

# The Suzuki, the Heck, and the Stille reaction — three versatile methods for the introduction of new C—C bonds on solid support

Robert Franzén

**Abstract:** Metal-catalyzed coupling reactions are very efficient and reliable methods for the introduction of new carbon-carbon bonds onto molecules attached to a solid support. This review summarizes recent advances in utilizing the three most used methods, the Suzuki reaction, the Heck reaction, and the Stille reaction, in the field of solid phase organic synthesis resulting in small organic molecule libraries.

**Key words:** metal-catalyzed coupling reactions, carbon-carbon bonds, solid phase synthesis, combinatorial chemistry, drug discovery.

**Résumé :** Les réactions de couplage catalysées par les métaux sont des méthodes efficaces et fiables pour l'introduction de nouvelles liaisons carbone-carbone dans des molécules attachées à un support solide. Cette revue résume les développements récents dans l'utilisation des trois méthodes les plus courantes, la réaction de Suzuki, la réaction de Heck et la réaction de Stille, dans le domaine de la synthèse organique en phase solide conduisant à l'élaboration de bibliothèques de petites molécules organiques.

**Mots clés :** réactions de couplage à catalyse métallique, liaisons carbone-carbone, synthèse en phase solide, chimie combinatoire, découverte de médicaments.

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## Introduction

Over the past 10 years, small molecule solid phase synthesis has become an important part in the discovery of new drugs (1, 2). In fact, most of the organic chemical libraries synthesized to date have been constructed using solid-phase methods. In the development of organic chemistry, the carbon-carbon bond formation has always been one of the most useful and fundamental reactions, (3-5) and numerous papers and reviews have detailed the progress of several reactions in solution phase since the end of the 19th century. The literature for new synthetic methods of carbon-carbon bond formation on solid-support has not been extensively reviewed. Recently, a short review by Andres et al. (6) on the utilization of some metal-catalyzed coupling reactions on solid phase was published. The current paper summarizes recent developments in metal-catalyzed coupling reactions performed on a polymeric material. The three following methods are investigated in detail: (i) the cross-coupling of aryl halides with aryl boronic acids (*the Suzuki coupling*); (ii) the palladium-catalyzed reaction between an aryl and

(or)alkyl halide and a vinyl functionality (*the Heck reaction*); and (iii) the palladium-catalyzed cross-coupling reaction of organotin reagents with a variety of organic electrophiles (*the Stille reaction*) on solid support. Only one remarkable preparation of compound libraries on solid phase utilizing the Stille reaction in the synthesis of hundreds of 1,4-benzodiazepine derivatives was reported by Plunkett and Ellman (7). The Suzuki reaction and the Heck reaction have not been applied for the preparation of compound libraries consisting of more than 20 compounds.

## The Suzuki coupling

Palladium-catalyzed coupling via Suzuki reactions are powerful methods for C—C bond formation (8-10). The reaction generally results in an excellent yield when performed at temperatures of 60-80°C. Therefore, it is of high interest to adapt this reaction to a resin mounted procedure.

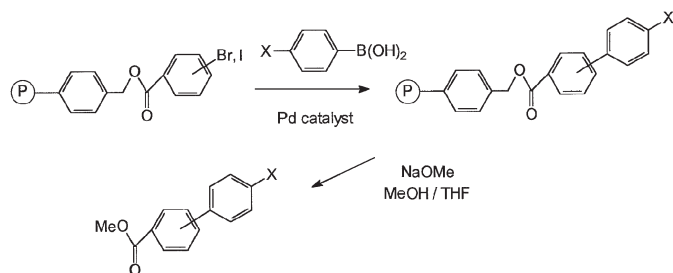
Solid-phase Suzuki coupling was first utilized in the preparation of biaryls. In the work by Frenette and Friesen (11) the cross-coupling reaction between aryl boronic acids and aryl bromides and iodides catalyzed by palladium on Merrifield resin was studied (Scheme 1). The biaryl products were released from the solid support by simple transesterification. A similar reaction was demonstrated by Guiles et al. (Scheme 2) (12). Han et al. (13) reacted several polymer bound arylhalides with a wide range of functionalized boronic acids under the Suzuki cross-coupling reaction conditions (Scheme 3) and produced several *ipso*-substitution products in good yields. Finally the Suzuki coupling for the production of biaryls has also been assisted by microwave irradiation as demonstrated by Larhed et al. (14) (Scheme 4).

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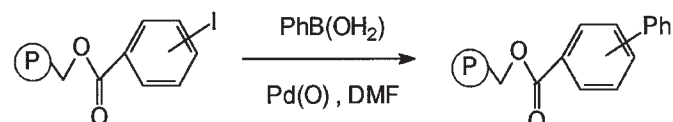
**R. Franzén.**<sup>1</sup> University of Helsinki, Division of Pharmaceutical Chemistry, Department of Pharmacy, P.O. Box 56, FIN-00014 Helsinki, Finland.

<sup>1</sup>Address for correspondence: Dr. Robert Franzén, Graduate School of Pharmaceutical Sciences, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan. Telephone—Fax: +81 3 5689.3522. e-mail: rfranzen@mol.f.u-tokyo.ac.jp

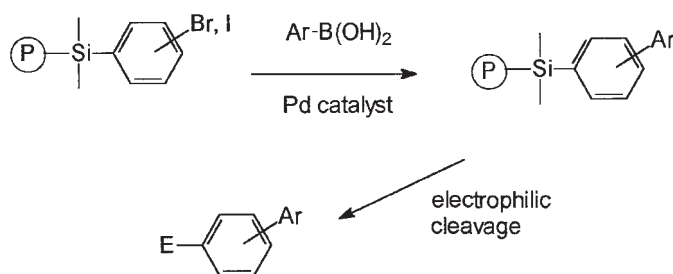
Scheme 1.



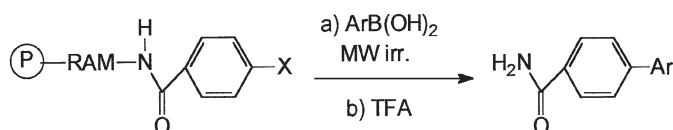
Scheme 2.



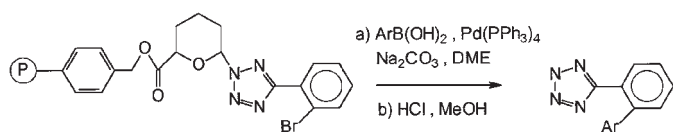
Scheme 3.



Scheme 4.

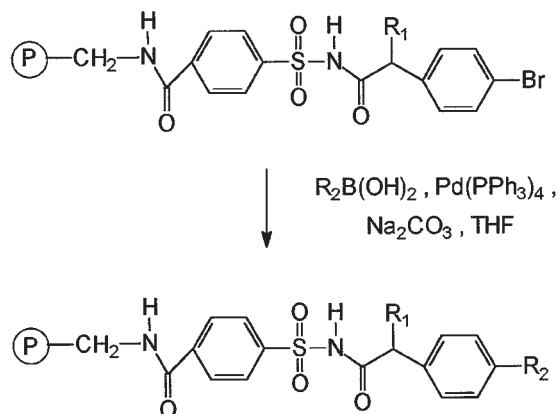


Scheme 5.

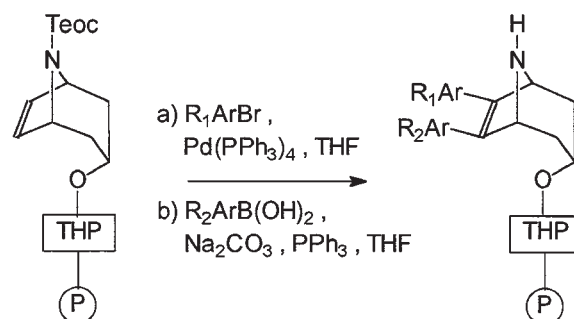


A Suzuki type solid-phase aryl-aryl coupling reaction for the preparation of various biphenyltetrazole derivatives was demonstrated by Yoo et al. (15) (Scheme 5). Marquis and Arlt (16) and Rottlander and Knochel (17) have also demonstrated that several biphenyls can be prepared from palladium-catalyzed reactions of aryl zinc bromides instead of phenyl boronic acids. Backes and Ellman (18) used the Suzuki reaction on solid support starting from a polymer supported acyl sulfonamide (Scheme 6) and in another paper Koh and Ellman (19) reported a palladium-mediated three component coupling (Scheme 7). In the work, several aryl boronic acids were used as coupling partners according to standard Suzuki coupling conditions. Ellman and co-workers (20) has also demonstrated that a Suzuki cross-coupling can

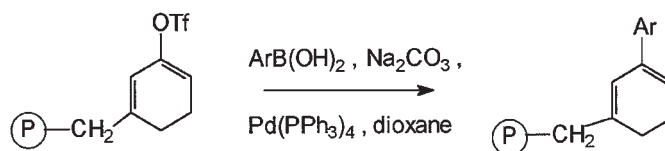
Scheme 6.



Scheme 7.



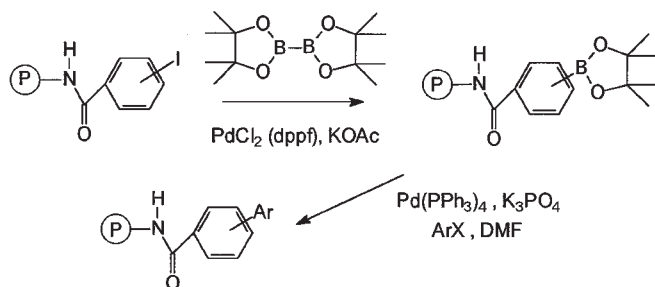
Scheme 8.



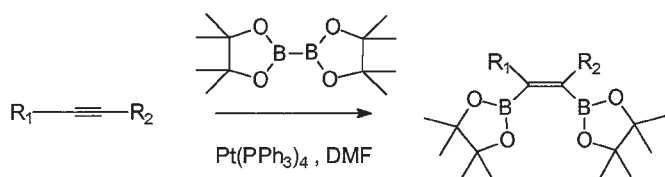
be performed in the synthesis of a 1,4-benzodiazepine-2,5-dione on solid support. Fraley and Rubino (21) utilized a Suzuki cross-coupling reaction between a vinyl triflate resin and boronic acid catalyzed by Pd(PPh<sub>3</sub>)<sub>4</sub> (Scheme 8). Also a variety of other boronic coupling agents (heteroaryl, alkyl, alkenyl, and alkynyl) have been optimized under conditions similar to those used for the phenyl boronic acid coupling (12). Commonly, it has been concluded that the optimal Pd catalyst varies strongly depending upon the boronic coupling partner (22). In this paper, the importance of resin type and solvent composition for Suzuki reactions wherein the boronic acid moiety is either in solution or attached to the resin, was noticed.

Piettre and Baltzer (23) modified the solid-phase reaction and treated polymer-bound aryl halides with pinacol ester of diboron under palladium (0) catalysis and produced polymer-bound boronates that could be used for Suzuki coupling reaction with a variety of aryl halides (Scheme 9). A coupling of a resin bound aryl iodide with phenyl boronic acid produced the biaryl compound in different yield depending on the catalysis system used in the reaction. When using the PdCl<sub>2</sub>(dcbf) as catalyst in the presence of triethylamine in DMF the best yield could be obtained. Ishiyama et al. (24)

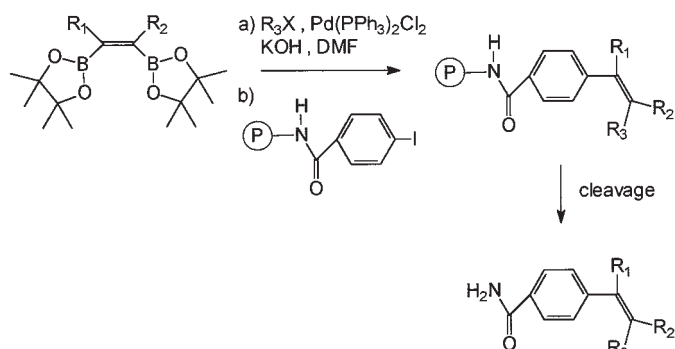
Scheme 9.



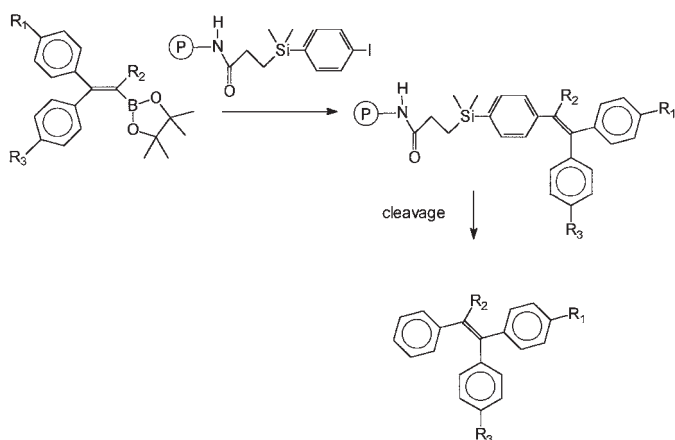
Scheme 10.



Scheme 11.

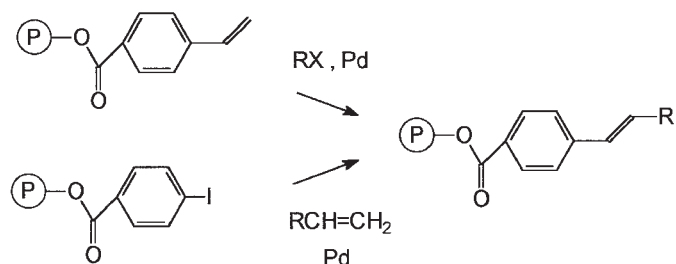


Scheme 12.

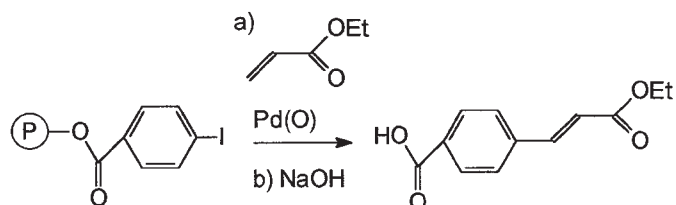


described the platinum-catalyzed diboration of alkynes to give bis(boryl)alkenes with very high *cis* selectivity (Scheme 10). Brown and Armstrong (25, 26) have utilized this approach in the preparation of tetra-substituted ethylenes (Scheme 11) and Tamoxifen derivatives (Scheme 12) on solid support via resin capture. The Suzuki

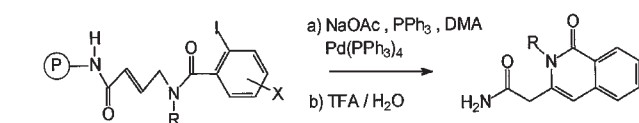
Scheme 13.



Scheme 14.



Scheme 15.



coupling reaction has also been utilized in the preparation of new linkers and resins to be used in combinatorial chemistry (27–29). Due to the high yield in the cross-coupling on solid-support, the reaction has been used for reaction monitoring in Spin Echo Magic Angle Spinning  $^1\text{H}$  NMR experiments (30).

### The Heck reaction

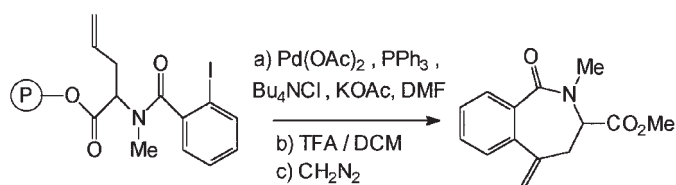
The Heck reaction (31, 32) has shown to be very useful for the preparation of especially disubstituted olefins. In the palladium catalyzed reaction the carbon–carbon bond is formed from a vinyl functionality and an aryl and (or) alkyl halide. The reaction is well adapted for automation due to the fact that it does not require inert atmosphere conditions. The intramolecular Heck reaction has been well-established as a powerful tool for the construction of complex polycyclic ring systems in the context of natural product synthesis. This process has been adapted in the solid-phase synthesis of several different types of molecules.

Yu et al. (33) used the reaction of polymer bound aryl iodide or styrene with olefins or arylhalides in the generation of 1,2-disubstituted olefin libraries (Scheme 13). Hiroshige et al. (34) studied the formation of a C–C bond in the palladium-promoted vinylation of aryl iodide bound to a solid support (Scheme 14). The solvent effect of Pd-catalyzed vinylation using different vinylic reagents was examined. The same group demonstrated also later that a macrocyclic molecule could efficiently be generated on solid support using a modified Heck reaction (35). This palladium-catalyzed intramolecular Heck reaction was also used by Goff and Zuckermann (36) (Scheme 15) for the solid-phase synthesis of substituted peptoid 1(2*H*)-isoquinolinones and by Yun

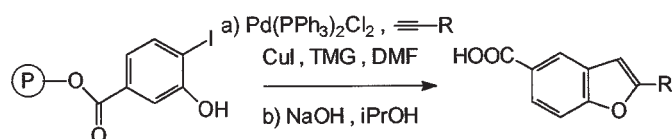
Scheme 16.



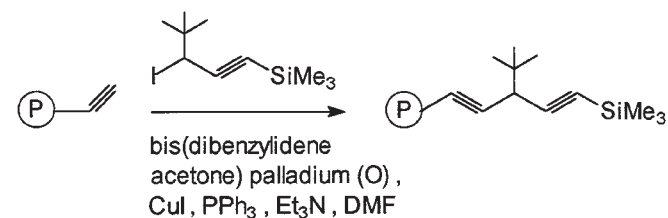
Scheme 17.



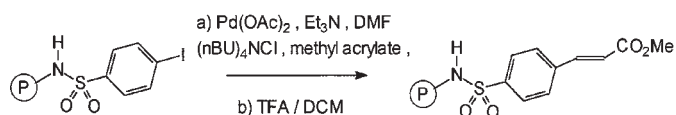
Scheme 18.



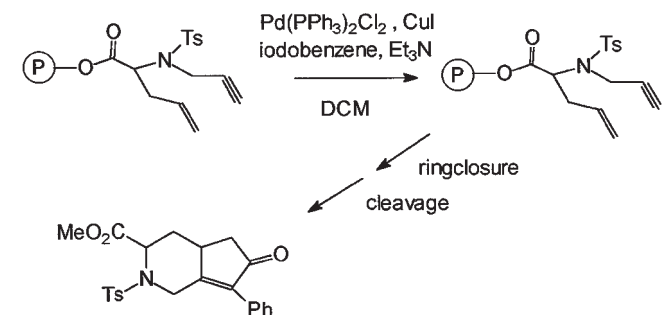
Scheme 19.



Scheme 20.

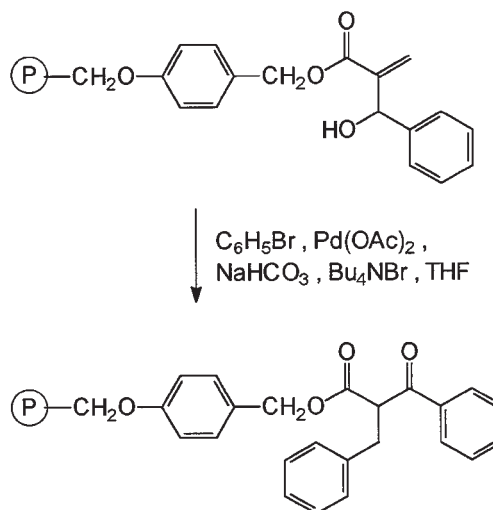


Scheme 21.

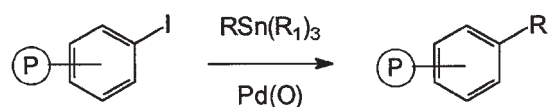


and Mohan (37) (Scheme 16) for the synthesis of indole analogues. A macrocyclization on solid-support using the Heck reaction has also been utilized by Akaji and Kiso (38) when a cyclic tetrapeptide derivative was synthesized. Lately, Bolton and Hodges (39) (Scheme 17) have prepared substi-

Scheme 22.



Scheme 23.



tuted benzazepines via intramolecular Heck cyclization on solid-phase.

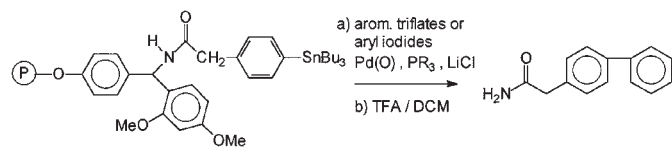
Fancelli et al. (40) utilized the solid-phase Heck-coupling in the preparation of 2-substituted benzofuran carboxylic acids (Scheme 18). The reaction between the resin-bound hydroxy iodide and several acetylenes was examined. In the synthesis of phenyl acetylene oligomers, the Heck reaction was employed between a resin-bound aryl iodide and a terminal acetylene (41) (Scheme 19).

Beaver et al. (42) (Scheme 20) have performed Heck reactions with sulfonamide resins. The resin-bound aryl iodide reacted with methyl acrylate in the presence of  $\text{Pd}(\text{OAc})_2$ . Following cleavage the  $\alpha,\beta$ -unsaturated methyl ester phenyl sulfonamide was obtained in high yield. The Heck reaction has also been used in the solid-phase synthesis of fused bicyclic amino acid derivatives (Scheme 21) (43) and in the monitoring of a solid-phase reaction by MAS NMR spectroscopy. Recently,  $\beta$ -keto esters have been prepared on solid support via a sequential Baylis-Hillman and Heck reaction (Scheme 22) (44).

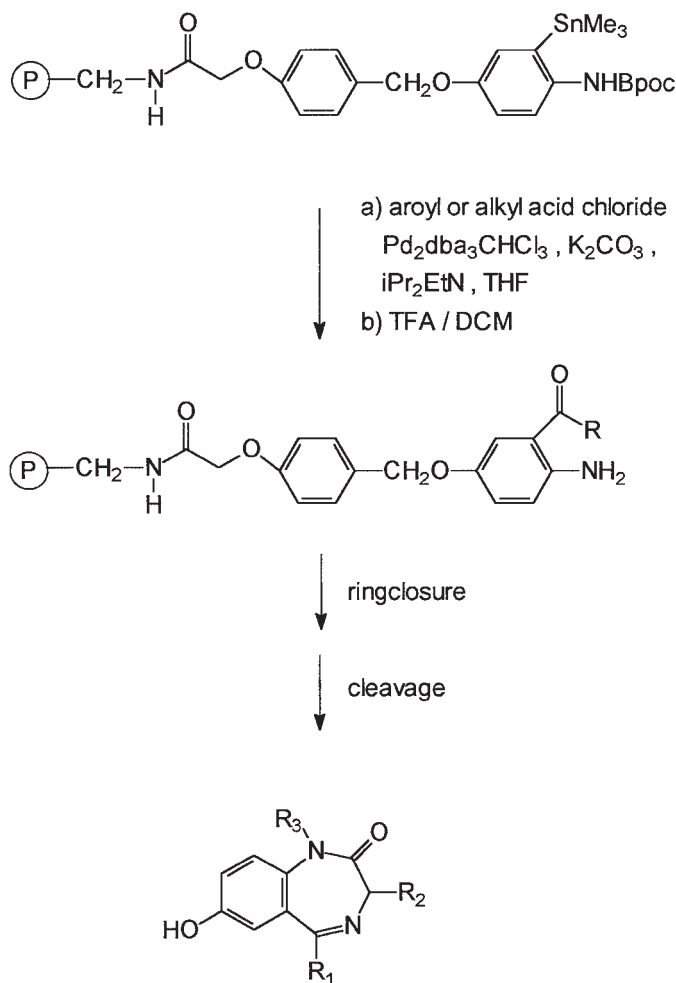
### The Stille reaction

Palladium-catalyzed substitution and addition involving organotin compounds (45–47) have been used by many research groups throughout the world for synthetic purposes. Several applications of the Stille reaction for efficient carbon-carbon bond formation on solid-support have been reported: (i) Desphande (48) used the Stille coupling reaction on solid support for the preparation of biaryls. In his report, he coupled vinyl and (or) aryl stannanes with polymer-bound aryl iodides (Scheme 23). The cross-coupled products were obtained following cleavage from the support in high yield. A year later, Forman and Sucholeiki (49) used the reaction for the preparation of biaryl derivatives and studied the reaction of polymer-bound aryl stannanes with aryl iodides

Scheme 24.



Scheme 25.

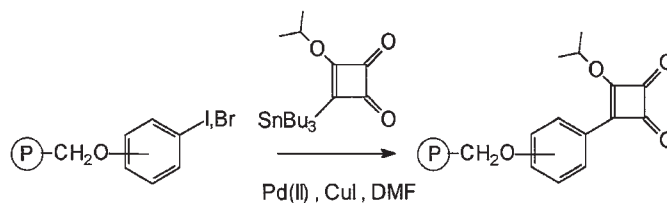


or triflates (Scheme 24). Tributylphenyltin was attached by an amide bond to the Rink amide resin and a palladium-mediated coupling with aryl triflates and aryl iodides was investigated.

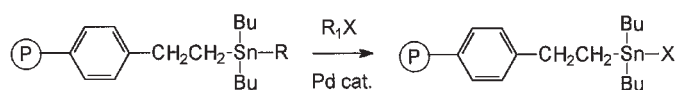
Ellman and co-workers (7, 50, 51) have demonstrated in several papers how the Stille coupling can be utilized in the preparation of small molecule libraries. His group discovered an excellent method (52) for the preparation of 1,4-benzodiazepine derivatives on solid-support and using the Stille coupling he could produce structurally diverse derivatives a few years later (7, 50, 51) (Scheme 25). Recently (53), the group has utilized the Stille coupling in the preparation of new traceless linkers to be used in solid-phase synthesis.

In the preparation of cyclobutenedione derivatives on solid-support, Tempest and Armstrong (54) used a Mitsunobu reaction (55) coupled with a tributyltin isopropyl squarate under Stille conditions (Scheme 26). The reaction

Scheme 26.



Scheme 27.



proceeded well and after TFA cleavage only the expected product was obtained in high yield. Finally, Kuhn and Neumann (56) (Scheme 27) investigated the Stille reaction carried out with polymer-supported organotin reagents. This work showed that organotin by-products could easily be separated by filtration and that the target molecule was free of toxic organotin materials.

## Concluding remarks

Carbon-carbon bond formation reactions on solid-support are highly useful and versatile methods needed for the development of modern drug discovery. This review encompasses most of the metal-catalyzed coupling reactions performed on solid-support starting from 1980. The review focuses on the investigation of the solid-phase adaption of the Suzuki, the Heck, and the Stille coupling reactions due to the fact that these have proven to be both reliable and efficient methods.

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