PART I

INTRODUCTION

CHAPTER 1

AN INTRODUCTION TO SOLID-PHASE PALLADIUM CHEMISTRY

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1 INTRODUCTION

Palladium chemistry has a central position in organic chemistry because of its ability to selectively form carbon–carbon and carbon–heteroatom bonds between organic fragments [1].

Palladium-catalyzed reactions represent one of the most powerful and versatile tools in organic synthesis for the preparation of fine chemicals, pharmaceutical intermediates, active pharmaceutical ingredients, and also bioactive drugs [2].

In recent years, the synthesis of combinatorial libraries has emerged as a valuable tool in the search for novel lead structures. The success of combinatorial chemistry in drug discovery is dependent, in part, on further advances in solid-phase organic synthesis (SPOS). The generation of molecular diversity to create libraries for drug discovery was originally focused on the synthesis of peptide and nucleotide libraries. However, the limitation of such libraries is the pharmacokinetic properties of large polymeric and often hydrophilic structures that make these molecules less suitable as leads in drug discovery [3]. It is therefore desirable to develop methods to prepare small, nonpolymeric molecules with sufficient diversity [4]. The rapid generation of such small-molecule libraries can be executed effectively by employing combinatorial or simultaneous parallel synthesis on solid supports [5–7]. Considerable work has been carried out to optimize many of the useful reactions from the organic chemists' arsenal for solid-phase conditions and to design versatile linkers [8, 9]. In this respect,

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palladium chemistry is a powerful synthetic methodology for the preparation of libraries of small organic compounds by multiparallel synthesis schemes on solid supports [10]. In particular, the development of reliable procedures with a wide scope for the formation of carbon–carbon bonds is of great importance together with the new solid-supported reagents, ligands, and catalysts [11, 12].

Some of the commonly employed palladium-catalyzed organic couplings that lead to the formation of carbon–carbon or carbon–heteroatom bonds have been named by prominent researchers in this field, such as Stille, Heck, Suzuki, Sonogashira, Kumada, Negishi, Nozaki–Hiyama, Buchwald–Hartwig, and Tsuji–Trost [13]. These reactions are usually very efficient, although the main drawback is that palladium is often retained by the isolated product. This is, however, a serious drawback because pharmaceutical ingredients official guidelines place exacting limits on the permissible levels of heavy-metal contaminants. In this sense, the use of resin-bound catalyst systems is particularly beneficial in reducing metallic contamination of the final products [14].

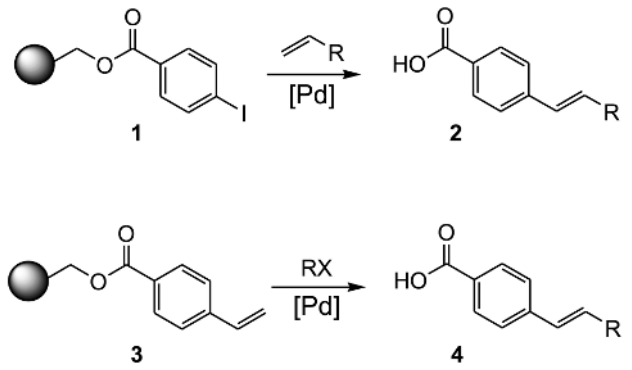
Numerous research groups have developed new metal complexes and ligands, expanding the scope of these transformations to give access to more complex molecules [15, 16]. The development of solid-phase palladium chemistry is also another approach to access such molecules, offering straightforward syntheses, without tedious and time-consuming purifications.

2 PALLADIUM-CATALYZED REACTIONS

Palladium-catalyzed coupling reactions are very efficient for the introduction of new carbon–carbon bonds onto molecules attached to solid supports. The mild reaction conditions, the compatibility with a broad range of functionalities, and high reaction yields have made this kind of transformation a very common tool for the combinatorial synthesis of small organic molecules.

2.1 Heck Reactions

This reaction has become one of the most powerful tools to bring up complex structural changes, in particular when conducted intramolecularly. Owing to the mild conditions employed and the toleration of many functional groups, the Heck reaction has been successfully adapted in a broad scope to organic synthesis in the solid phase [11, 17]. This reaction between



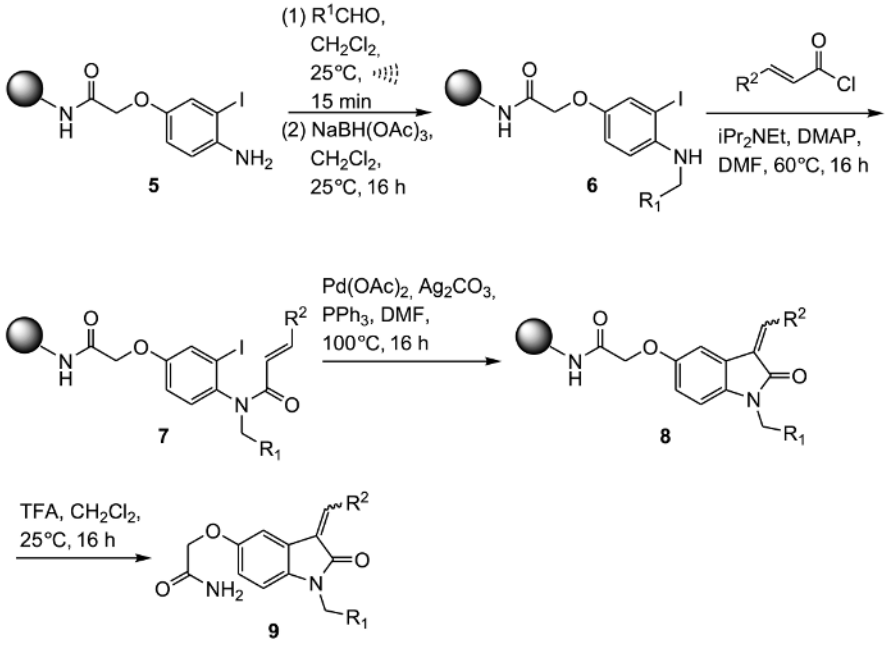
SCHEME 1 Heck reactions in solid-phase synthesis [18].

terminal olefins and alkyl/aryl halides has been widely employed in various intra- and intermolecular versions in solid phase, taking advantage of the ready accessibility of starting materials. The Heck reaction involves immobilized aryl or alkenyl halides with soluble alkenes as well as vice versa (Scheme 1) [18, 19].

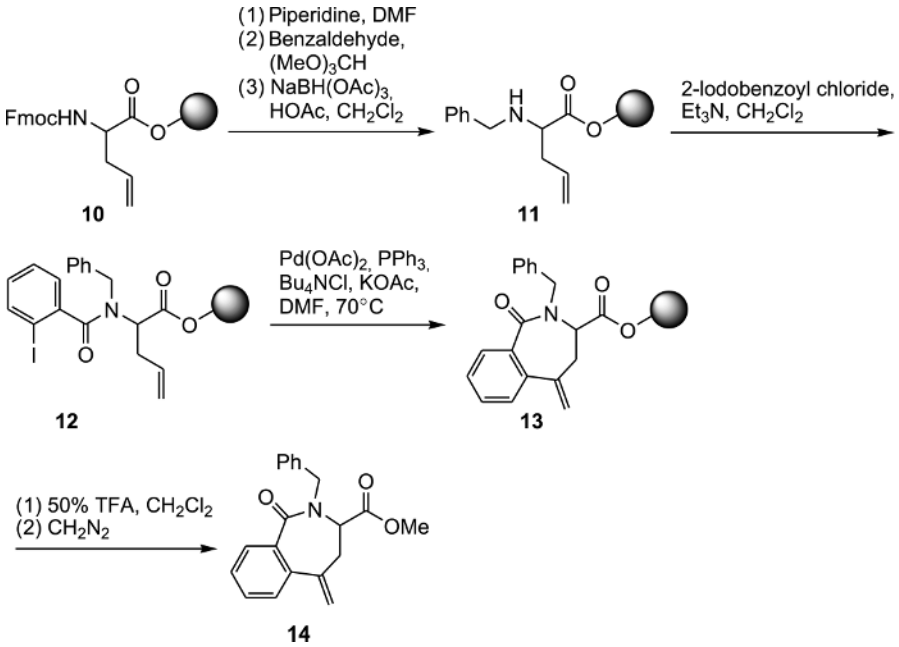
One of the most interesting applications of this cross coupling on solid phase has been the application in the preparation of medicinally relevant heterocycles [20]. For example, the synthesis of 2-oxindole derivatives on solid support was published by Arumugam et al. [21]. As shown in Scheme 2, the synthesis starts with reductive alkylation of the corresponding immobilized aniline **5**. After construction of the tertiary amide **7**, an intramolecular Heck reaction affords the oxindoles **9** as a mixture of (*E*)- and (*Z*)-isomers.

Bolton and Hodges [22] described the synthesis of benzazepines via intramolecular Heck cyclization as shown in Scheme 3. Deprotection of immobilized allylglycine ester **10**, followed by reductive amination with benzaldehyde cleanly produces the secondary amine **11**. Subsequent acylation with 2-iodobenzoyl chloride provides **12**, which undergoes efficient Heck cyclization to bicyclic lactam **13**. Acidic cleavage and esterification of this compound afforded **14** as a bicyclic aminoacid scaffold, which can be efficiently functionalized at various sites.

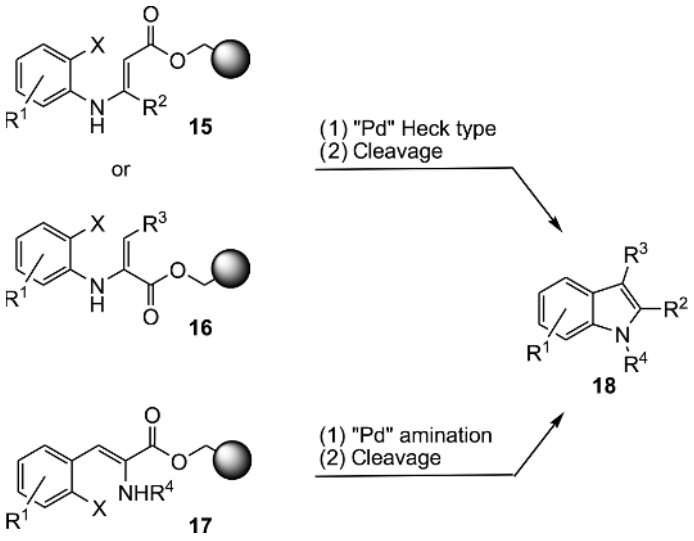
Cyclization of immobilized enaminoesters to indolecarboxylates was described by Yamazaki et al. via palladium-catalyzed reactions (Scheme 4) [23]. They described successfully the intramolecular palladium-catalyzed cyclization of the α- or β-(2-halophenyl)amino-substituted α,β-unsaturated esters employing in the solid-phase synthesis of indole 2- and 3-carboxylates with various functional groups on the benzene ring.



SCHEME 2 Synthesis of 2-oxindole **9** derivatives by Arumugam et al. [21].



SCHEME 3 Synthesis of benzazepines **14** via intramolecular Heck cyclization by Bolton and Hodges [22].

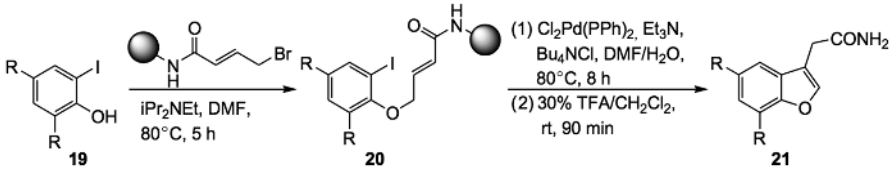


SCHEME 4 Palladium-assisted indole synthesis by Yamazaki et al. [23].

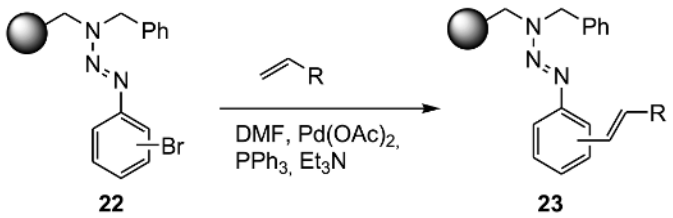
Zhang and Maryanoff reported the construction of benzofurans on a solid phase via palladium-mediated cyclizations [24], when different *ortho*-iodo phenols **19** were immobilized on functionalized Rink amide resin, followed by an intramolecular Heck-type reaction and cleavage with trifluoroacetic acid (TFA) to yield the benzofurans **21** in excellent purities and yields (Scheme 5).

A key step in SPOS is the development of a new kind of versatile linkers, which expand the possibilities of synthetic transformations. In this sense, Bräse et al. developed a traceless linker system of the triazene type to immobilize aryl halides **22**, with application to the Heck reaction with different olefins (Scheme 6) [25, 26].

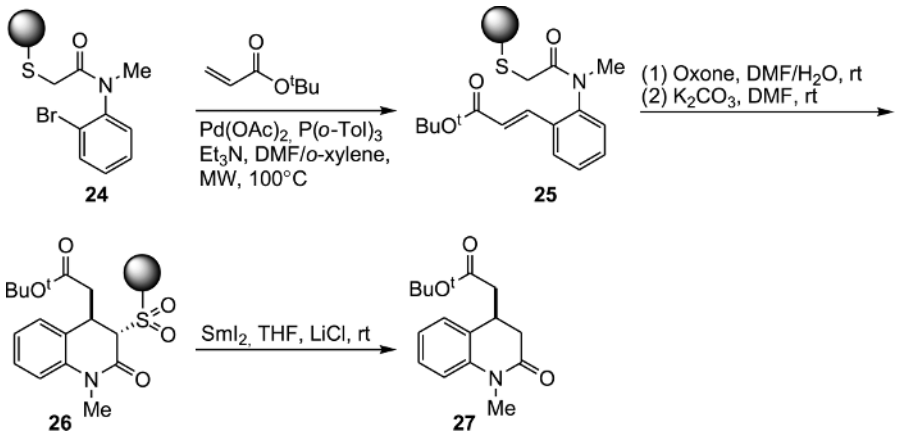
Another solid-phase approach to *N*-heterocycles was described by using a sulfur linker cleaved in a traceless fashion by reduction with samarium(II) iodide. The route to tetrahydroquinolones **26** involves a microwave-assisted



SCHEME 5 Solid-supported benzofuran synthesis by Zhang and Maryanoff [24].



SCHEME 6 Heck reaction on T1 triazene resins **22** [26].

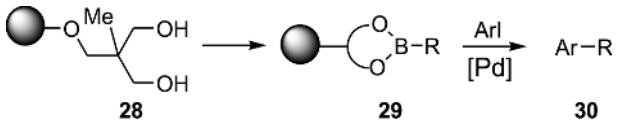


SCHEME 7 Solid-phase approach to tetrahydroquinolones **27** by using a sulfur linker [27].

Heck reaction followed by a Michael cyclization (Scheme 7) [27]. This route shows the compatibility of the linker system with a number of important reaction types and its utility for library synthesis.

2.2 Suzuki Reactions

The palladium-catalyzed coupling of boronic acids with aryl and alkenyl halides, known as Suzuki reaction, is one of the most efficient carbon–carbon cross-coupling processes used in reactions on polymeric support. The mild reaction conditions have made this reaction a powerful and widely used tool in organic synthesis. These coupling reactions require only gentle heating to 60–80°C, and the boronic acids employed are nontoxic and stable toward air and water. When the Suzuki reaction is transferred to a solid support, the boronic acid can be immobilized or used as a liquid reactant (Scheme 8) [28].

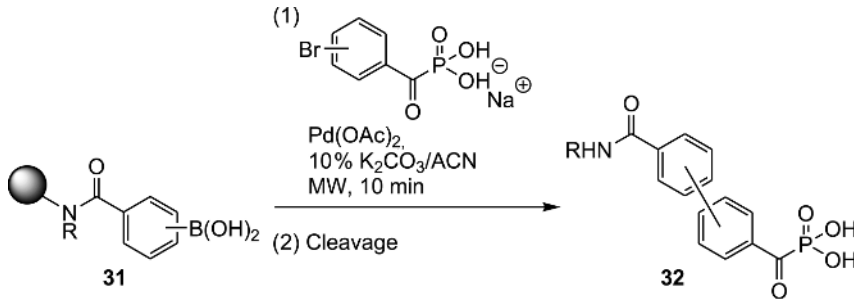


SCHEME 8 Solid-supported boronic acids as reagents for Suzuki couplings [29].

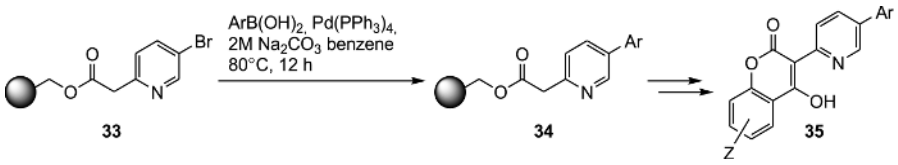
Solid-phase Suzuki reaction was first utilized in biaryls synthesis [30]. Since then, several examples for the synthesis of biologically active biaryl compounds have been described. Functionalized biaryl α-ketophosphonic acids **32** were obtained via microwave-assisted aqueous Suzuki coupling by using polymer-bound boronic acids **31** (Scheme 9) [31]. In addition, a 199-biphenyl member library containing three attachment points was synthesized by means of a catechol-based safety-catch linker strategy and a palladium-catalyzed Suzuki cross-coupling reaction employing polymer-bound bromo derivative [32].

In the past years, this methodology has been extended to the coupling of alkyl, allylic, 1-alkenyl, and 1-alkynyl halides with 1-alkenyl and even alkyl boron reagents. Mild reaction conditions, compatibility with most functional groups, and ready availability of starting material (boronic acids) have made this transformation a powerful tool also in SPOS. Additional benefits of the Suzuki reaction, relative to other cross-coupling processes, are the general nontoxicity and the thermal, air, and moisture stability of the boronic acids [11].

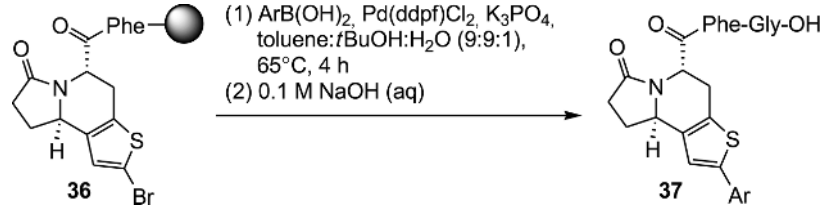
Suzuki coupling reactions in solid phase have been successfully used to derivatize heterocycles or natural products. By using this reaction, the cycloocta[*b*]indole skeleton of the macrolines has been decorated [33] and the pyridine moiety at C3 of a library of 3-(5-arylpyridin)-4-hydroxycoumarins **35** has been substituted (Scheme 10) [34].



SCHEME 9 Microwave Suzuki reactions to form biaryls **32** [31].



SCHEME 10 Synthesis of substituted 3-(5-arylpyridin)-4-hydroxycoumarins **35** [34].



SCHEME 11 Synthesis of aryl-substituted thienoindolizines **37** [35].

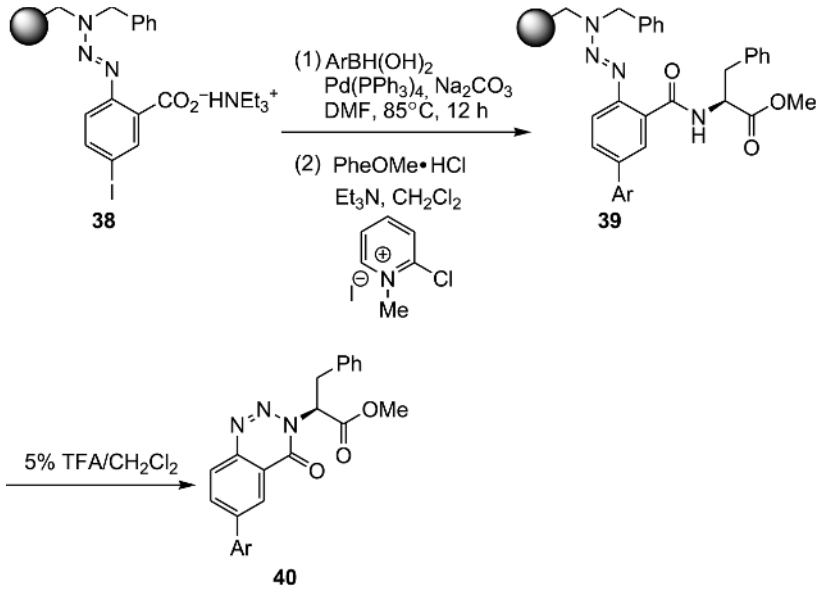
On the other hand, brominated thiophene-containing scaffolds **36** have provided a variety of aryl-substituted thienoindolizines **37** after Suzuki cross coupling with arylboronic acids (Scheme 11) [35].

A 72-member library of distamycin analogs with two points of diversification has been synthesized on SynPhase Lanterns, Suzuki coupling being one of the key steps [36]. Another example is the synthesis of a library of 6-aryl-3*H*-benzo-[*a*][1–3]triazinones **40**, obtained after cyclization of 38 suitable substituted benzamides **38** immobilized as triazenes and derivatized via a Suzuki-type reaction with arylboronic acids (Scheme 12) [37].

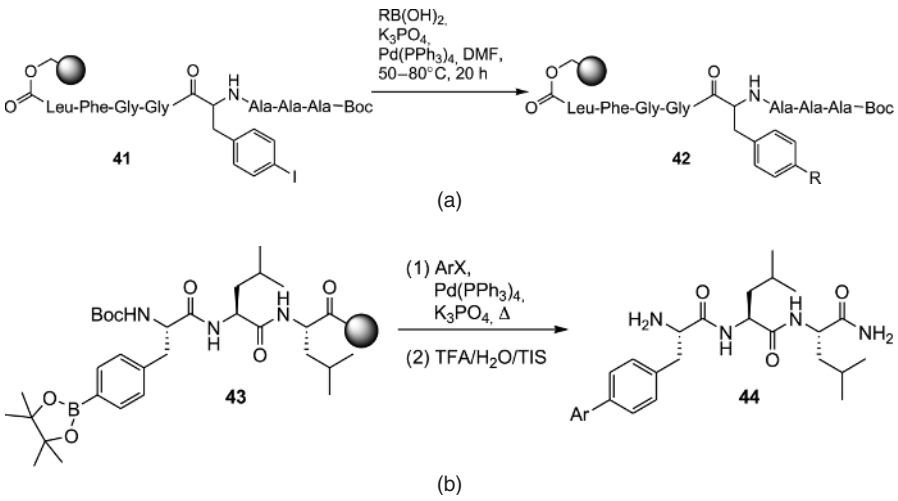
The Suzuki reaction also has shown effectiveness for solid-phase peptide modification in the preparation of large libraries of phenylalanine peptides **42** [38] or 5-arylhistidines derivatives [39]. In both cases, the couplings are based on the reaction between a polymer-bound halogenated aromatic amino acid and an arylboronic acid in solution. An alternative approach involving polymer-bound borylated peptides and aryl or heteroaryl halides has also been described, providing a large variety of 4-arylphenylalanine peptides **44** (Scheme 13) [40].

2.3 Stille Reaction

One of the first cross-coupling reactions performed on solid support was the Stille reaction. This reaction consists of a palladium-catalyzed reaction of a trialkylaryl or trialkylalkenyl stannane with an aromatic iodide,

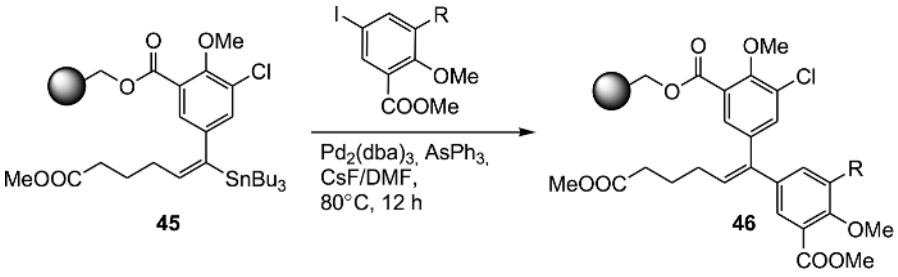


SCHEME 12 Synthesis of 6-aryl-3*H*-benzo-[*a*][1–3]triazinones **40** [37].



SCHEME 13 Solid-phase peptide modification by Suzuki reaction [38, 40].

bromide, or triflate. In contrast to the process in the solution phase, the organotin reagent is easily removed from the solid phase after washing processes. Immobilized aryl halides have been frequently coupled with aryl and alkenylstannanes, whereas stannanes attached to the solid support [41]



SCHEME 14 Synthesis of ADAM by a Stille reaction [43].

have been used less frequently for the Stille reaction [16]. A representative example of the application of the solid-supported Stille reaction is the synthesis of a benzodiazepine library by Plunkett and Ellman [42]. It was also interesting that the Stille cross-coupling reaction could be applied for the synthesis of alkenyldiarylmethane (ADAM) series of non-nucleoside HIV-1 reverse transcriptase inhibitors **46** (Scheme 14) [43].

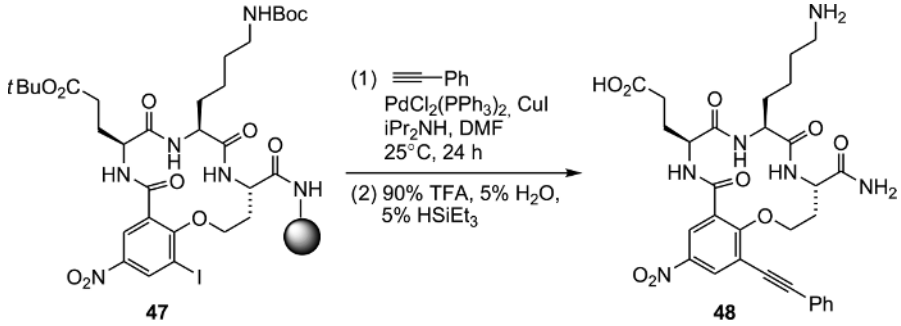
2.4 Sonogashira Reaction

The palladium-catalyzed arylation and alkenylation of terminal alkynes with aryl or alkenyl halides usually in presence of copper(I) salts as cocatalyst is called Sonogashira reaction. This alkynylation reaction is nowadays a key cross-coupling methodology, with growing applications in many different areas of chemistry, as natural product synthesis, and in the preparation of molecular organic materials [44, 45].

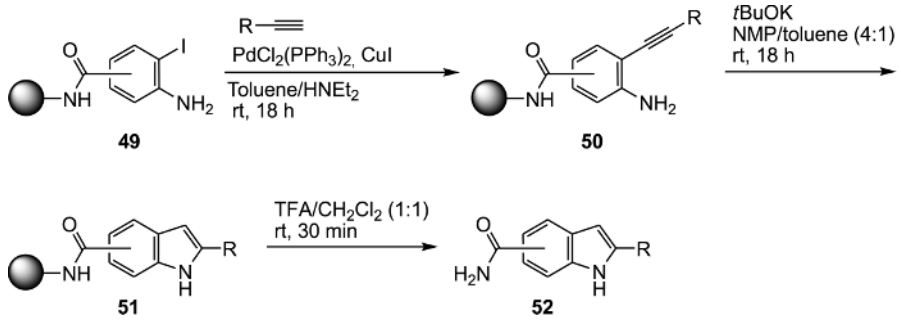
As in the other cross-coupling reactions described before, it is possible to immobilize the alkyne or the aromatic bromides, iodides, or triflates on solid support. Moreover, the triple bond can be converted into various new functionalities, making this reaction very useful for combinatorial library generation (Scheme 15). The main advantage of the Sonogashira reaction on solid support is the facile removal of the homodiyne side products [16].

This reaction and some variants have been successfully used for the preparation of precursors necessary for the synthesis of relevant heterocycles as indoles (Scheme 16) [47] or cinnolines (Scheme 17) [48]. Furthermore, isocoumarins, an important class of naturally occurring lactones, have been obtained in a two-step process involving a Sonogashira cross-coupling reaction between polymer-bound 2-bromobenzoates **56** and terminal alkynes (Scheme 18) [49].

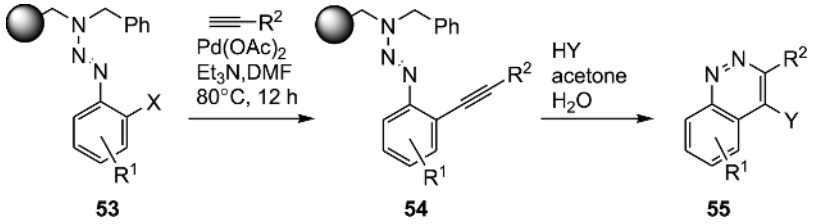
In order to execute large library syntheses, the variation of reaction types and linkers has to be predictable. In this sense, the development of different



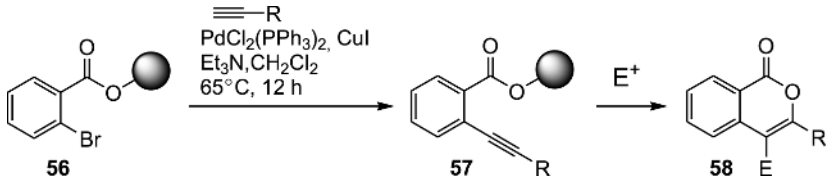
SCHEME 15 Structural diversity in macrocyclic systems via Sonogashira reaction [46].



SCHEME 16 Synthesis of polyfunctional indoles **52** by Koradin et al. [47].



SCHEME 17 Synthetic pathway to cinnolines **55** by Bräse et al. [48].



SCHEME 18 Synthesis of isocoumarins **58** on solid support by Peuchmaur et al. [49].

kinds of linkers and the study of their influence in palladium-catalyzed reactions are valuable tools for achieving molecular diversity [26, 50].

3 POLYMER-SUPPORTED REAGENTS AND CATALYSTS

The concept of immobilizing reagents on a solid support provides many advantages over both conventional solution-phase and solid-phase preparative routes. Moreover, it could be argued that this approach actually combines the best attributes from both these synthetic approaches, which results in a more efficient and powerful methodology [51].

As mentioned before, palladium-catalyzed cross-coupling reactions have benefited with the development of polymer-supported reagents such as boronic acid or stannanes, but supported palladium catalysts are becoming increasingly popular since the heterogeneous palladium can be easily filtered on completion of the reaction. These catalysts are in general air stable and easy to store and handle, making them highly amenable for routine and automated synthesis [52, 53].

When a catalyst is immobilized on a solid support, a number of advantages can be gained, such as easy recovery from reaction mixtures, no metal contamination of reaction solutions, easy handling of minute catalyst amount, and catalyst recycling. In addition, a combinatorial approach to catalyst design and optimization can be applied if catalysts are attached to a solid support.

Different polymer-supported catalysts from Merrifield polymer in two steps **59** [54], from the commercially available thiourea resin Deloxan® THP in one step **60** [55] and from resin-supported phosphine **61** [56] have been used for Suzuki reaction. All of them were shelf stable and reusable (Figure 1).

In this context, polymer-supported *N*-heterocyclic carbene (NHC) has been reported as a precursor for palladium complex **62**. This catalyst was able to decrease the reaction time with high efficiency, mainly because the catalytic sites were located only on the surface of the resin. It was also easily recovered quantitatively and reused many times with constant activity. It was used to catalyze Suzuki [57], Heck [58], and Sonogashira [59] reactions. Different efficient palladium NHC catalysts **63** were also successfully applied in Sonogashira and Suzuki cross-coupling reaction [60]. These catalysts proved to be stable toward TFA treatment when released from the solid support and in aqueous media, thus allowing for the Suzuki cross-coupling reactions to be performed in water. No loss of catalytic activity was observed when the catalyst was recycled and subjected to repetitive cycles of cross-coupling reactions in water. The use of water as solvent is particularly attractive in the context of green chemistry. In fact, during

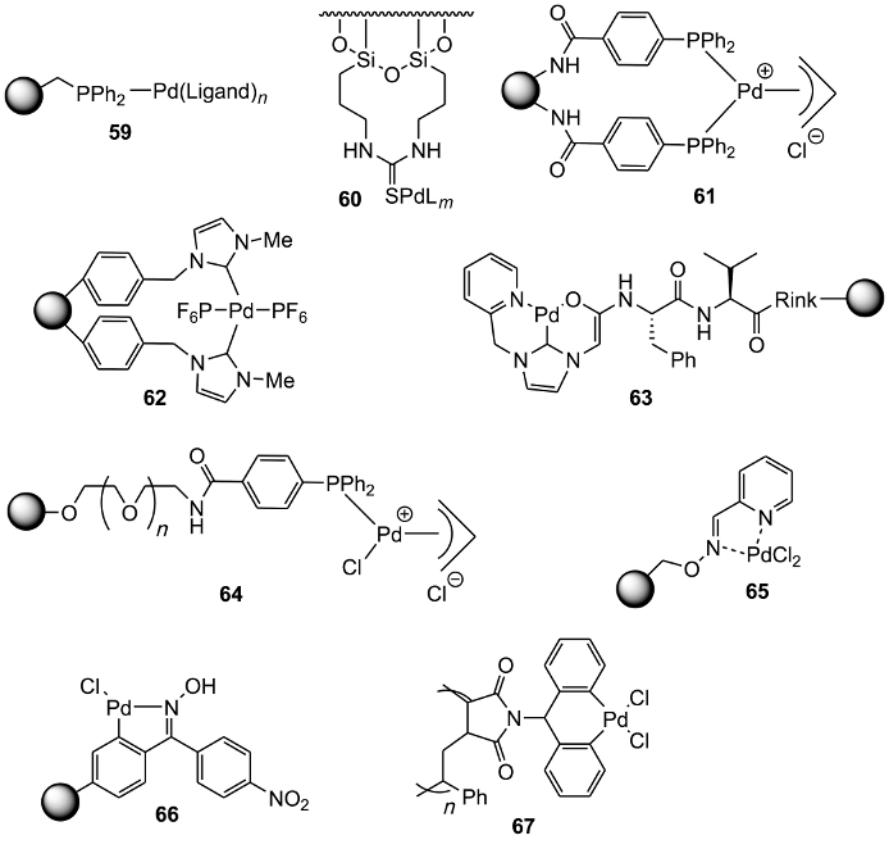
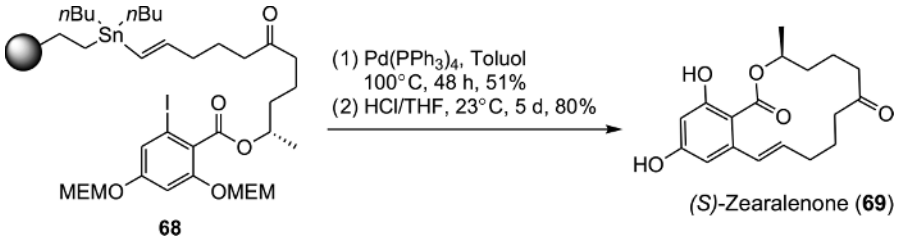


FIGURE 1 Polymer-bound catalysts.

the past years, organic chemists have shown a growing interest for heterogeneous palladium catalyst in water in response to the demand for more environmentally friendly procedures [61]. Since boronic acid has excellent stability in aqueous media, the development of heterogeneous catalyst to carry on Suzuki reaction in water has been highly successful. In addition, several efforts have been made to provide easy-to-handle catalysts of this type for other cross-coupling reactions.

For example, the polymer-supported palladium complexes developed by Uozumi et al. consist of an amphiphilic resin-supported triarylphosphine–palladium complex bound to a polyethylene glycol–polystyrene graft copolymer (PEG–PS resin) (**64**). This catalyst and other related with have been successfully employed for the aqueous heterogeneous catalysts, allowing Suzuki [56], Heck [62], Sonogashira [63], and even Tsuji–Trost reactions [64]. Polymer-supported oxime-based ligands as catalyst **65** and



SCHEME 19 A cleavage Stille coupling in the synthesis of the mycotoxin zearalenone (**65**) according to Nicolaou et al. [75].

66 [65–69] or pyridine ligands as catalyst **67** [70] have been used in a number of cross-coupling reactions in water.

The usefulness of this kind of catalyst is quite clear, and significant improvements should arise in the future [61].

4 PALLADIUM CLEAVAGE

It has been proved that palladium-catalyzed cross-coupling reactions on solid supports are efficient methods for library synthesis forming new carbon–carbon bonds under mild conditions. However, the cleavage of substrates from a solid support using palladium-promoted or -catalyzed reactions is also particularly interesting for several reasons. First, this type of cleavage is, in most cases, orthogonal to other procedures, thus enabling various types of transformations. Second, reactive intermediate organometallics can be suitable for further transformations [71].

For example, the group of allyl-based linkers developed by Kunz and Dombo [72] is of particular value, because they are removable under almost neutral conditions using palladium catalysis and are orthogonally stable to the commonly used acid and base-labile protecting groups [73]. Another interesting linker that allows an efficient cleavage–cross coupling strategy for solid phase is the triazene T1 linker. In this context, Heck, Suzuki, and Sonogashira reactions might lead to diversification [74].

Cleavage from solid supports by means of a palladium-catalyzed process has also been used to produce macrocyclic ring systems such as the natural product (*S*)-zearalenone (**69**) via Stille reaction (Scheme 19) [75].

5 CONCLUSION

It is clear that the main reason for immobilizing a molecule on a solid support for palladium-catalyzed coupling reactions relies on the simple

separation of the intermediates and, finally, on the separation of the products from the reagents and soluble by-products.

Owing to the central role in modern organic synthesis of palladium chemistry, catalytic coupling reactions were a logical target of the development of solid-phase synthesis.

Thus, solid-phase variants of the Stille, Heck, Suzuki, and Sonogashira couplings are nowadays well-recognized reactions. Despite the impressive progress, a number of challenges remain unclear, and research will continue in the future, giving rise to new reactions and novel, efficient catalysts.

In view of these advances, one can anticipate an increase in the use of palladium-catalyzed coupling reactions, particularly in industry and in drug discovery. Moreover, polymer-supported reagents and catalysts have emerged as important tools for the rapid generation of chemical libraries.

Palladium chemistry is at the core of organic chemistry. This fact, coupled with advances in polymeric supports, linkers, catalytic couplings conditions, or catalysts, suggests further exciting developments in solid-phase carbon–carbon and carbon–heteroatom bond-formation reactions and strategies.

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