

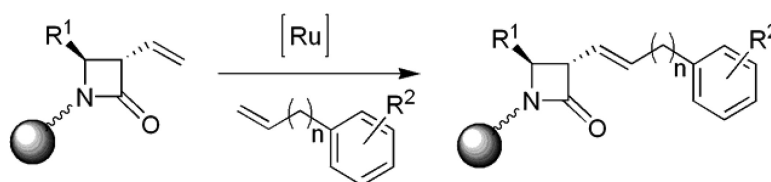
Perspective

**Prospect of Metal-Catalyzed C#C Forming Cross-Coupling
 Reactions in Modern Solid-Phase Organic Synthesis**

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Perspective

Prospect of Metal-Catalyzed C–C Forming Cross-Coupling Reactions in Modern Solid-Phase Organic Synthesis

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Solid-phase organic synthesis (SPOS) has evolved in the past few years to become a widely used tool for the preparation of a large number of structurally diverse compounds for combinatorial libraries. The generation of molecular diversity by solid-phase methodologies was originally focused on the synthesis of the peptide and oligonucleotide libraries.¹ However, after the pioneering work by Ellman² in the solid-phase synthesis of benzodiazepines, the scope of polymer-supported chemistry was expanded beyond the preparation of those biopolymers to reach the synthetically more complicated, drug-like, small organic molecules.

In recent years, an increasing interest from both academia and industry has motivated the adaptation to solid support of many procedures that were originally developed for liquid phase. As a result, multiple parallel syntheses in a combinatorial way have emerged as indispensable tools to speed up drug discovery in modern life science.

SPOS offers some advantages as compared to solution chemistry. Purification is facilitated by simple filtration, avoiding time-consuming separation techniques; consequently, building blocks and reagents can be added in excess to drive reactions to completion. Amenability to automate and the less favorable interference between functionalities linked to the solid support are other benefits of this chemistry. A result of the latter is the “pseudo-dilution effect”³ that makes intramolecular macrocyclization a suitable reaction that could be carried out efficiently

on solid-phase rather than in solution. Last, but not least, solid-phase techniques allow the use of high-boiling solvents because their evaporation is not an issue.

In this context, because of their central role in modern organic synthesis, catalytic coupling reactions were a logical target of the development of solid-phase synthesis from the very beginning of this methodology.⁴ Therefore, this type of reaction was soon established as a widespread tool for solid-phase synthesis, particularly, for carbon–carbon bond formation. For instance, solid-phase variants of the Stille, Heck, Suzuki, and Sonogashira couplings are now well recognized reactions. Despite this unquestionable development, the research in the area is far to be completed. Sometimes, the success of a reaction depends on the kind of support or linker used. On the other hand, new catalytic couplings and new versions of known catalytic couplings appear in the literature almost every month; new and more efficient catalysts are also frequently reported giving the opportunity to improve low-yielding procedures.

A quick overview of the state-of-the-art in metal-catalyzed carbon–carbon-forming reactions on solid support can help us to establish some guidelines for their future development. Because our emphasis will be on cross-coupling reactions, some excellent reviews can be consulted for a more comprehensive view of organometallic chemistry on solid phase.⁵

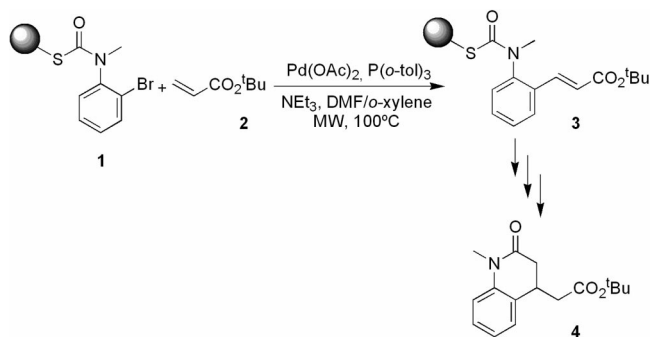
Heck Reaction

In the Heck reaction, an arene or heteroarene bearing a good leaving group (i.e., halide, triflate) is coupled with an alkene or

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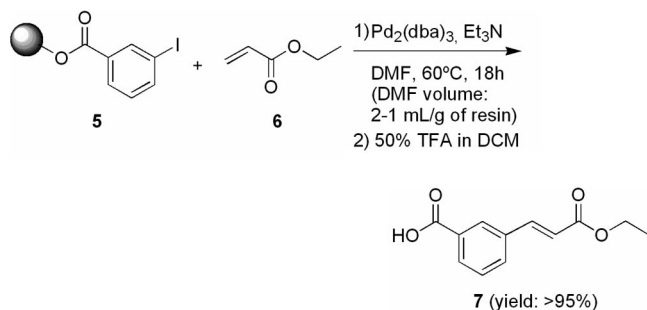
alkyne functionality in the presence of palladium (0) and a base to give disubstituted alkenes or alkynes. This is generally a very mild reaction and does not require strict anhydrous or inert conditions. Although this reaction has been successful either with aryl halides or alkenes tethered to the solid support, immobilized halides tend to give better results.⁶ Among aryl halides, iodides are by far the most used, while few examples of benzenesulfonate derivatives have also been reported.⁷ Yields are also very high for the coupling with an alkyne. It has also been reported that improved yields were occasionally observed when a Heck reaction was performed employing hindered phosphine ligands, such as tri-*o*-tolyl phosphine (P(*o*-tol)₃). However, ligandless catalysts, such as tris(dibenzylideneacetone)dipalladium(0) (Pd₂dba₃), have been found sometimes to be far more effective than traditional palladium acetate.^{6,8} As a representative recent example, Procter et al. have reported the Heck coupling between resin-bound *N*- α -halophenylamides (**1**) and *tert*-butyl acrylate (**2**) under microwave heating as a key step for the synthesis of tetrahydroquinolones (**4**) (Scheme 1).⁹

Scheme 1



A procedure using low solvent volumes in SPOS has been recently applied by Morphy et al.¹⁰ for a Heck reaction (Scheme 2). They start from the hypothesis that by reduction of the amount of solvent typically used in a solid-phase synthesis, it is possible to increase local concentration of reagents confining them solely to the interior of the polymer bead. Although this principle would require more generality, the prospect of better yield and less solvent, with their environmental implications, deserve to be taken into account in the near future.

Scheme 2

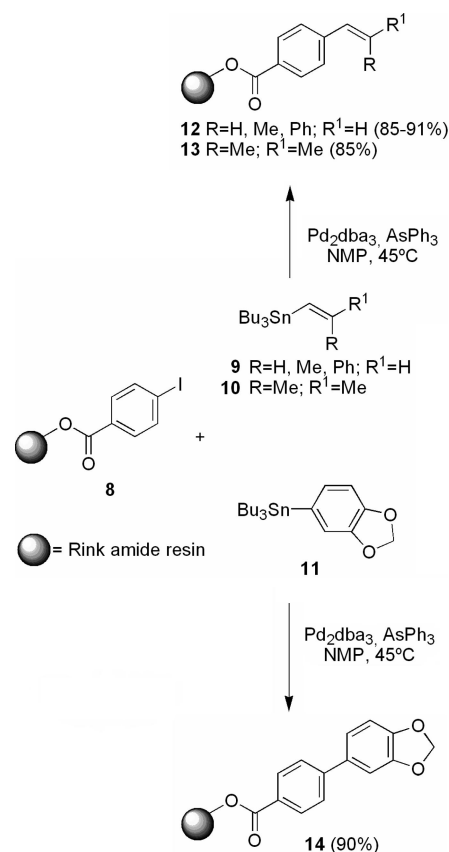


Because of the obvious advantage of the pseudodilution effect, intramolecular Heck reaction has been extensively used in solid-phase, particularly, for the preparation of heterocyclic compounds such as benzazepines, isoquinolines, indoles, benzofurans, and related structures.^{5a,11}

Stille Reaction

The Stille coupling is a versatile reaction in which a variety of C–C bonds can be obtained by reaction between stannanes and halides or pseudohalides. The major drawback of this reaction in solution-phase chemistry is the formation of stoichiometric tin byproduct that are generally difficult to remove.¹² As expected, solid-phase synthesis was soon considered as an alternative to avoid tedious purification. Hence, several versions of the Stille reaction have been performed on solid support. For example, vinyl and aryl stannanes (**9–11**) were coupled smoothly to solid-supported aryl iodides (**8**) to give the desired products (**12–14**) in very high yields (Scheme 3). It was demonstrated that the reaction is complete even with hindered (**10**) and aryl stannanes (**11**).¹³ Resin-bound stannanes have also been reported to be suitable for the immobilized version of this reaction.^{5c}

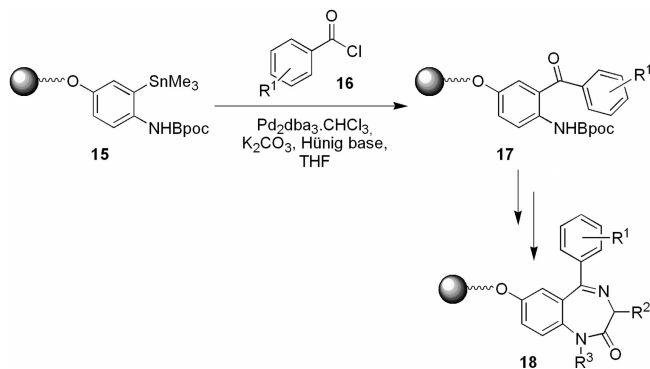
Scheme 3



In one of his brilliant approaches to the solid-phase synthesis of benzodiazepines, Ellman reported the coupling between a support-bound stannane and an aromatic acid chloride as a versatile methodology for the preparation of the benzophenone precursor (Scheme 4).¹⁴ The support-bound *N*-protected (2-aminoaryl)stannane (**15**) reacted, for example, with a benzoyl chloride (**16**) to give the corresponding *N*-protected 2-aminoaryl ketone (**17**). To avoid premature carbamate deprotection, Hünig base and potassium carbonate were added as acid scavenger. As was also observed in solid-phase Heck reaction, the use of ligandless catalyst (Pd₂dba₃, CHCl₃) gave better results than its phosphine ligand counterpart. In this way, palladium is more reactive, avoiding higher temperature conditions that led to some

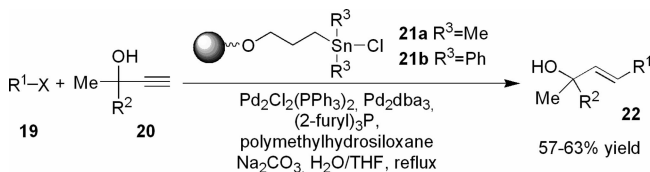
premature cleavage of the product from the resin. Now, for the same reason, the use of ligands with lower donor capacity toward Pd(II) than PPh₃, such as triphenylarsine, together with Pd₂dba₃ as palladium source, can be considered as the standard conditions for the solid-phase Stille coupling.¹⁵

Scheme 4



An interesting option to diminish unwanted tin byproduct was reported by Kilburn et al.¹⁶ Resin-bound dimethyl and dibutyltin chlorides (**21a** and **b**) were synthesized and successfully applied to a catalytic Stille coupling cycle (Scheme 5).¹⁷ Although 0.3 equiv of resin **21a** and **b** were necessary to obtain good yields, levels of tin in the organic products were low or negligible after removal of the solid support by filtration.

Scheme 5



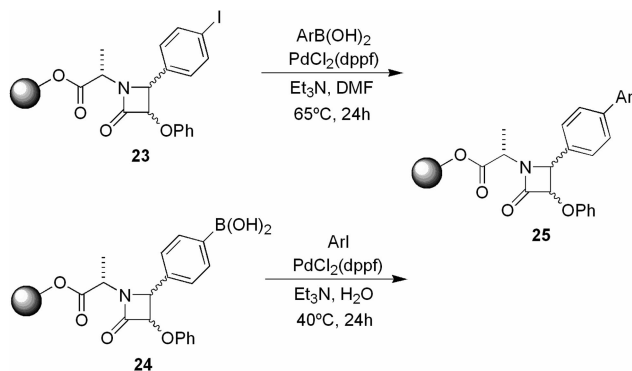
Suzuki–Miyaura Reaction

The Suzuki–Miyaura coupling is, by far, the most successful Pd-catalyzed reaction in solid-phase synthesis. In recent years, many examples have been reported in the literature. The Suzuki–Miyaura reaction is basically the reaction of arylboronic acids with aryl halides and triflates in the presence of palladium catalyst to form biaryl fragments, which are present in many biologically active molecules. The advantages of employing the Suzuki–Miyaura coupling include mild reaction conditions, tolerance to a wide range of functional groups, and availability of boronic acids which are, in turn, generally low in toxicity and a stable starting material.

One of the first examples of this cross coupling on solid phase was the synthesis of a library of biaryl substituted β-lactams (**25**) (Scheme 6).¹⁸ The best results were obtained when the immobilized 4-(4-halophenyl)-β-lactam (**23**) reacted with arylboronic acids using the bidentate phosphine-palladium complex: [1,1'-bis(diphenylphosphino)ferrocene] palladium(II) dichloride (PdCl₂(dppf)) as catalyst. The reaction was also successful when the boronic acid was attached to the resin (compound **24**). Although both strategies are possible, the use of resin-bound aryl halides as substrates is more common.

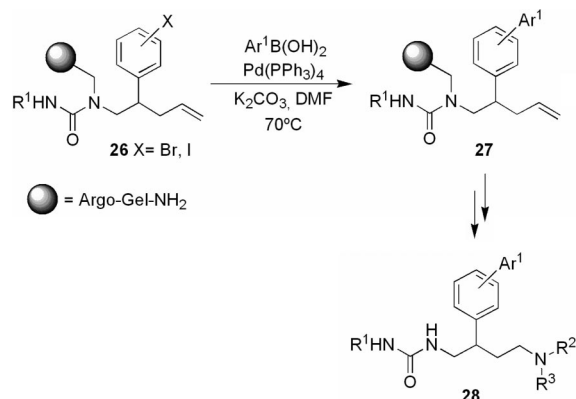
Although ligandless catalysts were recommended at the beginning, the use of more classical palladium catalysts, such as tetrakis(triphenylphosphine)palladium(0) [Pd(PPh₃)₄], cannot

Scheme 6



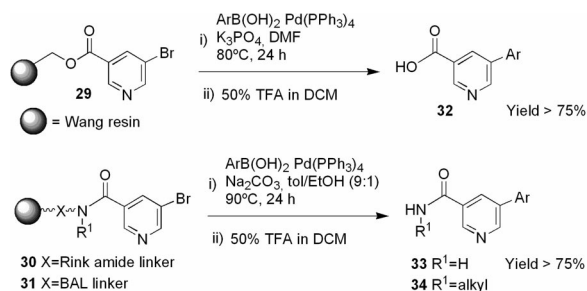
be discarded because they have been extensively used in recent years with great success. For example, the Suzuki–Miyaura coupling reactions have been applied to the generation of a solid-phase library of biaryl-containing compounds in the search for MCH1R antagonist (Scheme 7).¹⁹ With the use of an acid-labile Argo-Gel-NH₂ support, fifteen bromo and iodobenzyl derivatives (**26**) were reacted with various arylboronic acids in the presence of Pd(PPh₃)₄/K₂CO₃.

Scheme 7

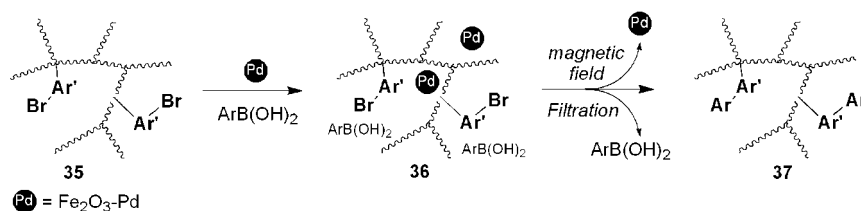


In solid-phase chemistry, it is clear that solid supports and linkers can influence the outcome of a particular reaction. In the case of the Suzuki–Miyaura coupling, Rink-amide and BAL resin linkers seem to require different conditions than ester-bound Wang resin to achieve total conversion. In a recent study dealing with the synthesis of 5-substituted nicotinic acid derivatives (**32–34**),²⁰ it was demonstrated that a fine-tuning of the experimental conditions for each resin, particularly in term of base, solvent, and temperature, is required for optimal results (Scheme 8). The authors also found that, for Wang resin, Pd(PPh₃)₄ gave better results than PdCl₂(dppf).

Scheme 8



Scheme 9



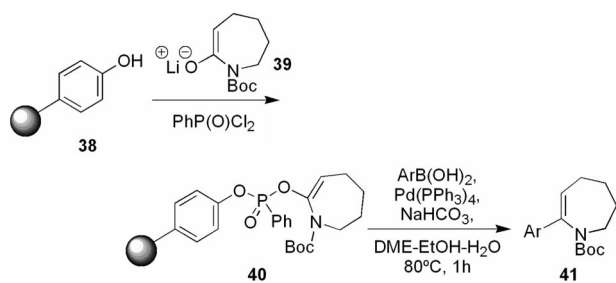
This coupling has also been employed to demonstrate the efficiency of magnetic nanoparticle-supported Pd catalyst in solid-phase chemistry. In this ingenious procedure,²¹ Pd catalyst was immobilized to the surface of a magnetic nanoparticle and applied to the Suzuki–Miyaura coupling of a resin-bound aryl halide (**35**) and a boronic acid (Scheme 9). After the reaction, the catalyst was magnetically isolated and recycled, while product-containing resin (**37**) was separated from the excess of boronic acid by a simple filtration. The small size of the nanoparticles allows their penetration inside the cross-linked polystyrene beads, carrying the catalyst closer of the immobilized aryl halide.

Ruhland et al. have recently reported the synthesis of biaryl structures by Suzuki–Miyaura coupling employing an interesting traceless support: a resin-bound Bismuth complex.²²

Although most of the examples of solid-supported Suzuki–Miyaura coupling are in the area of the biaryl and biheteroaryl compounds, other variants of this coupling have been translated to solid-phase chemistry. Thus, this methodology has been extended to the coupling of supported alkenyl halides with alkylboronates or arylboronic acids, and resin-bound aryl halides with alkyl and alkenyl boronates to give substituted olefins or alkyl-substituted aromatic compounds.^{5c} For instance, a resin-bound alkenylbromide reacted with alkenylboronates under Suzuki–Miyaura conditions to give a series of dienes as intermediates for the synthesis of vitamin D₃ derivatives.²³

Recently, Steel et al.²⁴ have described the adaptation to solid-phase supports of an interesting variant of the Suzuki–Miyaura reaction that involves a Pd-catalyzed coupling between vinyl phosphates and aryl or heteroaryl boronic acid.²⁵ The authors took advantage of this procedure for the development of a polymer-bound phosphonate which acts as a simple catch-and-release linker in the synthesis of 2-arylenamides. Immobilized enol phosphonate (**40**) was prepared from phenol resin (**38**), lithiated *N*-Boc caprolactam (**39**), and phenylphosphonic dichloride (PhP(O)Cl₂) (Scheme 10). Treatment

Scheme 10



of **40** under Suzuki–Miyaura conditions led to a concomitant cleavage and derivatization to give a small library of enamides (**41**) in moderate to good overall yields.

Sonogashira Reaction

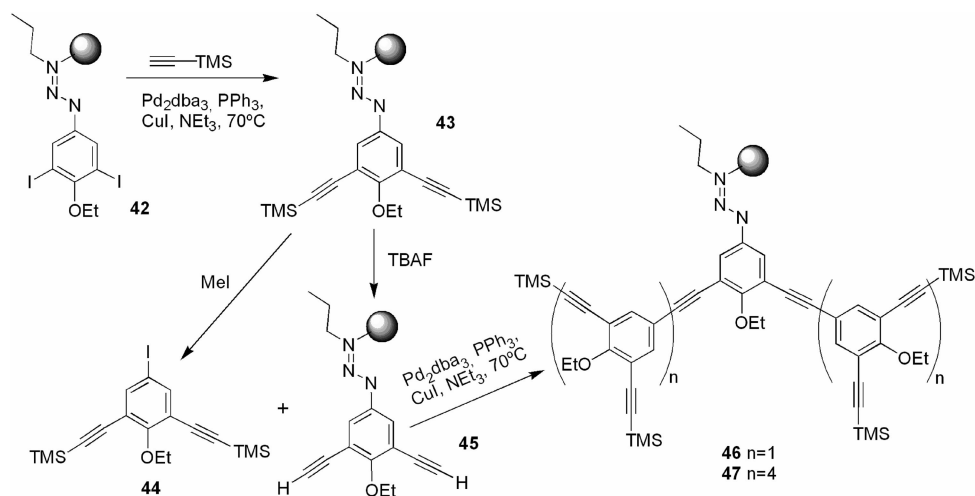
The Sonogashira coupling is a very reliable reaction that has been extensively applied to solid-phase synthesis. In this palladium-catalyzed reaction, aryl or vinyl halides or triflates couple to unactivated terminal alkynes in the presence of a Cu(I) cocatalyst, usually delivered in the form of CuI. Very mild conditions and tolerance to many other functional groups are among the advantages of this procedure. Moreover, the triple bond can be converted into various new functionalities, making this reaction very useful for combinatorial library generation. In particular, Sonogashira reaction on solid support has an extra advantage: the facile removal of the homodiyne side products.

Solid-phase variants of Sonogashira coupling have been successful in the case of aryl iodides and bromides, and also for vinyl triflates²⁶ but failed when propynoate esters were used as alkyne substrate.²⁷

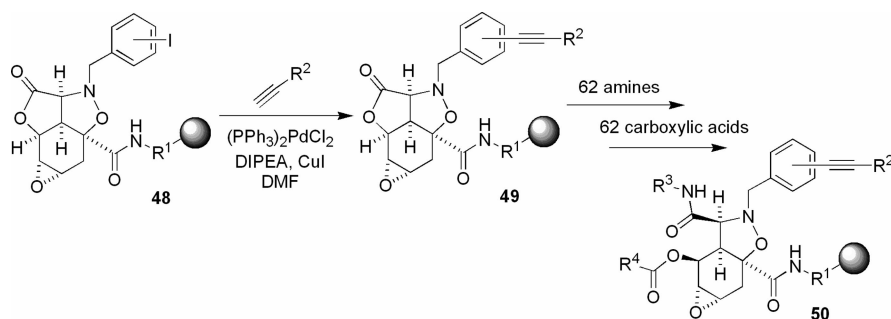
Probably, the most interesting application of the Sonogashira reaction is the preparation of acetylene oligomers and polymers. For example, using a triazene-linked 3,5-diodo-4-ethoxyaniline (**42**) as the starting material, phenylacetylene monodendrons were obtained by an iterative divergent/convergent synthetic strategy (Scheme 11).²⁸ Sonogashira coupling between resin **42** and trimethylacetylene in the presence of Pd₂(dba)₃ and CuI gave the resin-bound diacetylene **43**, which was then separated in two portions. One portion was treated with iodomethane to afford the nonimmobilized iodoarene **44**, and the other with TBAF to remove the trimethylsilyl group giving the intermediate **45**. Then, a new Sonogashira coupling between **44** and **45** afforded the polymer-supported monodendron **46**. This three-step sequence was repeated once to give a fourth generation polymer-supported monodendron **47**, which can be followed by detachment from the triazene linker with MeI to give the corresponding soluble phenylacetylene monodendron. Apart from synthesis and purification simplicity, this approach allows extra functionalization at both the core and periphery of the dendron employing the same Sonogashira reaction.

Exploring the diversity-oriented synthesis (DOS) principle, Schreiber et al. have employed the Sonogashira reaction for “decoration” of rigid polycyclic core structures.^{29,30} A group of eighteen different resin-bound tetracyclic structures (**48**)²⁹ reacted with 30 terminal alkynes under Sonogashira standard conditions to give the aryl alkynes

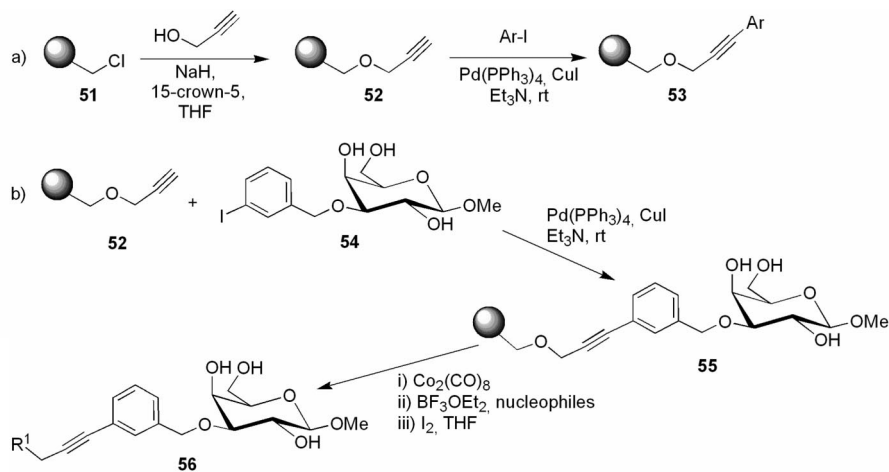
Scheme 11



Scheme 12



Scheme 13



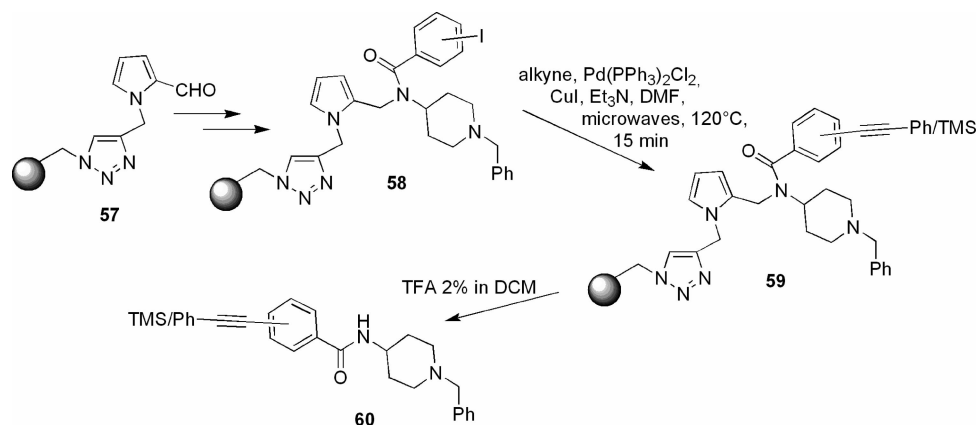
49, as part of a library of more than 2 million different compounds (**50**), obtained by a massive functionalization of the initial tetracyclic core (Scheme 12).

Although it is less common, the solid-phase Sonogashira reaction using resin-supported alkynes has also been reflected in literature. Recently, Kann and co-workers reported the use of Sonogashira coupling for the development of an interesting alkyne linkage. Polymer-bound alkyne **52** was prepared from Merrifield resin (**51**) by treatment with propargylic alcohol under Williamson conditions (Scheme 13a). Immobilized alkyne **52** can react with different aryl iodides to give resin **53**, a substituted aromatic systems linked to the polymer by an alkyne functionality.^{31,32} The Kann group has demonstrated that resin **53** is very suitable for the application of Nicholas reaction which

introduces diversity during cleavage, creating new carbon–carbon or carbon–oxygen bonds. This strategy has been successfully applied to the generation of a library of potential galactin inhibitors (Scheme 13b).³³ In that report, the 4-iodobenzyl galactoside (**54**) was attached to the solid-supported alkyne **52** under Sonogashira conditions to give the immobilized galactose **55**. Treatment of **55** with dicobalt octacarbonyl, boron trifluoride, and different nucleophiles (Nicholas reaction) afforded a library of soluble 3-*O*-alkynylbenzyl galactosides (**56**).

Gmeiner and co-workers have very recently described the use of microwave-assisted Sonogashira coupling in solid-supported synthesis.³⁴ This work was based on the “click resins”, a development from the same authors that takes advantages of the efficient 1,2,3-triazole formation reaction

Scheme 14



for attaching linkers to the solid support.³⁵ For example, using the FPMT (formyl pyrrolyl methyl triazole) linker (**57**), a parallel synthesis of dopaminergic phenylacetylenes (**60**) was developed by a four-step SPOS approach (Scheme 14).

Cadiot–Chodkiewicz Reaction

There are just a couple of examples of the solid-phase Cadiot–Chodkiewicz cross-coupling reaction. This reaction, known since middle of the 1950s,³⁶ deals with the coupling of a terminal alkyne with a 1-haloalkyne in the presence of a Cu(I) catalyst, to give unsymmetrical bisacetylenes. Because symmetrical coupling is a common byproduct, solid-supported synthesis offers a potential advantage over its homogeneous-phase counterpart. The use of an immobilized haloalkyne negates homocoupling.

In an earlier report, Kurth and co-workers³⁷ described the reaction of immobilized 1-chloro and 1-bromoalkynes with 1-octyne using CuCl as catalyst under standard Cadiot–Chodkiewicz conditions (hydroxylamine hydrochloride in 95% ethanol and *n*-propylamine). After separation from the resin, diynes were obtained with yields ranged from 34% to 84%.

A recent attempt to apply a Pd-catalyzed version of the solid-supported Cadiot–Chodkiewicz reaction to the synthesis of poly(triacetylene) oligomers was rather unsuccessful, giving low yield of the coupled compound in an inseparable mixture with other byproducts.³⁸

Negishi Reaction

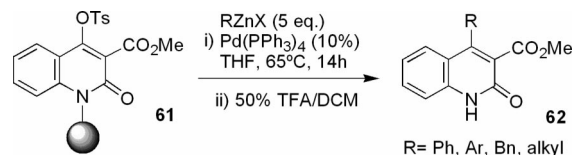
The Negishi coupling³⁹ was one of the first efficient Ni- or Pd-catalyzed cross-coupling reactions. As many others, this reaction has also been translated to solid-phase synthesis. This coupling of organozinc compounds with aryl and heteroaryl halides is a useful method for the synthesis of biaryls and related structures. Organozinc halides are usually derived from the corresponding Grignard reagents or aryl-lithium compounds, which is a disadvantage compared to other cross-coupling reactions that use more readily available substrates. The related Kumada coupling⁴⁰ has the advantage of being a direct coupling of organomagnesium compounds with aryl halides, avoiding the additional synthetic step of converting Grignard reagents to the zincates. However, the scope of the Kumada reaction is restricted to aryl halides that do not react with the organomagnesium counterpart, and

no reports dealing with the solid-phase version of this coupling have been published so far.

In solid-phase chemistry, immobilized bromides, iodides and triflates have been reported to couple with aryl, heteroaryl, and even alkylzinc halides.^{5c} A coupling of an in situ-generated arylzincate linked to a resin with aryl halides has also been described.⁴¹

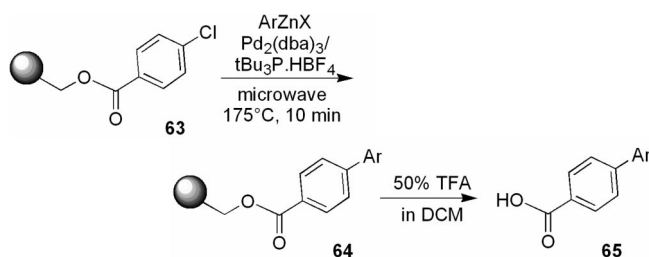
Recently, Xu and co-workers reported the application of Negishi coupling for the solid-phase synthesis of 4-substituted quinolinones (**62**) (Scheme 15).⁴² When a polymer-bound 4-tosyl quinolinone (**61**) was treated with different alkyl, aryl, and benzylzinc halides under Negishi conditions, very high yields of the coupled products (**62**) were obtained after detaching from the resin (63–90% isolated yields). Interestingly, in this work, Negishi reaction was better than Suzuki–Miyaura coupling because the highly reactive organozinc reagent allowed transmetalation and reductive elimination to compete favorably with hydrolysis, avoiding the formation of this undesired byproduct.

Scheme 15



The combination of microwave irradiation and Pd-catalyzed organozinc cross-coupling was recently applied to solid-supported chemistry by Kappe et al.⁴³ A resin-bound aryl chloride (**63**) reacted with arylzinc halides to give complete conversion in 10 min using 5 mol % of Pd₂(dba)₃/t-Bu₃P.HBF₄ as catalyst (Scheme 16). After cleavage from the support, the corresponding biaryl carboxylic acids (**65**) were obtained in high yield (87–90%).

Scheme 16

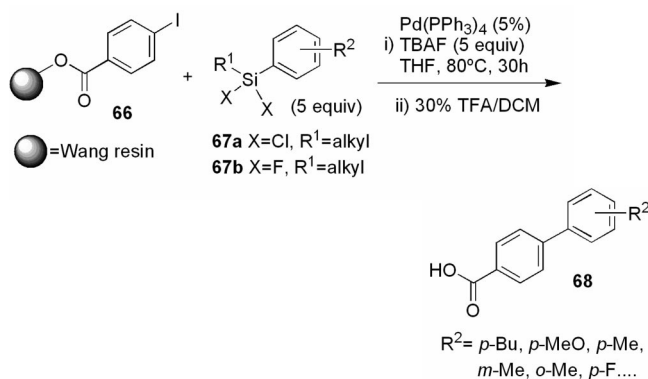


Hiyama Reaction

An interesting palladium-catalyzed C–C bond forming reaction is the Hiyama coupling.⁴⁴ Hiyama reaction is potentially one of the most attractive methods for obtaining biaryl compounds and involves the coupling of aryl, alkenyl, or alkyl halides or triflates with arylhalosilanes, which in turn, must be activated by a fluoride ion (TASF or TBAF) or a base. In general, organosilicon compounds are available at low cost or quite easily prepared; they are also nontoxic and compatible with other functionalities. Probably the reason for the limited success of this coupling, especially when compared with the Stille and Suzuki reactions, is that the organosilanes are rather unreactive nucleophiles. In the future, the prospect of this reaction will depend on the advances in the development of new and more efficient methods for organosilicon activation during the cross-coupling process.⁴⁵

Only two closely related articles dealing with the solid-phase version of Hiyama coupling have been published.^{46,47} In these reports, Hiyama and co-workers established the ideal conditions for the synthesis of a series of unsymmetrical biaryl compounds. A Wang resin-supported aryl iodide (**66**) reacted with arylhalosilanes (**67a** and **b**) in the presence of catalytic Pd(PPh₃)₄ and TBAF to give, after detaching from support, the desired products (**68**) in high yields in most of the cases (Scheme 17). As was corroborated in homogeneous-phase synthesis, aryl(dichloro)- (**67a**) and aryl(difluoro)silanes (**67b**) were the best organosilicon substrates in order to increase activation of the silane.

Scheme 17

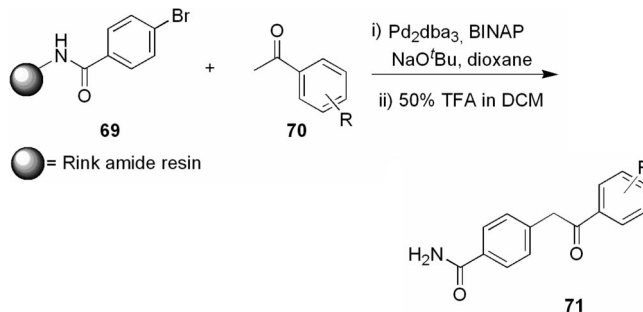


Buchwald–Hartwig Reaction

The α -arylation of ketones is a variant of the cross-coupling Buchwald–Hartwig reaction that is one of the few options of forming a C–C bond between an arene and a carbon α to a carbonyl group.⁴⁸ In this reaction, aryl halides react with enolates under palladium catalysis that is more efficient using bidentate phosphine ligands. Very recently, this cross-coupling reaction has been translated to solid-phase synthesis.⁴⁹ Under optimized conditions, α -arylated ketones (**71**) were obtained in moderate to high yields when an immobilized 4-bromobenzamide (**69**) reacted with excess of methyl ketones (**70**) in the presence of 20% mol of Pd₂dba₃, 80% mol of 2,2'-bis-(diphenylphosphino)-1,1'-binaphthyl (BINAP) as catalyst, and large excess of sodium *tert*-butyrate as base (Scheme 18). Only methyl ketones effectively

underwent the coupling, while aliphatic methyl ketones were fairly better than aromatic methyl ketones. On the other hand, heteroaromatic methyl ketones were more sensitive to by-reactions, such as bis-arylation, fragmentation, and heteroaromatic ring opening.

Scheme 18

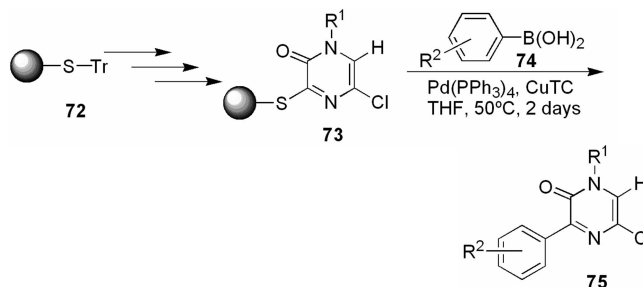


Liebeskind–Srogl Reaction

A very useful reaction is the Liebeskind–Srogl coupling, in which boronic acids couple to thiol esters or heteroaromatic thioethers under neutral conditions.^{50,51} Interestingly, this Pd(0)-catalyzed reaction uses stoichiometric amounts of copper(I) thiophenecarboxylate (CuTC) as a mediator.

So far, only one example of the solid-phase version of the Liebeskind–Srogl cross coupling has been reported. As expected, it was on the chemistry of the heteroaromatic compounds, specifically during the synthesis of highly substituted 2(1*H*)-pyrazinones (Scheme 19).⁵² By immobilization through a sulfur linker, Liebeskind–Srogl coupling allowed resin cleavage and concomitant derivatization at position C-3. Polymer-bound pyrazinone **73** was treated with excess of *m*- and *p*-substituted phenyl boronic acids (**74**) in the presence of Pd(PPh₃)₄ (6% mol) and CuTC (3 equiv) to give the soluble pyrazinones **75** in acceptable overall yields based on the starting thiol resin **72**. In this approach, Pd(PPh₃)₄ was better catalyst than Pd₂dba₃.

Scheme 19



Cross Metathesis Reaction

Cross metathesis is basically an intermolecular exchange of alkylidene fragments between two alkenes or one alkene and one alkyne, catalyzed by metal carbene complexes. With the emergence of commercially available and easily handled ruthenium precatalysts, this reaction has become one of the most powerful synthetic tools in modern organic and polymer synthesis.⁵³

While there is a considerable number of examples of metathesis reactions where a substrate has been immobilized to a solid phase, most of them refer to the ring-closing version of the coupling.⁵⁴ Surprisingly, few examples of solid-phase cross metathesis are in the literature, despite some fundamental advantages compared to its homogeneous-phase counterpart. Probably the major drawback of solution-phase cross metathesis is the difficulty of avoiding the formation of unwanted homodimeric products.⁵⁵ In contrast with one of the olefin substrates attached to a polymer, the olefin that remains in solution can be added in excess to drive the reaction to completion (its homodimer can be eliminated easily by simple filtration, avoiding time-consuming separation techniques). On the other hand, under certain conditions, homodimerization of the immobilized olefin is a less favorable process because of the site isolation on the polymeric matrix. Also problematic in homogeneous metathesis is the generation of ruthenium-contaminated products.⁵⁶ Under optimized conditions (see below), this disadvantage is negligible in the solid-supported version.

The ruthenium vinylalkylidene precatalyst **76**, known as first generation Grubbs precatalyst (Figure 1),⁵⁷ was scarcely used and with limited success in the initial reports on olefin cross metathesis,⁵⁸ as well as enyne cross metathesis⁵⁹ on solid support.

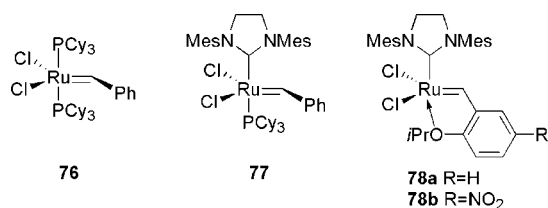
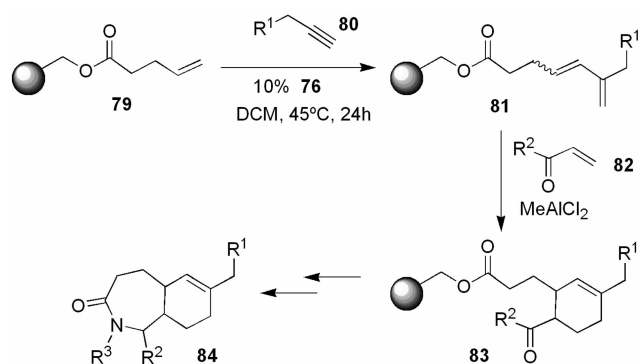


Figure 1

Among the most noteworthy of those reactions is the enyne metathesis in the presence of precatalyst **76** to give the 1,3-diene **81** that is amenable of further elaboration, such as a Diels–Alder cycloaddition to yield the cyclohexene **83** (Scheme 20).^{59c} Strategies with both immobilization of the alkyne and the olefin were equally efficient, giving products in about 20% overall yield.

Scheme 20

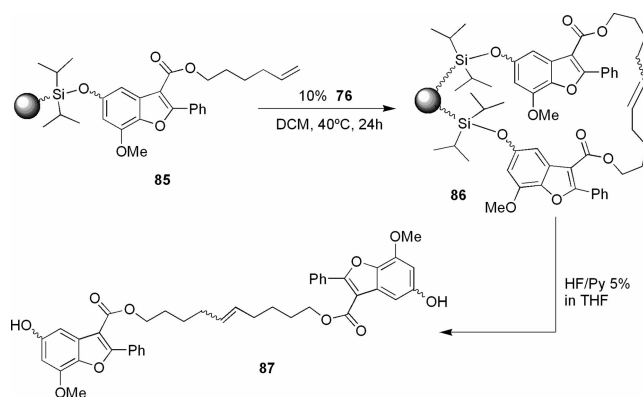


Clearly, the development of a new generation of precatalysts, such as second-generation Grubbs precatalyst (**77**)⁶⁰ and Hoveyda–Grubbs precatalyst (**78a**)⁶¹ (Figure 1) improves the chances of an efficient application of cross metathesis on solid support. The mild reaction conditions,

impressive functional group tolerance, high activity, and stability are the most outstanding features of these modern metathesis precatalysts.

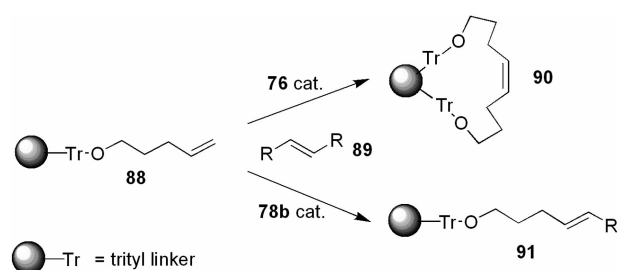
Probably the lack of success of first generation Grubbs precatalyst in solid-phase cross metathesis was the competition of the “intrasite” reaction, which is the reaction of two immobilized molecules linked to the same resin bead. Actually, some examples of the use of metathesis conditions for the synthesis of dimeric compounds have been reported.⁶² For instance, the synthesis of symmetrical benzo[*b*]furane derivatives (**87**) was carried out when the silyl-linker-based polystyrene resin **85** was treated with precatalyst **76** in dichloromethane at 40 °C for 24 h (Scheme 21). As a result, the neighbor olefin chains react each other to give dimer **86** that was finally detached from the resin to yield the symmetrical product **87**.^{62c}

Scheme 21



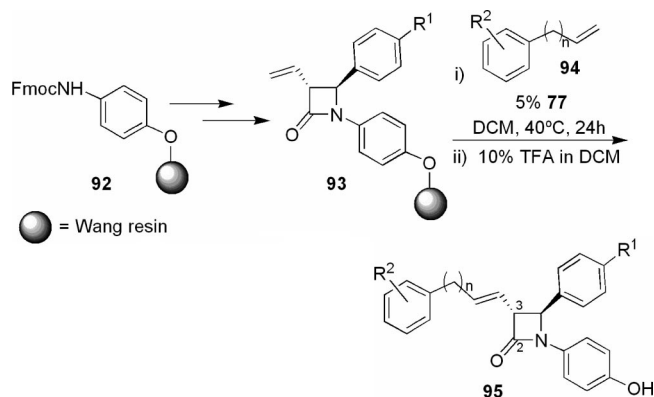
If the chains are close enough, the “intrasite” or “site–site” reaction is favored compared to the cross coupling between an immobilized alkene and a soluble one. Then, with a fairly active precatalyst like **76**, the “intrasite” reaction is expected to prevail and even to compete with the ring closing metathesis when using diene compounds as substrates.⁶³ With the introduction of more reactive second generation precatalysts, such as **77** or **78**, the reaction of an immobilized olefin or an immobilized dimer (in case of forming) with a nonimmobilized olefin is now a more favorable process and so is the formation of the heterodimer product. This assumption was corroborated by two independent results for the cross metathesis of tritylpolystyrene-bound 4-pentenol (**88**) and an alkene in the presence of precatalysts **76** and **78b**,⁶⁴ respectively (Scheme 22). In the first case, Blechert et al.^{58a} reported the resin-bound homodimer **90** as the only product, while the modern precatalyst **78b** led to good yields of the heterocoupling product **91**, as it has been recently reported.⁶⁵

Scheme 22



As a consequence of this evolution in ruthenium precatalysts, a renaissance of the solid-phase cross metathesis has just began. The undeniable attraction of this reaction led us to consider its application to the solid-phase synthesis of 3-(aryl)alkenyl- β -lactams (**95**), as cholesterol absorption inhibitor analogues (Scheme 23).⁶⁶ The olefin cross metathesis step was carried out in high yields, and the whole synthetic sequence gave good overall isolated yields of the desired β -lactams **95** with excellent 3,4-trans-selectivity and complete E selectivity at the C-3 side chain. It is also noteworthy that the use of low precatalyst loading (5 mol %) was enough to produce high conversion, avoiding the formation ruthenium metal byproducts. This work was the first example of an optimized solid-supported cross metathesis for the development of complex biologically interesting molecules.

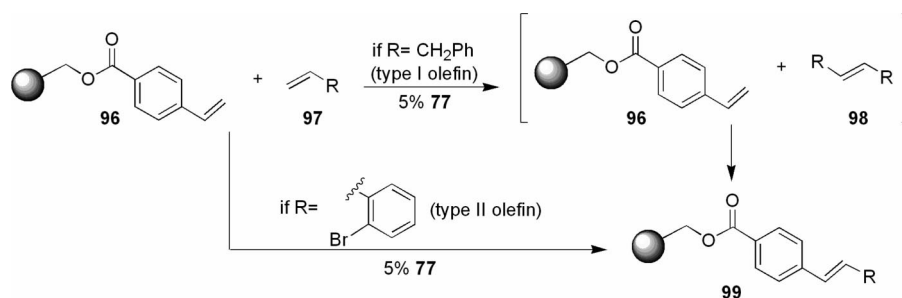
Scheme 23



Another important issue in cross metathesis on solid support is the role of the homodimerization of the nonimmobilized olefin during the reaction.⁶⁷ We found that since the nonimmobilized olefin is usually added in excess, the reaction output will depend on its trend to homodimerize and the reactivity of such homodimer. Very high yields were obtained when a type-I,⁵⁵ easily homodimerizable olefin was used, as long as that homodimer was also very reactive. Type-II olefins usually gave high yields since homodimerization was slow. Type-I olefins which undergo fast homodimerization to generate an unreactive dimer, generally afforded low cross metathesis yields (Scheme 24).

Hoveyda–Grubbs (**78a**) (Figure 1) is also a very interesting precatalyst, but there are just a few reports of its use in solid-phase chemistry. The general trend is that this precatalyst improves the reaction conversion, particularly, in the case of α,β -unsaturated carbonyl compounds.^{66–68} The use of microwave irradiation will be another tool for optimizing

Scheme 24



cross metathesis in solid phase; preliminary results show an increase in yields and a reduction in the reaction time comparing with conventional heating.⁶⁹

In summary, cross metathesis is just emerging as a versatile methodology for the solid-phase synthesis of biologically promising compounds. The reason for the delay in its development can be found in some not very stimulating initial results using the first generation Grubbs precatalyst. As it has been demonstrated by others and us, optimization of this reaction was not trivial and many variables have to be taken into account. However, once optimization is achieved, the comparative advantages of solid-phase cross metathesis are evident, and this procedure is now on its way to become a fundamental tool for creating C–C bonds.

Conclusions

The scope and generality of metal-catalyzed C–C-forming cross-coupling reactions in solid phase and their synthetic applications have grown substantially in the past decade. Pd-catalyzed cross-coupling reactions, such as the Suzuki–Miyaura and Sonogashira couplings, are at the front line of such development, being the most successful reactions of the area. The advantages of employing the Suzuki–Miyaura coupling have been recognized from the beginning: mild reaction conditions, tolerance to many other functional groups, and the use of boronic acids as a nontoxic, stable, and ready available substrate. In the case of Sonogashira coupling, apart from the advantages of very mild reaction conditions, functional group tolerance, and versatility of the triple bond for further synthetic transformations, the solid-phase version contributes with the extra “bonus” of facile removal of the homodiyne byproduct.

More recently developed reactions such as the Buchwald–Hartwig α -arylation and the Liebeskind–Srogl coupling demonstrates potential; just a few examples of their application to solid-supported chemistry have been reported. On the other hand, the Hiyama coupling is a very promising reaction which depends on the advances that can be achieved in terms of new and more efficient methods for organosilicon activation.

Because of the recent improvements, solid-phase cross metathesis represents a very interesting alternative to more traditional carbon–carbon bond-forming reactions. In addition to the mild reaction conditions, functional group tolerance, high activity and stability of modern metathesis precatalysts, cross metathesis requires little synthetic labor in the preparation of starting material compared to stannanes, halides and boronates, necessities for Stille, Heck, and Suzuki reactions. Olefins are readily available materials,

especially, because the alkene group is one of the most abundant functional groups in natural products. Furthermore, cross metathesis is useful in stepwise syntheses because it allows the use of functionalized olefin substrates and that functional groups can take part in subsequent reactions avoiding the employment of protecting groups. Last but not least, the natural occurrence of the alkene functional group makes this reaction attractive for the generation of solid-phase libraries of natural product derivatives.

In conclusion, although many challenges have been overcome, the research in metal-catalyzed chemistry will continue in the future, giving rise to new reactions and novel, more efficient catalysts.⁷⁰ Therefore, new and very interesting chemistries will be amenable for translating to solid phase, which will certainly improve the existing methodologies. Innovative technologies such as microwave and nanoparticles will also contribute to such improvement. Definitely, very stimulating developments can be anticipated in the area of metal catalyzed C–C forming cross reactions in solid phase and their application to the generation of libraries of complex pharmaceutically important molecules.

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