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Palladium-catalysed reactions in solid phase organic synthesis

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Contents

Keywords: cross-coupling reactions; combinatorial chemistry; solid support; palladium; Heck reaction; Suzuki coupling.

Abbreviations: ac, acetyl; acac, acetyl acetonate; Ad, adamantyl; Alloc (AOC), allyloxycarbonyl; BBN, borabicyclononane; Bn, benzyl; Bpoc, 2-(4-biphenylyl)-2-propyloxycarbonyl; BSA, bis(trimethylsilyl)acetamide; Bz, benzoyl; dba, dibenzylidene acetone; Cbz (Z), benzyloxycarbonyl; DIBAL-H, diisobutylaluminium hydride; DIPEA, diisopropylethylamine; DMA, *N*,*N*-dimethylacetamide; DMBA, dimethylbarbituric acid; DME, dimethoxyethane; DMF, *N*,*N*-dimethylformamide; DMSO, dimethylsulphoxide; dppe, 1,2-bis(diphenylphosphino)ethane; dppf, 1,1′-bis(diphenylphosphino)ferrocene; dppp, 1,2-bis(diphenylphosphino)propane; HOBt, *N*-hydroxybenzotriazole; Fc, ferrocenyl; Fmoc, fluorenylmethyloxycarbonyl; Ms, methylsulfonyl; MBHA, methylbenzylhydryl amine; NIS, *N*-iodosuccinimide; NMM, *N*-methylmorpholine; NMP, *N*-methylpyrrolidinone; Np, naphthyl; Ns, nosyl; n. r., not reported; PEG, polyethylene glycol; PEGA, polyethylene glycol/polyamide; PG, protecting group; Phth, phthalyl; PS, polystyrene; Pyr, pyridyl; TBAF, tetrabutylammonium fluoride; TBS, tertbutyldimethylsilyl; Teoc, trichloroethyl; Tf, trifluoromethylsulfonyl; TFA, trifluoroacetic acid; TFP, trifurylphosphine; THP, tetrahydropyranyl; TIPS, triisopropyl silyl; TM, tolymethyl; TMG, tetramethylguanidine; TMS, trimethylsilyl; TMU, tetramethyl urea; Tol, tolyl.

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1. Introduction and general remarks

From the synthesis of polypeptides, oligopeptides and saccharides, initialised by Merrifield[1] in 1963, solid phase organic synthesis (SPOS) has now become a cornerstone in the combinatorial synthesis of ‘drug-like’ small organic molecule libraries.[2] In the last decade, several research groups in academia and industry made efforts to transfer techniques, which were originally developed for the liquid phase, to the solid support. As a result, multiple parallel synthesis in a combinatorial way has emerged as an indispensable tool to speed up drug discovery in modern life science. For this purpose, palladium-catalysed transformations are one of the most versatile tools due to their potential in the synthesis of complex structures. The advantages of solid phase transformations such as the avoidance of tedious work-up procedures are particularly valuable for palladium-catalysed homogeneous reactions, because the soluble palladium catalyst can be easily removed by washing processes. A quasi high-dilution effect, high yields by employing excess of reagent, amenability to automatisation and the non-interference of various functionalities in the building blocks on solid supports are additional benefits of solid phase chemistry. In recent years, an increasing number of reports on well-established palladium-catalysed and mediated processes being performed on solid phases have been published. This review, which is divided into two parts, provides an extensive overview[3] of the use of palladium-catalysed and -mediated reactions in solid phase combinatorial chemistry and parallel synthesis.

The first part will discuss palladium-catalysed and mediated transformations on solid supports without cleavage of any higher molecular weight compounds from the support. Techniques for the attachment of building blocks and simple group transformations, such as hydrogenation reactions, are also included.

In the second part, cleavage reactions that give rise to soluble products as well as transformations that occur immediately after the cleavage step (derivatisation by cleavage) will be covered.

Throughout this review, the specific type of resin used will always be stated since a number of reactions can only be carried out on certain supports.[4] If not otherwise stated, the resin bead logo symbolises the terminal part of aromatic substructure (Fig. 1), and all polymers mentioned are cross-linked (in general, 1–2% divinylbenzene). This survey includes the available literature up to November 2002. No reference is made to reactions that were carried out only in the liquid phase without any combinatorial aspect.

The Tables are organised in the order of publication year to acknowledge the originality of the respective disclosure. Whenever no details of the reaction conditions are indicated in a Table or Scheme, the original publication did not provide this information. The yields and purities refer to those of the final product, when cleavage conditions are mentioned. The number of examples refers to the number of different compounds obtained. Throughout this review, Ar refers to carbocyclic arenes, whereas Hetaryl refers to furyl, thienyl, pyridyl and other heteroaromatic compounds.

2. Palladium-catalysed coupling reactions and transformations on solid supports

2.1. General remarks

Since the coupling of a suitable starting material to a solid support as well as the design of an appropriate linker are often the keys to successful solid phase synthesis, it is not surprising that considerable efforts have been made in the development of alternative methods to the standard peptide coupling protocols that were the first to be adapted for solid phase transformations. Among these new methods there is also a range of palladium-catalysed reactions such as cross-couplings,[5–7] substitutions and hydrogenations. It is noteworthy that almost every linker type used in solid phase chemistry has found applications in palladium-catalysed and mediated reactions.

2.2. Heck reaction on solid supports

The palladium-catalysed coupling between an alkyl/aryl halide and a vinyl component, the Heck reaction, is one of the most efficient transformations for C–C bond formation in the liquid as well as on the solid phase.[8,9] Over the last years, this reaction has become one of the most powerful tools for gaining complex structural changes, particularly when conducted intramolecularly. Due to the mild conditions and the toleration of many functional groups, the

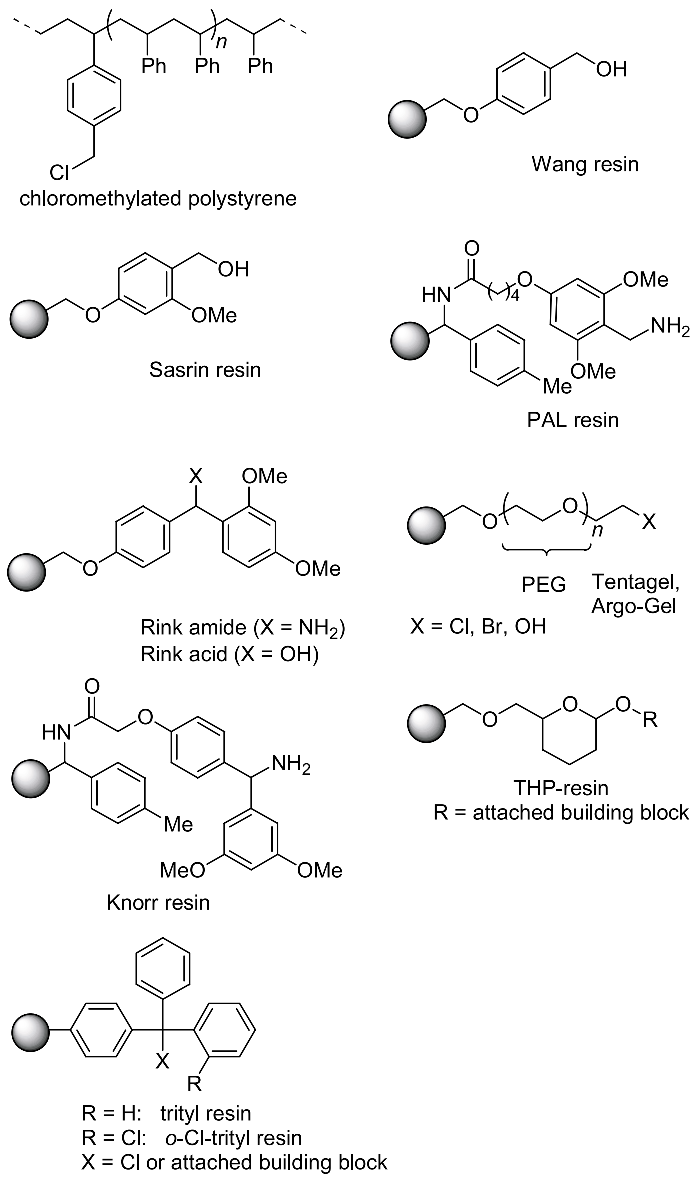


Figure 1. Types of functionalised polystyrene resins used for palladium-catalysed and -mediated reactions on solid supports (for reviews and explanations, see Ref. 4).

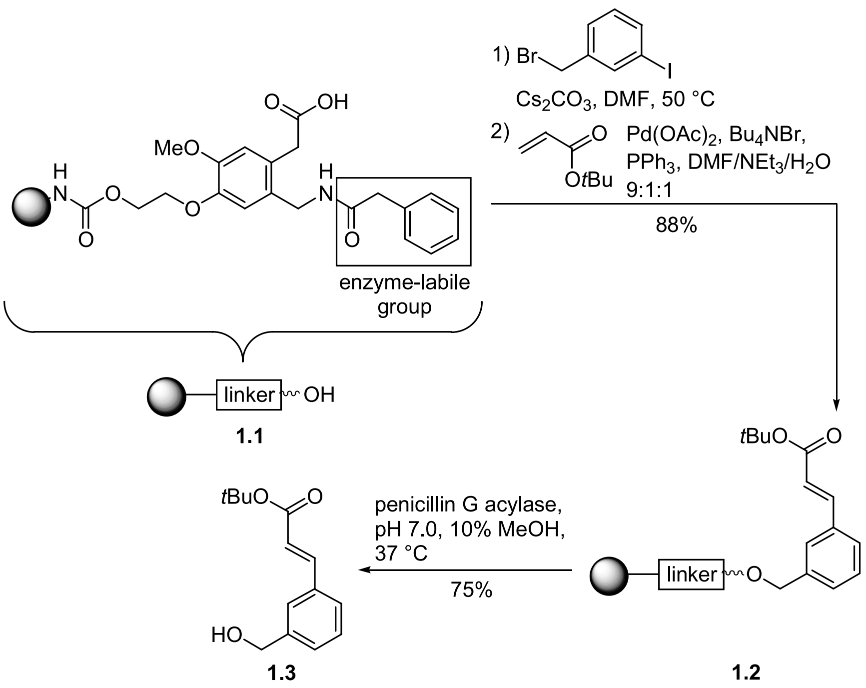
Heck reaction has been successfully adapted to a broad range of organic syntheses on the solid phase.

2.2.1. Intermolecular Heck reactions. Heck reactions on solid supports are extensively used due to the easy accessibility of the starting materials such as halo-alkenes or -arenes and alkenes. The reaction conditions used may be divided into the standard Heck conditions [$Pd(OAc)_2$, PPh_3 or $P(o\text{-}Tol)_3$, DMF, 80–100°C, 2–24 h][9] or the protocol developed by Jeffery [$Pd(OAc)_2$, PPh_3, Bu_4NCl, K_2CO_3, DMF, 20–80°C].[10] The yields obtained under Jeffery conditions were frequently enhanced by the addition of 10% water to the reaction mixture. In some cases, $Pd_2(dba)_3$ was found to be far more effective than $Pd(OAc)_2$.[11]

The Heck reaction was performed on immobilised aryl halides, mostly iodides, or iodonium salts with soluble alkenes (Table 1) or on immobilised alkenes with soluble aryl halides (Table 2). When performed on the same type of resin and with the same catalyst system, the immobilisation of aryl iodides appears to be more beneficial than that of alkenes.[12]

Waldmann et al. developed an enzyme-labile safety catch linker **1.1** and demonstrated its usefulness in various palladium-catalysed reactions.[13] The linker, which releases alcohols and amines through enzymatic cleavage of the benzylamide moiety and subsequent lactam formation, was attached to a soluble PEG 6000 polymer. After Heck reaction of the immobilised iodoarene with *t*-butyl acrylate to give cinnamate **1.2**, the coupling product **1.3** is cleaved off the solid support under very mild conditions (pH 7, 37°C) (Scheme 1).

2.2.2. Intramolecular Heck reactions. The main advantage of intramolecular Heck reactions on solid supports is the pseudo dilution of the starting material leading to an increased yield. The first application of this process was reported in 1995 for the synthesis of 20- to 24-membered



Scheme 1. Heck reaction of an iodoarene anchored by an enzyme-labile safety catch linker.[13]

Table 1. Intermolecular Heck reactions on solid supports: polymer-bound aryl iodides and related compounds

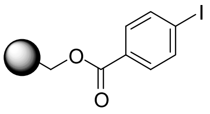
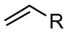
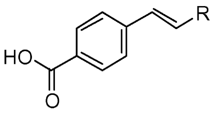
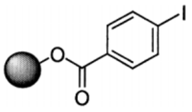
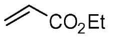
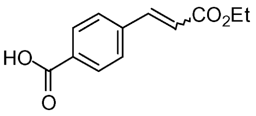
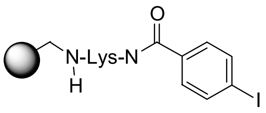
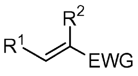
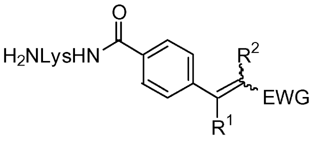
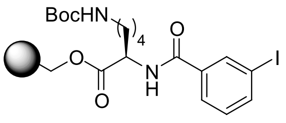
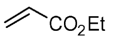
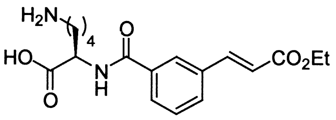
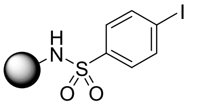
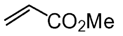
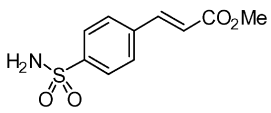
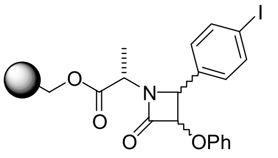
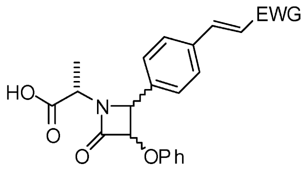
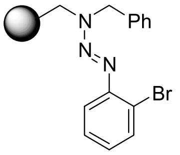
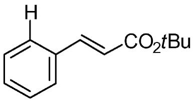
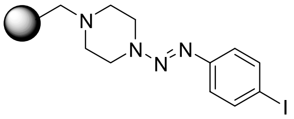
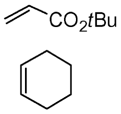
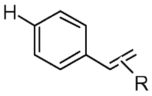
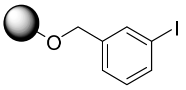
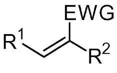
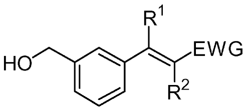
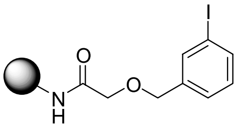
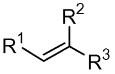
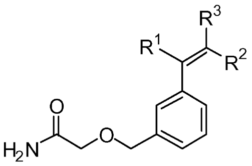
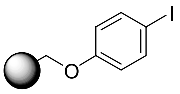
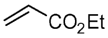
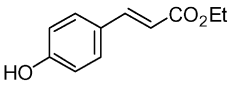
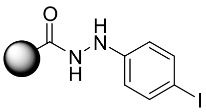
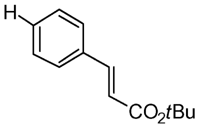
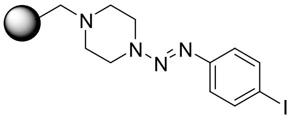
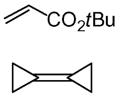
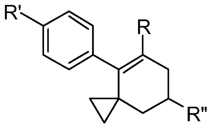
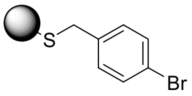
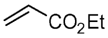
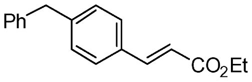
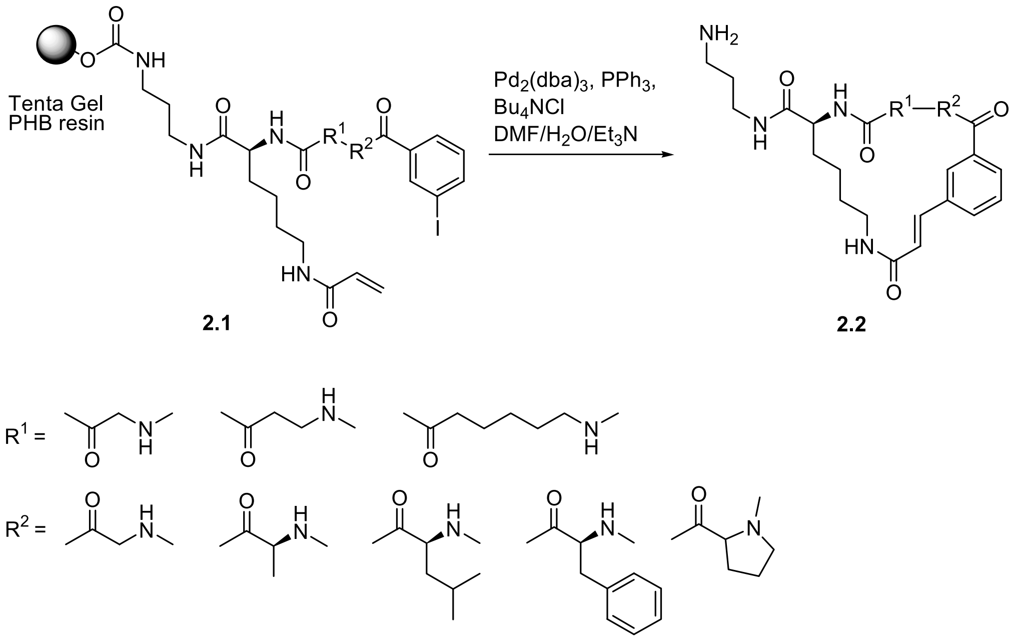
Entry	Starting material	Alkenes used	Product(s)	Reaction conditions	No of exps; yield (%)	Ref.
1	 Wang resin	 R=p-C$_6$H$_4$CO$_2$Me or CO$_2$Et	 Cleav.: 90% TFA, CH$_2$Cl$_2$, rt, 1 h	Pd(OAc)$_2$, Et$_3$N, n-Bu$_4$NCl, DMF, 80–90°C, 16 h	2 exps; 90–91	12
2	 Tentagel-OH		 Cleav.: TFA/CH$_2$Cl$_2$/PhOMe (50:47:3), rt, 30 min	Pd(OAc)$_2$, PPh$_3$, Bu$_4$NCl, sat. K$_2$CO$_3$, DMF/H$_2$O (9:1), 37°C, 4 h	>95 conv.	14
3	 Millipore PS-PEG-PAL	 EWG=CONH$_2$, CN; R^1=H, Ph; R^2=H, Me	 Cleav.: TFA/CH$_2$Cl$_2$/PhOMe (50:47:3), rt, 30 min	Pd(OAc)$_2$, PPh$_3$, Bu$_4$NCl, sat. K$_2$CO$_3$, DMF/H$_2$O (9:1), 37°C	6 exps; 54–>95	14
4	 Wang		 Cleav.: 90% TFA, CH$_2$Cl$_2$, 4 h	Pd(OAc)$_2$, P(o-Tol)$_3$, Et$_3$N, DMF, 60°C, 19 h	43	15
5	 Rink amide		 Cleav.: 20% TFA, CH$_2$Cl$_2$	Pd(OAc)$_2$, Bu$_4$NCl, Et$_3$N, 90°C, 18 h	1 exp	16

Table 1 (*continued*)

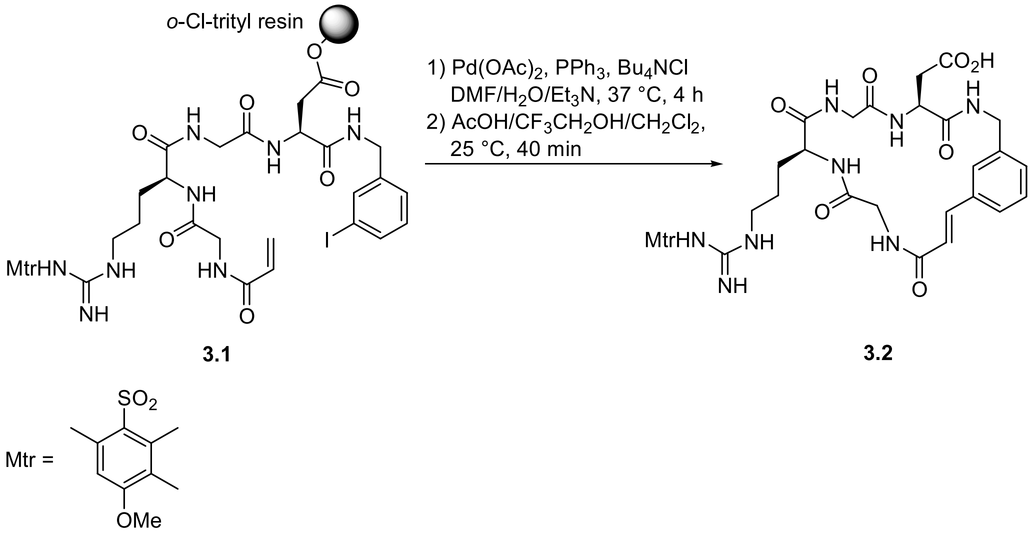
Entry	Starting material	Alkenes used	Product(s)	Reaction conditions	No of exps; yield (%)	Ref.
6	 Sasrin resin or ArgoGel-MB-OH	 EWG=CONH$_2$, CN, CO$_2$Et, CONMe$_2$	 Cleav.: 3–10% TFA, CH$_2$Cl$_2$	PdCl$_2$(dppf), Et$_3$N, Bu$_4$NI, DMF/H$_2$O (9:1), 40°C	4 exps; 60–91	17
7	 polystyrene		 Cleav.: HCl, THF, ultrasound, 50°C, 5 min	Pd(OAc)$_2$, PPh$_3$, Et$_3$N, DMF, ultrasound, 80°C, 24 h	2 exps	18
8	 polystyrene		 Cleav.: HCl, THF, ultrasound, 50°C, 5 min or HSiCl$_3$, CH$_2$Cl$_2$, 32°C, 10 min	Pd(OAc)$_2$, PPh$_3$, Et$_3$N, DMF, ultrasound, 80°C, 24 h	2 exps	18,19
9	 polystyrene with base-labile linker	 R^1=H, Me; EWG= CO$_2$*t*Bu, CO$_2$Me, CN, COEt, CONMe$_2$, SO$_2$Ph; R^2=H, Me	 Cleav.: NaOMe, MeOH/dioxane, rt, 24 h	Pd(OAc)$_2$, NaOAc, Bu$_4$NCl, DMA, 100°C, 24 h	7 exps; 48–96	20
10	 Rink resin	 R^1=H, Me, CO$_2$Me, Ph; R^2=H, Me, CO$_2$Me, CN, Ph, P(O)(OMe)$_2$, COEt, CONMe$_2$; R^3=H, Me, NHAc, COMe, CH$_2$CO$_2$Me, CN	 Cleav.: 20% TFA, CH$_2$Cl$_2$, rt, 5 min	Pd(OAc)$_2$, NaOAc, Bu$_4$NCl, DMA, 100°C, 24 h	11 exps; 40–96	20
11	 Wang resin		 Cleav.: 20% TFA, CH$_2$Cl$_2$	Pd$_2$(dba)$_3$·CHCl$_3$, P(*o*-Tol)$_3$, DMF, 110°C, 24 h	1 exp; >90	11
12	 polystyrene or TentaGel or ArgoPore		 Cleav.: Cu(OAc)$_2$, MeOH, pyr, rt, 2 h	Pd(OAc)$_2$, NaOAc, Bu$_4$NBr, DMA, 100°C, 24 h	1 exp; 83–96	21
13	 polystyrene		 Multicomponent reactions; see Scheme 7	Pd(OAc)$_2$, PPh$_3$, Et$_3$N, DMF, 80°C, 24 h	2 exps	22
14	 polystyrene with linker (see also Scheme 46)		 Cleav.: (1) Et$_3$O$^+$BF$_4^-$; (2) PhB(OH)$_2$, PdCl$_2$(dppf), K$_2$CO$_3$, THF, 60°C, 14 h	Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$, DMF, 70°C, 14 h	1 exp; 57	23



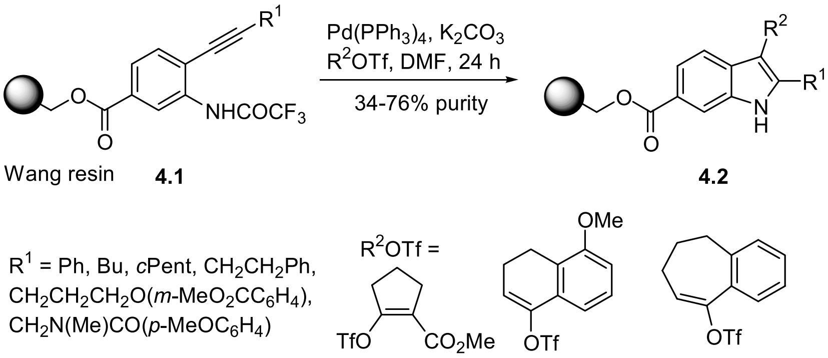
Scheme 2. Intramolecular Heck reaction for the synthesis of macrocycles.[30]

macrocyclic ring systems **2.2** starting from aryliodides **2.1** (Scheme 2).[30]

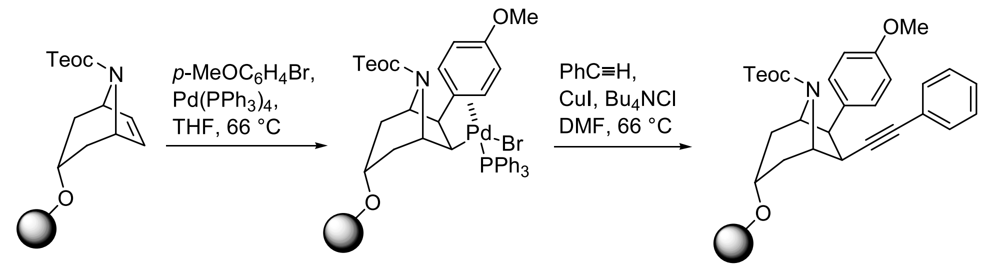
Similarly, a 20-membered ring **3.2** was formed and released from the *o*-chlorotrityl linker **3.1** (Scheme 3).[31] Recently, this methodology was applied in the synthesis of a 15-membered library having a diverse array of amino acids, combined with a variety of ring sizes.[32]



Scheme 3. Intramolecular Heck reaction for the synthesis of a macrocycle.[31]



Scheme 4. Carbometallation and cyclization of *o*-alkynylaniline derivatives.[40]



THP resin **5.1** **5.2** **5.3**

Scheme 5. Carbometallation on the tropane framework.[41]

Besides the preparation of macrocycles, the cyclisation to give heteroatom-containing five-, six- and seven-membered rings has been investigated (Table 3) and the construction of indoles, benzofurans, dihydroisoquinolines and benzazepines has been reported. Starting from aryl iodides with an appropriate alkenyl or alkynyl ether, the latter under reductive conditions, smooth cyclisations occur under standard conditions.

Intermolecular carbometallation of a triple bond in **4.1** by an organylpalladium triflate and subsequent intramolecular nucleophilic attack gives rise to the indoles **4.2** (Scheme 4),[40] the major advantage of this approach being that the triflate may be varied over a wide range.

An interesting sequential reaction, consisting of an intermolecular alkene carbometallation and subsequent intermolecular alkyne cross-coupling, has been reported by Ellman and co-workers (Scheme 5).[41] Starting from an immobilised tropane framework **5.1**, stoichiometric

Table 2. Intermolecular Heck reactions on solid support: polymer-bound alkenes

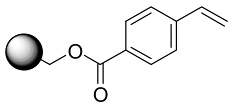
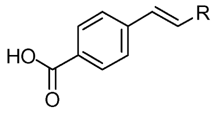
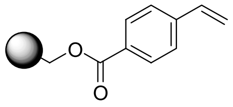
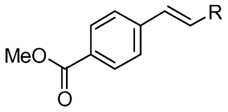
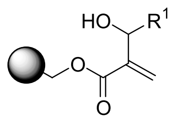
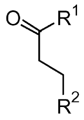
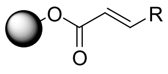
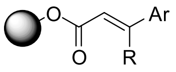
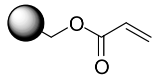
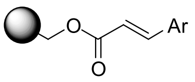
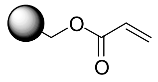
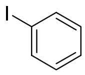
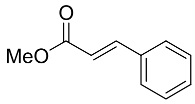
Entry	Starting material	Aryl halide or iodonium salt	Product(s)	Reaction conditions	No of exps; yield (%)	Ref.
1	 Wang resin	RX=PhI, 2-naphthyl-Br, 2-thienyl-Br, 3-Pyr-Br	 Cleav.: 20% TFA, CH_2Cl_2, rt, 1 h	$Pd_2(dba)_3$, P(o-Tol)$_3$, Et_3N, DMF, 100°C, 20 h or $Pd(OAc)_2$, Et_3N, n-Bu_4NCl, DMF, 80–90°C, 16 h	4 exps; 64–81	12
2	 polystyrene	$Ph_2I^+BF_4^-$; p-$(MeOC_6H_4)_2I^+BF_4^-$; $(2\text{-thienyl})_2I^+BF_4^-$	 Cleav.: NaOMe, MeOH/THF (1:4), reflux, 20 h	$Pd_2(dba)_3{\cdot}CHCl_3$, P(o-Tol)$_3$, $NaHCO_3$, DMF, 40°C, 20 h	3 exps; 55–80	24
3	 Wang resin; R^1=aryl, hetaryl, alkyl	R^2Br; R^2=aryl, hetaryl	 Cleav.: 75% TFA, CH_2Cl_2, rt, 1 h	$Pd_2(dba)_3$, P(o-Tol)$_3$, Et_3N, DMF, 100°C, 24 h	21 exps; 0–49	25
4	 MeO-PEG 5000 R=o-$MeOC_6H_4$, 1-Naphthyl, o-Tol, 2,4-$Cl_2C_6H_3$, 4-Pyr, cPr	ArI; Ar=p-Tol, p-BuC_6H_4, p-$MeOC_6H_4$	 Z/E=<1/99 to >99/1	$Pd(OAc)_2$, $NaHCO_3$, DMF, 145°C, 20 h	14 exps; 82–95	26
5	See Scheme 6					27
6		ArX; Ar=Ph, o-$H_2NC_6H_4$, o-HOC_6H_4		$Pd(OAc)_2$, P(o-Tol)$_3$, Et_3N, DMF, 40–100°C, 20 h	4 exps; 49–76 after cleavage	28
7	 REM resin		 Cleav.: NaOMe, MeOH, THF	$Pd(OAc)_2$, P(t-Bu)$_3$, DIPEA, super critical CO_2 (880 psi), 80°C, 16 h	1 exp; 98	29

Table 3. Synthesis of indoles, benzofurans, dihydroisoquinolines and benzazepines by Heck reactions on solid supports

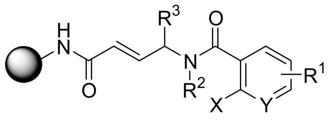
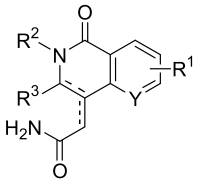
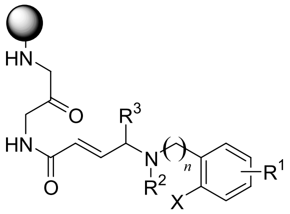
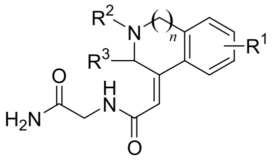
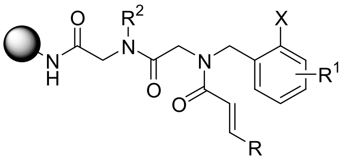
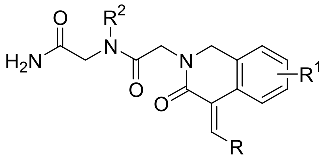
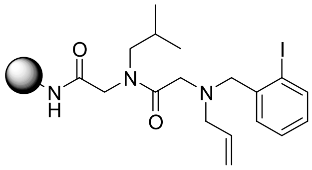
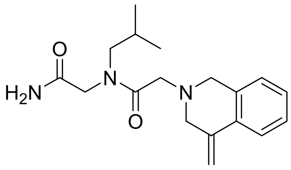
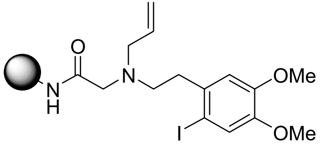
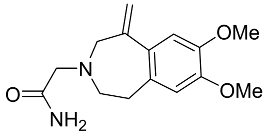
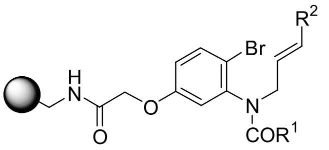
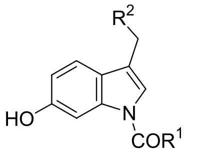
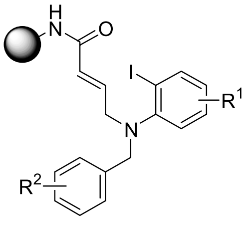
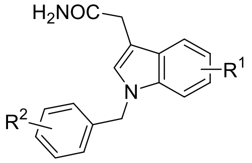
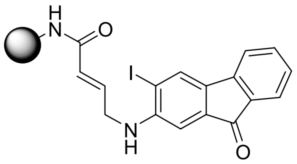
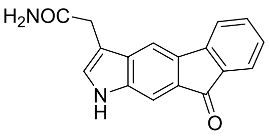
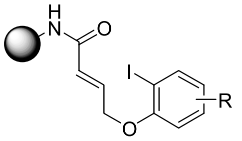
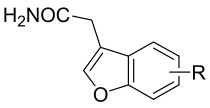
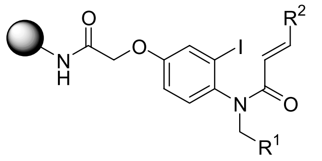
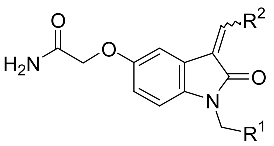
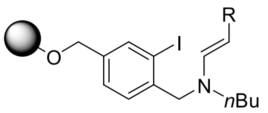
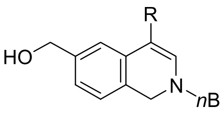
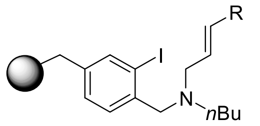
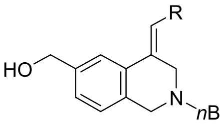
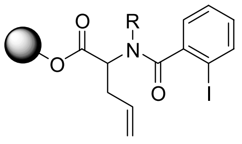
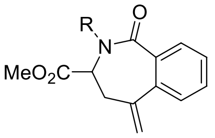
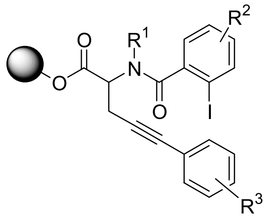
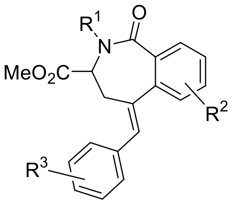
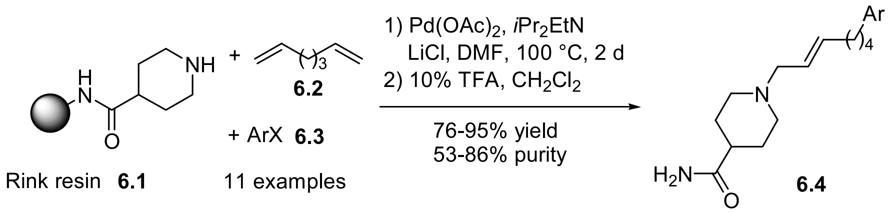
Entry	Starting material	Product(s)	Reaction conditions	No of exps; yield (%)	Ref.
1	 Rink amide; X=Br, I; Y=CH, N; R^1=Me, F, (OMe)$_2$, Cl, OMe; R^2=*i*Bu, CH$_2$CH$_2$Ph, Ph; R$_3$=H, Me	 Mixture of double bond isomers; cleav.: TFA/H$_2$O (95:5), rt, 20 min	Pd(PPh$_3$)$_4$, PPh$_3$, NaOAc, DMA, 85°C, 5 h	9 exps; 65–92	33,34
2	 Rink amide	 *n*=1–3; cleav.: TFA/H$_2$O (95:5), rt, 20 min		Several exps claimed	34
3	 Rink amide	 Cleav.: TFA/H$_2$O (95:5), rt, 20 min		Several exps claimed	34
4	 Rink amide	 Cleav.: TFA/H$_2$O (95:5), rt, 20 min	Pd(PPh$_3$)$_4$, PPh$_3$, NaOAc, DMA, 90–95°C, 8 h		34
5	 Rink amide	 Cleav.: TFA/H$_2$O (95:5), rt, 20 min	Pd(PPh$_3$)$_4$, PPh$_3$, NaOAc, DMA, 90–95°C, 7.5 h		34
6	 TentaGel S	 R^1=Et, *i*Pr, Ph, *m*-MeOC$_6$H$_4$; R^2=H, Me, Ph; cleav.: TFA (neat)	Pd(PPh$_3$)$_4$, PPh$_3$, Et$_3$N, DMA, 85°C, 5 h	8 exps; 65–94	35
7	 Rink amide AM or Rink amide resin	 R^1=H, 6-OMe, 5-CO$_2$Me; R$_2$=*p*-F, *p*-CF$_3$, *p*-F, *o*-Cl, *p*-OCF$_3$, *p*-Me, H; cleav.: 30% TFA, CH$_2$Cl$_2$	Pd$_2$(dba)$_3$·CHCl$_3$, P(*o*-Tol)$_3$, NaHCO$_3$, DMF, 40°C, 20 h	12 exps; 67–88	36

Table 3 (*continued*)

Entry	Starting material	Product(s)	Reaction conditions	No of exps; yield (%)	Ref.
8	 Rink amide AM or Rink amide resin	 Cleav.: 30% TFA, CH_2Cl_2	$Pd_2(dba)_3 \cdot CHCl_3$; $P(o\text{-}Tol)_3$, $NaHCO_3$, DMF, 40°C, 20 h	1 exp; 76	36
9	 Rink amide AM or Rink amide resin	 R=H, 5,7-$(Cl)_2$; cleav.: 30% TFA, CH_2Cl_2	$Pd_2(dba)_3 \cdot CHCl_3$, $P(o\text{-}Tol)_3$, $NaHCO_3$, DMF, 40°C, 20 h	2 exps; 81–83	36
10	 R^1=H, CH_2*c*Hex, *i*Bu; R^2=H, CH_3, Ph	 Cleav.: 25% TFA, CH_2Cl_2, 25°C, 16 h	$Pd(OAc)_2$, PPh_3, Ag_2CO_3, DMF, 100°C, 16 h	9 exps; 65–92; *E*/*Z* 2.7:15.9:1	37
11	 polystyrene with additional base-labile linker; R=CO_2Me, Ts, Ac	 Cleav.: MeONa, MeOH/dioxane (1:4), rt, 24 h	$Pd(OAc)_2$, PPh_3, Bu_4NCl, K_2CO_3, 100°C, 24 h	3 exps; 95–100	38
12	 polystyrene with additional base-labile linker, R=CO_2Me, Ts, Ac	 Cleav.: MeONa, MeOH/dioxane (1:4), rt, 24 h	$Pd(OAc)_2$, PPh_3, Bu_4NCl, K_2CO_3, 100°C, 24 h	2 exps; 90–100	38
13	 Wang resin; R=Me, Bn	 Cleav.: 50% TFA, CH_2Cl_2	$Pd(OAc)_2$, PPh_3, Bu_4NCl, K_2CO_3, 70°C	2 exps	39
14	 Wang resin; R^1=Ph, CH_2CH_2Ph; R^2=H, 7-Cl, 7,8-diOMe, R^3=H, *p*-CONHBu, *m*-CF_3	 Cleav.: (a) 50% TFA, CH_2Cl_2; (b) CH_2N_2	$Pd(OAc)_2$, PPh_3, Bu_4NCl, KOAc or HCO_2Na, 70°C	7 exps	39

carbopalladation yields a stable organopalladium intermediate **5.2**, which in the presence of copper(I) iodide undergoes coupling with an added terminal acetylene to give alkyne **5.3**.

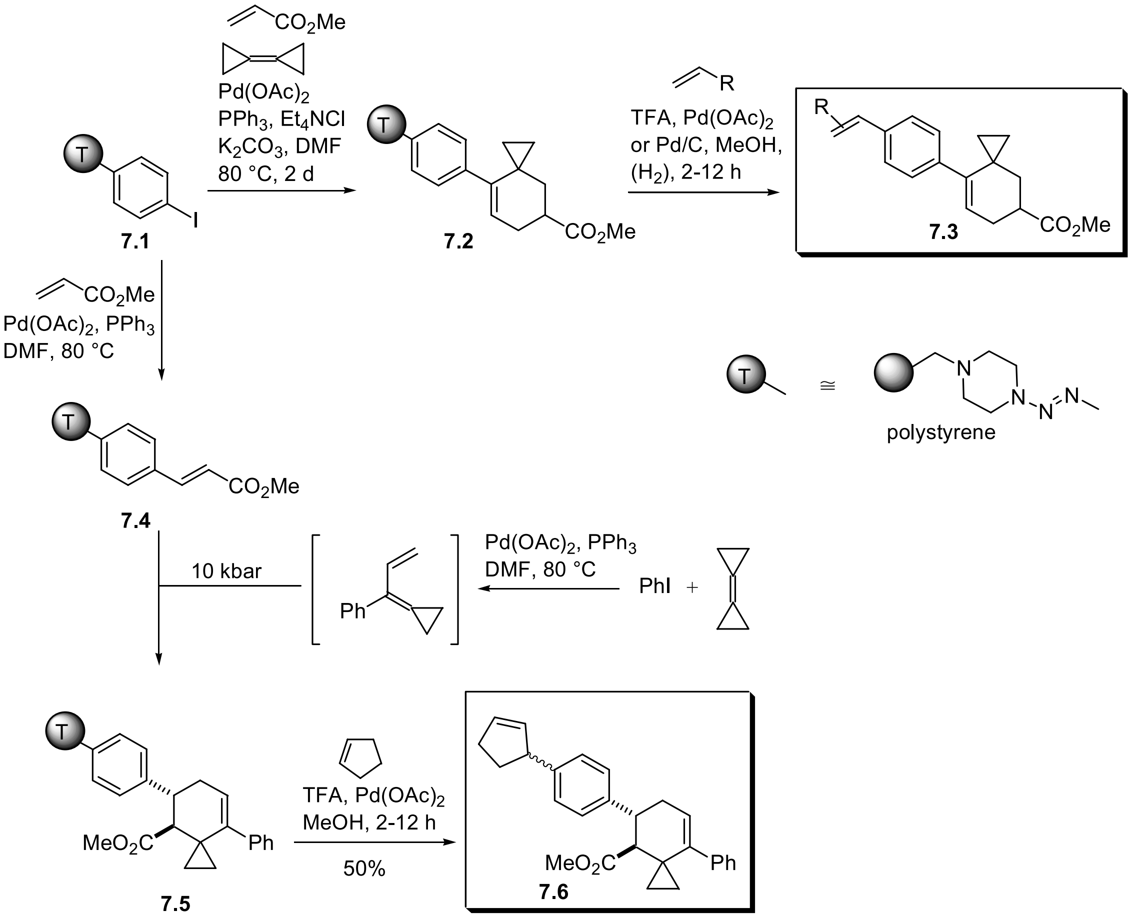
2.2.3. Multicomponent Heck reactions on solid supports. Multicomponent reactions (MCRs) are particularly feasible for combinatorial synthesis. The advantage of conducting an MCR on a solid support lies in the simplicity of removal of



Scheme 6. Coupling of a solid-supported piperidine with 1,5-hexadiene and aryl halides.[27]

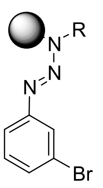
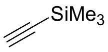
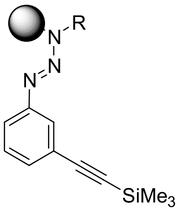
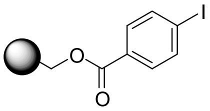
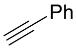
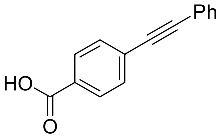
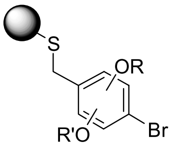
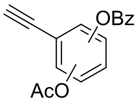
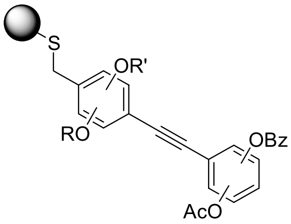
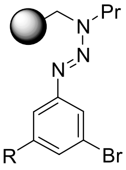
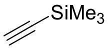
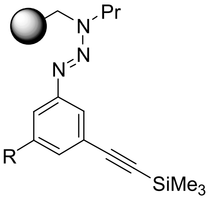
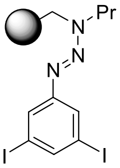
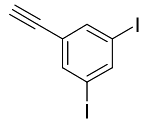
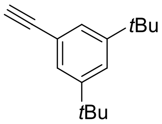
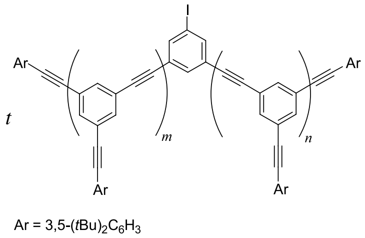
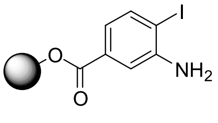
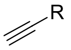
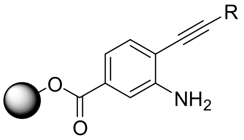
non-polymer-bound components and excess building blocks. A three-component reaction to highly diverse compounds, developed by Larock et al. using an aryl halide **6.3**, a non-conjugated diene **6.2** and a suitable nucleophile (mostly an amine), has been carried out on a solid phase using the immobilised amines **6.1** (Scheme 6).[27] The advantage of this procedure in comparison to the use of immobilised aryl halides is that any possible by-products formed from aryl halides, such as simple Heck coupling products, stay in solution and can be removed by washing processes. The yield of this three-component reaction is quite good and the purities of the products **6.4** are moderate to good. The flexibility of this approach using different starting materials (11 different aryl halides and five different resins) makes it very attractive.

The reactions of bicyclopropylidene with aryl halides under Heck conditions give rise to the formation of allylidenecyclopropanes, which in turn can react with dienophiles in a Diels–Alder reaction. This new three-component reaction has also been conducted on a solid support using the versatile triazene T1 linker (Scheme 7).[22,42] Heck coupling of an immobilised iodoarene **7.1** with bicyclopropylidene in the presence of an acrylate forms a polymer-bound spirooctene **7.2**. Alternatively, the iodoarene **7.1** can be first transformed by palladium-catalysed coupling into a polymer-bound cinnamate **7.4** with an acrylate. The cinnamate **7.4** itself can then act as a dienophile for the Heck coupling products of bicyclopropylidene and aryl iodides to give the polymer-bound spirooctene **7.5**. The latter transformation was conducted under high pressure, which facilitates both the Heck coupling and the Diels–Alder reaction. The triazene moieties could be cleaved to diazonium salts, which in turn act as precursors for Heck reactions with various alkenes to give the spirooctenes **7.3** and **7.6** in good yields and excellent purities. By employing palladium on charcoal for this transformation, the same catalyst may also be used in a subsequent catalytic hydrogenation of the double bond in the coupled alkene (see also Scheme 43).[42]



Scheme 7. Three-component Heck–Diels–Alder reactions on a solid support.[22]

Table 4. Arylation of terminal alkynes: immobilisation of the aryl halide

Entry	Starting material	Alkyne	Product(s)	Reaction conditions	No. of exps; yield (%)	Ref.
1	 3 different resins			$Pd_2(dba)_3$, PPh_3, CuI, DMF, 65°C, 24 h	3 exps	43
2	 Wang resin		 Cleav.: 90% TFA, CH_2Cl_2	$Pd_2(dba)_3$, P(*o*-Tol)$_3$, Et_3N, DMF, 100°C, 20 h	1 exp; 90%	12
3				$Pd(OAc)_2$, Et_3N, reflux, 4 h	Several exps claimed	46
4	 polystyrene, R=OC_6H_{13}, $CO_2C_6H_{13}$, CN			$Pd_2(dba)_3$, PPh_3, CuI, DMF, 65°C, 12 h	3 exps	47
5	 polystyrene	a)  b) capping with 	 Cleav.: MeI, 110°C, 12 h	$Pd_2(dba)_3$, PPh_3, CuI, DMF, piperidine, rt, 12 h	>18 exps	44
6	 Wang resin	 R=Ph, Bu, *c*Pent, CH_2CH_2Ph, $CH_2CH_2CH_2O$(*m*-$MeO_2CC_6H_4$), CH_2N(Me)CO(*p*-$MeOC_6H_4$)		$Pd(PPh_3)_2$, CuI, Et_2NH, DMF, 2 h	6 exps	40

(*continued on next page*)

Table 4 (*continued*)

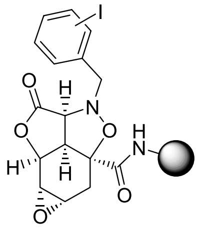
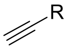
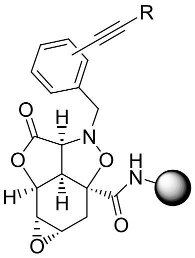
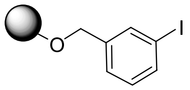
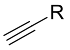
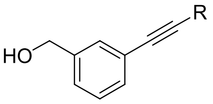
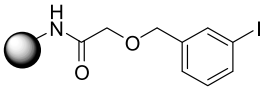
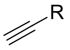
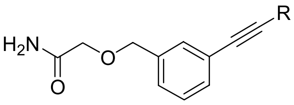
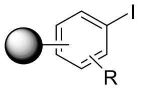
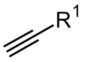
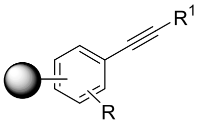
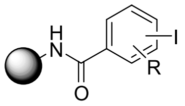
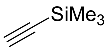
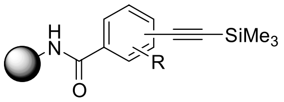
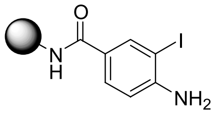
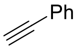
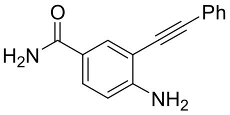
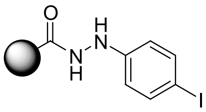
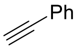
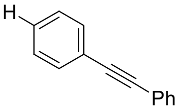
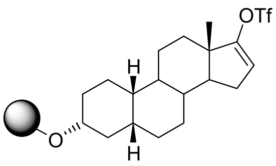
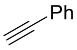
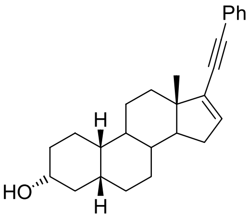
Entry	Starting material	Alkyne	Product(s)	Reaction conditions	No. of exps; yield (%)	Ref.
7	 Tentagel S NH_2	 31 different alkynes		$Pd(PPh_3)_2Cl_2$ CuI, *i*Pr_2EtN, DMF, rt, 15–45 min	ca. 100 exps	48
8	 Resin with base-labile linker	 R=*t*Bu, CH_2OH, CH(Me)OH, Bu Ph, CMe_2OH, CH_2NHBoc	 Cleav.: NaOMe, MeOH/dioxane, rt, 24 h	Pd(OAc)$_2$, NaOAc, Bu_4NCl, DMA, 100°C, 24 h	7 exps; 77–96	20
9	 Rink resin	 R=various Ar or HetAr	 Cleav.: 20% TFA, CH_2Cl_2, rt, 5 min	$Pd(PPh_3)_2Cl_2$ CuI, Et_3N or *i*Pr_2EtN, dioxane, rt–50°C, 24 h	7 exps; 79–95	49
10	 various scaffolds	 R^1=*t*Bu, *n*Bu, CH(OH)CH_3, CH(OTfa)CH_3, Ph, CH_2OH		$Pd(PPh_3)_2$ Cl_2 CuI, Et_3N, dioxane, rt, 24–30 h	14 exps; 52–97	49
11	 PS or PS-PEG with Rink linker, R=H, Me			$Pd(PPh_3)_4$, CuCl, THF/Et_3N (1:1), rt, 40 h	3 exps	50
12	 Rink amide		 Cleav.: 30% TFA, CH_2Cl_2	$Pd(PPh_3)_2Cl_2$ CuI, Et_3N/DMF (1:5), 80°C, 5–16 h	1 exp; 96; 96 pur.	51
13	 polystyrene or TentaGel or ArgoPore		 Cleav.: Cu(OAc)$_2$, *n*$PrNH_2$, rt, 2 h	$Pd(PPh_3)_2Cl_2$ CuI, Et_3N/dioxane (2:1), rt, 24 h	1 exp; 52–92	21
14	 polystyrene with fluoride-labile linker		 Cleav.: TBAF, TMU, 100°C, 1 h	Pd(OAc)$_2$, PPh_3, Bu_3N, DMF, 80°C, 2 h	1 exp; 46	52

Table 4 (*continued*)

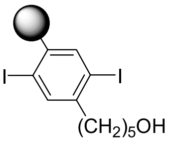
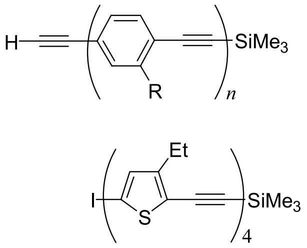
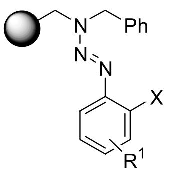
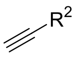
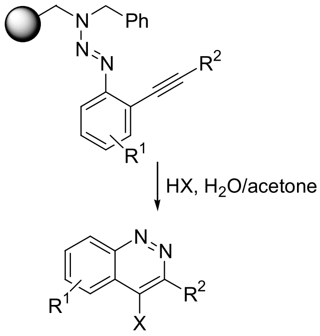
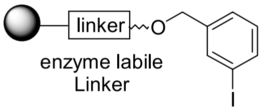
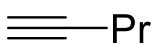
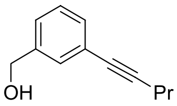
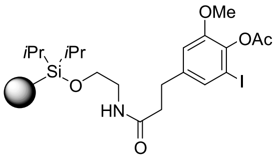
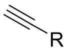
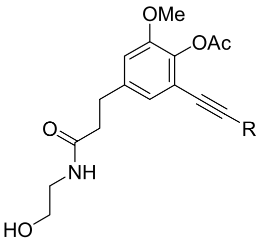
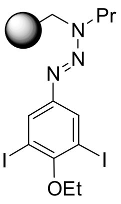
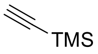
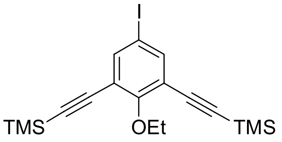
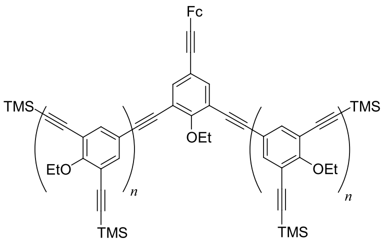
Entry	Starting material	Alkyne	Product(s)	Reaction conditions	No. of exps; yield (%)	Ref.
15	 polystyrene with THP-linker	 repetitive coupling, deprotection, up to n=17	Various scaffolds	$Pd_2(dba)_3$, PPh_3, CuI, Et_2NH/THF (1:4)	Various exps	53
16	 polystyrene; X=I, Br		 	$Pd(OAc)_2$, PPh_3, NEt_3, DMF, 80°C, 12–18 h	20 exps; >80	45
17	 POE 6000 (PEG resin) see Scheme 1		 Cleav.: penicillin G acylase, pH 7.0, 10% MeOH, 37°C	$Pd(PPh_3)_2Cl_2$, CuI, dioxane/NEt_3 2:1, 20°C, 24 h	1 exp; >88	13
18	 PS Macrobeads with linker	 R=Ph, NR_2, CH_2OAc, $(CH_2)_3CN$, CH(OH)*i*-Pr, $C(OH)R_2$, $C(NH_2)R_2$, $(CH_2)_3OTMS$	 Cleav.: HF/Py, THF, 25°C, 1 h, then TMSOMe, 25°C, 3 h	$Pd(PPh_3)_2Cl_2$, CuI, DIPEA, MeCN, 25°C, 24 h	12 exps; >95	54
19	 polystyrene	a)  b) deprotection, repetitive coupling, deprotection 	 Cleav.: Fc-C≡CH, $Pd(dba)_2$, PPh_3, CuI, NEt_3/THF 2:1, 70°C	$Pd(dba)_2$, PPh_3, CuI, NEt_3/THF 2:1, 70°C	1 exp	55

Table 5. Arylation and alkenylation of terminal alkynes: immobilisation of the alkyne

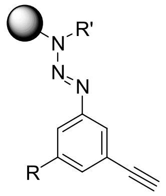
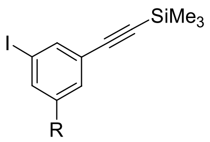
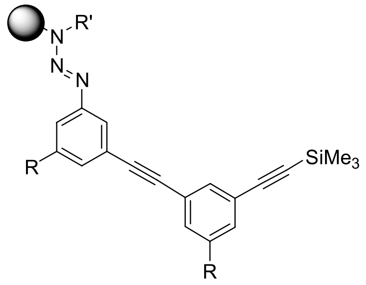
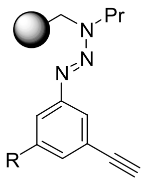
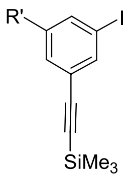
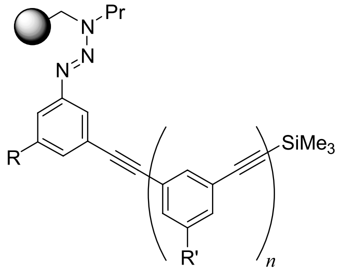
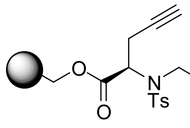
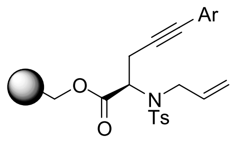
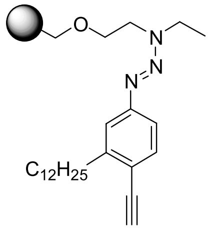
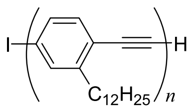
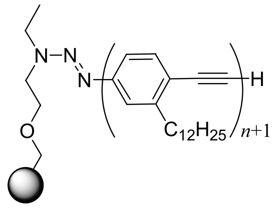
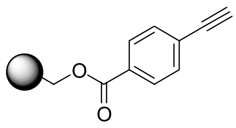
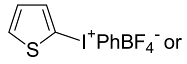
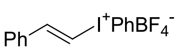
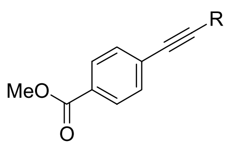
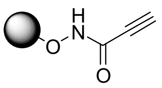
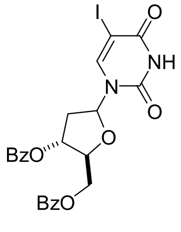
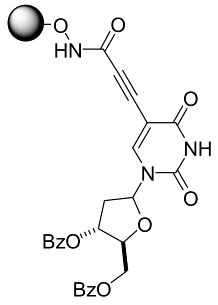
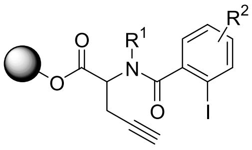
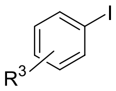
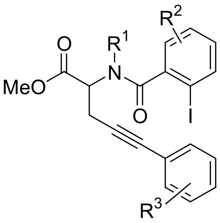
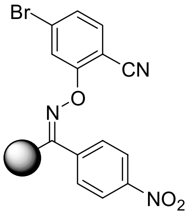
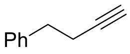
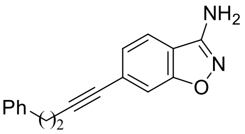
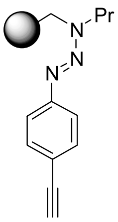
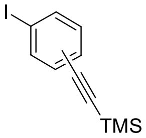
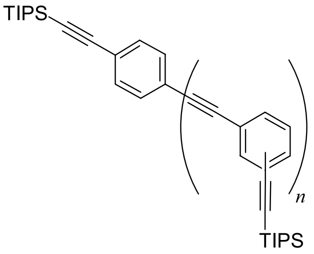
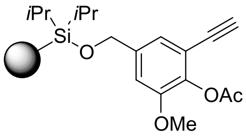
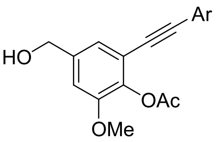
Entry	Starting material	Aryl halide	Product(s)	Reaction conditions	No. of exps; yield (%)	Ref.
1	 polystyrene with linker			$Pd_2(dba)_3$, PPh_3, CuI, DMF, 65°C, 24 h; 5 iterations (after deprotection)	61	43
2	 polystyrene; R=OC_6H_{13}, $CO_2C_6H_{13}$, CN	 Repetitive coupling and deprotection; up to n=5		$Pd_2(dba)_3$, PPh_3, CuI, DMF, 65°C, 12 h	Several exps described	47
3	 Wang resin	ArI; Ar=Ph, p-$MeOC_6H_4$ p-ClC_6H_4, p-$MeO_2CC_6H_4$		$PdCl_2(PPh_3)_2$, CuI, Et_3N, CH_2Cl_2, rt, 18 h	4 exps	56
4	 polystyrene	 repetitive coupling and deprotection; up to n=15		$Pd_2(dba)_3$, PPh_3, CuI, DMF, $i$$PrNH_2$/THF (1:5)	Various exps	57
5	 polystyrene	$RPhI^+BF_4^-$ = $Ph_2I^+BF_4^-$ p-MeOC6H_4I^+Ph BF_4^- or  	 Cleav.: NaOMe, MeOH/THF (1:4) reflux, 20 h	$Pd(PPh_3)_4$, CuI, $NaHCO_3$, DMF, 40°C, 20 h	4 exps; 50–75	24
6	 polystyrene with o-chlorotrityl linker			$Pd(PPh_3)_4$, CuI, Et_3N, DMF, 25°C	1 exp; >89	58

Table 5 (*continued*)

Entry	Starting material	Aryl halide	Product(s)	Reaction conditions	No. of exps; yield (%)	Ref.
7	 Wang resin		 R^1=Ph, CH_2CH_2Ph, Me, R^2=H, 7-Cl, 7,8-$(OMe)_2$; R^3=H, *p*-CONHBu, *m*-CF_3 Cleav.: (a) 50% TFA, CH_2Cl_2; (b) CH_2N_2	$Pd(PPh_3)_4$, CuI, Et_3N, CH_2Cl_2	7 exps; 39–73	39
8	See Table 4, entry 15					53
9	 polystyrene		 Cleav.: TFA/5 N aq. HCl (4:1); 55°C, 2 h	$Pd(PPh_3)_4$, CuI, Et_3N, THF, 55°C, 36 h	1 exp; 58; 93 pur.	59
10	 polystyrene	 Repetitive coupling and deprotection; up to *n*=3	 Cleav.: MeI, 110°C, then TIPS-C≡CH, $Pd_2(dba)_3$, PPh_3, CuI, NEt_3, 70°C, 12 h	$Pd_2(dba)_3$, PPh_3, CuI, NEt_3, 70°C, 12 h	18 exps; 16–47	60
11	 PS Macrobeads with linker	ArOTf; Ar=Ph, *p*-$NO_2C_6H_4$, α-naphtyl, β-naphtyl, *p*-Me(O)CC_6H_4 ArI; Ar=Ph, 2-thiophenyl, *p*-$NO_2C_6H_4$, *p*-FC_6H_4, *o*,*p*-$MeOC_6H_4$, β-naphtyl, *o*-MeC_6H_4	 Cleav.: HF/Py, THF, 25°C, 1 h, then TMSOMe, 25°C, 3 h	$Pd(PPh_3)_4$, CuI, DIPEA, THF/DMF, 25°C, 24 h	14 exps; 95–100	54

2.3. Arylations and alkenylations of terminal alkynes: Sonogashira-type coupling reactions

The palladium-catalysed coupling of aryl bromides or iodides with terminal alkynes in the presence of a copper(I) co-catalyst, the Sonogashira reaction, has been frequently used in SPOS (Tables 4 and 5). Since the C–C triple bond can be converted into various new functionalities or simply act as a spacer, any straightforward access to substituted alkynes is a valuable process.

An advantage of the Sonogashira coupling performed on solid supports is the facile removal of the by-products such as the diynes formed by homocoupling of the alkynes. Most terminal alkynes are suitable, although, propiolic esters have failed so far.[12] Moore et al. have reported one of the first alkyne couplings on a solid support utilising the versatile triazene linkage (Table 4, entry 1).[43] The repetitive coupling/desilylation sequence allowed the synthesis of arylacetylene oligomers. Using a triazene-linked iodoarene as the starting material, hyperbranched polymers with a narrow size distribution were synthesised on solid supports with 3,5-diiodophenyl)acetylene as a monomer.[44] Prior to detachment, capping with 3,5-di-*tert*-butylphenylethyne under palladium-catalysis was performed to enhance the solubility (Table 5). The resulting polymer had a molecular weight range of 5–25 kDa. With an alkynyl group attached *ortho* to a triazene linker, the latter yielding a diazonium ion moiety upon cleavage, cyclisation to form a cinnoline may occur (Table 4, entry 16).[45]

2.3.1. Carbometallations with subsequent nucleophilic attack. The heteroannelation of aryl iodides containing a potentially *ortho*-nucleophilic substituent (amino or

Table 6. Carboannelation of aminoiodoarenes

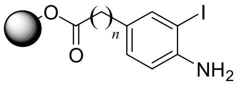
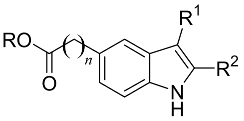
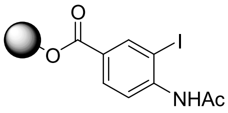
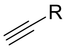
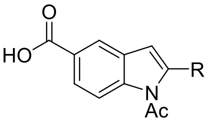
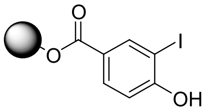
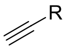
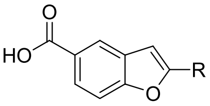
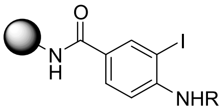
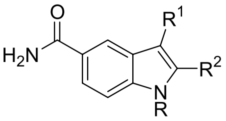
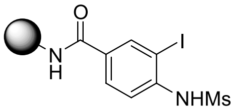
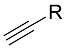
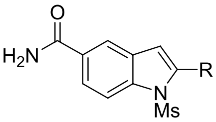
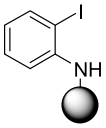
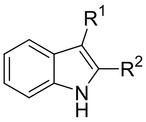
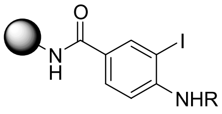
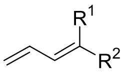
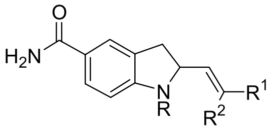
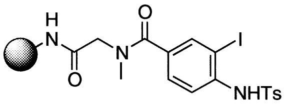
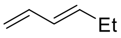
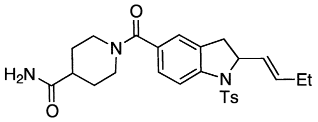
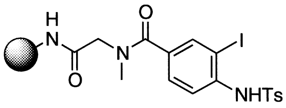
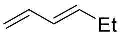
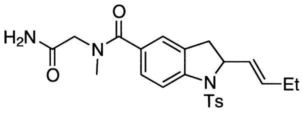
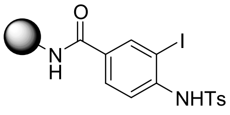
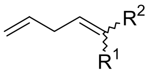
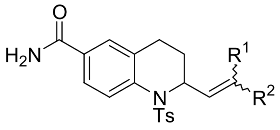
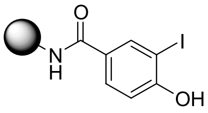
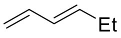
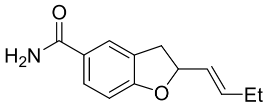
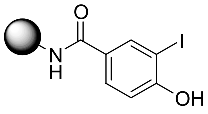
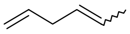
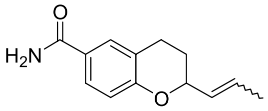
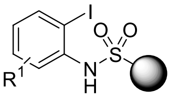
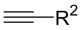
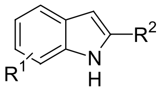
Entry	Starting material	Alkyne/alkene	Reaction conditions	Product(s)	No. of exps; yield (%)	Ref.
1	 Tentagel; n=0,1	$R^1-\equiv-R^2$ R^1=H, Me, Ph, CO_2Et; R^2=Me, C_6H_{13}, Ph, 2-Pyr, 2-(6-MeO-Naphthyl), CH_2cPent, *p*-Tol, *p*-$MeOC_6H_4$, $(CH_2)_2Cl$, *p*-ClC_6H_4 CH_2NMe_2, $(CH_2)_4OH$, *n*Bu	$Pd(PPh_3)_2Cl_2$ CuI, TMG, dioxane, 80–90°C, 24 h	 Cleav.: R=H: *i*PrOH/H_2O, 2 N NaOH, 40–50°C, 5 h; R=Me: MeOH/H_2O; R=Et: EtOH/H_2O	Several exps. described	66
2	 TentaGel S-OH	 R=Ph, *p*-ClC_6H_4, *p*-$MeOC_6H_4$, *p*-PrC_6H_4, $(CH_2)_3OH$, SPh, *i*Bu	$Pd(PPh_3)_4$, CuI, TMG, dioxane, 90°C, 18 h	 Cleav.: 0.03 M NaOH/*i*PrOH, 50°C, 5 h	7 exps; 78–90 pur.	67,68
3	 TentaGel S-OH	 R=Hex, *t*Bu, Ph, $(CH_2)_3Cl$, CMe_2OH, CH_2NH_2, CH_2NEt_2, $CH_2NHCONH$-*t*Bu,CH_2NH-CO_2tBu	$Pd(PPh_3)_4$, CuI, TMG, dioxane, 50°C, 16 h	 Cleav.: NaOH (aq.)/*i*PrOH	10 exps; 42–65	69
4	 R=H, Ac, CO*i*Pr Rink amide AM resin	$R^1-\equiv-R^2$ R^1=Me, Pr, Ph, CO_2Et, CH_2CH_2OH, CH_2CH_2Cl, CH_2CH_2(*m*-$MeOC_6H_4$), $CH_2(NC_4H_8)$; R^2=Pr, *t*Bu, Ph, $SiMe_3$	$Pd(OAc)_2$, $(PPh_3)_4$, LiCl or Bu_4NCl, K_2CO_3 or Na_2CO_3 or KOAc, DMF, 80°C, 7–20 h	 Cleav.: 30% TFA, CH_2Cl_2, 1 h	15 exps; 38–100; 53–92 pur.	63
5	 Rink amide	 R=Ph, Bn, C_5H_{11}, CH_2NMe_2	$Pd(PPh_3)_2Cl_2$, CuI, Et_3N/ DMF (1:5), 80°C, 5–16 h	 Cleav.: 30% TFA, CH_2Cl_2	4 exps; 87–96; 79–98 pur.	51
6	 polystyrene with THP linker	$R^1-\equiv-R^2$ R^1=Me, Et, Pr, Ph, CH_2CH_2OH; R^2=Pr, *t*Bu, Ph, $SiMe_3$	$Pd(PPh_3)_2Cl_2$, TMG, DMF, 110°C, 21 h	 Cleav.: 10% TFA, CH_2Cl_2	6 exps; 63–97	63

Table 6 (*continued*)

Entry	Starting material	Alkyne/alkene	Reaction conditions	Product(s)	No. of exps; yield (%)	Ref.
7	 Rink amide; R=SO_2Ar, COAr	 R^1=H, Me; R^2=Me, Et, CO_2Me, OAc	$Pd(OAc)_2$, LiCl, *i*Pr_2EtN, DMF, 100°C	 Cleav.: 30% TFA, CH_2Cl_2	12 exps; 87–96; 79–98 pur.	70
8	 Rink amide		$Pd(OAc)_2$, LiCl, *i*Pr_2EtN, DMF, 100°C	 Cleav.: 10% TFA, CH_2Cl_2	1 exp; 81; 86 pur.	70
9	 Rink amide R=SO_2Ar, COAr		$Pd(OAc)_2$, LiCl, *i*Pr_2EtN, DMF, 100°C	 Cleav.: 10% TFA, CH_2Cl_2	1 exp; 69; 85 pur.	70
10	 Rink amide	 R^1=H, Me; R^2=Me, Et, CO_2Me, OAc	$Pd(OAc)_2$, LiCl, *i*Pr_2EtN, DMF, 100°C	 Cleav.: 30% TFA, CH_2Cl_2	12 exps; 87–96; 79–>90 pur.	70
11	 Rink amide		$Pd(OAc)_2$, LiCl, *i*Pr_2EtN, DMF, 100°C	 Cleav.: 30% TFA, CH_2Cl_2	1 exp; 90; 88 pur.	70
12			$Pd(OAc)_2$, LiCl, *i*Pr_2EtN, DMF, 100°C	 Cleav.: 30% TFA, CH_2Cl_2	1 exp; 84; 88 pur.	70
13	 polystyrene; R^1=H, F, MeO, CO_2Me	 R^2=aryl, alkyl	$Pd(PPh_3)_2Cl_2$, CuI, Et_3N, DMF, 70°C	 Cleav.: TBAF, THF, 70°C, 5 h	17 exps; 65–100	71

(*continued on next page*)

Table 6 (*continued*)

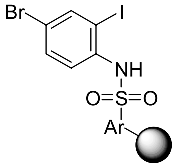
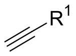
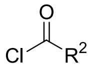
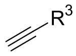
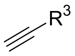
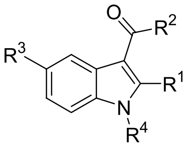
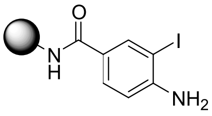
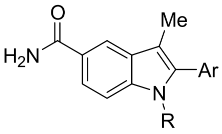
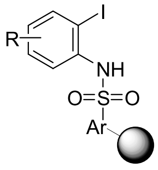
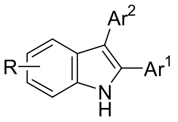
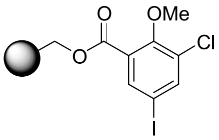
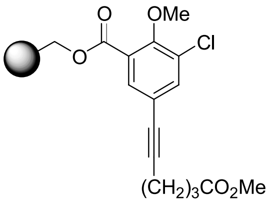
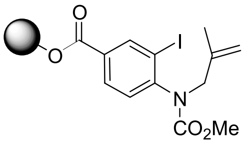
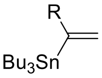
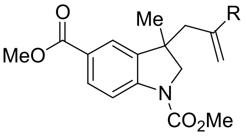
Entry	Starting material	Alkyne/alkene	Reaction conditions	Product(s)	No. of exps; yield (%)	Ref.
14	 polystyrene	 1) R^1=Ph, *o*-FC_6H_4, *p*-FC_6H_4, *p*-$MeOC_6H_4$, Pr, *p*-MeC_6H_4  2) R^2=Ph, *m*-FC_6H_4, *p*-FC_6H_4, Me, *c*-Hex, *c*-Pr, *p*-$MeOC_6H_4$, *i*-Pr, *m*-MeC_6H_4, *m*-$MeOC_6H_4$, *p*-(*t*Bu)C_6H_4, β-naphtyl, biphenyl 3) $(HO)_2BR^3$, R^3=Ph, *m*,*p*-$F_2C_6H_3$, *m*,*p*-$Cl_2C_6H_3$, *p*-$PhOC_6H_4$, *o*,*m*-$Me_2C_6H_3$, *o*-$CNOC_6H_4$, *p*-(*t*-Bu)C_6H_4, α-naphtyl, biphenyl or  3) R^3=Ph, *o*-FC_6H_4, *p*-FC_6H_4, Pr, Bn, *p*-$MeOC_6H_4$, *p*-MeC_6H_4	1) $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, DMF, 25°C, 24 h 2) $AlCl_3$, CH_2Cl_2, 12 h 3) $(HO)_2BR^3$: $Pd(dppf)Cl_2$, K_3PO_4, dioxane, 90°C, 24 h  $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, DMF, 70°C, 24 h	 Cleav.: R^4=H: *t*BuOK, THF, 25°C, 5 h R^4=Me: *t*BuOK, THF, 25°C, 5 h, then MeI; 2 h	39 exps; 10–20	72
15	 polystyrene	1) TMS—≡—Me 2) NIS, CH_2Cl_2 3) $(HO)_2BAr$ Ar=Ph, α-naphtyl, *p*-$MeOC_6H_4$, *p*-MeC_6H_4,	1) $Pd(OAc)_2$, PPh_3, *n*Bu_4NCl, Na_2CO_3, DMF, 80°C 3) $Pd(PPh_3)_4$, K_2CO_3, DMF/H_2O 9:1, 80°C	 R=H, Bn, *p*-F-Bn Cleav.: TFA, CH_2Cl_2	7 exps; 65–96, 89–98 pur.	73
16	 polystyrene; R=H, 5-CO_2Me	Ar^1—≡ Ar^1=Ph, *p*-MeC_6H_4, *p*-FC_6H_4, *p*-$NO_2C_6H_4$, 2) NBS, THF 3) $(HO)_2BAr^2$ Ar^2=Ph, *p*-pyr, β-naphthyl, α-naphthyl *p*-$MeOC_6H_4$, *p*-$ClOC_6H_4$, *p*-$MeO_2CC_6H_4$, *p*-MeC_6H_4, *p*-$MeSC_6H_4$	1) $Pd(PPh_3)_2Cl_2$, CuI, NEt_3, DMF, 70°C 3) $Pd(PPh_3)_4$, K_2CO_3, DMF, 90°C, 5–10 h	 Cleav.: TBAF, THF	12 exps; 85–99, 82–99 pur.	73

Table 6 (*continued*)

Entry	Starting material	Alkyne/alkene	Reaction conditions	Product(s)	No. of exps; yield (%)	Ref.
17		$\equiv$—$(CH_3)_3CO_2Me$	$Pd(OAc)_2$, CuI, NEt_3, DMF, 23°C, 12 h		n. r.	74
18	 Wang resin	 R=Ph, C(O)(NH)Ph, CH_2(NH)Ph, C(O)(NH)Bn, C(O)(NAc)Bn, CH_2Imid., *o*-$MeO_2CC_6H_4$, *o*-$AcHNC_6H_4$, HetAr, C(O)Me	$Pd_2(dba)_3$, P(2-furyl)$_3$, toluene, 0°C, 2 h, then 110°C, 8 h	 Cleav.: NaCN, NEt_3, MeOH/THF 1:3, 50°C, 48 h	11 exps; 58–86	75

hydroxy) with alkynes provides an elegant and straightforward access to substituted indoles and benzofurans (for reviews, Refs. 61,62). This reaction cascade, involving a carbometallation of a triple bond and subsequent nucleophilic displacement of the metal, has been frequently used and various reaction conditions have been reported (Table 6). While terminal alkynes were mostly coupled in the presence of a Cu(I) cocatalyst (Table 6, entries 1–3 and 5), internal alkynes were successfully converted under copper-free conditions (Table 6, entries 4[63] and 6[64]). In most cases, the most sterically demanding group on the triple bond (*t*Bu, $SiMe_3>Ph>CO_2Et$, Et, CH_2CH_2R, Me) is found in the 2-position of the indole or benzofuran and the substitution pattern in the product is therefore predictable. Since trimethylsilyl substituents are readily cleavable from the indole core, trimethylsilylalkynes serve as synthons for terminal alkynes, but the opposite regiochemistry is obtained.[63,64] The nitrogen atom of the iodoaniline may either be unprotected (Table 6, entries 1 and 4), acylated (Table 6, entries 2 and 4)[63] or even attached to the solid support as an aminal (Table 6, entry 6).[64]

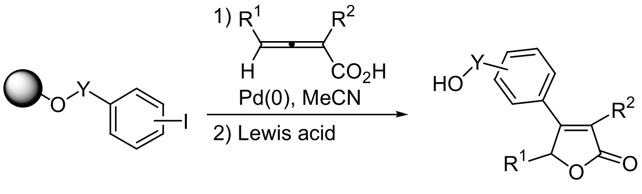
The coupling of 1,3- and 1,4-dienes with aryl halides bearing an *ortho*-nucleophilic group such as amino or hydroxyl groups was developed in the liquid phase by Larock et al.[65] and is one of the most versatile carboannelation reactions. Similarly, the reaction of an immobilised aminoiodoarene on a solid support with 1,3-butadienes (Table 6, entries 7–9 and 11) or 1,4-pentadienes (Table 6, entries 10 and 12) led to the formation of dihydroindoles, dihydrobenzofurans, tetrahydroquinolines and tetrahydrobenzopyranes, respectively.

Recently, the reactions of the polymer-bound aryl halides **8.1** with 2,4-disubstituted allenecarboxylic acids leading to the polymer-bound butenolides **8.2** have been reported. After cleavage from the polymer, the substituted butenolides can serve as important building blocks in the synthesis of natural products (Scheme 8).[76]

2.4. Cross-coupling reactions on solid supports

In general, cross-coupling reactions are extremely valuable tools for the construction of complex structures. The accessibility of suitable building blocks, in former times the bottleneck in library syntheses, has improved since a broad variety of alkenyl- or aryl-substituted stannanes or boranes can now be purchased from commercial suppliers.

2.4.1. Stille reactions. The Stille reaction was one of the first cross-coupling reactions performed on a solid support.[77] The reaction conditions employed for the palladium-catalysed coupling of aryl-, vinyl- or alkynyl-stannanes with aryl or alkenyl bromides, iodides or triflates, were chosen by analogy with the liquid phase procedures and often feature an arsine or trifurylphosphine as an added ligand. Due to the tedious separation of the inorganic tin and organotin reagents or by-products in the solution phase, this



8.1
Y = CO, $(CH_2)_{1,2}$

8.2

Scheme 8. Synthesis of butenolides.[76]

Table 7. Stille reactions with immobilised aryl halides

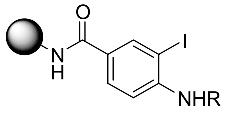
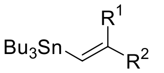
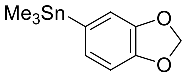
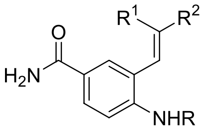
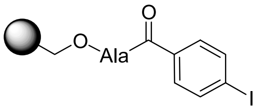
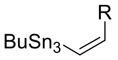
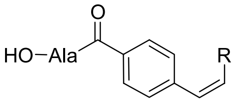
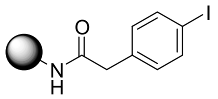
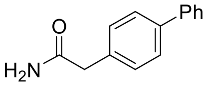
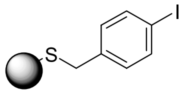
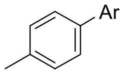
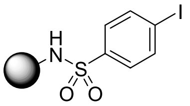
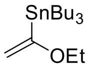
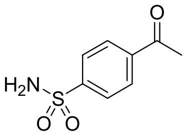
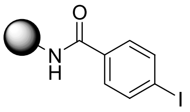
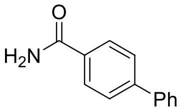
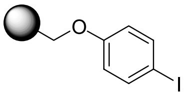
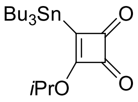
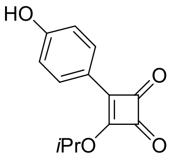
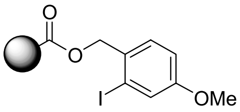
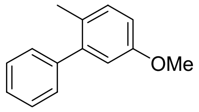
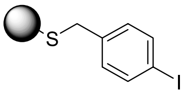
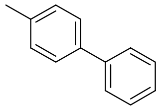
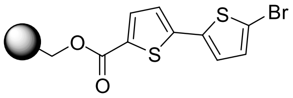
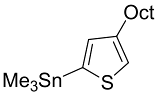
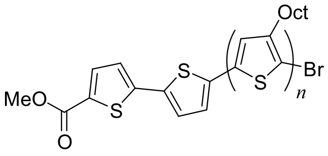
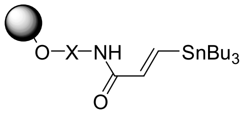
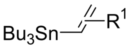
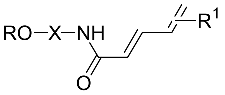
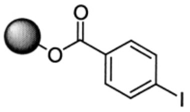
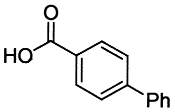
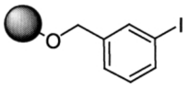
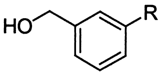
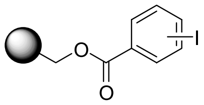
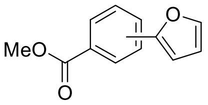
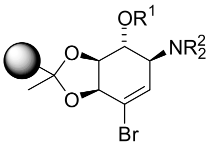
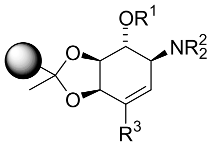
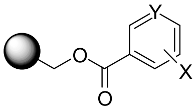
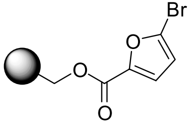
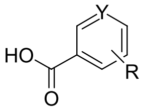
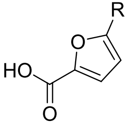
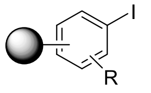
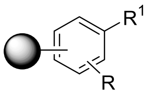
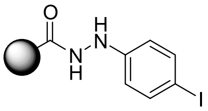
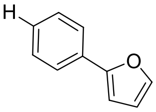
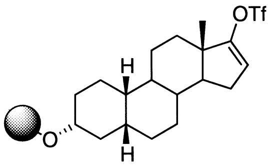
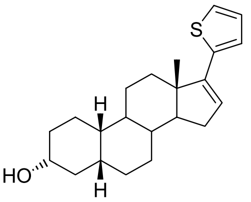
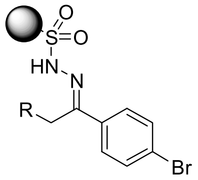
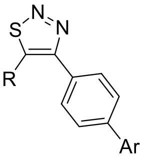
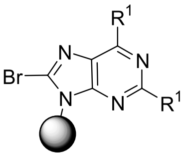
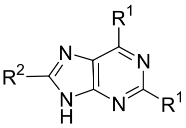
Entry	Starting material	Stannane	Product(s)	Reaction conditions	No. of exps; yield (%)	Ref.
1	 Rink amide	 R^1=H, Me; R^2=H, Me, Ph or 	 Cleav.: 5% TFA, CH_2Cl_2	$Pd_2(dba)_3$, $AsPh_3$, NMP, 45°C, overnight	5 exps; 85–91; >90 pur.	77
2	 Wang resin	 R=H, Me	 Cleav.: 95% TFA, CH_2Cl_2	$Pd_2(dba)_3$, $AsPh_3$, NMP, 45°C, overnight	2 exps; 88–92; >90 pur.	77
3	 Rink resin	Bu_3SnPh	 Cleav.: 5% TFA, CH_2Cl_2	$Pd_2(dba)_3$, P(2-Furyl)$_3$, LiCl, NMP, rt, 12 h	33 exps; ca. 90 pur.	79
4	 Rink amide with NpSSMpact linker	Me_3SnAr; Ar=Ph, *m*-$AcOC_6H_4$	 Cleav.: hν (350 nm), MeCN	$Pd_2(dba)_3$, P(2-Furyl)$_3$, LiCl, NMP, rt, 12 h	21–27 exps; ca. 80–90 pur.	79
5	 Rink amide		 Cleav.: 20% TFA, CH_2Cl_2	$Pd_2(dba)_3$, $AsPh_3$, NMP, rt, 15 h	1 exp	16
6	 Rink amide Tentagel	Bu_3SnPh	 Cleav.: 99% aq. TFA, 1 h	$Pd_2(dba)_3$, $AsPh_3$, NMP, microwave irradiation (3.8 min, 40 W)	1 exp; 85; >99 conv.	80
7	 Wang resin		 Cleav.: 20% TFA, CH_2Cl_2, rt, 20 min	$PdCl_2(PPh_3)_2$, CuI, DMF, rt, 30 h	1 exp	81
8	 polystyrene with magnetite core	Me_3SnPh	 Cleav.: $Pd(OAc)_2$, NH_4HCO_2, DMF, 65°C, 20 h	$Pd_2(dba)_3$, P(2-Furyl)$_3$, LiCl, NMP, 65°C, 22 h	1 exp	82

Table 7 (*continued*)

Entry	Starting material	Stannane	Product(s)	Reaction conditions	No. of exps; yield (%)	Ref.
9	 polystyrene with thio linker and with magnetite core	Me_3SnPh	 Cleav.: hν (350 nm), DMF, 6 h	$Pd_2(dba)_3$, P(2-Furyl)$_3$, LiCl, NMP, microwave irradiation, 2 h	1 exp; 8.5	82
10	 polystyrene		 Repetitive coupling and bromination; *n*=1 to 3; cleav.: NaOMe, THF, reflux then MeI, 18-c–6, reflux, 3 h	$PdCl_2(PPh_3)_2$, LiCl, DMF, 80°C	5 exps (trimer to tetramer), 89–95 pur.	83
11	 Wang or PEG; X=Gly, Phe, Ala-Aca, Arg(Pbf)-Aca	 Various substituents	 Cleav.: R=H; TFA/CH_2Cl_2/H_2O (80:15:5), rt, 1 h; R=Me: CH_2Cl_2, MeOH, DBU, rt, overnight	$Pd_2(dba)_3$, $AsPh_3$, NMP, rt, overnight	>60 exps	84
12	 Tentagel S with photocleavable linker	Bu_3SnPh	 Cleav.: hν (Hg pressure, >320 nm)	$Pd_2(dba)_3$, $AsPh_3$, NMP, 50°C, 42 h	1 exp; 50; 93 pur.	85
13	 polystyrene with base labile linker	Bu_3SnR; R=Aryl, Hetaryl or Alkenyl	 Cleav.: 6 equiv. NaOMe, MeOH/dioxane (1:4), rt, 24 h	$Pd_2(dba)_3$, $AsPh_3$, dioxane, 50°C, 24 h (preferentially) or $Pd(PPh_3)_4$, dioxane, 100°C, 24 h	49–95 exps	86
14	 polystyrene on SynPhase crown	Bu_3Sn(2-Furyl)	 Cleav.: 0.1 M NaOMe, THF/MeOH (4:1), rt, 20 h	$Pd_2(dba)_3$, $AsPh_3$, THF	2 exps; quant; 75–>90 pur.	87
15	 Wang type diol linker	Bu_3SnR^3; R^3= various alkenyl groups		$Pd(PPh_3)_4$, dioxane, 100°C, 24 h	11 exps	88
16	  polystyrene; Y=CH, H	Bu_3SnR; R=Ph, Ethenyl, 2-Furyl, 2-Thienyl, *o*-$Et_2NC(O)C_6H_4$, *o*-$Et_2NC(O)OC_6H_4$	  Cleav.: LiOH/H_2O/MeOH/THF	$Pd(PPh_3)_4$, DMF, 60°C, 24–48 h	22 exps; 71–>95	89

(*continued on next page*)

Table 7 (*continued*)

Entry	Starting material	Stannane	Product(s)	Reaction conditions	No. of exps; yield (%)	Ref.
17	 various scaffolds	R^1SnBu_3: R^1= 2-Furyl, 2-Thienyl 2-Pyr, 3-Pyr, Ethenyl		$Pd_2(dba)_3$, $AsPh_3$, dioxane, 50°C, 24 h	9 exps; 37–95	49
18	 polystyrene or TentaGel or ArgoPore	Bu_3Sn(2-Furyl)	 Cleav.: $Cu(OAc)_2$, MeOH, pyr, rt, 2 h	$Pd_2(dba)_3$, $AsPh_3$, dioxane, 60°C, 24 h	1 exp; 50–90	21
19	 polystyrene with fluoride-labile linker	Bu_3Sn(2-Thienyl)	 Cleav.: TBAF, TMU, 100°C, 1 h	$Pd(PPh_3)_4$, LiCl, DMF, 110°C, 3 h	1 exp; 38	52
20	 polystyrene	Bu_3SnAr; Ar=Ph, *p*-F-C_6H_4	 Cleav.: $SOCl_2$, $ClCH_2CH_2Cl$, 60°C, 5 h	$PdCl_2(PPh_3)_2$, DMF, 90°C, 24 h	3 exps; 76–80	90
21		R^2SnBu_3: R^2=Ph, 2-Furyl, C(OEt)CH_2, 2-Pyr, C≡CPh, *m*-EtOC_6H_4, Ethenyl	 Cleav.: 20% TFA, $ClCH_2CH_2Cl$	$Pd(OAc)_2$, dppp, Cu_2O, NMP, 100°C, 20 h	8 exps; 21–>98	91,92

carbon–carbon bond-forming reaction is particularly suitable for solid phase synthesis.

Immobilised aryl halides have been coupled with aryl- and alkenylstannanes to a large extent (Table 7). Stannanes attached to a solid support have been used less frequently for Stille reactions (Table 8), but they have been used in Ellman's benzodiazepine synthesis

Table 8. Stille reaction with polymer-bound stannanes

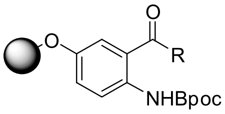
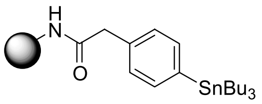
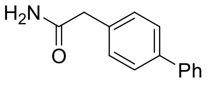
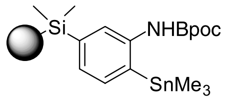
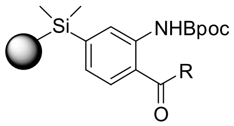
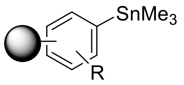
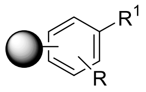
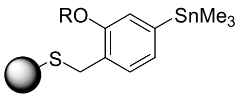
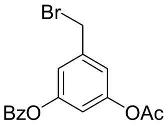
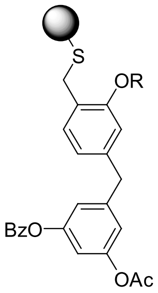
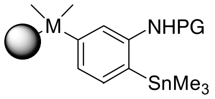
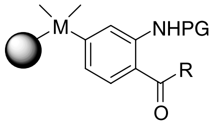
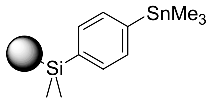
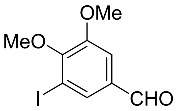
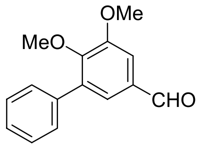
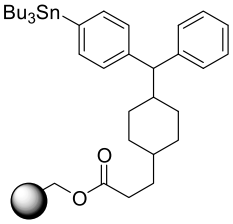
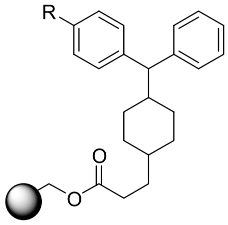
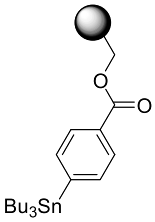
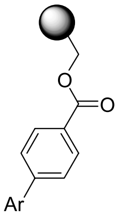
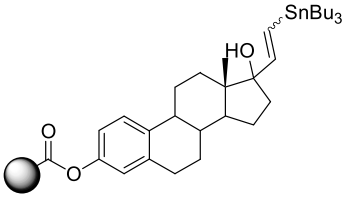
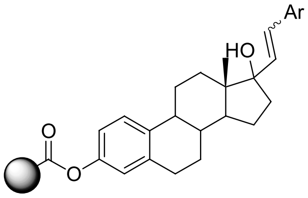
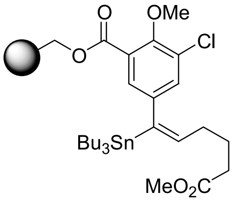
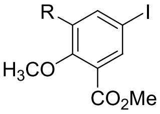
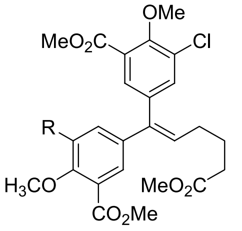
Entry	Starting material	Electrophile	Product(s)	Reaction conditions	No. of exps; yield (%)	Ref.
1	 polystyrene with linker	RCOCl; R= *o,m,p*-MeOC_6H_4, *c*Hex, 2-Me-5-NCC_6H_4, *m*-$CF_3C_6H_4$, *p*-*t*BuC_6H_4, *o*-ClC_6H_4, 1-(*p*-ClPh)*c*Pent, $CH_2CH_2CO_2Me$, Thienyl, 2-Furyl, 1-Ad, 3-(1,2-methylene-dioxo)C_6H_3, 2-Naphthyl		$Pd_2(dba)_3\cdot CHCl_3$, K_2CO_3, THF, rt	52–82 exps; >80 pur.	93,94

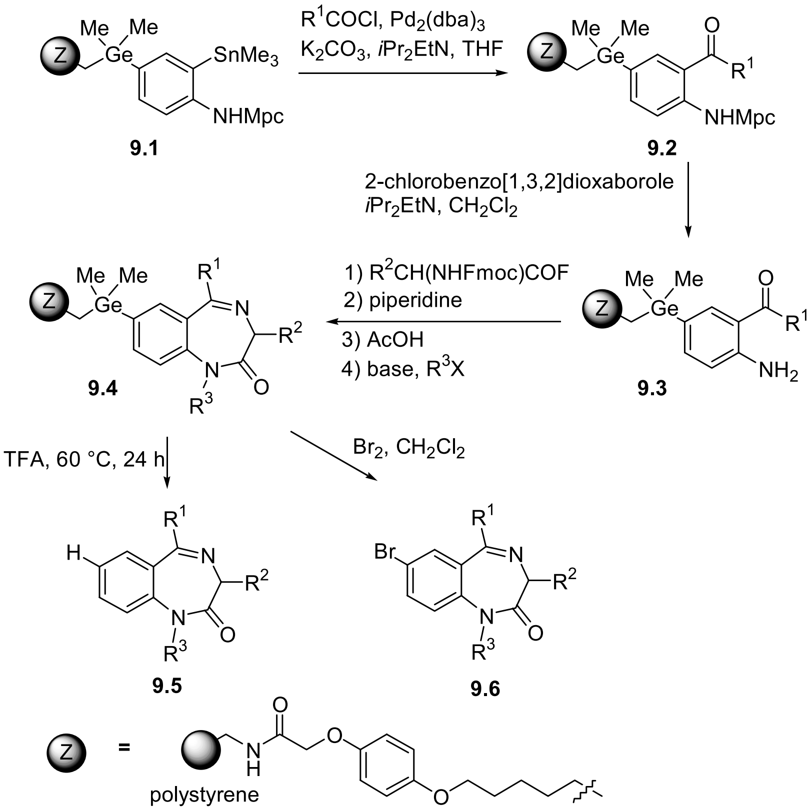
Table 8 (*continued*)

Entry	Starting material	Electrophile	Product(s)	Reaction conditions	No. of exps; yield (%)	Ref.
2	 Rink amide	PhI or PhOTf	 Cleav.: 5% TFA, CH_2Cl_2	$Pd_2(dba)_3$, TFP, LiCl, NMP, rt, 12 h	PhI: 15 exps; PhOTf: 3 exps	79
3	 polystyrene with linker	RCOCl; R= *m*,*p*-$MeOC_6H_4$, 1-Ad, Ph		$Pd_2(dba)_3$· $CHCl_3$, K_2CO_3, THF, *i*Pr_2NH, rt, 1 h	>50	78
4		R^1X; R^1X=ArOTf, $ArCH_2Br$		$PdCl_2(PPh_3)_2$, LiCl, DMF, 120°C, 28 h	Several exps. claimed	46
5	 Tentagel			$Pd(PPh_3)_4$, Et_3N, reflux, 4 h	Several exps. claimed	46
6	 M=Si, PG=Bpoc or M=Ge, PG=Mpc	RCOCl; R= *m*,*p*-$MeOC_6H_4$, 1-Ad, 3-(1,2-methylene-dioxo)C_6H_3, 2-Naphthyl		$Pd_2(dba)_3$· $CHCl_3$, K_2CO_3, THF, rt, 1 h	>58 exps	95
7	 R=H, OMe polystyrene with linker		 Cleav.: 50% TFA, CH_2Cl_2	$Pd(PPh_3)_4$, aq. Na_2CO_3, DME, reflux, 12 h	1 exp	96
8	 polystyrene	RBr; R=2-, 3-Pyr, Ph, 2-Thienyl and other hetaryl		$Pd(PPh_3)_4$, LiCl, DMF, 100°C	10 exps	97

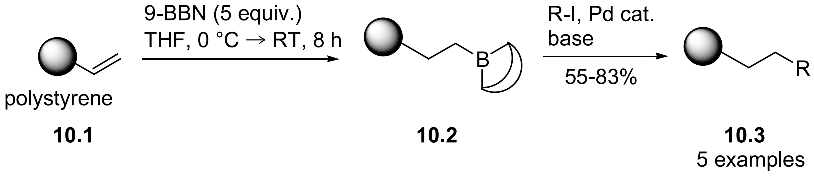
(*continued on next page*)

Table 8 (*continued*)

Entry	Starting material	Electrophile	Product(s)	Reaction conditions	No. of exps; yield (%)	Ref.
9		ArX; X=Br, I		Palladacycle, LiCl, NMP, 90°C	6 exps; 80–>95	98
10	 oxidized Wang linker	ArX	 Cleav.: 5 N NaOH, MeOH/dioxane	Pd(PPh$_3$)$_4$, 3,5-di-*t*Bu-4-hydroxy-toluene, toluene, N$_2$, 90–100°C, 24 h	8 exps; 17–75	99
11		 R=H, Me	 Cleav.: NaOMe, THF/MeOH 2:1, reflux, 20 h	Pd$_2$(dba)$_3$, AsPh$_3$, CsF, DMF, 80°C, 12 h	2 exps; 75–85 pur.	74



Scheme 9. Synthesis of benzodiazepines.[78]



Scheme 10. Derivatisation of a borane.[101]

(Scheme 9[78]). Starting from the stannane **9.1**, palladium-catalysed Stille coupling with acid chlorides furnished ketones **9.2**. The latter were deprotected to give anilines **9.3**. The benzodiazepine moiety **9.4** was elaborated in a four step sequence. Final cleavage from solid support gave hydrocarbons **9.5** via traceless cleavage of arylbromides **9.6**.

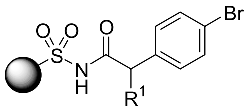
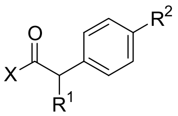
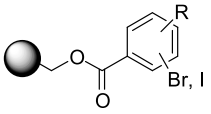
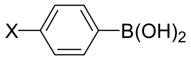
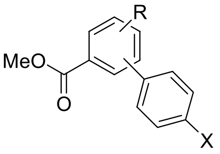
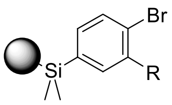
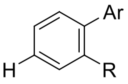
Various aryl bromides and iodides can be used in this reaction. The reaction conditions may include microwave irradiation (Table 7, entry 6). It is interesting to note that a Stille coupling reaction can be performed on a polymer-bound halobenzyl ester, which was subsequently cleaved by palladium-catalysed hydrogenation to give the corresponding substituted methylarenes in the liquid phase (Table 7, entry 8).

2.4.2. Suzuki coupling reactions. The palladium-catalysed Suzuki reaction of aryl halides and aryl triflates with arylboronic acids to form biaryls has emerged as a powerful tool in organic synthesis (for a review, see Ref. 100). In the last few 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. The mild reaction conditions, the compatibility with most functional groups and the ready availability of the starting material (boronic acids) has made this transformation a powerful tool also in SPOS. Additional benefits of the Suzuki reaction, relative to other cross-coupling processes, are the general non-toxicity and the thermal, air and moisture stability of the boronic acids.

Starting from a vinyl-substituted resin **10.1**, hydroboration with 9-BBN furnishes the homobenzylborane **10.2** (Scheme 10). This intermediate can be coupled with various functionalised aryl iodides as well as vinyl and alkyl iodides giving rise to resins **10.3** with amide, ester or protected hydroxy functionalities.[101] Similarly, bromostyrene could be coupled with functionalised boranes for the attachment of preformed handles, e.g. for the construction of the silicon traceless linker (Table 9, entries 11,[102] 54 and 55[103])

In the case of aromatic iodides, the couplings were performed using $Pd(OAc)_2$ (0.3 equiv.), PPh_3 (0.9 equiv.), NaOH (3 equiv.), a phase transfer agent (Triton B, 1.5 equiv.) and the iodide (4 equiv.) in DMF at 85°C for 14 h. The alkenyl and alkyl iodides were coupled using $PdCl_2(dppf)$ as a catalyst and K_2CO_3 as a base. The microwave-assisted coupling of aryl- and heteroaryl boronic acids with polymer-bound bromo- and iodobenzoic acids proceeds under quite mild condition within short reaction

Table 9. Suzuki reactions with immobilised aryl or alkenyl halides and triflates

Entry	Starting material	Aryl- and alkyl-borane/boronic acid	Product(s)	Reaction conditions	No of exps; yield (%)	Ref.
1	 polystyrene with linker; R^1=H, Me, Et, *i*Pr, Bn	$R^2B(OH)_2$ or *i*Bu-9BBN; R^2=Ph, *p*-$F_3CC_6H_4$, *p*-$MeOC_6H_4$, 2,6-$Cl_2C_6H_3$,	 Cleav.: 1) CH_2N_2; 2) OH^- (X=OH) or amine (X=NR^3_2)	$Pd(PPh_3)_4$, Na_2CO_3, THF, 65°C	10 exps; 87–100	106
2	 polystyrene; R=H, Me, OMe	 X=H, OMe, Me, NO_2	 Cleav.: 0.2 equiv. NaOMe	$Pd(PPh_3)_4$, (optimum) or $Pd(PPh_3)_2Cl_2$ or $Pd(C_3H_5)_2Cl_2$/ PPh_3 or $PdBn(PPh_3)_2Cl$	9 exps; 90>95	107
3	 Wang resin with linker	$ArB(OH)_2$; Ar=Ph, *p*HOC_6H_4	 Cleav.: TFA	$Pd(PPh_3)_4$, aq. 2 M Na_2CO_3, EtOH, 90°C, 16–24 h	2 exps	108, 109

(*continued on next page*)

Table 9 (*continued*)

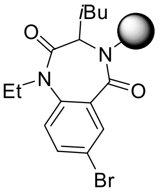
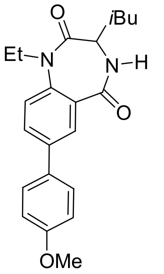
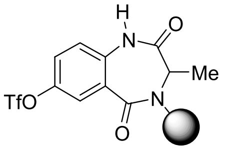
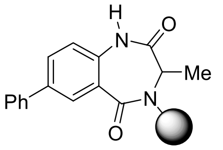
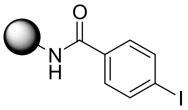
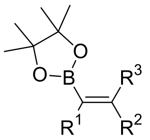
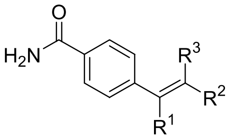
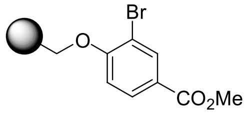
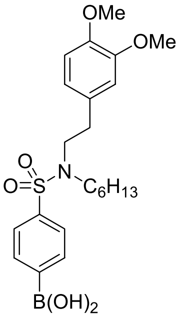
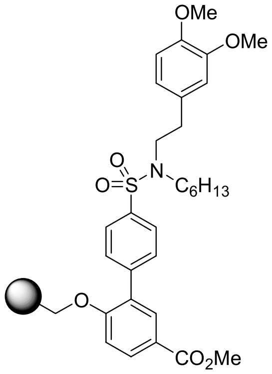
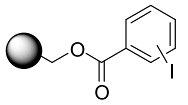
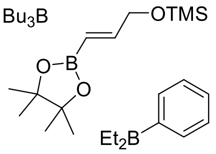
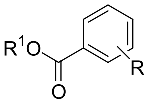
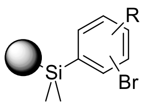
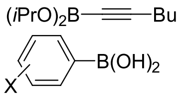
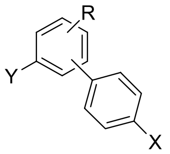
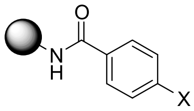
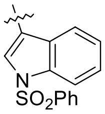
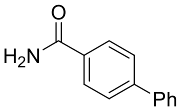
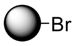
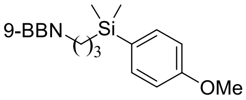
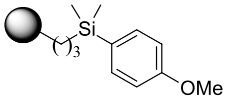
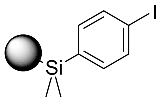
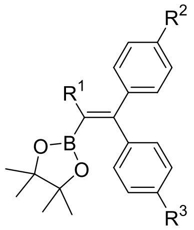
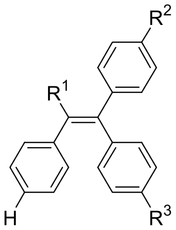
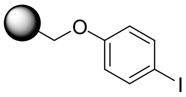
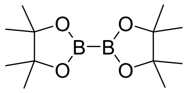
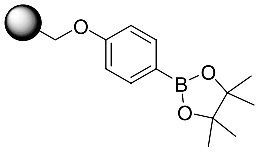
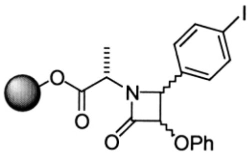
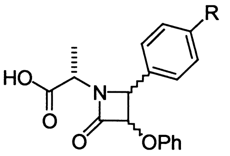
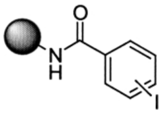
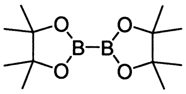
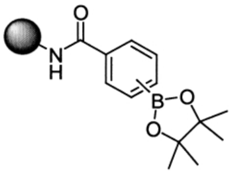
Entry	Starting material	Aryl- and alkyl-borane/boronic acid	Product(s)	Reaction conditions	No of exps; yield (%)	Ref.
4	 polystyrene with PAL type linker	p-MeOC$_6$H$_4$B(OH)$_2$	 Cleav.: TFA/Me$_2$S/H$_2$O (90:5:5), 36 h	Pd(PPh$_3$)$_4$, 2 M aq. K$_2$CO$_3$, THF, reflux, 18 h	1 exp; 62	110
5	 polystyrene with additional linker	PhB(OH)$_2$		Pd(PPh$_3$)$_4$, K$_3$PO$_4$, dioxane, 85°C, 8.5 h	1 exp	111
6	 Rink amide		 Cleav.: 30% TFA, CH$_2$Cl$_2$	Pd(PPh$_3$)$_2$Cl$_2$, 3 M KOH, DME, 80°C	10 exps; 75–>95	112
7	 polystyrene			Pd(PPh$_3$)$_4$, 2 M aq. Na$_2$CO$_3$, EtOH, 80°C, 25 h	1 exp; detection by MAS ^{1}H NMR	113
8	 Sasrin or Wang resin	R–B(OH)$_2$ R=Ph, 2-Thienyl 	 Cleav.: R^1=H: TFA, CH$_2$Cl$_2$, RT, 30 min; R^1=Me: 3 equiv. NaOMe, MeOH, THF, 1 h	Pd(PPh$_3$)$_4$, or Pd(dppf)$_2$Cl$_2$ or Pd$_2$(dba)$_3$ (optimum); K$_2$CO$_3$, DMF, rt.	6 exps; 50–91; 100 conv.	114

Table 9 (*continued*)

Entry	Starting material	Aryl- and alkyl-borane/boronic acid	Product(s)	Reaction conditions	No of exps; yield (%)	Ref.
9	 Wang resin with linker, R=H, OMe	 X=H, *p*-Me, *p*-MeO, *p*-HOCH$_2$, *p*-Cl, *m*-NO$_2$	 Cleav.: Y=H: TFA; Y=I: ICl; Y=Br: Br$_2$/pyr	Pd(PPh$_3$)$_4$, Na$_2$CO$_3$, DME, reflux or Pd(PPh$_3$)$_4$, Et$_3$N/DMF reflux, 24 h	22 exps; 36–99	115
10	 Rink amide Tentagel; X=I, Br	RB(OH)$_2$; R=Ph, 2-Naphthyl, 2-Thienyl, *p*-MeOC$_6$H$_4$, *p*-FC$_6$H$_4$, *o*-MeOC$_6$H$_4$, *m*-NO$_2$C$_6$H$_4$, 	 Cleav.: 99% aq. TFA, 1 h	Pd(PPh$_3$)$_4$, Na$_2$CO$_3$, H$_2$O, EtOH, DME, microwave irradiation (3.8 min, 40 W)	8 exps; 93–99	80
11	 polystyrene			Pd(PPh$_3$)$_4$, Na$_2$CO$_3$, DME, 80°C, 24 h	1 exp	102
12	 ArgoGel amine with linker	 (generated in situ) R^1=Me, Et, Pr; R^2=H, OMe, R^3=various substituents	 Cleav.: 30% TFA, CH$_2$Cl$_2$	Pd(dppf)Cl$_2$, KOH, DME, 25°C, 18 h	13–59; 1–4 isomers each	116
13	 Wang resin			Pd(0), KOAc, DMSO, 80°C, 2 h	1 exp	81
14	 Sasrin resin or ArgoGel-MB-OH	RB(OH)$_2$; R=Ph, *o*,*m*-MeOC$_6$H$_4$, *m*-NO$_2$OC$_6$H$_4$, *m*-(MeCONH)C$_6$H$_4$, 2-Thienyl	 Cleav.: 3–10% TFA, CH$_2$Cl$_2$	PdCl$_2$(dppf), Et$_3$N, DMF, 65°C, 12–24 h	7 exps; 65–83	17
15	 Rink amide on TentaGel			PdCl$_2$(dppf), KOAc, DMF, 80°C, 16 h	1 exp; >99 conv.	117

(*continued on next page*)

Table 9 (*continued*)

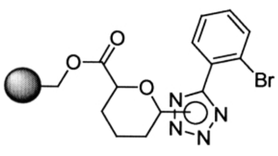
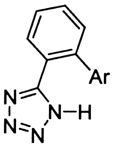
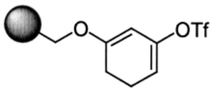
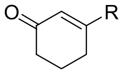
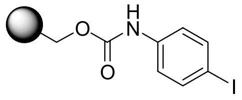
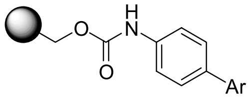
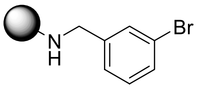
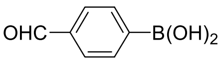
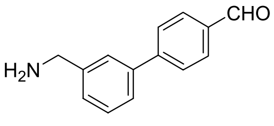
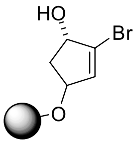
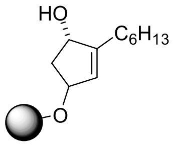
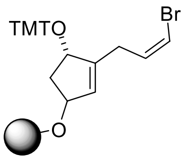
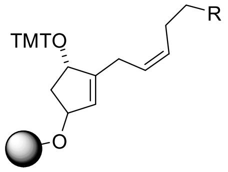
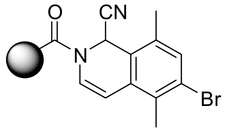
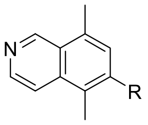
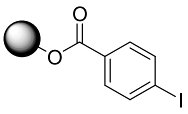
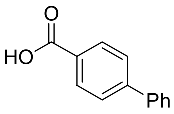
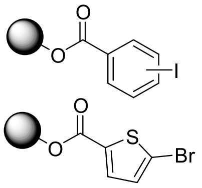
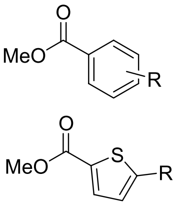
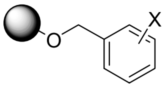
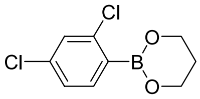
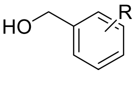
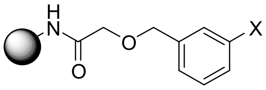
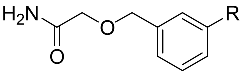
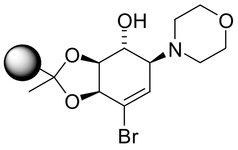
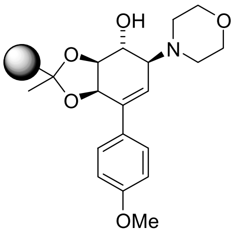
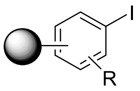
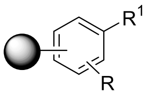
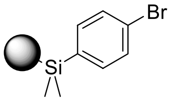
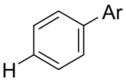
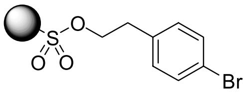
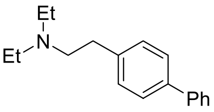
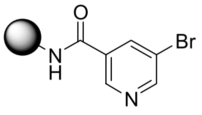
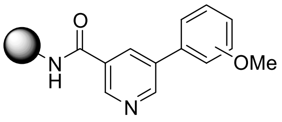
Entry	Starting material	Aryl- and alkyl-borane/boronic acid	Product(s)	Reaction conditions	No of exps; yield (%)	Ref.
16	 polystyrene	$ArB(OH)_2$; Ar=Ph, Tol	 Cleav.: 99% aq. TFA, 1 h	$Pd(PPh_3)_4$, Na_2CO_3, DME, 80°C, 24 h	2 exps; 53–57	118
17	 Rink resin	$RB(OH)_2$; R=aryl or Thienyl	 Cleav.: 5% TFA, Me_2CO	$Pd(PPh_3)_4$, aq. 2 M Na_2CO_3, dioxane, 90°C, 2.5 h	9 exps; 28–47; >95 pur.	119
18	 Wang resin	$ArB(OH)_2$; Ar=Tol, *p*-$MeOC_6H_4$		$Pd(PPh_3)_4$, Na_2CO_3, DME, 90°C, 24 h	2 exps; 32–33; 92–94 pur.	120
19	 Rink resin		 Cleav.: 5% TFA, CH_2Cl_2	Pd(0), aq. K_2CO_3, EtOH, xylene	1 exp; 60	121
20	 (presumably polystyrene) with dibutylsilyl linker	C_6H_{13}–9-BBN		$Pd(PPh_3)_4$, THF, Na_2CO_3, 65°C	1 exp	122
21	 (presumably polystyrene) with dibutylsilyl linker	RC_2H_4–9-BBN; R=$(CH_2)_2OMe$, Bu, $NHSO_2Ph$, NHBn, OEt, OMe, O*i*Pr		$Pd(PPh_3)_4$, THF, Na_2CO_3, 65°C	7 exps	122
22	 polystyrene	$RB(OH)_2$; R=Ph, 3-Thienyl	 Cleav.: 1 M aq. KOH	$Pd(PPh_3)_4$, DME, Na_2CO_3, 80°C, 36 h	2 exps; 17–19	123
23	 Tentagel S with photocleavalbe linker	$PhB(OH)_2$	 Cleav.: hv (Hg high pressure lamp, >320 nm)	$PdCl_2(dppf)$, Et_3N, DMF, 65°C, 18 h	1 exp; 72; 93 pur.	85

Table 9 (*continued*)

Entry	Starting material	Aryl- and alkyl-borane/boronic acid	Product(s)	Reaction conditions	No of exps; yield (%)	Ref.
24	 MeO-PEG 4000, 5000 or 6000	$RB(OH)_2$; R=aryl and hetaryl	 Cleav.: Et_3N, MeOH	$Pd(PPh_3)_4$, 2 M Na_2CO_3, DMF, 110°C, 10 h	18 exps; 46–93	124
25	 polystyrene with base-labile linker, X=Br, I	 RB(OH)2 (various subst. arom. and heteroarom. structures); C_6H_{13}–9BBN	 Cleav.: 6 equiv. NaOMe, MeOH/dioxane (1:4), rt, 24 h	$Pd(OAc)_2$, K_2CO_3, dioxane/H_2O (6:1), 100°C, 24 h	21 exps; 51–97	86
26	 polystyrene with Rink linker	p-$OHCC_6H_4B(OH)_2$, o-$MeC_6H_4B(OH)_2$	 Cleav.: 20% TFA, CH_2Cl_2, rt, 5 min	$Pd(OAc)_2$, K_2CO_3, dioxane/H_2O (6:1), 100°C, 24 h or $Pd(OAc)_2$, K_2CO_3, $MeOCH_2CH_2OH$ 100°C, 24 h	2 exps; 40–89	86
27	 polystyrene with Wang type linker	p-$MeOC_6H_4B(OH)_2$		$Pd(OAc)_2$, dioxane/H_2O (6:1), 100°C, 24 h; double coupling	1 exp	88
28	 various scaffolds	$R^1B(OH)_2$; R^1=aryl, Hetaryl		$Pd_2(dba)_3$, $AsPh_3$, dioxane, 50°C, 24 h	>10 exps; 37–95	49
29	 R=H, OMe polystyrene with linker	$ArB(OH)_2$; Ar=Ph, 1-Naphthyl, Tol, $(OHC)(MeO)C_6H_3$	 Cleav.: 50% TFA, CH_2Cl_2	$Pd(PPh_3)_4$, aq. Na_2CO_3, DME, reflux, 12 h	7 exps and a 100 cpd. library	96
30	 polystyrene with spacer	p-$MeC_6H_4B(OH)_2$	 Cleav.: Et_2NH, 60°C, 18 h	$Pd(PPh_3)_4$, Na_2CO_3, toluene, EtOH, 90°C, 20 h	1 exp; 23; 90 pur.	125
31	 Rink amide	o,p-$MeOC_6H_4B(OH)_2$		$Pd(PPh_3)_4$, Na_2CO_3, toluene, EtOH, 90°C, 20 h	2 exps; >25	126

(*continued on next page*)

Table 9 (*continued*)

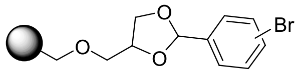
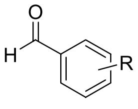
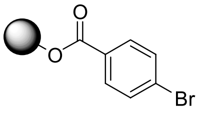
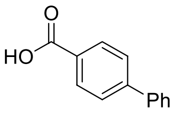
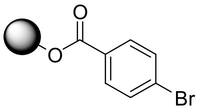
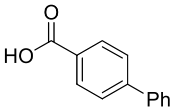
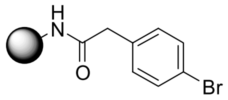
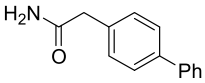
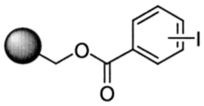
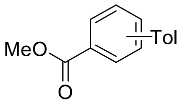
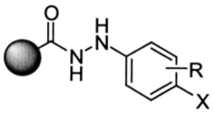
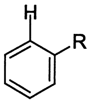
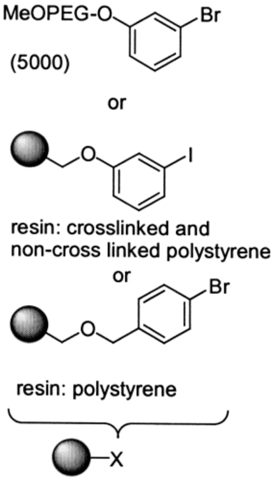
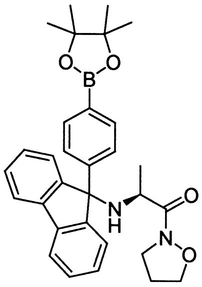
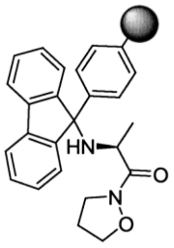
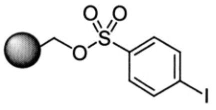
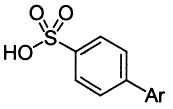
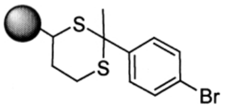
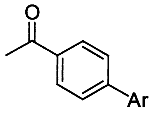
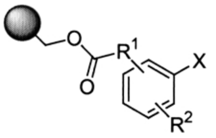
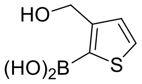
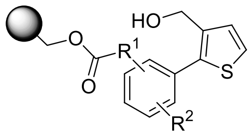
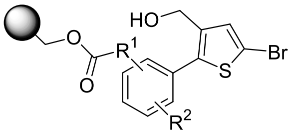
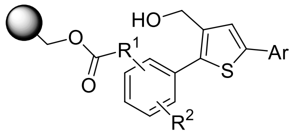
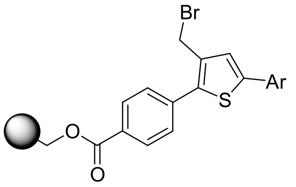
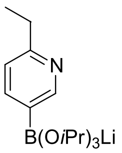
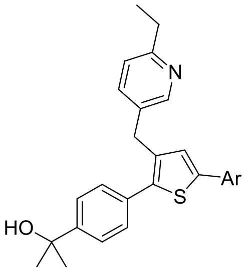
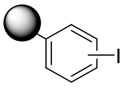
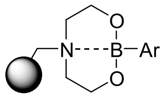
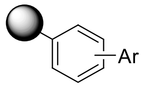
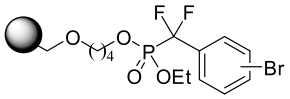
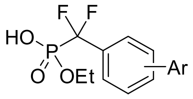
Entry	Starting material	Aryl- and alkyl-borane/boronic acid	Product(s)	Reaction conditions	No of exps; yield (%)	Ref.
32	 polystyrene	RB(OH)$_2$; R=Aryl or Hetaryl	 Cleav.: 3 M HCl/dioxane (1:1)	Pd(PPh$_3$)$_4$, Na$_2$CO$_3$, DME, reflux, 24–48 h	15 exps; 45–>95	127
33	 polystyrene with 9-phenyl-fluorenyl-9-yl linker (PhFI)	PhB(OH)$_2$	 Cleav.: 20% TFA, CH$_2$Cl$_2$/MeOH (9:1)	Pd(PPh$_3$)$_4$, Na$_2$CO$_3$, DME, 80°C, 16 h	1 exp; 68; >95 pur.	128
34	 polystyrene with 9-phenyl-fluorenyl-9-yl linker (PhFI acetic acid)	PhB(OH)$_2$	 Cleav.: 20% TFA, CH$_2$Cl$_2$/MeOH (9:1), 2h	Pd(PPh$_3$)$_4$, Na$_2$CO$_3$, DME, 80°C, 16 h	1 exp; 72; >95 pur.	129
35	 polystyrene with Knorr linker	PhB(OH)$_2$	 Cleav.: TFA, CH$_2$Cl$_2$ 2 h	Pd(PPh$_3$)$_4$, Na$_2$CO$_3$, THF/H$_2$O (4:1), 60°C, 2 d	1 exp; 72; >95 pur; reaction in Micro-Tube™	130
36	 polystyrene on SynPhase crown	*p*-TolB(OH)$_2$	 Cleav.: 0.1 M NaOMe, THF/MeOH (4:1), rt, 20 h	Pd(OAc)$_2$, K$_2$CO$_3$, THF/H$_2$O (6:1), 60°C, 2 d	2 exps; quant; 83–94 pur.	87
37	 polystyrene or TentaGel or ArgoPore X=Br, I; R=H, Me, F	RB(OH)$_2$; R=*p*-MeOC$_6$H$_4$; *p*-OHCC$_6$H$_4$, 2-Thienyl	 Cleav.: Cu(OAc)$_2$, *n*PrNH$_2$, rt, 2 h	Pd(PPh$_3$)$_2$Cl$_2$ or Pd(PPh$_3$)$_4$	5 exp; 60–93	21
38				PdCl$_2$(dppf), aq. 2 M Na$_2$CO$_3$, DMF, 80°C, overnight	4 exps; 50–90	131

Table 9 (*continued*)

Entry	Starting material	Aryl- and alkyl-borane/boronic acid	Product(s)	Reaction conditions	No of exps; yield (%)	Ref.
39	 Argogel-MBOH	$ArB(OH)_2$; Ar=Ph, *p*-MeC_6H_4, *p*-$MeOC_6H_4$, *o*-MeC_6H_4	 Cleav.: 20% TFA, CH_2Cl_2, rt, 1 h	Pd_2dba_3, K_2CO_3, DMF, CH_2Cl_2, 80°C, 23°C or 45°C, 18 h	4 exps; 51–58	132
40	 polystyrene	$ArB(OH)_2$; Ar=Ph, *p*-ClC_6H_4, *p*-$MeOC_6H_4$	 Cleav.: 2.5 equiv. $PhI(Tfa)_2$, CH_2Cl_2/EtOH/H_2O (4.5:4.5:1), rt, 30 min	$Pd(PPh_3)_4$, Na_2CO_3, DMF, DME, 80°C, overnight; repeat coupling	3 exps; 28–33	133
41	 X=Br or I; 19 different Wang or Merrifield resins			X=Br: $Pd(PPh_3)_4$, 2 M Na_2CO_3, DME, reflux, 7 h; X=I: $Pd(PPh_3)_4$ or Pd_2dba_3, rt	19 exps	134
42		7 $ArB(OH)_2$		$Pd(PPh_3)_4$, 2 M Na_2CO_3, DME, reflux, 7 h		134
43	 Ar=3,4-di-$MeOC_6H_3$		 Cleav.: a) MeMgBr, THF/toluene; b) NH_4Cl, EtOAc	$Pd(PPh_3)_4$, H_2O, DME, 80°C, 3 h	1 exp; 35; 65 pur.	134
44	 various linkers	 polystyrene		$Pd(PPh_3)_4$, various cond.	3 exps; 25–100	105
45	 non-crosslinked polystyrene	$ArB(OH)_2$	 Cleav.: 4 equiv. Me_3SiI, CH_2Cl_2, rt, 4 h	$PdCl_2(PhCN)_2$, K_2CO_3, DMF, rt, 24 h	28 exps; 43–90	135

(*continued on next page*)

Table 9 (*continued*)

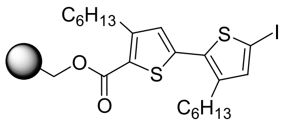
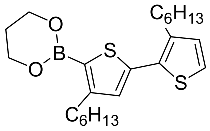
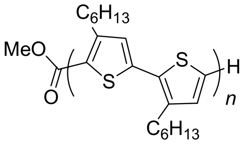
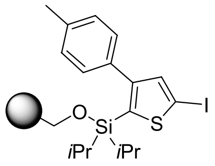
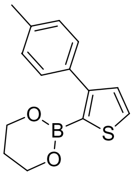
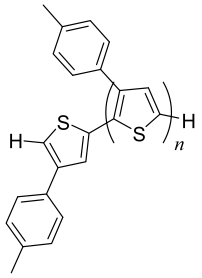
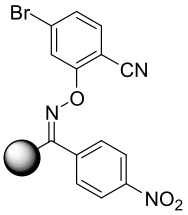
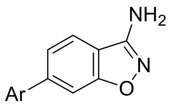
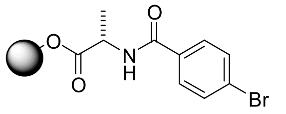
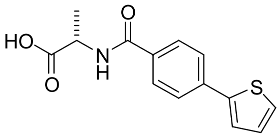
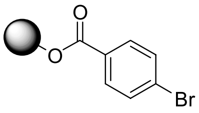
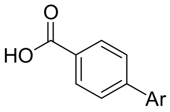
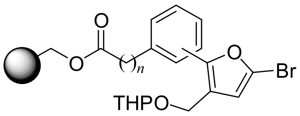
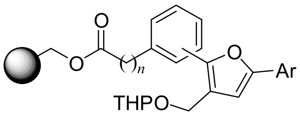
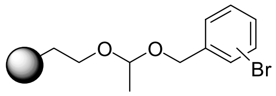
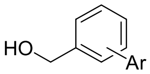
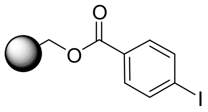
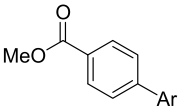
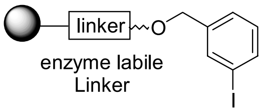
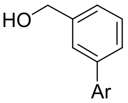
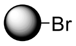
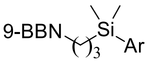
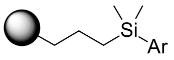
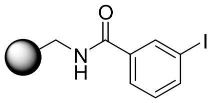
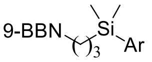
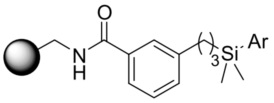
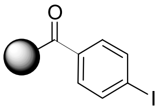
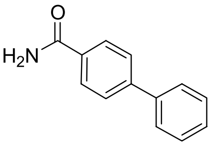
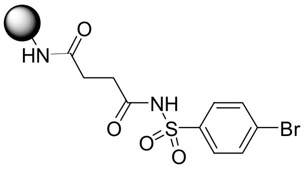
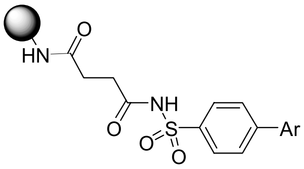
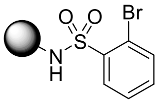
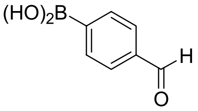
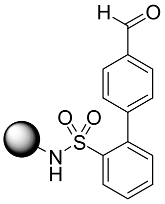
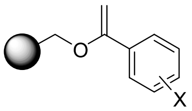
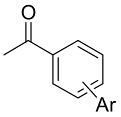
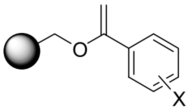
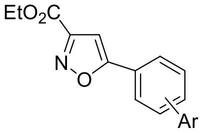
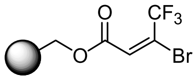
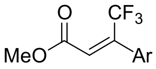
Entry	Starting material	Aryl- and alkyl-borane/boronic acid	Product(s)	Reaction conditions	No of exps; yield (%)	Ref.
45	 polystyrene		 Repetitive coupling and iodination; n=2 to 6; cleav.: a) Bu_4NOH; b) MeI	$Pd(PPh_3)_4$, CsF, THF, reflux, Ar	5 exps (dimer to hexamer), 15–93	136
46	 polystyrene		MeI  Repetitive coupling and iodination; n=1 to 3; cleav.: TBAF, THF	$Pd(PPh_3)_4$, $NaHCO_3$, THF, reflux, 8 h	5 exps (dimer to tetramer), 48–87	136–139
47	 polystyrene	$ArB(OH)_2$; Ar=Ph, 3,5-$(Cl)_2C_6H_3$, 3,5-$(CF_3)_2C_6H_3$, *p*-$OHCC_6H_4$	 Cleav.: TFA/5 N aq. HCl (4:1), 55°C, 2 h	$Pd(PPh_3)_4$, THF, 55°C, 36 h	4 exps; 41–54; 81–>96 pur.	59
48	 polystyrene with Rink type linker	(2-thienyl)$B(OH)_2$	 Cleav.: 1% TFA, CH_2Cl_2, 75 min	$Pd(PPh_3)_4$, aq. Na_2CO_3, DMF, 80°C, 24 h	1 exp; >90; >90 pur.	140
49	 MeO-PEG 5000	$ArB(OH)_2$; Ar=Ph, *p*-FC_6H_4, *m*-$O_2NC_6H_4$, *p*-ethenylC_6H_4	 Cleav.: a) 1 N NaOH; b) 12 N HCl	$Pd(PPh_3)_4$, 2 M K_2CO_3, DMF, 70–80°C, 3–4 h	3 exps; 55–60	141
50	 Wang resin; n=0,1	$ArB(OH)_2$; Ar=*m*-$NO_2C_6H_4$, *m*,*p*-ClC_6H_4, *m*-$MeOC_6H_4$, *p*-$tBuNHSO_2C_6H_4$		$Pd(OAc)_2$, PPh_3, 2 M Na_2CO_3, DME, 85–90°C	7 exps	142
51	 Wang with linker	$ArB(OH)_2$; Ar=Ph, *p*-MeC_6H_4		$Pd(PPh_3)_4$, Na_2CO_3, DME, 80°C, 24 h	4 exps; 60–68	143

Table 9 (*continued*)

Entry	Starting material	Aryl- and alkyl-borane/boronic acid	Product(s)	Reaction conditions	No of exps; yield (%)	Ref.
52	 REM resin	ArB(OH)$_2$; Ar=Ph, *p*-MeC$_6$H$_4$	 Cleav.: NaOMe, MeOH, THF	Pd(OAc)$_2$, P(*t*-Bu)$_3$, DIPEA, supercritical CO$_2$ (880 psi), 80°C, 16 h	2 exps; 67–70	29
53	 POE 6000 (PEG resin) see Scheme 1	ArB(OH)$_2$; Ar=*p*-MeOC$_6$H$_4$	 Cleav.: penicillin G acylase, pH 7.0, 10% MeOH, 37°C	Pd(PPh$_3$)$_4$, K$_3$PO$_4$, DMF, 80°C, 20 h	1 exp. 68	13
54	 polystyrene	 Ar=*p*-BrCH$_2$C$_6$H$_4$, *p*-HOCH$_2$C$_6$H$_4$, 2-(2′-HOCH$_2$)-Naphthyl, 2-(4-HOCH$_2$)-Thienyl		Pd(PPh$_3$)$_4$, Na$_2$CO$_3$, DMF, 75°C, 48 h	4 exps	103
55	 polystyrene	 Ar=*p*-HOCH$_2$CH$_2$C$_6$H$_4$, *N*-Boc-naphthylalanine methyl ester		Pd(PPh$_3$)$_4$, K$_3$PO$_4$, DMF, 75°C, 48 h	2 exps	103
56	 polystyrene resins with different levels of cross-linking (0.3–6.0% DVB), rink linker	PhB(OH)$_2$	 Cleav.: TFA/H$_2$O/CH$_2$Cl$_2$ 95:2.5:2.5	Pd(PPh$_3$)$_4$, K$_2$CO$_3$, DMF, 80°C	1 exp; 20–95 after 2 h, 100 after 48 h, depending on cross-linking	104
57		ArB(OH)$_2$; Ar=Ph, *p*-F$_3$CC$_6$H$_4$, *o*-MeC$_6$H$_4$		Pd(PPh$_3$)$_4$, Na$_2$CO$_3$, DMF/H$_2$O 15:1, 80°C, 45 h	3 exps; 88–97	144
58	 polystyrene with HMPB linker			Pd$_2$(dba)$_3$, P(*t*-Bu)$_3$, Cs$_2$CO$_3$, DMF 80°C, 4 h	1 exp; 97	145
59	 Wang or Merrifield resin; X=*m*-I, *p*-Br	ArB(OH)$_2$; Ar=*p*-OHCC$_6$H$_4$, *m*-O$_2$NC$_6$H$_4$, *m*-NHAcC$_6$H$_4$, *p*-HO$_2$CC$_6$H$_4$, *p*-NCC$_6$H$_4$, *m*-(F$_3$C)$_2$C$_6$H$_3$, 3-Thienyl	 Cleav.: 3% TFA, CH$_2$Cl$_2$, 25°C, 30 min	Pd(OAc)$_2$, dppf, K$_2$CO$_3$, DMF, 90°C, 16 h	6 exps; 60–79; >95 pur.	146

(*continued on next page*)

Table 9 (*continued*)

Entry	Starting material	Aryl- and alkyl-borane/boronic acid	Product(s)	Reaction conditions	No of exps; yield (%)	Ref.
60	 Wang or Merrifield resin; X=m-I, p-Br	(1) ArB(OH)$_2$; Ar=p-OHCC$_6$H$_4$, m-O$_2$NC$_6$H$_4$, m-NHAcC$_6$H$_4$, p-HO$_2$CC$_6$H$_4$, p-NCC$_6$H$_4$, m-(F$_3$C)$_2$C$_6$H$_3$, 3-Thienyl; (2) ethyl chlorooximido-acetate, NEt$_3$, THF, 1 h, four times	 Cleav.: 5% TFA, CH$_2$Cl$_2$, 25°C, 30 min	Pd(OAc)$_2$, dppf, K$_2$CO$_3$, DMF, 90°C, 16 h	7 exps; 38–80; ~90 pur.	146
61	 Wang resin	ArB(OH)$_2$; Ar=phenyl, 3-Thienyl, m-MeOC$_6$H$_4$, m-O$_2$NC$_6$H$_4$, m-EtOC$_6$H$_4$, p-FC$_6$H$_4$, p-MeOC$_6$H$_4$, p-MeSC$_6$H$_4$, 1	 Cleav.: MeONa in MeOH.THF (1/4), followed by flash chromatography	Pd(PPh$_3$)$_4$, Na$_2$CO$_3$, xylene/EtOH 80°C, 24 h	8 exps. 27–49 >95 pur.	147

Yield in parentheses refers to the bromobenzamide as starting material.

times (4 min, 40 W).[80] The yields were between 55 (alkyl) and 85% (aryl iodides) as determined by quantitative IR analysis of representative carbonyl bands.

Synthetically interesting is the conversion of aryl halides into the corresponding boronates. Treatment of polymer-bound aryl iodides with a pinacol ester of diborane under palladium-catalysis gave the corresponding polymer-bound boronates (Table 9, entries 13 and 15). The Suzuki coupling reaction was then carried out using a variety of aryl halides. Cleavage from the solid support delivered diverse biaryl libraries in good yields with high purities of the individual compounds (Table 10, entries 4 and 6).

The relation between the cross-linking in polystyrene resins and its effect on reaction rates was investigated for the

Table 10. Suzuki reactions with polymer-bound aryl and alkyl boranes

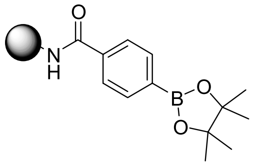
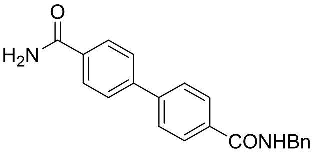
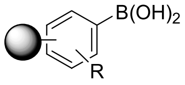
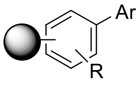
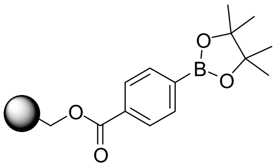
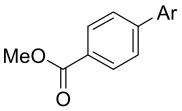
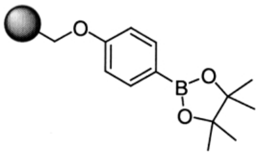
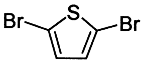
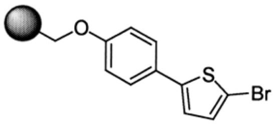
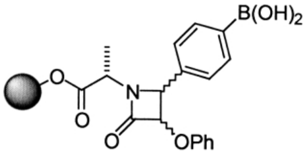
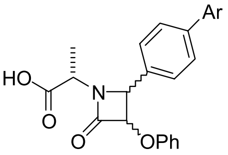
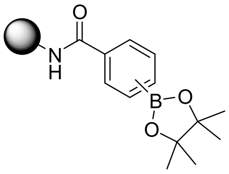
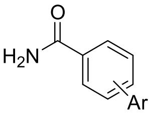
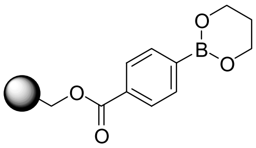
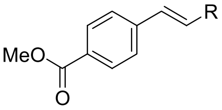
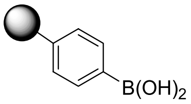
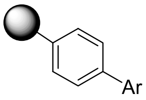
Entry	Starting material	Aryl halide	Product(s)	Reaction conditions	No. of exps; yield (%)	Ref.
1	 Rink amide	p-IC$_6$H$_4$CONHBn	 Cleav.: 30% TFA, CH$_2$Cl$_2$	Pd(PPh$_3$)$_4$, DMF, 80°C	10 exps; 75–>95	112
2		ArI		Pd(PPh$_3$)$_4$, EtOH, K$_2$CO$_3$, toluene, reflux, 12 h	Various examples claimed	46
3	 Wang resin	ArX; Ar=Ph, o-NO$_2$C$_6$H$_4$, m-MeOC$_6$H$_4$, o-NCC$_6$H$_4$	 Cleav.: a) 50% TFA, CH$_2$Cl$_2$ 30 min; b) Me$_3$SiCHN$_2$, CHCl$_3$, MeOH	Pd(PPh$_3$)$_4$, K$_2$CO$_3$, DMF	4 exps; 43–77 conv.	114
4	 Wang resin			Pd(0), aq. KOH, DME, 80°C, 2 h	1 exp	81

Table 10 (*continued*)

Entry	Starting material	Aryl halide	Product(s)	Reaction conditions	No. of exps; yield (%)	Ref.
5	 Sasrin resin or ArgoGel-MB-OH	ArI; Ar=Ph, *m*-$NO_2C_6H_4$, *p*-$MeOC_6H_4$	 Cleav.: 3–10% TFA, CH_2Cl_2	$PdCl_2$(dppf), Et_3N, H_2O, DMF, 40°C, 12–24 h	3 exps; 100 conv.; 60–86	17
6	 Rink amide Tentagel	ArX; X=Br, I; Ar=Ph, 2-Naphthyl, *p*-NCC_6H_4, *m*-NCC_6H_4, 6-MeO-Tropolonyl, *p*-$CF_3C_6H_4$, 2-(8-MeO)Naphthyl	 Cleav.: 20% TFA, CH_2Cl_2	$Pd(PPh_3)_4$, K_3PO_4 DMF, 80°C, 2.5–20 h	9 exps; 26–95	117
7	 polystyrene	$Ph_2I^+BF_4^-$; *p*-$MeOC_6H_4I^+BF_4^-$; 2-ThienylI$^+BF_4^-$; (*E*)-PhCH=CH-I$^+BF_4$	 Cleav.: NaOMe, MeOH/THF (1:4) reflux, 20 h	$Pd(PPh_3)_4$, Na_2CO_3, DMF, rt, 20 h	4 exps; 60–86	24
8	See Scheme 10					101
9	 polystyrene	ArBr Ar=*p*-$HO_2CC_6H_4$, *p*-$HOCH_2C_6H_4$, *p*-HOC_6H_4, $P(C_6H_4)_3$, *p*-$H_2NCH_2C_6H_4$, *p*-$H_2NSO_2CH_2C_6H_4$, 2-Thienyl, 2-Furyl		$Pd(PPh_3)_4$, Na_2CO_3, DME, 70°C, 72 h	9 exps; 23–86	148

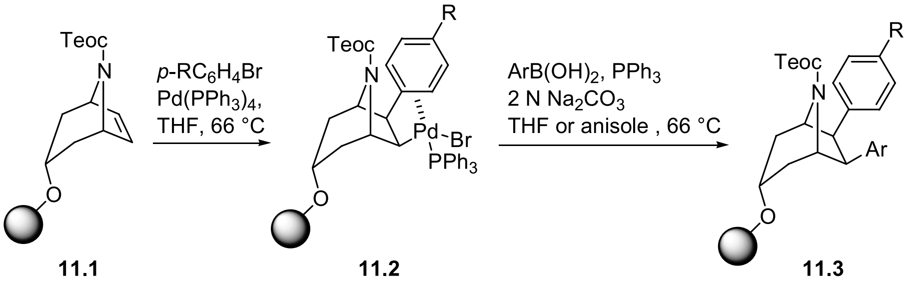
Suzuki coupling of immobilised 4-iodobenzoic acid with phenylboronic acid (Table 9, entry 56).[104] As expected, the reaction rate for the coupling process on low cross-linked resin (0.3% divinylbenzene (DVB)) is about 11-fold faster than on resins with higher cross-linking (2.7% DVB), but an unusual behaviour of higher cross-linked resins (3.0 and 6.0% DVB) has been observed. On these polymeric supports, only 3–5% yields of the cross-coupling product are obtained, presumably due to the limited site accessibility of the bulky $Pd(PPh_3)_4$ catalyst.

The organopalladium intermediate **11.2**, obtained from the carbopalladation of polymer-bound tropane derivative **11.1**, undergoes coupling with various aryl boronic acids to give the derivative **11.3** (Scheme 11).[41]

In general, Suzuki reactions with immobilised aryl halides (Table 9) appear to be more successful than with polymer-bound boronic acids (Table 10). A recent report describes the use of solid supported arylboronic acids in a resin-to-resin Suzuki coupling (RTR Suzuki strategy, Table 9, entry 43).[105]

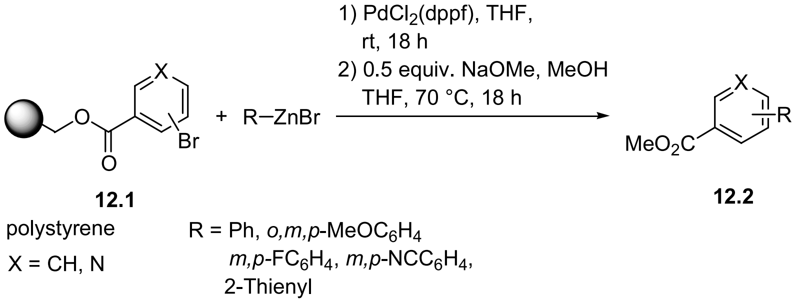
2.4.3. Cross-coupling reactions involving zincates (Negishi couplings).

The cross-coupling between (het)-arylzincates and aryl halides (Negishi coupling) provides a



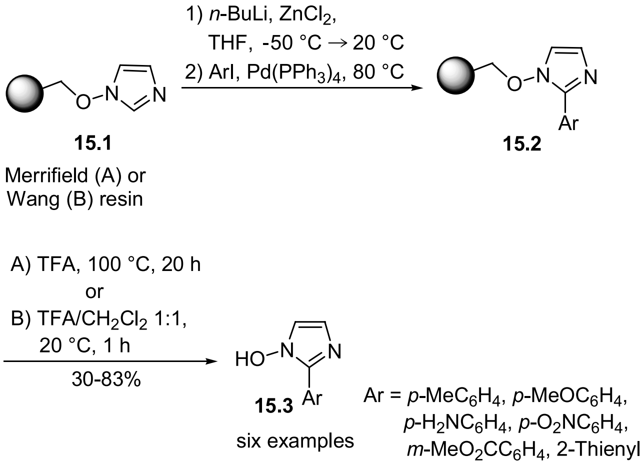
11.1 **11.2** **11.3**

Scheme 11. Carbometallation on the tropane framework.[41]

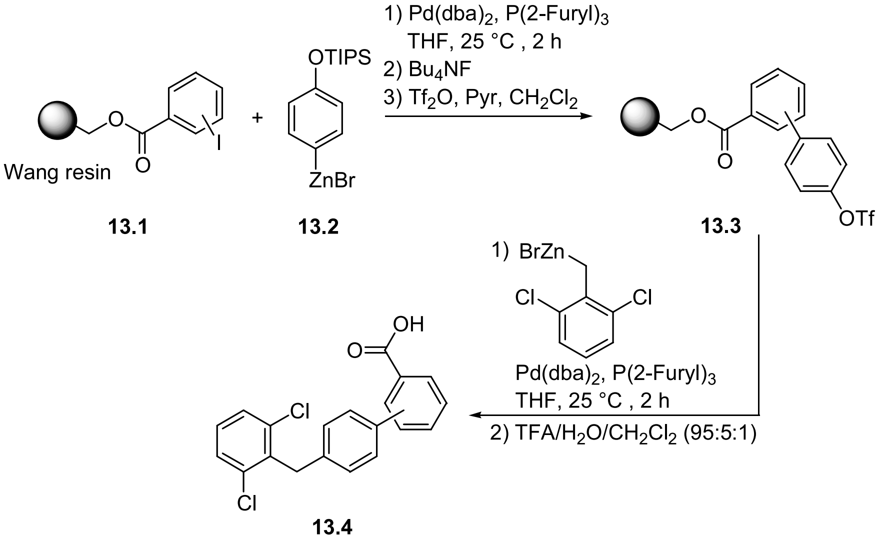


Scheme 12. Aryl–aryl cross-coupling reactions with polymer-bound aryl bromides.[149]

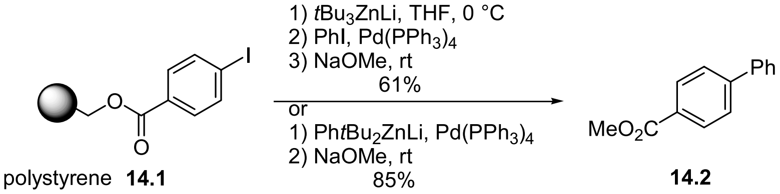
general access to (het)biaryls. Since zincates leave quite a large number of functional groups unaffected and are readily available from Grignard reagents or aryllithium compounds, this approach is very appealing. Polymer-bound aryl bromides **12.1** (Scheme 12),[149] iodides **13.1** and triflates **13.3** (Scheme 13)[150] have been coupled with various zincates such as **13.2**, furnishing after cleavage, esters **12.2** and acids **13.4**, respectively. Recently, the coupling of an immobilised arylzincate, prepared in situ from the corresponding aryl iodide **14.1** and *tert*-butylzincate (Scheme 14),[151] has been reported. The arylation of a polymer-bound imidacylzincate, synthesised from the imidazole **15.2**, gave the immobilized arylimidazoles **15.2** and subsequently, after cleavage from the resin, the hydroxyimidazoles **15.3** (Scheme 15).[152]



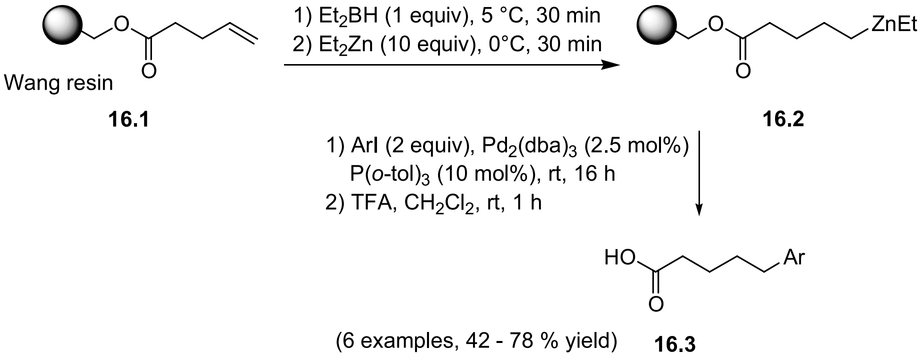
Scheme 15. Arylation of a polymer-bound imidacylzincate.[152]



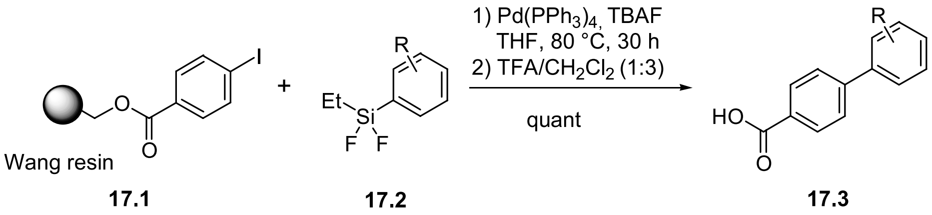
Scheme 13. Aryl–aryl cross-coupling reactions with polymer-bound aryl iodides and triflates.[150]



Scheme 14. Aryl–aryl cross-coupling reactions with polymer-bound arylzincates.[151]



Scheme 16. Utilisation of alkyl zinc species on a solid support.[154]



Scheme 17. Synthesis of unsymmetrical biaryls.[156,157]

In addition to benzylzincates, thymidine derivatives bearing carbonyl functionalities have been successfully employed in this reaction.[153] According to a recent report, however, nickel catalysis might be superior to palladium-catalysis for this type of coupling reactions.[154]

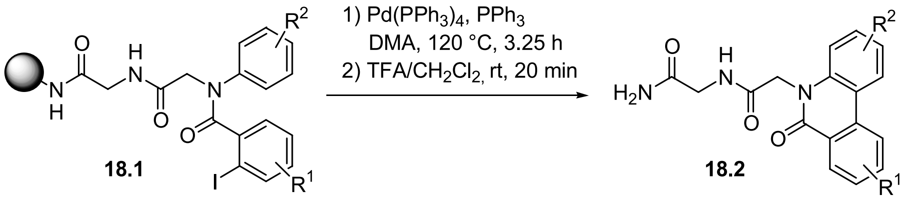
The same class of resin was used for the solid phase synthesis of 2-furylarenes, which were further elaborated in a Suzuki coupling (Table 9, entry 46).[142]

There is also one example of an immobilised alkylzincate and its Pd-catalysed coupling to aryl iodides.[155] The zincates were generated from a terminal olefin via hydroboration followed by transmetallation with diethylzinc (Scheme 16).

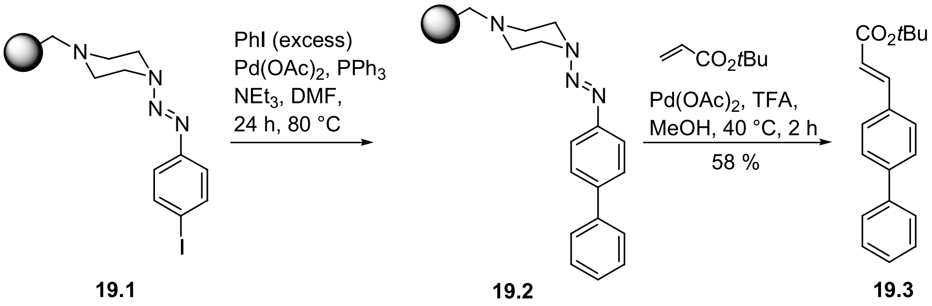
2.4.4. Cross-coupling reactions involving silicon compounds. A very recent example has been reported for the cross-coupling of arylfluorosilanes **17.2** with aryliodides **17.1** attached to solid support to give, after cleavage, the biaryl acids **17.3** (Scheme 17).[156,157] Optimisation of the reaction parameters has led to a complete conversion within 30 h.

2.4.5. Biaryl synthesis by arylation of arenes. The intramolecular arylation of arenes **18.1** on a polymeric support to produce a library of phenanthridones **18.2** has been disclosed in a patent (Scheme 18).[34]

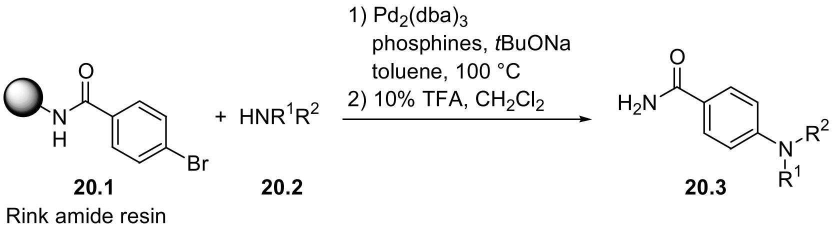
2.4.6. Reductive coupling of aryl halides leading to biaryls. The reductive coupling of iodobenzene to a triazene T1 linker-bound iodoarene **19.1** has been reported (Scheme 19).[18] The resulting biaryl **19.2** was cleaved off using another Heck coupling of the intermediate diazonium salt



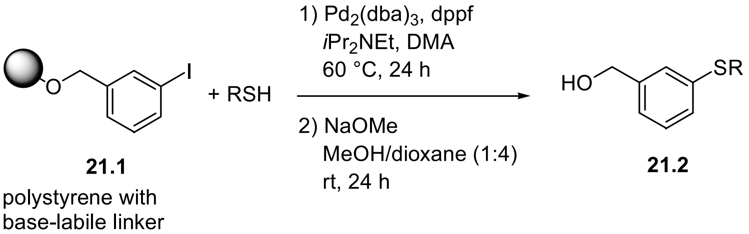
Scheme 18. Dimerisation leading to biaryls.[34]



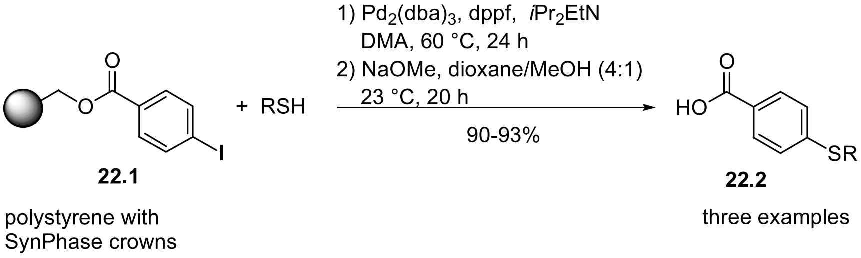
Scheme 19. Reductive coupling of aryl halides leading to biaryls.[18]



Scheme 20. Amination of polymer-bound aryl halides.[159]



Scheme 21. Coupling between thiols and resin-bound aryl iodides.[86]



Scheme 22. Coupling on SynPhase crowns.[87]

with acrylate, giving rise to a cinnamonic acid derivative **19**.**3** (see also Scheme 43).[42]

2.5. Arylations of amines, alcohols and thiols

The heterofunctionalisation of haloarenes on a solid support is a versatile method to create small-molecule libraries of high diversity. Starting with simple resins, arylamines **20.3** can be prepared in good to excellent yield by the amination of polymer-bound aryl halides **20.1** employing the Hartwig–Buchwald protocols (BINAP or P(*o*-Tol)$_3$, *t*BuONa; for a review, see Ref. 158) (Scheme 20).[159,160] Primary and secondary alkylamines and anilines **20.2** can be employed and, in the case of cyclic amines, BINAP was found to be the optimal ligand for the arylation.[160]

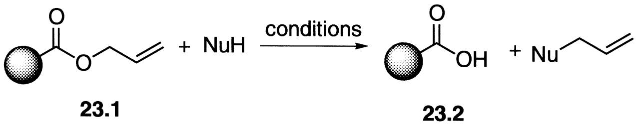
The arylation of thiols has also been investigated (Schemes 21 and 22). Starting from immobilised aryl iodides **21.1** or **22.1**, smooth reaction occurs with various thiols using dppf as the preferred ligand. Cleavage from the resins resulted in the formation of the alcohols **21.2** and acids **22.2**, respectively.[86,87]

2.6. Reactions involving π-allyl complexes

The chemistry of π-allyl complexes on solid supports may be divided into protecting group/linker chemistry and C–C/C–heteroatom bond-forming reactions.

2.6.1. Deprotection of allyl esters and ethers.

The deprotection of allyl esters and ethers under palladium catalysis has frequently been employed in various syntheses of pharmaceutically relevant molecules, peptides or carbohydrates. Kunz et al.[161–163] and Guibé et al.[164] have developed this deprotection of allyl esters on a solid support with the aid of a palladium catalyst.[165] The mild reaction conditions are suitable for enantiomerically pure compounds that are prone to racemisation. The allyloxy-based protecting group is completely orthogonal to *t*-butyloxy and fluorenyloxy groups. The removal of traces of palladium can be accomplished by treatment with sodium diethyldithiocarbamate in DMF.[166] It is noteworthy, that, in general, stoichiometric amounts of the palladium complex have been used. While there is agreement that Pd(PPh$_3$)$_4$ is usually the best catalyst of choice, the nature of the nucleophile may be crucial for the success of the reaction (Scheme 23 and Table 11).[129,164,166–186] The Fmoc group can be removed if morpholine is used as the nucleophile. In this case, phenyltrihydrosilane[187,188] or dimethylamine/borane[189] should be used as neutral group scavengers.

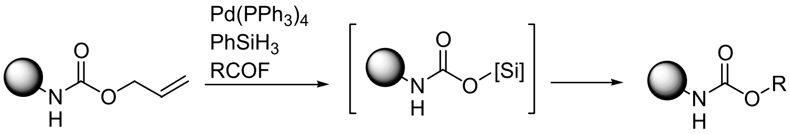


Scheme 23. Deprotection of allyl esters on solid supports.

Table 11. Deprotection of allyl esters on solid supports (recent examples)

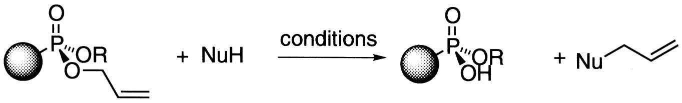
Entry	Resin	Nucleophile	Reaction conditions	Yield (%)	Ref.
1	Polystyrene	PhNHMe	Pd(PPh$_3$)$_4$, DMSO, THF, aq. HCl	n. r.	167
2	PEG–PS	Morpholine	Pd(PPh$_3$)$_4$, DMSO, THF, aq. HCl	n. r.	168
3	PEG–PS	NMM	Pd(PPh$_3$)$_4$, CHCl$_3$	n. r.	166
4	n. r.	Morpholine	Pd(PPh$_3$)$_4$, DMSO, THF, aq. HCl	n. r.	169
5	Polystyrene	Dimedone	Pd(PPh$_3$)$_4$, CH$_2$Cl$_2$/THF (1:1)	n. r.	173
6	PAC–PS	NMM, AcOH	Pd(PPh$_3$)$_4$, CHCl$_3$	n. r.	170
7	Rink amide	NMM, AcOH	Pd(PPh$_3$)$_4$, CHCl$_3$	n. r.	171
8	*o*-Cl-trityl	Me$_3$SiN$_3$	Pd(PPh$_3$)$_4$, ClCH$_2$CH$_2$Cl$_2$	n. r.	177
9	Wang type	Dimedone	Pd(0), CH$_2$Cl$_2$	98[a]	172
10		DMBA	Pd(PPh$_3$)$_4$, THF	n. r.	176
11	Wang	HOBt	Pd(PPh$_3$)$_4$, CH$_2$Cl$_2$, DMF, PPh$_3$	n. r.	202
12	PhF1 on PS	Morpholine	Pd(PPh$_3$)$_4$, CH$_2$Cl$_2$	n. r.	129
13	Wang	PhNHMe	Pd(PPh$_3$)$_4$, DMSO/DMF (1:1)	n. r.	174
14	Trityl	NMM, AcOH	Pd(PPh$_3$)$_4$, CHCl$_3$	n. r.	175
15	Rink linker on different supports	Dimedone	Pd(PPh$_3$)$_4$, CH$_2$Cl$_2$	n. r.	181

[a] Crude yield; yield of product was 57%.



24.1 **24.2** **24.3**

Scheme 24. In situ deprotection and peptide coupling with Alloc-protected amines.[204]



25.1 **25.2**

Scheme 25. Deprotection of allylphosphonates.[206–208]

Allyloxycarbonyl is a useful protecting group, especially for primary amines,[165] as it is easily cleaved in the presence of a suitable palladium catalyst.[190] It has found widespread interest in peptide, oligonucleotide and glucopeptide synthesis ever since it was introduced. Various sources for the nucleophile have been reported including tin hydrides,[164,178] formic acid salts,[191,192] azides,[193,194] *N*-methylaniline,[195] acetates,[196,197] dimedone,[190,198] morpholine,[199] *N*-methylmorpholine[200] pentamethylsilyl-amine/trimethylsilyl trifluoroacetate,[201] HOBt[202] or dimethylamine–borane complex[203] for the deprotection of secondary amines. In addition, a one-pot deprotection/peptide coupling strategy was investigated using the Alloc protected amines **24.1** consisting of a silyl hydride as the nucleophile, which also gives rise to the intermediate silyl ester **24.2** (Scheme 24). In the presence of an acid fluoride, the newly formed carbamates **24.3** were isolated.[204]

Table 12. Deprotection of allylphosphonates

Entry	Resin	Nucleophile	Reaction conditions	Yield (%)	Ref.
1	Wang	Morpholine	Pd(PPh$_3$)$_4$, DMF	n. r.	208
2	Wang	BuNH$_2$, HCO$_2$H	Pd(PPh$_3$)$_4$, THF	100[a]	206
3	Wang	NMM, AcOH	Pd(PPh$_3$)$_4$, CHCl$_3$	n. r.	207

[a] Conversion.

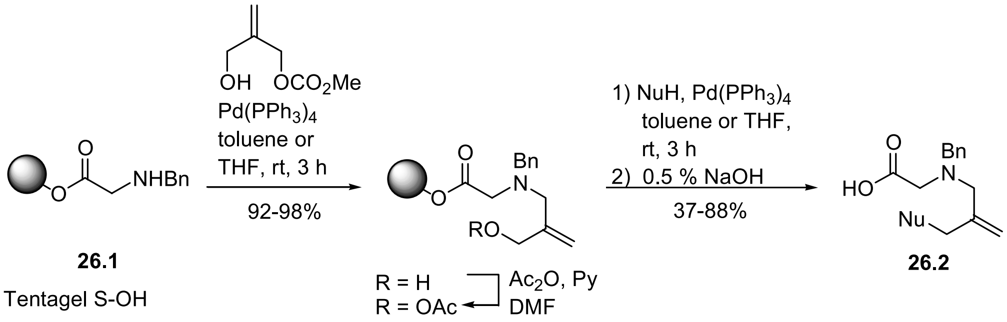
The Alloc deprotection is additionally applicable to the automated solid-phase synthesis of oligonucleotides,[191,192] and linear and cyclic peptides.[205]

In a manner similar to carboxylic acid derivatives, allylphosphonates **25.1** can be cleaved under mild conditions to give phosphonates **25.2** (Scheme 25 and Table 12).[206–208]

Benzylphosphonates can be deprotected with palladium acetate under increased hydrogen pressure with simultaneous cleavage from the support.[209]

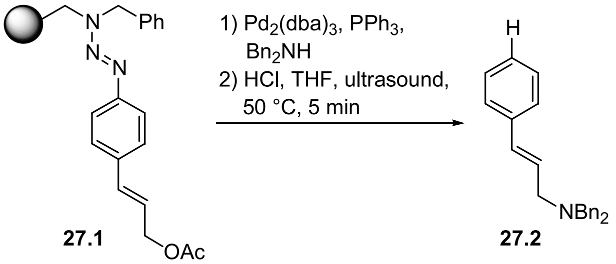
A recent report describes a new protocol for the cleavage of allyl ethers on a solid support using a palladium(0)-catalysed allyl transfer reaction to *p*-toluenesulfinic acid.[210]

2.6.2. Coupling of building blocks to solid supports via π-allylpalladium complexes. The reactions of immobilised nucleophiles with π-allylpalladium precursors have been described for various combinations.[18,211–214] A double allylation reaction has been shown using the immobilised nitrogen nucleophile **26.1** with 2-hydroxymethyl allylmethyl carbonate. After the first allylic substitution, acylation and a subsequent coupling with various nucleophiles provided access to the substituted glycine derivatives **26.2** (Scheme 26).[211]

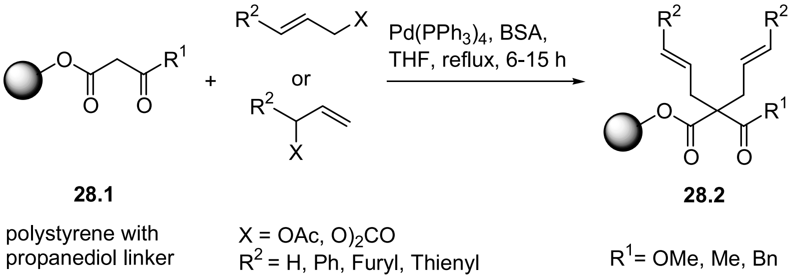


Nu = various prim. and sec. amines, sulfinates, thiols

Scheme 26. A synthesis applying bisallylic building blocks.[211]



Scheme 27. Allylic substitution on a triazene-linked cinnamoyl acetate.[18]

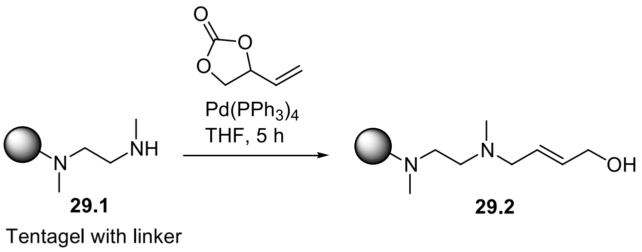


Scheme 28. Allylic substitution with polymer-bound nucleophiles.[212]

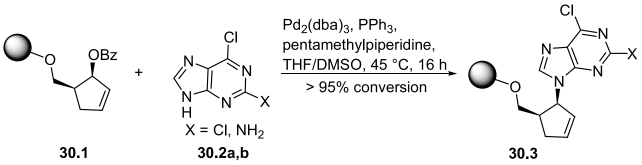
The versatile triazene T1 linker has been applied to create a template for an allylic substitution with dibenzylamine on the immobilised cinnamoyl acetate **27.1**. Traceless cleavage furnished the tertiary amine **27.2** in good yield and purity (Scheme 27).[18]

Starting from the oxygen-linked 1,3-dicarbonyl compounds **28.1** (malonates or acetoacetates), Tietze et al. have demonstrated an allylic substitution at the α-position of various substrates (allyl acetates, carbonates and chlorides).[212] Under the conditions employed, bisalkylation was observed in all cases. Since the acetoacetates **28.2** could be alkylated by hard electrophiles at the γ-position, a broad spectrum of compounds can be obtained. The cleavage from the resin was performed using DIBAL-H obtaining the corresponding diols (Scheme 28).

A chain elongation of a polymer-bound secondary amine **29.1** was achieved by palladium-catalysed allylic substitution on a vinyldioxolanone giving 0°C the allylic alcohol **29.2** (Scheme 29). This carbonate provides neutral conditions for the alkylation reaction.



Scheme 29. Allylation of a polymer-bound amine with a vinyldioxolanone under palladium catalysis.[213]

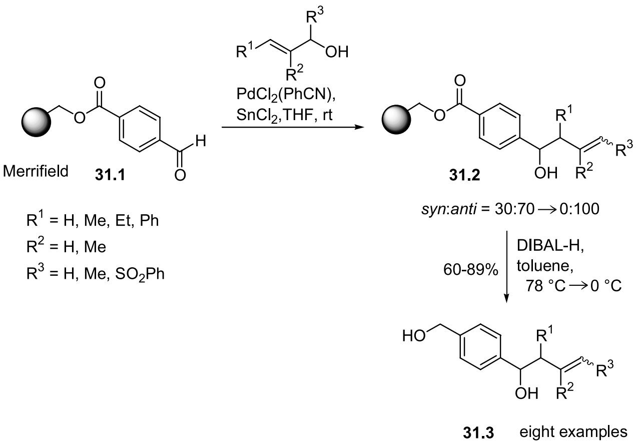


Scheme 30. Synthesis of carbocyclic nucleoside analogues.[214]

Allyl benzoates **30.1** have been used in the synthesis of carbocyclic nucleoside analogues **30.3** (Scheme 30). Both 2,6-dichloropurine **30.2a** and 2-amino-6-chloropurine **30.2b** were effective nucleophiles in the presence of a bulky tertiary base and the palladium catalyst.[214]

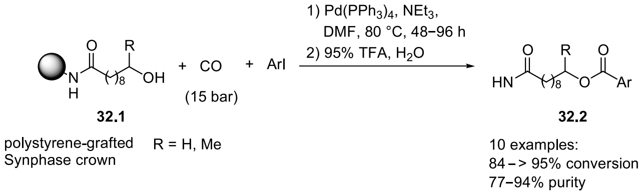
Recently, *N*-allylation of an *o*-nosyl-protected *N*-terminus of a peptide with allyl methyl carbonate has been reported.[215]

The carbonyl allylation of the polymer-bound aldehyde **31.1** with a variety of allylic alcohols under Lewis-acidic



Scheme 31. Carbonyl allylation of a polymer-bound aldehyde.[216]

conditions leads to homoallylic alcohols **31.2** (Scheme 31).[216] The coupling process proceeds via a $SnCl_2$-mediated umpolung of a π-allylpalladium complex and furnishes predominantly the anti isomers of the immobilised homoallylic alcohols. The latter can be cleaved from the resin with DIBAL-H.



Scheme 32. Carbonylative coupling reaction on a solid support.[217]

2.7. Carbonylative coupling and cyanation reactions

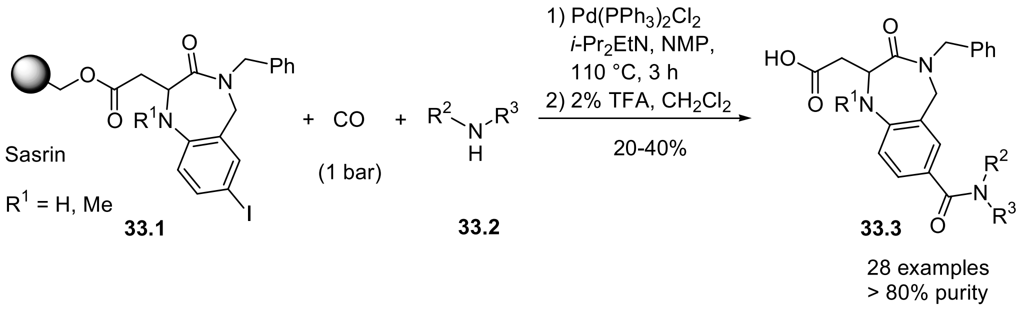
The carbonylation of aryl halides in the presence of suitable nucleophiles such as alcohols and amines offers an attractive approach to benzoic acid derivative and the reaction of polymer-supported primary and secondary alcohols **32.1** with aryl iodides under a carbon monoxide atmosphere was therefore investigated (Scheme 32). Under the reported reaction conditions, this three-component reaction proceeded in good yields and, after cleavage, the products **32.2** were obtained in moderate to good purities.[217] Following this general procedure, the authors described the preparation of a peptide library using a combination of five solid-supported amines and 10 aryl iodides.

Complex amines were used in the synthesis of a benzodiazepine library (Scheme 33).[218] Starting from an iodoarene **33.1**, treatment with various amines **33.2** in the presence of a slight pressure of carbon monoxide proceeds smoothly to give the corresponding benzamides, which upon cleavage under mildly acidic conditions furnish the desired products **33.3** in good purities.

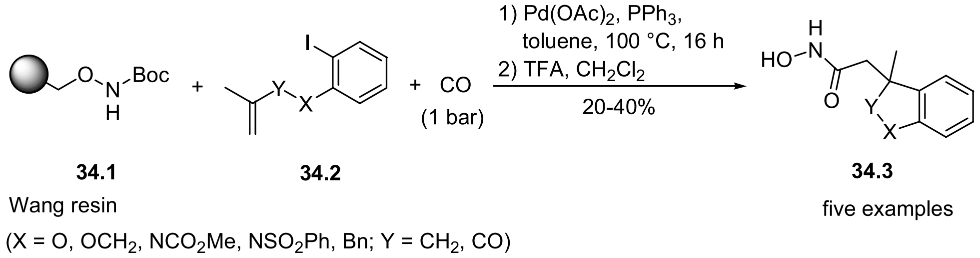
Grigg et al. have recently demonstrated a cascade consisting of an intramolecular carbopalladation, carbonylation and nucleophilic attack by an immobilised hydroxamic acid ester **34.1** using iodoarenes **34.2** to yield benzoannelated heterocycles **34.3** (Scheme 34).[219]

In a three-component Stille reaction, a polymer-bound arylstannane **35.1** serves as coupling partner for a broad variety of aryl bromides and iodides in the presence of carbon monoxide.[220] After cleavage from the solid support, the resulting diaryl ketones **35.2** were obtained in good yields and purities, usually >80% (Scheme 35).

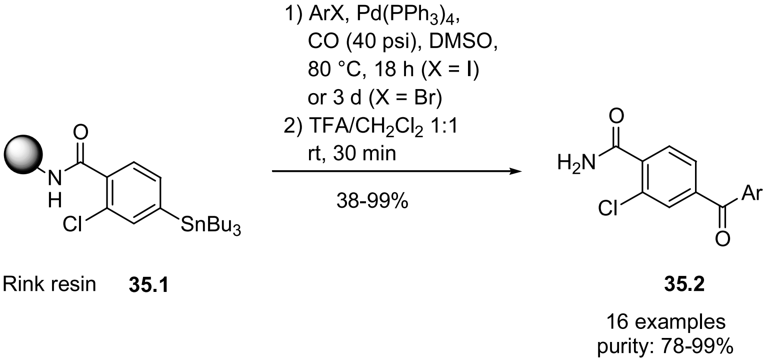
The coupling of an immobilised aryl iodide **36.1** with



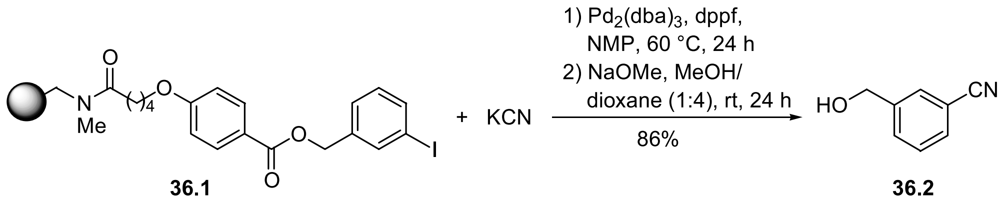
Scheme 33. Synthesis of a benzodiazepine library on a solid support.[218]



Scheme 34. Carbonylation cascade reaction on a solid support.[219]



Scheme 35. Synthesis of diaryl ketones through a three-component Stille coupling reaction.[220]



Scheme 36. Coupling between cyanide and a resin-bound aryl iodide.[20]

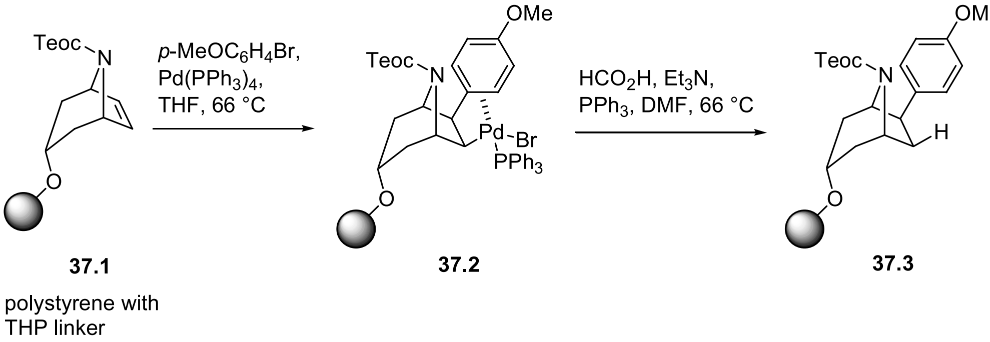
potassium cyanide has been found to yield the corresponding nitrile **36.2** in good yield (Scheme 36).[20]

2.8. Hydrogenation reactions

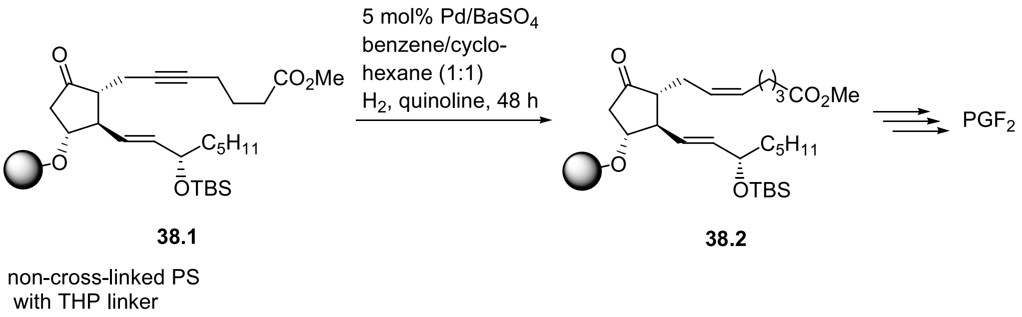
The various types of hydrogenation reactions that have been performed on solid supports consist of hydrodepalladations of σ-organyl complexes, hydrogenations of double and triple bonds as well as the hydrogenolytic removal of triple bonds as well as the hydrogenolytic removal of benzyl-type protecting groups.

2.8.1. Hydrodepalladations of σ-organylpalladium. The formal reduction of σ-organylpalladium, replacing a C–Pd by a new CH bond may be achieved by the use of e.g. formic acid.[41] The intermediate σ-complexes usually arise by carbopalladation of a multiple bond (Scheme 37). This has been demonstrated by a sequence of carobometallation on the tropane **37.1** to yield the palladacycles **37.2**, which was subsequently reduced to give the aryltropane **37.3**.

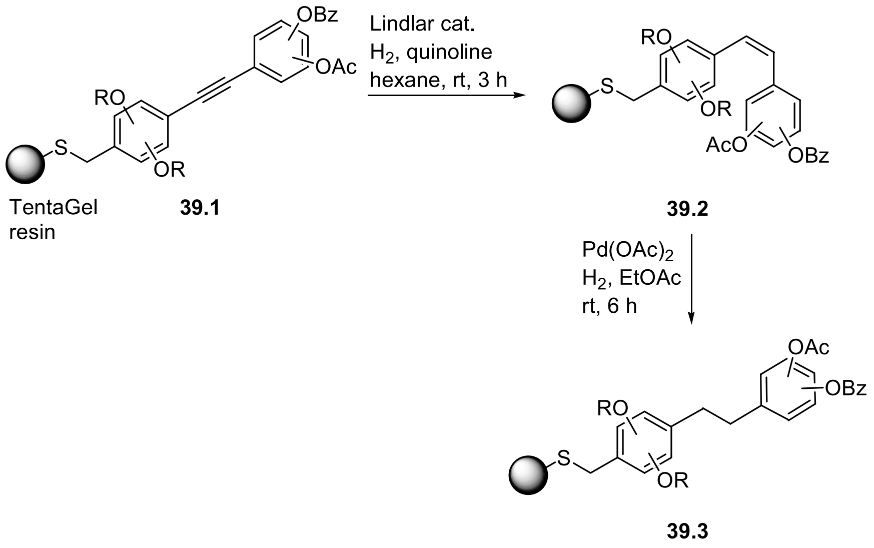
2.8.2. Catalytic hydrogenation of triple and double bonds. The catalytic hydrogenation of a triple to a double



Scheme 37. Carbometallation on the tropane framework.[41]



Scheme 38. Prostaglandin synthesis on a solid support.[222]

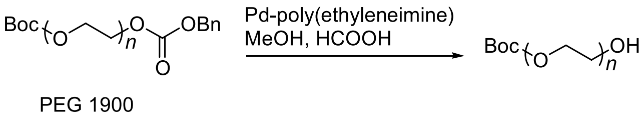


Scheme 39. Hydrogenation on a solid support.[46]

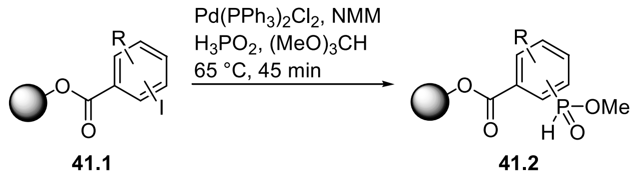
bond has been performed on non-cross-linked polystyrene,[221] which demonstrates the suitability of this support.[222,223] This transformation has been applied to the polymer-bound version of the classical prostaglandin synthesis starting from the alkyne **38.1** to give the (*Z*)-alkene **38.2** (Scheme 38).[222]

On the other hand, even cross-linked polystyrene was used in the reduction of the immobilised alkynes **39.1** with the Lindlar catalyst to give the alkene **39.2**.[46] The subsequent hydrogenation to alkane **39.3** was achieved with palladium acetate as a precatalyst (Scheme 39).[46]

2.8.3. Deprotection of benzyl ethers. Benzyl ether and benzyloxycarbonyl groups in compounds on a PEG support can be cleaved by catalytic hydrogenation with a heterogeneous palladium catalyst[224,225] or with homogeneous palladium acetate.[226] In some cases, palladium-poly(ethylene imine) has been found to be more effective than palladium black (Scheme 40).[227] Very recently, Wong et al. have reported the use of Pd-nanoparticles for the removal of benzyl protecting groups on carbohydrates attached to solid supports such as TentaGel and PEGA resins.[228]



Scheme 40. Benzyl ether deprotection on PEG.[227]



41.1

Wang resin

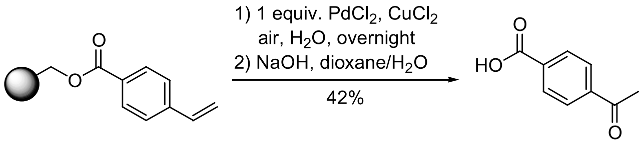
41.2

Scheme 41. Synthesis of arylphosphinic acid derivatives.[229]

2.9. Miscellaneous reactions

The coupling of aryl iodides **41.1** on solid supports with hydrophosphoric acid in the presence of trimethyl orthoformate (Scheme 41) has been described in a recent patent.[229] The resulting polymer-bound methyl aryl phosphonates **41.2** were subsequently derivatised.

2.9.1. Wacker-type reactions. The Wacker oxidation of the alkene **42.1**, bound to a macroporous polystyrene resin, yielded the expected methyl ketone **42.2** (Scheme 42), whereas in the case of an alkene bound to a low-cross-linked Merrifield resin no product formation could be found. The results correlate with the relative permeability of each of these resins towards the aqueous solvent employed.[230] It is interesting to note that the catalytic version of this process gave nearly the same yield as the stoichiometric reaction.



42.1

macroporous polystyrene resin

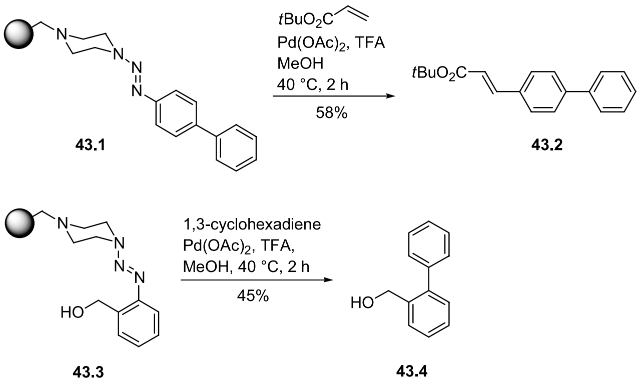
42.2

Scheme 42. Wacker-type oxidations on a solid support.[230]

3. Palladium-catalysed cleavage from the solid support and concomitant derivatisation

3.1. General remarks

The cleavage of substrates from a solid support using palladium-promoted or -catalysed reactions has some advantages over other cleavage methods. Since most protecting groups and functionalities are resistant towards the palladium catalyst, a selective surgical cut-off is often possible. In addition, the intermediate π-allyl- and



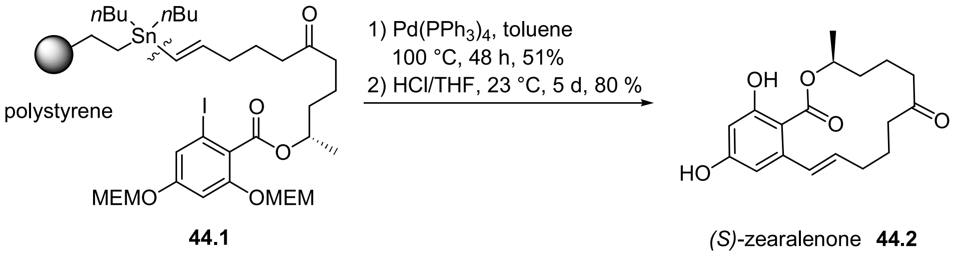
Scheme 43. Cleavage with ensuing Heck coupling using the triazene linker.[42]

σ-aryl-palladium complexes can, in principle, be used for further derivatisation with the use of suitable linker types.

3.2. Cleavage with ensuing cross-coupling reactions on solid supports

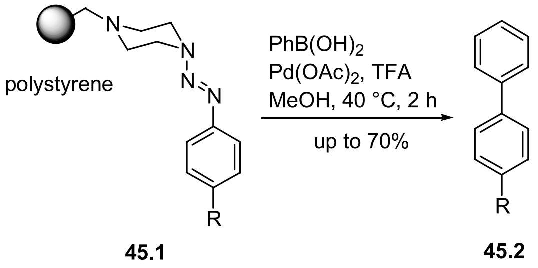
3.2.1. Heck reactions. A cleavage with a subsequent Heck reaction was developed utilising the T1 triazene linker (Scheme 43). Upon treatment of the immobilised biaryl **43.1** with trifluoroacetic acid, a diazonium ion is first formed and this can couple with an added alkene under palladium catalysis, yielding the styrene derivative **43.2**. The coupling proceeds well with simple terminal alkenes, styrenes and di- and even tri-substituted alkenes.[42] The coupling with 1,3-cyclohexadiene by cleavage of the benzylalcohol resin **43.3** eventually then yields biaryl **43.4**, apparently by a facile dehydrogenation of the primary coupling product.[42] The advantage of this process is clearly the possibility of using volatile alkenes (and alkynes) without contamination by any salt or other less volatile by-products.

3.2.2. Stille coupling reactions. A polymer-bound tin hydride has been used to hydrostannylate alkynes under palladium-catalysis to give immobilised alkenylstannanes.[231] Alternatively, the latter could be prepared from a polymer-bound tin chloride and an alkenyl-lithium or -magnesium halide reagent. These alkenylstannanes were employed in both inter- and intramolecular Stille reactions. The intermolecular reactions provided the coupling products in good yields. In addition, the stannylated resin produced in the cleavage–coupling can be recycled. Although the obtained products were not contaminated by any stannane, they have to be separated from an excess of the reactive electrophiles that had to be applied in the cleavage-coupling step. The intramolecular mode which was used by Nicolaou et al. to produce macrocyclic ring system such as the natural product (*S*)-zearalenone (**44.2**) from precursor **44.1** does not have this drawback (Scheme 44).[232]



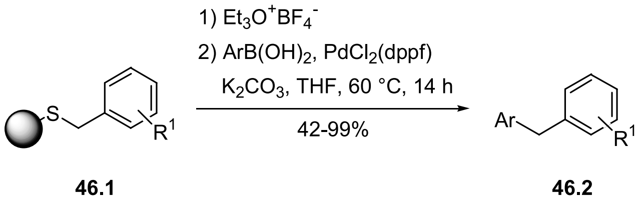
Scheme 44. Cleavage Stille strategies using a stannane linker.[232]

3.2.3. Suzuki coupling reactions. Suzuki couplings followed by a cleavage reaction are potentially applicable in a multidirectional sense, but due to the likely homocoupling of the boronic acid derivative, it is necessary to apply additional ligands and less volatile boronic acid derivatives. In addition, a more or less tedious work-up is required after these types of transformations. A few studies have shown that certain functionalities generated during cleavage may act as the leaving groups for a subsequent Suzuki reaction, e.g. the diazonium group, which can be generated by cleavage of the triazene T1 linker (Schemes 7, 19, 27, 43 and 50). While the Heck-type coupling with alkenes gave good yields of the desired products (Scheme 43), the analogous reaction of the resins **45.1** with phenylboronic acid to give biaryls **45.2** appeared to be difficult due to problems in the work-up (Scheme 45).[42]

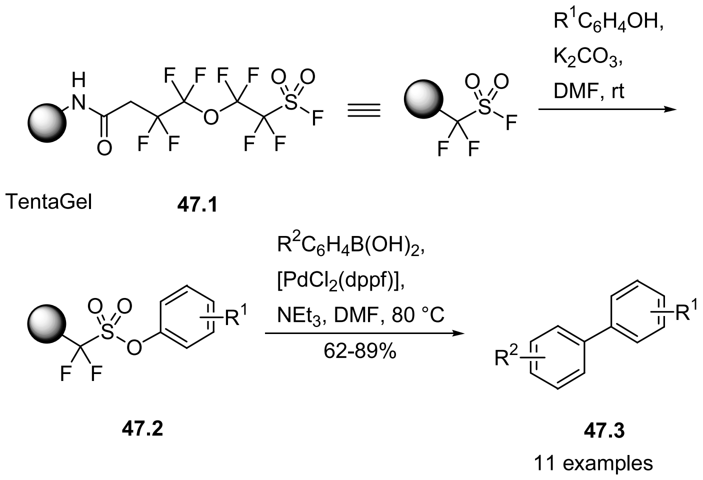


Scheme 45. Cleavage with subsequent Suzuki coupling.[42]

Arylmethyl(homobenzyl)ethylsulphonium salts are also suitable substrates for the Suzuki-type coupling reactions. In this type of reaction performed on a polymer-bound sulphonium tetrafluoroborate, the benzyl fragment on the sulphur was transferred to the boronic acid residue. The sulphonium salt was prepared from an alkylthiol resin **46.1** by alkylation with a substituted benzyl halide and subsequent alkylation with triethyloxonium tetrafluoroborate. The final product on reaction with a boronic acid derivative was the diarylmethane **46.2** (Scheme 46).[23]



Scheme 46. Cleavage Suzuki coupling protocol using sulphonium salts.[23]

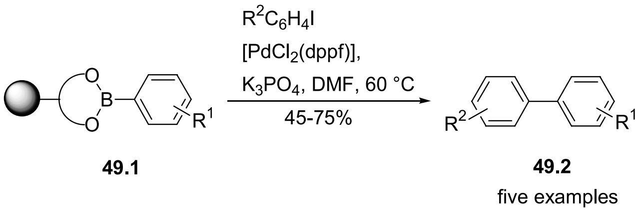


Scheme 47. Suzuki cleavage/cross-coupling of polymer-bound perfluoroalkylsulfonates.[233]

Recently, immobilised perfluoroalkylsulfonates were reacted with a broad variety of arylboronic acids to furnish biaryls in a traceless cleavage/cross-coupling sequence (Scheme 47).[233] Under mild conditions, phenols were attached to a perfluoroalkylsulfonyl fluoride resin **47.1**. The resulting polymer-bound aryl triflate species **47.2** act as electrophiles in the following Suzuki reaction with various arylboronic acid derivatives, releasing the desired products **47.3** from the solid support.

A boronic acid ester, which contains an aryl iodide moiety attached by an suitable ether, can act as an intramolecular arylation agent. Burgess et al. developed a polymer-bound precursor **48.1**, which by a biaryl coupling and subsequent cleavage furnished a macrocyclic constrained β-turn peptide mimetic **48.2** (Scheme 48).[234]

An intermolecular cleavage Suzuki coupling protocol was conducted with immobilised boronic acid esters and aryl iodides, allowing the synthesis of functionalised biaryl compounds (Scheme 49).[235] Aryl boronic acids were attached to a macroporous solid support, giving rise to the boronic acid esters **49.1**, which upon treatment with aryl iodides under Suzuki coupling conditions yield the biphenyl derivatives **49.2**.



Scheme 49. Intermolecular cleavage–Suzuki coupling of immobilised boronic acid esters.[235]

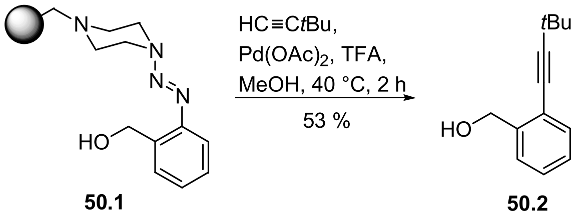
3.2.4. Sonogashira-type coupling reactions.

The coupling of alkynes with diazonium salts has been reported in the context of the T1 linker like the triazene **50.1**. In this case, the product **50.2** was isolated in moderate yield. Obviously, it had to be separated by chromatography from alkyne homodi- and trimers (Scheme 50).[42]

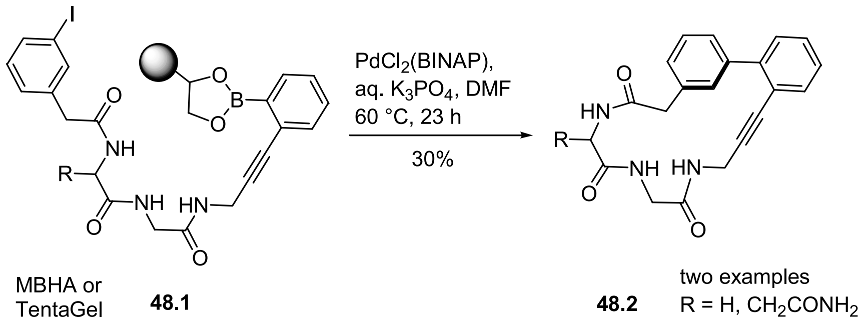
3.3. Reactions involving π-allyl complexes

3.3.1. Deprotection of allyl esters: allylic linkers for solid phase synthesis.

The advantages of cleaving a linker under palladium catalysis are the mild reaction conditions[165] and their orthogonality to various protecting groups. Kunz et al.[236–238] developed the first and most simple linker using



Scheme 50. Sonogashira coupling associated with cleavage.[42]



Scheme 48. Intramolecular cleavage–Suzuki coupling protocol.[234]

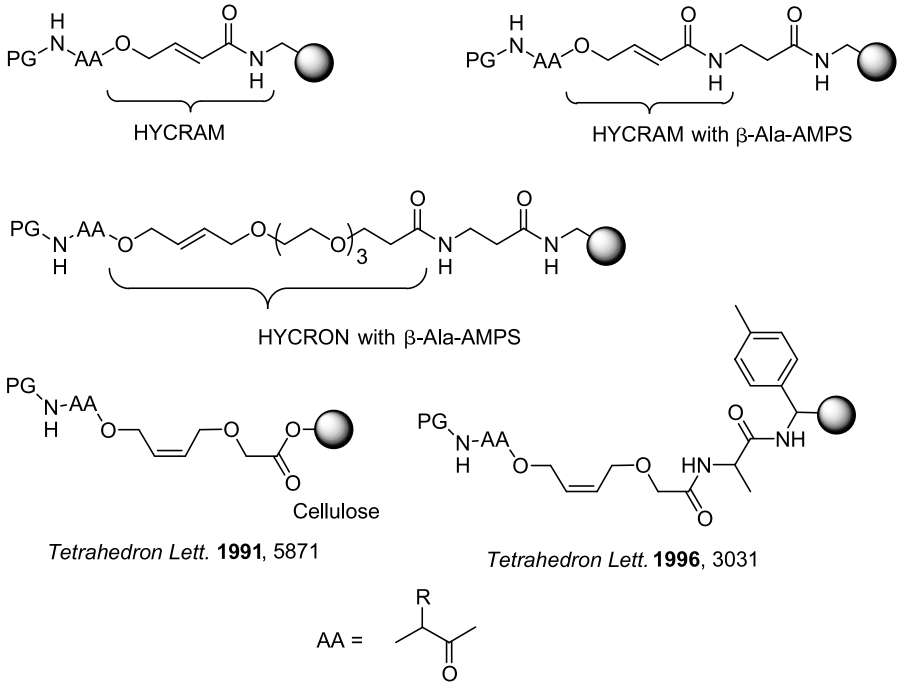
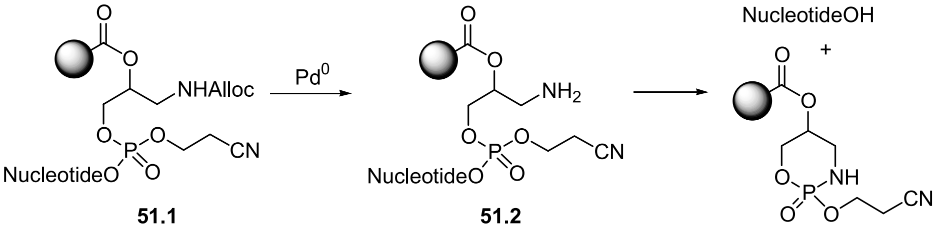


Figure 2. Allylic alcohol linkers.[165]

the π-allyl detachment strategy. Starting from 2-bromocrotonic acid, attachment to an amino group on a resin and further reaction with the caesium salt of a suitable protected amino acid or peptidic structure yields the hydroxycrotonylamide (HYCRAM) resin (Fig. 2).[239] The allylic cleavage proceeds with $Pd(PPh_3)_4$ and morpholine or hydroxybenzotriazole.[240] The readily available HYCRON linker[161,241–245] is based on a similar concept. In this case, however, a handle comprising an amino acid and a preformed linker has been used to minimise the risk of racemisation upon cleavage. A higher stability towards unwanted nucleophilic cleavage was achieved in comparison with the HYCRAM linker. The incorporation of β-alanine facilitates monitoring of the reaction. Several other similar constructs have been used for comparable purposes.[246–253] Recently, the semi-synthesis of vancomycin on a solid support was accomplished using an allylic anchor.[180]

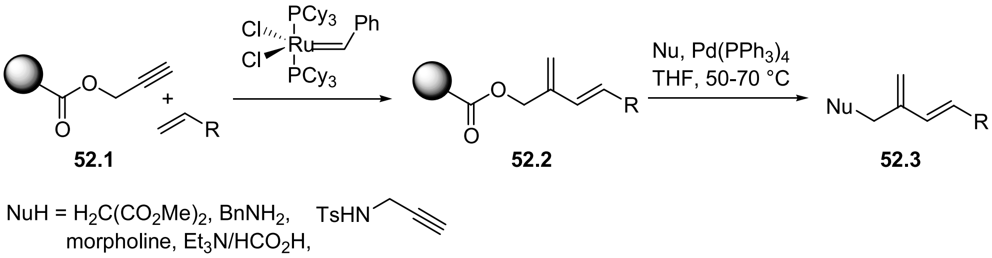
An indirectly (=safety catch) π-allyl-cleavable linker was developed for the synthesis of DNA on a solid support. Starting from a linker containing an Alloc-protected amino group, conventional phosphoramidite chemistry was carried out to synthesise the desired nucleotide **51.1**. Removal of the Alloc group under palladium-catalysis and neutral conditions generates the intermediate **51.2**. The nucleotide was liberated from the solid support by the intermolecular attack of the free amino group on the activated phosphonate (Scheme 51).

3.3.2. Functionalisation during cleavage. The cleavage of polymer-bound allyl esters with a palladium catalyst



51.1 **51.2**

Scheme 51. Safety-catch palladium-activated linker.[196,197]

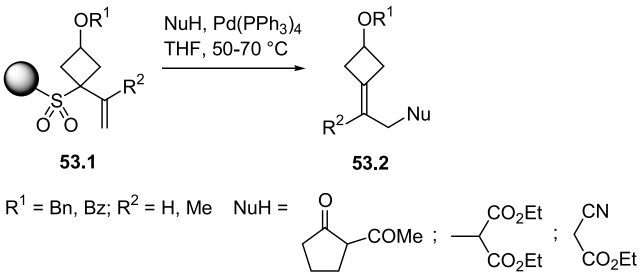


52.1 **52.2** **52.3**

Scheme 52. Cleavage with formation of π-allyl intermediates.[254]

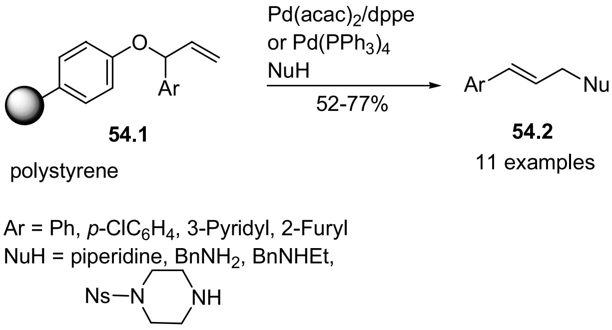
provides a general access to π-allyl complexes, which in turn may react with various nucleophiles. Blechert et al. used an ene–yne cross-metathesis of the immobilised alkene **52.1**, followed by a subsequent cleavage of the resulting diene **52.2** in the presence of various nucleophiles to yield the corresponding functionalised dienes **52.3** (Scheme 52).[254]

Similarly, solid-bound 1-alkenylcyclobutyl sulfones **53.1** were cleaved from a resin in the presence of suitable nucleophiles to the give substituted cyclobutylidene derivatives **53.2** (Scheme 53).[255]



Scheme 53. Cleavage with formation of π-allyl intermediates.[255]

Immobilised aryl allyl ethers can also provide palladium π-allyl complexes suitable for concomitant derivatisation. As shown in Scheme 54, the allyl ethers **54.1** are readily cleaved by various primary and secondary amines in the presence of either Pd(acac)/dppe or $Pd(PPh_3)_4$ to form the allylic amines **54.2** in moderate yields.[256]

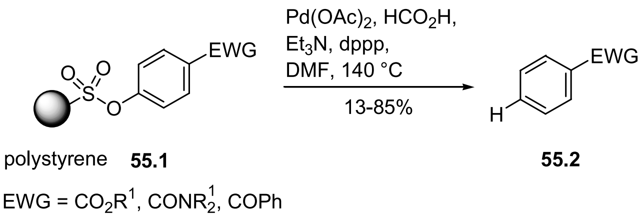


Scheme 54. Palladium-catalysed nucleophilic cleavage of allyl ethers.[256]

3.4. Hydrogenolytic cleavage

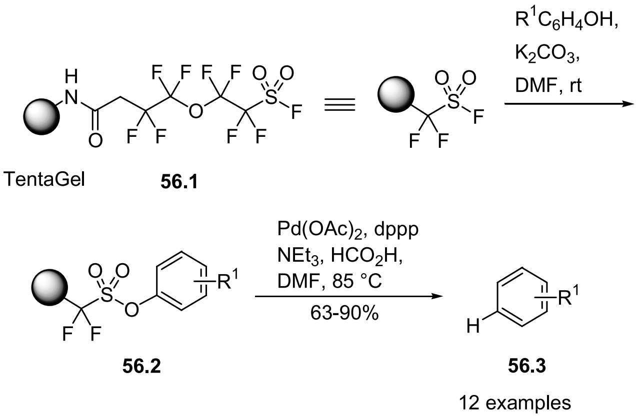
Hydrogenolytic removal of substrates from solid supports is important as this cleaves the substrate with hydrogen at the former site of the polymer binding. These types of linkers are also called traceless linkers, reflecting the memory of the point of attachment.[257]

3.4.1. Hydrogenation of sulphonates. The detachment of the substituted arylsulphonates **55.1** in the presence of a reducing agent such as formic acid provides a traceless cleavage to the arenes **55.2** (Scheme 55). In this case, it is important that the arene core is substituted with electron-withdrawing substituents to enhance the yields significantly.[258] This approach has been described (without experimental details) in 1995 in a patent including the possible derivatisation of the intermediate σ-arylpalladium aryl complex.[259]



Scheme 55. Hydrogenolytic cleavage of a polymer-bound substrate.[258]

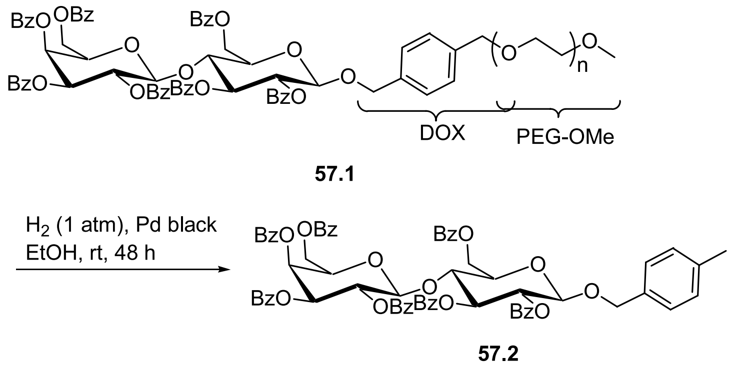
Recently, this strategy has been expanded to a wider range of substrates by the employment of a perfluoroalkylsulphonyl fluoride resin **56.1** (Scheme 56).[260] Attachment of phenols affords the corresponding arylsulphonates **56.2**, which upon palladium-mediated reductive cleavage release the parent arenes **56.3** in purities of around 90%.



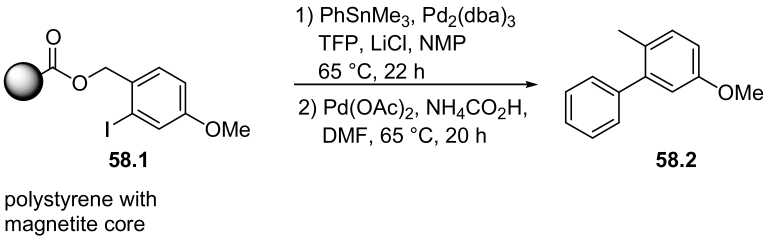
Scheme 56. Palladium-catalysed reductive cleavage of arylsulfonates.[260]

3.4.2. Deprotection of benzyl ethers and esters. The cleavage of specially designed polymeric benzyl-type protecting groups has been achieved by heterogeneous palladium black. In these cases, the catalytic hydrogenation furnishes methyl-substituted arenes as side products or targets. An early example takes advantage of the properties of the MeO-PEG-type support for the synthesis of di- and oligosaccharides. It is interesting to note that the DOX linker in **57.1** enables the cleavage from the PEG structure to give methylarene **57.2**, leaving the *p*-methylbenzyl (TM) group attached under certain conditions (Scheme 57)[261] (but cf. Scheme 60).[262] Similarly, the cleavage for polystyrene resin was achieved using homogeneous palladium catalysts (palladium acetate) with either formate reduction using the resin **58.1** to give methylarene **58.2**[82] (Scheme 58) or under an atmosphere of hydrogen (Scheme 59).[46]

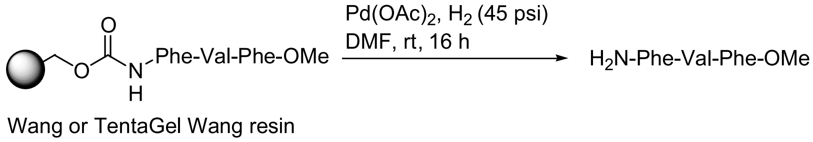
Alternatively, the benzyl group was attached to the solid



Scheme 57. Syntheses of methylarenes on a soluble polymer.[261]

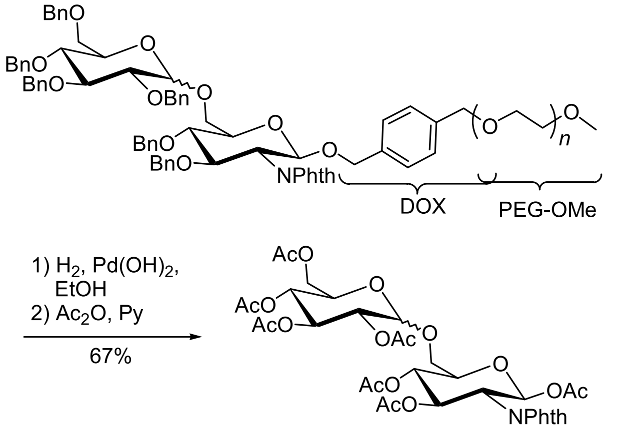


Scheme 58. Syntheses of methylarenes on a solid support.[82]



Scheme 59. Detachment from benzyl-type protecting groups on a solid support.[46]

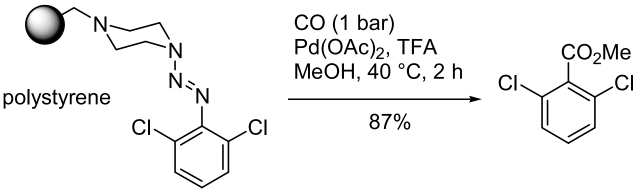
support. In this case, the hydrogenolytic cleavage used to detach the molecules then leads to molecules with an oxygen or nitrogen functionality (cleavage of benzylic C–O and C–N bonds, respectively).[226,262–264] The polymers in these cases are formally immobilised Cbz groups. Interestingly, TentaGel and polystyrene provide the products in comparable yields under identical conditions. Benzylic linkers can also advantageously be used in the presence of other benzylic protecting groups, since they can be removed in the same step (Scheme 60).[226,262] Palladium-catalysed removal of the Cbz group was also conducted after (non-palladium-catalysed) detachment from the solid support.[265]



Scheme 60. Detachment from benzyl-type protecting groups on a soluble polymer.[262]

3.5. Carbonylative cleavage

The cleavage with ensuing carbonylation has been conducted with the T1 linker system **61.1** in methanolic trifluoroacetic acid to generate the methyl esters **61.2** in good yields (Scheme 61).[42] This overall process constitutes a transformation of an aniline to the corresponding methyl carboxylate.



Scheme 61. Detachment/carbonylation reaction.[42]

4. Conclusions[267–271]

Due to the mild reaction conditions, good selectivities and generally high yields, palladium-catalysed reactions are commonly used in SPOS. In particular, C–C bond formations are of great importance for the efficient synthesis of pharmaceutically important molecules. Palladium-catalysed cross-coupling reactions are by far the dominating family of transformations applied in SPOS for this purpose.

In general, the catalyst is easily removed by simply washing the resin. This can be extremely important since transition metals often interfere with high throughput screening assays to be performed with the final products.

The possible functionalisations during cleavage are gaining increasing importance as they add yet another dimension of diversity. When soluble supports are used, the removal of the catalyst and excess may not be as trivial. This problem may be solved by the use of immobilised palladium catalysts in association with volatile reagents. Another option, which has not yet been pursued, is to use efficient scavenger resins to sequester the catalyst. This possibility will also give some new impulses to liquid phase combinatorial chemistry.

Some other aspects of catalysis such as the control of stereochemistry with chiral ligands have not yet been widely explored in SPOS. Up to now, most compound libraries simply contained racemates and frequently even mixtures of diastereomers. Stereoselectivity will be surely one of the next challenges in combinatorial solid phase synthesis.[266]

Acknowledgements

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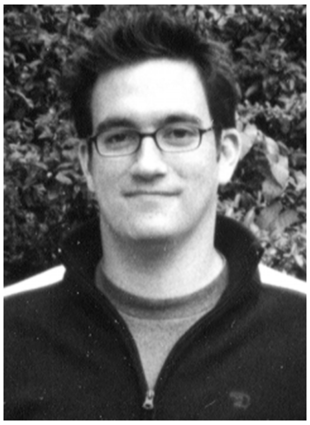

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