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Review

# Organometallic chemistry on solid phase. An overview☆

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**Abstract**

Solid-phase organic synthesis (SPOS) is the most important method for the production of combinatorial libraries and with the development of high-throughput screening, libraries are widespread in pharmaceutical and agricultural chemistry. Amongst all the synthetic transformations successfully applied to solid phase, the use of organometallic reagents for the formation of a new carbon–carbon bond has been scarcely pursued. In this overview we collected the most recent examples of the use of organometallic reagents of Li, Mg, Cu, Zn, Si and B for C–C bond formation. The use of organometallic reagents in Pd-catalysed cross-coupling reactions was not reviewed. Highly basic organometallics as organo-lithium and -magnesium reagents have been more largely employed than cuprates and zincates, suggesting that several kinds of resins can withstand relatively strong reaction conditions. © 2002 Published by Éditions scientifiques et médicales Elsevier SAS.

*Keywords:* Organometallic chemistry; Solid phase synthesis; Combinatorial chemistry

The impact of Combinatorial Chemistry and related technologies in Medicinal Chemistry has been tremendous in the last decade [1–3]. Drug discovery requires finding molecules that interact selectively with biological targets. With the developments of High Throughput Screening, the availability of new molecules became a bottleneck in pharmaceutical research. Consequently, the combinatorial chemistry approach has been very actively pursued, with the hope of finding new leads for rapid access to new pharmaceuticals. Libraries of discrete molecules have been prepared from a series of molecular structures connected in various sequences by a repetitive application of specific chemical reactions. The target was to start from a multifunctional core and to decorate it with the highest possible structural diversity. The extensive use of repetitive procedures on a common scaffold made organic synthesis on solid (insoluble) support (solid-phase organic synthesis (SPOS)) the most popular technique to generate large libraries. Hundreds of "classical" organic transformations have been adapted to solid phase with excellent results in terms of efficacy and variety of structures prepared, as documented by several reviews on the arguments [4,5]. Heteroatom–carbon bond formation has been the most deeply investigated but several examples of carbon–carbon bond formation have also been described. Although the literature documented the possibility of employing highly basic organometallic reagents in SPOS, the examples reported are much less than those where the new C–C bond is formed with metal-mediated reactions.

This overview is intended to cover the usage of organometallic reagents in the formation of new C–C bond in SPOS. The term "organometallic reagent" is used to define the series of compounds described by E. Neghishi in his famous book: "*Organometallics in Organic Synthesis*" [6]. The aim is to demonstrate, with selected examples, that organometallic chemistry can be carried out on solid phase and to persuade organic and medicinal chemists to use these reagents in the preparation of libraries on solid phase. Moreover, the small number of examples on the use of some "classical" organometallic reagents in SPOS can stimulate research in the field.

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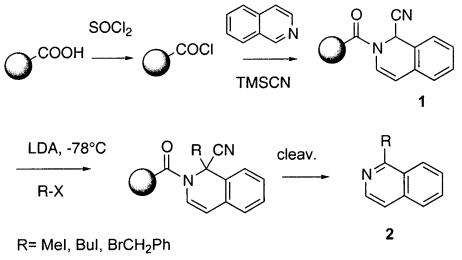
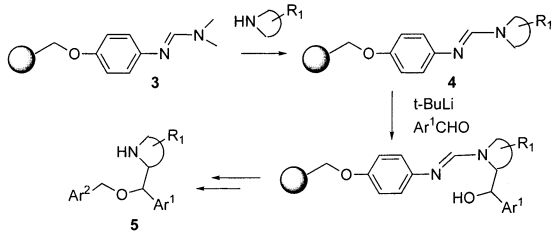
This overview is organised as the index of the Neghishi book. Some of the arguments contained here have been recently reviewed [4].

## 1. Li

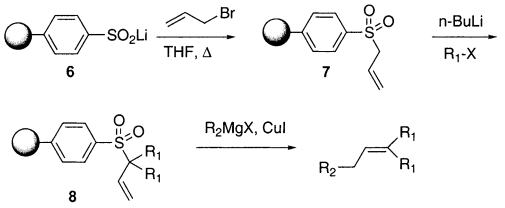
The organometallic reagents of this element can be generated by deprotonation of a relatively acid proton followed by alkylation with different electrophiles, by addition of an organolithium on a multiple bond or by metal halogen exchange. Two contemporary cases are possible: the organometallic reagent can be generated on the resin or it can be added in solution to a supported electrophile. The example selected deals with both these cases.



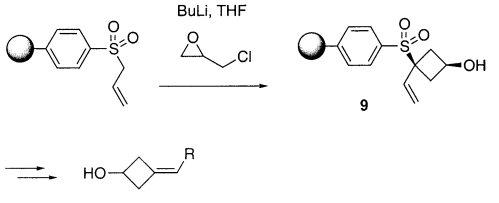

Scheme 1.




Scheme 2.




Scheme 3.




Scheme 4.

The alkylation of Reissert complex **1** was studied on solid phase for obtaining novel isoquinoline–isoxazoline heterocycles [7].

Isoquinoline substituted at C1, with basic containing substituents, are known to show a wide range of biological applications and an efficient method of incorporating substitution at C1 of isoquinolines makes use of the alkylation of Reissert compounds taking advantage of the increased acidity of the 2-acyl-1,2-dihydroxyquinaldonitriles.

Polymer bound benzoylchloride was obtained from a polystyrene–divinylbenzene benzoic acid functionalised resin and the Reissert complex formation accomplished by treatment with isoquinoline and TMSCN at room temperature. While solution phase Reissert alkylation traditionally uses NaH as base, in this case the best results were obtained using an excess of the base LDA. Three different C1-substituted isoquinolines **2** were prepared from methyl iodide, butyl iodide and benzylbromide (Scheme 1). Analysis of these reaction mixtures showed that nearly complete alkylation occurred as, in all cases, only very minor traces ($< 5\%$) of not alkylated isoquinoline could be detected. These intermediates have been further elaborated to synthesise novel isoquinoline–isoxazoline heterocycles.

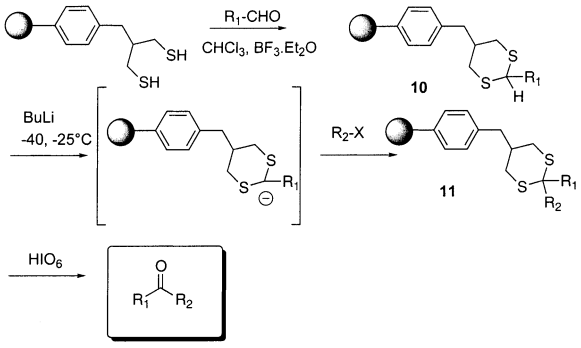
The alkylation of anions generated from solid-supported amidines of structure **4** with aromatic aldehydes was also investigated [8], to obtain the α-substituted hydroxy compounds **5**.[1]

Thus, the solid-supported dimethyl formamidine **3** was treated with a set of secondary amines by an amine exchange reaction and the new generated amidine **4** reacted with *t*-BuLi in pentane at $-70\,^{\circ}C$ and then with the aldehyde (Scheme 2). After alkylation and cleavage a series of ether-substituted amino compounds **5** were obtained.

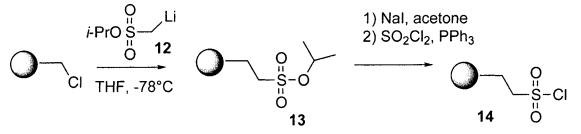
Polymer-bound lithium phenylsulfinate **6** reacted with allylbromide to give allylphenylsulfone beads **7** (Scheme 3).

Dianion formation could then be easily achieved using *n*-BuLi in THF and α–α′-dialkylated sulfone **8** was delivered by an excess of alkylating agent [11]. Copper-mediated sulfinate displacement regenerated the starting resin and released a trisubstituted alkene. Six different alkenes were prepared by this method. Unsymmetrical trisubstituted alkenes could also be prepared via monoalkylation of allyl secondary sulfones. However, bis alkylation of the dianion derived from primary sulfone with two different alkylating agents led to unresolved mixtures of products.

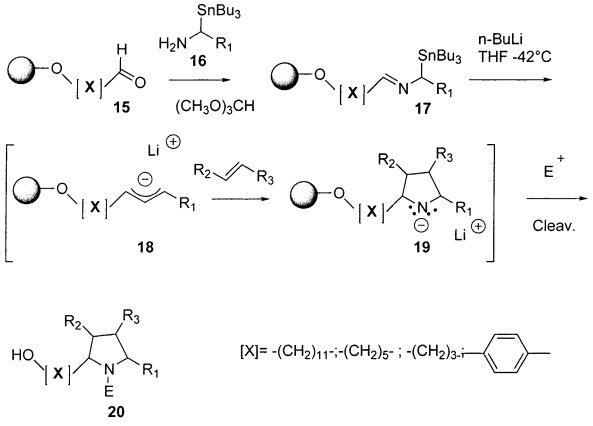
[1] A similar alkylation was extensively studied in solution phase by Meyers and colleagues [9,10] including studies regarding the regioselectivity of anion formation and asymmetric carbon–carbon bond formation, but no solid-phase methods had been previously described.



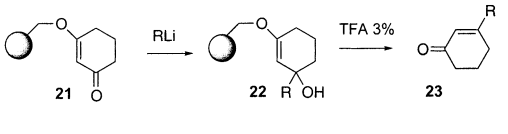
Scheme 5.



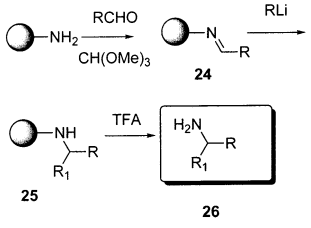
Scheme 6.



Scheme 7.



Scheme 8.



Scheme 9.

This chemistry has also been modified to accommodate the formation of cyclobutane **9** by sulfone dianion alkylation with epychloridrine [12] and subsequent "traceless" resin release by $S_N2'$ sulfinate displacement. (Scheme 4).

The resulting cyclobutanes may prove useful as a molecular scaffold for library production.

Polymeric reagents containing propane 1,3 dithiol were used to link aldehydes [13,14]. Also in this case the linkers behave as a protecting group for the carbonyl function. Dithiane **10** was treated with *n*-BuLi to provide a carbanionic intermediate active towards nucleophilic substitution on alkyl halydes (Scheme 5). Ketones **11** were then released upon dithiane ring cleavage with periodic acid.

Alkylation of Merrifield chloromethyl resin was developed using the lithium anion of isopropylmethanesulfonate **12** [15].

Isopropyl sulfonate resin **13** was converted to the sulfonylchloride resin **14**, which was used as a suitable linker to support sugar residues for polymer-supported oligosaccharide synthesis (Scheme 6).

Lithium derivatives are known to add on multiple bonds and some examples of this reactivity have been reported on polymer-supported substrates.

A method for generation of libraries of pyrrolidines was described in which the key step of the reaction sequence is represented by the generation of a polymer-supported 2-azaallylanion [16]. The procedure took advantage of the condensation of a polystyrene resin-supported aldehyde **15** with aminostannane **16**, to generate the corresponding imine **17** (Scheme 7).

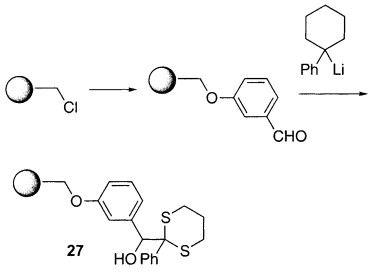
Imines are suitable precursors for 2-azaallylanions which have been employed in cycloaddition methodology, resulting in the generation of pyrrolidines. Treatment with *n*-BuLi at the optimal temperature of $-42$ °C produced 2-azaallylanion **18** which was transformed into the *N*-lithium pyrrolidine **19** in the presence of an alkene. Finally, quenching with electrophiles lead to **20**. Several pyrrolidines were prepared using two different alkenes, four aldehydes and two electrophiles.

Organolithium 1,2 addition was described on a hydroxymethyl polystyrene resin-bound vinylogous ester [17]. Treatment of a suspension of **21** with excess of organolithium reagent in anhydrous THF at 0 °C provided alcohol **22** which, under cleavage, released enone **23** in high yields and excellent purity (Scheme 8).

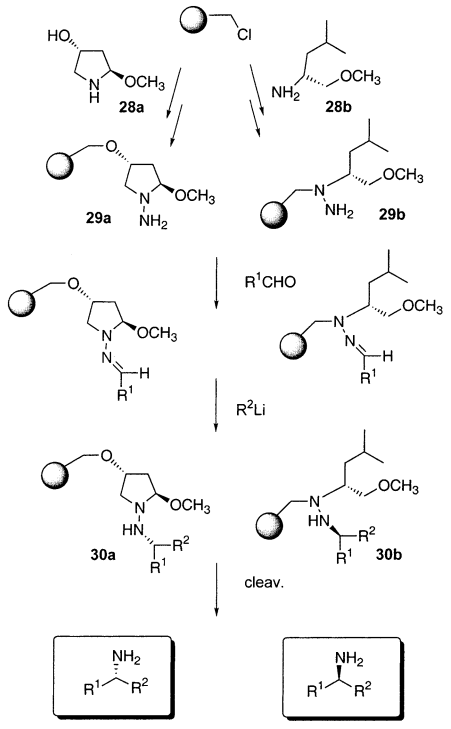
A wide range of primary amines was prepared in good to excellent yields via a nucleophilic addition of organometallic regents to aldimines immobilised on Rink resin [18]. The resin behaved both as a solid support and as NH protecting group.

Aldimines **24** were reacted with a range of organolithium reagents at $-78$ °C to give **25** (Scheme 9). After TFA cleavage, the corresponding primary amines **26** were recovered in good yields and purity. Aldimines derived from both electron-rich and electron-deficient aldehydes were successfully employed.

Nucleophilc addition on polymer-supported benzaldehydes was described using the lithium anion of 2-phenyl-1,3-dithiane [19]. 3-Hydroxybenzaldehyde was attached to chloromethyl–polystyrene resin and then reacted to provide a dithiane protected 3-alkoxybenzoine **27** which was shown to behave as a new photolabile linker for solid phase organic synthesis (Scheme 10).

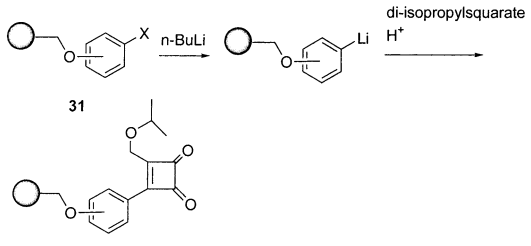



Scheme 10.




$R^2Li$ = *n*-Hex-Li; *t*-Bu-Li; Ph-Li; *n*-Bu-Li.

Scheme 11.




Scheme 12.

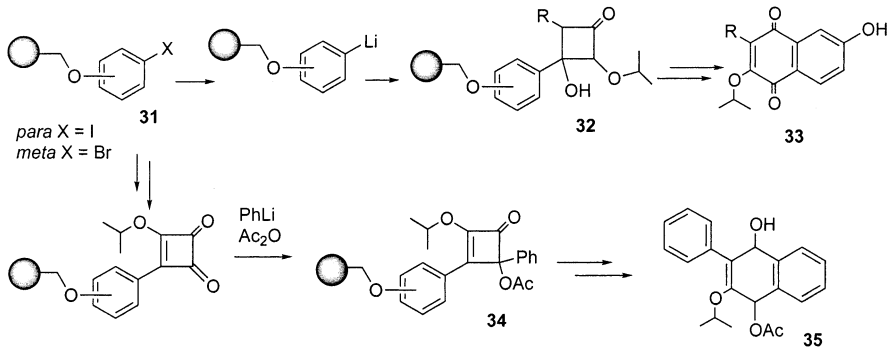
The asymmetric solid-phase synthesis of non-racemic α-branched primary amines was described by addition of both alkyl or aryl lithium reagents to polymer-bound aliphatic and aromatic aldehyde hydrazones [20]. Two novel chiral hydrazine resins for asymmetric solid phase synthesis were developed. The enantiopure β-methoxyamino auxiliaries, derived from *trans*-4-hydroxyproline **28a** or (*R*)-leucine **28b** were attached to a Merrifield resin, transformed into their corresponding hydrazines **29a**,**b** and coupled with aliphatic and aromatic aldehydes. Stereoselective addition on C–N double bond was achieved by treatment with different organolithium reagents to give enantiopure hydrazines **30a**,**b**. These compounds furnished the corresponding α-branched amines, after cleavage, in good yield and enantiomeric excess (Scheme 11).

The lack of effective preparative methods for obtaining immobilised organometallic compounds represents one of the drawbacks for the application of organometallic chemistry on solid phase. Consequently the development of new ways for the selective metallation of small supported molecules is of great importance for research development in this field. The following examples will be especially devoted to this topic.

Halogen–metal exchange is one of the more efficient ways for generating new organometallic compounds. Generation of anions on solid support through lithium halogen exchange has been reported [21]. To this aim halogenated phenols were coupled to Wang resin. Reaction of aromatic halogenides **31** with 10 equiv. of *n*-butyllithium in THF at −78 °C for 15 min led to complete exchange of the halogen (Scheme 12). After the supported anion was formed it was quenched with excess diisopropylsquarate to give the 1,2-addition product which rearranged under acid catalysis.

This approach was applied to develop two versions of resin-mediated synthesis of substituted naphtylenes. The first involved the condensation of a resin-bound organolithium species with a squaric acid precursor to obtain the intermediate **32** which could be further elaborated to naphtylene **33** (Scheme 13). The second involved the addition of an organolithium compound generated in solution to a squaric acid derivative linked to the resin, to obtain the intermediate **34** which was further elaborated to generate **35**.

Directed lithiation of aromatic compounds followed by reaction with an electrophile has a broad potential and has been used extensively [22]. In many cases, proton–lithium exchange provides the most direct route to the target structure and is thus preferred over halogen–lithium exchange. Consequently, lithiated solid-phase bound aromatic substrates can be useful for the introduction of a variety of functional groups by trapping with a broad range of electrophiles.




Scheme 13.

A single example of lithiation was reported [23] in which resin-bound silyl ether **36** was subjected to *ortho*-lithiation and then quenched with DMF to give a supported aldehyde **37** (Scheme 14).

The first systematic investigation of directed *ortho*-lithiation through deprotonation of a polymer-supported substrate appeared 2 years later and was based on the selective deprotonation of 1-hydroxyimidazole with *n*-BuLi [24]. 1-Benzyloxy group in benzyloxyimidazole was known [25] to serve as a directing group in *ortho*-metallation. The process was adapted to a solid-phase protocol using chloromethyl polystyrene as support. Resin-bound 1-hydroxyimidazole **38** was lithiated and reacted with a series of representative electrophiles (Scheme 15). Lithiation was performed using 5 equiv. of *n*-BuLi at $-50$ °C. Subsequent addition of carbon, halogen or sulfur electrophiles provided resin-bound 2-substituted imidazole derivatives.

Compound **38** was successfully transformed into benzoyl derivative **39** using benzoyl chloride. When the same reaction was carried out in solution the expected tertiary alcohol **40** was formed.

The study of *ortho*-metallation reaction has been further extended to the commonly used benzamide moiety [26]. In this case the amide functionality acts both as the directing group and as the linker. Polytetrahydrofuran (PTHF) cross-linked resins carrying a $NH_2$ group **41** was treated with benzoylchlorides and triethylamine to yield **42** (Scheme 16). Sequential treatment with tetramethylene diamine (TMEDA) and *sec*-BuLi was followed by addition of differently substituted 4-anisaldehydes to afford alcohols **43**. Phtalides **44** were then obtained by refluxing the resin with toluene.

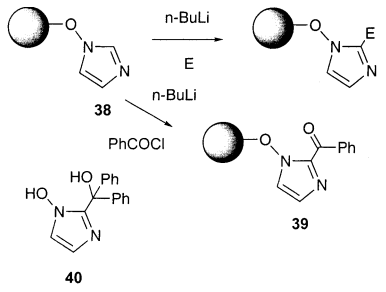
It should be noted that commercial DVB polystyrene and Tentagel® resins provided lower yields. Further optimisation of the reaction showed that even higher yields were obtained when *n*-BuLi was used in the absence of TMEDA. A phtalide 24-member library was obtained by treating three different benzamides with eight aromatic aldehydes. Yields were comparable with those observed in solution-phase chemistry [22].

## 2. Mg

The use of Grignard reagents in SPOS has already been reviewed and we cover here examples not cited in this literature [27].

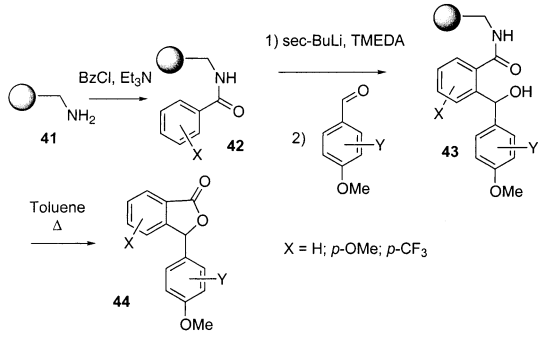
Very few examples of Grignard reagents generated on solid phase have been reported and always by halogen–magnesium exchange. The field was explored by Knochel and his group [28] that prepared several substituted heterocycles on solid phase. Furans **45** were


Scheme 14.



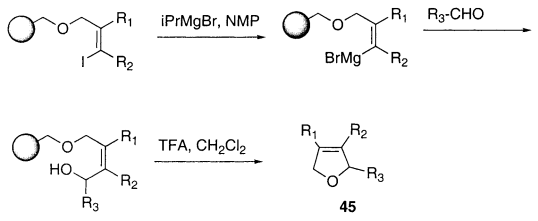

E = MeI, PhCHO, $HCONMe_2$, $C_2Cl_6$, $CBr_4$, $Me_2S_2$, $Ph_2S_2$, PhCOCl

Scheme 15.

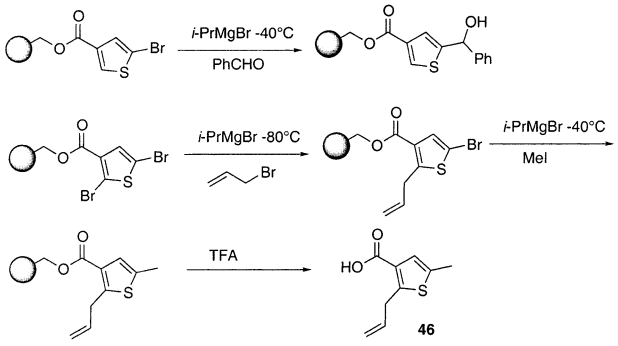



X = H; *p*-OMe; *p*-$CF_3$

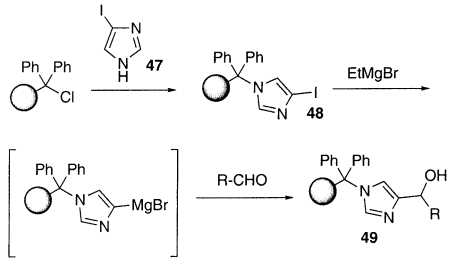
Scheme 16.



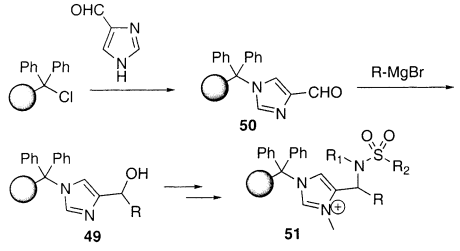

Scheme 17.



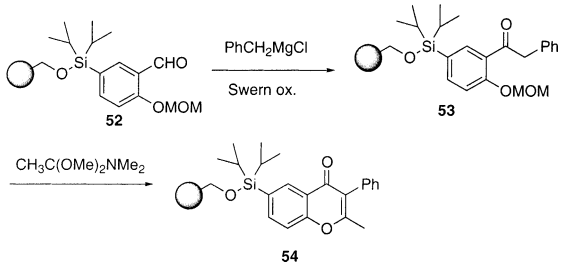

Scheme 18.




Scheme 19.




Scheme 20.




Scheme 21.

prepared on a Wang resin after generation of an alkenyl Mg reagent with *i*-PrMgBr in NMP followed by reaction with aldehydes and cleavage from the resin through acid ring closing (Scheme 17).

Analogously substituted thiophenes **46** were prepared on solid phase [29] using different heterocyclic bromides attached to the resin (Scheme 18). Treatment with an excess of *i*-PrMgBr (10 equiv.) at low temperature followed by reaction of various electrophiles afforded, after cleavage from the resin, a range of polyfunctionalised thiophenes.

It is noteworthy that, as happens in solution, the reactivity of two different bromides can be modulated working at different temperatures with a consecutive introduction of different electrophiles on the thiophen ring.

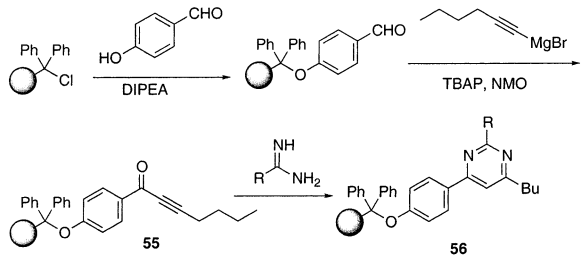
The same approach was employed in the preparation of a library of 4-substituted imidazoles [30] by loading 4-iodoimidazole **47** on a trytyl resin, followed by iodomagnesium exchange and reaction with different electrophiles (Scheme 19).

Aldehydes, ketones, acyl chlorides nitriles and isocyanates were used as electrophiles with excellent results affording the supported substituted imidazoles **49**, which could be further functionalised before cleavage.

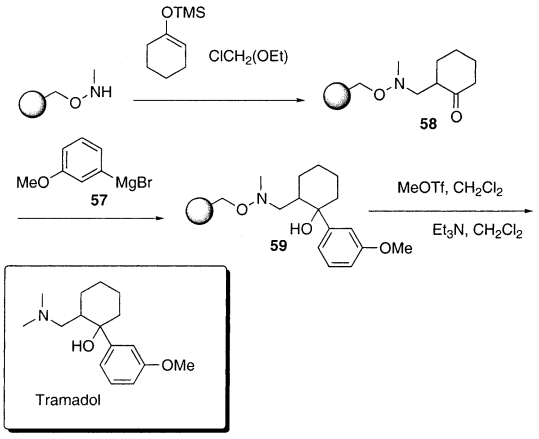
Imidazole containing derivatives **49** were also prepared, with the opposite approach, on a trytyl resin [31] (Scheme 20). Resin-bound imidazolyl aldehyde **50** was reacted with different Grignard reagents to give the corresponding alcohols that are the same compounds prepared from the previous reviewed authors. After 5–6 additional steps a library of 4-substituted imidazole sulfonamides **51** was prepared and tested in search of new antifungal compounds.

Another aldehyde **52**, loaded on a resin through a silyl linker, was reacted with a Grignard reagent to give an alcohol that was further oxidised to a keton **53** and finally transformed into a substituted benzopyranone **54** with dimethylacetamide dimethylacetal [32] (Scheme 21).

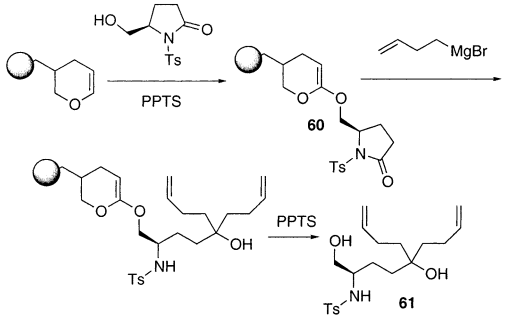
The reaction of aldehydes with Grignard reagents to give alcohols, that could be further oxidised to ketons, was also used [33] in the preparation of libraries of pyrimidines on a trityl resin as reported in Scheme 22. The Grignard was prepared from a series of alkynes



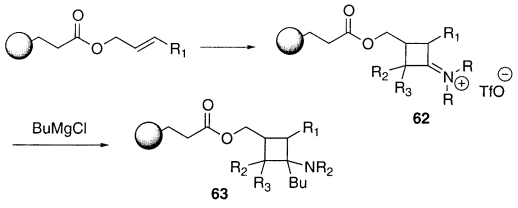

Scheme 22.



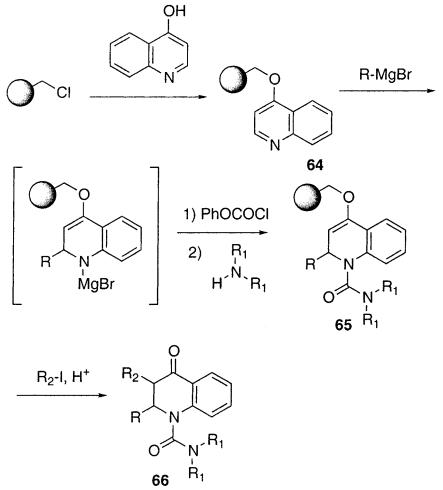

Scheme 23.




Scheme 24.




Scheme 25.




Scheme 26.

with EtMgBr to give, after oxidation, the propargyl keton **55** that is a versatile intermediate for the preparation of heterocyclic compounds, as the trisubstituted pyrimidine **56** (Scheme 22).

A keton was used as the electrophile in the preparation of the analgesic Tramadol on solid phase, using a methyl hydroxylamine linker [34].

3-Methoxyphenyl magnesium bromide **57** reacted with the resin bound keton **58** to give a tertiary alcohol **59** (Scheme 23). After quaternarisation of the resin bound alcohol, cleavage with $Et_3N/CH_2Cl_2$ gave Tramadol in 57% yield.

(5*S*)-*N*-Tosyl-5-hydroxymethyl-pyrrolidin-2-one coupled to a DMP-linked polystyrene resin **60** was another useful supported electrophile for Grignard reagents [35]. Ring opening of the pyrrolidinone ring occurred with different organometallic nucleophiles (including magnesium and lithium compounds) to give a small library of substituted enantiomerically pure *N*-tosyl amines **61** (Scheme 24).

Supported imminium ions can be also used as electrophiles for the preparation of amines as in the case of the reaction of the cyclobutylketeneimminium ion **62** in Scheme 25 [36].

Addition of a Grignard reagent to this supported species gave amine **63**. This transformation was noteworthy, as an earlier example of the analogous reaction in solution had been reported to be much less efficient.

Nucleophilic addition of a Grignard reagent onto the C=N double bond of the supported quinoline **64** gave an intermediate urethane **65** that was additionally decorated to give a series of substituted 2,3-dihydroquinolin-4-ones **66** [37] (Scheme 26).

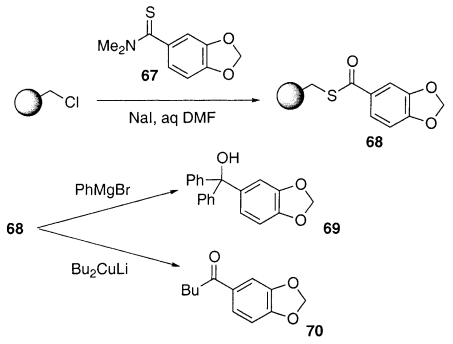
The resin used was a simple Merrifield support and the cleavage was carried out with addition of an electrophile to the enol-ether formed after the addition of the Grignard to the pyridine ring.

Finally, Grignard reagents were employed in the cleavage of functionalised resin bound thioesters as reported by M. Bradley and his group [38] (Scheme 27).

In this case several aromatic thiocarboxyamides **67** were linked to a Merrifield type resin and, after transformation on the aromatic ring, products **68** were reacted with Grignard reagents or organocuprates to give alcohols **69** or ketons **70**.

## 3. Cu, Zn

The existence of electrophilic functional groups has been a limit for the use of highly basic reagents on immobilised small molecules, therefore the search of new ways for the chemoselective metallation of highly functionalised supported molecules is considered very important in this area.




Scheme 27.

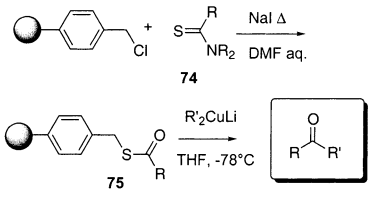

Scheme 28.

Many efforts have been made for the preparation of organometallic compounds with electrophilic substituents in solution chemistry and among others, organocopper and organozinc reagents have been proved to be very efficient.

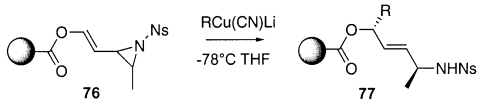
Immobilized organocuprate **71** and zincate **72** species have been prepared by halogen–metal exchange reaction using copper and zinc ate-complexes and their reactivity with electrophiles has been studied [39] (Scheme 28).

Halogen–zinc exchange reaction proceeded smoothly on 4-iodobenzoate resin **73** using LTBZ (lithium tri-*tert*-butylzincate) at 0 °C (Scheme 29). Careful control of the reaction temperature was necessary in order to avoid cleavage of the ester linkage. Halogen copper exchange reaction was also examined. $(TMS)_2Cu(CN)–Li_2$ was reported as the chosen metallating agent. However, the best conditions to achieve immobilised organocuprates **71** were by treating the immobilised organozincate **72** with lithium cyanothienylcuprate.

Alkylation of organozincates **72** with benzaldehyde, allyl and methyl iodide was described. Treatment of cuprates **71** with 2-cyclohexenone gave 1,4 adduct. Pal-

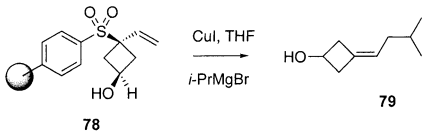



Scheme 30.




Ns = Nosylate, p-Nitrobenzenesulfonate

Scheme 31.




Scheme 32.

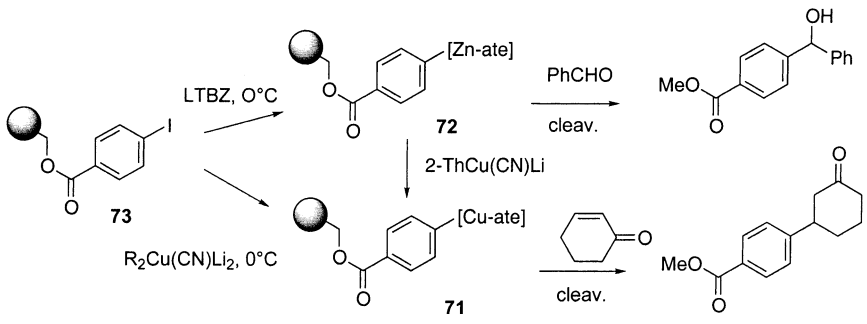
ladium-catalysed cross-coupling reactions with iodobenzene were also reported.

Cuprates $R_2CuLi$ were employed to cleave resin-bound thioesters to chemoselectively afford ketones (Schemes 30 and 27) [38]. Heating an aqueous DMF solution of a thioamide **74** with sodium iodide and Merrifield resins gave **75**, which could be efficiently employed as a "traceless linker". Reaction of **75** with cuprates afforded ketons in good yields.

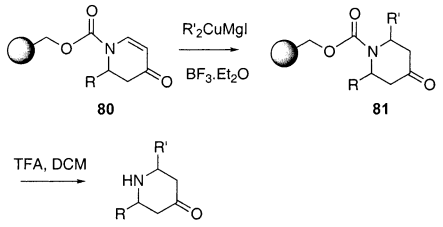
Alkylcyanocuprates were employed in the solid phase synthesis of (*E*)-alkene peptide isosters [40]. Alkenylaziridine supported on a Wang resin **76** reacted with cyanocuprates at low temperature to afford the corresponding amino esters **77** (Scheme 31).

Cuprates derived from organolithium, -magnesium or zinc precursors were proved to be equally effective.

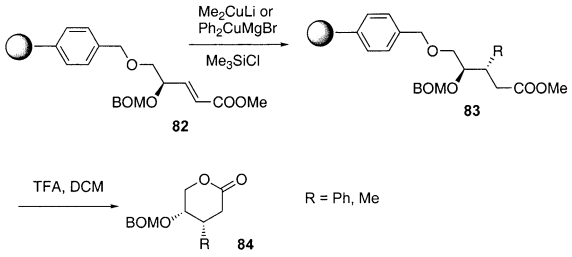
Kurth and co-workers [12] employed a cuprate addition in the synthesis of cyclobutylidenes. Organocuprate, formed by combination of isopropylmagnesium bromide and CuI, was added to the allylsul-



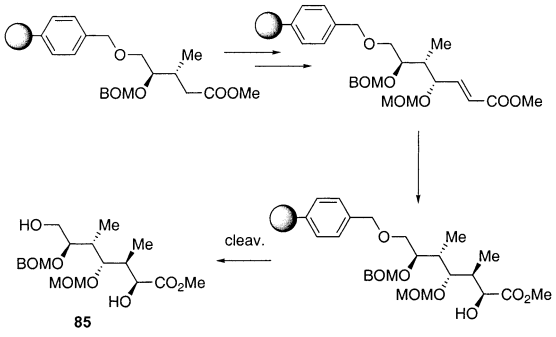

Scheme 29.



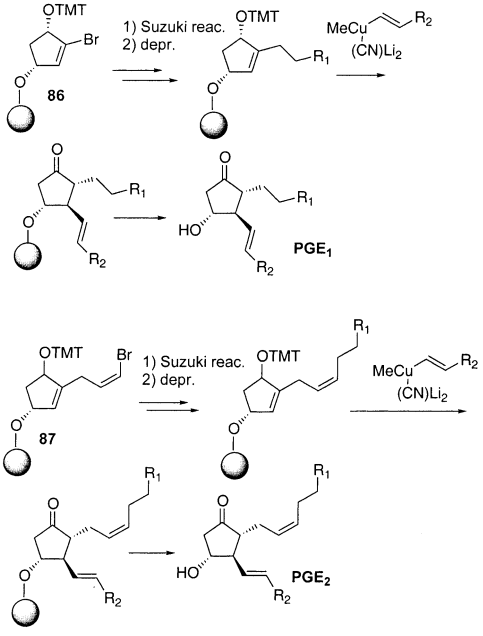

Scheme 33.




Scheme 34.




Scheme 35.




Scheme 36.

fone **78** to give cyclobutylidene **79** through an $S_N2'$ displacement of the sulfinate (Scheme 32).

Reactions of organocuprates have found their major application in 1,4-addition on α,β-unsaturated substrates.

1,4-Addition was applied in the solid phase synthesis of piperidin-4-ones employing RECAP technology [41]. Polymer-supported dihydropyridones **80** were reacted with cuprates in the presence of $BF_3{\cdot}Et_2O$ to furnish, after cleavage, piperidin-4-ones **81** in good yields and purities (Scheme 33).

Michael addition followed by alkylation of the resulting enolate provided a reaction sequence which was efficiently employed by Hanessian in the synthesis of contiguous stereogenic centres [42]. This stereoselective synthesis started by attaching a chiral α,β-unsaturated ester to Wang resin (Scheme 34). Treatment of **82** with a cuprate reagent gave the corresponding adducts **83** which were cleaved to afford enantiopure lactones **84**.

The tandem stereocontrolled addition of a cuprate followed the enolate hydroxylation, previously successfully realised in solution [43], was also applied to SPOS (Scheme 35). Hanessian showed that polypropionate **85** could be prepared on solid phase with excellent 1,2-stereocontrol through two cuprate additions and two enolate hydroxylation cycles.

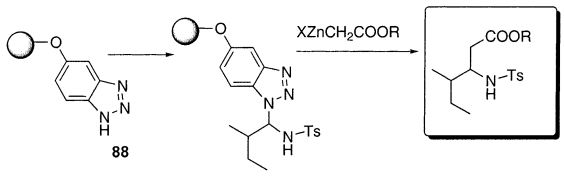
Michael addition has been successfully employed in the polymer-supported synthesis of prostaglandins. Solid-phase synthesis of diverse E- and F-series prostaglandin was described [44]. Two different core structures were prepared and loaded on a dibutylsilyl chloride-substituted resin: core structure **86** provided access to $PGE_1$-series PGs, while core structure **87** provided access to $PGE_2$-series derivatives (Scheme 36). A Suzuki cross-coupling thus introduced the first lateral chain, while diversity in the lower side chain was introduced by the addition of vinylcuprates, which were prepared in situ by hydrozirconation of terminal alkynes followed by transmetallation. All the prostaglandin products were obtained in greater than 95% diastereomeric purity as would be expected on the basis of analogous cuprate addition chemistry in solution.

This procedure was applied to the parallel synthesis of diverse prostaglandins by the preparation of a set of 26 $PGE_1$ analogues designed to target the unique binding pocket within the designed TA202 mutant of the prostaglandin $EP_3$ receptor [45].

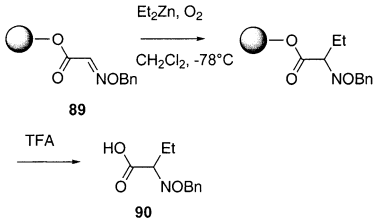
Reaction of organozinc derivatives has been less studied on solid phase. There are few reports and they are mainly devoted to cross-coupling Pd- or Ni-catalysed reactions.

Reformatsky reagents have been employed to test the reactivity of resin-bound Mannich bases derived from a benzotriazole containing resin **88** [46].

Reaction was performed in THF at 60 °C and the corresponding β-amino esters were released in good yield (Scheme 37).




Scheme 37.




Scheme 38.

Diethylzinc was reported to promote stereoselective solid-phase radical reactions [47].

The addition of an ethyl radical generated from diethyl zinc and $O_2$ to oxime ether anchored to Wang resin **89** proceeded smoothly and with high yield even at low temperature to afford, after cleavage, hydroxylamino acid **90** (Scheme 38). In the same reaction, a high degree of stereocontrol could be achieved using Oppolzer's camphorsultam as chiral auxiliary (Scheme 39). The addition product **92** was obtained with excellent diastereoselectivity starting from compound **91**.

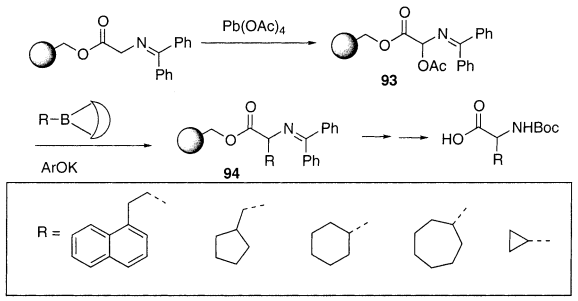
Different radical precursors could also be used under iodine-atom transfer reaction conditions.

## 4. B, Si

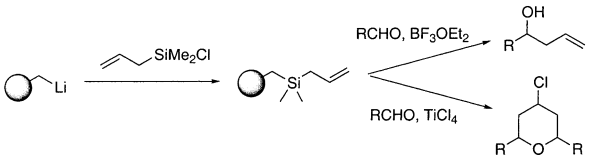
Although organoboranes [48] and organosilanes [49] have been largely used in organic synthesis for the formation of new carbon–carbon bonds, very few examples deal with their use in SPOS.

Unnatural amino acids were synthesised on solid phase by reaction of a resin-bound Schiff base with organoboranes in the presence of potassium 2,6-di-*tert*-butyl-4-methylphenoxide [50] (Scheme 40).

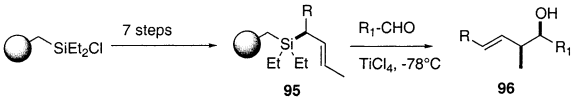
A solid phase glycine cation equivalent **93** was prepared by treatment of a suitable Schiff base loaded on




Scheme 40.




Scheme 41.




Scheme 42.

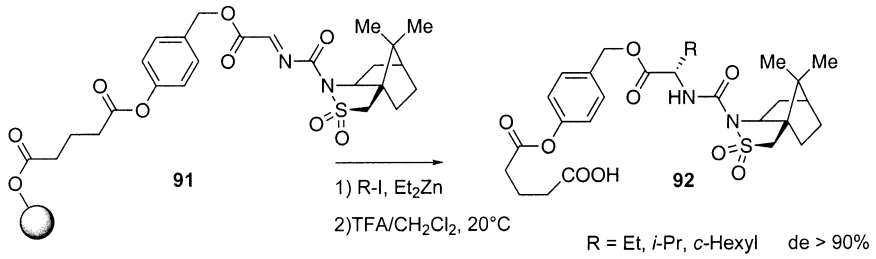
a Wang resin with $Pb(OAc)_4$. Reaction of this acetate with different boranes gave the products **94** that was finally released using standard techniques.

Allylsilanes supported on resins have been reported as substrates for metathesis reactions [51]. Subsequently they have been used for reactions with aldehydes in the presence of Lewis acids to generate homoallyl alcohols or tetrahydropyrans in solution [52] (Scheme 41).

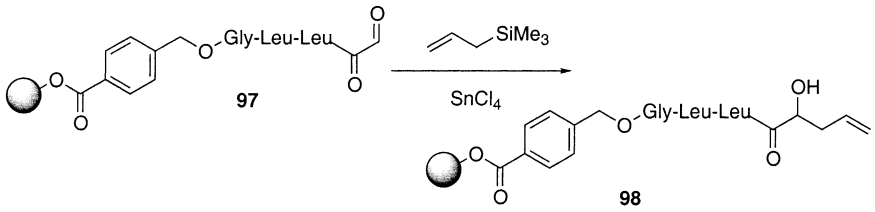
A highly enantioenriched allylsilane **95** was also prepared on solid phase [53] and further reacted with aldehydes to give *syn*-homoallylic alcohols **96** with high diastereoselectivity and ee (from 93 to 99%) (Scheme 42).

Meldal [54] described the use of allyltrimethylsilane in the Sakurai reaction with solid phase bound N-terminal peptide aldehyde **97** leading to peptide isostere **98** (Scheme 43).

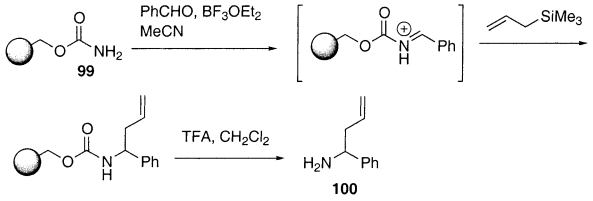
Hiemstra and Rutjes [55] described the use of allyltrimethylsilane in solution in the reaction with aldehydes and supported carbamate **99** (Scheme 44).



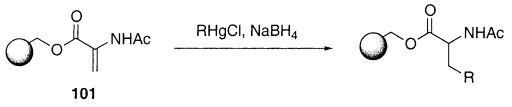

Scheme 39.




Scheme 43.




Scheme 44.




Scheme 45.

The use of $BF_3OEt_2$ in MeCN was compatible with a Wang linker and a library of allylamines **100** was obtained after TFA cleavage.

## 5. Hg

Alkylmercury compounds were used to generate radicals on solid phase [56]. *N*-Acetyldehydroalanine **101** was bound to a Wang resin and subjected to alkyl radical generated in situ by reaction of alkylmercury chloride and $NaBH_4$ (Scheme 45).

## 6. Conclusions

In conclusion we observed that several methods employing organometallic reagents are available for generating new C–C bonds on solid phase. Notwithstanding the current opinion that mild reaction conditions are required on solid phase, the most widely employed reagents were organolithium and organomagnesium. Less basic organocuprates and zincates have found less applications and surprisingly neutral organometallic reagents as organoboranes and silanes were poorly investigated. No examples on the use of organostannanes or organoaluminium reagents for C–C bond formation on solid phase have been reported yet, except in the case of Pd-catalysed coupling reactions.

It is expected that these reagents will soon be applied to SPOS, thereby making possible the preparation of new libraries with new biological activity.

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