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# Non-conventional methodologies for transition-metal catalysed carbon–carbon coupling: a critical overview.

## Part 1: The Heck reaction

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### Contents

1. General introduction	11772
1.1. Substrates	11773
1.2. Catalytic systems	11773
1.3. Solvents	11774
1.3.1. Supercritical fluids (SCFs)	11774
1.3.2. Ionic liquids (ILs)	11774
1.3.3. Fluorous media	11775
1.3.4. Aqueous solvents	11775
1.4. Reaction conditions	11775
1.4.1. Physical activation	11776
1.4.1.1. Microwave	11776
1.4.1.2. Ultrasound	11776
1.4.1.3. High pressure	11776
1.4.2. Physicochemical activation	11776

**Keywords:** Heck reaction; Supercritical fluids; Ionic liquids; Fluorous media; Aqueous solvents; Microwave; Ultrasound; High pressure; Nanofiltration; Microreactors; Ball-milling conditions.

**Abbreviations:** A, ampere; AAEMA, deprotonated form of 2-(acetoacetoxy)ethyl methacrylate; acac, acetylacetonate; Ad, adamantyl; A336, tricaprylmethylammonium chloride; atm, atmosphere; bbim, 1,3-di-*n*-butylimidazolium; *b*, block copolymer; bmim, 1-butyl-3-methylimidazolium; BINAP, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl; Boc, *tert*-butoxycarbonyl; BTF, benzotrifluoride ( $\alpha,\alpha,\alpha$ -trifluorotoluene); Cbz, benzyloxycarbonyl; *co*, copolymer; COD, 1,5-cyclooctadiene; Cy, cyclohexyl; DAB, 1,4-diaminobutane; dba, dibenzylideneacetone; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DEA, *N,N*-diethylacetamide; DEC, dendrimer-encapsulated catalyst; dendr, dendrimer; DIPEA, diisopropylethylamine; DMA, *N,N*-dimethylacetamide; DMF, dimethylformamide; DMG, *N,N*-dimethylglycine; dppp, 1,3-diphenylphosphinopropane; EDG, electron-donating group; EWG, electron-withdrawing group; Fc, ferrocenyl; F-dppp, fluorine-tagged 1,3-bis(diphenylphosphino)propane; HDAPS, *N*-hexadecyl-*N,N*-dimethyl-3-ammonio-2-propanesulfonate; Hex, hexyl; IL, ionic liquid; LDH, layered double hydroxide; M, metal; MCM-41, hexagonally packed mesoporous molecular sieves; MW, microwave; Nf, nonaflate (nonafluoro-*n*-butane-1-sulfonyl); NMP, *N*-methylpyrrolidinone;  $P_c$ , critical pressure; PAMAM, poly(amidoamine); PEG, poly(ethylene glycol); pmim, 1-*n*-pentyl-3-methylimidazolium; PNIPAM, poly(*N*-isopropylacrylamide); PNP, *p*-nitrophenyl; PS, polystyrene; Py, pyridyl; RCM, ring-closing metathesis; ROMP, ring-opening metathesis polymerisation; rt, room temperature; SAPO, silico aluminophosphate; sc, supercritical; SCF, supercritical fluid; SCM, shell cross-linked micelles; SDS, sodium dodecyl sulfate; TBAA, tetra-*n*-butyl ammonium acetate; TBAB, tetra-*n*-butyl ammonium bromide; TBAC, tetra-*n*-butyl ammonium chloride; TBAF, tetra-*n*-butyl ammonium fluoride; TEAC, tetraethylammonium chloride; Tf, trifluoromethanesulfonyl; TPPDS, bis(*p*-sulfonatophenyl)phenylphosphane dipotassium salt; Na-TPPMS, mono(*m*-sulfonatophenyl)diphenylphosphane monosodium salt; *m*-TPPTC, tris(*m*-carboxyphenyl)phosphane trilithium salt; TPPTS, tris(*m*-sulfonatophenyl)phosphane trisodium salt; TXPTS, tris(4,6-dimethyl-3-sulfonatophenyl)phosphane trisodium salt;  $T_c$ , critical temperature; THF, tetrahydrofuran; THP, tetrahydropyranyl; TFA, trifluoroacetic acid; Tol, tolyl; TOF, turnover frequency (mol of product per mol of catalyst  $h^{-1}$ ); TON, turnover number (mol of product per mol of catalyst); Ts, *p*-toluenesulfonyl; ttmp, tris-(2,4,5-trimethoxyphenyl)phosphane; wt, weight; XAFS, X-ray absorption fine structure.

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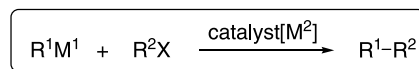
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1.4.2.1. Micellar solutions	11776
1.4.2.2. Microemulsions	11777
1.4.3. Electrochemical activation	11777
1.5. Miscellaneous non-conventional techniques	11777
1.5.1. Nanofiltration	11777
1.5.2. Microreactors	11777
1.5.3. Ball-milling conditions	11778
2. Objectives and organisation	11778
3. Introduction to the Heck reaction	11778
4. Substrates	11778
4.1. Alternative arylating agents	11778
4.2. Supported substrates	11782
5. Catalytic systems	11785
5.1. Ligands: ligand-free catalytic systems	11785
5.2. Catalysts: supported catalysts	11787
5.2.1. Carbon	11787
5.2.2. Metal oxides and other inorganic materials	11788
5.2.3. Clays, zeolites and molecular sieves	11795
5.2.4. Polymers	11798
5.2.5. Dendrimeric systems	11803
6. Solvents	11806
6.1. Supercritical fluids	11806
6.2. Ionic liquids	11808
6.3. Fluorous media	11814
6.4. Aqueous solvents	11817
7. Reaction conditions	11820
7.1. Physical activation	11820
7.1.1. Microwave	11820
7.1.2. Ultrasound	11822
7.1.3. High pressure	11822
7.2. Physicochemical activation	11823
7.2.1. Micellar solutions	11823
7.2.2. Electrochemical activation	11824
8. Miscellaneous non-conventional techniques	11824
8.1. Nanofiltration	11824
8.2. Microreactors	11825
8.3. Ball-milling conditions	11826
9. General conclusions	11826
References and notes	11826
Biographical sketches	11835

## 1. General introduction

The formation of carbon–carbon bonds is a fundamental reaction in organic synthesis the efficiency of which has interested organic chemists for a long time ago. Aryl–aryl bond formation has been known for more than a century and was one of the first reactions involving a transition metal.<sup>1</sup> Modern synthetic chemistry is also sustained by the use of transition-metal catalysts as powerful tools for carbon–carbon bond-forming processes.<sup>2</sup> Among these, carbon–carbon coupling reactions through the activation of carbon–hydrogen bonds,<sup>3</sup> as well as addition reactions,<sup>4</sup> have experienced an increasing interest in the preparation of molecules, the access to which is not so straightforward using other methodologies. On the other hand, the transition-metal catalysed carbon–carbon bond formation developed in the 1970s represented a milestone in synthetic organic chemistry that allowed the cross coupling of substrates in ways that would have previously been thought impossible.<sup>5</sup> This protocol has been substantially improved

and expanded over the past 30 years, providing an indispensable and simple methodology for preparative organic chemists (Scheme 1).



M<sup>1</sup> = Li (Murahashi)  
Mg (Kumada-Tamao, Corriu)  
B (Suzuki-Miyaura)  
Al (Nozaki-Oshima, Negishi)  
Si (Tamao-Kumada, Hiyama-Hatanaka)  
Zn (Negishi)  
Cu (Normant)  
Zr (Negishi)  
Sn (Migita-Kosugi, Stille).....  
M<sup>2</sup> = Fe, Ni, Cu, Pd, Rh,.....  
X = I, Br, Cl, OSO<sub>2</sub>R,.....

Scheme 1.

In spite of the fact that it would seem that most of the research on developing carbon–carbon coupling strategies has been done, some new challenges on this topic have emerged in the narrow boundary between the 20th and 21st century. A new mentality of the organic chemist is focussed on the design of new tendencies and methodologies able to make the already known chemical transformations simpler, faster, cheaper, greener and in general, more efficient processes. In particular, increasing attention has been paid to the ‘green chemistry’ of these processes, this concept being understood as the set of principles<sup>6</sup> that reduce or eliminate the use or generation of hazardous substances.<sup>7</sup> The idea of atom-economical reactions may be also a useful concept in helping to promote thinking in the direction of sustainable chemistry.<sup>8</sup> In order to achieve all the goals mentioned above, several valuable and distinctive techniques,<sup>9</sup> which do not find daily use in the laboratory, can be applied by the organic chemist to operate at different levels including (a) the type of substrates, (b) the catalyst, (c) the solvent, (d) the reaction conditions, (e) the separation techniques and (d) the reaction vessel. An introductory commentary to remark the importance of any of these parameters follows.

### 1.1. Substrates

The majority of studies of metal-catalysed cross-coupling reactions involve a halide or sulfonate as the electrophile and an organometallic reagent as the nucleophile in which the carbon atoms to be coupled are all  $sp^2$ -hybridized. There is, however, a substantial need for the development of successful cross-coupling reactions involving either alkyl halides or sulfonates. Organic halides also take part in Heck-type reactions. On the other hand, all these processes have in common some lack of atom economy,<sup>8</sup> since the corresponding inorganic salts are obtained and require proper isolation and treatment.

In the past decade, there have been developments in palladium-catalysed coupling systems for Heck, Suzuki, Stille and Sonogashira reactions among others, as a consequence of the great interest in the development of coupling partners that are both more economical and readily accessible. In spite of the fact that organoboranes and organostannanes have been the reagents of choice for some of these reactions, there are still some drawbacks in their use: certain organostannanes such as the trimethyltins,  $Me_3SnX$  and their by-products are toxic, whereas organoboranes have a lack of stability, particularly alkyl- and alkenylboranes.

Consequently, the search for novel substrates for the cross-coupling reactions has been the focus of much attention, for example, carboxylic acids, anhydrides and esters, as well as sulfonium salts, thiol esters and thioethers, have emerged as interesting alternatives to aryl halides.<sup>10</sup> In particular, carboxylic acids do not generate large amounts of waste and they work in the absence of phosphane ligands. There is, however, no general advantage in terms of atom economy and their generation is not always readily accessible, producing stoichiometric amounts of salts as by-products. The Stille, Suzuki and Kumada reactions with alkyl and aryl fluorides is a recent and promising research area leading to

the cross-coupled products under generally mild reaction conditions.<sup>11</sup> The stability of vinylic tellurides has also been used in palladium-catalysed cross-coupling reactions for the preparation of stereochemically defined enynes and enediynes. The fact that these reagents work in the presence of sensitive functional groups and under mild reaction conditions makes them interesting substitutes for vinylic halides and triflates.<sup>12</sup>

On the other hand, potassium trifluoro(organo)borates are promising alternatives to the use of the known organo-boronic acids, exhibiting higher reactivity and exceptional stability.<sup>13</sup> Germanium reagents have been recently used in cross-coupling reactions,<sup>14</sup> exhibiting intermediate reactivity between that of organotin<sup>15</sup> and organosilicon compounds,<sup>16</sup> avoiding the toxicity of certain organotin reagents and being more reactive than silicon.

In recent years, an increasing interest has been shown in the possibility of anchoring the substrates to a solid support, facilitating their use in automated parallel synthesis in a combinatorial manner. The main advantages of these solid-phase transformations are the avoidance of tedious workup procedures, the quasi high-dilution effect (high yields by employing an excess of reagent), amenability to automatization and the non-interference of various functionalities in the building blocks on a solid support.<sup>17</sup>

### 1.2. Catalytic systems

The form in which the catalyst is present in the reaction media is fundamental to drive the reaction in an effective manner. A wide range of possibilities can be explored, depending on the different combinations of the components of the catalytic system, for example, the catalyst can be present as nanoparticles, ligandless, unsupported, supported, etc.

Transition-metal nanoparticles have attracted a great deal of attention during the last 10 years as catalytic systems with great potential, due to the large surface area of the particles. It has been suggested that metal colloids are very efficient catalysts because of the ratio of atoms remaining at the surface. In fact, these catalysts are microheterogeneous systems bearing nanoparticles. The application of transition-metal nanoparticles to the formation of carbon–carbon bonds is still, however, in its infancy.<sup>18</sup>

Recent interest in the development of environmentally benign syntheses and in minimising the cost of the precious metal catalysts has led to the development of polymer-bound metal catalysts for the carbon–carbon coupling reaction that maintain high activity and selectivity. The supported complexes can be recovered from the reaction mixtures, they do not contaminate the product solution and they can be recycled and used for the rapid production of compound libraries. Often, however, there is metal leaching during the course of the reaction and they are often not recyclable. As a result, many efforts have been focussed on the development of new ligand-derivatised polymeric supports for the attachment of metals and on the design of new methods to increase both the activity and the selectivity.<sup>19</sup> In particular, dendrimers as soluble supports

have recently attracted much attention in homogeneous catalysis, since these well-defined macromolecular structures enable the construction of precisely controlled catalyst structures. Moreover, the globular shapes of the higher generations of dendrimers are particularly suited for membrane filtration.<sup>20</sup>

Alternatively, the immobilisation of catalysts can be effected on inorganic matrices, having several important potential advantages such as: (a) the remarkable ease of handling and use, (b) reduced product contamination by having the catalyst fully bound to the solid support, (c) relatively safe handling owing to full chemisorption of the possible toxic chemicals, (d) reduced environmental impact upon work-up, (e) good thermal and chemical stabilities, (f) good dispersion of the active catalytic sites, with a significant improvement in the reactivity and (g) improvement in the reaction selectivity, due to the constraints of the pores and the characteristics of surface adsorption.<sup>21</sup> In general, they offer superior chemical, mechanical and thermal stability compared with the use of organic polymeric supports.

### 1.3. Solvents

Since most of the chemical reactions are performed in the solution phase, the solvent plays a crucial role to implement any transformation, either on a laboratory or industrial scale.<sup>22</sup> For a given process, the solvent will always condition the work-up, recycling and disposal techniques employed for the appropriate treatment of the reaction mixture and every one of its components. Within the context of green and sustainable chemistry, the endeavour to replace volatile organic solvents in organometallic catalysis for alternative more practical and environmentally friendly solvents must be highlighted.<sup>23</sup> Interesting approaches include catalysis based on aqueous systems, ionic liquids, supercritical media, or fluorinated phases.

Nonetheless, it is known that many reactions proceed efficiently in the solid state. In fact, in some cases, solid-state organic reactions occur more efficiently and selectively than their solution counterparts, since molecules in a crystal are arranged tightly and regularly. In addition, the solvent-free reactions make syntheses simpler for process and handling, saving energy and preventing solvent waste, hazards and toxicity.<sup>24</sup>

**1.3.1. Supercritical fluids (SCFs).** Supercritical fluids are well established as useful solvents for extraction, chromatography and a few specialised reactions.<sup>25</sup> In spite of the fact that they have been used for large-scale industrial production for most of the 20th century, only during the last decade have their special properties made them attractive solvents for modern synthetic chemistry.<sup>25d,26</sup> The properties of SCFs are different from those of ordinary liquids and gases and are tunable simply by changing the pressure and temperature. They form a single-phase mixture with gaseous reactants, sometimes avoiding a rate-limiting mass-transfer step and therefore, enhance the reaction rates.

scCO<sub>2</sub> is readily accessible, with a  $T_c$  of 31 °C and a  $P_c$  of 73 atm and is abundant, inexpensive, non-flammable, non-

toxic and environmentally benign. Non-polar organic solvents have a high solubility in scCO<sub>2</sub> and the solubility of polar, ionic, or polymeric compounds can be increased by the addition of a polar additive or an appropriate surfactant. In addition, scCO<sub>2</sub> facilitates the separation of reactants, catalysts and products, being a substitute for environmentally less acceptable solvents.<sup>27</sup>

Water near its critical point ( $T_c$  374 °C and  $P_c$  218 atm) also offers environmental advantages and possesses properties very different from those of ambient liquid water. The dielectric constant is much lower and the formation of hydrogen bonds is less favoured. As a result, high temperature water behaves like many organic solvents in allowing a high solubility of organic compounds in near-critical water and complete miscibility in supercritical water.<sup>28</sup>

**1.3.2. Ionic liquids (ILs).** Ionic liquids can be generally defined as liquid electrolytes composed entirely of ions. By applying the melting point criterion, they can be considered as salts with a melting point below the boiling point of water. They are, however, better described as liquid compounds that display ionic-covalent structures. Most ILs have an organic cation and an inorganic polyatomic anion. The most commonly used cations in room temperature ionic liquids are alkylammonium, alkylphosphonium,<sup>29</sup> *N,N'*-dialkylimidazolium and *N*-alkylpyridinium cations and the most commonly utilised alkyl chains are methyl, ethyl, butyl, hexyl, octyl and decyl. Although the pyridinium- and imidazolium-based chloroaluminate ionic liquids share the disadvantage of being reactive with water, the more recent tetrafluoroborate, hexafluorophosphate, nitrate, sulfate and acetate salts are stable towards hydrolysis. Their physical and chemical properties can be finely tuned for a range of applications by varying the cations or anions.<sup>30</sup>

This fascinating group of chemicals exhibits a great potential to improve development in organic chemistry, due to their particular properties: a very wide liquid range, relatively wide electrochemically stable window, good electrical conductivity, high ionic mobility with strong ion–ion interactions, negligible vapour pressure, non-flammability, excellent chemical and thermal stability and ability to act as catalysts. Reactions in ILs have different thermodynamic and kinetic behaviour, which often lead to improved process performance. Moreover, ILs allow an enhanced stability of organometallic reagents and biocatalysts and an easy recovery, as well as possible recycling of homogeneous catalysts.

The potential for recyclability, ability to dissolve a variety of materials and the non-volatile nature of the ILs are some of their unique attributes responsible for their popularity. Although originally studied in electrochemistry, ILs are currently being explored as environmentally benign solvent substitutes in a variety of applications such as chemical synthesis, liquid–liquid separations, extractions, dissolution processes, catalysis, biocatalysis and polymerisation.<sup>31</sup> More recently, they have also found application in asymmetric synthesis,<sup>32</sup> as well as in the synthesis of nanoparticles and other inorganic nanostructures.<sup>33</sup>

It has recently been shown that there is a possibility of performing chemical reactions in ILs in conjunction with microwave irradiation,<sup>34</sup> as well as with separation routes utilising binary ionic liquid–scCO<sub>2</sub> systems.<sup>35</sup>

In spite of the fact that ILs are generally considered as environmentally friendly substitutes for volatile organic solvents, the environmental fate and any potential toxicity issues for most ionic liquids are not known, particularly with respect to alkylimidazolium systems.<sup>36</sup> In fact, so far, only a few toxicological and ecotoxicological data are available for this group of chemicals. More information seems to be needed in order to assess ILs with regard to sustainability and the principles of green chemistry.<sup>37</sup> On the other hand, although ILs are easy to obtain, their conventional preparation involves an excess of solvents and alkyl halides and, therefore, new efforts have emerged in a direction to minimize, at least, the amount of solvents in the reaction medium.<sup>38</sup>

**1.3.3. Fluorous media.** Fluorous chemistry can be considered as a complementary type of liquid-phase synthetic and separation methodology involving the use of fluorine-containing reagents and solvents.<sup>39</sup> Fluorous solvents offer a unique perspective on a chemical reaction that allows one or more stages to be carried out without the need for volatile or noxious organic solvents, making the process simpler and more energy efficient and reducing the separation steps. Perfluoroalkanes, perfluorodialkyl ethers and perfluorotrialkylamines are the most common fluorous solvents used, which are practically non-toxic. These solvents can be used in conjunction with a fluorous reaction component (reagent, catalyst, pre-catalyst, ligand, product, scavenger, protecting group, etc.), to which a fluorous tag has been deliberately attached in order to make it soluble in fluorous solvents. It must be taken into account that the attachment of fluorous ponytails can significantly change the reactivity of the fluorous reaction component, the insertion of two or three methylene groups before the fluorous ponytail being necessary, in many cases, to decrease their strong electron-withdrawing effects.

The foundation of this methodology resides in the fact that the fluorous solvent has a low miscibility with common organic solvents. At a certain increased temperature, it is miscible with organic solvents but, when cooled, it splits into a biphasic system. A fluorous biphasic system can therefore, consist of a fluorous phase containing a fluorous-soluble reaction component and a second product phase, which may be any organic or non-organic solvent with limited solubility in the fluorous phase.<sup>40</sup> The fluorous biphasic reaction at the operating temperature can proceed either in the fluorous phase or at the interface of the two phases, depending on the solubilities of the reactants in the fluorous phase. When the reaction is complete, simply cooling the system makes the fluorous solvent immiscible in the organic phase. The fluorous biphasic system therefore, combines the advantages of a one-phase reaction with biphasic product separation.

The fluorous biphasic concept has been successfully applied in stoichiometric chemical reactions utilising organic, inorganic, or organometallic fluorous-soluble reagents. Because of the nature of the fluorous media, the application

of fluorous reagents is limited to apolar substrates, since the reactions of polar substrates may be too slow for practical applications. This concept has also found application in catalysis (where only transition-metal complexes have been converted into fluorous soluble entities through ligand modification), in multistep organic synthesis and in combinatorial chemistry.<sup>41</sup>

The fluorous phase, together with ionic liquid approaches and supercritical fluid systems, offers a whole new repertoire of solvents that overcome many of the problems of volatile organics.

**1.3.4. Aqueous solvents.** In the most recent decades, the use of water as a reaction solvent or co-solvent has received much attention in synthetic organic chemistry, with sometimes surprising and unforeseen results.<sup>42</sup> Despite the different advantages that the previous mentioned solvents can offer, water can still be considered as a unique solvent. Moreover, water is the ‘solvent of Nature’ and, therefore, its use in common chemistry can be regarded as biomimetic and biocompatible. There are many potential reasons to replace the classical organic solvents by water, such as cost, safety and environmental concern. In fact, aqueous procedures are often referred to as green, environmentally friendly, or benign. In addition, the unique solvation properties of water have been shown to have beneficial effects on many types of organic reactions in terms of both the rate and selectivity. Furthermore, experimental procedures may be simplified, since isolation of organic products and recycling of water-soluble catalysts and other reagents can be achieved by simple phase separation.

The main obstacle to the use of water as reaction solvent is the negligible solubility of the majority of organic compounds in water. This problem can be addressed by using aqueous organic solvents or phase-transfer agents. As will be shown in this review, aqueous-phase transition-metal catalysis, including asymmetric catalysis, has emerged as an important tool in the formation of carbon–carbon bonds.<sup>43</sup>

## 1.4. Reaction conditions

While some reactions occur spontaneously, most of them require activation. For carbon–carbon coupling reactions, chemical activation modes (i.e., catalysis) are indispensable in order to make processes effective and selective. The association of several activation modes, however, emerges as a powerful synthetic strategy when the respective kinetic effects are convergent. Besides the classical thermal activation mode, new methods have emerged in the recent years, such as physical or physicochemical activation techniques, among others. Thus, microwaves and ultrasonic and high-pressure techniques have been added to the chemist’s repertoire as physical methods for accelerating chemical reactions. On the other hand, physicochemical activation results from interactions between the medium and the reactive molecules and can arise from the solvent or from added complexing molecules. Physicochemical activation can be applied through the action of solvophobic effects (microemulsions and vesicles), host–guest chemistry, etc.



### 1.4.1. Physical activation.

**1.4.1.1. Microwave.** Microwaves are a form of electromagnetic radiation. When molecules with a permanent dipole are placed in an electric field, they become aligned with that field. If the electric field oscillates, then the orientations of the molecules will also change in response to each oscillation. Most microwave ovens operate at 2.45 GHz, wavelength at which oscillations occur  $4.9 \times 10^9$  times per second. Molecules subjected to this microwave radiation are extremely agitated as they align and realign themselves with the oscillating field, creating an intense internal heat that can escalate as quickly as  $10^\circ\text{C}$  per second. Non-polar molecules such as toluene, carbon tetrachloride, diethyl ether and benzene are microwave inactive, while polar molecules such as DMF, acetonitrile, dichloromethane, ethanol and water are microwave active. This technique proves to be excellent in cases where traditional heating has a low efficiency because of poor heat transmission and, hence, local overheating is a major inconvenience.<sup>44</sup>

Microwave-assisted synthesis is a relatively young science of increasing research interest, as evidenced by the number of papers and reviews appearing in the literature.<sup>45</sup> The most important advantage of microwave-enhanced chemistry is the reduction in the reaction times. Reactions that require hours or days of conventional heating may often be accomplished in minutes under microwave heating. Moreover, reactions are not only faster, but proceed with higher purity and, consequently, higher yields. The dramatic acceleration and increased purity and yields of microwave-assisted reactions make them attractive to the increased demands in industry and, in particular, for combinatorial drug discovery.<sup>46</sup> In addition to being energy efficient, the possibility of employing milder and less toxic reagents and solvents, or even solvent-free systems, offers a further advantage of this heating technology.

**1.4.1.2. Ultrasound.** Ultrasound generally designates acoustic waves with frequencies in the range of 20–100 MHz. This energy is insufficient to cause chemical reactions, but when ultrasound travels through media a series of compressions and rarefactions are created, the rarefaction of liquids leading to cavities. During rarefaction, the negative pressure developed by power ultrasound is enough to overcome the intermolecular forces binding the fluid and tear it, producing cavitation bubbles. The succeeding compression cycle can cause the microbubbles to collapse almost instantaneously with the release of large amounts of energy. The enormous rise in local temperatures and pressures produces a dramatic beneficial effect of reaction acceleration, with relatively short times being required for completing the reaction such that the decomposition of thermally labile products is minimised.<sup>47</sup>

The frequency of ultrasound has surprisingly little influence on the reactions within the range in which cavitation occurs. Of significance is the fact that ultrasound affects both homogeneous and heterogeneous reactions.

**1.4.1.3. High pressure.** Pressure represents a mild non-destructive activation mode, generally respecting the molecular structure by limiting decomposition or further

evolution of the products. Therefore, the specific effects of high pressure can be of important value for organic synthesis.<sup>48</sup> The kinetic pressure effect is primarily determined by the variation of volume due to changes in the nuclear positions of the reactants during the formation of the transition state. Related to volume requirements are steric effects since the bulkiness of the molecules involved in the transition state conditions the magnitude of the steric interactions. As a consequence, pressure affects volume changes and should have an effect on steric congestion.

As a mild activation mode, pressure may be considered of value in the synthesis of thermally fragile molecules, permitting a lowering of the temperature. In addition, the selectivity is generally preserved or even improved under such conditions.

On the other hand, pressure can be combined with solvophobic effects. The effect of pressure on organic reactions in aqueous solutions is complex. The activation volume relative to hydrophobic effects is positive (meaning deceleration by pressure), whereas the activation volume due to hydrogen bonding is negative. In addition, electrostatic effects may also be involved in many reactions (negative activation mode). Nevertheless, the combination of pressure and solvophobic activation may be an interesting method to increase the reactivity of reluctant polar molecules.

### 1.4.2. Physicochemical activation.

**1.4.2.1. Micellar solutions.** Micelles are dynamic colloidal aggregates formed by amphiphilic surfactant molecules. These molecules can be ionic, zwitterionic, or non-ionic, depending on the nature of their head groups, their micelles being classified in the same way. In dilute solutions, amphiphile molecules exist as individual species in the media and these solutions have completely ideal physical and chemical properties. As the amphiphile concentration increases, aggregation of monomers into micelles occurs and, as a consequence, these properties deviate gradually from ideality. This concentration is called the critical micellisation concentration.

During the formation of micelles, head group repulsions are balanced by hydrophobic attractions and for ionic micelles, also by attractions between head groups and counterions. Hydrogen bonds can be also formed between adjacent head groups.

It is well known that the rates and pathways of all kinds of chemical reactions can be altered by performing the reactions in micellar media instead of pure bulk solvents.<sup>49</sup> Micelles are able to (a) concentrate the reactants within their small volumes, (b) stabilise substrates, intermediates or products and (c) orientate substrates so that ionisation potentials and oxidation–reduction properties, dissociation constants, physical properties, quantum efficiencies and reactivities are changed. Thus, they can alter the reaction rate, mechanism and the regio- and stereochemistry. For many reactions, rate increments of 5–100-fold over the reactions in homogeneous solutions have been reported. In some cases, rate increments may be much higher and increments in the order of  $10^6$ -fold have been observed.

**1.4.2.2. Microemulsions.** When water is mixed with an organic liquid immiscible with water and an amphiphile, generally a turbid milky emulsion is obtained which, after some time, separates again into an aqueous and an organic phase. On the water-rich side, the mixtures consist of stable dispersions of oil droplets in water, which coagulate with rising temperature. A spongelike structure is obtained if the mixtures contain approximately equal amounts of water and oil. On the oil-rich side, dispersed water droplets are found, which coagulate with decreasing temperature. The size of the domains is a function of the amphiphile concentration and the volume fractions of water and oil.<sup>50</sup>

Since microemulsions contain both a polar component (water) and a non-polar component (oil), they are capable of solubilising a wide spectrum of substrates. The mechanism of solubilisation is similar to that in micellar solutions. The micelles are replaced by the oil domains, which are capable of solubilising all kinds of hydrophobic substances. The solubilisation of polar substances takes place analogously through the aqueous domains of the microemulsion. The solubilisation capacity of microemulsions is generally superior to that of the micellar solutions and can therefore, affect the rate and course of a certain reaction.

**1.4.3. Electrochemical activation.** Electrochemistry represents a convenient synthetic method in which electrons constitute clean and energetically efficient reactants. The development of the potentialstat turned electrochemistry into a common tool for organic synthesis.<sup>51</sup> In spite of the procedural simplicity, absence of side products derived from reagents and high ability for accomplishing selective oxidoreductions under very mild conditions, electro-synthesis still appears to be undervalued, even though some industrial-scale work has demonstrated its appealing features.

The apparatus required for electrosynthesis can be as simple as a beaker containing a pair of electrodes connected to a direct-current voltage source. A stirrer, thermometer, jacket, inert gas inlet, or any combination, can be added. For some reactions, the separation of the electrodes by a diaphragm is mandatory to prevent the products from one electrode diffusing to the other and being destroyed. A proper solvent and supporting electrolyte will be also required.

In some cases, chemical techniques turn out to be quite difficult in the preparation of certain organometallic species. Electrochemistry can, however, provide an easy way to generate a desired oxidation state of a metal complex that becomes the active catalytic species for an organic reaction. In the particular case of redox processes, the active catalytic species can be recycled continually by the electrode oxidation or reduction reactions. In these processes, the electrons are consumed stoichiometrically with respect to the substrate. Therefore, it is the electrons that are used as clean, controlled and non-polluting redox agents. In non-redox reactions, electrochemistry is used only to generate the catalytic system. It has been observed that electro-generated species can be more reactive than their chemically prepared analogues.<sup>52</sup>

## 1.5. Miscellaneous non-conventional techniques

The techniques mentioned below are rather specific and so far have only been described for a limited number of examples.

**1.5.1. Nanofiltration.** It is important to recognise that the total efficiency of synthesis is also conditioned by the ability to separate the products from the unchanged starting materials, excess reagents and catalysts. Within the green chemistry context, it is also interesting to develop techniques that enable the separation and re-use of catalysts and reagents. Thus, separation protocols additional to those described above (i.e., perfluorinated systems, sc fluids, ionic liquids, solid-phase supported reagents and catalysts, etc.), which are easily automated to enable rapid purification by simple operations, are welcome.<sup>53</sup>

In the field of homogeneous catalysis, separation of the catalyst from the product mixture is rather complicated, preventing large-scale industrial processes. An interesting and promising development in the area of homogeneous catalyst recycling is the attachment of homogeneous catalysts to soluble organic supports. In this way, macromolecular catalysts anchored on soluble supports such as polymers and dendrimers are created, which can be recovered by ultra- or nanofiltration techniques and re-used again.

Recently, solvent-stable ultra- and nanofiltration membranes have been introduced showing high retentions for medium-sized soluble molecules.<sup>54</sup> In the field of membrane filtration, ultra- and nanofiltration techniques are defined to retain macromolecules with dimensions between 8–800 and 0.5–8 nm, respectively.

**1.5.2. Microreactors.** Microreactor devices consist of a network of micron-sized channels (10–300  $\mu\text{m}$ ), with a high surface-area-to-volume, etched into a solid substrate.<sup>55</sup> For solution-based chemistry, the channel networks are connected to a series of reservoirs containing chemical reagents and products to form the complete device with overall dimensions of a few cm. Reagents can be brought together in a specific sequence, mixed and allowed to react for a specified time in a controlled region of the channel network using electrokinetic (electro-osmotic and electrophoretic) or hydrodynamic pumping. For electrokinetically driven systems, electrodes are placed in the appropriate reservoirs to which specific voltage sequences can be delivered under automated computer control. This control offers an effective method of moving and separating reagents within a microreactor, without the need for moving parts. Hydrodynamic pumping uses conventional, or microscale, pumps to manoeuvre solutions around the channel network, but, this technique has the disadvantage of requiring either large external pumps or complex fabrication of small moving parts.

Many reactions have been demonstrated to show altered reactivity, product yield and selectivity when performed in microreactors, as compared with conventional benchtop glassware. In fact, the desired product is often produced in higher yield and purity and more quickly. Process

parameters such as pressure, temperature, residence time and flow rate are more easily controlled, thus minimising risk and side reactions. Furthermore, solvent-free mixing, in situ reagent generation and integrated separation techniques can all help to make the chemistry greener.<sup>56</sup> One of the immediate applications is therefore in drug and process discovery, where the generation of compounds with different reagents under variable conditions is an essential factor and also allows, in a short time and with greater safety, a process to be transferred to the pilot and production scale.<sup>57</sup>

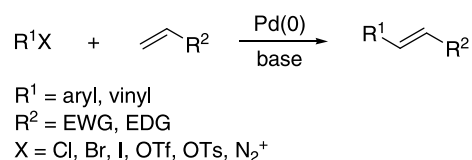
**1.5.3. Ball-milling conditions.** Ball-mill chemistry is of interest because of the mild conditions under which it operates and also the absence of any solvent and easy work up. This technique has, however, been scarcely studied and applied to very few reactions.<sup>58</sup> Apparently, the rotation of the steel balls creates a high pressure in contact with the walls of the container, allowing the reagents to interact and promoting the process.

## 2. Objectives and organisation

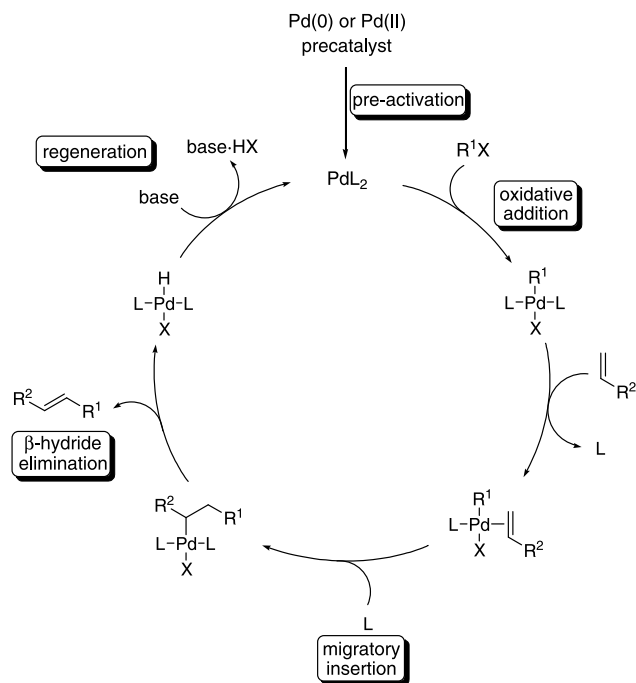
In principle, we wanted to present in this report the application of recent non-conventional methodologies to the transition metal-catalysed carbon–carbon coupling reaction. Heck, Suzuki, Sonogashira, Stille, Negishi and Kumada reactions, among others, were the reactions originally to be covered. Because of the abundant literature found on this topic, however, we decided to dedicate this first part only to the Heck reaction, whereas the rest of the reactions will be studied in the second part in due course. Nonetheless, the above introduction is common for any of the parts of the review. Other carbon–carbon bond forming reactions such as the transition-metal catalysed coupling reactions through the activation of carbon–hydrogen bonds, nucleophilic substitution (Tsuji–Trost reaction), or acylation of carbon nucleophiles are beyond the scope of this review. Some of the reports dealing with the diverse topics to be tackled here have been previously and properly reviewed elsewhere and will not be covered to their full extent. Instead, a summary together with the more recent contributions until 2004 will be provided. The review is organised according to the sub-headings presented in the general introduction, taking into account the different components and variety of conditions involved in the Heck reaction. Many of the contributions to this review are also analysed from a critical point of view, with the aim of discussing the advantages and disadvantages that the different techniques offer and trying to select the best choice, when possible. A short conclusion can be found at the end of each section.

## 3. Introduction to the Heck reaction

The Heck reaction is broadly defined as Pd(0)-mediated coupling of an aryl or vinyl halide or sulfonate with an alkene under basic conditions. Since its discovery, this methodology has been found to be very versatile and applicable to a wide range of aryl species and a diverse range of olefins (Scheme 2).<sup>59</sup> The major steps of the



Scheme 2.



Scheme 3.

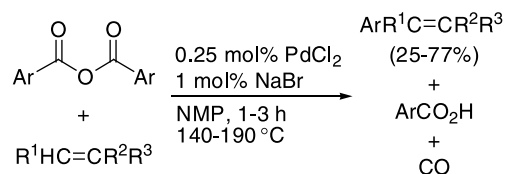
general and traditional mechanism for the Heck reaction are depicted in Scheme 3.<sup>60</sup>

## 4. Substrates

### 4.1. Alternative arylating agents

In all the Heck reactions described in Scheme 2, a stoichiometric amount of base is required to neutralise the acid that is formed during the reaction (see Scheme 3). As a consequence, the corresponding equivalent amount of halide salt is obtained as waste. In the search for a cheap aryl source that does not lead to the formation of halide salts, de Vries et al. introduced the use of aromatic carboxylic anhydrides as the arylation source.<sup>61</sup> For instance, heating benzoic anhydride and *n*-butyl acrylate in a *N*-methylpyrrolidinone (NMP) solution containing PdCl<sub>2</sub> and NaBr at 160 °C for 90 min, led to the formation of (*E*)-*n*-butyl cinnamate with high conversion, 90% selectivity and good yield. Although a catalytic amount of a chloride or bromide was necessary for optimal activity, phosphane ligands were not required. *p*-Methoxybenzoic anhydride and 2-furanoic acid anhydride were also successfully used as arylation agents. A variety of olefins were arylated under similar conditions at 140–190 °C (Scheme 4). Olefins with electron-withdrawing groups gave better yields, although, due to the relatively high reaction temperature, double-bond isomerisations and less





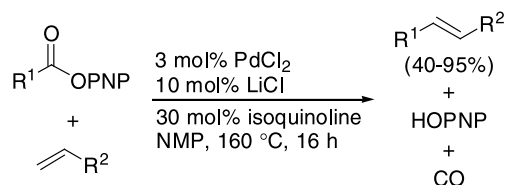
Ar = Ph, *p*-MeOC<sub>6</sub>H<sub>4</sub>, 2-furyl  
 R<sup>1</sup> = H, OCy, CO<sub>2</sub>Bu<sup>n</sup>, N(CH<sub>2</sub>)<sub>3</sub>CO  
 R<sup>2</sup> = H, Me, CO<sub>2</sub>Bu<sup>n</sup>  
 R<sup>3</sup> = H, Ph, CO<sub>2</sub>Bu<sup>n</sup>, CN, *n*-C<sub>8</sub>H<sub>17</sub>

Scheme 4.

regioselective arylations were observed in some cases. It is noteworthy that the only side products in the reaction are benzoic acid (easily recovered by extraction with hot water) and carbon monoxide (which could be transformed into carbon dioxide in industrial processes).

Further investigation on this topic by Schmidt and Smirnov showed that the use of lithium chloride instead of sodium bromide increased the catalyst activity and productivity, since chloride accelerates CO elimination from the oxidative addition product more than bromide.<sup>62</sup>

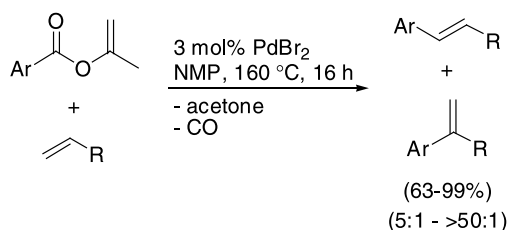
Gooßen et al. studied the decarbonylative olefination of aryl esters in an attempt to minimise the production of waste.<sup>63</sup> Starting from the *p*-nitrophenyl ester of the carboxylic acid, the corresponding alcohol formed in the Heck reaction could be recycled back into the starting ester, with CO and water being the only by-products in the overall reaction.<sup>63a</sup> Lithium chloride and isoquinoline proved to increase the effectiveness and stability of the catalyst in such a manner that higher yields were obtained. A wide variety of benzoates of electron-deficient phenols (e.g., *p*-nitrophenol) were found to be suitable substrates, whereas both electron-rich and electron-poor olefins gave similar yields, with regioselectivities ranging from 4:1 to 20:1 (Scheme 5). If we compare this methodology with that described above, the scope of this Heck olefination seems to be wider. The catalytic system, however, requires larger amounts of all of its components, as well as the presence of a substantial amount of isoquinoline that must be removed at the end of the process. The lower reactivity of the benzoic esters in comparison with the benzoic anhydrides is also reflected in the reaction times.



PNP = *p*-nitrophenyl  
 R<sup>1</sup> = *p*-YC<sub>6</sub>H<sub>4</sub> (Y = MeO, NC, MeCO, CHO, CF<sub>3</sub>, Cl, Pr<sup>i</sup>OCO), *m*-YC<sub>6</sub>H<sub>4</sub> (Y = Me, NO<sub>2</sub>, AcO), *o*-FC<sub>6</sub>H<sub>4</sub>, 2-naphthyl, 3-thienyl, 3-pyridyl, *trans*-cinnamyl  
 R<sup>2</sup> = H, Ph, CO<sub>2</sub>Bu<sup>n</sup>, CONHPr<sup>i</sup>, CN, 2-norbornyl

Scheme 5.

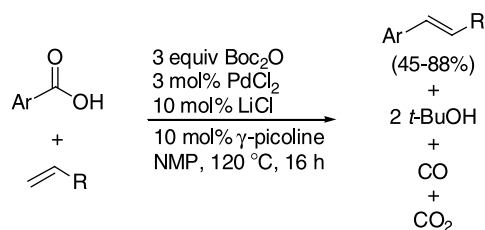
The above idea was extended recently to the use of isopropenyl arenecarboxylates as arylating agents in a salt-free medium.<sup>63b</sup> These arylating reagents were synthesised through a waste-free reaction involving ruthenium-catalysed addition of the carboxylic acids to propyne. Concerning the coupling reaction, instead of waste salts, CO and acetone are the only by-products, the volatility of which allows easy workup. Electron-rich and electron-deficient aryl, heteroaryl and vinyl carboxylic acid esters were coupled with several olefins (styrene in most cases) in good to excellent yields (Scheme 6). In contrast to the beneficial features of the whole process, the reaction temperature is rather high and is probably the reason for the moderate regioselectivities generally obtained (5:1–15:1), except in the case of *n*-butyl acrylate (> 50:1).



Ar = Ph, *p*-YC<sub>6</sub>H<sub>4</sub> (Y = CHO, Cl, MeO, MeCO, CF<sub>3</sub>), *m*-YC<sub>6</sub>H<sub>4</sub> (Y = CN, OAc, NO<sub>2</sub>), *o*-FC<sub>6</sub>H<sub>4</sub>, 2-naphthyl, 3-thienyl  
 R = Ph, CO<sub>2</sub>Bu<sup>n</sup>, 2-norbornyl

Scheme 6.

In the examples shown in Schemes 4 and 5, there is the necessity to generate the starting material in an extra reaction step and separate the olefin products from the carboxylic acids or phenols, these being practical disadvantages for small-scale preparations. Gooßen et al. utilised mixed anhydrides of carbonic and aromatic carboxylic acids, easily prepared in situ by mixing the carboxylic acids with di-*tert*-butyl dicarbonate (Boc<sub>2</sub>O), as arylating agents in the Heck olefination.<sup>64</sup> Different aromatic and heteroaromatic carboxylic acids (including electron-rich carboxylic acids) were coupled mainly with styrene, to give the expected products in moderate to good yields (45–88%) and selectivities (5:1–28:1) (Scheme 7). The reaction could be performed at a lower temperature (120 °C), in comparison to the examples described above, although  $\gamma$ -picoline was necessary to stabilise the palladium

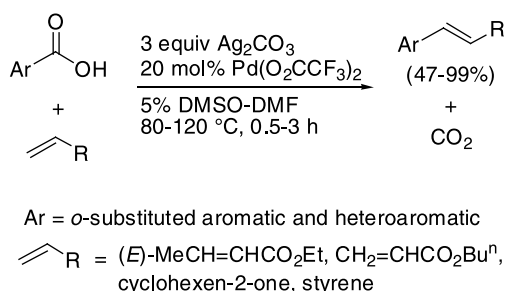


Ar = *p*-YC<sub>6</sub>H<sub>4</sub> (Y = MeO, Cl), *m*-YC<sub>6</sub>H<sub>4</sub> (Y = Me, MeCO<sub>2</sub>), *o*-FC<sub>6</sub>H<sub>4</sub>, 3,4,5-tri-MeOC<sub>6</sub>H<sub>2</sub>, 2-naphthyl, 2-thienyl, 2-furyl, 3-thienyl, 3-furyl  
 R = Ph, CO<sub>2</sub>Bu<sup>t</sup>, 2-norbornyl

Scheme 7.

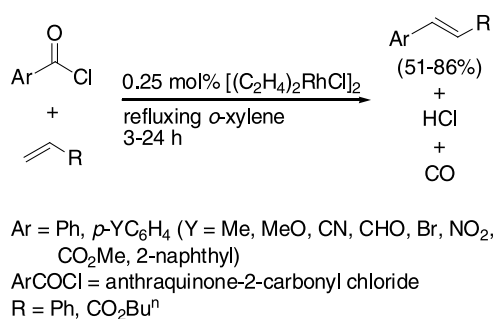
and to avoid precipitation and loss of activity at reasonable reaction rates.

Myers et al. subjected a wide range of arenecarboxylates to efficient Heck-type decarboxylative coupling with olefinic substrates under relatively mild reaction conditions and in short reaction times (Scheme 8).<sup>65</sup> The key additive, silver(I) carbonate, presumably functions both as a base and as a stoichiometric oxidant, enlarging the lifetime of the active catalyst. Good yields of the coupled products were obtained for both electron-rich and electron-withdrawing substituents on the aromatic carboxylic acid and olefinic partners such as styrene, acrylates, (*E*)-ethyl crotonate and cyclohexenone. Certainly this methodology allows the direct use of aromatic carboxylic acids without any previous transformation, although the experiments suggested that at least one *ortho* substituent is necessary for successful decarboxylative palladation to occur. The relatively high catalyst loading and the large amount of the silver salt used are the main disadvantages of this methodology, which probably would limit its application to a laboratory scale.



Scheme 8.

In 1982, Blaser and Spencer demonstrated that aryl chlorides could react with activated alkenes, under Pd(OAc)<sub>2</sub> catalysis in the presence of a tertiary amine at 120–130 °C, to give the expected (*E*)-aryllkenes stereospecifically and in high yields.<sup>66</sup> More recently, Miura et al. have utilised the rhodium complex [(C<sub>2</sub>H<sub>4</sub>)<sub>2</sub>RhCl]<sub>2</sub> for the catalytic decarboxylative Heck-type coupling of aryl chlorides with styrene and *n*-butyl acrylate.<sup>67</sup> This methodology is very interesting, since the reactions are carried out in the absence of any phosphane ligand and base and with low catalyst loading, although refluxing *o*-xylene (143–145 °C) is needed to obtain the products with good yields at reasonable reaction times (Scheme 9). In addition, the workup seems to be significantly simple, that is, filtration, evaporation and washing with an appropriate



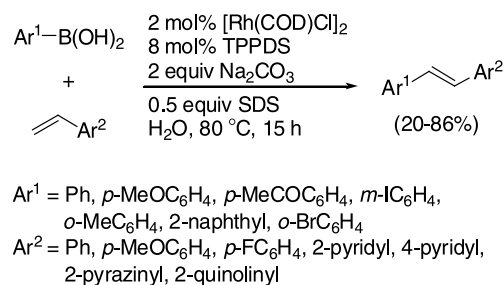
Scheme 9.

solvent such as methanol. A slow stream of nitrogen is, however, required to sweep away the HCl and CO evolved during the reaction, what can be a limitation for large-scale processes. Under similar conditions, cyclic alkenes such as norbornenes also reacted with aryl chlorides accompanied by cyclisation to afford the indanone derivatives.

Andrus et al. have recently applied a palladium-catalysed decarboxylative Heck-type reaction of aryl chlorides to the synthesis of resveratrol using palladium acetate, an imidazolium carbene-type ligand and a non-coordinating amine base, *N*-ethylmorpholine.<sup>68</sup> The overall yield starting from the inexpensive resorcylic acid (53%) was higher compared to the aryldiazonium or mixed anhydride approach.

Boronic acids have been used as arylating agents in Heck-type reactions by several groups.<sup>4b</sup> Uemura et al. showed, in 1994, that arylboronic acids reacted with alkenes in acetic acid at 25 °C in the presence of a catalytic amount of palladium(II) acetate, together with sodium acetate, to give the corresponding aryl-substituted alkenes in high yields.<sup>69</sup> Alkenylboronic acids also reacted with alkenes under similar conditions to give the corresponding conjugated dienes stereospecifically, but the product yields were lower compared with those from the arylboronic acids. A similar treatment of sodium tetraphenylborate (NaBPh<sub>4</sub>) with alkenes afforded the corresponding phenylated alkenes in high yields, together with biphenyl and benzene as side products. Oxidative addition of a carbon–boron bond to Pd(0), formed in situ, to give an organopalladium(II) species was assumed to be the key step of these cross-coupling reactions.

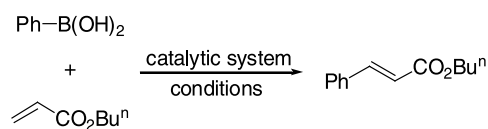
More recently, Lautens et al. utilised a rhodium complex to catalyse the coupling reaction of arylboronic acids and styrenes in an aqueous media (Scheme 10).<sup>70</sup> The best results were obtained with [Rh(COD)Cl]<sub>2</sub> and TPPDS as the water-soluble ligand. It was, however, necessary to add 0.5 equiv of sodium dodecyl sulfate (SDS) as a phase-transfer agent to avoid hydrolytic deboronation when the arylboronic acid had polar functional groups. Genêt et al. found out that, using *m*-TPPTC [tris(*m*-carboxyphenyl)phosphane trilitium salt] as the water-soluble ligand instead of TPPDS, no SDS was necessary, due to the inherent surfactant effect of *m*-TPPTC.<sup>71</sup> This ligand exhibited a similar performance in comparison with TPPDS, but was shown to be superior to TPPTS under the same conditions depicted in Scheme 10, but in the absence of SDS. Lautens' methodology was very recently extended to the coupling of a wide variety of aryl- and hetero-arylboronic acids with acrylates, acrylamides and vinyl sulfones.<sup>72</sup> The high selectivities and yields obtained were



Scheme 10.

believed to result from the use of the bulky, electron-rich, water-soluble ligand *tert*-butyl-amphos chloride [*N*-2-(*di-tert*-butylphosphino)ethyl-*N,N,N*-trimethylammonium chloride].

Different catalytic systems have been developed recently for the Heck-type reaction of boronic acids and electron-deficient olefins (Scheme 11). Pd(OAc)<sub>2</sub>, [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> and RhCl<sub>3</sub> were utilised as catalysts by Mori,<sup>73</sup> Brown,<sup>74</sup> Zou,<sup>75</sup> and their corresponding co-workers, respectively. Despite the palladium and rhodium catalytic systems exhibiting better yields, higher temperatures were also required in comparison with the ruthenium catalytic system. Stoichiometric amounts of Cu(OAc)<sub>2</sub> were needed as a re-oxidising agent for palladium and ruthenium, the latter including 3-quinuclidinone as a base in order to obtain the highest turnover.



Catalytic system	Conditions	Yield
10 mol% Pd(OAc) <sub>2</sub> 2 equiv Cu(OAc) <sub>2</sub> 3 equiv LiOAc	DMF 100 °C 3 h	84%
2.5 mol% [Ru( <i>p</i> -cymene)Cl <sub>2</sub> ] <sub>2</sub> 2.5 equiv Cu(OAc) <sub>2</sub> 2.5 equiv 3-quinuclidinone	CH <sub>2</sub> Cl <sub>2</sub> rt 24 h	66%
3 mol% RhCl <sub>3</sub> 12 mol% Ph <sub>3</sub> P	PhMe, H <sub>2</sub> O 100 °C, 20 h	83%

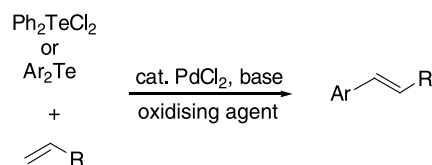
Scheme 11.

The groups of Jung and Larhed independently introduced molecular oxygen as a re-oxidising agent in the palladium(II)-catalysed coupling of organoboron compounds and olefins. The optimised catalytic system reported by Jung et al. was composed of 10 mol% Pd(OAc)<sub>2</sub>, O<sub>2</sub> and Na<sub>2</sub>CO<sub>3</sub> in DMF at 50 °C for 3–10 h.<sup>76</sup> Under these conditions, electron-rich and electron-poor olefins could be coupled with several boronic acids and esters, with generally good yields and stereo- and regioselectivities. The catalyst loading was diminished to 1 mol% by Larhed et al. in a catalytic system composed of Pd(OAc)<sub>2</sub>, O<sub>2</sub>, *N*-methylmorpholine and 1.2 mol% 2,9-dimethyl-1,10-phenanthroline in MeCN at 50 °C for 3–24 h. This oxidative Heck protocol was applied to the coupling of arylboronic acids with unsubstituted acrylates<sup>77a</sup> and electron-rich olefins.<sup>77b</sup> The internal regioselectivity observed for the coupling with *n*-butyl vinyl ether and enamides was attributed to the phenanthroline ligand, which also seemed to mediate the re-oxidation of palladium(0) with molecular oxygen, allowing a low catalyst loading.

Together with boronic acids, arylsilanols<sup>78</sup> and arylstannanes<sup>78c,79</sup> have been used as arylating agents in the Heck reaction with electron-deficient olefins. There are, however, some evident disadvantages of these materials, when compared with the carboxylic acid derivatives. Firstly, these starting materials are not so readily available, their

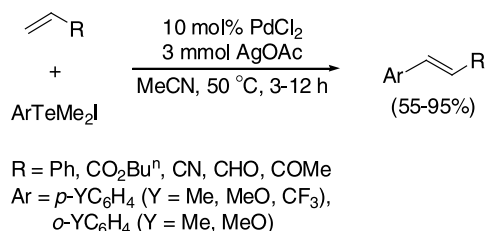
preparation involving less common and more expensive reagents, with the corresponding generation of waste. Secondly, boric acid, silanols and stannanes are formed as by-products in the Heck reactions, which can make the purification of the products difficult with a low possibility of recycling. Thirdly, the presence of large amounts of Cu(II) salts as re-oxidants, phosphanes and organic bases is required for a maximum efficiency.

Uemura et al. found that diphenyltellurium(IV) dichloride reacted with a variety of olefins in the presence of a catalytic amount of PdCl<sub>2</sub>, together with NaOAc in HOAc to afford the corresponding arylated (*E*)-olefins in variable yields (3–98%) (Scheme 12).<sup>80</sup> A suitable oxidant such as *tert*-butyl hydroperoxide or copper(I) or copper(II) chloride had to be added for the reaction to proceed catalytically on palladium. The stereoselectivity was very high, except for acrylonitrile (*Z/E* 26:74). Transmetalation of tellurium with palladium was suggested as the key step of the reaction. Alternatively, diaryltellurides could be used as arylating agents for a variety of olefins in the presence of Et<sub>3</sub>N as base and AgOAc as oxidant (40–99% product yield).<sup>81</sup>



Scheme 12.

As an alternative to the above reagents, Kamigata et al. used aryl(dimethyl)tellurium iodides for the palladium-catalysed Heck-type reaction with electron-deficient olefins and styrene, in the presence of a stoichiometric amount of silver(I) acetate.<sup>82</sup> For the tellurium salt partner, the best results were obtained when the aryl moiety bore electron-donating substituents at the *para* position, those at the *ortho* position retarding the reaction (Scheme 13). The yields are good to excellent, although a 3-fold excess (with respect to the olefin) of the expensive silver acetate is needed for the anion exchange and oxidation steps in the catalytic cycle. In contrast with the reactions with organic tellurides, for which the crude mixtures must be purified to remove the excess reagent, in the reactions with the tellurium salts the pure products were obtained by simple filtration using silica gel to remove the solids in the reaction mixture.

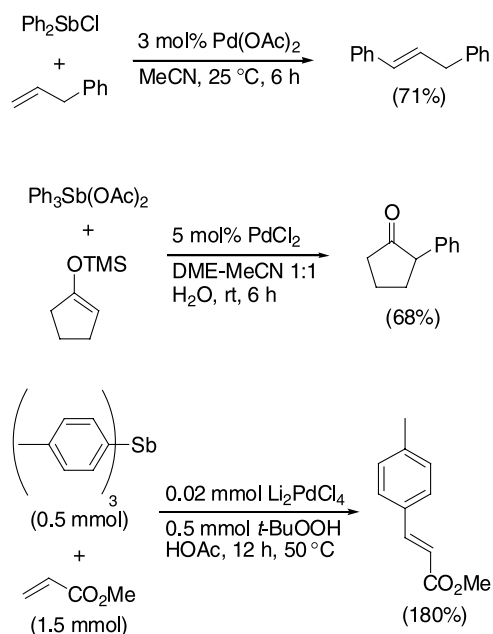


Scheme 13.

Unfortunately, the organic tellurides and tellurium salts are not commercially available. Diaryltellurium(IV) dihalides are normally prepared from TeCl<sub>4</sub> with activated arenes, arylmercury chlorides or arenediazonium salts.

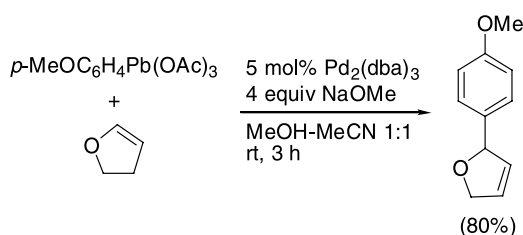
Symmetrical diaryltellurides can be prepared from alkali tellurides and non-activated aryl halides, sodium telluride or potassium tellurocyanate and arenediazonium fluoroborates, tellurium(IV) halides and arylmagnesium halides, or elemental tellurium and diarylmercury compounds. Alkyl aryl tellurides are the precursors of the corresponding telluronium salts and are generally prepared by sequential arylation–alkylation of sodium telluride or from organyl tellurolates, generated by tellurium insertion into organomagnesium or organolithium reagents.<sup>83</sup> In short, the preparation of these arylating agents represents a major disadvantage that adds to the toxic and mutagenic properties of the starting materials, tellurium and  $\text{TeCl}_4$ , respectively, and to the possible toxicity of the organotellurium compounds.<sup>84</sup>

A variety of organoantimony compounds have also found application in the arylation of olefins with different catalytic systems, including: (a) triphenylstibine with  $\text{AgOAc}$  and catalytic  $\text{Pd}(\text{OAc})_2$ ,<sup>85</sup> (b) diphenyl- and phenylantimony chloride with catalytic  $\text{Pd}(\text{OAc})_2$  under air,<sup>86</sup> (c) triarylantimony diacetates under  $\text{PdCl}_2(\text{MeCN})_2$  catalysis<sup>87</sup> and (d) triarylstibines<sup>88</sup> or tetraphenylantimony(V) carboxylates<sup>89</sup> in the presence of equimolecular amounts of a peroxide and catalytic amounts of  $\text{Li}_2\text{PdCl}_4$  or  $\text{PdCl}_2$  (see some selected examples in Scheme 14). In spite of the fact that these antimony compounds cannot be considered as usual reagents, all of them have an interesting feature in common, namely that the coupling reactions can be carried out under very mild reaction conditions, normally at room temperature or 50 °C.



Scheme 14.

Less common is the use of organolead(IV) compounds as arylating agents for olefins. Kang et al. described in 1998 for the first time that aryllead triacetates could be coupled with a variety of electronically different olefins under mild reaction conditions and palladium catalysis (see one example in Scheme 15).<sup>90</sup> Most of the reactions proceeded at room temperature with moderate to good yields, although



Scheme 15.

the homocoupling reaction competed in some of the experiments reported. It was presumed that the oxidative addition step was facilitated by the formation of the organolead trimethoxide,  $\text{ArPb}(\text{OMe})_3$ , to give a polar reactive intermediate,  $\text{ArPdPb}(\text{OMe})_3$ , which allowed the coupling under mild conditions. On the other hand, the aryllead triacetates are not commercially available and are rather toxic reagents.

Most of the alternative arylating agents presented in this report have the main advantage of minimising by-product formation, therefore facilitating the work-up. Except in the case of the carboxylic acids, however, the rest of the reagents are not commercially available and the generation of waste in their preparation is inevitable. In addition, rather high temperatures are needed for the coupling reactions in order to achieve reasonable conversions.

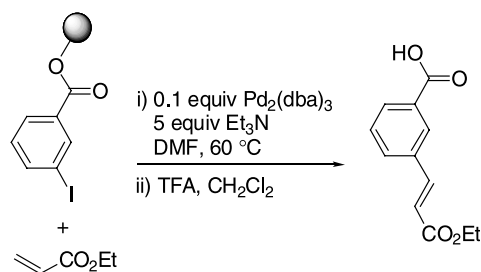
## 4.2. Supported substrates

Intermolecular Heck reactions on solid supports have been extensively used in synthetic organic and combinatorial chemistry, due to the easy accessibility of the starting haloalkenes or -arenes and alkenes. The reactions involve immobilised aryl halides, mostly iodides, or iodonium salts with soluble alkenes, or immobilised alkenes with soluble aryl halides. When performed on the same type of resin and with the same catalytic system, the immobilisation of aryl iodides appears to be more beneficial than that of alkenes. Two main protocols have been applied: (a) the standard Heck conditions [ $\text{Pd}(\text{OAc})_2$ ,  $\text{Ph}_3\text{P}$  or (*o*-Tol) $_3\text{P}$ , DMF, 80–100 °C], 2–24 h] and (b) the Jeffery conditions [ $\text{Pd}(\text{OAc})_2$ ,  $\text{Ph}_3\text{P}$ , TBAC,  $\text{K}_2\text{CO}_3$ , DMF, 20–80 °C]. The intramolecular Heck reaction on solid supports has found application in the preparation of macrocycles and heteroatom-containing five-, six- and seven-membered rings, as well as in the construction of indoles, benzofurans, dihydroisoquinolines and benzazepines. The pseudo dilution effect exhibited by the starting material in the intramolecular version has led to an increased yield. Both inter- and intramolecular Heck reactions on a solid support have been recently reviewed<sup>17</sup> and, therefore, it is not our objective to repeat all of this information here. Instead, we will deal with the more recent and representative examples and present a general conclusion at the end of this section.

Morphy et al. observed that the use of low solvent volumes in solid-phase Heck reactions resulted in large increases in yield, compared with the standard dilution conditions.<sup>91</sup> 3-Iodobenzoyl chloride was reacted with Wang resin, the resulting aryl halide being coupled with ethyl acrylate under palladium catalysis, followed by resin cleavage with TFA.



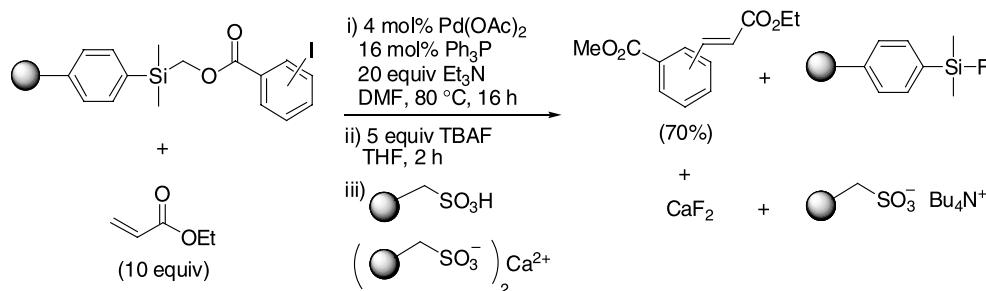
After reaction at 60 °C for 2 h at standard dilution (1 ml), a conversion of 40% was observed, compared to 80% when only 0.05 ml of solvent was used. The reaction was complete after 18 h for a low solvent volume with only 54% conversion under standard dilution conditions (Scheme 16). The optimal amount of solvent represented  $\leq 2 \mu\text{L}/\text{mg}$  of resin, significantly less than that required to totally swell the resin used and lead to a separate solvent phase. This methodology is certainly advantageous, since it minimises the use of solvent and provides high conversions under mild reaction conditions. Unfortunately, all reactions were performed on a very small scale (0.05 mmol of resin-bound 3-iodobenzoic acid) with excess of ethyl acrylate (2 equiv) and  $\text{Et}_3\text{N}$  (5 equiv) and, therefore, the behaviour of this catalytic system on a larger scale remains uncertain.



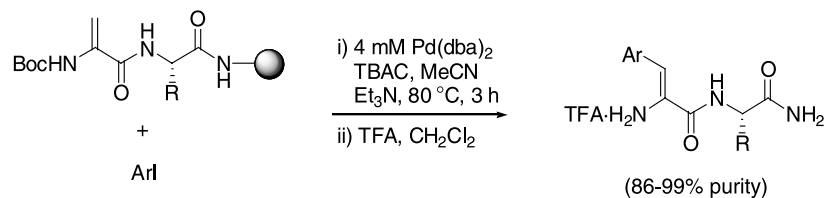
DMF (ml)	t (h)	Conversion (%)
1	2	40
0.05	2	80
1	18	54
0.05	18	> 95

Scheme 16.

A small library of cinnamate esters was prepared by Genêt et al., based on the use of a new stable silylated polystyrene, PS-SiMe<sub>2</sub>CH<sub>2</sub>Cl.<sup>92</sup> This chloromethyl resin was esterified with various iodobenzoic acids (*o*-, *m*- and *p*-derivatives),



Scheme 17.



R = H, Me, Bu<sup>t</sup>

Ar = *p*-MeOC<sub>6</sub>H<sub>4</sub>, *o*-MeC<sub>6</sub>H<sub>4</sub>, *m*-MeC<sub>6</sub>H<sub>4</sub>, *p*-MeC<sub>6</sub>H<sub>4</sub>, 1-naphthyl

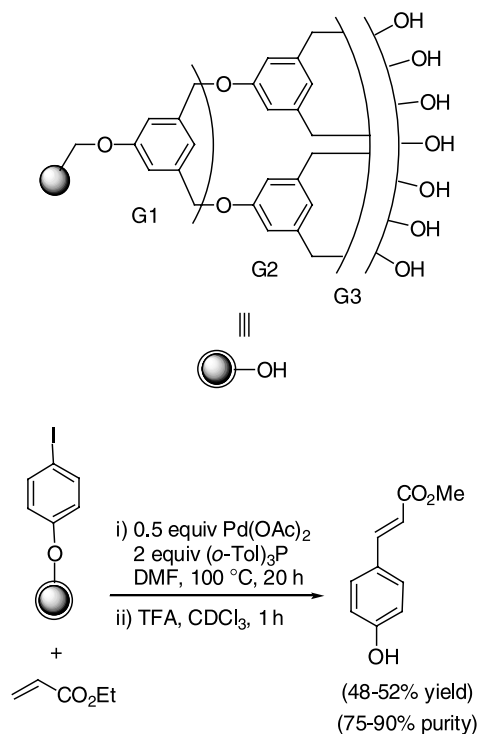
Scheme 18.

followed by a cross-coupling reaction with ethyl acrylate in DMF in the presence of Pd(OAc)<sub>2</sub>-PPh<sub>3</sub> as the catalytic system, the latter transformation taking place with complete conversion. The expected esters were released from the resin by treatment with TBAF in THF (Scheme 17). Owing to the difficulties of eliminating the excess of TBAF, however, further treatment with Amberlyst A-15 and its calcium salt as scavengers was needed to purify the reaction mixture. Despite the final products being obtained in good yields and the mild resin-cleavage step, this methodology does not seem to introduce any advantage with respect to the use of the more conventional resins. Firstly, the silylated resin is not commercially available and had to be prepared from a 1% divinylbenzene–styrene copolymer by lithiation and trapping with chloro(chloromethyl)dimethylsilane, a relatively expensive electrophile. Secondly, the cesium carboxylate had also to be prepared to increase its nucleophilicity in the S<sub>N</sub>2 reaction to attach the resin. Thirdly, a special resin-cleavage protocol was needed, leading to more waste (additional to the excess of reagents) and to the generation of a new silylated resin with no chance of being recycled.

Takahashi et al. recently described the stereoselective synthesis of 36 peptides containing unnatural amino acids, utilising the Pd(0)-catalysed Mirozoki–Heck reaction of dehydroalanine derivatives in combination with an asymmetric hydrogenation on polymer support.<sup>93</sup> In this case, the alkene partner was supported on Synphase Rink-amino PS-Crowns™, whereas the aryl iodides were in solution. It was found that 4 mM Pd(dba)<sub>2</sub> in MeCN at 80 °C for 3 h in the presence of TBAC and Et<sub>3</sub>N were the optimal reaction conditions. Products were obtained with a high purity, except for aryl iodides bearing electron-withdrawing substituents, where a low purity (45–60%, *p*-AcC<sub>6</sub>H<sub>4</sub>I) or no reaction (*p*-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>I) was observed (Scheme 18). Asymmetric hydrogenation and final cleavage with TFA–CH<sub>2</sub>Cl<sub>2</sub> furnished the corresponding phenylalanine

derivatives with high stereocontrol. Unfortunately, the authors did not give any information about the isolated yields of the final products, making it difficult to evaluate the efficiency of the whole process.

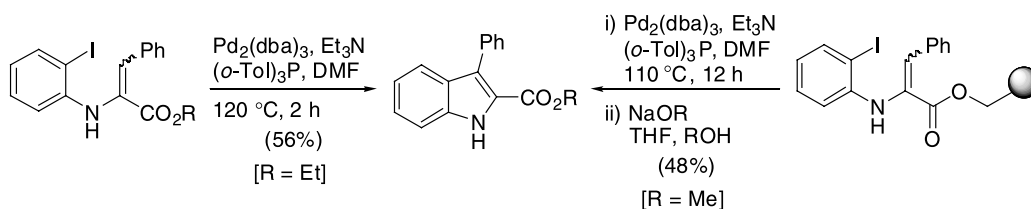
Portnoy et al. synthesised various poly(aryl benzyl ether) dendrimers on a solid support, based on the initial immobilisation of commercially available 5-hydroxyisophthalate onto the Wang resin, followed by ester reduction. Repetitive Mitsunobu coupling and ester reduction led to the formation of a second and third-generation of dendrimers.<sup>94</sup> The three resins were subjected to Mitsunobu reaction with *p*-iodophenol, followed by Heck coupling with methyl acrylate, with complete conversions being achieved for every resin. Only moderate yields and fair purities were, however, obtained for any of the resins tested upon TFA-induced cleavage (Scheme 19). In fact, this methodology has no advantage with respect to that developed by Hanessian et al.<sup>95</sup> in which the aryl iodide was directly attached to the Wang resin. In this case, the free cinnamic ester was obtained in 90% overall yield under the same reaction conditions, but minimising the number of steps and consequently, the generation of waste, making the process more economic and time saving.



Scheme 19.

In a study on indole synthesis, Kondo et al. described the palladium-catalysed intramolecular cyclisation of enaminoesters in the solution phase and on solid supports.<sup>96</sup> In the solution phase, the expected ethyl 3-phenyl-2-indolecarboxylate was obtained in 56% yield after treatment with a catalytic amount of Pd<sub>2</sub>(dba)<sub>3</sub>, (*o*-Tol)<sub>3</sub>P and Et<sub>3</sub>N in DMF at 120 °C for 2 h (Scheme 20). The polymer-supported version of this reaction involved the attachment of the substrate to a hydroxymethyl-polystyrene resin, treatment with the same catalytic system at 110 °C for 12 h, and final transesterification of the resulting polymer-bound indole carboxylate using NaOMe in MeOH–THF. In this case, the product was obtained in 48% yield after further purification by column chromatography. It seems clear that the solution-phase reaction is advantageous, since it reduces the reaction time in the intramolecular coupling, less steps are used, and the yield is slightly improved. Similar solid-phase indole synthetic strategies have been published recently by the same research group.<sup>97</sup>

It is clear that the main reason for immobilising a molecule on a solid support for the Heck or any other reaction relies on the simple separation of the intermediates and, finally, of the products from the reagents and soluble by-products. This fact, which represents a major advantage, compared to the solution-phase chemistry, may hide some inherent inconveniences and limitations that can curtail the whole efficiency of the process, for example, (a) reactions can be driven to completion in most cases, but only in return for consuming an excess of reagent, (b) suitable, robust and versatile linkers are required, which have to be cleaved selectively under mild reaction conditions without destroying the product, (c) a second functionality in the starting material is normally necessary for attachment to the support, as exemplified by the intermolecular Heck reaction, in which the polymer-bound aryl iodides must bear an additional group (carboxy, hydroxy, amino, etc.) that remains at the end in the product, whereas most of the polymer-bound alkenes studied are derived from  $\alpha,\beta$ -unsaturated carboxylic acid derivatives, (d) the selection of usable solvents and the temperature range can be quite restricted (100 °C is at the upper limit), (e) the chemistry involving heterogeneous catalysts such as palladium on charcoal is incompatible with solid-phase synthesis methods, (f) the difficulty of analysing the outcome of a given reaction makes it necessary for the cleavage of the products from the support to be analysed by normal methods and (g) in the case of solid-phase combinatorial chemistry, additional investment is essential for laboratory automation, robotics and mechanical and tag-reading/sorting devices enabling the simultaneous performance of multiple tasks. In short, there is a need for more solid-phase methodology, including the development of traceless linkers.



Scheme 20.

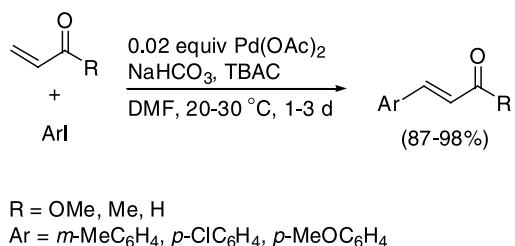
## 5. Catalytic systems

The selection of a proper catalytic system is fundamental for achieving the best efficiency in a given Heck reaction. In order to design such an efficient catalytic system, however, we have to focus not only on its catalytic activity or selectivity, but also on other important topical issues, such as the possibility of recovery of the components, or their toxicity and environmental impact, especially for application to an industrial scale. In fact, industrial applications are rare, because the cheap aryl chlorides or many readily available bromides do not react with sufficiently high yields, turnover numbers and selectivities, even in the presence of the traditional phosphane catalysts.<sup>98</sup> Significant efforts have been made in recent years to develop more efficient catalytic systems, trying to simplify these reactions as much as possible.

### 5.1. Ligands: ligand-free catalytic systems

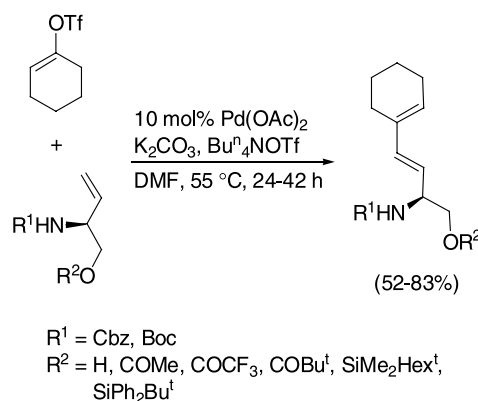
Tertiary phosphane ligands have traditionally been used to ensure catalyst stability, in spite of the fact that they can have some detrimental effect on the rate of the individual steps of the coupling reaction. The use of phosphorus ligands in fine-chemical and industrial processes, however, is less desirable. They are usually toxic, unrecoverable and frequently hamper the isolation and purification of the desired product, as well as the performance of consecutive catalytic steps of the total synthesis. In spite of the fact that numerous phosphane-free ligand systems have been developed, including palladacycles, nucleophilic carbene ligands and others,<sup>99</sup> these catalytic systems suffer from some drawbacks. The high ligand sensitivity to air and moisture, their tedious multistep synthesis, the high cost of the ligands and the use of various additives curtails their applications. On the other hand, the ligand-free Heck catalytic systems have very recently emerged as more advantageous at all levels, operationally, economically and environmentally.<sup>100</sup>

We have described in Section 4.1 a series of methodologies involving the use of alternative arylating agents to aryl halides in the Heck reaction, most of which have a common and advantageous feature, that is, no ligand was added to the reaction mixture. The ligandless approach to carbon–carbon coupling was, however, pioneered independently by Beletskaya<sup>101</sup> and Jeffery.<sup>102</sup> The latter author reported, in 1984, the palladium-catalysed vinylation of organic iodides under solid–liquid phase-transfer conditions at, or near, room temperature, using TBAC as the phase-transfer agent and sodium hydrogen carbonate as a base in the absence of any ligand.<sup>102a</sup> The reactions proceeded with excellent yields (85–98%) and with high regio- and stereoselectivity. Aryl iodides furnished the (*E*)-products exclusively (Scheme 21), whereas (*E*)-1-iodohexen-1-ene gave a 1:15 diastereomeric mixture in favour of the (*E,E*)-product. The mild conditions allowed this type of reaction to be generalised to thermally unstable vinylic substrates such as methyl vinyl ketone or acrolein. Fortunately, the vinylation of vinylic iodides was greatly accelerated (1–5 h) by using potassium carbonate instead of sodium hydrogen carbonate as the inorganic base, with a parallel improvement of the stereoselectivity.<sup>102b</sup>



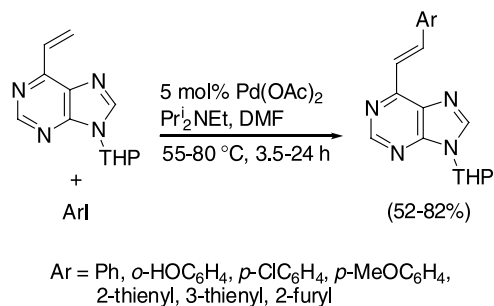
Scheme 21.

More recently, a slightly modified catalytic system was applied by Crisp et al. to the Heck coupling of the chiral non-activated alkenes, 2-aminobut-3-en-1-ols, with cyclohexenyl triflate.<sup>103</sup> In this case, tetra-*n*-butylammonium triflate was used instead of TBAC under mild reaction conditions, the produced dienes being isolated in moderate to good yields and with little or no racemisation (Scheme 22). The high reactivity observed with tetra-*n*-butylammonium triflate was attributed to the high rate of dissociation of the triflate anion from the neutral palladium(II) intermediate and the formation of a very reactive cationic palladium species. Some beneficial influence was observed when a small amount of water (5 equiv) was added to the reaction mixture. Little can be said about the scope of this reaction, since cyclohexenyl triflate was the only triflate tested.



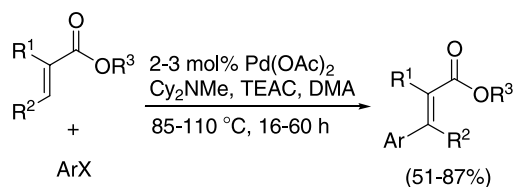
Scheme 22.

A very simple catalytic system was used by Gundersen et al. in the coupling of vinylpurine with a variety of aryl iodides (Scheme 23).<sup>104</sup> Better results were obtained when Pd(OAc)<sub>2</sub> alone was employed as the catalyst compared with catalysts containing phosphane ligands such as triphenylphosphane. All the couplings were highly stereoselective, including the coupling of vinylpurine with (*E*)-methyl 3-iodo-2-methylacrylate.



Scheme 23.

Buchwald et al. introduced the bulky amine base, methyl(dicyclohexyl)amine, into a phosphane-free catalytic system that found application in the coupling of aryl iodides and bromides with 1,1- and 1,2-disubstituted olefins to give trisubstituted olefins (Scheme 24).<sup>105</sup> The method was applicable to the coupling of both electron-deficient and electron-rich substrates and displayed good stereoselectivity and a high degree of functional-group compatibility. A combination of the bulky amine and tetraethylammonium chloride (TEAC) made the reaction faster and increased the *E/Z* selectivity, in comparison with other amines.



R<sup>1</sup> = Me; R<sup>2</sup> = H; R<sup>3</sup> = Bu<sup>n</sup>  
 R<sup>1</sup> = CH<sub>2</sub>CO<sub>2</sub>Me; R<sup>2</sup> = H; R<sup>3</sup> = Me  
 R<sup>1</sup> = H; R<sup>2</sup> = Ph, Me; R<sup>3</sup> = Me  
 Ar = Ph, *p*-YC<sub>6</sub>H<sub>4</sub> (Y = F, OMe, NMe<sub>2</sub>, Bu<sup>t</sup>, CN),  
*o*-YC<sub>6</sub>H<sub>4</sub> (Y = Me, Et, OMe, CN), *m*-MeOC<sub>6</sub>H<sub>4</sub>,  
 3-thienyl, 2-naphthyl  
 X = Br, I

Scheme 24.

Reetz et al. discovered that Pd(OAc)<sub>2</sub> in the presence of the additive, *N,N*-dimethylglycine (DMG), is a simple, reactive and selective catalytic system for the Heck reaction of aryl bromides with olefins.<sup>106</sup> The reaction of bromobenzene and styrene in NMP took place with >95% *trans*-selectivity with only traces of side products in the presence of a 20:1 DMG/Pd ratio (Scheme 25). It had been interesting to know the isolated yields instead of the conversions, as well as the experimental procedure for the product purification, above all taking into account the presence of the additive DMG and the high boiling point solvent NMP.



Scheme 25.

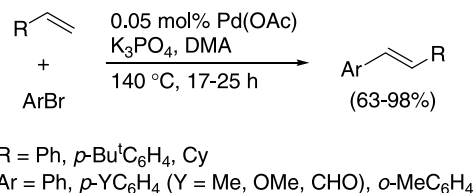
Another simple catalytic system recently developed by Schmidt et al. was found to catalyse the reaction of bromoarenes with styrene in air in the absence of any ligands.<sup>107</sup> Conversions of around 95% were achieved by the use of 0.04–1.6 mol% PdCl<sub>2</sub>, 18% HCO<sub>2</sub>Na and 112% NaOAc in DMF after 10 min at 140 °C or 180 min at 100 °C (Scheme 26). The presence of sodium formate as a reducing agent accelerated the reaction, although it had no effect on the yield of stilbene. It was corroborated that colloidal palladium particles formed in the course of the reaction are the main reservoir of catalytically active homogeneous Pd(0) complexes. The low catalyst loading, the availability and the low prices of the components of the catalytic system, together with the absence of an inert atmosphere,



Scheme 26.

makes this methodology attractive to be applied at a larger scale. The 6-fold excess of bromoarene required is, however, an important limitation, above all taking into account that bromoarenes are rather expensive and that an additional recycling strategy should be developed for better process efficiency. In our opinion, this work demands further study on the applicability to some other aryl bromides and alkenes, as well as a study on the compatibility of different functional groups attached to the substrates with the reaction conditions.

In this context, Pd(OAc)<sub>2</sub> in combination with K<sub>3</sub>PO<sub>4</sub> in DMA exhibited a high catalytic activity for the Heck reaction of both activated and deactivated aryl bromides in the absence of any stabilising ligands or additives.<sup>108</sup> Styrenes and vinylcyclohexene led to the expected coupling products with good to excellent isolated yields (63–98%) when the reaction was performed at 140 °C for about 20 h (Scheme 27). It is, however, surprising that the more activated terminal olefins such as *n*-butyl acrylate gave low yields.



Scheme 27.

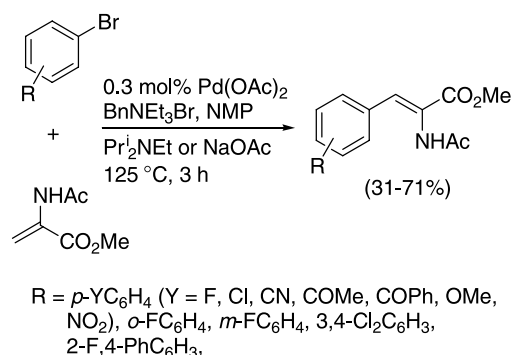
The group of de Vries has recently concentrated much effort in developing ligand-free palladium catalytic systems for Heck reactions, for example, they reported a practical and cost-effective coupling methodology based on the recovery and re-use of the palladium catalyst,<sup>109</sup> with different Heck reaction mixtures being separated from precipitated palladium on Celite by filtration. The addition of 2 equiv of iodine or bromine in NMP dissolved the recovered palladium and allowed the performance of eight successive runs without significant loss of activity. This re-activated palladium catalyst, which is homogenous in character, was suggested to exist as a mononuclear anionic species, although the presence of nanoparticles was not excluded.

The same research group proved that the catalytic system reported by Reetz et al.<sup>106</sup> (see Scheme 25) could work nicely in the absence of the additive DMG and with a lower catalyst loading. A broad range of aryl bromides was reacted with both electron-deficient and electron-rich olefins in the presence of 0.05 mol% Pd(OAc)<sub>2</sub>, and 2.4 mmol of NaOAc in NMP at 135 °C for 1–15 h, affording the products in 80–100% conversion.<sup>110</sup> The fact that this method was scaled up to a few Kg, together with the low cost of the catalytic



system, the relatively low solvent volume used and the easy workup procedure, makes it very attractive for large-scale production.

As an example of a specific application, a ligand-free palladium-catalysed Heck reaction of methyl 2-acetamidoacrylate and aryl bromides was used by de Vries et al. as the key step in the synthesis of enantiopure substituted phenylalanines.<sup>111</sup> All reactions were performed in NMP at 125 °C in the presence of Pd(OAc)<sub>2</sub>, BnNEt<sub>3</sub>Br and Pr<sub>2</sub>NEt or NaOAc as base. A variety of aryl bromides with different electronic character was tested, giving rise to the corresponding products, purified by simple crystallisation, in moderate yields (Scheme 28). It is noteworthy that one of the reactions took place in 55% yield, even in the absence of the tetraalkylammonium salt, simplifying the catalytic system even more.



Scheme 28.

The absence of any ligand in the reaction medium, especially phosphane ligands, is very desirable. This absence, however, normally implies the presence of other additives to stabilise the in situ generated palladium species, which nonetheless can be removed more easily. At any rate, more efforts are needed for the ligand-free Heck reaction in order to decrease the reaction temperature, above all in the coupling of aryl bromides.

## 5.2. Catalysts: supported catalysts

Although the Heck reaction is also very attractive also for industrial applications, the homogeneous Heck reaction has no practical application in industry.<sup>112</sup> The loss of catalyst, which usually cannot be recovered and the need for aryl bromides or iodides as the starting materials are the major drawbacks that have prevented a more extensive exploitation of this reaction at an industrial level. The loss of catalyst could perhaps be tolerated if the cheaper and much more readily available aryl chlorides could be employed as the starting materials.

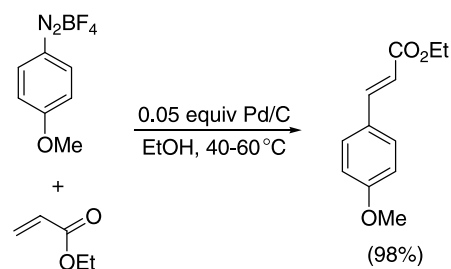
In principle, heterogeneous catalysts or heterogenised homogeneous catalysts can be used to solve some of the above-mentioned technical applications in the Heck reaction.<sup>113</sup> Among the heterogeneous catalysts we should mention the supported metal catalysts, zeolite-encapsulated catalysts, colloid-nanoparticles and intercalated metal compounds. The homogeneous metal complexes catalysts can be heterogenised using modified silica catalysts,

polymer-supported catalysts, biphasic catalysts, supported liquid-phase catalysts, non-ionic liquid solvents, perfluorinated solvents and re-usable homogeneous complexes. All these types of catalysts can be easily recovered from the reaction mixture and recycled, if they do not deactivate too quickly under duty. In addition, the palladium in heterogeneous catalysts would already be present as metal crystallites dispersed onto the solid support, so that precipitation of palladium black should not occur. In general, the heterogeneous catalysts have a major drawback of lower selectivity towards Heck coupling and metal leaching, whereas the heterogenised metal complexes operate under milder reaction conditions.

Since an important part of this topic has been tackled in diverse reviews, we are going to deal mainly with some selected examples of the most recent literature covering the study of catalysts supported on carbon, metal oxides, molecular sieves, clays, zeolites, polymeric and dendrimeric materials, among others.

**5.2.1. Carbon.** Palladium on carbon proved to be active for Heck coupling under several different conditions and is one of the most frequently investigated catalysts.<sup>113</sup> In general, carbon-supported catalysts do not seem to differ significantly in activity from their homogeneous counterparts, since the proportion of the metal to the limiting reagent, reaction temperatures, times and yields are comparable to those observed for homogeneous catalysts. Palladium supported on carbon, however, often causes unwanted hydrodehalogenation of the haloaromatic compounds and suffers from substantial palladium leaching.<sup>114</sup> Palladium leaching is also relevant to the mechanism of Pd/C-catalysed Heck couplings. In fact, it is still the subject of debate as to whether the reaction takes place on the solid palladium surface or the true catalyst is the dissolved palladium that has been leached from Pd/C, which acts simply as a palladium reservoir.

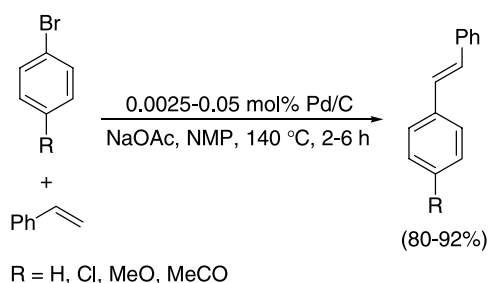
It is worth mentioning the publication by Beller et al. which described the first Heck reaction of aryldiazonium salts using heterogeneous catalysts.<sup>115</sup> Palladium on carbon was shown to be a very effective catalyst in this reaction under very mild conditions (40–60 °C) (Scheme 29). There was no need to add stoichiometric amounts of base or stabilising ligands such as phosphanes and these are major advantages. Unfortunately, the catalyst exhibited an important reduction in activity after its first use. The lack of commercial availability of the starting anilines and the additional step of conversion into the corresponding aryldiazonium salts



Scheme 29.

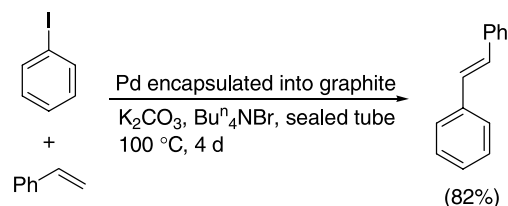
would be the only possible disadvantages of this methodology.

A very interesting and detailed study was reported by Köhler et al. concerning the Heck reaction of aryl bromides with olefins in the presence of a variety of Pd/C catalysts.<sup>116</sup> The activity of the catalysts was shown to be strongly dependent upon the palladium dispersion, palladium oxidation state in the fresh catalyst, the water content and the conditions of catalyst preparation. A high palladium dispersion, low degree of palladium reduction, high water content and uniform palladium impregnation led to the most active catalyst. The fact that uniformly impregnated Pd/C catalysts showed higher activities than eggshell catalysts supported the hypothesis that leached palladium is the active species, for which the solid Pd/C acts as a reservoir that delivers catalytically active palladium species into solution. In fact, Arai et al. have demonstrated that palladium exists on the support, in solution and in the form of free colloidal particles during and after the Heck reaction, which can be redeposited on the support.<sup>117</sup> The optimised Pd/C catalyst exceeded by at least one order of magnitude the activity of any heterogeneous palladium catalyst reported in the literature in the reaction of bromoarenes with olefins (Scheme 30). In general, all the catalysts studied exhibited a high activity and selectivity, without the exclusion of air and moisture, extremely low palladium concentrations, easy and complete separation from the product mixture, easy and quantitative recovery of palladium and commercial availability. Although the TONs were still lower than those of the most active homogeneous catalytic systems for the activation of aryl bromides, the TOFs were higher, the activity at the beginning of the reaction being extremely high before deactivation of the catalyst occurred. In contrast to the results of Arai et al.,<sup>118</sup> who observed up to 80% hydrodehalogenation, no hydrodehalogenation of bromoarenes was observed in any experiment.



Scheme 30.

Hara et al. obtained quasi 2-dimensional palladium nanoparticles encapsulated into graphite, which proved to be active catalysts for the Heck reaction.<sup>119</sup> Thus, an 82% yield of the coupled product, stilbene, was isolated by reacting 1 mmol of styrene with 2 mmol of iodobenzene in the presence of 4 mmol of potassium carbonate, 2 mmol of tetra-*n*-butylammonium bromide and 10.2 mg of the quasi two-dimensional palladium particles encapsulated in graphite (37%) in DMF using a sealed tube at 100 °C for 4 days (Scheme 31). No coupling product was observed with chlorobenzene. The nanoparticles remained inside the



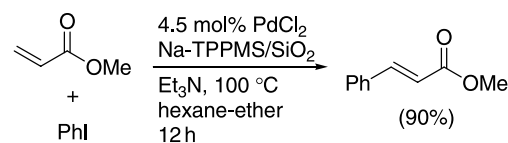
Scheme 31.

carbon lattice after the Heck reaction and could not be washed out, the catalyst therefore being stable. Despite this catalytic system completely avoiding palladium leaching, its preparation is rather time consuming and somewhat complex. In addition, harsh reaction conditions and long reaction times are required.

For the application of Pd/C in combination with ionic liquids, see Section 6.2.

**5.2.2. Metal oxides and other inorganic materials.** The catalytic activity and selectivity of palladium supported on various metal oxides in the Heck reaction have attracted the interest of many research groups, both the nature of the oxide support and the Pd dispersion playing a crucial role in the activity of the catalytic system.<sup>120</sup> On the other hand, there is a considerable interest in determining the heterogeneous or homogeneous nature of the mechanisms involved in these reactions.<sup>121</sup>

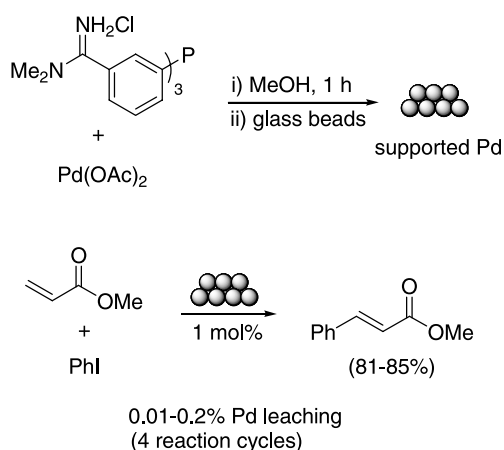
Silica, within the family of metal oxides, has been, by far, the most utilised support in the Heck reaction.<sup>122</sup> In one of the first reports on this topic, Strauss et al. used 0.18% palladium on porous glass tubing for Heck reactions conducted continuously or batchwise.<sup>123</sup> This support offered resistance to oxidative deterioration and could be re-used several times for repeating, or for different, reactions, but the regio- and stereoselectivity was lower than expected. In parallel with this work, Mirza et al. developed a supported liquid-phase catalytic system for the Heck reaction of iodobenzene and methyl acrylate in a batch reactor, based on a combination of sulfonated triphenylphosphine–palladium complexes (Na-TPPMS and PdCl<sub>2</sub>) supported upon porous glass beads and solvated with ethylene glycol (Scheme 32). Under these conditions, the catalyst complex was held in solution, whilst the reactants and products were restricted to a nonmiscible solvent phase.<sup>124</sup> Leaching was eliminated to the limits of detection, but the activity of the supported liquid-phase catalyst decreased significantly after recycling. With regard to the nature of the catalysis occurring within the system, evidence suggests that this is predominantly homogeneous via the formation of an organic-soluble catalyst complex. Alternatively, potassium acetate was used by Arai et al. as an inorganic base instead of triethylamine in a very similar



Scheme 32.

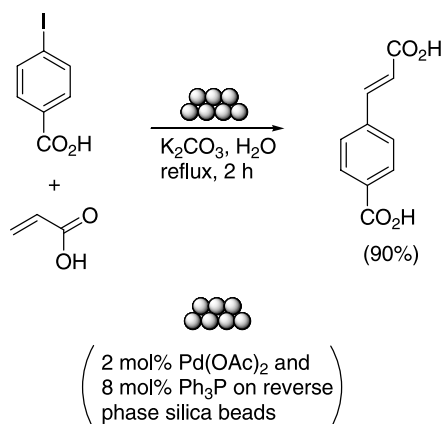
catalytic system,<sup>125</sup> whilst tri-*n*-butylamine gave higher reaction rates than triethylamine.<sup>126</sup>

A supported palladium catalyst on glass beads, generated from a guanidinium phosphane and palladium acetate, showed a high activity and low leaching of catalyst in the Heck reaction of aryl iodides and alkenes (Scheme 33).<sup>127</sup> The low catalyst loading, as well as the high yields achieved and the low leaching maintained over four reaction cycles, are clear advantages of this catalytic system. The main inconvenience is the preparation of the ligand which involves four steps, that is, Grignard reaction of commercially available 2-(*N,N*-bis-trimethylsilylamino)phenylmagnesium chloride with phosphorus trichloride, nitrogen deprotection, hydrochloride formation and condensation with dimethyl cyanamide.



Scheme 33.

The same research group prepared a new catalyst by treatment of reverse-phase silica beads with Pd(OAc)<sub>2</sub> and Ph<sub>3</sub>P in cyclohexane.<sup>128</sup> The reverse-phase bead catalyst formed was assumed to contain (Ph<sub>3</sub>P)<sub>2</sub>Pd(OAc)<sub>2</sub> and was stable in air and easy to handle. This catalyst was applied to the Heck reaction between iodobenzoic acid and acrylic acid, the expected product being obtained in a high yield and with low palladium leaching (Scheme 34). Heteroaromatic halides were also coupled with methyl acrylate with lower yields and low palladium leaching. The reverse-phase beads could be recovered from the reaction mixture and were



Scheme 34.

re-used seven times without any apparent loss of activity. Some reactions could be performed in water or with no added solvent. The real advantage of using the reverse-phase silica support seems to be that more polar substrates can be employed.

The catalysts shown in Chart 1 are all stable and active heterogeneous catalysts based on chemically modified silica, prepared by building up a suitable ligand structure, containing an aminopropyl moiety, on the surface of the silica, followed by complexation to the M(II). All of these catalysts have been recently reported and shown to be effective in Heck reactions, complex **1** furnished 82% conversion in the coupling of iodobenzene and methyl acrylate with Et<sub>3</sub>N in MeCN at 82 °C for 24 h.<sup>129</sup> This catalyst was successfully re-used without a noticeable loss of activity and with no detectable amounts of palladium leached. The same complex **1**, but prepared from PdCl<sub>2</sub> instead of Pd(OAc)<sub>2</sub> on ordered mesoporous silica FSM-16, was active for the coupling of aryl iodides and bromides with methyl acrylate, giving 100% conversion in 1–5 h at 130 °C. Aryl bromides with electron-donating substituents were particularly sluggish in their reactivity, but the reactivity could be increased by the addition of TBAB. Seven reaction cycles were applied in the vinylation of 4-bromoacetophenone with methyl acrylate without a significant loss of reactivity.<sup>130</sup> Complex **2** was prepared by heating 3-(4,5-dihydroimidazol-1-yl)-propyltriethoxysilanedichloropalladium(II) with mesoporous silica nanotube particles.<sup>131</sup> A 1.5% palladium-imidazoline complex **2**

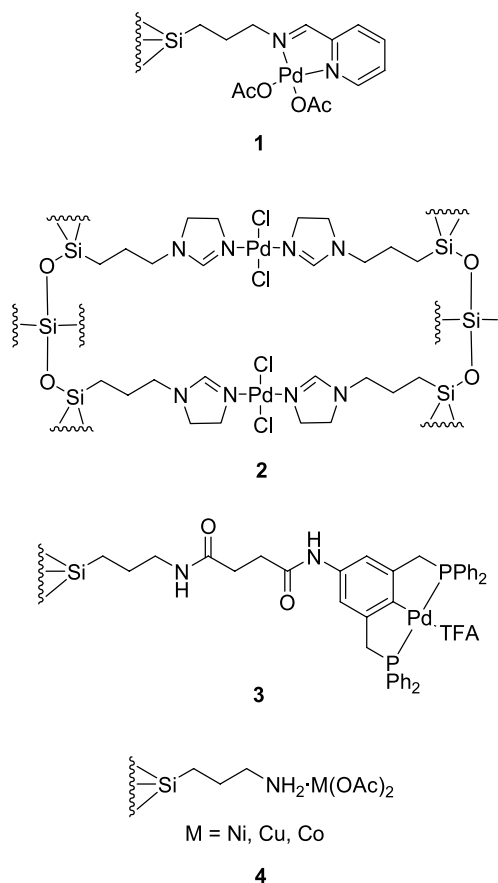


Chart 1.

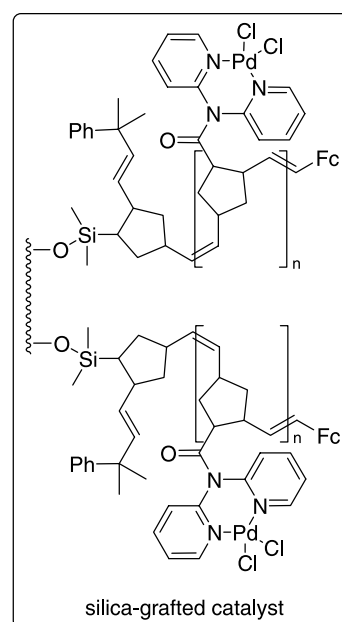
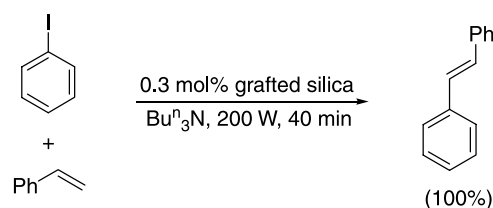
with  $\text{Cs}_2\text{CO}_3$  in dioxane at  $80^\circ\text{C}$  for 2–3 h gave excellent yields (79–94%) of coupled products obtained for a wide array of bromides or iodides with styrene. In all cases where recycling of the catalyst was attempted, however, small decreases in activity were observed from one run to the next. A higher reaction temperature ( $140^\circ\text{C}$ ) was required for catalyst **3** in the reaction of iodobenzene and *n*-butyl acrylate using sodium carbonate as base in NMP.<sup>132</sup> High TONs were obtained and the catalyst was recycled three times with high activity, whereas a lower reactivity was observed for styrene, with both *E/Z* stilbenes being formed in a 7:1 ratio. A higher loading of catalyst was necessary in the case of 4-bromotoluene and a lower yield was found after three runs. Zheng et al. prepared silica-supported poly- $\gamma$ -aminopropylsilane-transition metal complexes **4**, which were also active and stereoselective for the Heck vinylation reaction of aryl iodides with olefins at  $120$ – $150^\circ\text{C}$ .<sup>133</sup> All of the complexes were treated with  $\text{KBH}_4$ –EtOH before use. The supported Ni complex furnished the expected products in 86–98% yield and the Co and Cu complexes in 71–96% yield, although the reaction of iodobenzene and styrene gave stilbene in only 40% yield with the latter complexes. An induction period of  $>2$  h was observed for these catalysts. The reaction temperature could be reduced by up to  $70$ – $100^\circ\text{C}$  using a similar, but new, silica-supported poly- $\gamma$ -aminopropylsilane- $\text{Cu}^{2+}$ - $\text{Pd}^{2+}$  complex.<sup>134</sup>

Although there is no doubt about the efficiency and the possibility of recycling of the above-described catalysts, a comment must be made concerning their preparation. A minimum of three reaction steps are involved in the preparation of the catalysts (10 steps for catalyst **3**) and, in addition, other multiple operations such as filtration, washing, drying under vacuum or high temperature, or conditioning by refluxing in a solvent, as well as long reaction times, are needed for some of the steps (up to 4 days). Therefore, taking into account the yield reduction when increasing the number of steps, as well as the waste produced along the synthesis of the catalysts and the price of the starting materials and metallic salts, the catalysts **4** seem to be the most convenient from a practical point of view and for the larger-scale preparations.

In relation to the above catalytic system described by Zheng et al. this research group prepared silica-supported palladium(0) complexes from  $\gamma$ -chloropropyl- and  $\gamma$ -aminopropyltriethoxysilane via immobilisation on fumed silica, followed by reaction with ethylenediamine and salicylaldehyde and then reaction with  $\text{PdCl}_2$  and reduction with  $\text{KBH}_4$ .<sup>135</sup> In this case, the reaction temperature was reduced to  $90^\circ\text{C}$  for the Heck reaction of aryl iodides (*p*- $\text{RC}_6\text{H}_4\text{I}$ ,  $\text{R} = \text{H}, \text{MeO}, \text{CO}_2\text{H}$ ) with acrylic acid, methyl acrylate and styrene. The catalysts could be recovered and re-used without loss of activity. A comparable performance was observed for the silica-supported palladium(0) complex similarly prepared from poly- $\gamma$ -cyanopropyltriethoxysilane.<sup>136</sup>

*N,N*-di(pyrid-2-yl)norborn-2-ene-5-ylcarbamide was surface grafted or coated onto various silica-based carriers through a ring-opening metathesis polymerisation (ROMP) in the presence of  $\text{Mo}(N\text{-}2,6\text{-Me}_2\text{C}_6\text{H}_3)(\text{CHCMe}_2\text{Ph})[\text{OCMe}(\text{CF}_3)_2]_2$ .<sup>137</sup> The silica-based materials were used

in slurry reactions under standard conditions, as well as under microwave irradiation, the latter case leading to a drastic reduction of the reaction times. A quantitative conversion was achieved for iodoarenes, while activated bromoarenes required prolonged reaction times. Typically, less than 2.5% palladium was leached into the reaction mixture. Nonetheless, the preparation of the supported catalysts is very sophisticated in order to finally achieve similar results to those obtained with simpler supported catalytic systems. An example using 0.3 mol% of the silica-based slurry is depicted in Scheme 35.



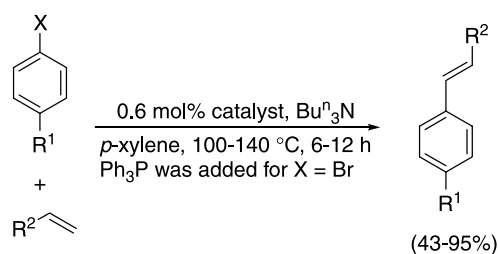
Scheme 35.

In 1997, Cai et al. described the preparation of a silica-supported poly- $\gamma$ -mercaptopropylsiloxane-palladium(0) complex that gave high yields (86–96%) in the arylation of styrene and acrylic acid ( $\text{Bu}_3\text{N}$ , xylene,  $100^\circ\text{C}$ , 6 h) and could be recovered and re-used with a low decrease in activity.<sup>138</sup> The same ligand, but supported on FSM-16 mesoporous silica, was shown to be an active and stable catalyst for the Heck reaction of 4-bromoacetophenone and ethyl acrylate (KOAc, NMP,  $130^\circ\text{C}$ , 92% yield), the catalyst being re-used at least five times with no indication of catalyst deactivation. The less reactive electron-rich aryl bromides, 4-bromoanisole and bromobenzene, however, resulted in moderate yields (58 and 62%, respectively), whereas 4-chloroacetophenone gave a low yield (18%).<sup>139</sup>

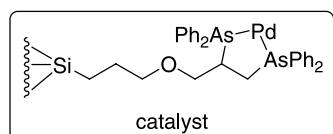
Based on the above original methodology and, more recently, Cai's group has prepared a silica-supported bidentate arsine-palladium(0) complex from 4-oxa-6,7-dichloroheptyltriethoxysilane via immobilisation on fumed



silica, followed by reaction with potassium diphenylarsenide and palladium chloride and then reduction with hydrazine hydrate.<sup>140</sup> This complex exhibited a high activity in the stereoselective arylation of styrene and acrylic acid with aryl halides, affording a variety of *trans*-stilbenes and substituted *trans*-cinnamic acids in high yields (Scheme 36). The arylation of styrene with aryl iodides proceeded smoothly at 100 °C, whereas that of aryl bromides took place at 140 °C with added triphenylphosphane. The substituent effects in aryl iodides appeared to be less significant than those in aryl bromides, the reactivity of the latter with electron-withdrawing substituents being higher than that of aryl bromides with electron-donating substituents. The bidentate arsine ligand seems to efficiently prevent palladium leaching, since a yield variation of only 91 to 89% was observed after four consecutive runs. Similar results to those described above were obtained in the coupling of aryl halides with acrylic acid. It is worthy of note that the catalyst activity did not remarkably decrease after exposure to air for 7 days. The methodology was extended to the arylation of acrylonitrile, furnishing (*E*)-cinnamitriles in high yields.<sup>141</sup> Some disadvantages include the fact that the starting 4-oxa-6,7-dichloroheptyltriethoxysilane and potassium diphenylarsenide are not commercially available and must be prepared, the potential toxicity of the arsenic products and waste, and the higher temperature and presence of Ph<sub>3</sub>P required for aryl bromides. The same group prepared a silica-supported poly- $\gamma$ -methylselenopropylsiloxane-palladium(0) complex (from poly- $\gamma$ -chloropropylsiloxane and sodium methylselenolate, followed by reaction with PdCl<sub>2</sub> and final reduction with hydrazine hydrate), which was also a highly active and stereoselective catalyst for the arylation of conjugated alkenes.<sup>142</sup>



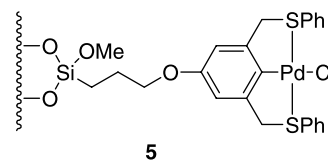
R<sup>1</sup> = H, Cl, Me, MeO, NO<sub>2</sub>, MeOCO  
 R<sup>2</sup> = Ph, CO<sub>2</sub>H  
 X = Br, I



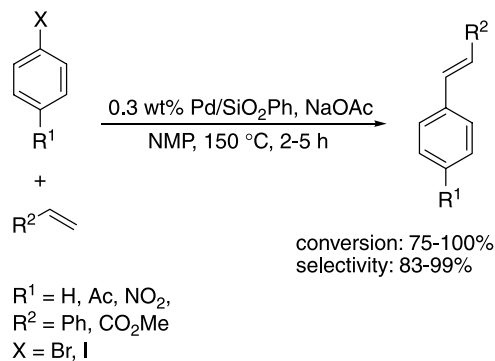
Scheme 36.

A palladium(II)–SCS–pincer complex was immobilised on porous silica and the resulting catalyst **5** was applied to the reaction of iodobenzene and *n*-butyl acrylate with Et<sub>3</sub>N in DMF at 120 °C for 1.5 h.<sup>143</sup> The catalyst was recycled three times with high yields (>99, 97 and 94%, respectively), with induction periods between subsequent runs indicating that the silica-immobilised catalyst acted as a precatalyst,

with the real active species being generated in situ during the reaction. It would worthwhile knowing about the substrate scope and limitations of this catalytic system.



Molnár et al. prepared two series of catalysts by modifying silica with various chlorohydrosilanes, followed by reaction with a saturated solution of PdCl<sub>2</sub> or a 1.25 × 10<sup>-3</sup> PdCl<sub>2</sub> solution to obtain five palladium-on-silica catalysts with different Pd loadings and another five palladium catalysts with an equal palladium loading of 0.3 wt%, respectively.<sup>144</sup> These catalysts were found to exhibit a high activity in the Heck coupling of aryl halides with styrene or methyl acrylate to afford the corresponding *E* isomers with good to excellent selectivities. The 0.3 wt% Pd-silica catalysts showed a lower activity, but increased selectivities, with 0.3 wt% Pd/SiO<sub>2</sub>Ph being the best catalyst (Scheme 37). The catalytic performance seemed to be related to the organophilicity of the surface, since the catalysts prepared from precursors with a single organic group as the surface modifier (Pd/SiO<sub>2</sub>Me and Pd/SiO<sub>2</sub>Ph) showed a higher activity than those containing two organic groups (Pd/SiO<sub>2</sub>Me<sub>2</sub> and Pd/SiO<sub>2</sub>Ph<sub>2</sub>). In a comparative study, the properties of these organically modified silicas were considered to be identical with those of 10 wt% Pd/C. Despite the reactions being carried out in a sealed tube at 150 °C, the experimental procedure for the preparation of these catalysts is very straightforward and their performance is remarkable. In addition, the catalyst performance did not change in successive experiments in which no special precaution was taken to exclude air or moisture.

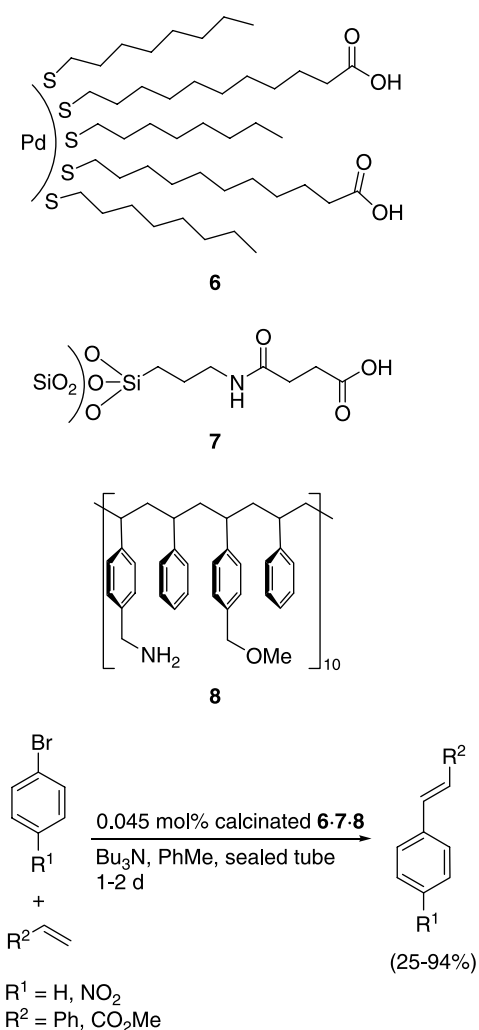


R<sup>1</sup> = H, Ac, NO<sub>2</sub>,  
 R<sup>2</sup> = Ph, CO<sub>2</sub>Me  
 X = Br, I

Scheme 37.

Rotello et al. reported a highly reactive, recyclable, heterogeneous catalyst in which palladium mixed monolayer protected clusters were simultaneously used as building blocks and active catalytic units.<sup>145</sup> Palladium nanoparticle **6** (obtained by place exchange of 11-mercapto-undecanoic acid onto 1 nm octanethiol-covered particles) was dissolved in MeOH and, to this, was added silica particles **7** and amine polymer **8**. The active catalysts were prepared through calcination of the nanocomposite materials, providing total removal of organics and

preserving intact the highly porous nature of the systems. The calcinated **6·7·8** was able to catalyse the Heck reaction of activated and neutral bromoarenes with styrene and methyl acrylate (Scheme 38). A large difference in reactivity was observed for bromobenzene and *p*-nitro-bromobenzene, the former leading to much lower yields (25–30%). The main drawbacks of this catalytic system seem to be the fact that the starting materials are not readily available and the relatively long reaction times required for the coupling reaction (1–2 days).



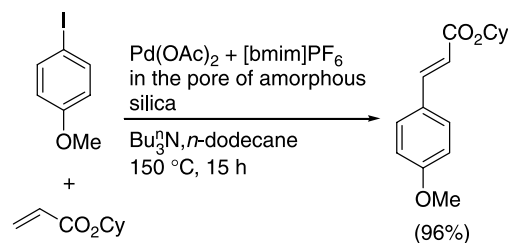
Scheme 38.

More recently, the introduction of a hydrosilane function on the pore channels of a mesoporous silica SBA-15 allowed the obtention of a highly dispersed palladium colloid layer on the pore walls of the support material.<sup>146</sup> This heterogeneous catalyst system was successfully applied to the Heck coupling of styrene and methyl acrylate with iodobenzene and electron-deficient aryl bromides, although bromobenzene gave poor conversions. The catalyst (0.02 mol% Pd-SBA-15) showed a high stability against leaching of the active species into the liquid phase and could be recycled (by filtration, washing and drying) without any apparent decrease in its catalytic activity. On the other hand, the reaction temperatures were rather high (120–170 °C,

20 min–48 h) and the catalytic system had a narrow range of substrate applicability.

Blum et al. described the easy preparation of silica sol-gel entrapped  $\text{PdCl}_2(\text{PPh}_3)_2$  as a heterogeneous catalyst for the coupling of iodobenzene and *p*-nitroiodobenzene with styrenes and acrylic acid derivatives.<sup>147</sup> The reactions were performed with  $\text{Pr}_3\text{N}$  as a base in toluene at 90–110 °C for 8–12 h and both the yields and stereoselectivities ranged from low to good, the aryl bromides reacting sluggishly. Recycling of the catalyst (by filtration and sonication) without any loss of activity was only possible in the reaction of styrene and iodobenzene. The arylation products derived from acrylonitrile were accompanied by some polymerisation products.

Ionic liquids have been used to immobilise palladium on porous silica supports and applied to ligandless Heck reactions. Exploiting the unique properties of ionic liquids, Marr et al. prepared a silica aerogel structure containing palladium nanoparticles that led to 100% conversion in the Heck reaction of *n*-butyl acrylate and iodobenzene in 2 h at 80 °C.<sup>148</sup> The selectivity towards *trans*-*n*-butyl cinnamate remained at 100% after catalyst recycling by filtration, washing and drying. In this context, Hagiwara et al. supported  $\text{Pd}(\text{OAc})_2$  on amorphous silica with the aid of the ionic liquid  $[\text{bmim}]\text{PF}_6$  through a simple procedure.<sup>149</sup> In this case, the Heck reactions involved cyclohexyl acrylate and aryl halides of different electronic character (59–96% yield), and were carried out in a hydrocarbon solvent in order to prevent removal of the ionic liquid layer from the silica (the best result is shown in Scheme 39). The catalyst was air- and thermally-stable and was re-used six times, giving high yields. The reaction temperature was, however, rather high and it would be interesting to know the possibility of application of the methodology to other more conventional acrylates and other olefins. In fact, methyl acrylate furnished low to moderate yields of the coupled product with iodobenzene.

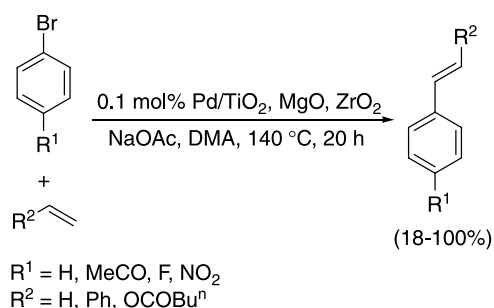


Scheme 39.

Recently, palladium nanoparticles were generated from  $\text{Pd}(\text{PPh}_3)_4$  in a mixture of tetra(ethylene glycol) and tetramethoxysilane, followed by encapsulation in a silica matrix by treatment with water. The only reported application to the Heck reaction was for the coupling of methyl *p*-iodobenzoate with styrene using 0.75 mol% catalyst and  $\text{NaOAc}$ , in DMF at 120 °C for 17 h, leading to the expected product in 80% yield. The possible re-usability of the catalyst in the Heck reaction was not tested.<sup>150</sup>

Besides silica, other metal oxides and inorganic compounds have proved to be useful supports for palladium in Heck reactions.<sup>151</sup> Iyer et al. studied the activity of Ni/Al<sub>2</sub>O<sub>3</sub>, Ni/HY-zeolite, Cu/Al<sub>2</sub>O<sub>3</sub> and Co/Al<sub>2</sub>O<sub>3</sub> in the reaction of aryl iodides (RC<sub>6</sub>H<sub>4</sub>I, R=MeO, Cl, NO<sub>2</sub>) with styrene, ethyl acrylate and ethyl methacrylate in the presence of K<sub>2</sub>CO<sub>3</sub> in NMP at 150 °C for 5–48 h.<sup>152</sup> With few exceptions, the behaviour of all catalysts was quite similar, giving a variable yield of products. The reaction temperature was rather high, taking into account that only iodides could be activated, none of the catalysts being able to activate aryl bromides or chlorides. A considerable amount of the heterogeneous catalyst underwent leaching under the reaction conditions, with a consequent loss in activity in the recycling.

Köhler et al. carried out a detailed study on the coupling of aryl bromides with olefins catalysed by palladium supported on various metal oxides.<sup>153</sup> In this case, all the supports were commercially available or easily prepared and fixation of palladium to the oxide support was easily accomplished by hydrogen reduction of a Pd(acac)<sub>2</sub> solution in the presence of the support, followed by thermal treatment. The yields of the coupled products varied from low to excellent, depending upon the substituents in the starting materials, the selectivity being high in all cases (Scheme 40). The alkenes, butyl acrylate and (the uncommon) ethylene, could also be converted, although with lower yields than for styrene. Roughly, the order of activity followed the trend TiO<sub>2</sub> > ZrO<sub>2</sub> > MgO > ZnO > SiO<sub>2</sub>. The catalysts could be recycled and reused without loss of activity. According to the authors, there were some indications of a heterogeneous reaction mechanism, but, the participation of resolved palladium species (colloids or complexes) was not excluded. In fact, this group has recently brought out clear experimental evidence for the correlation between the dissolution of palladium from the supported catalyst surface and the reaction rate.<sup>154</sup>

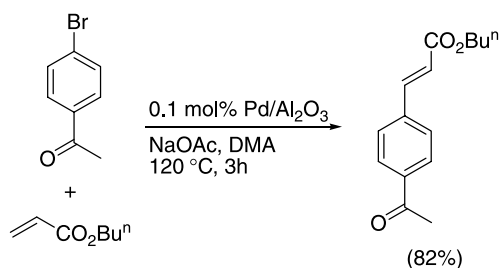


Scheme 40.

The above-mentioned oxides, together with a variety of zeolites and carbon, were used as supports in the palladium-catalysed Heck arylation of cyclohexene and cyclopentene with 4-bromoacetophenone at 120–140 °C for 20 h.<sup>155</sup> In general, almost all catalysts gave mixtures of the three possible regioisomers, although less hydrodehalogenation was observed for the zeolite-entrapped molecular palladium species than for the supported Pd(0) particles. The former catalyst also prevented double arylation, probably due to shape selectivity. Certainly, this thorough research is

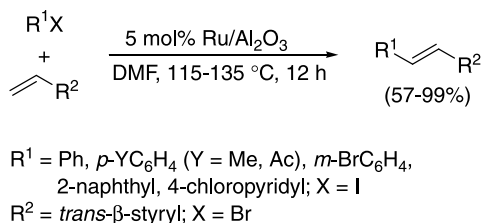
interesting from a comparative and mechanistic point of view, and involves some less well-studied olefins. The generally moderate to low regioselectivity, however, and the predictable difficulties in separating the regioisomers make any of these methodologies of little practical application.

A 5% Pd/MgO catalyst was shown to be superior to Pd/γ-Al<sub>2</sub>O<sub>3</sub> and Pd/C in the Heck arylation of acrylonitrile with iodobenzene.<sup>156</sup> Cinnamionitrile was the major product in an acetonitrile medium with Pd(acac)<sub>2</sub> and Pd/MgO catalysts in impregnated and reduced forms. 3,3-Diphenylacrylonitrile was formed as a minor product, although, very interestingly, it turned out to be the major product by changing the solvent to methanol. On the other hand, Pd/Al<sub>2</sub>O<sub>3</sub> was very active catalyst in the Heck reaction of 4-chloroacetophenone with *n*-butyl acrylate in DMA at 120 °C for 3 h (Scheme 41).<sup>157</sup> The high amount of leached palladium (79%) was utilised in additional tests exhibiting practically the same activity as in the original catalyst, and this representing strong evidence that heterogeneous palladium metal catalysts employed for Heck reactions are mainly sources of soluble palladium(II) complexes, which are the actual catalytic species.<sup>158</sup>



Scheme 41.

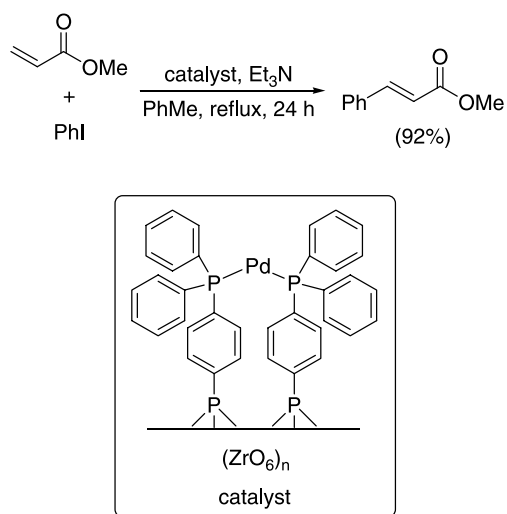
Chang et al. observed that the supported zerovalent ruthenium catalyst Ru/Al<sub>2</sub>O<sub>3</sub> was superior to the homogeneous precursor [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> in the Heck olefination of aryl iodides and an alkenyl bromide (Scheme 42).<sup>159</sup> In fact, the immobilised species displayed a wider substrate scope and higher selectivity, even under milder reaction conditions, what was related to catalysis by ruthenium colloids of the zero oxidation state. The supported catalyst was quantitatively recovered at the end of the reaction by simple centrifugation and could be re-used for an additional three runs with constant reactivity. Ruthenium leaching from the support was negligible.



Scheme 42.

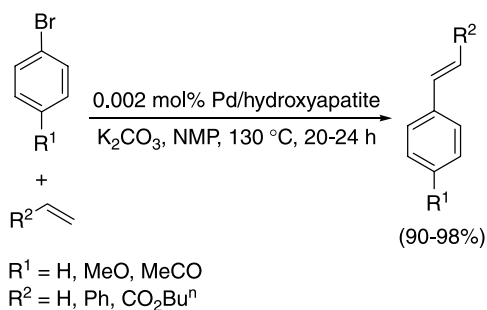
Villemin et al. prepared a palladium complex supported on zirconium phosphite–phosphonate from triphenylphosphane–phosphonic acid.<sup>160</sup> The phosphonic acid was

complexed with palladium(II) chloride, treated with zirconium chloride octahydrate (heated for 3 days), and reduced to palladium(0) with triethylsilane to give the supported catalyst. This catalyst exhibited a high activity in the coupling of iodobenzene and methyl acrylate under relatively mild reaction conditions (Scheme 43). Unfortunately, the catalyst was oxygen sensitive and had to be kept under an inert atmosphere in order to avoid deactivation and maintain its high activity over several runs.



Scheme 43.

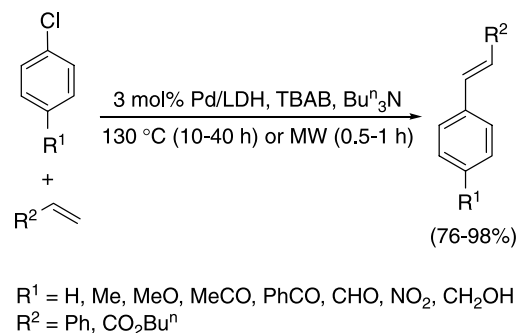
A hydroxyapatite-supported palladium complex was obtained by treatment of the non-stoichiometric Ca-deficient hydroxyapatite Ca<sub>9</sub>(HPO<sub>4</sub>)(PO<sub>4</sub>)<sub>5</sub>(OH) with an acetone solution of PdCl<sub>2</sub>(PhCN)<sub>2</sub>.<sup>161</sup> This catalyst exhibited a remarkable activity in the Heck reaction of aryl bromides with olefins, high TONs and excellent yields being obtained independently of the electronic character of the substituents (Scheme 44). The fact that no palladium leaching was observed indicated that the reaction proceeded on the Pd/hydroxyapatite surface and not with dissolved palladium species. Additional experiments seemed to support this Heck reaction not proceeding via the traditional Pd<sup>0</sup>/Pd<sup>II</sup> cycle, but via the Pd<sup>II</sup>/Pd<sup>IV</sup> mechanism. The hydroxyapatite, although not commercially available, was easily prepared by a precipitation method from Ca(NO<sub>3</sub>)<sub>2</sub>·4H<sub>2</sub>O and (NH<sub>4</sub>)<sub>2</sub>HPO<sub>4</sub>, the only limitation of this methodology being that the reactions must be performed in an argon atmosphere.



Scheme 44.

Various palladium-containing Mg–Al hydrotalcites were synthesised from the soluble metal salts by the co-precipitation method, and were applied to the Heck reaction of aryl iodides and bromides with styrenes and methyl acrylate.<sup>162</sup> Reactions with aryl iodides proceeded in the presence of a 4% Pd loading and Et<sub>3</sub>N in DMF at 120 °C for 5–20 h (59–88% yield). The less reactive aryl bromides required a higher temperature (150 °C) and catalyst loading in the presence of K<sub>2</sub>CO<sub>3</sub> in NMP. The catalyst was recycled in the case of iodobenzene and methyl acrylate without any treatment, but some decrease in the yield was observed.

A very interesting study must be highlighted carried out by the group of Choudary et al., who prepared a layered double hydroxide (LDH)-supported nanopalladium catalyst as a unique and highly effective catalyst for the Heck reaction of chloroarenes and olefins.<sup>163</sup> The reactions were conducted in TBAB as the solvent, in place of the most commonly used NMP, at 130 °C. The products were obtained with excellent yields and >99% trans-selectivity, albeit requiring relatively long reaction times. The duration of the experiments was, however, dramatically reduced under microwave conditions from 10–40 to 0.5–1 h without affecting the yields and selectivity (Scheme 45). The activity of the Pd/LDH was demonstrated to be higher than that of Pd/C, Pd/Al<sub>2</sub>O<sub>3</sub> and Pd/SiO<sub>2</sub>, the basicity of the support facilitating the oxidative addition of palladium(0) to the starting aryl chloride. As in the above example, the heterogeneity studies disclosed that the reaction occurred at the heterogeneous surface of the nanopalladium particle. In spite of the support not being commercially available and the higher catalyst loading, its recovery by simple filtration and re-use with consistent activity makes it a prime choice for the high-performance coupling of chloroarenes and olefins. LDH-supported Pd(TPPTS)<sub>2</sub>Cl<sub>2</sub> was also successfully used in the Heck arylation of olefins with bromo- and iodobenzenes in the presence of Et<sub>3</sub>N in DMF at 120 °C under a nitrogen atmosphere.<sup>164</sup> The re-usability of this catalyst for five cycles was excellent.

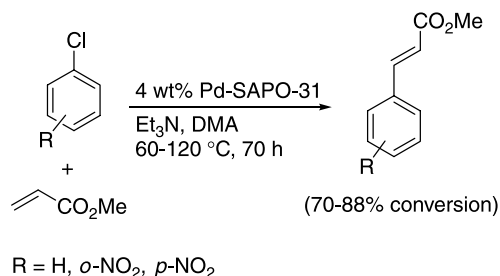


Scheme 45.

Recently, a study of the preparation of 3 mol% Cu-, Ni- and Pd- containing silicoaluminophosphate-31 (SAPO-31) materials and their catalytic activity in the coupling of iodobenzene and aryl chlorides with several styrenes and acrylates has been reported.<sup>165</sup> The Ni and Cu catalysts exhibited a lower activity than the Pd catalyst, the latter giving complete conversion of iodobenzene in the Heck



coupling reaction with methyl acrylate after 1.5 h in DMF and  $K_2CO_3$  at 120 °C. More interesting was the activity shown by the Pd catalyst for chlorobenzenes, although long reaction times and the presence of electron-withdrawing groups were needed in order to achieve good aryl chloride conversions (Scheme 46). A phenomenon of palladium leaching and redeposition was observed and the Pd-SAPO-31 catalyst could be recovered by filtration and recycled three times without significant loss in activity. This catalyst was found to be more active and efficient than other heterogeneous catalysts such as Pd/C, Pd/graphite, Pd/MgO, or Pd/Al<sub>2</sub>O<sub>3</sub>.



Scheme 46.

Natural and alkali-exchanged sepiolites containing PdCl<sub>2</sub> behaved as bifunctional catalysts in the Heck reaction of iodobenzene and bromobenzene with styrene in *o*-xylene at 145 °C for 24 h in the absence of base.<sup>166</sup> Only iodobenzene gave good yields, but, a considerable decrease in activity was observed in a second cycle after filtration. This decrease in activity could be due to the deactivation of the metal or to the consumption of the basic sites.

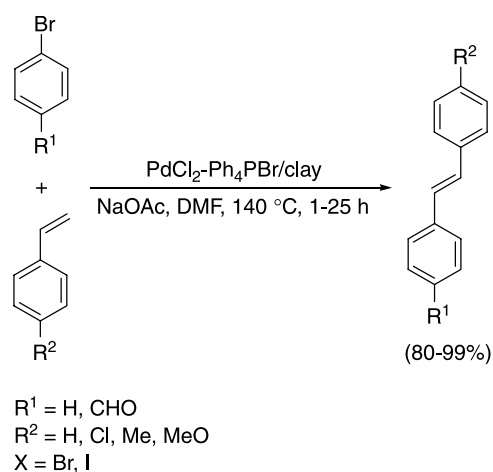
Arisawa et al. prepared a palladium catalyst on sulphur-terminated GaAs(001), using an ammonium sulfide solution followed by the adsorption of Pd(PPh<sub>3</sub>)<sub>4</sub> at 100 °C.<sup>167</sup> This novel catalyst was applied only to the coupling of iodobenzene and methyl acrylate with Et<sub>3</sub>N as a base in MeCN at 100 °C for 12 h. Repeated use of the catalyst resulted in a decrease in its catalytic activity (93–57% after five runs), which could be restored in part by further treatment with a Pd(PPh<sub>3</sub>)<sub>4</sub> solution (89–30% after ten runs).

**5.2.3. Clays, zeolites and molecular sieves.** Clay minerals consist of layered silicates which occur abundantly in nature and their high surface area, sorptive and ion-exchange properties have been exploited for catalytic applications for decades. In particular, clay-supported reagents and catalysts have found application in a wide range of organic transformations,<sup>21c</sup> although very little utility in carbon-carbon coupling reactions.

The group of Choudary was one of the pioneers in the application of clays to the Heck reaction in the early 1990s. This group discovered that a montmorillonite-ethylsilyldiphenylphosphane-palladium(II) chloride complex was a highly active and stereoselective heterogenised homogeneous catalyst for the arylation of stilbene and acrylates with iodobenzene in Bu<sub>3</sub>N at 100 °C for 2–8 h.<sup>168</sup> The coupled products were obtained in excellent yields (90–98%) and with near-quantitative *trans*-selectivity. In

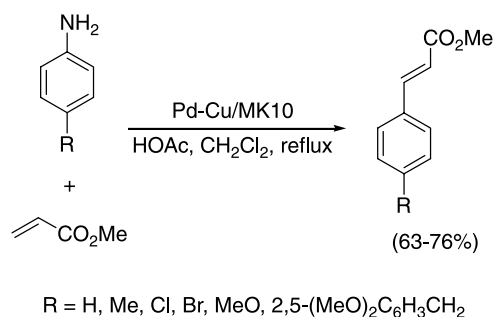
addition, the clay-anchored catalyst could be recycled four times with very little deactivation (98–92% yield). The performance of this catalytic system has subsequently been difficult to equal.

More recently, Varma et al. prepared a palladium(II) chloride and tetraphenylphosphonium bromide intercalated clay by simply refluxing (48 h) the sodium-exchanged clay with a PdCl<sub>2</sub> solution and tetraphenylphosphonium bromide, filtration, washing and drying at 100–110 °C overnight.<sup>169</sup> The catalyst gave excellent yields in the coupling at 140 °C of aryl bromides and iodides with styrenes bearing either electron-withdrawing or electron-releasing substituents (Scheme 47). The re-use of the catalyst without loss in activity and the faster reactivity, when compared to the corresponding homogeneous reaction conditions, makes this a useful and attractive protocol.



Scheme 47.

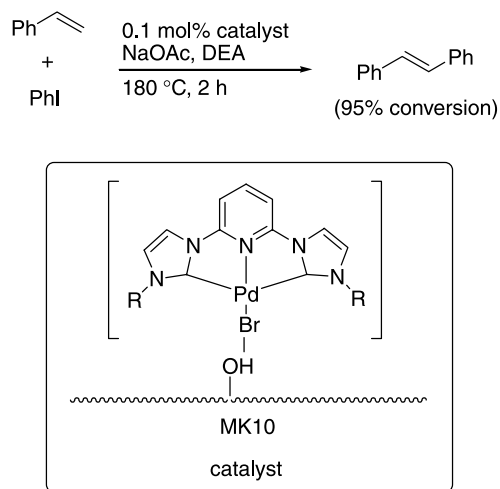
A variation of the Heck reaction was introduced by Rigo et al. involving the reaction of different anilines with vinyl acetate, catalysed by palladium(II) chloride- and copper(II) nitrate-intercalated montmorillonite K10 (MK10) clay.<sup>170</sup> The corresponding methyl cinnamates were obtained in fair yields, without the formation of by-products (Scheme 48). The catalyst was easily prepared by exchanging the clay with dilute aqueous PdCl<sub>2</sub> and Cu(NO<sub>3</sub>)<sub>2</sub> at room temperature for 24 h, followed by washing and drying at 110 °C for 12 h, and could be re-used without losing its activity. This catalyst had already demonstrated activity in the vinylation of aryl halides, mainly iodides.<sup>171</sup> With



Scheme 48.

respect to the aryl iodides, however, anilines are more readily available and, consequently cheaper, which together with the absence of adding base, makes this an interesting alternative for the larger-scale applications of the Heck vinylation of substituted aromatics.

A series of bis-carbene-pincer complexes of palladium(II) have been immobilised on montmorillonite K10 and utilised in a standard Heck reaction (Scheme 49).<sup>172</sup> The supported catalyst, obtained by the solvent impregnation method, showed a catalytic activity similar to that of its homogeneous counterparts. The leaching observed was practically negligible and, consequently, the catalyst could be recycled up to ten times, without significant loss of activity. The same catalytic system was applied to the more unreactive aryl halides, bromobenzene and 4-bromobenzaldehyde, yielding very high conversions in the presence of TBAB, but 4-chlorobenzaldehyde gave only 15% of the expected coupled product.



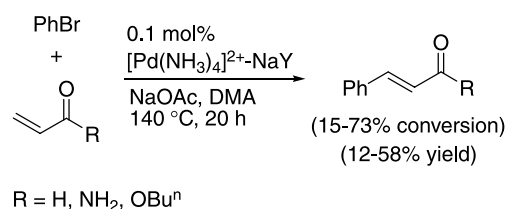
Scheme 49.

The group of Djakovitch has studied in detail the capability of palladium complex-loaded zeolites of catalysing the Heck reaction of aryl bromides with olefins, using standard reaction conditions. The high activity exhibited by these palladium-modified zeolites has been recently reviewed.<sup>21b</sup> Summarising the characteristics of these catalysts, it may be stated that the most studied NaY zeolites utilise low amounts of palladium (0.1 mol%), which can be easily separated and re-used after washing. In general, no remarkable palladium leaching was observed, the stability of the palladium active species against leaching apparently being correlated with the temperature of decomposition of the immobilised palladium complexes in the zeolite cages. It is worthy of note that even aryl chlorides can be directly activated by this type of catalyst, which is an additional advantage, besides that of the simple preparation of the palladium loaded zeolites.

Mordenite is one of the rarer, but still somewhat more widespread, members of the zeolite group of minerals. More specifically, it is a hydrated calcium sodium potassium aluminium silicate.  $\text{Pd}(\text{NH}_3)_4^{2+}$ /mordenite and  $\text{Pd}(0)$ /mordenite behaved as truly heterogeneous catalysts in the

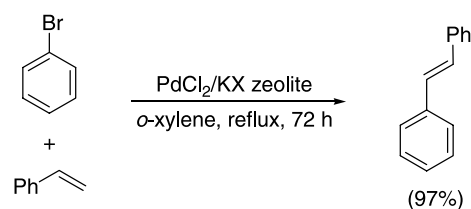
Heck reaction of iodobenzene and aryl bromides with styrene and acrylates, using  $\text{Bu}_3\text{N}$  as a base in toluene at  $130\text{ }^\circ\text{C}$ .<sup>173</sup> The best results were obtained for the coupling of iodobenzene with *n*-butyl acrylate, the other examples furnishing low to moderate conversions with rather long reaction times. The possibility of catalyst re-use was not tested. An in-depth study included the reaction of 4-bromoacetophenone and *n*-butyl acrylate under the above conditions.<sup>174</sup> Despite the conversions still being low, a continuous Heck experiment was designed to obtain 3.5 g product per g Pd and per h with hardly detectable palladium leaching.

Djakovitch et al. described the Heck arylation of acrylic compounds, including the little-studied acrolein, using the homogeneous Herrmann's palladacycle and the zeolite-supported palladium catalyst  $[\text{Pd}(\text{NH}_3)_4]^{2+}\text{-NaY}$ .<sup>175</sup> In general, better conversions and yields were obtained with the palladacycle, although the supported catalyst was more specific for the monoarylation reactions (Scheme 50). At any rate, lower yields were observed for acrolein and acrylamide than for *n*-butyl acrylate for both catalysts.



Scheme 50.

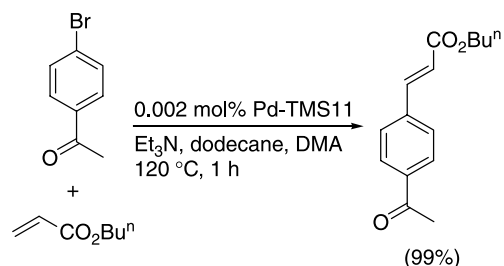
García et al. reported the preparation of  $\text{K}^+$ - and  $\text{Cs}^+$ -exchanged X zeolites containing  $\text{PdCl}_2$ , which behaved as bifunctional catalysts in the Heck reaction of iodo- and bromobenzene with styrene.<sup>176</sup> The reactions were performed in toluene or polymethylbenzenes at reflux without any extrinsic base, due to the basic character of these zeolites. The reaction of PhI and styrene produced variable amounts of 1,1-diphenylethene in all cases,  $\text{PdCl}_2\text{-CsX}$  giving predominantly 1,1-diphenylethene. On the other hand, the reaction of PhBr and styrene in the presence of  $\text{PdCl}_2\text{-KX}$  provided 97% stilbene with a long reaction time (72 h) (Scheme 51). Although no leaching of palladium was observed, the activity of the basic zeolites decreased after the second use, albeit a notable recovery of the activity being achieved by washing the zeolites with KOH or CsOH solutions. When methyl acrylate was used instead of styrene, the PhI conversion was not complete, due to partial polymerisation of methyl acrylate under the reaction conditions.



Scheme 51.

Platinum and palladium nanoparticles bound at high surface coverage on (3-aminopropyl)trimethoxysilane NaY zeolites catalysed the Heck arylation of iodobenzene with styrene in the presence of Et<sub>3</sub>N in DMA at 120 °C for 2 h.<sup>177</sup> High conversions (~95%) were achieved, even after filtration of the catalyst in a third cycle. The stereoselectivity was low, however, giving about a 10:90 cis–trans ratio. The palladium nanoparticles were shown to be firmly bound to the zeolite support, predominantly through the amine groups, preventing leaching during the different reactions.

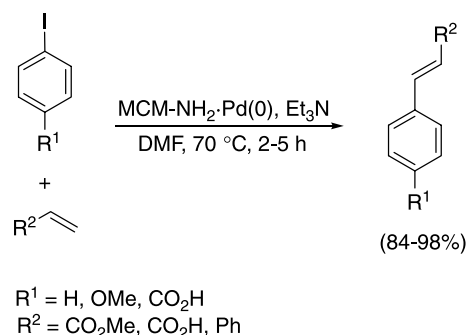
Mesoporous molecular sieves (MCM-41) are also of particular interest for catalysis involving bulky substrates because of their large pore sizes (> 20 Å) and they have been a challenge for zeolitic materials, due to their pore-opening restrictions (4–12 Å).<sup>21b</sup> In the context of the application of these materials in the Heck reaction, Ying et al. synthesised a palladium-grafted mesoporous material that utilised mesoporous Nb-MCM-41 as the support framework for the deposition of the catalytically active species.<sup>178</sup> A vapour-grafting method followed by reduction was employed for the preparation of the active catalyst, which, in addition, was silanised to reduce the palladium content, while maintaining a uniform palladium distribution. The new material Pd-TMS11 catalysed the Heck reaction of activated and non-activated aryl bromides with styrene and *n*-butyl acrylate in air at 120–170 °C. The activated aryl bromides reacted rapidly (20 min–8 h) and with excellent conversions and yields, whilst bromobenzene and chlorobenzene led to lower conversions (16–67%) with longer reaction times (32–48 h), the selectivity being remarkably high in all cases. A selected example is depicted in Scheme 52. These studies revealed a reaction mechanism based on a heterogeneous catalytic cycle. The main drawbacks of this methodology are the rather complex preparation of the active catalyst, the use of the expensive niobium(V) ethoxide, the removal of the high-boiling-point solvents, dodecane and DMA and the agglomeration of palladium and partial structural damage of the Nb-MCM-41 support shown after filtration.



**Scheme 52.**

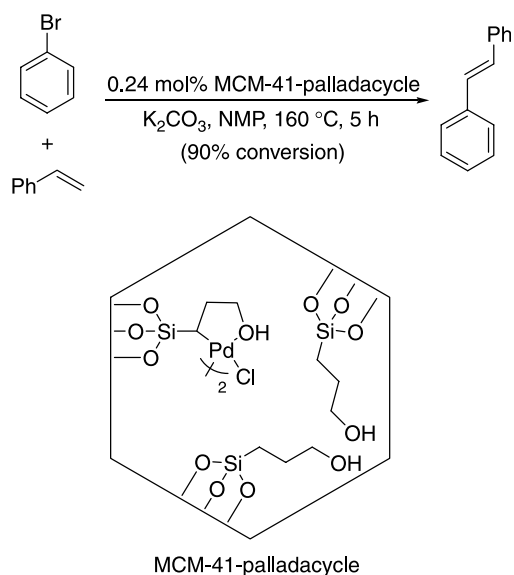
A new MCM-41-supported aminopropylsiloxane-palladium(0) complex was prepared by Zhou et al., which was a highly active and stereoselective catalyst for the Heck reaction of aryl iodides and conjugated olefins.<sup>179</sup> The catalyst was easily prepared from the MCM-41-supported aminopropylsiloxane and PdCl<sub>2</sub> in EtOH, followed by reduction with NaBH<sub>4</sub>. The corresponding products were obtained exclusively with trans stereochemistry and in high yields after 2–5 h at 70 °C (Scheme 53). Unfortunately, the catalyst was not effective with bromo- and chlorobenzene.

Concerning its re-use, a 1–3% decrease in yield was observed after each recycle. A very similar behaviour was observed for an MCM-41 supported aminopropylsiloxane-palladium acetate catalyst.<sup>180</sup>



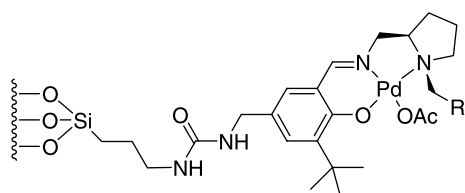
**Scheme 53.**

A C-metallated palladacycle, prepared in the pores of (3-hydroxypropyl)triethoxysilane-functionalised MCM-41 has recently found application in the coupling of bromobenzene and styrene.<sup>181</sup> Four steps were used for the preparation of the catalyst, the final of which involved palladation of the hydroxypropyl moiety of the MCM-41 with Li<sub>2</sub>PdCl<sub>4</sub> and NaOAc in MeOH under reflux for 2 days. The highest conversion in the Heck reaction (90%) was achieved at 160 °C for 5 h with K<sub>2</sub>CO<sub>3</sub> in NMP (Scheme 54), which was much superior (but proceeded at a higher temperature) to that achieved with the Pd-TMS11 catalyst described above. Unfortunately, little can be said about the scope of the reaction, since no other starting materials have been studied.



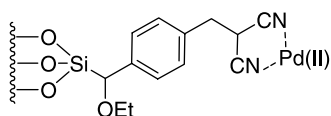
**Scheme 54.**

Many other research groups have recently focussed their attention on the development of new palladium(II) complexes anchored on MCM-41, with the aim of obtaining efficient and recyclable catalysts for the Heck reaction. Iglesias et al. prepared various catalysts of the type 9 (Chart 2), which were applied to the coupling of

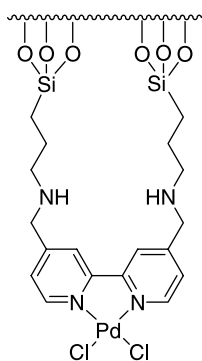


R = Ph, 1-naphthyl, 2-naphthyl

9



10



11

Chart 2.

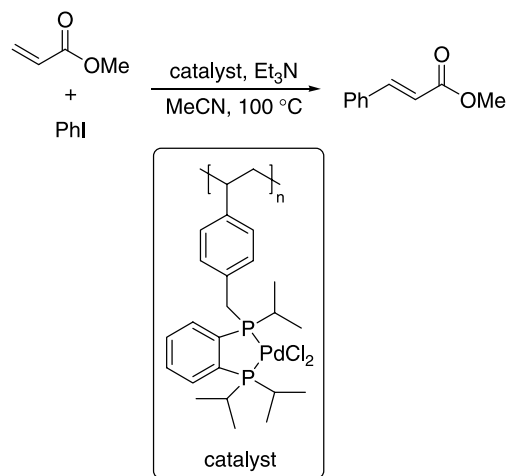
iodobenzene with  $\alpha$ -methylstyrene and two acrylates in a biphasic mode (ethylene glycol–toluene) with KOAc at 140 °C for 24 h.<sup>182</sup> Despite the fact that the catalyst was air and moisture stable, and that it could be recycled (by separation of the ethylene glycol phase) at least six times without apparent loss of activity, the conversions were low (10–64%). In addition, the catalysts and their preparation were rather sophisticated. The dicyano-functionalised MCM-41-anchored palladium complex **10** demonstrated a good catalytic activity towards the vinylation of aryl iodides and bromides with methyl acrylate, in the presence of Et<sub>3</sub>N and DMF for 4–8 h at 70–120 °C.<sup>183</sup> Exclusive formation of the trans products was achieved in 87–92% yield, the activity being constant through four cycles, due to the very little palladium leaching observed. The palladium-bipyridyl complex **11**, anchored inside the channels of nanosized MCM-41, exhibited a generally good performance in the Heck reaction of aryl iodides and bromides with styrene and alkyl acrylates,<sup>184</sup> most of the yields ranging from 70 to 98% by using Bu<sub>3</sub>N in NMP at 100–170 °C for 16–96 h. The catalytic activity remained intact after four re-use runs. High TONs were reached in most cases (up to 10<sup>6</sup> for each cycle), although the aryl bromide activation required harsher reaction conditions and the coupling with styrene was not completely stereoselective (~90:10 cis–trans).

A palladium-loaded ETS-10 molecular sieve exhibited good activity and selectivity towards the carbon–carbon coupling of aryl halides with olefins at low concentrations of Pd (0.009–1.4 mol%). In the case of the coupling of ethyl

acrylate with iodobenzene, 96% conversion of iodobenzene with >98% selectivity could be obtained within 1 h over a 0.2 wt% Pd-loaded catalyst. The catalyst activated both aryl bromides and chlorides, and appeared to be heterogeneous.<sup>185</sup>

**5.2.4. Polymers.** In the introductory section, we have already highlighted the ongoing interest in immobilising palladium on polymeric supports in organic synthesis and, in particular, in carbon–carbon coupling reactions.<sup>19</sup> The Heck reaction using polystyrene-bound phosphanes was pioneered by Teranishi et al.<sup>186</sup> and studied in detail by Andersson et al. in the mid-1980s.<sup>187</sup> It is also worthwhile mentioning that Zhang et al. developed in the late-1980s a [poly(styryl)phenanthroline]palladium(0) catalyst that exhibited a high activity in the Heck reaction of olefins with substituted iodobenzenes and that could be recycled up to ten times with no decrease in activity.<sup>188</sup>

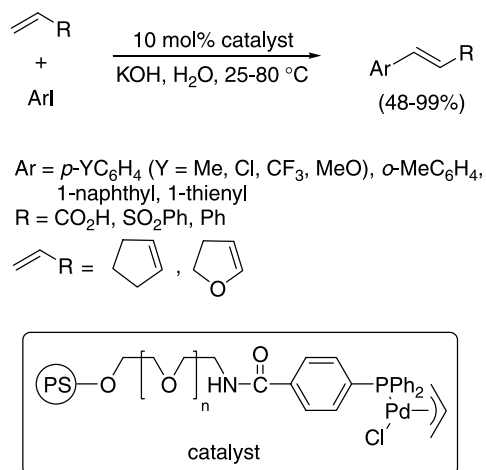
An interesting publication by Fox et al. appeared in 1994 comparing the catalytic efficiency of monomeric and polystyrene-supported 1,2-bis(diisopropylphosphino)benzene-palladium(II) in the Heck reaction.<sup>189</sup> The coupling of iodobenzene and methyl acrylate was used as a model reaction (Scheme 55), which led to the following conclusions in favour of the palladium-supported version: (a) the polymer-supported palladium(II) complex showed a higher activity than the analogous monomeric complex, (b) the products were easily separated from the heterogeneous catalyst by simple filtration and (c) the recycled polymer-supported complex was stable to air and retained its original catalytic activity after many turnovers.



Scheme 55.

More recently, Uozumi et al. developed an amphiphilic polystyrene-poly(ethylene glycol) resin-supported palladium–phosphane complex that exhibited a very high performance in the Heck reaction of aryl iodides and olefins in water.<sup>190</sup> A wide array of electronically different aryl iodides and alkenes were tested under very mild reaction conditions (25–80 °C), most of the yields being >92% (Scheme 56). Bromobenzene showed a lower reactivity (52%), even at 80 °C. Although the palladium loading was high (10 mol%), recyclability of the catalyst was successful, leading to a 92% average yield after five continuous runs.





Scheme 56.

Bergbreiter et al. synthesised various pincer-type SCS ligands that were attached to soluble poly(ethylene glycol) via ether or amide linkages. Both the PEG-bound 5-oxo (**12**) and 5-amido (**13**) palladium complexes were active as catalysts in the Heck reaction of aryl iodides and acceptor alkenes in DMF and air at 110 °C for 5–6 h using 0.1 mol% of catalyst (71–99% product yield) (Chart 3).<sup>191</sup> Catalyst **12**, however, slowly decomposed, leading to a black precipitate of palladium that precluded the possibility of recycling. In contrast, the PEG-bound 5-amido-SCS-Pd complex **13** was recycled three times via solvent precipitation (in diethyl ether) with no observed catalyst deactivation. Perhaps the main inconvenience of this methodology is the large number of steps needed for the synthesis of the catalysts, although the yields are generally high. Based on this methodology, different thiol pincer groups attached to four different resins were complexed with palladium and their performance tested in the coupling of 4-bromoacetophenone with styrene.<sup>192</sup> The best conversion (88%) was obtained for the cyclohexyl-bearing thiol pincer ligand bound to polystyrene in a dioxane-NaOAc system.

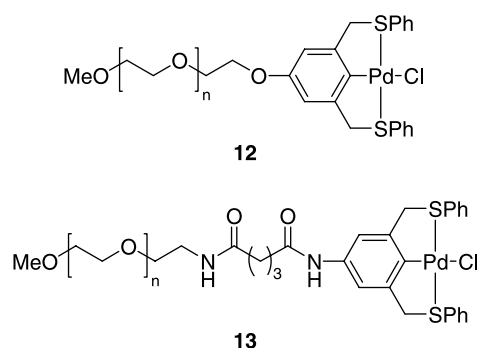


Chart 3.

Bergbreiter's group studied a new technique of product isolation and catalyst recovery, based on liquid–liquid biphasic systems that exhibit an increase in phase miscibility at elevated temperature, together with soluble polymer-bound catalysts that have a strong phase preference at ambient temperature. The catalysis in this type of system was termed thermomorphic catalysis. The Heck reactions of aryl iodides and olefins were conducted in the presence of a

poly(*N*-isopropylacrylamide) (PNIPAM)-bound phosphane or a polymer-supported tridentate SCS-Pd catalyst,<sup>193</sup> for example, using 2 mol% (PNIPAM-PPh<sub>2</sub>)<sub>4</sub>Pd(0) (**14**) and Et<sub>3</sub>N in heptane–90% aqueous EtOH, iodobenzene and *tert*-butyl acrylate completely reacted within 48 h at 70 °C (Chart 4). The system was allowed to cool to room temperature to induce phase separation. Removal of the heptane phase and solvent evaporation furnished the expected product in 71% yield. Catalyst recycling was achieved by adding a fresh heptane solution of the reactants and reheating the system to 70 °C for an additional 48 h. Interestingly, the yields increased in each cycle, becoming virtually quantitative after the third cycle. This catalyst was, however, air sensitive. The recyclability and application of catalyst **14** in aqueous or aqueous-organic media were confirmed by other workers.<sup>194</sup> A DMA–heptane system was used for the thermomorphic catalysis with the PNIPAM-bound methyl red dye **15** (2 mol%) (Chart 4). In this case, complete conversion in the reaction between iodobenzene and styrene was observed after 48 h at 90 °C. Catalyst **13** (0.2 mol%) was also shown to be effective in coupling various aryl iodides and alkenes in a DMA–heptane system at 95 °C with Et<sub>3</sub>N, with the advantage of being an air-stable catalyst. A similar performance to catalyst **13** was observed for catalyst **16** (Chart 4).

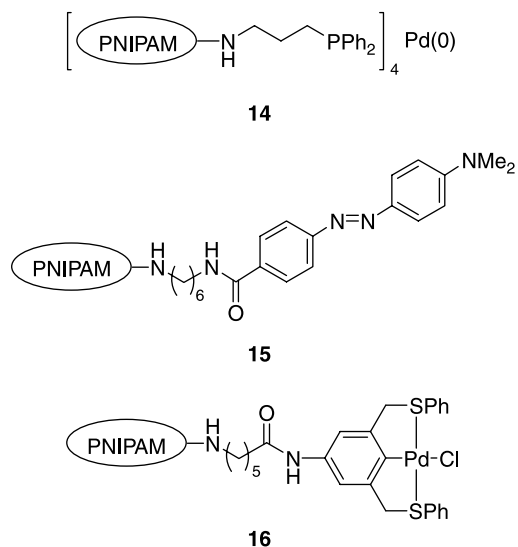


Chart 4.

By changing the *N*-alkyl group in PNIPAM to the more lipophilic octadecyl, the polymer solubility was inverted so that it selectively dissolved in the non-polar phase of a biphasic mixture, but stayed in solution at elevated temperature (inverse thermomorphic separation).<sup>195</sup> Thus, poly(*N*-octadecyl-acrylamide-*co*-*N*-acryloxysuccinimide) was prepared and modified to support an air- and heat-stable SCS-Pd(II) Heck catalyst **17** (Chart 5). This polymer-bound catalyst was active in a thermomorphic heptane–DMA mixture at 110 °C, its activity being comparable to that of the PNIPAM-bound SCS-Pd(II) catalyst **16**. In fact, it was used for up to nine cycles in the formation of cinnamic acid from iodobenzene and acrylic acid, showing a 90% conversion in the ninth cycle at 24 h. The palladacycles **18**, derived from an azo dye ligand coupled to either a

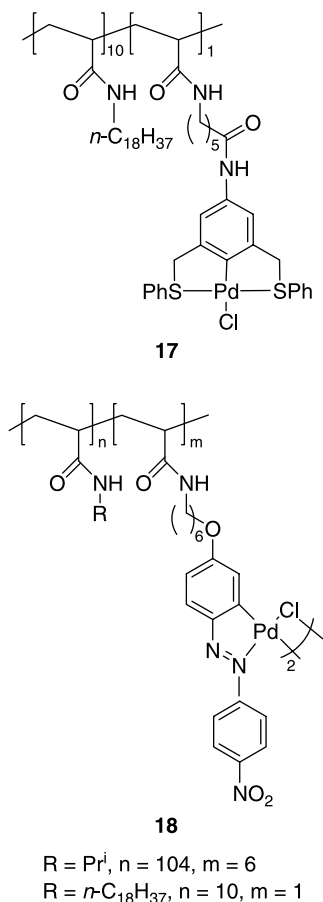


Chart 5.

poly(*N*-isopropylacrylamide) or a poly(*N*-octadecylacrylamide), were also active Heck catalysts (Chart 5).<sup>196</sup> While the polymer recovery was very high (>99.9%) and easily assayed by UV spectroscopy, however, a small amount of catalyst decomposition was observed, making these palladacycles less suitable than the above-described catalysts.

Herrmann et al. attached palladium(II) complexes of *N*-heterocyclic carbenes to polystyrene-based Wang resins through ether linkages (Chart 6).<sup>197</sup> The catalysts **19** exhibited a high activity in the coupling of aryl bromides with styrene and *n*-butyl acrylate. Full conversions were obtained for *p*-bromoacetophenone after 15 h with a low catalyst loading (0.02–0.15 mol%). Even deactivated bromobenzenes bearing electron-donating groups were converted with TONs of 10<sup>3</sup>–10<sup>4</sup>. When styrene was employed as the vinylic substrate, however, the conversions were lower and substantial amounts of isomeric compounds were obtained. Unfortunately, chlorobenzenes did not react, even under harsh reactions conditions. Despite the fact that catalyst preparation was not straightforward (even the starting *N,N'*-diimidazolylmethane had to be synthesised), the catalyst was used 15 times without a detectable loss of activity and was not sensitive to air and moisture. In contrast, catalyst **20** was readily prepared in two steps from commercially available aminomethyl-functionalised polystyrene beads and its activity studied in the coupling reaction of iodobenzene and styrene in NMP with Pr<sub>3</sub>N as a base at 100–140 °C.<sup>198</sup> This catalyst showed a comparable

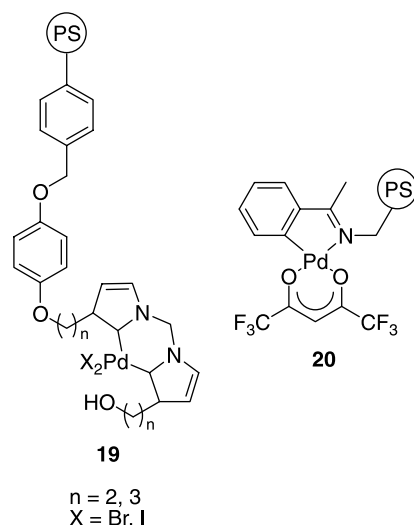


Chart 6.

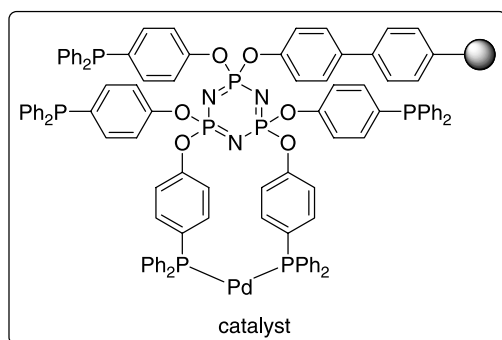
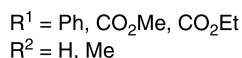
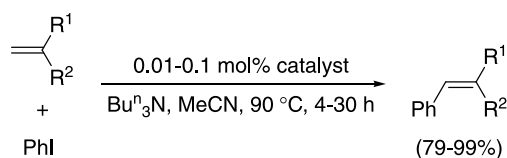
level of activity in the first run (140 °C, 11 h, 100% yield, TON 15625) to that of some homogeneous analogues. It proved, however, to be completely inactive in a consecutive run. This provided evidence about the soluble character of the catalytically active species, which must be formed under loss of the ligand. In fact, **20** proved to be thermally labile to such an extent that even moderate heating during the synthesis of the palladacycle caused precipitation of some palladium black.

A PS-supported palladium catalyst (PS-C<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>PPh<sub>2</sub>...[Pd]) was also applied in intramolecular Heck reactions after RCM of a series of *N*-alkenyl-*N*-allyl-2-bromo(or iodo)benzenesulfonamides. The corresponding bridged ring systems were obtained in 40–69% yield after treatment of the RCM products with 10% mol PS-bound palladium catalyst and 2 equiv of Ti<sub>2</sub>CO<sub>3</sub> in toluene at 110 °C for 16 h.<sup>199</sup> Despite the attractiveness of this cascade process, the use of 2 equiv of Ti<sub>2</sub>CO<sub>3</sub> is a clear disadvantage, due to its high toxicity (mutagen and reproductive effector).

A β-ketoesterato polymeric palladium complex, obtained by co-polymerisation of Pd(AAEMA)<sub>2</sub> [AAEMA is the deprotonated form of 2-(acetoacetoxy)ethyl methacrylate] with ethyl methacrylate and ethylene glycol dimethacrylate, was also active in the Heck reaction of activated and non-activated iodo- and bromoarenes with styrene, acrylonitrile and methyl acrylate.<sup>200</sup> The reactions with aryl iodides were performed with KOAc in DMF at 90 °C for 2–6 h, giving high yields of products, but moderate trans-selectivity. In the case of aryl bromides with styrene, the reactions were carried out at 160 °C in the presence of DMG for 10–12 h, the yields also being high with improved trans-selectivity. A negligible loss of activity was observed after five recycles of the catalyst.

A palladium complex of a pendant cyclophosphazene-containing cross-linked polymer was synthesised by Chandrasekhar et al. by reacting hexachlorocyclotriphosphazene with 1 equiv of 4-hydroxy-4'-vinylbiphenyl, followed by reaction with 5 equiv of *p*-diphenylphosphinophenol, copolymerisation with divinylbenzene,

palladium complexation and final reduction.<sup>201</sup> This polymer-supported catalyst was successfully used in the coupling reaction of iodobenzene with several olefins, giving the expected products with exclusive trans stereochemistry (Scheme 57). Slightly longer reaction times were needed in comparison with the monomeric catalyst and bromobenzene did not react. It is worthy of note that even the 1,1-disubstituted olefin, methyl methacrylate, reacted stereoselectively and in good yield (79%). The recovered catalyst tested in three successive cycles maintained almost the original activity, which was in agreement with the fact that the reaction took place due to the polymeric catalyst and not to the leached palladium species.



Scheme 57.

The structures in Chart 7 were both obtained by a ring-opening ROMP metathesis polymerisation strategy of norbornene derivatives. The synthesis of ligand **21** was achieved in four steps from *p*-benzoquinone and was applied to the Heck reaction of iodobenzene and methyl acrylate in the presence of Pd(OAc)<sub>2</sub> (5 mol%) and TBAA in DMF at 80 °C for 12 h (95% yield).<sup>202</sup> A 10% decrease in yield was observed after five catalytic cycles. The preparation of complex **22** was not so straightforward, since even the starting bis(pyrimid-2-yl)amine had to be prepared by palladium-catalysed amination of 2-chloropyrimidine.<sup>203</sup> This catalyst, however, showed a high activity in the coupling of activated 4-bromobenzonitrile and 4-chloroacetophenone with styrene (DMA, Bu<sub>3</sub>N, 150 °C, 72 h) to afford 4-cyanostilbene and 4-acetylstilbene in 98 and 70% isolated yields, respectively. The addition of TBAB was needed for the effective coupling of the aryl chloride.

More recently, Portnoy et al. have prepared representative members of five different families of supported phosphane and phosphinite ligands from common polymer-bound aminoalcohols.<sup>204</sup> These include β-aminophosphines, *N*,β-diphosphinoamines, α,β-diphosphinoamines, β-amino-phosphinites and *N*-phosphino-β-aminophosphinites. The

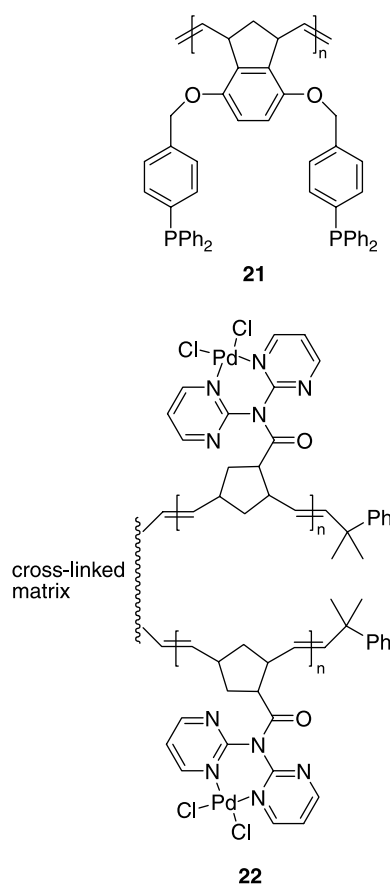


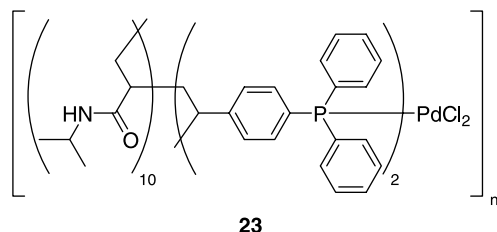
Chart 7.

ligands were complexed with Pd(OAc)<sub>2</sub> and tested in the Heck reaction of iodo- and bromobenzene with methyl acrylate in the presence of Et<sub>3</sub>N in NMP at 110 °C for 18 h. All ligands furnished equally high yields (90%) in the Heck reaction of iodobenzene. Low to moderate conversions (8–63%) and yields (1–56%) were, however, obtained in the reaction with bromobenzene, showing clear differences in the activity of the various ligands tested.

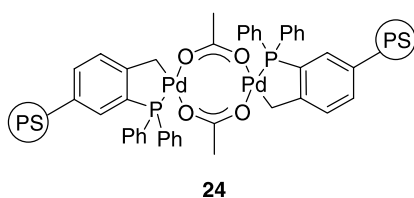
A polymer (fibre)-supported palladium catalyst containing imidazolanyl rings was synthesised easily from commercially available polyacrylonitrile fibre.<sup>205</sup> The catalyst (0.01 mol%) was successfully used in the Heck reaction of iodobenzene with different alkyl acrylates in the presence of Et<sub>3</sub>N in dioxane at 100 °C for 1–2 h (94–97% yield). The fibre catalyst could be recycled more than 20 times without any loss of activity or selectivity.

Ikegami et al. developed a supramolecular complex prepared from a self-assembly of (NH<sub>4</sub>)<sub>2</sub>PdCl<sub>4</sub> and a non-cross-linked amphiphilic phosphine polymer poly[(*N*-isopropylacrylamide)<sub>5</sub>-*co*-(4-diphenylstyrylphosphine)] (**23**).<sup>206a</sup> This catalyst was shown to be very effective in the coupling of electronically different aryl iodides with alkyl acrylates and styrene. The reactions proceeded with Et<sub>3</sub>N as a base in toluene at 100 °C for 5–20 h, the yields being in all cases above 90%. Very high TONs were reached (up to 1,150,000) and the complex could be recycled up to five times, still retaining its activity with only 5 × 10<sup>-5</sup> mol equiv. In this case, the polymer is not commercially available and

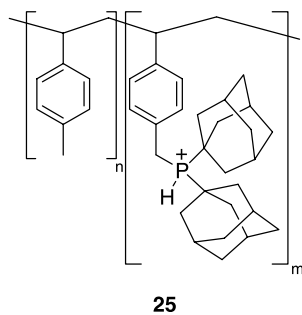
must be synthesised by radical copolymerisation of *N*-isopropylacrylamide and the expensive diphenyl(4-styryl)phosphine, but this is compensated for the effectiveness of the catalyst. This methodology was applied to the synthesis of resveratrol and was demonstrated to also work effectively using water as a solvent.<sup>206b</sup>



The polystyrene-supported palladacycle **24** was obtained in 20% overall yield after six steps from 4-methylacetophenone.<sup>207</sup> This catalyst (0.002–0.05 equiv) promoted the Heck reaction of methyl acrylate with iodobenzene and aryl bromides containing either electron-rich or electron-withdrawing groups, in the presence of NaOAc in DMA at 100 °C for 8–48 h in excellent yields (92–99%). In a model reaction, the yield of the product was > 80% after recycling the catalyst four times using ether as the solvent to precipitate the catalyst.



Plenio et al. reported the synthesis of a polymer-enlarged catalyst formed from (1-Ad)<sub>2</sub>P-substituted poly(methylstyrene) (**25**) and a suitable palladium source [Pd(dba)<sub>2</sub>].<sup>208</sup> The polymer **25** was obtained by anionic polymerisation of 4-methylstyrene, bromination and reaction with (1-Ad)<sub>2</sub>PH. The catalyst (0.5 mol%) was utilised in the coupling of 4-bromoacetophenone, 4-bromoanisole and bromobenzene with *n*-butyl acrylate in NMP–Pr<sub>2</sub>NH at 100 °C for 16 h. The coupling yields were 80–87%, but, the catalyst could not be recycled, since attempting nanofiltration in the highly polar and aprotic medium resulted in severe membrane damage.



Poly(vinylpyridine) nanospheres were used by Thompson et al. as a stable support for dispersing polymer-stabilised palladium nanoparticles (1–4 nm) by a one-step adsorption from colloidal solution.<sup>209</sup> Monodispersed nanospheres

were prepared by emulsifier-free emulsion polymerisation techniques under free-radical initiation of the monomer with 4 wt% divinylbenzene as the cross-linking agent. The catalyst (0.1 mol%) was successfully applied to the coupling of 4-nitrobromobenzene and *n*-butyl acrylate in DMA and Et<sub>3</sub>N at 120 °C for 12 h. The catalyst was found to be air-stable and did not show any decrease in activity after six months stored in air. Although there was no substantial palladium loss or swelling under the reaction conditions, the coverage and palladium loading over the beads were relatively higher, compared to those of Antonietti's system described below (see Section 7.2.1). It would be interesting to know about the scope of the catalytic system when applied to other haloarenes and olefins.

The palladium complex supported on Tenta Gel<sup>®</sup> resin **26** (Chart 8), containing a pyridylbis-*N*-heterocyclic carbene ligand derived from isonicotinic acid, could be recycled up to 14 times (by filtration, washing and drying) in the Heck coupling of iodobenzene and methyl acrylate.<sup>210</sup> The different cycles were carried out with 1 mol% **26**, Et<sub>3</sub>N and DMA at 165 °C for 48 h under an inert atmosphere to avoid Pd black formation. Very low levels of palladium leaching from the resin were detected. The reaction conditions are, however, still rather harsh (165 °C, sealed tube, 48 h) and the methodology seems to be restricted to only iodobenzene and methyl acrylate. Buchmeiser et al. have reported the synthesis of new polymer-supported palladium(II)bis(3,4,5,6-tetrahydropyrimidin-2-ylidenes) of the type **27** (Chart 8), derived from Merrifield resin, Wang resin and crosslinked poly(norbor-2-ene).<sup>211</sup> These supported catalysts were used in the Heck reaction of *n*-butyl acrylate and styrene with various aryl iodides and bromides in DMA at 145 °C. No general trend in terms of optimum support was, however, observed under the chosen conditions, most of the yields being rather low. The strong variations in reactivity seem to support the coupling

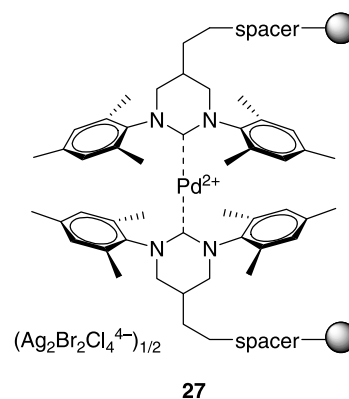
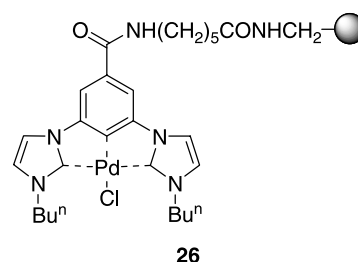
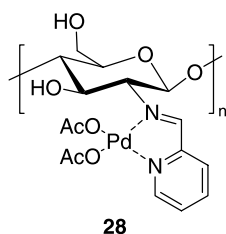


Chart 8.



reactions proceeded via supported species. In addition, catalyst deactivation and leaching of palladium were observed when re-used, this precluding any possible catalyst recycling.

Chitosan or poly[ $\beta$ -(1-4)-2-amino-2-deoxy-D-glucan] is produced by deacetylation of chitin, a major naturally occurring biopolymer. Recently, different groups have used it as a support in the palladium-catalysed Heck reaction. Macquarrie et al. modified chitosan by the introduction of a palladium iminopyridyl complex.<sup>212</sup> The resulting complex **28** catalysed the reaction of iodobenzene and *n*-butyl acrylate, in the presence of Et<sub>3</sub>N, giving *n*-butyl cinnamate in 82% yield after 42 h at 100 °C (for a substrate-to-Pd molar ratio of 1325). The coupling of styrene and bromobenzene was accomplished at a substrate-to-Pd ratio of 1420, giving stilbene in 88% yield after 42 h. By doubling the amount of catalyst, the reaction times were reduced by 50%. But the possibility of catalyst recycling was not explored in the Heck reaction. A chitosan-immobilised palladium(0) complex was prepared by other workers by refluxing chitosan with PdCl<sub>2</sub> in EtOH and this was also applied to the Heck reaction with yields varying from 12 to 99%.<sup>213</sup> For the application of palladium on chitosan in ionic liquids, see Section 6.2.

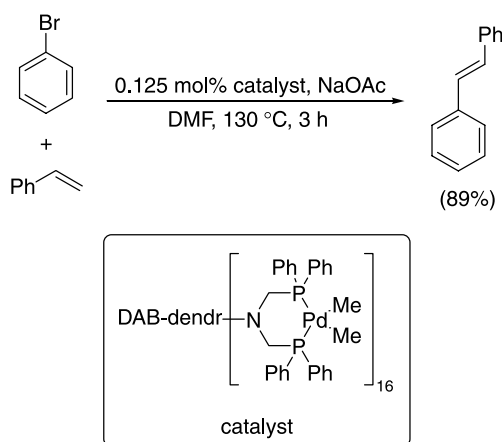


The inorganic and polymeric supported catalysts reported here were demonstrated to be very advantageous from the point of view of catalyst recycling and product purification. The generally high reaction temperatures needed in order to obtain reasonable conversions and the often observed palladium leaching are still, however, the main limitations of these methodologies.

**5.2.5. Dendrimeric systems.** The synthesis of dendrimers with defined inner and outer structural elements provides access to macromolecular materials having special properties and functions that can be useful for applications in catalysis.<sup>214</sup> Such materials can be at the interface between homogeneous and heterogeneous catalysis. Dendrimers are particularly attractive hosts for catalytically active nanoparticles since (a) the dendrimer templates yield well-defined nanoparticle replicas, (b) the nanoparticles are stabilised by encapsulation within the dendrimer and do not agglomerate, (c) the nanoparticles are retained within the dendrimer primarily by steric effects and, therefore, a substantial fraction of their surface is unpassivated, (d) the dendrimer branches can be used as selective gates to control the access of small molecules to the encapsulated nanoparticles and (e) the dendrimer periphery can be tailored to control the solubility of the hybrid nanocomposite and to facilitate linking to surfaces and other polymers.<sup>214</sup> Metal-containing dendrimers have, however,

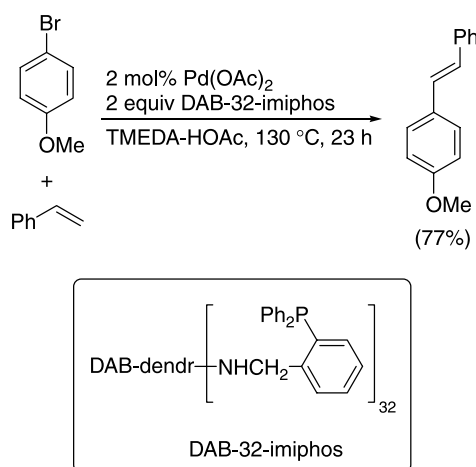
been scarcely prepared for use as catalysts in the Heck reaction.

In 1997, Reetz et al. reported the preparation of a dendritic diphosphane-metal complex from a commercially available DAB-based (DAB = 1,4-diaminobutane) polyamino dendrimer DAB-dendr-(NH<sub>2</sub>)<sub>16</sub>, by double phosphinomethylation of each of the primary amino groups and metal complexation.<sup>215</sup> Coupling of bromobenzene and styrene in the presence of 0.125 mol% catalyst furnished 89% stilbene, together with 11% 1,1-diphenylethylene at a conversion of 85–90% (Scheme 58). The catalyst could be recovered by precipitation with diethyl ether and used once more with comparable catalytic activity. Unfortunately, the selectivity of the method is not very high.



Scheme 58.

More recently, Screttas et al. have described the synthesis of the iminophosphane ligand, DAB-dendr-[1,2-*N*=CHC<sub>6</sub>H<sub>4</sub>-PPh<sub>2</sub>]<sub>32</sub> (DAB-32-imiphos), from the polyamino dendrimer DAB-dendr-(NH<sub>2</sub>)<sub>32</sub> and 2-diphenylphosphinobenzaldehyde, which was tested in the palladium-catalysed reaction between *p*-anisyl bromide and styrene.<sup>216</sup> The highest conversion (93%) was achieved under the reaction conditions specified in Scheme 59. An equimolar mixture of a tertiary amine and acetic acid was shown to be superior to any other solvent tried, this solvent system



Scheme 59.

behaving as an ionic liquid. It must be pointed out that this catalytic system is not recoverable, due to degradation of the ligand and extensive formation of palladium black under the reaction conditions.

Portnoy et al. synthesised various poly(aryl benzyl ether) and polythioether dendronised polystyrene resins in which the terminal hydroxyl groups were esterified with 4-(diphenylphosphino)benzoic acid, followed by complexation with Pd(0) using a Pd(dba)<sub>2</sub> precursor (Chart 9). In the polyether series, the maximum conversion (100%), yield (100%) and selectivity (>200) in the Heck reaction of bromobenzene and methyl acrylate was achieved with the third-generation-derived catalyst at 80 °C for 72 h in NMP–Et<sub>3</sub>N.<sup>217</sup> A similar behaviour was observed for styrene as the substrate, although the effect on the activity and selectivity was somewhat smaller. In the case of *n*-butyl vinyl ether, three isomeric products were obtained in all cases. Precipitation of palladium occurred during the reaction, indicating that, probably, the catalysis is performed by palladium nanoparticles stabilised inside the dendritic matrix. In the polythioether series, the starting monomer is not commercially available and was synthesised from the corresponding oxygenated derivative.<sup>218</sup> In this case, the third-generation of the polystyrene-polythioether dendron/Pd(0)-phosphane (2.5% Pd) was effective in the reaction of bromobenzene and methyl acrylate in NMP–Et<sub>3</sub>N at 120 °C for 14 h (89% yield). Moreover, for iodobenzenes as substrates, there was no need for phosphino groups on the dendron, since each isophthalate-derived unit in the interior of the dendron can serve as a precursor to the pincer complex of the SCS monoanionic tridentate ligand, which behaves as an efficient and recyclable catalyst.

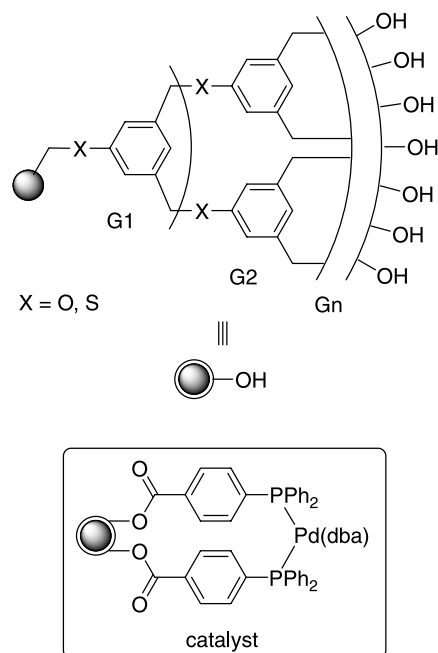


Chart 9.

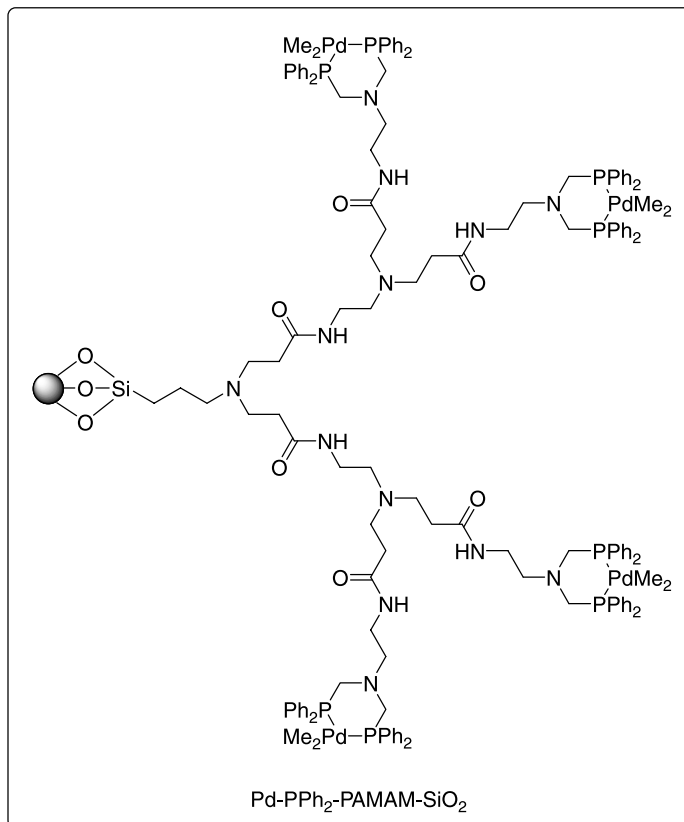
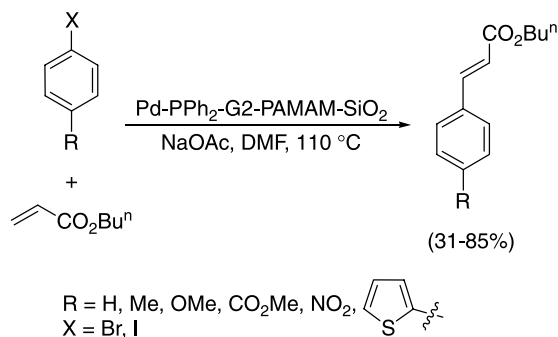
Christensen et al. studied the behaviour of palladium nanoparticles encapsulated in poly(amidoamine) (PAMAM) dendrimers in the Heck reaction of aryl iodides

and bromobenzene with acrylic acid.<sup>219</sup> Thus, 0.025 mol% Pd in the form of Pd<sub>60</sub>[G4PAMAM-OH] catalysed the coupling of different substituted aryl iodides and acrylic acid in DMA–NaOAc at 140 °C for 12 h, furnishing the corresponding *trans*-cinnamic acids in 67–92% isolated yields. A much lower yield was obtained for bromobenzene (35%), whereas chlorobenzene did not react. On the other hand, the lifetime of the catalyst was not satisfactory, as a loss of catalytic activity was observed, due to a gradual thermal degradation of the dendrimer.

A palladium-nanoparticle-cored G3 dendrimer, derived from Fréchet-type dendritic polyaryl ether disulfide of generation three, was found to possess approximately 300 Pd atoms in the metallic core and an average diameter of 2 nm, to which were attached 14 G3 dendrons.<sup>220</sup> These dendrons inhibited metal agglomeration without adversely affecting the chemical reactivity. In fact, nearly 90% of the metal nanoparticle surface was unpassivated and available for catalysis, for example, the Pd-G3 dendrimer ( $2 \times 10^{-3}$  mol%) catalysed the Heck reaction of iodobenzene and ethyl acrylate in toluene–Et<sub>3</sub>N at reflux for 24 h, giving ethyl *trans*-cinnamate in 75% yield. The use of styrene as the substrate, however, led to a mixture of stilbene and 1,1-diphenylethylene in rather low yields, 38 and 8%, respectively. The reactions took place under homogeneous conditions, and, after removal of the toluene and addition of ether, the Pd-G3 catalyst was easily removed, and was shown to be stable for several months, both as a powder and as a dilute solution in dichloromethane.

Alper et al. developed dendritic silica-supported bidentate phosphine ligands of the type PPh<sub>2</sub>-PAMAM-SiO<sub>2</sub>, obtained from a commercial aminopropylsilica gel by Michael addition of the pre-existing amino group to methyl acrylate, amidation of the ester units with ethylenediamine, phosphinomethylation of each terminal amino group, and palladium complexation.<sup>221</sup> The second-generation Pd-PPh<sub>2</sub>-G2-PAMAM-SiO<sub>2</sub> dendrimer showed the highest catalytic activity and found application in the coupling of different bromoarenes and iodobenzene with *n*-butyl acrylate (Scheme 60).<sup>222</sup> In contrast to the expected behaviour, electron-withdrawing substituents on the arene gave relatively low yields and conversions, while electron-donating groups gave moderate to good yields of the coupled products.

Kaneda et al. recently described the immobilisation of a palladium complex catalyst within the cavity of poly(propylene imine) dendrimers through ionic bonds.<sup>223</sup> The peripheral groups on the third to fifth-generation of the dendrimer were modified with decanoyl chloride and 3,4,5-triethoxybenzoyl chloride, respectively, to give the alkylated and arylated dendrimers. The dendritic palladium complexes catalysed the Heck reaction of iodobenzene with *n*-butyl acrylate in the presence of KOAc in toluene at 100 °C, the reaction rates increasing with increasing generations of dendrimers. The fifth-generation dendrimer complex was also applied to the high-yielding coupling of 1-iodonaphthalene with *n*-butyl acrylate and styrene. It is worthy of note that, in the reaction of *p*-diiodobenzene with *n*-butyl acrylate, the monosubstituted product was obtained



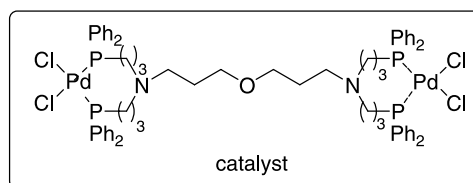
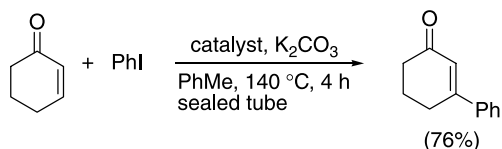
Scheme 60.

with 92% selectivity. The possibility of catalyst recycling in the Heck reaction was not, however, tested.

Poly(ether imine) dendrimer peripheries were modified with alkyldiphenylphosphine ligandies and converted into catalytically active phosphine–Pd(II) complexes.<sup>224</sup> The first to third-generation of dendrimeric catalysts found application in the Heck coupling of iodobenzene with a variety of conjugated olefins (see one example in Scheme 61). In general, an increase in the substrate conversion could be noticed for the first-generation palladium catalyst, although, for styrene, the reaction was sluggish and took longer than for any other substrate. The catalytic performance of the regenerated catalysts decreased, when compared to the corresponding fresh catalyst, limiting the possibilities of their being re-used.

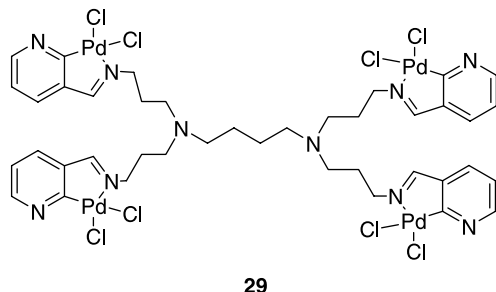
Dendritic poly(propyleneimine)-iminopyridyl-palladium complexes achieved high conversions in the reaction of iodobenzene with methyl acrylate, styrene and 1-octene.<sup>225</sup>

In particular, the pyridylimine palladium dendrimer **29** achieved high conversions in refluxing acetonitrile, although electronic factors seem to play a decisive role in determining the regiochemistry of the reaction. The reactions with methyl acrylate yielded mainly  $\beta$ -arylated



Scheme 61.

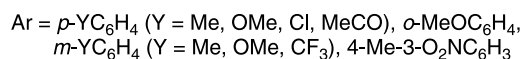
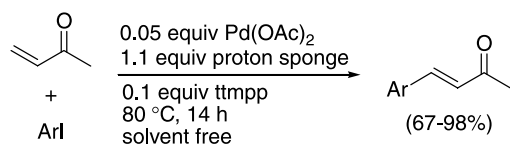
products, whereas 1-octene yielded a mixture of *cis*–*trans* isomers and  $\beta,\beta$ -disubstituted compounds. At any rate, the dendritic complex **29** exhibited a higher conversion and the reactions proceeded faster, compared to the reaction with the mononuclear iminopyridyl-palladium analogue or PdCl<sub>2</sub>. Unfortunately, iodobenzene was the only aryl halide tested and no recycling studies were carried out.



In general, the catalytic activity and selectivity exhibited by dendrimeric systems as catalysts in the Heck reaction are comparable, or even lower, than those observed for other unsupported or supported systems. It is clear that the easy separation of the catalyst by precipitation in a proper solvent is very advantageous from the re-utilisation point of view. The preparation of the catalysts, especially those of higher generations, is, however, not straightforward in most cases, involving sometimes non-commercially available substrates and different synthetic steps with the concomitant generation of waste.

## 6. Solvents

The standard Heck reaction uses a conventional solvent to place the different components in close proximity, allowing the reaction to take place either under homogenous or heterogeneous conditions. Recently, however, Cacchi et al. reported an interesting study on the Heck reaction of butenone with aryl iodides under solvent-free conditions.<sup>226</sup> A number of aryl iodides containing electron-donating and electron-withdrawing substituents gave the corresponding vinylic substitution products in good to excellent yields (67–98%) (Scheme 62). Only iodoanisole produced the Heck derivative in a low yield (32%). The presence of both a proton sponge and *tris*-(2,4,5-trimethoxyphenyl)-phosphane (ttmpp) was required in order to obtain the best results, minimising the formation of hydroarylation products. The absence of a solvent reduced the toxicity and flammability, and simplified the work-up.



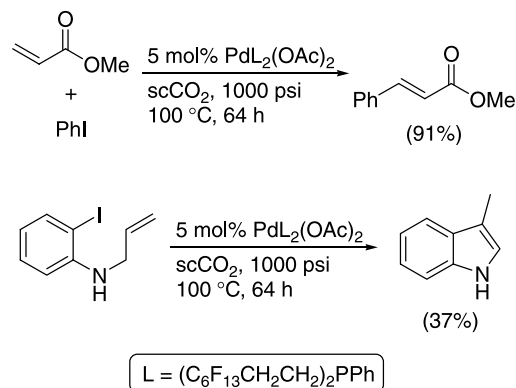
Scheme 62.

Chandrasekhar et al. found that PEG having a molecular weight of 2000 was an efficient medium for the palladium-

catalysed Heck reaction of aryl bromides with ethyl acrylate, styrene, and *n*-butyl vinyl ether.<sup>227</sup> The reactions were carried out with 5 mol% Pd(OAc)<sub>2</sub> and Et<sub>3</sub>N at 80 °C for 8–16 h (80–95% yield). Interestingly, and in sharp contrast to the results obtained when the reaction was performed in ionic liquids (see Section 6.2), exclusive attack of the arylpalladium species on the  $\beta$ -carbon of *n*-butyl vinyl ether was observed (*Z/E* 70:30–100:0). The reaction mixture was extracted with diethyl ether and the PEG and Pd(OAc)<sub>2</sub> were solidified and subjected to subsequent runs with a low decrease in yield (88–70% for six runs).

## 6.1. Supercritical fluids

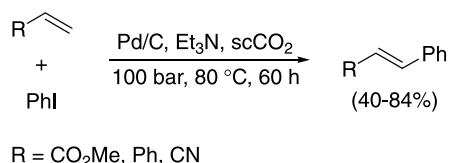
Highly fluorinated compounds have been shown to have an unusually high solubility in scCO<sub>2</sub>, and their incorporation into phosphane-based ligands was expected to improve the solubility of the corresponding metal complexes. The groups of Holmes and Tumas independently reported<sup>228,229</sup> in 1998 the first palladium-catalysed carbon–carbon coupling reactions in scCO<sub>2</sub> using fluorinated ligands. Holmes et al. demonstrated that the Heck reaction of iodobenzene and methyl acrylate in scCO<sub>2</sub> with (C<sub>6</sub>F<sub>13</sub>-CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>PPh as the ligand occurred in a superior yield to that reported for conventional solvents. Under these reaction conditions intramolecular processes were also possible (Scheme 63).<sup>228</sup> Despite the work-up procedure being easy, the reaction time was considerably long and the fluorinated ligand had to be prepared from C<sub>6</sub>F<sub>13</sub>CH<sub>2</sub>CH<sub>2</sub>MgI and PhPCl<sub>2</sub>. Very high conversions and selectivities were also obtained by Tumas et al. in the coupling of iodobenzene with either methyl acrylate or styrene in the presence of Pd(OAc)<sub>2</sub> and the ligands, [3,5-(CF<sub>3</sub>)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>]<sub>3</sub>P or (C<sub>6</sub>F<sub>5</sub>)<sub>3</sub>P.<sup>229</sup> In this case, a slightly lower temperature (90 °C) and a shorter reaction time (24 h) were reported, but applying a 5-fold pressure (345 bar).



Scheme 63.

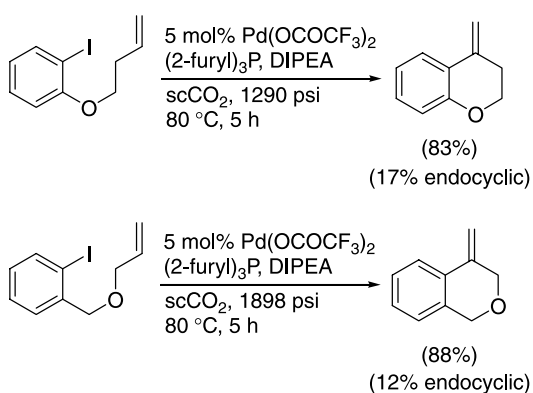
Cacchi et al. introduced Pd/C as a catalyst in the reaction of iodobenzene with methyl acrylate, styrene and acrylonitrile in scCO<sub>2</sub> to give the vinylic substitution products in moderate to good yields (Scheme 64).<sup>230</sup> Unfortunately, the reaction of iodobenzene, *p*-iodoanisole and *p*-iodoacetophenone with butenone gave rise to a mixture of the vinylic substitution products and hydroarylation (formal conjugate addition) products, whereas the reaction of *p*-iodoanisole with *n*-butyl vinyl ether afforded a mixture of  $\alpha$ - and  $\beta$ -arylation products.





Scheme 64.

Rayner et al. demonstrated that the use of fluorinated palladium sources for Heck reactions in scCO<sub>2</sub> gave superior results to those previously reported, including a low catalyst loading at moderate temperatures and commercially available ligands.<sup>231</sup> Conversions of >95% were obtained for the reaction of iodobenzene with methyl acrylate or styrene with catalytic Pd(OCOCF<sub>3</sub>)<sub>2</sub> or Pd(F<sub>6</sub>-acac)<sub>2</sub> and (2-furyl)<sub>3</sub>P as a ligand, and DIPEA as a base, at 75–80 °C for 15–17 h, under 1600 psi CO<sub>2</sub>. These catalysts, however, gave dark precipitates in the crude product, presumably due to metallic palladium residues obtained by decomposition. The same group applied the above catalytic system to significantly reduce double-bond isomerisation in intramolecular Heck reactions (Scheme 65).<sup>232</sup> A comparative study using conventional solvents and scCO<sub>2</sub> demonstrated that double-bond migration was suppressed to a large extent by using scCO<sub>2</sub> as the reaction medium.



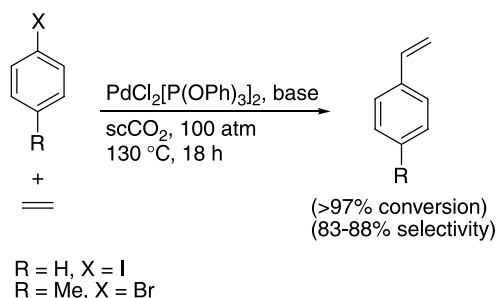
Scheme 65.

The group of Arai et al. has concentrated much effort on the development of efficient Heck reactions based on the use of multiphase catalysis and supercritical carbon dioxide.<sup>233</sup> In one contribution, they highlight the significant enhancement in the solubility of the substrates in scCO<sub>2</sub> by the addition of a co-solvent such as water or ethylene glycol to the reaction medium. Heck vinylation of iodobenzene with butyl acrylate and styrene was carried out in scCO<sub>2</sub> at 80 and 140 bar, respectively, in the presence of Pd(OAc)<sub>2</sub>, TPPTS, Et<sub>3</sub>N and water or ethylene glycol, for 17 h. In spite of the good catalyst stability, high selectivity and easy separation of the reactants and products (in the organic phase) from the catalyst (in the co-solvent phase), the conversions were very disappointing (<29%).

The same group studied the palladium-catalysed Heck reaction of iodobenzene and styrene in compressed CO<sub>2</sub> (12 MPa) using different fluorinated-phosphine compounds as ligands at 70 °C.<sup>234</sup> Although the solubility of the fluorinated ligands was very high in dense CO<sub>2</sub>, marginal improvements were found in this reaction, when compared

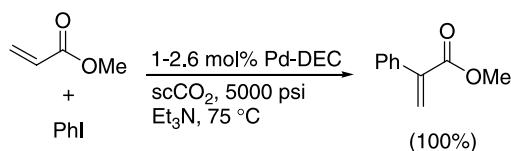
with the non-fluorinated ligand, triphenylphosphane. The activity exhibited by the palladium complexes was shown to strongly depend on the type of phosphane used, following the trend bis(pentafluorophenyl)phenylphosphane > triphenylphosphane, tris(pentafluorophenyl)phosphane > diphenyl(pentafluorophenyl)phosphane, tris(*p*-fluorophenyl)phosphane > tris(*p*-trifluoromethyl phenyl)phosphane, 1,2-bis[bis(pentafluorophenyl)phosphino]ethane. This order of effectiveness was different from that obtained in conventional organic solvents.

Ikariya et al. reported the Mirozoki–Heck arylation of ethylene catalysed by palladium complexes bearing triphenyl phosphite ligands in an scCO<sub>2</sub>–liquid biphasic system, giving rise to a mixture of arylated products (styrene, stilbene and 1,1-diarylethylene derivatives).<sup>235</sup> PdCl<sub>2</sub>[P(OPh)<sub>3</sub>]<sub>2</sub> was the best choice of catalyst for the arylation, because of its excellent activity and suitable solubility under the reaction conditions at 130 °C and 100 atm (Scheme 66). Very high conversions were obtained either for iodobenzene or for the less reactive *p*-bromotoluene, using Et<sub>3</sub>N or a mixture of DBU and 1-ethylpiperidine as bases, respectively. Notably, the yield and selectivity were higher in comparison with other reaction media, the selectivity for the styrene formation being remarkably improved with an increase in the pressure of CO<sub>2</sub> above the critical pressure. As an additional advantage, the product was effectively extracted into the scCO<sub>2</sub> phase, because of its reasonable high vapour pressure and high solubility in scCO<sub>2</sub> under the reaction conditions.



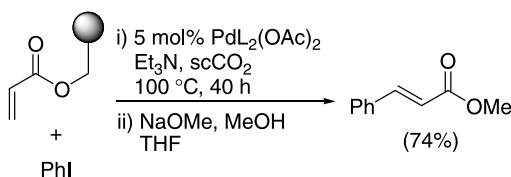
Scheme 66.

Palladium nanoparticles sequestered within fifth-generation poly(propylene imine) dendrimers, having perfluoro-2,5,8,11-tetramethyl-3,6,9,12-tetraoxapentadecanoyl perfluoropolyether chains covalently attached to their periphery, could be easily solubilised in scCO<sub>2</sub>. These dendrimer-encapsulated catalysts (DECs) were shown to be active in the Heck coupling of iodobenzene and methyl acrylate in the presence of Et<sub>3</sub>N at 75 °C and 5000 psi.<sup>236</sup> In contrast to the other methodologies, methyl 2-phenylacrylate was obtained as the only reaction product, instead of the regioisomeric methyl cinnamate (Scheme 67). The high selectivity obtained was attributed in part to the steric environment that the dendrimer template imposes on the reaction intermediate, although, primarily, it was suggested to result from the scCO<sub>2</sub> solvent. Unfortunately, this study was limited to the coupling shown in Scheme 67, the behaviour of other substrates remaining unknown.



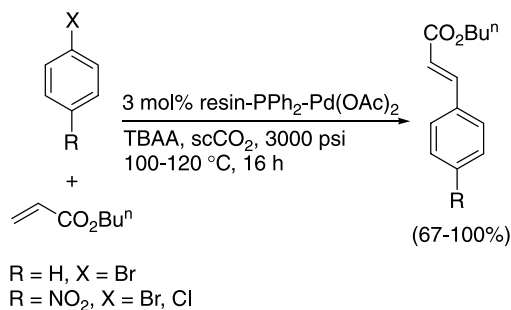
Scheme 67.

Holmes et al. showed that the combination of Pd(OAc)<sub>2</sub> with Bu<sub>3</sub>P catalysed the Heck coupling of iodobenzene with methyl and *n*-butyl acrylate in scCO<sub>2</sub>. This completely non-fluorous catalytic system (5–10 mol% Pd) furnished the coupling products in 77–92% isolated yields using Et<sub>3</sub>N or DIPEA as bases at 100 °C for 16 h.<sup>237</sup> Alternatively, and taking advantage of the ability of scCO<sub>2</sub> to plasticise polymers, the acrylate substrate was supported on an REM resin, which underwent a Heck reaction with iodobenzene employing a catalytic system of Pd(OAc)<sub>2</sub> and the highly fluorinated phosphane, (C<sub>6</sub>F<sub>13</sub>CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>PPh, to give (*E*)-methyl cinnamate in 74% yield after resin cleavage (Scheme 68).



Scheme 68.

The same research group carried out some investigations on the Heck reaction in scCO<sub>2</sub>, where the base or the catalyst were immobilised on commercially available supports.<sup>238</sup> A polystyrene-supported amine base (PS-NEt<sub>2</sub>) was shown to be as effective as other CO<sub>2</sub>-soluble amine bases (e.g., DIPEA) in the coupling of differently substituted iodoarenes with *n*-butyl acrylate using Pd(OAc)<sub>2</sub> or Pd(TFA)<sub>2</sub> with or without Bu<sub>3</sub>P at 80–100 °C and 3000 psi for 16 h. The novelty of this approach is based on the easy work-up, in which both the amine and the bulk of the palladium trapped in the polymer matrix can be removed by filtration of the solvent, into which the CO<sub>2</sub> reaction mixture is vented. Successful experiments were also carried out by using a polymer-supported phosphane catalyst, resin-PPh<sub>2</sub>-Pd(OAc)<sub>2</sub>. It is noteworthy that, in this case, the less reactive bromobenzene, *p*-nitrobromobenzene and even *p*-nitrochlorobenzene reacted with *n*-butyl acrylate, in the presence of tetra-*n*-butylammonium acetate (TBAA), to give the expected products in good to excellent yields (Scheme 69). Alternatively, palladium(II) acetate was



Scheme 69.

microencapsulated in polyurea, furnishing a heterogeneous catalyst able to effectively catalyse the cross-coupling reaction of aryl halides (iodides, bromides and chlorides) with styrene and *n*-butyl acrylate in scCO<sub>2</sub> under similar conditions to those reported above.<sup>239</sup> The catalyst could be recovered by simple filtration and recycled up to four times.

Heck reactions involving various arenes and alkenes were also studied in supercritical water at 400 °C.<sup>240</sup> These reactions were shown to be more sensitive to steric hindrance and electronic effects than the analogous reactions in organic solvents. Supercritical water promoted the loss of alkene functionality to a much greater extent than normal organic conditions. Bromide, chloride, carboxylate and, to some extent, hydroxyl losses were all observed in scH<sub>2</sub>O. Moreover, hydrogenolysis and hydrogenation processes were favoured under these supercritical conditions, leading to increased side products and, therefore, to a poor selectivity.

It is worthy of note that the Heck coupling of iodobenzene with styrene could be promoted in scH<sub>2</sub>O without using any catalyst.<sup>241</sup> The conversion reached 70% within 10 min in the presence of KOAc as a base, the yield of stilbene being 56%, as a 1:4 mixture of *cis*- and *trans*-diastereoisomers. Again, the selectivity was very low and, therefore, these reactions in scH<sub>2</sub>O, although very interesting, seem not to be very practical.

From the information presented in this section, it can be inferred that the main advantage of using SCFs is the easy work-up. No liquid–liquid partition is necessary, since a simple pressure change in the sc reactor allows the gaseous–liquid reaction medium to be vented. On the other hand, it must be taken into account that an expensive stainless steel reactor with sapphire windows is needed to perform reactions in sc media and the CO<sub>2</sub> or H<sub>2</sub>O used must be of a very high purity, which consequently increases their prices. The presence of fluorinated compounds, dendrimeric-encapsulated catalysts, or polymer-supported substrates and reagents normally increases the reactivity in the sc system and facilitates the purification step. Additional synthetic chemistry is, however, needed for their preparation. Finally, and in contrast with the supported catalysts described in the previous section, there is a lack of information about the possibility of catalyst recycling in most of the sc systems studied, which, in our opinion, must be a very important topic to be taken into account in any new non-conventional methodology developed.

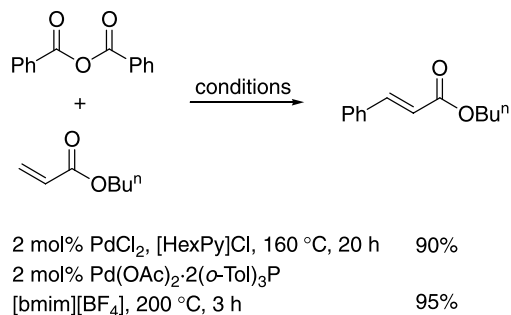
## 6.2. Ionic liquids

Ionic liquids have been widely studied as alternative solvents in the Heck reaction, since the pioneering work by Kaufmann et al. in 1996.<sup>242</sup> In particular, ionic liquids such as 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF<sub>6</sub>]) are virtually insoluble in water and alkanes, but dissolve many transition metal catalysts. Such biphasic liquid systems enable the products of the reaction to be separated from the ionic liquid and catalyst by solvent extraction with an organic solvent or by distillation from the reaction vessel. Furthermore, if a hydrophobic IL is chosen (e.g., [bmim][PF<sub>6</sub>]), then water can also be used as an

extraction solvent to remove the salt by-products formed in the reaction.

Kaufmann et al. found that Heck reactions proceeded in a melt of hexadecyltri-*n*-butylphosphonium bromide, tetra-*n*-butylammonium bromide and tetra-*n*-octylammonium bromide with high efficiency.<sup>242</sup> Different palladium(0) catalyst precursors such as  $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ ,  $\text{PdCl}_2$  or  $\text{Pd}(\text{OAc})_2$  were appropriate for the Heck reactions without additive ligands. Bromobenzene and *p*-methoxybromobenzene reacted with *n*-butyl acrylate in high yields in the presence of  $\text{Et}_3\text{N}$  at 100 °C, chlorobenzene did not react under these conditions, whereas *p*-nitrochlorobenzene gave a 52% yield of the expected product. The observed activity for these reactions was explained by a stabilising effect of the palladium(0) by the phosphonium or ammonium salts.

Later, in 1999, Earle et al. reported the Heck reaction in a number of low-melting-point *N,N'*-dialkylimidazolium or *N*-alkylpyridinium ILs with halide, hexafluorophosphate, or tetrafluoroborate anions. For the cations, 1-butyl-3-methylimidazolium (bmim), 1-*n*-pentyl-3-methylimidazolium (pmim), or *N-n*-hexylpyridinium (HexPy) species were chosen.<sup>243</sup> The Heck reaction of iodobenzene and ethyl acrylate in ionic liquids with 2 mol%  $\text{Pd}(\text{OAc})_2$  in the presence of  $\text{Et}_3\text{N}$  or  $\text{NaHCO}_3$  furnished *trans*-ethyl cinnamate in excellent yields. For the reactions carried out in the chloride salts, the *N-n*-hexylpyridinium salts led to higher yields than the corresponding reactions in imidazolium salts. The reactions carried out in hexafluorophosphate or tetrafluoroborate ILs needed higher temperatures, the tetrafluoroborate IL giving the higher yields. In contrast to the chloride-based systems, the addition of a phosphine ligand (such as  $\text{Ph}_3\text{P}$ ) promoted the reaction in the imidazolium salt, [bmim][PF<sub>6</sub>]. Even more interesting was the use of benzoic anhydride as a source of the aryl moiety, since a base was not required for the reaction and the by-products were  $\text{CO}_2$  and  $\text{CO}$ . The reaction of *n*-butyl acrylate with benzoic anhydride gave *trans-n*-butyl cinnamate in 90–95% yield. A considerable difference in reactivity was observed between imidazolium and pyridinium ILs, although relatively high temperatures were needed in both cases (Scheme 70). Typically, the product and by-product could be extracted with ether and fresh reagents could be added to re-use both the IL and the catalyst.

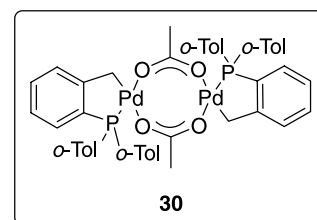
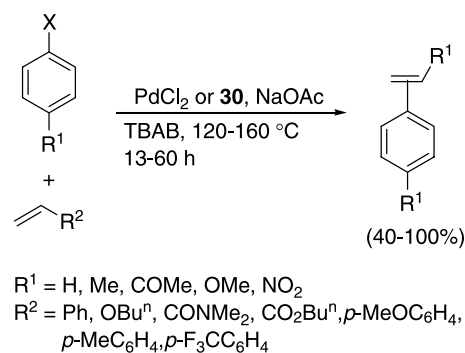


Scheme 70.

In almost parallel studies, Howarth et al. demonstrated that the IL, [bmim]PF<sub>6</sub>, could replace DMF in the Heck coupling of aryl bromides and iodobenzene with methyl acrylate.<sup>244</sup>

The reactions were performed with  $\text{Pd}(\text{OAc})_2$  and  $\text{Ph}_3\text{P}$  in the presence of  $\text{NaOAc}$  as the base at 140 °C for 17 h, affording the corresponding cinnamates exclusively as the *E*-isomers. It is worthy of note that the products could be distilled under high vacuum directly from the reaction mixture, after separation from the aqueous layer, avoiding the use of an extraction solvent. Both the solvent and catalyst were re-usable several times.

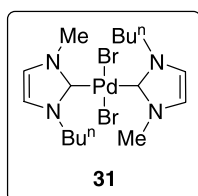
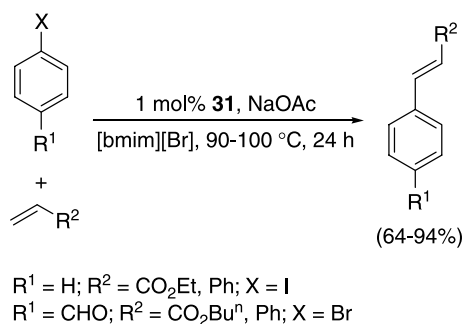
Herrmann et al. carried out a detailed study on the Heck vinylation of aryl halides using non-aqueous ILs.<sup>245</sup> In particular, TBAB improved the catalyst efficiencies, compared to all of the previously described molecular solvents. The phosphapalladacycle **30** (Herrmann's catalyst), or even the less active  $\text{PdCl}_2$ , were able to catalyse the coupling of chloroarenes, bromoarenes, iodoarenes and benzoic acid anhydride with *n*-butyl acrylate, different substituted styrenes, *n*-butyl vinyl ether and the disubstituted  $\alpha$ -methyl-*n*-butyl acrylate (Scheme 71). In general, the activity for the electron-rich *n*-butyl vinyl ether and 4-methoxystyrene was lower. Electron-rich substrates (e.g., *p*-bromoanisole) favoured  $\alpha$ -arylation, whereas electron-poor aryl derivatives (e.g., *p*-bromoacetophenone) strongly favoured  $\beta$ -arylation. Perhaps one main inconvenience of this methodology is the low regio- and stereoselectivity achieved in those cases. The excellent yields obtained in the coupling of chloroarenes with styrene (except for *p*-chloroanisole) must, however, be highlighted. The insoluble by-products such as  $\text{NaBr}$  and palladium black could be separated by filtration after several recycling runs, whereas the soluble catalyst and the  $[\text{NBu}_4^+]\text{Br}$  could be re-used, although a decrease in the product yields was observed. An additional inconvenience was that careful drying and degasification of the IL was necessary for optimum results.



Scheme 71.

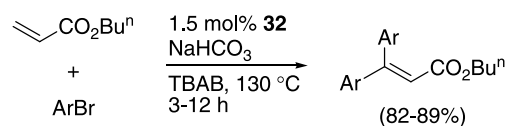
Xiao et al. studied the olefination of aryl halides in [bmim][Br] and [bmim][BF<sub>4</sub>] by heating (90–125 °C) a mixture of the aryl halide and an acrylate or styrene, in the presence of  $\text{NaOAc}$  and 1 mol%  $\text{Pd}(\text{OAc})_2$ , in the IL for 24 h.<sup>246</sup> As

expected, the reactions proceeded more efficiently with aryl iodides and activated aryl bromides, whereas a low or no conversion was observed for the less reactive bromobenzene and chlorobenzene, respectively. The coupling reactions were found to be markedly more efficient in [bmim][Br] than in [bmim][BF<sub>4</sub>], decomposition of the latter salt being observed with the formation of palladium black. The most important feature of this publication is, however, the finding that the IL, [bmim][Br], reacts readily with Pd(OAc)<sub>2</sub> to give *N*-heterocyclic carbene complexes of palladium, which are active catalysing the Heck reaction. The carbene complex **31** was isolated as a mixture of rotamers and applied, under similar conditions to those used with Pd(OAc)<sub>2</sub>, to the olefination of iodobenzene and *p*-bromobenzaldehyde by acrylates in [bmim][Br] (Scheme 72). Surprisingly, complex **31** showed a very low activity in the Heck reaction in [bmim][BF<sub>4</sub>].

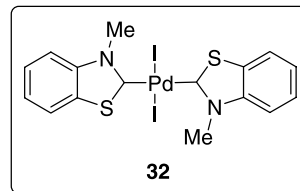


Scheme 72.

Calò et al. synthesised a palladium catalyst **32** with benzothiazole carbenes as ligands, which proved to be effective for a variety of Heck reactions in ILs.<sup>247</sup> Thus, 1 mol% of catalyst at 130 °C and 2% of sodium formate (as reducing agent for palladium) in TBAB as solvent catalysed the coupling of aryl bromides and *n*-butyl acrylate in the presence of NaHCO<sub>3</sub> as a base for 1–5 h, to furnish the corresponding cinnamic esters in high yields (85–95%).<sup>248</sup> Even *p*-nitrochlorobenzene gave the nitrocinnamic ester in 95% yield after 1 h. Styrene also reacted with 4-bromotoluene in <2 h under the above-mentioned conditions, but leading to a 9:1 mixture of *trans*-4-methylstilbene and 1-(4-methylphenyl)-1-phenylethene, respectively. The same catalytic system was applied to the coupling of *trans*-cinnamates with both electron-rich and electron-poor aryl bromides and *p*-nitrochlorobenzene, affording the tri-substituted olefins with 100% conversion, but with very poor stereoselectivity.<sup>249</sup> Several β,β-diarylacrylates were, however, obtained in a one-pot synthesis by the reaction of an excess of aryl bromides with *n*-butyl acrylate under the above conditions (Scheme 73).

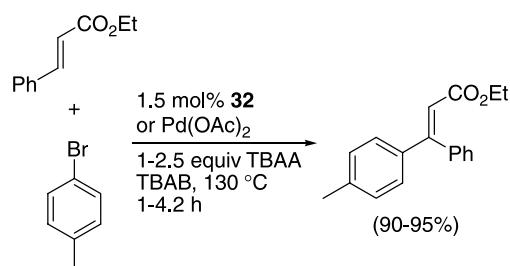


Ar = Ph, *p*-MeC<sub>6</sub>H<sub>4</sub>, *p*-MeOC<sub>6</sub>H<sub>4</sub>, 1-naphthyl



Scheme 73.

The problem of the low diastereoselectivity observed in the reaction of *trans*-cinnamates with aryl halides (mainly aryl bromides) was overcome by using palladium nanoparticles, generated by the reaction of catalyst **32** or Pd(OAc)<sub>2</sub> with TBAA dissolved in TBAB.<sup>250</sup> The corresponding β-aryl-substituted cinnamic esters were obtained in excellent yields and remarkable diastereoselectivity (see one example in Scheme 74). The observed stereoselectivity was ascribed not only to a better solubility of TBAA in TBAB, but also to an intramolecular neutralisation of PdH, still ligated to the olefin, by an acetate ion in the metal coordination shell through a five-membered transition state. The absence of acetate in the coordination shell would allow the PdH isomerisation, leading to a thermodynamic mixture of isomeric olefins. This palladium nanoparticle-catalysed Heck arylation was extended to *n*-butyl methacrylate and α-methylstyrene. Unfortunately, a 3:1 mixture of regioisomers was obtained in favour of the terminal olefins, together with variable amounts of double-arylated products.<sup>251</sup>

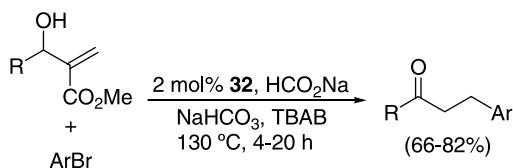


Scheme 74.

Closely related to the work described above, Cacchi et al. conducted the coupling of aryl iodides and methyl cinnamate with catalytic Pd(OAc)<sub>2</sub> in a molten TBAA–TBAB mixture at 100 °C, obtaining the corresponding β-aryl-substituted cinnamic esters also with excellent (*E*)-stereoselectivity.<sup>252</sup>

Catalyst **32** also allowed the reaction of various bromoaromatics with hydroxymethylenealkanoates to give β-arylketones, but not the expected Heck products, β-oxoalkanoates (Scheme 75).<sup>253</sup> The exclusive formation of the former ketones was rationalised in terms of a fast decarboxymethoxylation in TBAB of the expected β-oxoalkanoates.



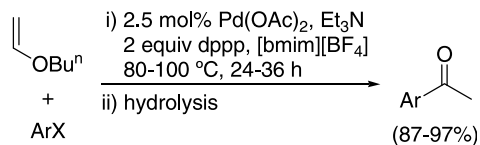


R = Me, Ph, Pr<sup>n</sup>, Pr<sup>i</sup>, *n*-C<sub>8</sub>H<sub>17</sub>  
 Ar = Ph, *p*-YC<sub>6</sub>H<sub>4</sub> (Y = Me, Ac, OMe), 1-naphthyl

Scheme 75.

The catalyst could be recycled maintaining a roughly equal activity after three cycles.

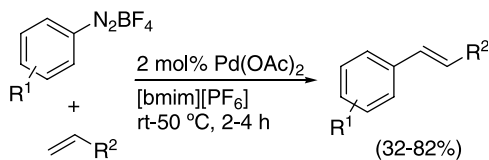
The group of Xiao et al. focussed on the palladium-catalysed arylation of the electron-rich olefin, *n*-butyl vinyl ether, in the IL, [bmim][BF<sub>4</sub>], using aryl iodides and bromides as the arylating agents.<sup>254</sup> The reactions proceeded with excellent conversion, yield and regioselectivity, regardless of the nature of the substituents on the aromatic ring, giving exclusively the  $\alpha$ -arylated products, which were hydrolysed to the corresponding aryl methyl ketones (Scheme 76). Although the reaction conditions were relatively mild (80–120 °C), 2 equiv of dppp were needed for maximum efficiency. It was suggested that an IL effect stabilising the active palladium-phosphine species was involved in these reactions.



Ar = Ph, *p*-YC<sub>6</sub>H<sub>4</sub> (Y = Me, OMe, COMe, CO<sub>2</sub>Me, CHO, CN, F), 1-naphthyl; X = Br  
 Ar = 1-naphthyl; X = I

Scheme 76.

Recently, Kabalka et al. have reported the palladium-catalysed reaction of methyl acrylate and methyl acrylonitrile with arenediazonium salts in the IL, [bmim][PF<sub>6</sub>].<sup>255</sup> The reactions could be performed at room temperature for methyl acrylate and at 50 °C for acrylonitrile in the absence of base and in relatively short reaction times (Scheme 77). The catalytic system was recycled at least four times without loss of activity, although electron-rich olefins did not react and styrenes produced dimerisation products.



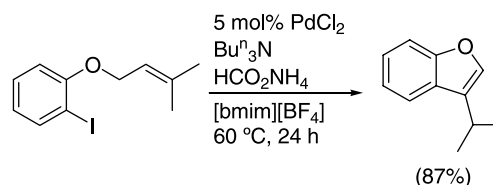
R<sup>1</sup> = H, *p*-X (X = Br, Cl, I, OMe), *o*-CN  
 R<sup>2</sup> = CO<sub>2</sub>Me, CN

Scheme 77.

The phosphonium salt IL, trihexyl(tetradecyl)phosphonium chloride, proved to be an excellent medium for the Heck

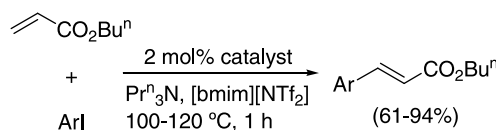
reaction of aryl iodides and bromides with acrylates and styrene with catalytic Pd(OAc)<sub>2</sub> (1–4 mol%), NaOAc–H<sub>2</sub>O or Et<sub>3</sub>N at 50–100 °C for 2–4 h.<sup>256</sup> The products were obtained in very high yields (81–99%) with complete stereo- and  $\beta$ -regioselectivity. The IL layer containing the palladium catalyst was used in three consecutive recycled rounds with a low decrease in activity (98–94%).

Substituted benzofurans were obtained in modest to good yields by palladium-catalysed intramolecular Heck reaction in [bmim][BF<sub>4</sub>] (see one example in Scheme 78).<sup>257</sup> It seemed that the less hindered the double bond or the better the aryl leaving group, the lower the yield of the benzofuran. In general, the yields of the substrates with a substituent on the aryl group were lower, although the character of the substituent did not have a significant effect on the reaction yield. The catalyst in the IL phase could be re-used by the addition of another portion of substrate, Bu<sub>3</sub>N and HCO<sub>2</sub>NH<sub>4</sub>, the catalytic activity varying from 71 to 57% after four cycles.

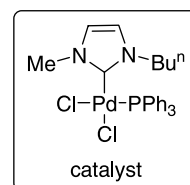


Scheme 78.

The low viscosity IL, [bmim][NTf<sub>2</sub>], exhibited a comparable efficiency to the frequently used high-viscosity ILs, such as [bmim][PF<sub>6</sub>] and [bmim][BF<sub>4</sub>], in the coupling of aryl iodides with *n*-butyl acrylate using a palladium-carbene complex as catalyst (Scheme 79).<sup>258</sup> After separation of the product by a triphasic workup (hexane-water-IL), the IL phase containing the palladium catalyst was recycled for six runs without any detectable loss of activity. Despite the high yields obtained for the *trans*-cinnamates, no information was provided about the possibility of application to other aryl halides or electronically different olefins. This methodology was extended to a microflow system with efficient catalyst recycling for the coupling of iodobenzene with *n*-butyl acrylate (see also Section 8.2).<sup>259</sup>

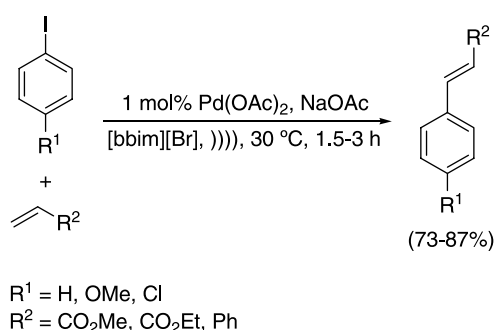


Ar = Ph, *p*-YC<sub>6</sub>H<sub>4</sub> (Y = Me, MeO, MeCO, NO<sub>2</sub>),  
*o*-MeC<sub>6</sub>H<sub>4</sub>, *m*-MeC<sub>6</sub>H<sub>4</sub>



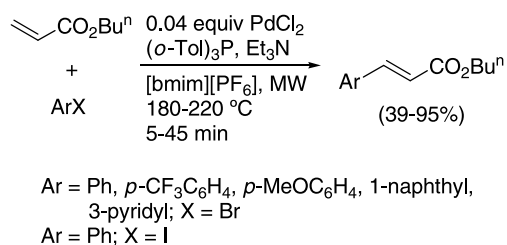
Scheme 79.

The first ultrasound-promoted Heck reaction in ILs at ambient temperature (30 °C) was reported by Srinivasan et al.<sup>260</sup> The reaction took place smoothly for the coupling of iodobenzenes with methyl acrylate, ethyl acrylate and styrene to furnish the corresponding trans products in short reaction times and high yields (Scheme 80). The products were separated from the catalyst by extraction with 10% EtOAc in petroleum ether, leaving the palladium catalyst in the dissolved state in the immiscible ionic liquid. The recovered catalyst as a solution in the IL was re-used up to three times without loss of activity. The products, however, required further purification by column chromatography. Under the sonochemical conditions, the conversion of a Pd-biscarbene complex to a highly stabilised cluster of zero-valent palladium nanoparticles was also established.



Scheme 80.

Microwave heating in sealed tubes was found to accelerate the Heck arylation of iodobenzene and different aryl and heteroaryl bromides with *n*-butyl acrylate and *n*-butyl vinyl ether in ILs (Scheme 81).<sup>261</sup> The presence of (*o*-Tol)<sub>3</sub>P was necessary for the coupling with *n*-butyl acrylate, whereas the bidentate ligand dppp controlled the internal arylation of *n*-butyl vinyl ether. The ionic catalyst phase could be recycled at least five times.



Scheme 81.

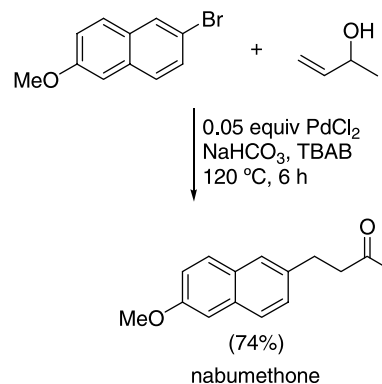
Pd/C (3 mol%) was found to disperse well in [bmim][PF<sub>6</sub>] and to catalyse the Heck reaction of aryl iodides and bromides with olefins (acrylonitrile, styrene, methyl acrylate, methyl vinyl ketone and ethyl vinyl ketone) in the presence of Et<sub>3</sub>N at 100 °C for 1–24 h.<sup>262</sup> The yields obtained ranged from moderate to high, except in the case of the vinyl ketones, where they were low. The products were extracted by stirring with *n*-hexane or diethyl ether, followed by decantation. The IL containing Pd/C could be re-used although a certain decrease in the yields was observed, due to accumulation of triethylammonium iodide. Washing the IL with water, however, recovered the catalytic activity to the same level as in the fresh system. A Pd(II)/

SiO<sub>2</sub> catalyst with 2 equiv of Et<sub>3</sub>N in [bmim][PF<sub>6</sub>] was shown, in general, to be more active than Pd/C and Pd(0)/SiO<sub>2</sub> in [bmim][PF<sub>6</sub>], or supported palladium catalysts in DMF, for the Heck reaction of iodobenzene and 4-methyl-iodobenzene with alkyl acrylates.<sup>263</sup> The easy product separation and catalyst recycling without loss of activity are, again, the main advantages of this study.

More recently, Perosa et al. reported a 10-fold acceleration in the Pd/C-catalysed Heck coupling of aryl iodides with electron-deficient olefins and styrene in the presence of the liquid phase-transfer catalyst, Aliquat 336 (A336) and Et<sub>3</sub>N at 100 °C.<sup>264</sup> This enhancement was also observed when A336 was used in catalytic amounts in a multiphase isooctane-water system. Under these conditions, A336 forms a third phase that allows the catalyst, products and reagents and the base (Et<sub>3</sub>N), to be kept separate. The reaction seems not to be of general applicability, however, since the conversion and product distribution are very dependent on the substituents on the aryl moiety and the olefin. Aryl bromides reacted even more sluggishly, only the more reactive bromides undergoing the Heck reaction.

Pd/C (3 mol%) was used in conjunction with the ionic liquid, 1-octanyl-3-methylimidazolium tetrafluoroborate and microwave heating in the absence of phosphane ligands for the coupling of aryl halides with acrylates and styrene.<sup>265</sup> Despite the possibility of re-using the catalytic system and the short reaction times (1.5–2.0 min), good product yields were only achieved for very specific activated substrates, aryl chlorides being very reluctant to couple, even on increasing the power of the microwave radiation and the reaction time.

Muzart et al. described the Heck coupling of aryl iodides and bromides with allylic alcohols at 80–120 °C in molten TBAB using NaHCO<sub>3</sub> as base and PdCl<sub>2</sub> as catalyst without extra ligands, leading to the corresponding β-arylated carbonyl compounds regioselectively and in moderate yields.<sup>266</sup> No reaction was observed with chlorobenzene or employing benzoic anhydride as the arylating agent, whereas re-use of PdCl<sub>2</sub> and TBAB in the reaction with iodobenzene exhibited an important decrease in the isolated yield. Nonetheless, a successful application of this methodology to the synthesis of the nonsteroidal anti-inflammatory drug, nabumethone, was reported (Scheme 82).



Scheme 82.

The new palladium complex **33** was synthesised by Alper et al. and proved to be an effective catalyst for the Heck reaction using [bmim][PF<sub>6</sub>] as the solvent under phosphane-free conditions (Chart 10).<sup>267</sup> The versatility of the complex **33** was demonstrated in the high yields and conversions achieved in the coupling of bromobenzene, iodobenzene and a variety of iodoarenes containing electron-withdrawing or electron-donating substituents with several alkyl acrylates, *t*-butyl vinyl ether, styrene and 4-chlorostyrene. The reactions were generally performed with 2 mol% **33** and 1.5 equiv of Et<sub>3</sub>N, in [bmim][PF<sub>6</sub>] at 120 °C, giving exclusively the corresponding (*E*)-cinnamates. In addition, a double Heck reaction could be effected, either by using an excess of iodoarene, or sequentially (with different types of arenes), leading to β,β- or β,β'-diarylacrylates, respectively. The catalytic system was recycled five times without any loss of catalytic activity, the only inconvenience being that the complex has to be prepared in three steps (30% overall yield) from *N*-methylimidazole, although it is insensitive to oxygen or moisture. The cyclopalladated complex **34** also exhibited a good performance in the coupling of iodoarenes with methyl acrylate in [bmim][BF<sub>4</sub>] (Chart 10). In this case, the catalyst was recycled more than ten times, maintaining a satisfactory catalytic activity.<sup>268</sup>

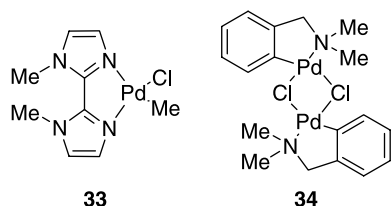
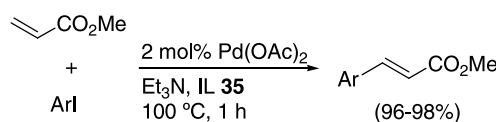


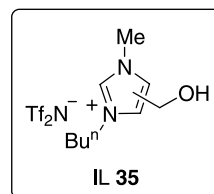
Chart 10.

Zou's group has reported an aqueous-ionic liquid biphasic reaction medium based on high-melting-point hydrophobic alkylammonium tetrafluoroborates and its application to the Heck reaction with a ligandless palladium catalyst.<sup>269</sup> Thus, 2 mol% PdCl<sub>2</sub> in a water- or toluene-ammonium biphasic system (ammonium = Bu<sub>4</sub>N<sup>+</sup> or C<sub>5</sub>H<sub>10</sub>NBu<sub>2</sub><sup>+</sup>) catalysed the Heck coupling of iodobenzene with *n*-butyl acrylate, in the presence of K<sub>2</sub>CO<sub>3</sub> or Et<sub>3</sub>N, giving the expected *trans*-cinnamate in 84–93% yield. Bromobenzene was, however, almost inactive and re-use of the catalytic system remained unclear.

Handy et al. have utilised fructose as the starting material for the preparation of a new class of room temperature ILs, which were obtained in four steps (about 45% overall yield) as a 9:1 mixture of regioisomers.<sup>270</sup> The behaviour of these ILs was excellent in the Heck reaction of three aryl iodides and methyl acrylate at 100 °C (Scheme 83). The reactions were fast (about 1 h) and the catalytic system could be recycled up to five times, by extracting the cinnamate products with cyclohexane, maintaining the original high performance. Unfortunately, the reaction was limited to iodoarenes, with no reaction being observed for bromobenzene, even at 140 °C. When compared with the [bmim] salts, the IL **35** showed a slower reaction rate, although the



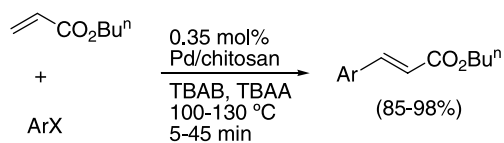
Ar = H, *p*-MeCOC<sub>6</sub>H<sub>4</sub>, *p*-MeOC<sub>6</sub>H<sub>4</sub>



Scheme 83.

magnitude of this difference was less than a factor of two. An interesting accelerating effect of catalytic amounts of certain halide ions on the coupling of iodobenzene and methyl acrylate was observed.<sup>271</sup>

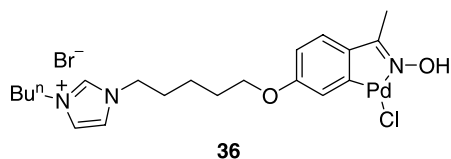
The chitosan support described in Section 5.2.4 was also utilised by Calò et al. to immobilise palladium nanocolloids that were applied to the Heck reaction of iodobenzene, aryl bromides and activated aryl chlorides with *n*-butyl acrylate in TBAB as solvent and TBAA as base at 100–130 °C (Scheme 84).<sup>272</sup> The reactions were very fast (15 min in most cases) and gave very high yields of products, which were extracted with cyclohexane, leaving both the IL and catalyst ready to be recycled. Unfortunately, the efficiency of the catalyst decreased after each cycle, with concomitant leaching of palladium from the complex.



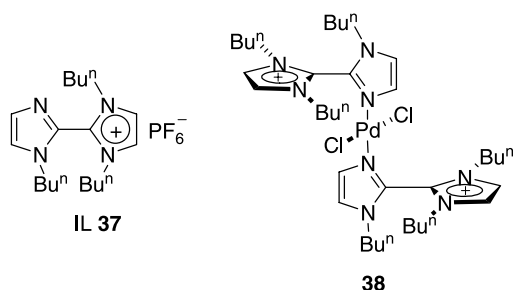
Ar = Ph; X = I  
Ar = Ph, *p*-MeC<sub>6</sub>H<sub>4</sub>, *p*-MeOC<sub>6</sub>H<sub>4</sub>, 6-MeO-2-naphthyl;  
X = Br  
Ar = *p*-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>, *p*-PhCOC<sub>6</sub>H<sub>4</sub>; X = Cl

Scheme 84.

New catalysts have been recently developed with the aim of increasing their ionophilicities by the introduction of an imidazolium group covalently attached to the rest of the palladium complex. Corma et al. reported the four-step synthesis of complex **36**, which was soluble in [bmim][PF<sub>6</sub>] and not extractable by ether.<sup>273</sup> Unfortunately, the catalytic activity of this palladium complex was unsatisfactory, providing very low yields (<26%) in the coupling of halobenzenes with styrene (NaOAc as a base at 130 °C). A marginal increase in the catalytic activity was observed when the reaction was performed in [bmim][PF<sub>6</sub>]-scCO<sub>2</sub>, which reduced the medium viscosity. The low activity of complex **36** was attributed to the poor stability of imidazolium ILs to bases.



Shreeve et al. showed that the monoquaternary product of 2, 2'-biimidazole with iodobutane was an IL that could act both as a solvent and a ligand in the palladium-catalysed Heck reaction.<sup>274</sup> The palladium complex prepared from the ionic liquid **37** and PdCl<sub>2</sub>, **38**, gave good to high yields (75–91%) in the coupling of iodo- and chlorobenzene with methyl acrylate and styrene (2 mol% **38**, Na<sub>2</sub>CO<sub>3</sub>, IL **37**, 100 °C, 4 h). The products were easily separated from the reaction mixture by simple extraction with ether. The catalyst-IL could be recovered by washing with water to remove the sodium salt and drying under vacuum before using. The high performance exhibited by the catalytic system even after ten cycles and using the less reactive chlorobenzene, must be highlighted.



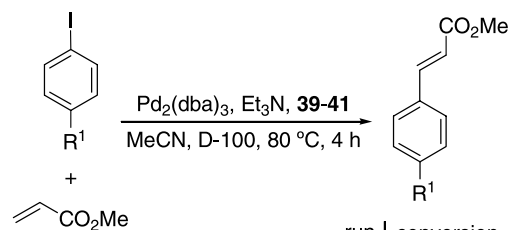
Hardacre et al. carried out an interesting investigation on the palladium species present during the Heck reaction in room temperature ILs based on XAFS.<sup>275</sup> A variety of ILs was tested using palladium ethanoate as a palladium metal source and their behaviour was studied in the presence or absence of the reagents or a phosphane. In general, palladium clusters of diameters between 0.8–1.6 nm were formed, the size and stability of which varied according to the system in which they were present. The stabilising effect exerted by the IL on the palladium clusters allowed complete recyclability and simple product separation without the incorporation of palladium in the product or the loss of catalyst from the reaction medium.

It can be concluded in this section that the Heck reaction based on the use of ILs is clearly advantageous from the point of view of product separation and re-use of the catalytic system. The overall effect is a reduction in the number of separation steps required, the product being directly distilled in some cases from the IL without any solvent extraction. In addition, most of the reactions can be performed in the absence of added phosphane ligands. We must not, however, ignore other features of these solvents that can curtail their use, above all on a larger scale. ILs are rather expensive solvents and are therefore used in small-scale reactions, normally involving 1–2 g of the IL. Careful drying and degasification of the IL were also necessary in order to achieve good results. Moreover, and especially when Et<sub>3</sub>N is used as a base, by re-utilising the catalytic system it becomes more viscous, due the high concentration

of triethylammonium salts. Therefore, further washing with water and drying in vacuo is required in order to return the IL to its original state.

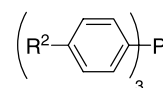
### 6.3. Fluorous media

The Heck reaction in fluorous systems is a very young field of research, as demonstrated by the fact that practically all the related reports have been published in the 21st century. The pioneering work in this field was described by Sinou et al. in 1999,<sup>276</sup> this group carrying out the palladium-catalysed reaction of aryl iodides with methyl acrylate in a biphasic system with the perfluorocarbon-soluble triarylphosphanes **39–41** (Scheme 85). The fluorous-soluble palladium complexes were prepared by stirring Pd<sub>2</sub>(dba)<sub>3</sub> or Pd(OAc)<sub>2</sub> and a solution of the perfluorinated phosphanes in the perfluorinated solvent D-100 (mainly *n*-perfluorooctane). An acetonitrile solution of the aryl iodide and methyl acrylate was added, the biphasic system being stirred at 80 °C for 4 h. The coupling product, in the acetonitrile phase, was easily separated by decantation, whereas the palladium catalyst remained in the fluorous phase. Both the conversion and selectivity were high in the first run, but a decrease in the conversion was observed after recycling of the catalyst, due to the formation of some metallic palladium or the loss of the perfluorinated ligand in the acetonitrile phase.



R<sup>1</sup> = H, NO<sub>2</sub>, MeO

run	conversion
1	84–100%
2	60–93%
3	40–70%



R<sup>2</sup> = OCH<sub>2</sub>(*n*-C<sub>7</sub>F<sub>15</sub>) (**39**)

R<sup>2</sup> = *n*-C<sub>6</sub>F<sub>13</sub> (**40**)

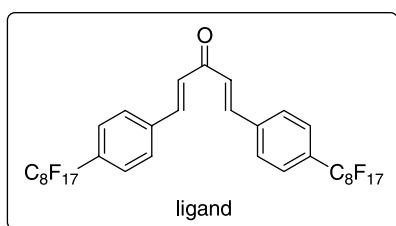
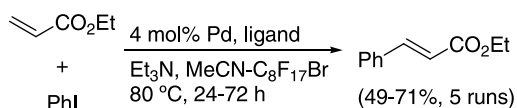
R<sup>2</sup> = O(CH<sub>2</sub>)<sub>2</sub>OCH<sub>2</sub>CF<sub>2</sub>[CF(CF<sub>3</sub>)CF<sub>2</sub>]<sub>m</sub>(OCF<sub>2</sub>)<sub>n</sub>OCF<sub>3</sub>;  
m = 3.38; n = 0.11 (**41**)

#### Scheme 85.

A fluorous biphasic system was also used for intramolecular Heck reactions after RCM of a series of *N*-alkenyl-*N*-allyl-2-bromo- or -2-iodobenzenesulfonamides. The corresponding bridged-ring systems were obtained in 0–67% yield after treatment of the RCM products with 10 mol% Pd(OAc)<sub>2</sub>, 20 mol% **40** and 2 equiv of Ti<sub>2</sub>CO<sub>3</sub> in the perfluorous system at 110 °C for 16 h.<sup>199</sup> The yields were lower in comparison with those obtained with a PS-bound palladium catalyst. As already mentioned in Section 5.2.4, the use of 2 equiv of Ti<sub>2</sub>CO<sub>3</sub> is a clear disadvantage in this methodology, due to its high toxicity (mutagen and reproductive effector).

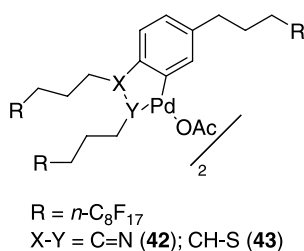


The group of Moreno-Mañas and Pleixats discovered the stabilisation effect exerted by fluorous compounds on palladium nanoparticles and studied their activity as recoverable catalysts under fluorous biphasic conditions in the Heck reaction of iodobenzene with ethyl acrylate, ethyl cinnamate and cinnamitrile.<sup>277</sup> The palladium nanoparticles, generated from the ligand, 1,5-bis[4,4'-bis(perfluorooctyl)phenyl]-1,4-pentadien-3-one and PdCl<sub>2</sub> using MeOH as the reducing agent, were shown to be soluble in perfluorinated solvents through the stabilisation by the fluorinated ligand. The reaction with ethyl acrylate proceeded in 49–71% yield for five consecutive runs (Scheme 86), whereas the reactions with ethyl cinnamate and cinnamitrile did not reach completion, the final product being accompanied by the starting alkene and minor amounts of biphenyl. Despite the ligand being easily prepared by aldol condensation of 4-perfluorooctylbenzaldehyde with acetone, the former starting material was not commercially available and had to be prepared in three steps from methyl 3-iodobenzoate.

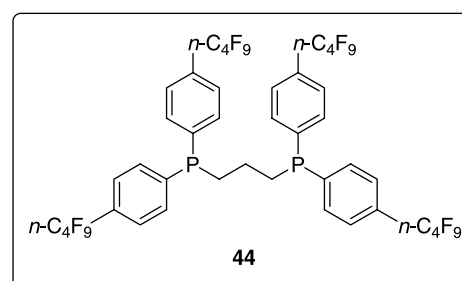
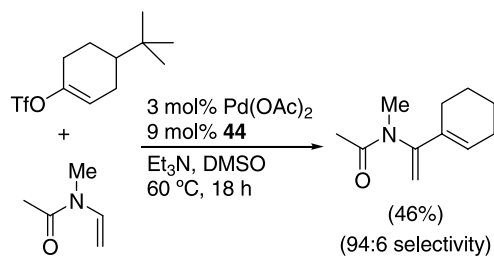


Scheme 86.

The palladacycles **42** and **43**, which were prepared by Gladysz et al. in seven steps from *p*-iodobenzaldehyde, behaved as catalyst precursors in the Heck reaction of aryl bromides and iodides with methyl acrylate and styrene.<sup>278</sup> The turnover TONs exceeded 10<sup>6</sup> with iodobenzene under homogeneous conditions, in the presence of Et<sub>3</sub>N at 140 °C and in the absence of fluorous solvents, freshly distilled DMF being used. The catalytic system could be recycled after the addition of the fluorous solvent, *n*-C<sub>8</sub>F<sub>17</sub>Br, to give a biphasic system, albeit with a progressive loss of activity being observed after each cycle. Transmission electron microscopy indicated the formation of soluble, highly active palladium nanoparticles. The most important feature of this catalytic system is the remarkable TONs achieved, although its re-use is not as effective as desired and the synthetic route for the ligands is rather long.

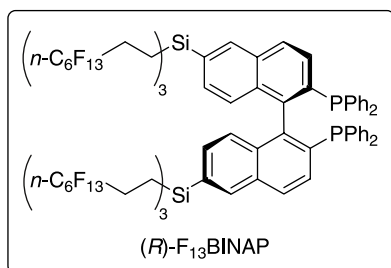
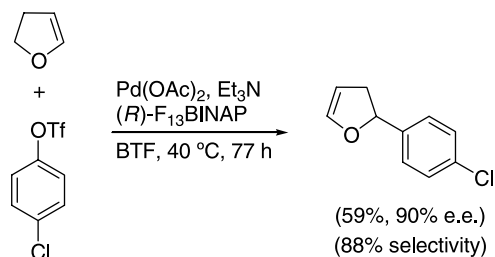


New bidentate, fluorous-tagged 1,3-bis(diphenylphosphino)propane (F-dppp) ligands were synthesised by Curran, et al. and their efficiency was checked in the Heck vinylation of enamides and arylation of *n*-butyl vinyl ether.<sup>279</sup> As an example, the Heck reaction of the enol triflate derived from 4-*tert*-butylcyclohexanone with the electron-rich enamide, *N*-methyl-*N*-vinylacetamide, was conducted under the conditions specified in Scheme 87, in the presence of the F-dppp ligand **44**. The performance of this ligand was very similar to that of the nonfluorous dppp, although the selectivity was slightly lower. The free ligand, palladium-complexed ligand and oxidised ligand were all removed from the reaction medium by direct solid fluorous phase separation using the MeOH–H<sub>2</sub>O eluting system. The MeOH was removed under reduced pressure and the salts were withdrawn by water–ether extraction. Unfortunately, attempts to re-use the isolated phosphine mixture as the catalytic mixture in a second vinylation failed, with no Heck product being detected. The ligand **44** was also shown to be as effective as dppp in the internal arylation of *n*-butyl vinyl ether with 1-naphthyl triflate (100% conversion, >99:1 selectivity, 5 h), whereas F-dppp ligands bearing larger fluorous tails reduced the reaction rate and selectivity. The synthesis of the F-dppp ligands was accomplished in 56–62% isolated yields (three steps) from the corresponding fluorinated aryl bromides, which are not commercially available.



Scheme 87.

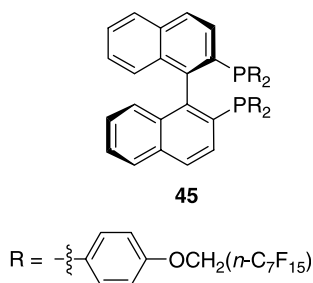
A fluorous chiral BINAP, (*R*)-F<sub>13</sub>BINAP, was prepared and applied to the asymmetric Heck reaction between 2,3-dihydrofuran and 4-chlorophenyl triflates in benzonotrifluoride (BTF,  $\alpha,\alpha,\alpha$ -trifluorotoluene).<sup>280</sup> The reaction rate was lower and the enantioselectivity similar, compared to the original reaction with (*R*)-BINAP. The expected coupling product was obtained in 59% yield together with the corresponding 2,5-dihydrofuran derivative (8%) (Scheme 88). By carrying out the reaction in benzene or in a benzene/FC-72 biphasic system, the enantioselectivity was slightly higher (93% ee), but the chemical yield and selectivity were much lower. The (*R*)-F<sub>13</sub>BINAP could be



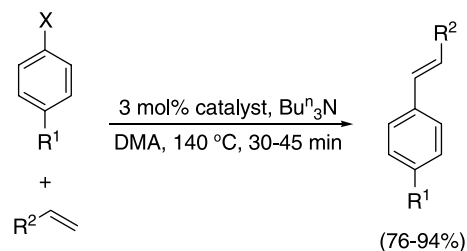
Scheme 88.

recovered, mainly as the corresponding oxide, in 70% yield by using a fluorous reverse-silica gel. In fact, the test for recycling of the catalyst failed, probably due to inactivation by ligand oxidation. Therefore, this study does not contribute to any improvement of the original work<sup>281</sup> since the catalyst could not be recycled, the ligand had to be synthesised, and the fluorinated solvents are rather expensive.

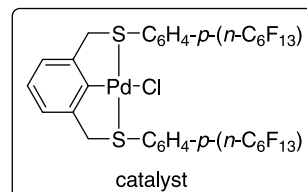
The above-depicted reaction was also studied by Sinou et al. under the same reaction conditions, but in the presence of the ligand **45** instead of (R)-F<sub>13</sub>BINAP.<sup>282</sup> Quantitative conversion was observed after 89 h at 40 °C to furnish the product, 2-(chlorophenyl)-2,3-dihydrofuran, in better regioselectivity (97%), but worse enantioselectivity (68%), compared with the use of the ligands, (R)-F<sub>13</sub>BINAP or (R)-BINAP. Again, a long synthetic sequence was needed to prepare the ligand and re-use of the catalyst seems unclear, since ligand **45** does not contain enough fluorine to be used in a fluorous biphasic system.



A new fluorous SCS pincer palladium complex was recently synthesised by Curran et al. and this was shown to efficiently promote the Heck reaction under thermal or microwave heating.<sup>283</sup> Aryl bromides, iodides and a single triflate were coupled with methyl acrylate and styrene in short reaction times and high yields at 140 °C (Scheme 89). The catalyst could be recovered largely intact by fluorous solid-phase extraction and re-used, either crude or after crystallisation. The fluorous complex was prepared in three



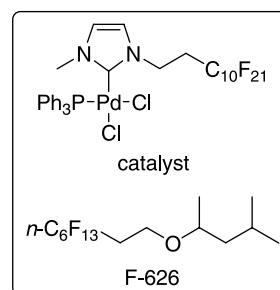
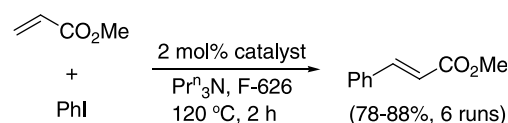
X = Br, I, OTf  
R<sup>1</sup> = H, MeO, CN, COMe, NO<sub>2</sub>  
R<sup>2</sup> = CO<sub>2</sub>Me, Ph



Scheme 89.

steps (21% overall yield) from a commercially available perfluoroalkylaryl bromide and shown to be a stable solid.

The fluorous ether, 1*H*,1*H*,2*H*,2*H*-perfluorooctyl 1,3-dimethylbutyl ether (F-626), was used by Ryu et al. as the sole reaction medium in the Heck β-arylation of α,β-unsaturated acids and esters with aryl iodides, in the presence of a fluorous palladium carbene complex (that can be prepared in situ).<sup>284</sup> The insolubility of the acid-type coupling products in F626 allowed facile separation by simple filtration, whereas, for the ester-type coupling products, a traditional fluorous-organic biphasic work-up using EtOH-perfluorohexanes was necessary to separate the products and the fluorous ether F-626 containing the fluorous catalyst. The recovered F-626 phase, containing the palladium catalyst, was re-used for a further five runs without any detectable loss in catalytic activity (Scheme 90). The fluorous solvent utilised, although recyclable, is rather sophisticated and is not readily available.



Scheme 90.

In a different context, Crooks et al. reported the preparation of perfluorinated polyether-derivatised poly(propyleneimine) dendrimers containing Pd<sup>0</sup> nanoparticles by

introducing Pd<sup>2+</sup> into the interiors of amine-terminated poly(propyleneimine) dendrimers, which were previously end-group derivatised (>90%) with perfluorinated polyether chains.<sup>285</sup> Two generations of dendrimer-encapsulated nanoparticle catalysts were investigated for the coupling of iodobenzene, bromobenzene and *p*-bromonitrobenzene with *n*-butyl acrylate using a fluorocarbon–hydrocarbon solvent-based catalyst recovery system. All reactions proceeded with 100% trans-selectivity, the best result being obtained for iodobenzene (70% yield) in the presence of Et<sub>3</sub>N (59% in its absence) at 90 °C. Unfortunately, a large decrease in reactivity was observed for the coupling of aryl bromides, whereas aryl chlorides were unreactive. The nanoreactors were recovered after each reaction, the fluorous phase retaining the dark-coloured catalyst with no palladium leaching. The catalytic activity decreased significantly, however, upon successive recovery-catalysis cycles, probably due to changes in the morphology of the palladium nanocluster surface.

From the information presented above, it can be concluded that the application of fluorous media methodologies requires the preparation of the perfluorinated ligands, in most cases through long synthetic pathways and from relatively expensive starting materials. The fluorinated solvents used are also rather expensive and are not always readily available. In addition, the recycling of the catalyst through the fluorous biphasic technique is not always as effective as expected, and this difficulty cannot compensate the economic and time investment in these methodologies.

#### 6.4. Aqueous solvents

The pioneering work in this field was carried out by Beletskaya et al. in 1989.<sup>286</sup> Her group discovered that the palladium-catalysed coupling reaction of aryl halides with acrylic acid and acrylonitrile in the presence of a base (NaHCO<sub>3</sub> or K<sub>2</sub>CO<sub>3</sub>) in water at 80–100 °C provided a novel and efficient method for the synthesis of substituted cinnamic acids and cinnamitriles in high yields. The reactions could be carried out alternatively faster and at a lower temperature (50–60 °C) using KOAc as a base.

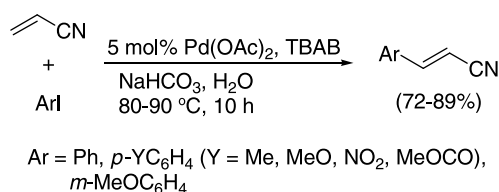
Since then, the transition-metal-catalysed Heck reaction in aqueous solvents has been developed following three major protocols: (a) methods without phosphane ligands using transition-metal salts in neat water or aqueous organic solvents, (b) aqueous phosphane-assisted methods using hydrophilic phosphane ligands in aqueous organic solvents and (c) recyclable phase-separation methods using heterogeneous systems with the aqueous phase holding the catalyst, and the hydrophobic organic phase holding the stock of substrates and receiving the products of the reaction. Some other protocols involving the use of superheated or subcritical water were also reported, but showed, in general, very poor selectivity.<sup>287</sup>

This subject has been properly tackled in the multiple reviews which have essentially covered the bibliographic data published until 2000.<sup>42,43</sup> Therefore, and in order to avoid an oversized review, we will deal only with the most representative publications which have appeared since 2001.

One of the most attractive protocols uses neat water as solvent in the presence of a proper phase-transfer agent. In this context, Xia et al. used PEG both as a polymeric support and phase-transfer catalyst for the Heck coupling of PEG-supported 4-iodobenzoate with styrene and acrylic acid.<sup>288</sup> The reactions were performed with 5 mol% Pd(OAc)<sub>2</sub> and Na<sub>2</sub>CO<sub>3</sub> in water at 60 °C for 1–4 h, and, after resin cleavage, afforded the expected products in 94 and 76% yield, respectively.

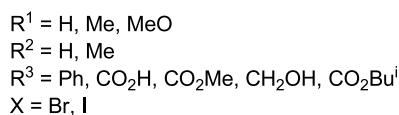
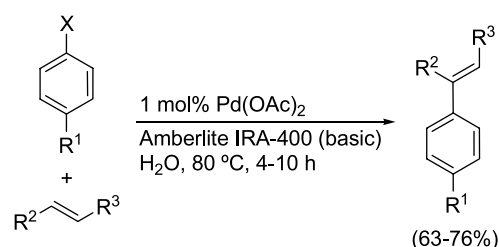
The combination of water as solvent with microwave irradiation proved to be very efficient in the coupling of a series of aryl iodides (ArI, Ar = *p*-HO<sub>2</sub>CC<sub>6</sub>H<sub>4</sub>, *p*-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>, *o*-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>, *p*-MeC<sub>6</sub>H<sub>4</sub>) with styrene, methyl acrylate and acrylic acid,<sup>289</sup> 5 mol% Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> being used as catalyst, together with TBAB and K<sub>2</sub>CO<sub>3</sub> in water under MW irradiation (375 W) for 10 min in an argon atmosphere. The work-up of these reactions was readily carried out by simple extraction with diethyl ether, the coupled products being obtained exclusively as the trans-diastereoisomers in high yields (86–93%).

Cai et al. described the Heck arylation of acrylonitrile with a variety of aryl iodides in neat water.<sup>290</sup> The reactions proceeded smoothly for aryl iodides bearing both electron-donating and electron-withdrawing substituents, leading to the corresponding (*E*)-cinnamitriles in good yields (Scheme 91). This methodology was extended to the Heck arylation of *n*-butyl acrylate and acrylamide with aryl iodides, giving the corresponding (*E*)-cinnamates and (*E*)-cinnamamides in good yields.<sup>291</sup>



Scheme 91.

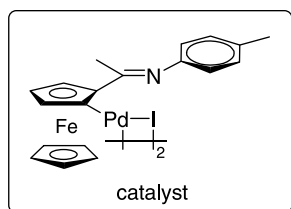
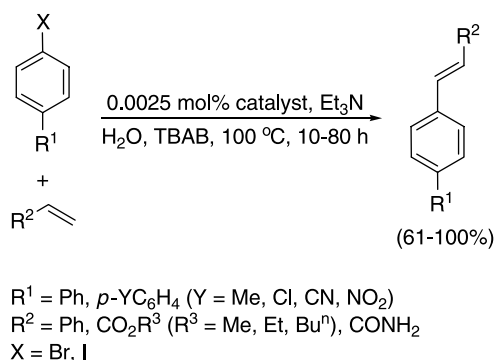
Amberlite IRA-400 (basic) was found to have a dual role in assisting the Heck reaction as a base and as a phase-transfer catalyst after salt formation.<sup>292</sup> This catalytic system exhibited a good performance in the stereoselective Heck reaction of bromobenzene, *p*-iodotoluene and *p*-iodoanisole with a representative variety of olefins (Scheme 92). The



Scheme 92.

work-up procedure was very simple and the resin could be regenerated and recycled.

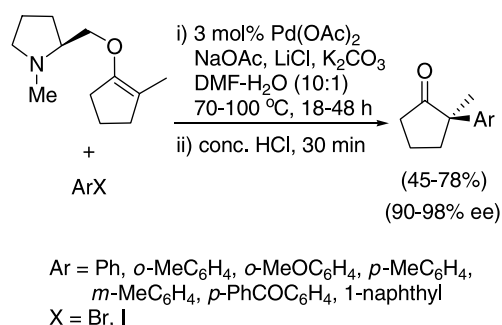
An insoluble phosphane-free cyclopalladated ferrocenyl-imine, at very low concentrations, was successfully applied to the Heck coupling of aryl iodides and bromides with different olefins in neat water (Scheme 93).<sup>293</sup> The optimised reaction conditions involved the use of TBAB and Et<sub>3</sub>N as the phase-transfer agent and base, respectively. All the reactions were conducted in air under reflux, furnishing the expected coupled products in moderate to excellent yields (most of the yields were >90%). In spite of the fact that the catalyst had to be prepared from the relatively expensive, acetyl ferrocene, the amounts used in each reaction were very low.



Scheme 93.

Another protocol consists of using an aqueous biphasic medium (instead of neat water), also in the absence of phosphane ligands. Williams et al. studied in detail the Heck reaction between iodobenzene and *n*-butyl acrylate with various combinations of polar solvent, solvent-water mixtures, ligand and added base.<sup>294</sup> The results showed that DMF or DMF–H<sub>2</sub>O were the solvents of choice, the origin of the catalyst [Pd(OAc)<sub>2</sub> or Pd(dba)<sub>2</sub>] making little difference to the yield. *n*-Butyl cinnamate was obtained in 95% yield using 0.1 equiv Pd(OAc)<sub>2</sub> and Et<sub>3</sub>N in a 1:1 DMF/H<sub>2</sub>O mixture at 80 °C for 24 h in the absence of any added ligand. Unfortunately, the reaction with bromobenzene or 4-bromobenzene failed under the above reaction conditions.

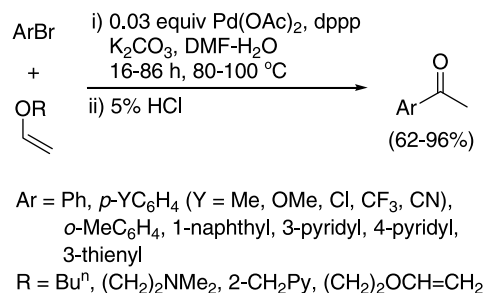
Based on a similar catalytic system, Hallberg et al. reported a highly asymmetric chelation-controlled Heck arylation of a prolinol vinyl ether, as an alternative approach to the synthesis of 2-aryl-2-methylcyclopentanones.<sup>295</sup> The phosphane-free catalytic system, utilised in a 1:10 H<sub>2</sub>O/DMF solvent mixture and under air, provided moderate to good yields and excellent enantioselectivities of the isolated cyclopentanones (Scheme 94). An *N*-chelated



Scheme 94.

$\pi$ -intermediate was suggested to account for the excellent regio- and stereochemical outcome of the arylation.

A different protocol was applied by the same group concerning the palladium-catalysed regioselective internal arylation of alkyl vinyl ethers with aryl and heteroaryl bromides, which was carried out in aqueous DMF, with K<sub>2</sub>CO<sub>3</sub> as base and dppp as bidentate ligand.<sup>296</sup> The arylated products were transformed into the corresponding aryl methyl ketones after acidic treatment, which were obtained in good to high yields and excellent regioselectivities (Scheme 95). In addition, vinyl bromides were converted into the corresponding  $\alpha,\beta$ -unsaturated methyl ketones, albeit with rather low yields. Contrary to the internal couplings with aryl bromides, the analogous aryl iodides delivered essentially nonselective regioisomeric product mixtures. Unfortunately, the reaction times are quite long, although an example was reported in which the reaction time was shortened to 1 h at 122 °C in a microwave synthesiser.

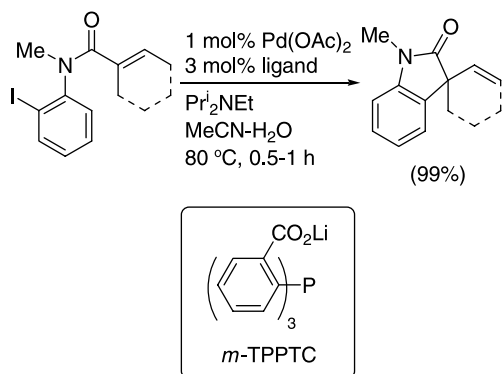


Scheme 95.

A new water-soluble phosphane ligand bearing carboxylate groups, *m*-TPPTC, was prepared by Genêt et al. and tested in the Heck arylation of ethyl acrylate and styrene with iodobenzene in aqueous organic solvents.<sup>297</sup> Complete conversion of ethyl acrylate was achieved in the presence of 1 mol% Pd(OAc)<sub>2</sub> and 3 mol% ligand, using Et<sub>3</sub>N as a base in a 6:1 MeCN/H<sub>2</sub>O mixture at 80 °C for 45 min. For styrene, 76% conversion was obtained using the same catalytic system, but with Pr<sub>2</sub>NH as a base, at 80 °C for 22 h. Alternatively, an NMP–H<sub>2</sub>O solvent mixture also provided good results at a higher temperature (110 °C). The palladium-catalysed coupling of 4-methoxyiodobenzene with 2,3-dihydrofuran, using 5 mol% Pd(OAc)<sub>2</sub> and 15 mol% ligand in a MeCN–H<sub>2</sub>O mixture at 40 °C, led to the corresponding 2,3-dihydrofuran derivative in 95% yield and 95:5 regioselectivity. Moreover, when this catalytic

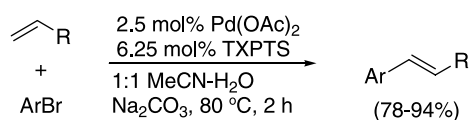


system was applied to the intramolecular Heck reaction of two iodoanilides, the desired lactams were obtained in 99% isolated yields after 1 h at 80 °C (Scheme 96).

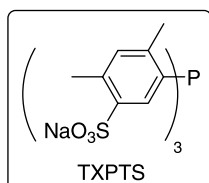


Scheme 96.

The sterically demanding, water-soluble tris(4,6-dimethyl-3-sulfonatophenyl)phosphane trisodium salt (TXPTS), was applied by Shaughnessy et al. to the aqueous-phase Heck coupling of aryl bromides with styrene and sodium acrylate.<sup>298</sup> The catalyst derived from TXPTS gave higher yields, in comparison with the more common TPPTS, and under relatively mild reaction conditions (Scheme 97). Both electron-donating and electron-withdrawing substituents on the aryl bromide gave high yields of products, whereas an ortho substituent decreased the yield. Due to partial hydrolysis under the coupling reactions, sodium acrylate had to be used instead of the corresponding *n*-butyl ester. Under very similar reaction conditions, the ligand, 2-(di-*tert*-butylphosphino)ethyltrimethylammonium chloride, was also found to be superior to TPPTS.<sup>299</sup> Attempts to couple an activated aryl chloride, as well as to use other solvents such as water or water–toluene, were, however, unsuccessful. As a result, the catalyst could not be recycled.



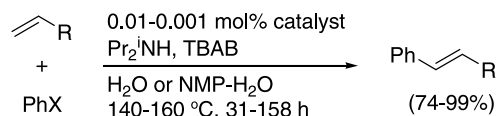
Ar = *p*-YC<sub>6</sub>H<sub>4</sub> (Y = Me, MeO, MeCO), *o*-MeC<sub>6</sub>H<sub>4</sub>,  
2-Me,4-MeOC<sub>6</sub>H<sub>3</sub>  
R = Ph, CO<sub>2</sub>Na



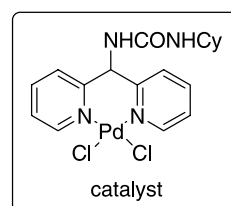
Scheme 97.

Nájera et al. designed a new palladium-dipyridylmethylamine complex that found application in the homogeneous Heck reaction of iodo-, bromo- and chlorobenzene with acrylates and *p*-chlorostyrene in DMF, NMP–H<sub>2</sub>O and H<sub>2</sub>O.<sup>300</sup> TBAB had to be added to the reaction mixture in the case of bromo- and chlorobenzene. In general, very high yields were obtained for the coupled products derived from

iodobenzene and bromobenzene, either in neat water or in a 3:1 NMP/H<sub>2</sub>O mixture (Scheme 98). Chlorobenzene, however, only reacted with *p*-chlorostyrene in NMP–H<sub>2</sub>O at 160 °C using 0.5 mol% catalyst, leading to a 2:1 mixture of regioisomers. Despite the ligand being readily prepared after four steps (62% overall yield) and the TONs being high, the TOFs are rather low and relatively harsh reaction conditions are required, in comparison to the above-described methodologies.

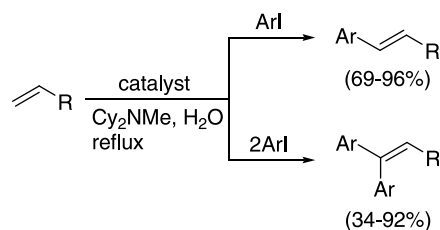


R = CO<sub>2</sub>Bu<sup>t</sup>, CO<sub>2</sub>Bu<sup>n</sup>, *p*-ClC<sub>6</sub>H<sub>4</sub>  
X = Br, I

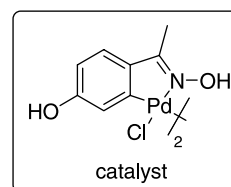


Scheme 98.

More recently, Nájera's group reported the mono- and β,β-diarylation of α,β-unsaturated carbonyl compounds with electron-deficient and electron-rich aromatic iodides in water, under the catalysis of a *p*-hydroxyacetophenone oxime-derived palladacycle.<sup>301</sup> The reactions were carried out in refluxing water or under microwave heating using (dicyclohexyl)methylamine as a base and a low catalyst loading (≤ 1 mol%), the expected products being obtained in moderate to excellent yields (Scheme 99). The mono- and diarylation reactions could be controlled in most of the cases, although they both failed when aryl bromides were used instead of aryl iodides. In general, lower yields were obtained for the diarylated products, the diarylation only failing with *p*-fluorobenzene. The catalyst remained active



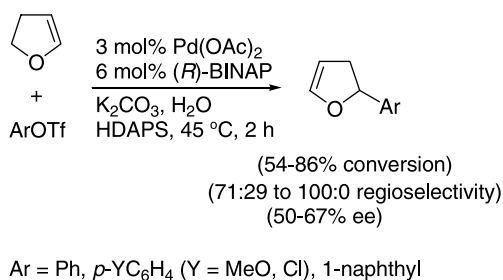
R = CO<sub>2</sub>Bu<sup>t</sup>, CONMe<sub>2</sub>, CN, COMe  
Ar = Ph, *p*-XC<sub>6</sub>H<sub>4</sub> (X = F, Cl, MeO)



Scheme 99.

upon addition of more substrates in both the mono- and diarylation processes, with total conversion after four consecutive cycles. This methodology, applied to the arylation of different styrenes, allowed the preparation of methylated resveratrol and analogues in high yields, with total *E* stereoselectivity and variable regioselectivity.<sup>302</sup>

Sinou et al. described the asymmetric arylation of 2,3-dihydrofuran with aryl triflates in water, in the presence of the surfactant, *n*-C<sub>16</sub>H<sub>33</sub>N<sup>+</sup>Me<sub>2</sub>(CH<sub>2</sub>)<sub>3</sub>SO<sub>3</sub><sup>-</sup> (HDAPS) and (*R*)-BINAP as the chiral ligand.<sup>303</sup> The reactions proceeded with high regioselectivity under mild conditions, but both the conversion and the enantiomeric excess were moderate (Scheme 100).



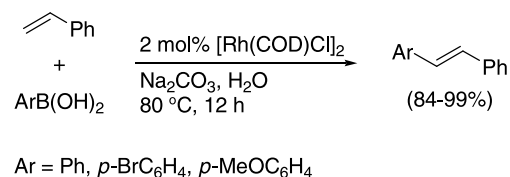
Scheme 100.

We have already commented in Section 5.2.4 on the high performance exhibited by an amphiphilic polystyrene-poly(ethylene glycol) resin-supported palladium-phosphane complex in the Heck reaction of aryl iodides and olefins in water (see Scheme 56). In contrast to some of the examples presented above, the catalyst could be recycled, leading to a 92% average yield after five continuous runs.<sup>190</sup>

In the context of heterogeneous palladium-catalysed Heck reactions, Sasson et al. reported the reaction of aryl chlorides, bromides and iodides with styrene, catalysed by Pd/C in water.<sup>304</sup> The reactions were carried out with catalytic amounts of Pd/C (0.7 mol%) and PEG-400 (8.5 mol%) in the presence of sodium formate as reducing agent and water as solvent in an autoclave (100 °C) for 5.5 h. In addition to the expected Heck products (12–61%), the formation of the hydrogenated Heck products (2–25%), together with some hydrogenation of styrene to ethylbenzene (8–22%), plus the respective homocoupling (9–43%) and hydrodehalogenation (11–76%) products, were observed. Filtration experiments demonstrated that the Pd/C alone was responsible for the catalysis. This methodology, although interesting from the point of view of the separation and possible re-use of the catalyst, needs to be improved as regards the conversion and selectivity, in order to have a more practical application.

It is noteworthy that Heck-type reactions involving arylboronic acids and styrenes could be carried out under rhodium catalysis in aqueous media. This methodology is based on the use of water-soluble ligands such as TPPDS, TPPTS or *m*-TPPTC and has been studied independently by the groups of Lautens<sup>70</sup> and Genêt (see Scheme 10 and comments in Section 4.1).<sup>71</sup> Despite the advantageous properties shown by *m*-TPPTC in Genêt's report, the

coupling reactions of boronic acids and styrene derivatives proceeded with better yields in the absence of any phosphane ligand under the same reaction conditions, this certainly being the main improvement in this methodology (Scheme 101).



Scheme 101.

To use water to replace totally or partially an organic solvent is, without any doubt, beneficial from the environmental point of view. The advantage of using water (mainly as the cosolvent) in Heck reactions is also confirmed by the introduction of this methodology as a crucial step in total synthesis.<sup>305</sup> Nonetheless, we believe that the trend in the near future of the Heck reaction in aqueous media must improve and combine the use of neat water (limiting the use of organic solvents only for extraction, if necessary), together with a recoverable and re-usable catalyst.

## 7. Reaction conditions

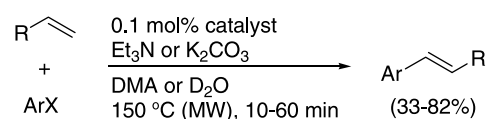
### 7.1. Physical activation

**7.1.1. Microwave.** During the preparation of this manuscript, a book about microwave-assisted organic synthesis has been published,<sup>45n</sup> in which Larhed and Kristofersson have dedicated one chapter to review and update the microwave assisted carbon-carbon coupling reactions, including the Heck reaction. This revision, in addition to some other recent revisions which have appeared in the literature,<sup>45j-p</sup> make it unnecessary to present herein the different studies carried out in this area. Instead, a short analysis of the application of this non-conventional technique to the Heck reaction, together with some contributions in 2004, follows.

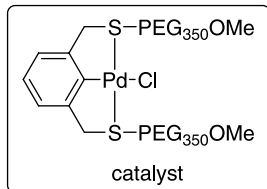
The first examples of Heck reactions promoted by microwave heating were conducted by the group of Larhed in 1996 in a single-mode cavity in septum-sealed Pyrex vessels.<sup>306</sup> Since then, MW heating has been applied extensively in the Heck reaction using different substrates, catalysts and reaction conditions.<sup>45j-p</sup> Aryl bromides, iodides and triflates, as well as vinyl triflates, worked well and regioselectively in the coupling with both electron-poor and electron-rich olefins, including even enols. The versatility of MW allowed the Heck couplings to be performed following different protocols such as in water under phase-transfer conditions or utilising water-soluble ligands, with ligand-free catalytic systems, under heterogeneous conditions with supported catalysts, in the absence of solvent or, most commonly, in solvents. In general, the same product patterns were essentially observed as in the reactions performed with thermal heating. The rapid heating induced by the radiation, however, led to the formation of

products under mild reaction conditions with short reaction times, avoiding decomposition or side reactions, and sometimes increasing the yields.

As a recent example of microwave-promoted Heck reactions, Bergbreiter et al. utilised an air-stable, water-soluble oligo(ethylene glycol)-bound SCS palladacycle to catalyse the coupling of several aryl halides and alkenes at 150 °C employing microwave heating.<sup>307</sup> Either DMA or D<sub>2</sub>O were used as the solvents for organic-soluble or water-soluble coupling partners. The products were obtained in moderate to good yields and in short reaction times (Scheme 102). Catalyst recycling was carried out using a thermomorphic solvent mixture consisting of aqueous DMA–heptane, the products being directly isolated from the heptane phase. No added solvent was necessary for the product and catalyst isolation and the catalyst recycling only required the addition of a fresh substrate solution to the mixed aqueous solution of catalyst.

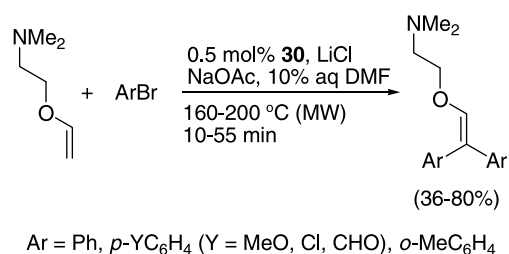


R = Ph, 4-pyridyl, CO<sub>2</sub>H, CO<sub>2</sub>Me, CO<sub>2</sub>Bu<sup>t</sup>, CONMe<sub>2</sub>  
 Ar = Ph, *m*-HO<sub>2</sub>CC<sub>6</sub>H<sub>4</sub>, 2-Me,5-HO<sub>2</sub>CC<sub>6</sub>H<sub>3</sub>,  
 1-naphthyl  
 X = Br, I



Scheme 102.

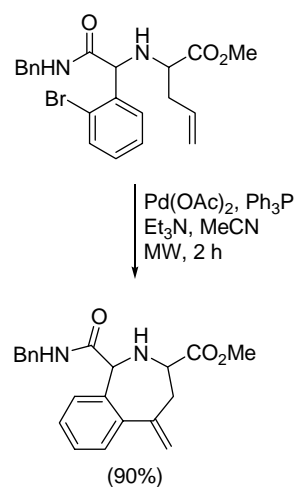
Larhed et al. have recently developed a rapid protocol for microwave-assisted regioselective double  $\beta$ -arylation of the chelating vinyl ether *N,N*-dimethyl-(2-ethenyloxy)ethanamine, using Herrmann's catalyst **30** as the palladium source.<sup>308</sup> By proper selection of the experimental parameters, it was possible to achieve symmetrical and nonsymmetrical terminal  $\beta,\beta$ -diarylations with both electron-rich and electron-poor aryl bromides. The symmetrical diarylation was carried out in sealed vessels under air, affording mixtures of the  $\alpha,\beta$ - and  $\beta,\beta$ -diarylated products in a 29:71–5:95 ratio (Scheme 103). Fortunately, the latter products could be purified by column chromatography.



Scheme 103.

Classic heating at 180 °C furnished almost identical reaction results to microwave heating. Using almost identical reaction conditions, aryl bromides were reacted with  $\beta$ -arylated olefins, giving rise to unsymmetrical  $\beta,\beta$ -diarylated products with a  $\beta,\beta$  selectivity of >91:9, but a low stereoselectivity.

As a recent example of microwave-assisted intramolecular Heck cyclisation, Gracias et al. subjected several  $\gamma,\delta$ -unsaturated amino esters, derived from an Ugi four-component reaction and bearing a haloaryl moiety, to Heck cyclisation under microwave heating.<sup>309</sup> In this case, the reaction required the presence of Ph<sub>3</sub>P, the resulting nitrogenated heterocyclic compounds being obtained in high yields and short reaction times (see one example in Scheme 104).



Scheme 104.

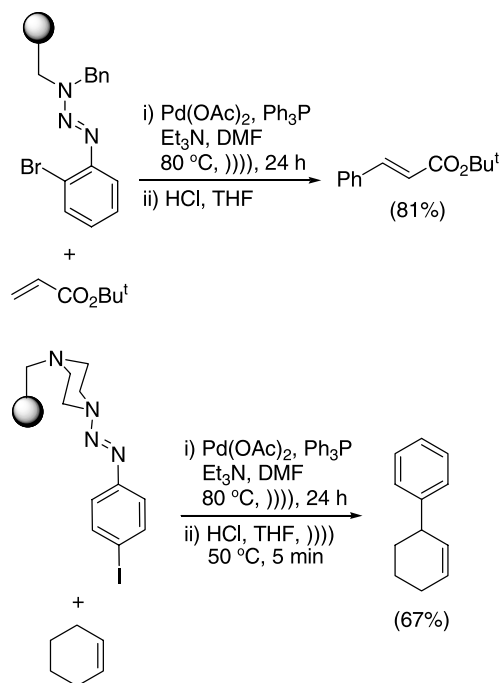
Despite the clear advantages that microwave-assisted synthesis offers,<sup>310</sup> there are still some issues which require further studies in order to be properly addressed. The health hazards of microwave radiation are still under investigation and it is not yet known whether a low-level exposure is detrimental. The recommended safety levels tend to move in the direction of lower doses of radiation, so great care should be taken to minimise microwave leakage. Another potential hazard is the formation of electric arcs in the cavity. Although microwave-heated organic reactions can be smoothly conducted in open vessels, closed vessels sealed under an inert gas atmosphere to reduce the risk of explosions are recommended, especially if superheating or high-pressure conditions are desired.

Both the multi- and monomode microwave reactors have been shown to work successfully for small-scale organic synthesis, in particular for the rapid optimisation of reaction conditions and in the context of the drug-discovery process. There is, however, a clear need to develop larger-scale microwave-assisted organic synthesis techniques, which can ultimately provide products on a kilogram scale. In this context, it is worthy of note that the feasibility of direct scale-up from a single-mode microwave reactor to a larger multimode system has been recently demonstrated by Kappe et al. in the Heck reaction.<sup>311</sup> For scale-up, both

homogeneous and heterogeneous palladium-coupling conditions were employed for experiments on a  $4 \times 20$  mmol scale in the multimode batch reactor, the yields obtained closely agreeing with those in the small-scale experiments.

**7.1.2. Ultrasound.** Standard Heck reactions, which are carried out in polar solvents such as DMF and NMP, generally involve long reaction times (8–72 h) at temperatures ranging from 80 to 140 °C. Even in ILs, these parameters are still high. To the best of our knowledge, Srinivasan et al. have reported the only example of a Heck reaction promoted by ultrasound using an IL as solvent at ambient temperature.<sup>260</sup> The reactions were carried out in a thermostatted ultrasonic cleaning bath of frequency 50 KHz at 30 °C with complete conversion of iodobenzenes in 1.5–3 h (see Scheme 80 and the corresponding comments). No reaction, even in trace amounts, could be observed under ambient conditions in the absence of ultrasound. Unfortunately, the reaction did not proceed with aryl chlorides and bromobenzene under the reported sonochemical conditions.

Bräse et al. developed a traceless linker system of the triazene type to immobilise aryl halides, with application to the Heck reaction with a variety of olefins under ultrasonic conditions (Scheme 105).<sup>312</sup> The halogenated resins were air and water stable, they could be stored for long periods without loss of activity, and the recovered resins could be re-used with a slight loss of activity (<10%). In this case, no comment was made about the advantages of using ultrasound, compared to the standard Heck conditions.



Scheme 105.

On the other hand, ultrasound was also utilised to induce the reduction of Pd(II) salts to Pd(0), the activity of the latter species being examined in the Heck reaction. When a 1:2 mixture of Pd(OAc)<sub>2</sub> and myristyltrimethylammonium bromide was subjected to sonochemical reduction in THF

or MeOH at room temperature, nanoscale particles of palladium metallic clusters were obtained.<sup>313</sup> Apart from its stabilising effect, the ammonium salt was suggested to act as a reducing agent, probably due to the decomposition that occurs at the liquid-phase region immediately surrounding the collapsing cavity, providing reducing radicals. The sonochemical reduction of Pd(II) could be enhanced by the addition of 0.2 M EtOH–MeOH in the THF process, its highly volatile nature producing various reducing radicals inside the collapsing bubble. UV–vis spectroscopic analysis revealed the initial formation of a Pd(II)–NR<sub>4</sub>X complex, which, in turn, was reduced to Pd(0). Elemental analysis of the resulting solid after sonication showed that the THF process yielded NR<sub>4</sub>X stabilised-palladium clusters, whereas the methanol process produced pure Pd agglomerates. These Pd nanoclusters, either in situ supported on charcoal or NR<sub>4</sub>X stabilised, were catalytically active towards the Heck reaction between bromobenzene and styrene in the absence of phosphine ligands, but to a moderate extent of 30% conversion.

The little work published on ultrasound applied to the Heck reaction makes it difficult to balance the advantages and disadvantages. Some of the advantages have been clearly demonstrated in the above examples, together with some other more general benefits such as the simplicity of the method, involving little work-up, its adaptability to heterogeneous reactions and the possibility of it being applied to large-volume reactions. On the other hand, the lack of generality, cost of equipment and hazardous temperature control may be mentioned as general disadvantages of this technique.

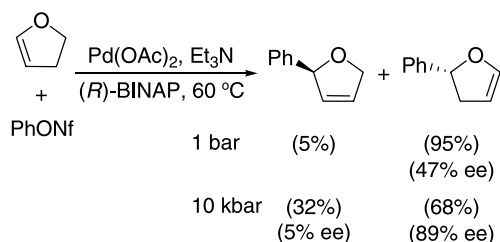
**7.1.3. High pressure.** Pressure in the range of 1–20 kbar strongly influences the rate and equilibrium position of processes accompanied by a decrease in volume such as carbon–carbon bond formation. These processes, in which the distance between two carbon atoms decreases from the van der Waals distance of ca. 3.6 Å to the bonding distance of ca. 1.5 Å, are accelerated by pressure and the equilibria are shifted towards the side of the products.

Considering the generally accepted mechanism for the Heck reaction, it is evident that several steps in the catalytic cycle should be pressure dependent. The following steps are considered to be accelerated under high-pressure conditions, because they might have negative activation volumes: (a) formation of the active Pd(0) species, (b) oxidative addition of Pd(0) to the carbon–halogen bond, (c) complexation of palladium species with the olefin and (d) formation of the quaternary ammonium salt. The insertion, migration and re-insertion steps should be invariant, whereas the reductive elimination and decomplexation of the catalyst should be disfavoured by pressure. The net volume balance has a negative sign and, therefore, pressure may be a very useful parameter to activate Heck reactions, which otherwise would not occur or would take place only sluggishly. In addition, the activity of the palladium catalyst does not decrease at high pressure, which is capable of stabilising PdL<sub>n</sub> species by enforcing ligand coordination.<sup>314</sup>

Pioneering work in this field was carried out by the groups

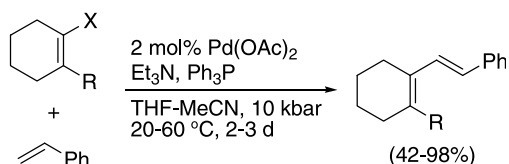


of Reiser<sup>315</sup> and de Meijere<sup>316</sup> in 1993 and 1994, respectively. Reiser et al. described the dramatic influence on the regioselectivity and the ligand-induced enantioselectivity of the palladium-catalysed arylation of 2,3-dihydrofuran by high pressure.<sup>315</sup> Firstly, it was observed that, at normal pressure, the addition of triphenylphosphane led to little change in the regioselectivity, and this was always in favour of the 2,3-dihydrofuran derivative. In contrast, the 2,5-dihydrofuran derivative became the major product by adding triphenylphosphane at 10 kbar. This behaviour was also observed when Pd-BINAP was used as a chiral catalyst, together with a substantial improvement in the enantioselectivity for the 2,3-dihydrofuran derivative (Scheme 106).



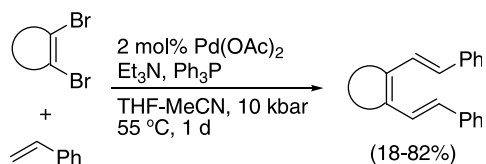
Scheme 106.

De Meijere et al. also studied the palladium-catalysed coupling of 2-bromocyclohexene with styrene under 10 kbar to furnish 1-styrylcyclohexene in 82% yield after 2 days at 20 °C, whereas a control experiment under ambient pressure led only to traces of the product (Scheme 107).<sup>316</sup> Alternatively, the product was obtained in 51% yield starting from 1-(trifluoromethylsulfonyloxy)cyclohexene, instead of the bromide, under the same reaction conditions. Coupling of styrene to dienyl halides under 10 kbar at 20–60 °C afforded the 1,6-disubstituted 1,3,5-hexatrienes in near-quantitative yields, while no product was observed under the same conditions at ambient pressure (Scheme 107). Moreover, when 1,2-dibromocyclopentene, 1,2-dibromocyclohexene and *o*-dibromobenzene were treated with styrene under these conditions, but at 55 °C, the 2-fold coupling products were obtained in 18–82% yield, no product being formed at ambient pressure (Scheme 108).



R = H, CH=CHCN, CH=CHCO<sub>2</sub>Me  
X = Br, Cl, OTf

Scheme 107.



Scheme 108.

The different advantages of using high pressure on Heck reactions were additionally supported by the studies of Sugihara et al. in the coupling of aryl iodides with ethyl acrylate,<sup>314</sup> of Reiser et al. in the coupling of iodobenzene with 2,3-dihydrofuran, *N*-ethoxycarbonyl-2,3-dihydropyrrole and cyclopentene,<sup>317</sup> and of Tietze et al. in the intramolecular Heck reaction for the synthesis of isochromanes, isoquinolines and benzazepines.<sup>318</sup> These publications were recently reviewed in detail by Reiser et al.<sup>319</sup> In general, the catalyst performance was improved by high pressure, leading to higher yields, better TONs numbers and rates, and increased selectivity, demonstrating that the ligand exchange on catalytic species is viable under pressure.

More recently, a very interesting and detailed contribution by de Meijere et al. was reported, in order to better understand the mechanism and influence of high pressure on the Heck reaction.<sup>320</sup> To achieve a more accurate kinetic analysis, this group applied quantitative on-line FT-IR spectroscopy for measuring concentrations in the Heck reaction of iodobenzene with methyl, ethyl and *tert*-butyl acrylate, and of both 4-nitrophenyl iodide and 4-nitrophenyl triflate. The results obtained revealed that the activation volumes correlated with the degrees of steric congestion for the variation of the alkyl groups in the acrylates and of the leaving group in the nitrophenyl derivatives. The more highly congested systems provided more negative activation volume values, while the activation enthalpies and entropies were virtually independent of the reactants. The rate coefficients for the coupling of iodobenzene with the alkyl acrylates followed the trend: *tert*-butyl > ethyl > methyl acrylate, while those for the coupling of the nitrophenyl derivatives with methyl acrylate followed the trend: *p*-nitrophenyl triflate > *p*-nitrophenyl iodide. These orders were consistent with the notion that the coordination and insertion steps of the acrylate are rate determining. Therefore, the rate-determining step of the overall catalytic cycle of the Heck reaction under high-pressure conditions is not the oxidative addition, as this is assumed to be the rate-determining step at ambient pressure.

It has been shown that the high-pressure technique not only activates the Heck reaction, but also can have a decisive role in controlling the regio- and stereoselectivity of the process. This technique is normally excellent in reproducibility although it is mainly applied to low-volume and homogeneous reactions, because of the difficulty of mixing. In addition, the cost of equipment and the safety issues can limit its application.

## 7.2. Physicochemical activation

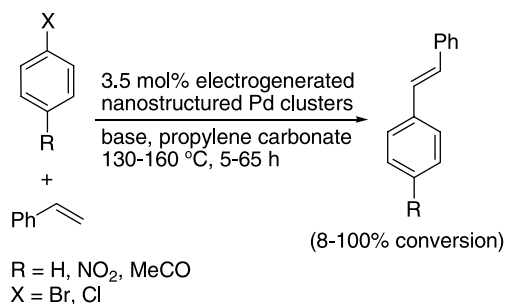
**7.2.1. Micellar solutions.** Hybrid palladium colloids in the core of amphiphilic block copolymer micelles showed catalytic activity in the Heck reaction. These dispersions of nanometer-sized palladium colloids were prepared in block copolymer micelles of polystyrene-*b*-poly-4-vinylpyridine and exhibited a very high stability.<sup>321</sup> The activities of these colloids compared well with those of the standard materials. The yields were high in the coupling of activated bromoarenes with styrene and *n*-butyl acrylate (60–99%) at 140 °C in toluene and Bu<sub>3</sub>N. In general, however, the

reactions were very slow (up to 5 days), very low yields being obtained for non-activated haloarenes, and no comment was made concerning the possibility of catalyst recycling.

Sakurai et al. prepared shell cross-linked micelles (SCM), where the polysilane core was surrounded by a partially cross-linked shell of poly(methacrylic acid), and used then as the template for the synthesis of metal nanoparticles.<sup>322</sup> Reduction of Pd(II) with the polysilane SCM produced Pd(0) particles, which were highly dispersed in water. SCM–Pd (0.01 mol%) catalysed the Heck reaction of styrene or methyl acrylate with iodobenzene in DMF and Et<sub>3</sub>N at 120 °C, giving the coupled products in 82 and 96% yield, respectively. Despite the very interesting nature of this catalytic system, its preparation is rather sophisticated, involving some non-commercially available starting materials and reagents.

**7.2.2. Electrochemical activation.** Electrochemical reactions with catalytic amounts of low-valent nickel and palladium species, generated in situ from Ni(II) or Pd(II) precursors, have found application in one step coupling processes.<sup>323</sup> These electrolyses are conducted generally at relatively low reduction potentials, avoiding the direct reduction of the organic compounds. Most synthetic applications in electrochemically assisted nickel- and palladium-catalysed carbon–carbon bond-forming reactions have, however, been carried out in the field of reductive coupling, while the electrochemical version of the Heck reaction has been little studied.

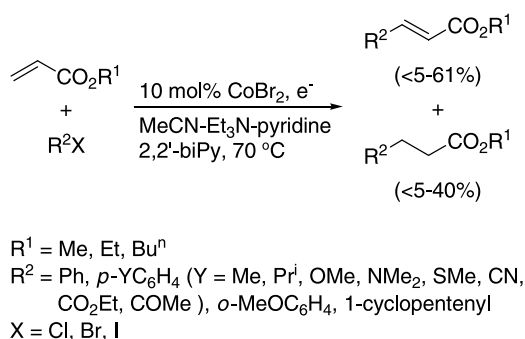
In 1996 Reetz et al. devised an electrochemical process to transform palladium bulk into nanostructured palladium clusters, using a palladium sacrificial anode as the metal source in a simple electrolysis cell containing NaCl in propylene carbonate (with 5% ethanol) at 60 °C.<sup>324</sup> The electrochemical process involved the anodic dissolution of the palladium sheet with the intermediate formation of Pd(II) ions, which migrate to the cathode, where they were reduced back to the zero-valent state. Propylene carbonate was used as a stabilising agent for the clusters to prevent metal powder formation. These palladium clusters showed a good performance in the Heck reaction of activated bromobenzenes with styrene at 130 °C (70–100% conversion, 79–96% yield), whereas unactivated bromo- and chlorobenzene showed only poor to moderate conversion even at 160 °C (Scheme 109). The black palladium cluster solution was stable at 155 °C for several days, although any other manipulation (removal of the solvent or immobilis-



Scheme 109.

ation on a solid support) led to large amounts of palladium powder that could not be redispersed in propylene carbonate.

More recently, Gosmini et al. developed a consumable anode process for the electrochemical Heck reaction between aromatic or vinylic halides and acrylic esters, using cobalt(II) bromide as catalyst associated with 2,2'-bipyridine as ligand, in a mixture of MeCN–Et<sub>3</sub>N–pyridine at 70 °C (Scheme 110).<sup>325</sup> All reactions were conducted in a one-compartment cell at a constant current intensity of 0.2 A with an iron consumable anode, associated with a stainless-steel grid as the cathode, in the presence of tetra-*n*-butylammonium tetrafluoroborate to ensure ionic conductivity. Unfortunately, the reaction showed little selectivity leading to a mixture of the expected substitution and conjugate addition products, together with some other minor by-products. The presence of triethylamine, pyridine and 2,2'-bipyridine enabled a higher substitution versus addition product ratio.



Scheme 110.

Despite the advantages of the electrochemical methods outlined in the introductory section, very little research has emerged on this technique applied to the Heck reaction. Much effort is still required in order to improve both the yield and selectivity of the work reported so far, as well as to have a better knowledge of the scope and limitations of this technique.

## 8. Miscellaneous non-conventional techniques

### 8.1. Nanofiltration

Livingston et al. developed a new approach for the separation and recycling of homogeneous Heck catalysts from post-reaction mixtures, based on the use of solvent-resistant nanofiltration membranes.<sup>326</sup> Different catalytic systems were tested for the standard Heck coupling of iodobenzene and styrene. In contrast with the continuous operation mode for nanofiltration-coupled catalysis, the catalysis and nanofiltration stages were still coupled, but operated independently, allowing more flexible operating conditions and lower reactor occupancy. For all the reactions studied, neither the product nor the remaining reactants were retained during the filtration, the membrane selectivity towards the catalyst being high ( $\leq 96\%$  palladium rejection). The ammonium salt formed as a

by-product precipitated out and could be easily removed from the reactor, before refilling it for the subsequent run. Consequently, a cleaner form of the product in the corresponding solvent was obtained on the permeate side. In the first catalytic system,  $\text{Pd}(\text{OAc})_2(\text{PPh}_3)_2$  was recycled 6-fold before the reaction rate dropped below 20% of the original value, with a cumulative TON of 690 in 120 h. Substantial improvements in the system performance were obtained by employing catalysts with a greater chemical stability. An imidazolydinene catalyst yielded an equal TON for six recycles in 40 h with less reaction rate decline, whereas  $\text{Pd}(\text{OAc})_2$  stabilised by a quaternary phosphonium salt gave six recycles under 30 h. The higher reaction rates achieved with the two latter catalytic systems minimised both the reactor occupancy and the waste generated by downstream processing.

Zeolite membranes were utilised by Santamaría et al. to separate palladium complexes in mixtures representing possible post-Heck scenarios.<sup>327</sup> The reaction of 4-bromobenzonitrile with methyl acrylate was chosen as a Heck example reaction, the catalyst being  $[\text{Pd}(\mu\text{-Cl})(\text{PPh}_3)_2]_2(\text{BF}_4)_2$ . Separation experiments using a first mixture composed of the Pd complex, DMA and the product were unsuccessful. In contrast with this work, good separation was attained in experiments where dichloromethane was used as the solvent. Complete retention of the Pd complex occurred with simultaneous permeation of both the solvent and the product.

We have already commented in Section 5.2.4 on the application of a polymer-enlarged catalyst, formed from (1-Ad)<sub>2</sub>P-substituted poly(methylstyrene) (**25**) and  $[\text{Pd}(\text{dba})_2]$ , to the Heck reaction of aryl bromides with *n*-butyl acrylate.<sup>208</sup> Nanofiltration of the NMP solution was estimated to render less than 0.5% polymer leaching, with a retention of the catalyst by the membrane >99.95%. Even after diluting the NMP solution with a large amount of cyclohexane, the catalyst performance decreased significantly after the second cycle. The coupling yields were 80–87%, but the catalyst could not be recycled since attempting nanofiltration in the highly polar and aprotic medium resulted in severe membrane damage.

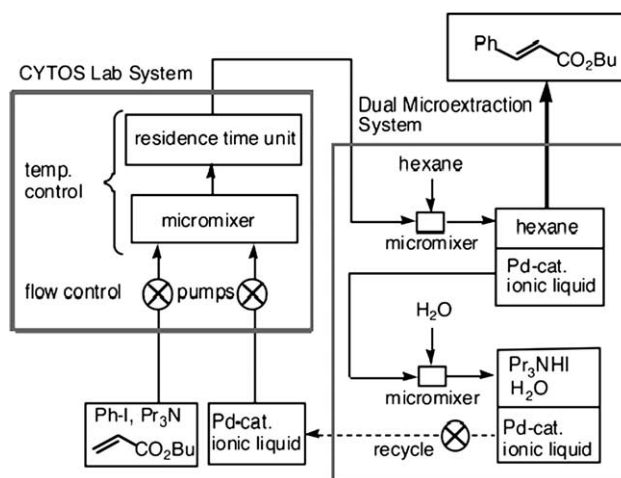
The membrane technology seems to be a very promising technique for the Heck reaction using homogeneous catalysts. Its application involves the design of special reactors together with the selection of optimum parameters such as the membrane pore and composition, solvent and flux system, or the transmembrane pressure. At any rate, the development of more resistant membranes and improving the reactor technology is desirable, since these factors largely determine the applicability of membrane technology in homogenous catalyst recycling.

## 8.2. Microreactors

Two examples of the application of continuous-flow microreactors to the Heck reaction have appeared recently in the literature. Kirschning et al. developed a continuous-flow microreactor with an interior monolithic glass-polymer composite that was loaded with palladium particles by ion exchange, followed by reduction.<sup>328</sup> This microreactor

allowed the coupling of 4-iodoacetophenone with *n*-butyl acrylate and of 4-iodoanisole with isobutyl acrylate in DMF as solvent and  $\text{Et}_3\text{N}$  as base at 110–130 °C for 0.5–2.5 h (>78% yield). The work-up was very simple and the catalytic system could be re-used more than 20 times after washing.

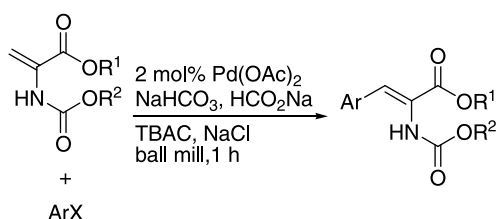
The methodology developed by Ryu et al. for the coupling of aryl iodides with *n*-butyl acrylate using the low-viscosity IL,  $[\text{bmim}][\text{NTf}_2]$  (see Scheme 111),<sup>258</sup> was extended to a continuous microflow system and applied to the particular Heck reaction of iodobenzene with *n*-butyl acrylate.<sup>259</sup> A CPC CYTOS Lab System was used as the microreaction apparatus, in combination with a microextraction-catalyst recycling system, to continuously recycle the reaction medium. A palladium–carbene complex soluble in the IL was used as the catalyst, the low viscosity of the IL being essential to ensure a smooth flow by the action of the pump. The temperature of both the microreactor and the residence time unit was controlled at 130 °C, with a residence time of 17 min at a total flow rate of 1.0 ml/min. The ammonium salt could be removed from the resulting IL layer by washing with copious amounts of water. Under these reaction conditions, yields >90% were obtained and the recovered IL could be used again in the next run without any drop in the product yield (90–99%). Alternatively, microextraction units were attached to the microflow reaction system in order to facilitate the extraction of the product and the ammonium salt and to pump back the IL layer containing the palladium catalyst. A total of 115.3 g of *n*-butyl cinnamate could be prepared in 80% yield at a rate of 10 g/h. Scheme 111 represents a schematic drawing of the automated microflow apparatus. The whole methodology is remarkable in the sense that the great effort needed to design the apparatus in an automatic manner was compensated for the possibility of a multi-ten gram-scale preparation of *n*-butyl cinnamate, a task very difficult to achieve using any other of the methodologies described in this review. Nonetheless, the complete apparatus has a high economical cost and the product required further purification by silica gel chromatography, with the consequent and proportional use of silica gel and eluting solvents (for 115 g of product).



Scheme 111.

### 8.3. Ball-milling conditions

To the best of our knowledge, the only Heck reaction under ball-milling conditions has been recently reported by Frejd et al., involving the synthesis of unsaturated unnatural amino acids from protected amino acrylates and aryl halides.<sup>329</sup> These reactions were performed using a Fritsch Planetary Micro Mill model, housing two stainless-steel cups, each containing eight stainless steel balls, and sealed by a stainless-steel lid fitted with a Teflon gasket. The presence of TBAC was crucial for the success of the reaction, whereas the addition of sodium formate as a reductant for Pd(II) improved the yields. The Z-products were obtained in yields ranging from low to good for aryl iodides and bromides, but no reaction was observed for aryl chlorides (Scheme 112).



R<sup>1</sup> = Me, Bn

R<sup>2</sup> = Boc

Ar = Ph, *p*-YC<sub>6</sub>H<sub>4</sub> (Y = NH<sub>2</sub>, MeO), *m*-NCC<sub>6</sub>H<sub>4</sub>,  
3-furyl, 2-thienyl

X = Br, I

Scheme 112.

### 9. General conclusions

We have presented in this report some recent trends in the Heck reaction that highlight the efforts and interest in developing more efficient processes according to the new requirements of the chemistry of the 21st century. A vast array of methodologies has been described, any of which intervenes in a non-conventional way over one or more of the different parameters involved in the reaction: substrates, catalytic system, solvent, reaction conditions, or work-up. Very often, however, the dynamic of the research seems to be driven more because of the current fashions than because of the real need in achieving practical procedures. As a result, we can enjoy a variety of methodologies that are very interesting from an academic point of view, but most of these are useless from a practical point of view.

Anyway, we would like to point to a series of present issues, that in our opinion, still need to be addressed, as well as to outline the possible future direction of the research in order to achieve the goals mentioned in the introduction section. (a) Most of the methodologies which have appeared in this review deal with the simpler reactions involving the most reactive substrates, that is, the reaction of aryl iodides or activated aryl bromides with acrylates; in contrast, little work has been done concerning the use of the more desirable, but reluctant to react, aryl chlorides or other olefinic substrates (e.g., electron-rich olefins). (b) Only highly regio- and stereoselective reactions are worthwhile, the formation of by-products being a procedural and

economical problem due to the additional purification steps and the difficulty of separating compounds of similar polarity. (c) Whenever possible, commercially available starting materials, reagents, ligands, catalysts, or solvents must be used; it is contradictory that we try to recycle a catalytic system (e.g., to minimise waste generation and to make the process more economical) and that rather long or minimally-effective experimental work is needed to prepare the different reaction components. (d) The catalyst must be recyclable and/or display high TONs; high TONs are essential to avoid contamination problems, above all on a larger scale and in the pharmaceutical industry. (e) Ligandless catalysts, recoverable ligands or stabilised nanoparticles allow better recovery and lower cost; in this sense, heterogeneous catalysts are preferable, above all when metal leaching is prevented. (f) It is very rare to find a genuine catalyst for the Heck reaction, in which filtration of the reaction mixture produces a catalytically active solid and an inactive filtrate; this is the only case that can be considered a strictly recyclable catalyst. (g) The usual high reaction temperatures (> 120 °C), sometimes imposed by the high stability of the catalyst (e.g., palladacycles), are often detrimental for the selectivity. (h) In general, reproducible, as well as atom-economy, low-cost, scalable and practical procedures, are needed to extend the methodologies from the academic laboratory to the industrial plant; most of the reactions reported in this review were carried out on a few mmol scale and the scale up was not attempted. (i) The expensive equipment or reaction medium utilised in some methodologies cannot compensate for the little or no improvement observed in many cases with respect to the conventional methodologies; in addition, the application of these methodologies is normally restricted to a small scale. (j) Finally, further research must be undertaken in order to clarify the reaction mechanisms involved in the different processes, which remain unclear in most cases; it is crucial to have a better knowledge of the nature and properties of the real catalytic species in order to improve any given reaction.

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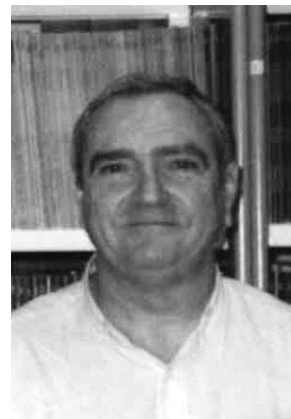
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**Biographical sketch**

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



Miguel Yus was born in Zaragoza in 1947. He received the BSc (1969), MSc (1971), and PhD (1973) degrees from the University of Zaragoza. After spending 2 years as a postdoc at the Max Planck Institut für Kohlenforschung in Mülheim a.d. Ruhr, he returned to the University of Oviedo where he became Associate Professor in 1977, being promoted to full Professor in 1987 at the same university. In 1988 he moved to a chair in organic chemistry at the University of Alicante, where he has been the head of the Organic Chemistry Department until 2004, when he was appointed to Director of the newly created Institute of Organic Synthesis (ISO) at the same university. Professor Yus has been visiting professor at different institutions such as ETH-Zürich and the universities of Oxford, Harvard, Uppsala, Marseille, Tucson, Okayama, Paris VI and Strasbourg. He is member or fellow of the chemical societies of Argentina, England, Germany, Japan, Spain, Switzerland and United States. He is co-author of more than 350 papers and three patents, mainly in the field of the development of new methodologies involving organometallic intermediates in synthetic organic chemistry. Among others, he has recently received the Spanish–French Prize (1999), the Japan Society for the Promotion of Science Prize (2000) and the Stiefvater Memorial Lectureship Award (2001). Professor Yus belongs to the advisory board of the journals *Tetrahedron*, *Tetrahedron Letters*, *European Journal of Organic Chemistry*, *Chemistry Letters* and *Trends in Organic Chemistry*. Last year, he and other members of the ISO founded the new chemical company MEDALCHEMY, S. L. to commercialise fine chemicals.



Irina Beletskaya received her Diploma degree in 1955, her PhD Degree in 1958, and her Doctor of Chemistry degree in 1963 from Moscow State University. The subject for the latter was Electrophilic Substitution at Saturated Carbon. She became a Full Professor in 1970 and in 1974 a Corresponding Member of the Academy of Sciences (USSR), of which she became a full member (Academician) in 1992. She is currently Head of the Laboratory of Organoelement Compounds, Department of Chemistry, Moscow State University. Irina Beletskaya is Chief Editor of the *Russian Journal of Organic Chemistry*. She was President of the Organic Chemistry Division of IUPAC from 1989 to 1991. She was recipient of the Lomonosov Prize (1979), the Mendeleev Prize (1982), and the Nesmeyanov Prize (1991). She is the author of more than 500 articles and 4 monographs. Her current scientific interests are focused on (i) transition-metal catalysis in organic synthesis; (ii) organic derivatives of lanthanides; and (iii) carbanions and nucleophilic aromatic substitution.