ARYL - ARYL STILLE AND SUZUKI - MIYAURA CROSS COUPLING REACTIONS ON SOLID SUPPORT

by

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Abstract

The Stille and Suzuki-Miyaura cross coupling reactions in solution phase have proven to be effective methods for the formation of new carbon-carbon bonds. The work contained herein describes the adaptation of these reactions to the solid support.

Chapter 1:

The Stille cross coupling reaction on solid support using an ester linker is described. New cleavage condition of the ester linker involving LiOH hydrolysis is reported. Merrifield resin - linked halo benzoates undergo Pd(0) catalysed coupling with a wide range of stannanes to produce after cleavage styryl, biaryl and heterobiaryl carboxylic acids in 71->95% isolated yields.

Chapter 2:

The synthesis of biaryl and heterobiaryl aldehydes in 45->95% yields by Suzuki-Miyaura cross coupling reaction on Merrifield – Leznoff acetal – linked halo benzaldehydes followed by mild acid hydrolysis is reported; synthetic utility for heterocycles based on solution phase Directed *ortho* Metalation chemistry is demonstrated in two prototype cases. Phenanthridine and 6*H*-dibenzo[*b*,*d*]pyran-6-one were synthesised in, 90% and 71%, respectively, overall isolated yields.

Acknowledgements

Les recherches dont ce mémoire est la synthèse ont été effectuées à l'Université de Waterloo, sous la direction de Monsieur le Professeur Victor Snieckus à qui j'exprime toute ma gratitude pour la bienveillance qu'il m'a témoignée et l'intérêt constant qu'il a manifesté pour mes travaux pendant toute la durée de mon séjour dans son équipe. Je le remercie vivement de m'avoir donné la possibilité de travailler dans ce nouveau domaine de la chimie.

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Je voudrais bien sûr remercier de tout cœur mes parents qui m'ont donné la chance de poursuivre de si longues études, pour leur aide au cours de toutes ces années et pour leur encouragement permanent.

Ich danke Marc von ganzem Herzen für seine ständige Unterstützung und Geduld. Seine Liebe hat mir die Kraft für alles gegeben.

A mes parents,

A Marc,

A tous ceux qui me sont chers

«Chercher n'est pas une chose et trouver une autre,

mais le gain de la recherche,

c'est la recherche elle-même.»

Saint Grégoire de Nysse (v. 335- v. 395)

Homélies sur l'Ecclésiaste

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Abbreviations

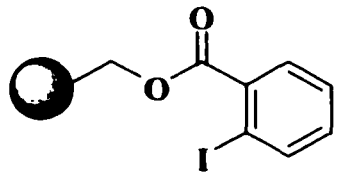
Aca	aminocaproic acid
acac	acetylacetonate
AIBN	2,2′-azobisisobutyronitrile
Ala	alanine
AM	aminomethyl
aq	aqueous
Ar	aryl
binap	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bpoc	2-(4-biphenyl)isopropyloxycarbonyl
brine	saturated aqueous solution of NaCl
CI	chemical ionization
CSA	camphorsulfonic acid
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DIBAL	diisobutylaluminium hydride
DIC	diisopropylcarbodiimide
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMG	directed *ortho* metalation group

DMS	dimethylsulfide
DoM	directed *ortho* metalation
dppf	1,1′-bis(diphenylphosphino)ferrocene
DreM	directed remote metalation
DVB	divinylbenzene
EDG	electron donating groups
EI	electron impact
EWG	electron withdrawing groups
FAB	fast-atom bombardment
Fmoc	9-fluorenylmethoxycarbonyl
FT	Fourier transform
HMBA	4-hydroxymethylbenzoic acid
HMP	4-hydroxymethylphenoxyacetic acid
HMPA	hexamethylphosphoramide
HOBT	1-hydroxybenzotriazole
L	ligand
LG	leaving group
MBHA	methylbenzhydrylamine
MEM	methoxyethoxymethyl
Met	metal
MOM	methoxymethyl
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMP	*N*-methylpyrrolidone

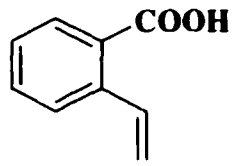
PEG	polyethyleneglycol
PTSA	*p*-toluenesulfonic acid
pyr	pyridine
RBF	round bottom flask
SASRIN	super acid-sensitive resin
SPOS	solid phase organic synthesis
TBAF	tetrabutylammonium fluoride
***t*-Boc**	*tert*-butoxycarbonyl
TEA	triethylamine
Teoc	[[(trimethylsilyl)ethyl]oxy]carbonyl
TFA	trifluoroacetic acid
TFE	trifluoroethanol
TFMSA	trifluoromethanesulfonic acid
TFP	tri-2-furylphosphine
THP	tetrahydropyran
Tips	triisopropylsilyl
TMEDA	*N,N,N′,N′*-tetramethylethylendiamine
TMS	trimethylsilyl or tetramethylsilane
TMSCI	chlorotrimethylsilane
xs	excess

List of Experimental Procedures

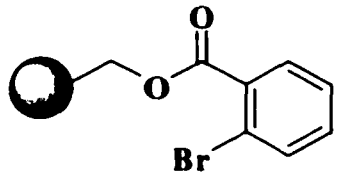
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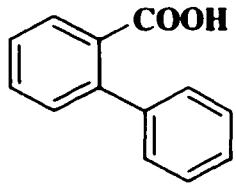
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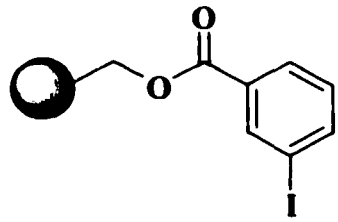
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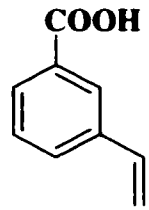
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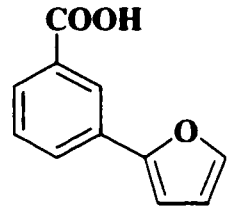
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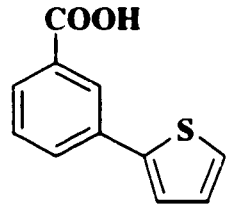
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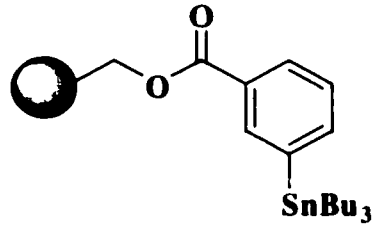
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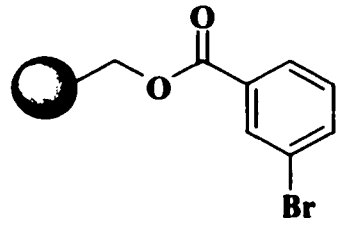
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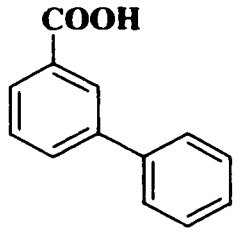
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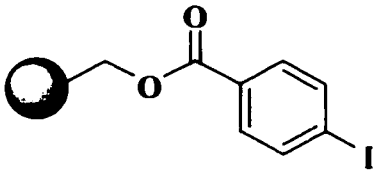
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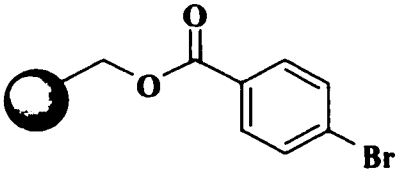
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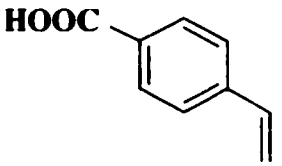
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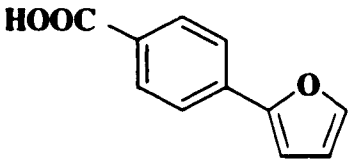
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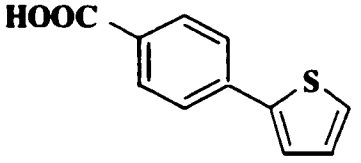
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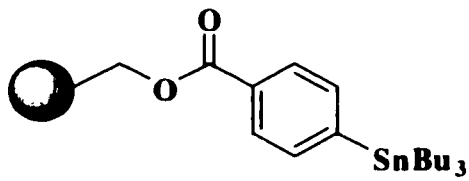
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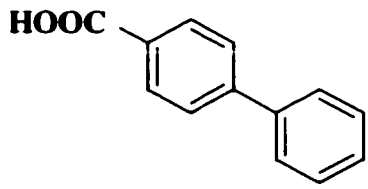
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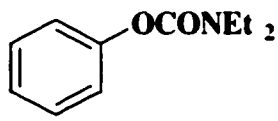
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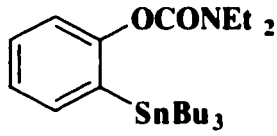
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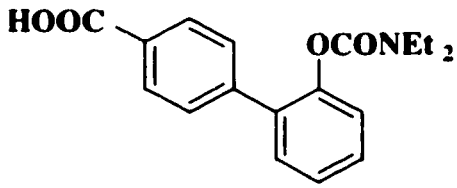
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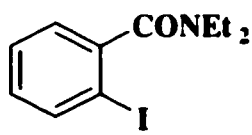
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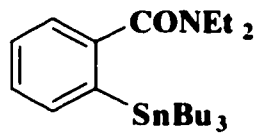
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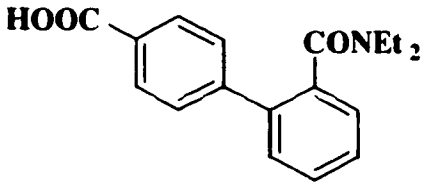
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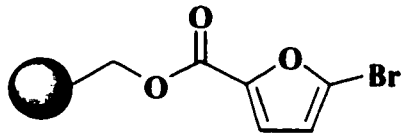
N,N-Diethyl 2-tributylstannylbenzamide (1.123)..... 107



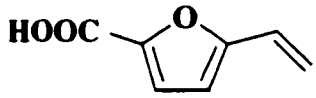
4-(2-*N,N*-Diethylcarboxamidophenyl)benzoic acid (1.120)..... 108



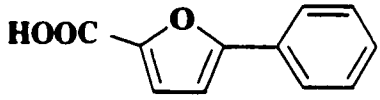
Resin-bound 5-bromo-2-furoic acid (1.131)..... 108



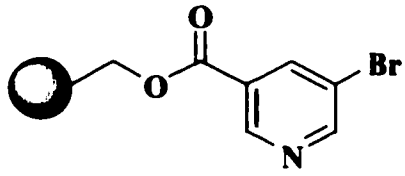
5-Vinylfuran-2-carboxylic acid (1.132)..... 109



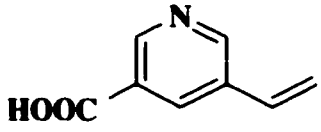
5-Phenylfuran-2-carboxylic acid (1.133)..... 110



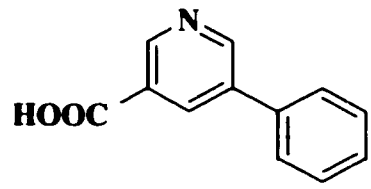
Resin-bound 5-bromonicotinic acid (1.128)..... 111



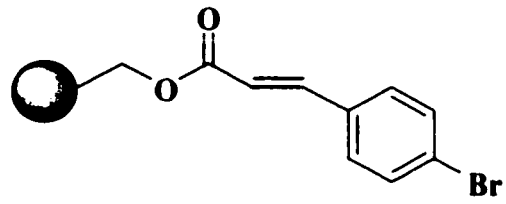
5-Vinylnicotinic acid (1.129)..... 111



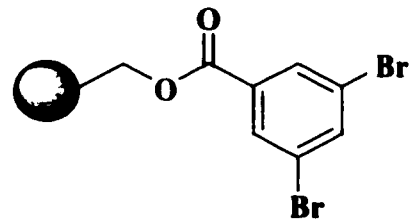
5-Phenylnicotinic acid (1.130)..... 112



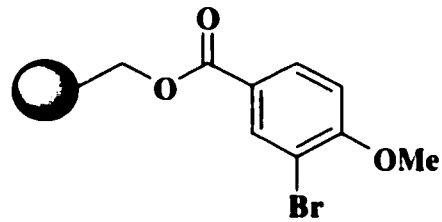
Resin-bound 4-bromocinnamic acid (1.140)..... 113



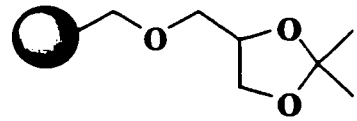
Resin-bound 3,5-dibromobenzoic acid (1.141)..... 113



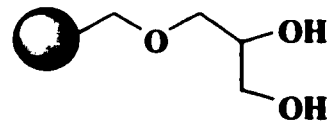
Resin-bound 3-bromo-4-methoxy-benzoic acid (1.142)..... 114



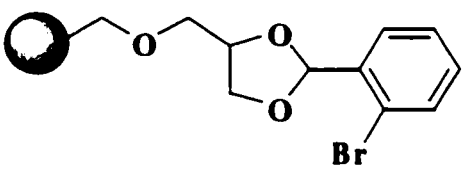
Resin-bound 1-O-benzyl-2,3-isopropylidene glycerol (2.50)..... 161



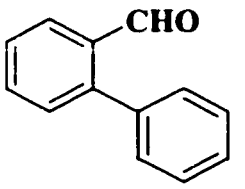
Resin-bound 3-benzyloxypropan-1,2-diol (2.51)..... 162



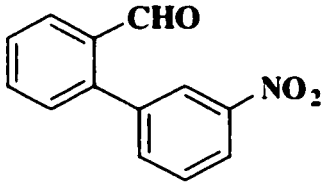
Resin-bound 2-bromobenzaldehyde (2.59)..... 162



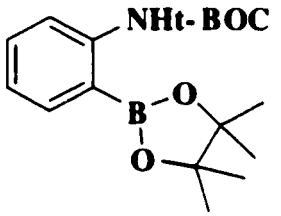
Biphenyl-2-carbaldehyde (2.60)..... 163



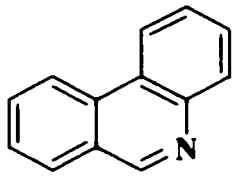
2-(3-Nitrophenyl)benzaldehyde (2.63)..... 164



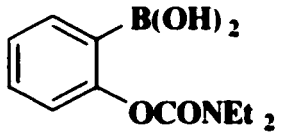
Pinacol[*N*-(*tert*-butoxycarbonyl)-2-amino-1-phenyl]boronate (2.108)..... 165



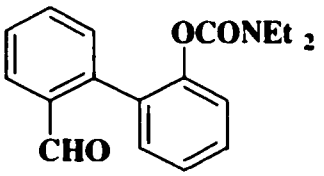
Phenanthridine (2.110)..... 165



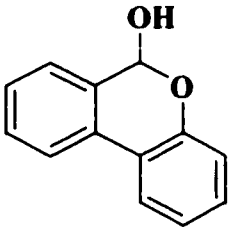
2-*N*,*N*-Diethylcarbamoylphenylboronic acid (2.104)..... 166



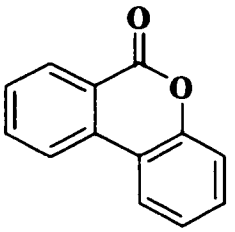
2-(2-*N,N*-Diethylcarbamoylphenyl)benzaldehyde (2.120)..... 167



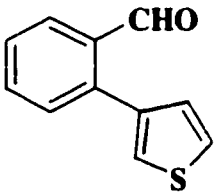
6*H*-Dibenzo[*b,d*]pyran-6-ol (2.121)..... 168



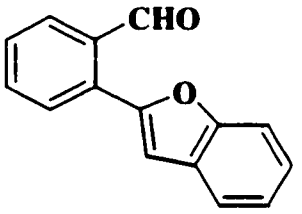
6*H*-Dibenzo[*b,d*]pyran-6-one (1.62)..... 168



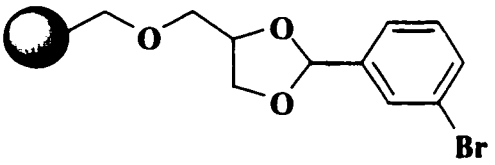
2-(3-Thienyl)benzaldehyde (2.77)..... 169



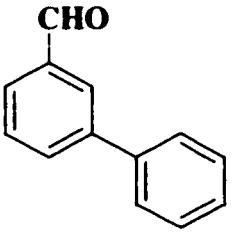
2-(2-Benzofuranyl)benzaldehyde (2.79)..... 170



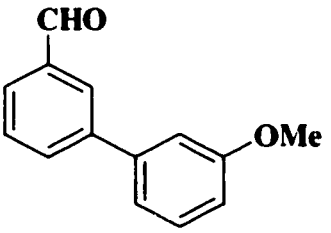
Resin-bound 3-bromobenzaldehyde (2.64)..... 171



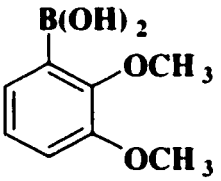
Biphenyl-3-carbaldehyde (2.65)..... 171



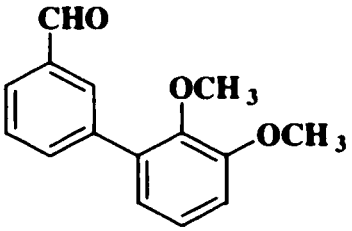
3-(3-Methoxyphenyl)benzaldehyde (2.67)..... 172



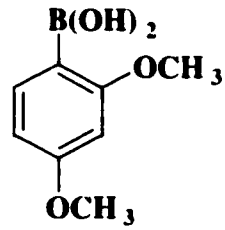
2,3-Dimethoxyphenylboronic acid (2.100)..... 173



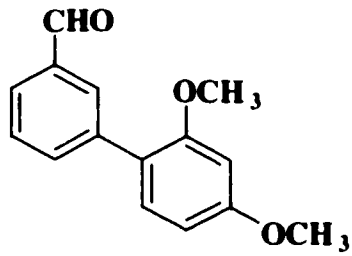
3-(2,3-Dimethoxyphenyl)benzaldehyde (2.101)..... 173



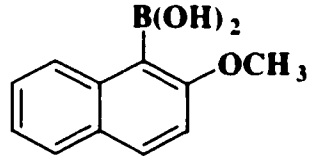
2,4-Dimethoxyphenylboronic acid (2.98)..... 174



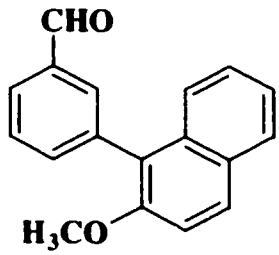
3-(2,4-Dimethoxyphenyl)benzaldehyde (2.99)..... 175



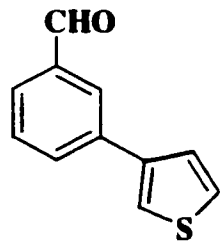
2-Methoxy-1-naphthyl-boronic acid (2.102)..... 176



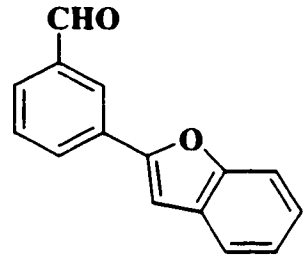
3-(2'-Methoxy-1-naphthyl)benzaldehyde (2.103)..... 177



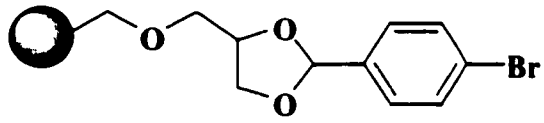
3-(3-Thienyl)benzaldehyde (2.80)..... 178



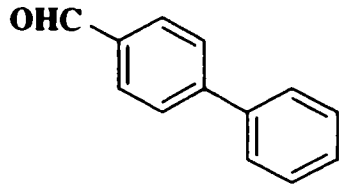
3-(2-Benzofuranyl)benzaldehyde (2.81)..... 179



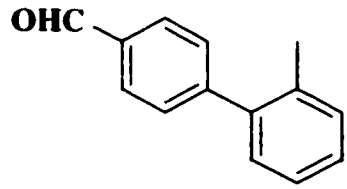
Resin-bound 4-bromobenzaldehyde (2.68)..... 180



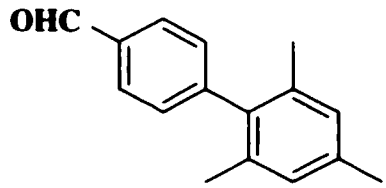
Biphenyl-4-carbaldehyde (2.69)..... 180



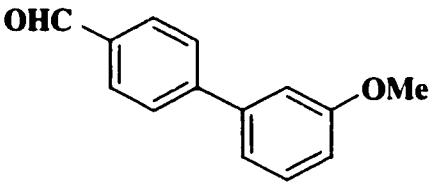
4-(2-Tolyl)benzaldehyde (2.71)..... 181



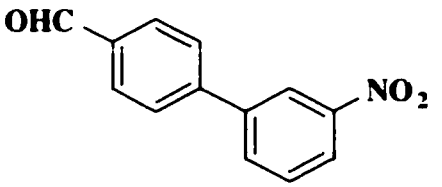
4-(2,4,6-Trimethylphenyl)benzaldehyde (2.73)..... 182



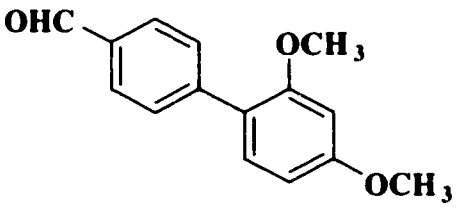
4-(3-Methoxyphenyl)benzaldehyde (2.74)..... 183



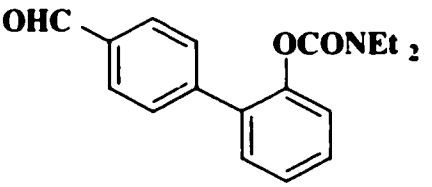
4-(3-Nitrophenyl)benzaldehyde (2.75)..... 184



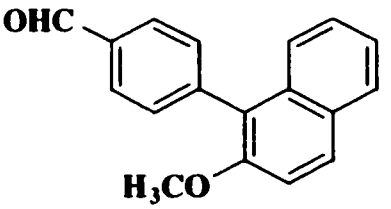
4-(2,4-Dimethoxyphenyl)benzaldehyde (2.106)..... 185



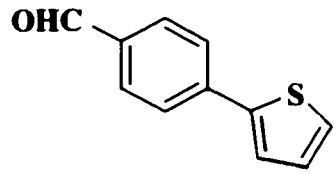
4-(2-*N,N*-Diethylcarbamoylphenyl)benzaldehyde (2.105)..... 186



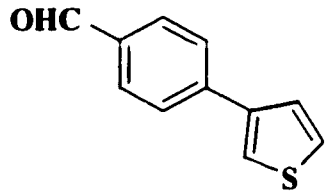
4-(2'-Methoxy-1-naphthyl)benzaldehyde (2.107)..... 187



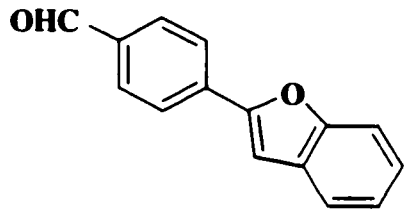
4-(2-Thienyl)benzaldehyde (2.84)..... 188



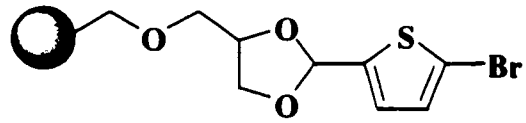
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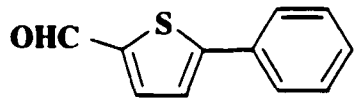
4-(2-Benzofuranyl)benzaldehyde (2.85)..... 190



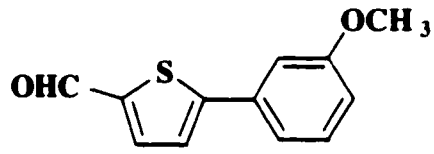
Resin-bound 5-bromo-thiophene-2-carbaldehyde (2.92)..... 191



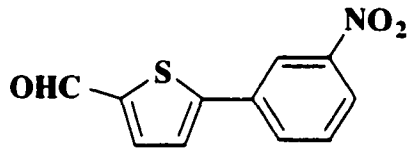
5-Phenylthiophene-2-carbaldehyde (2.95)..... 191



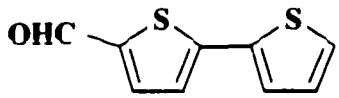
5-(3'-Methoxyphenyl)thiophene-2-carbaldehyde (2.96)..... 192



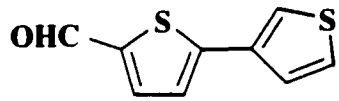
5-(3'-Nitrophenyl)thiophene-2-carbaldehyde (2.97)..... 193



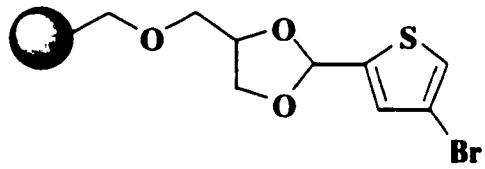
5-(2'-Thienyl)-2-thiophenecarbaldehyde (2.93)..... 194



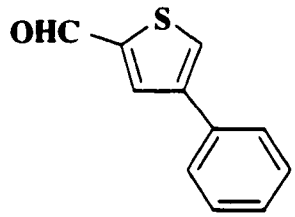
5-(3'-Thienyl)-2-thiophenecarbaldehyde (2.94)..... 195



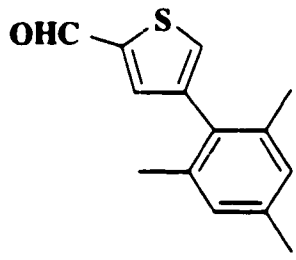
Resin-bound 4-bromo-thiophene-2-carbaldehyde (2.86)..... 196



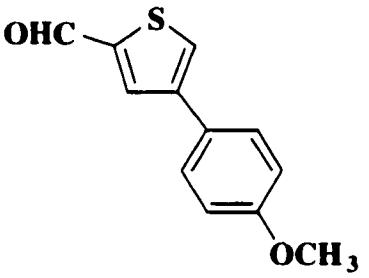
4-Phenylthiophene-2-carbaldehyde (2.88)..... 197



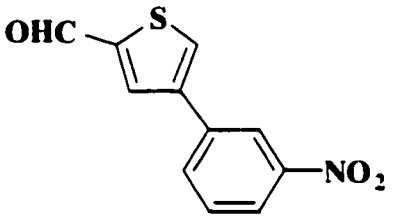
4-(2',4',6'-Trimethylphenyl)thiophene-2-carbaldehyde (2.90)..... 198



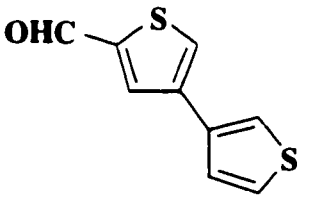
4-(4'-Methoxyphenyl)thiophene-2-carbaldehyde (2.91)..... 199



4-(3'-Nitrophenyl)thiophene-2-carbaldehyde (2.89)..... 200



4-(3'-Thienyl)-2-thiophenecarbaldehyde (2.87)..... 201



Chapter 1

1. Introduction

1.1. Combinatorial Chemistry

Due to robotisation and miniaturisation, the task of biological screening of small molecules has made tremendous progress during the last decade. The number of compounds that can be screened daily has increased from tens to thousands and the availability of a large number of compounds to feed the screening robots has become a major bottleneck.[1] The number of possible organic compounds with a molecular weigh < 750 g / mol is estimated to be 10^{200},[2] and the number of chemical compounds described in the literature to 1991 was about 11 million.[3] In the 1950s, the traditional basis of drug lead discovery (coupled in many cases with folk medicine) relied on natural sources like plants, animals or fermentation broths.[4] These required sophisticated purification and structural elucidation and their synthesis could be complicated and time-consuming. Compounds were also available from in-house samples accumulated over the years, synthesised by chemists. These sources were limited and reflected the history of each chemical company rather than a real chemical diversity. Initial hits, established from random screening of naturally occurring and synthetic compounds were systematically modified by medicinal chemists using bioassays as guides to develop the structure-activity relationships (SARs).[5] This approach required the synthesis of comprehensive series of organic compounds, an army of synthetic chemists, and considerable time for developing a limited variety of structures. Nowadays, a marketable drug requires 12

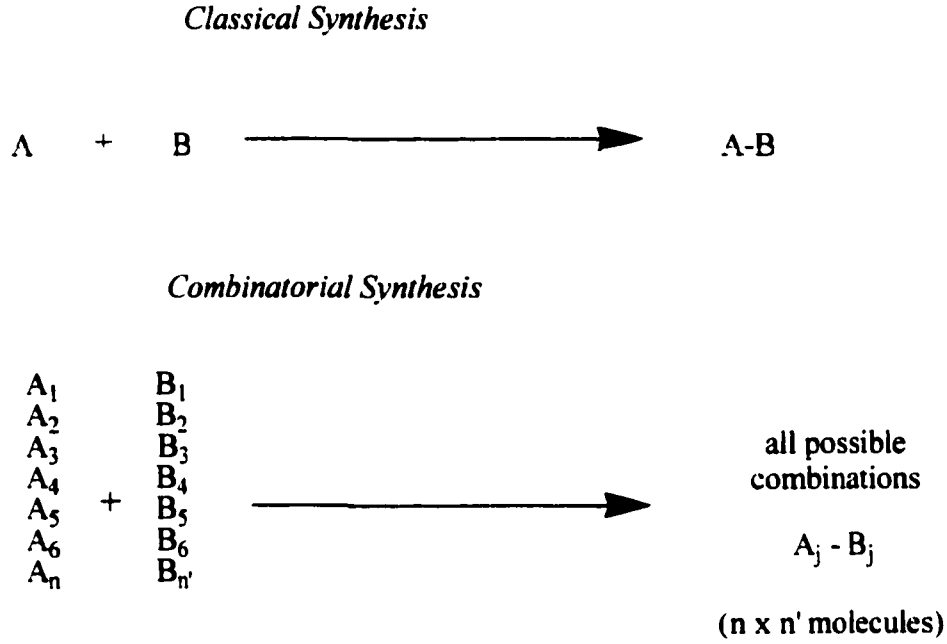
years of research and several studies have shown that the average cost of creating a new molecular entity in a major pharmaceutical company is around $ 7500 / compound.[6]

The increasing pressure to abbreviate both the time and the cost,[7] coupled with the availability of high-throughput screening regimens, prompted chemists to design new strategies for a single inexpensive and easy synthesis of a large number of structurally diverse compounds.[8] That is how the new area of combinatorial chemistry began. Although very much in its infancy, this new tool has made a powerful impact on the methodology and time-scale of all industrial drug discovery programs by allowing the rapid generation of large and diverse compound libraries.[9] The great interest in combinatorial chemistry is well illustrated by the sharp increase of the number of papers involving this chemistry.[10]

The technique of combinatorial chemistry was first reported by Mario Geysen in 1984.[11] Another pioneer in this field is Arpad Furka[12] from the University of Budapest who introduced the split and mix method at international scientific meetings in Prague and Budapest in 1988; however, the concept was not published until 1991 in three papers from the groups of Furka,[13] Houghten,[14] and Lam.[15]

The principle of combinatorial chemistry is illustrated on **Scheme 1.1.** Instead of using single molecular species of each reagent (A and B) as in classical chemistry and expecting to obtain a major product A-B, groups of building blocks are allowed to undergo reaction in a combinatorial process. A group of n building blocks (A_1 to A_n) is allowed to react simultaneously with another group of n' building blocks (B_1 to $B_{n'}$) leading to a mixture of all possible combinations (A_1B_1 to $A_nB_{n'}$). Thus starting from n+n' building blocks, n×n' products

are obtained. Using this basic principle, combinatorial chemistry allowed a dramatic increase in the number of compounds synthesised; especially when several combinatorial steps are repeated, the number of compounds formed increasing exponentially.[16]



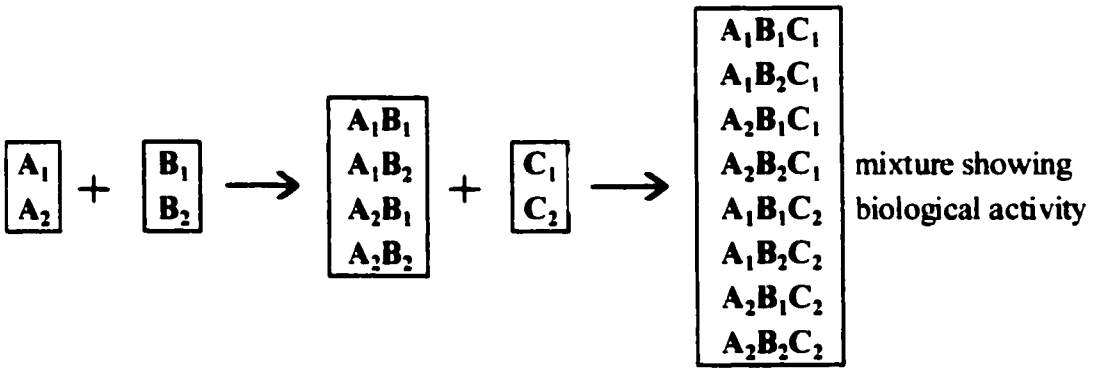
Scheme 1.1. Principle of combinatorial chemistry.

Because, historically, in the biological assays of natural product extracts, many compounds were screened simultaneously to discover active components,[17] early pioneers in combinatorial chemistry developed the concept of intentionally making mixtures for the purpose of more rapid screening. This concept has been widely accepted even if the generation of mixtures goes against the traditional practices in synthetic chemistry. Nevertheless, several problems emerge from this technique. When a mixture shows no activity, all the compounds in the mixture are assumed to be inactive. This implies that no compound affects the assay of another one or even that the products do not undergo reaction with each other. Another major

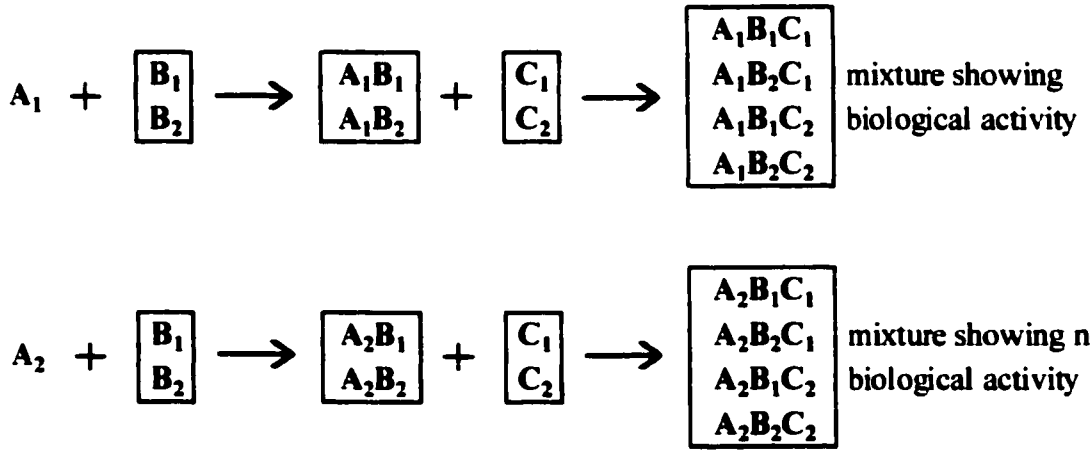
concern arising when making mixtures is the necessity to find reactions that are suitable for a large variety of reagents leading to the expected products in high yield. Otherwise, inextricable mixtures that would hinder any structural elucidation would be obtained.

Since these early days, solutions such as identifications of active compounds from mixtures by deconvolution,[18] split mix methods[19] and parallel synthesis[20] were found and tremendous improvements have been achieved. The deconvolution strategy was initially proposed by Houghten.[21] It constitutes a reliable but time-consuming method. It involves an iterative procedure in which libraries containing a decreased number of compounds are prepared successively until a unique structure is identified (**Scheme 1.2.**).

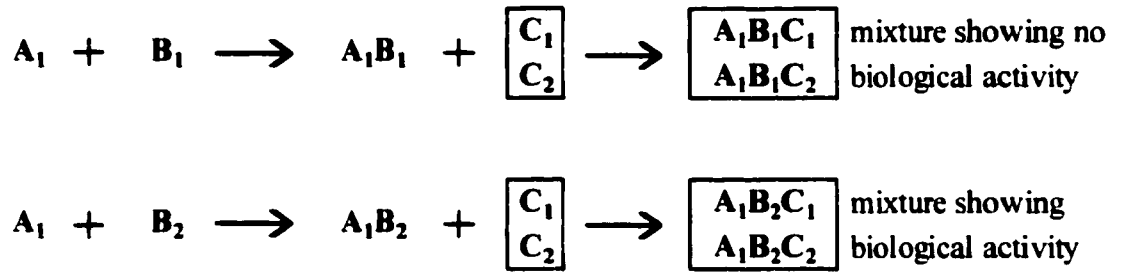
Combinatorial library synthesis



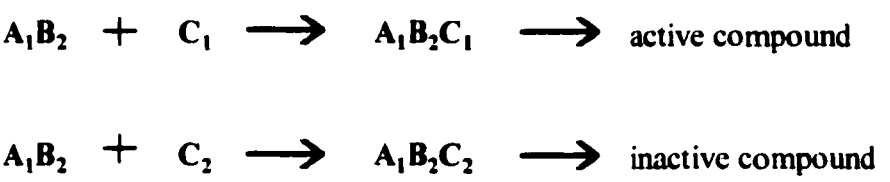
1st deconvolution procedure



2nd deconvolution procedure



3rd step deconvolution procedure

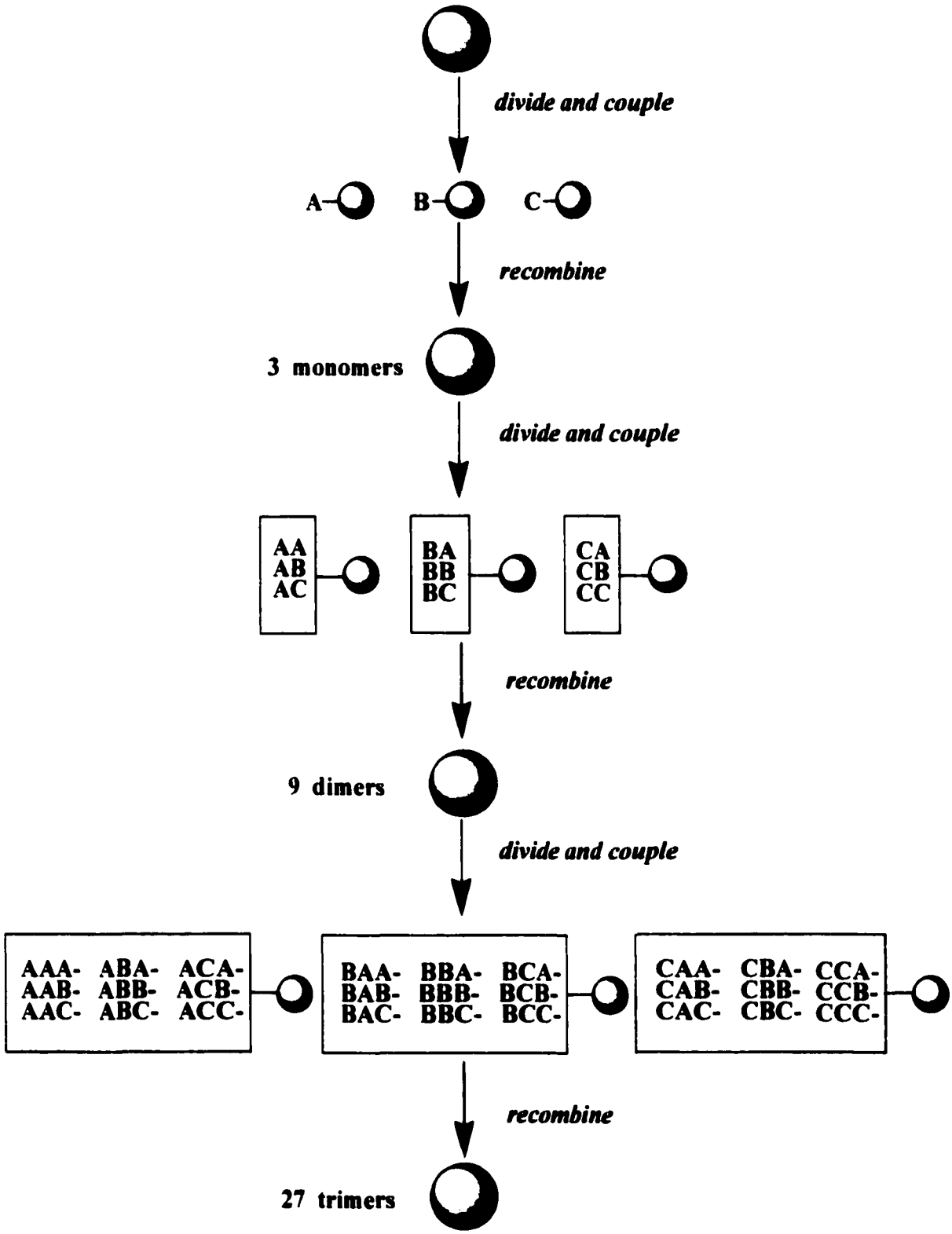


Scheme 1.2. Deconvolution principle.

A library of eight components $[A_1B_1C_1]$,.... $[A_2B_2C_2]$ is formed by a combinatorial synthesis involving the coupling of two components mixtures $[A_1A_2]$, $[B_1B_2]$, $[C_1C_2]$ at each step. If an activity is detected in this mixture, the identification of the active compound in the eight components mixture can be performed by a 3 steps deconvolution procedure. In the first step, two sublibraries are synthesised, in which the first position is fixed. By determining the biological activity of each of these two sublibraries, it can be determined whether A_1 or A_2 is responsible for the activity initially detected in the mixture. If A_1 is identified as the active block, a second deconvolution step can be carried out to determine whether B_1 or B_2 is responsible for the biological activity by building two new sublibraries in which position 1 is A_1 and position 2 is B_1 for one of the sublibraries and B_2 for the other one. By repeating this method for the third position, the identification of a unique active structure is achieved.

Further analyses of the deconvolution method and its inherent problems have been described by Freier.[22]

The early form of combinatorial chemistry involved solid phase synthesis and presented a major risk. Large excess of mixtures of soluble buildings blocks were allowed to react with polymer bound substrates to accelerate reactions and force them to completion. When the different building blocks had various reaction rates, the most reactive building blocks were over represented in the final-bound mixture. Furka[13] first reported the so-called spit-mix method in order to avoid this problem. The method consists of dividing the resin before each combinatorial step and couple each building block separately in a different vessel. After the coupling, the different samples of the resin are recombined and divided before being submitted to the next combinatorial step. **Scheme 1.3.** illustrates the split-mix synthesis of 27 monomers by three synthetic cycles with three monomers (A, B, C).



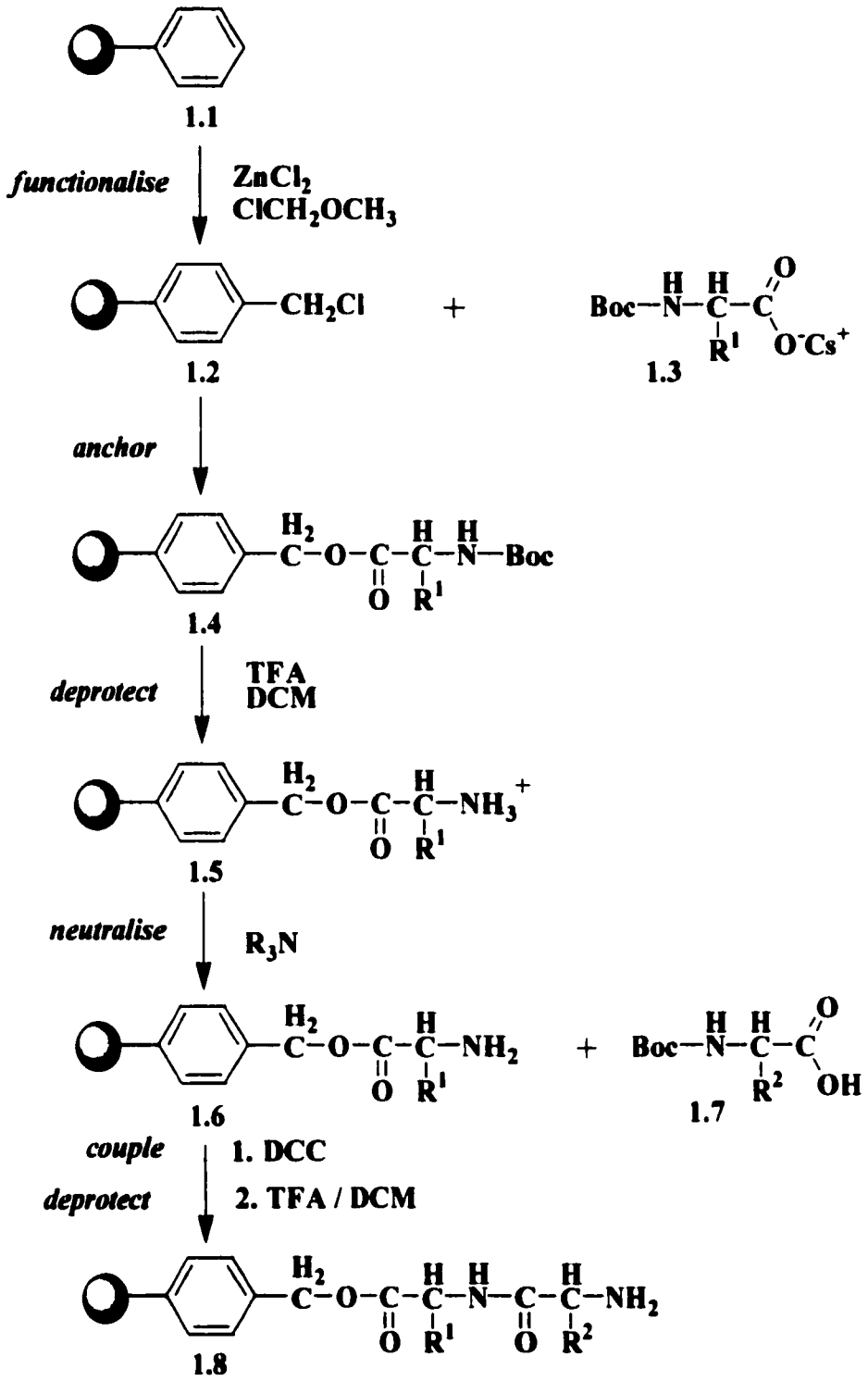
Scheme 1.3. Split-mix synthesis method.

To avoid the tedious processes necessary for the identification of the active compounds in mixtures. the technique of parallel synthesis is gaining more and more interest among combinatorial chemists.[23] *N* substances are synthesised in *n* different vessels using an automated reaction process. The identity of any compound is given by its spatial location and can be confirmed by analytical methods. The multipin approach was developed by Geysen[11] for the synthesis of peptides. The synthesis is usually performed using 96 pins placed into a supporting block so that each pin fits into a separate well of a 96-well plate holder. Each pin, which consists of an amino-functionalised polyacrylic-acid-grafted polyethylene rod, serves then as a distinct reaction vessel. The lower portion of the apparatus can be immersed in a heated or cooled ultrasound bath to provide both agitation and temperature control. Above the holder block, a manifold permits the maintenance of an inert atmosphere. This technique was applied successfully to the synthesis of non-peptidic compounds such as benzodiazepines[24] and 4-aminoproline analogues.[25] Parke-Davis designed the Diversomer technology and demonstrated its utility in the successful preparation of hydantoin, benzodiazepine, benzisothiazolone, and quinilone library syntheses.[26] An 8 pin or 40 pin apparatus is coupled to robots allowing automatic resin loading, reaction cycle monitoring, washing cycles, and parallel purification by solid-phase extraction methods.[27]

Combinatorial chemistry represents a new wave in drug discovery. The rapid improvement of its efficiency relies on the development of many research areas such as new analytical methods, new computer modelling, new database-related challenges, new synthetic approaches, new types of reagents and new types of assays in order to prepare the libraries and find the active compounds. In this context, the methods of solid-phase synthesis, pioneered by Merrifield, provide a major advantage to combinatorial chemistry.

1.2. Solid Phase Synthesis

From the pioneering efforts of Merrifield[28] and Letsinger[29] in the early sixties, solid phase synthesis has become the standard technique for the preparation of peptides and oligonucleotides.[30] Merrifield was awarded the Nobel Prize for his work on solid-phase synthesis in 1984.[31] In 1963, he reported the first examples of solid-phase synthesis of peptides using chloromethylated-polystyrene-containing, immobilised N-protected amino acid building blocks. **Scheme 1.4** shows the Merrifield approach. The reactions used are the same as in standard synthesis, but one of the reactants is anchored onto a solid support. One of the amino acids protected by a *t*-Boc group **1.3** is coupled to the CH_2Cl side chain of the resin **1.2** (anchor). The Boc group is then removed by hydrolysis with TFA (deprotect) and the second amino acid **1.7** is coupled to the first using DCC (couple). The second Boc group is removed, resulting in a dipeptide still anchored to the polymer **1.8**. If the dipeptide is the desired product, it can be cleaved from the polymer by various methods,[32] one of which is the treatment of the resin with HF. If a longer peptide is desired, additional amino acids can be added by repeating the coupling and the deprotection steps.



Scheme 1.4. Merrifield approach to the solid phase synthesis of peptides.

The basic advantage of this technique is that the polymer and all chains attached to it are easily separated from all the by-products, excess reagents, and solvents by washing cycles. The purification of the polymeric species can be then complete and rapid. In the 1980's automated peptide synthesiser technology was in its infancy. Today, the synthesis may be fully automated.[33] However, peptides and oligonucleotides were of limited use as drug candidates owing to their *in vivo* instability and poor oral availability and this provided the next challenge – the synthesis of small molecules on solid support.[34] Despite the work of Leznoff,[35] Patchornik,[36] Rapoport,[37] and Fréchet[38] in the 1970's, who showed that polystyrene bead-supported organic chemistry worked well, this approach did not go far.[39] One can think of at least two reasons for this lack of interest. Small quantities of compounds were produced and, since before 1980, when NMR analysis required larger samples due to the absence of high-field Fourier transform machines, products of solid-phase synthesis were problematic to analyse. The synthesis of large libraries of compounds was not a major goal because, at that time, the testing of new compounds was the rate-limiting step in the drug discovery process. Thus, until 1992, the solid-phase synthesis field remained the domain of peptide chemistry. It changed in 1992 with the report by Bunin and Ellman concerning the generation of combinatorial libraries of small molecules.[40] They provided the first illustration of polymer supported methodology for the synthesis of 192 structurally diverse 1,4-benzodiazepines, a well-established class of bioactive therapeutic agents. In the short period since then, solid phase chemistry and combinatorial chemistry have become intense main stream activities of industrial laboratories world-wide, as it clearly evidence by having a cursory glance at current literature.[41] Classical organic reactions are being transferred from solution phase to solid phase[42] and therefore combinatorial chemistry at a rapid pace, such that review articles are outdated by the time of their appearance. Today, combinatorial and parallel-synthesis

techniques are not only used in the drug discovery area but also in such diverse fields as material science, cosmetics, catalysis, and plant protection. Although, to date, only a small percentage of solution chemistry has been translated into solid-phase chemistry, the clear advantages of solid-phase for high-throughput synthesis are numerous:

a) Large excess of reagents can be used to force reactions to go to completion, reducing the complexity of final mixtures. Excess reagents, soluble by-products, and solvents are easily washed away by filtration of the resin.[43]

b) Side product formation is often minimised when the reaction schemes are designed on solid support.[44]

c) All the synthesised products remain linked to the polymer until the end of the synthesis avoiding losses during extraction or precipitation procedures (which are typically used in solution synthesis).

d) The isolation of intermediates at each step is carried out by simple filtration.

e) Odourless polymers of reduced toxicity may be prepared containing functionalities which, in low molecular weight compounds, would be associated with significant toxicity or noxious odours.

f) The solid support may be used to monoprotect bifunctional symmetrical molecules in such a way that the compound of interest may be fished out of a complex mixture of reactants or from excess unreacted starting material. This procedure, called the fishhook principle, can be exploited to allow selective modification of bifunctional molecules.[45]

g) Reactions exhibiting poor selectivity in solution may often be directed to give only the desired product by attachment of the appropriate component on the solid support.[46]

h) The technique is highly amenable to automation enabling many compounds to be prepared simultaneously in parallel reactors.[47]

i) By applying split-mix methodology, libraries containing from tens to millions of compounds may be rapidly synthesised.[48]

The principle drawbacks of solid phase organic synthesis are:

a) Due to the inability to purify intermediate resin-bound products, high yielding schemes (90-100%) are obligatory as are sequences not requiring purification so as to minimise the number of side-products. Although it may be argued that this increases the diversity of the library, it is almost impossible to do a successful deconvolution of such a library.

b) Extra labour is required to develop a solid phase route. Even if the starting point is the conditions described in solution phase chemistry (reagents, solvents, temperature), the translation to suitable solid phase synthesis conditions is usually a time-consuming process due to restrictions in the use of certain solvents and reagents.

c) Heterogeneous reactions on the solid phase are likely to be different from those in solution.

d) Solid-phase synthesis requires two additional steps to attach the starting material and release the product from the solid support. Bioassays are not very well adapted to compounds still bound to the polymers as the beads and linkers present conformational restrictions that may prevent binding to the receptor. Furthermore, for pharmaceutical applications, compounds need to act in solution and thus ideally need to be tested in solution.

e) The means of monitoring the reactions in real time on solid support are limited.

f) The current range of commercially available supports and linkers is limited.

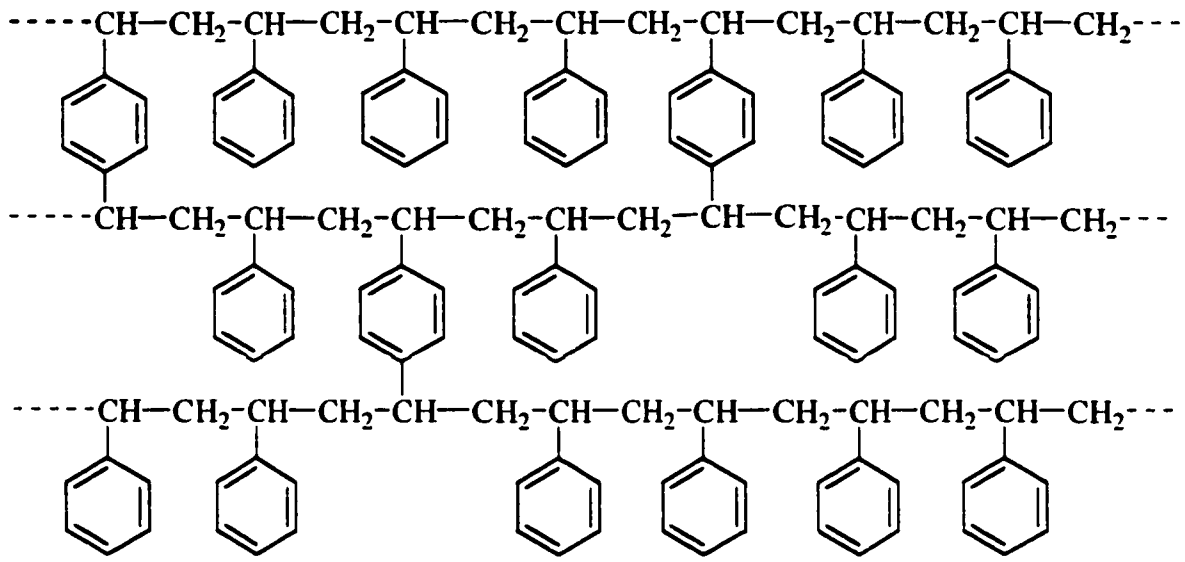
g) In order to be able to automate the chemistry, working with extreme temperatures should be avoided.

h) < 100 mg of final products are usually prepared.

When developing a solid phase synthesis, consideration should be given to the following factors. The solid support should be stable to a wide range of organic solvents and reactions. The linker should be cleavable under mild conditions suitable to automation but stable to the proposed reaction conditions. The target molecule should be synthesised in high yield and purity. Analytical techniques should be available for the reaction monitoring of the synthesis.

1.2.1. Solid Supports Used in Solid Phase Organic Synthesis

To date, the majority of the published solid phase organic syntheses has been carried out on two main types of solid support: polystyrene cross-linked with 1 or 2% of divinylbenzene (PS-DVB) and PEG-PS.[47b] Early pioneering work of Merrifield in peptide synthesis on solid support has made the use of cross-linked polystyrene a standard resin for routine solid-phase organic chemical reactions (**Scheme 1.5.**).



Scheme 1.5. Styrene – divinylbenzene copolymer.

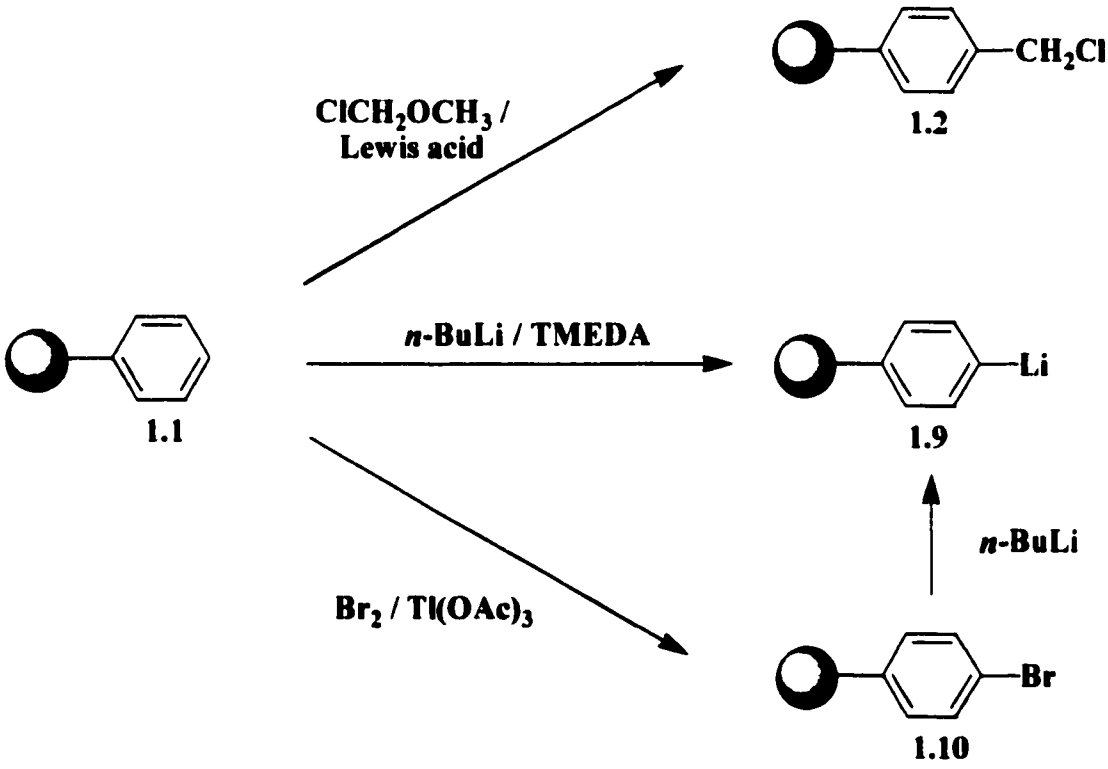
This type of support is however not suitable to all types of chemical reaction conditions and new supports such as PEG-PS have been used advantageously by combinatorial chemists.[49]

A resin is characterised by its loading, its functionality, its particle size, and the nature of its backbone that will affect its swelling properties and its stability towards reagents and temperature.

The loading of a resin designates the number of mmol of functional group present per gram of resin. In styrene-divinylbenzene copolymer, the level of substitution is about 100 pmol per bead. Knowing that 1 g of resin has 4-10 x 10^6 beads, the loading is in the range 0.4 mmol / g - 1 mmol / g. Higher loading resins are being developed and one can find loading as

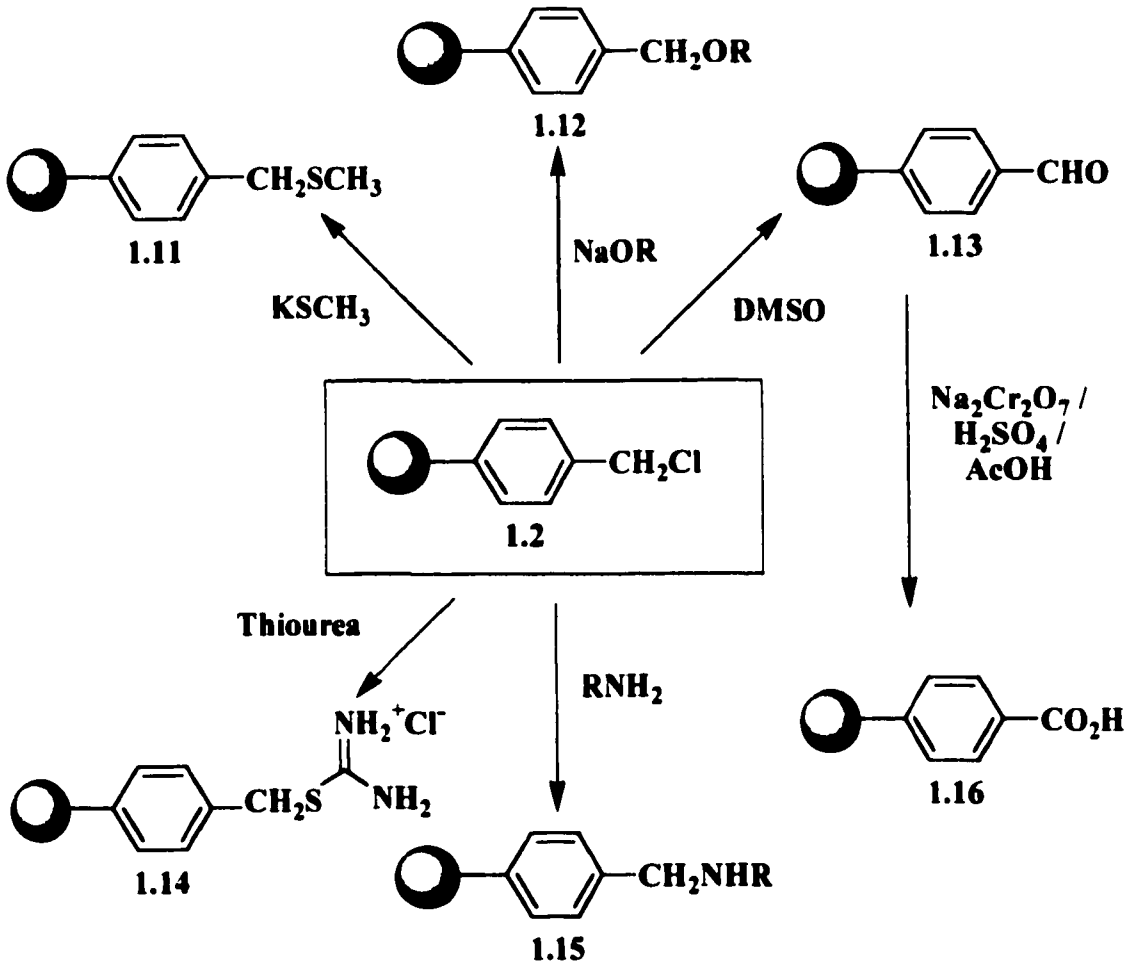
high as 4 mmol / g. PEG-PS copolymers are characterised by lower loadings. They are in the order of 0.2 to 0.5 mmol / g.

A wide range of functionalities has been introduced into the polymer supports.[43] They may be incorporated during the synthesis of the support itself or, preferably, they may be introduced by chemical modification of non-functionalised preformed support matrices. The most common functionalisation techniques of polymers are chloromethylation, using a Lewis acid catalyst and chloromethyl methyl ether as the solvent[50] and lithiation, using *n*-BuLi and TMEDA or the metal halogen exchange of bromo PS using *n*-BuLi[51] (**Scheme 1.6.**).



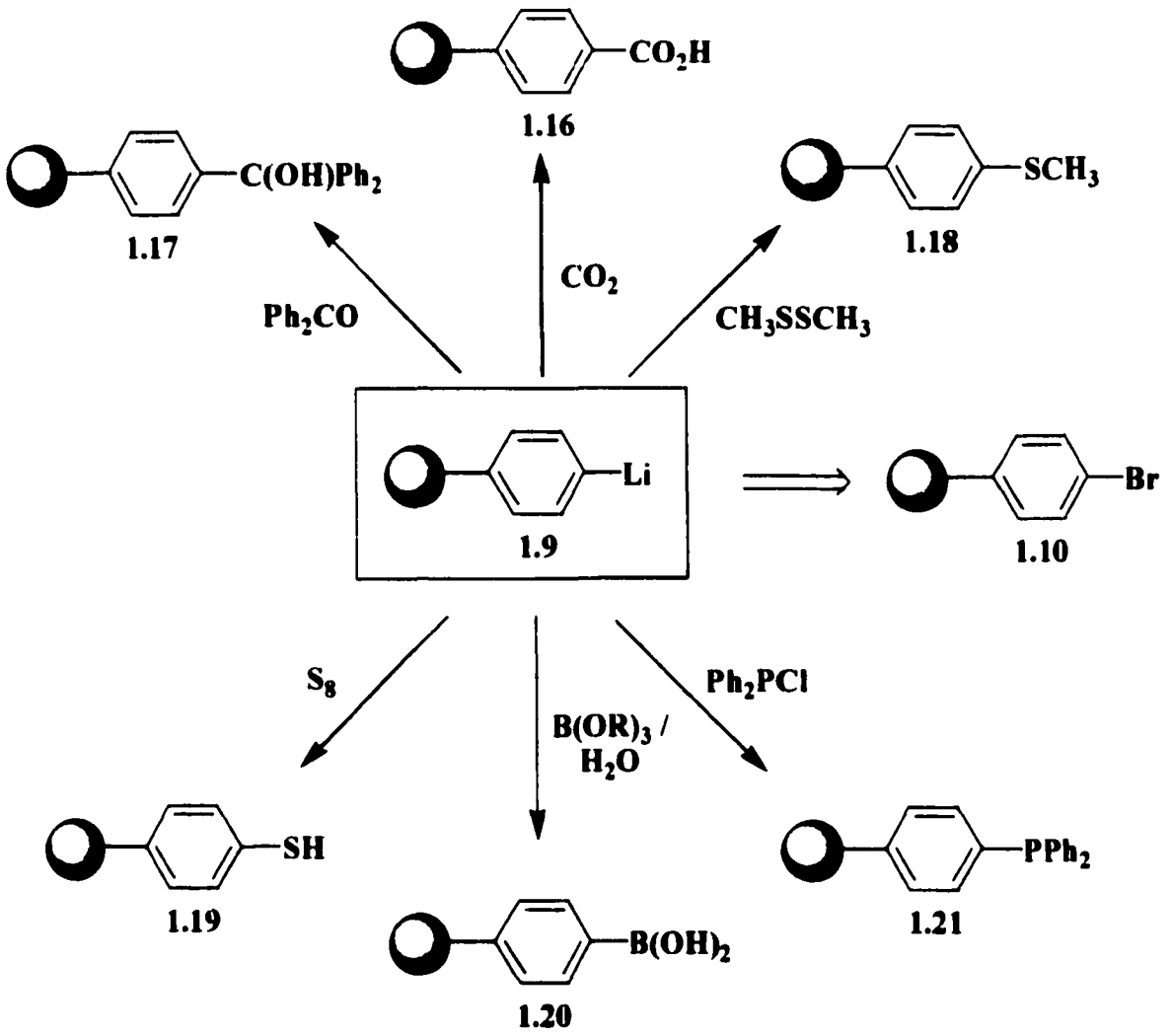
Scheme 1.6. Functionalisations of PS-DVB.

The chloromethylated resin known as Merrifield resin **1.2**,[52] has been widely used for solid phase peptide synthesis and as precursor to numerous other polymers, due to the ease with which its chlorine atoms can be displaced by nucleophilic substitutions (**Scheme 1.7.**). For example, amine,[53] formyl,[54] carboxylic acid,[54a] polyether,[55] thioether[56] groups as well as thiouronium salts[57] have been introduced. After derivatisation of the resin, unreacted chloromethyl functions can be reduced by radical reaction with Bu_3SnH.[58]



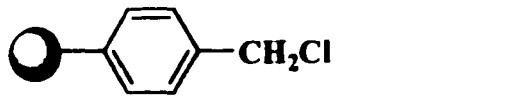
Scheme 1.7. Functionalisations of chloromethylated Merrifield resin by nucleophilic substitutions.

By reaction of the lithiated PS- DVB with a large number of electrophiles, the introduction of diverse functionalities such as carboxylic acid, thioether, phosphine, boric acid and triphenylcarbinol has been achieved (**Scheme 1. 8.**).[51b]

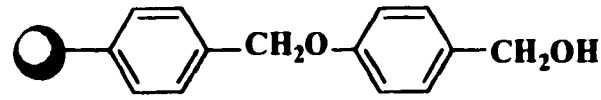


Scheme 1.8. Functionalisations of lithiated resin by electrophilic substitutions.

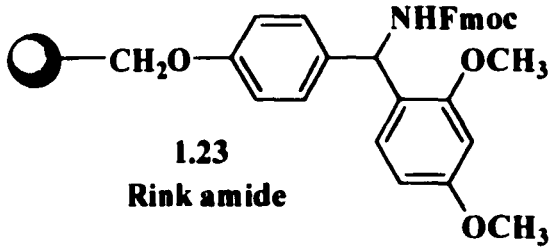
Beside Merrifield resin **1.2**, Wang **1.22**,[59] Rink amide **1.23**,[60] MBHA **1.24**,[61] Trityl **1.25**,[62] and SASRIN **1.26**,[63] resins are among the standard polymer supports for solid phase organic synthesis (**Scheme 1.9.**).



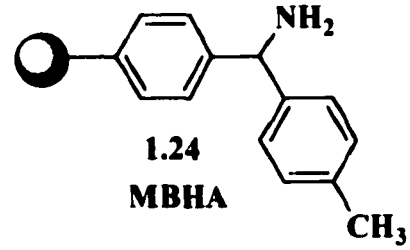
1.2
Merrifield



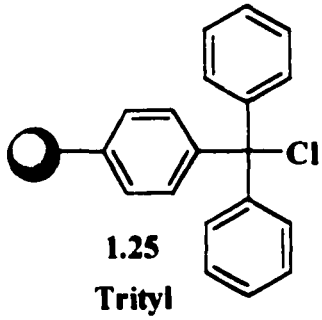
1.22
Wang



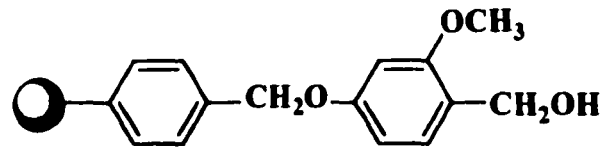
1.23
Rink amide



1.24
MBHA



1.25
Trityl



1.26
SASRIN

Scheme 1.9. Common resins for solid phase organic synthesis.

As the polymerisation of resins for solid phase synthesis takes place in microdroplets, the beads have a spherical shape. The consistency of size is ensured by sieving. While in PEG-PS copolymers, the particle size is variable, in polystyrene-divinylbenzene copolymers, the main particle sizes are either 100-200 mesh (150-75 μm) or 200-400 mesh (75-38 μm).

Three main types of polymers may be distinguished: linear, cross-linked, and macroporous.[64]

Linear polymers are long chain species consisting of many monomeric units linked together; these polymers are extremely fragile and not suitable to solid-phase synthesis. However, they can be used as supports for reactions carried out in solution, in a homogeneous medium, with equal accessibility to all functional groups of the polymer. The advantages in terms of purification are lost because the separation of the polymer from low molecular weight contaminants may be difficult.

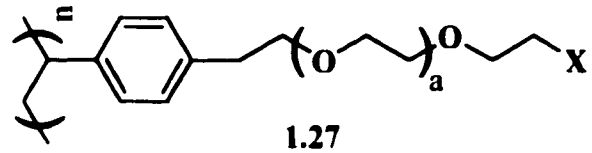
Cross-linked polymers are infinite networks in which linear chains are interconnected; they are obtained by copolymerisation of a monovinyl monomer with a divinyl compound, for example. In cross-linked polystyrene the divinylbenzene gives the mechanical strength and insolubility while still permitting the flexibility during swelling.

Considerable differences in the properties depend on the degree of cross-linking. The pore size is inversely proportional to the degree of cross-linking. A wide range of reactions conditions may be used. The resin is stable from -78°C to 155°C. This temperature range depends on the cross-linking; at low cross-linking (<1%) the thermal stability is limited to 110°C. For routine synthesis, cross-linked 1%-DVB polystyrene is the preferred support and the 2% cross-linked material is generally reserved for reactions involving high temperature and organometallics. Many reagents are compatible with this support such as TFA, alkyllithium reagents, LAH, mCPBA, and Pd catalysts.

Cross-linked polymers are microporous, that means that they are not porous when dry. When a good solvent is added to a cross-linked polymeric network, it may become highly expanded and extremely porous, forming a gel and allowing the diffusion of the reactants. Non polar solvents such as methylene chloride cause the resins to expand while polar solvents such as methanol, water, and acetonitrile cause the support to contract and affect the level of reactivity, due to the poor reaction site accessibility. In order to quantify the degree of swelling of beads, swelling ratios are calculated from the equation: $S\ (\%) = (V_S - V_D) / V_D$ (where V_S = volume of swollen beads (cm^3) and V_D = volume of dry beads (cm^3)).[65] In practice, an organic solvent is added to a known volume of dry beads contained in a graduated cylinder, the air bubbles entrapped are removed by gentle stirring and the resin is allowed to swell at rt for 24 h. The volume occupied by the swollen resin is then measured.[66] Merrifield[67] studied the solvation and swelling phenomena for the solid phase synthesis of peptides and deduced distinct procedures depending on the final loading in peptide per gram of resin. Systematic study of the swelling abilities of an array of thirty six common solvents and of three mixed solvents on resins has been recently published by Santini and co-workers,[68] providing an appreciable help for choosing the suitable solvent for solid phase organic synthesis.

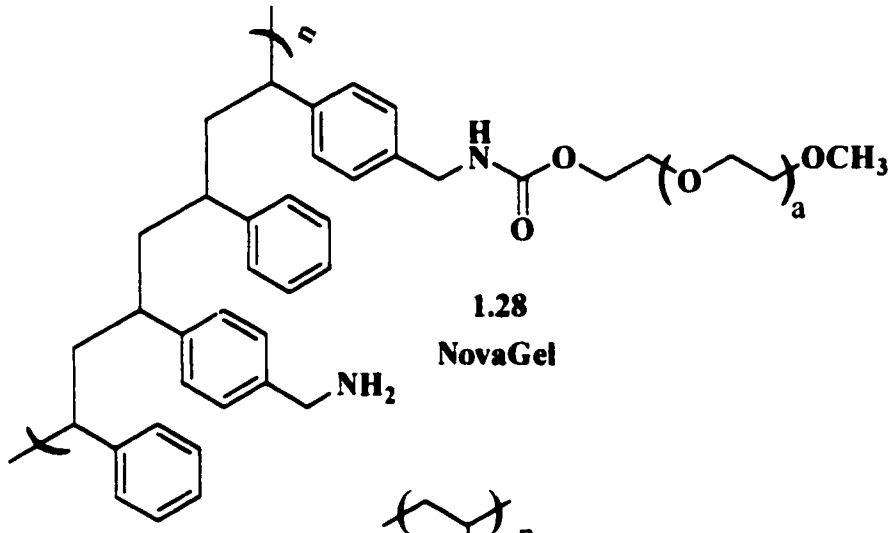
When PS-DVB resins do not swell sufficiently, the diffusion of reagents into the polystyrene matrix is low and the chemical reactions can not take place. This limited utility of PS-DVB has prompted combinatorial chemists to develop new supports with much broader spectrum of solvent compatibility ranging in polarity from toluene to water. PEG-PS DVB copolymers show good swelling properties in polar solvents. They contain a polystyrene core with long grafted polyethyleneglycol chains (50-60 ethylene oxide units). The PEG is up to

70% of the resin weight. There are many resins of these types commercially available such as TentaGel **1.27**, NovaGel **1.28**, ArgoGel **1.29** resins (**Scheme 1.10.**).[20c]



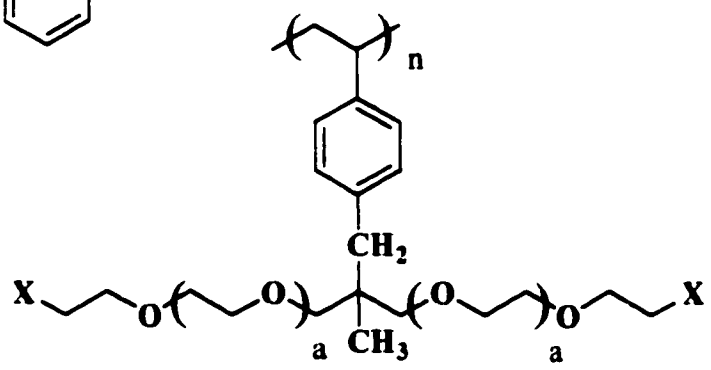
1.27

TentaGel



1.28

NovaGel



1.29

ArgoGel

Scheme 1.10. PEG-PS copolymers.

Rapp and Bayer prepared a PEG-PS resin by polymerising ethylene oxide onto a primary alcohol located on the cross-linked polystyrene (the resin is marketed as Tentagel resin).[30b] Millipore has prepared PEG-PS by attaching preformed polyethylene glycol onto the polystyrene bead. The backbone of PEG-PS is less robust than that of polystyrene. The major advantage of PEG-PS resins in synthesis is that the reacting groups project into solution, at the end of long, flexible spacers so they are highly accessible rather than being anchored close to the polymer backbone. This distance between the reacting groups and the polystyrene core makes them less affected by hydrophobic PS matrix, thus explaining the good swelling properties of PEG-PS in all types of solvents. This support is most often used in applications requiring direct release of the target molecules into the aqueous media and is the favoured resin for support bound assays due to its good solvation characteristics. The main drawbacks of PEG-PS are its cost (ten times more expensive than PS-DVB), its lower mechanical stability (stirring or vigorous shaking results in significant losses of material) and its reduced loadings.

Studies have been carried out on the effect of the nature of polymer supports on the kinetics of seven solid phase organic reactions.[69] Li and Yan showed that there is no single polymer that favours all reactions and the choice between PS-DVB and PEG-PS should rely on the requirements of the reaction for polar or non polar medium.

The third category of polymers is the macroporous resins, which are completely insoluble in all solvents. They are prepared by polymerisation of PS using higher amounts of the cross-linking agent. While gel resins in their swollen state are more reactive than their macroporous counterparts, the latter have a more rigid structure with permanent pores that

allow their use in almost any solvent and may facilitate reactions involving ionic or sparingly soluble species. Their reactivity is not a function of the swelling properties.

PEG-supported synthesis of small molecules has recently shown increasing interest.[70] PEG represents an alternative polymeric support to PS-DVB or PEG-PS and combines the advantages of syntheses in solution with those of solid-phase syntheses.[71] PEG is a soluble support in most of the common solvents[72] but can be crystallised by addition of large amount of diethyl ether.[73] The reaction conditions of the free substrates in solution can usually be applied to the PEG-bound substrates; only in a few cases the reactivity appears to be different.[74] PEG resins present many advantages. The transfer of known solution phase conditions to PEG-supported synthesis is rapid because there is no prior requirements to develop workable solid-phase coupling and linking techniques. In order to follow the reaction, the use of classical analytical methods such as NMR can be performed when the reaction products are still attached to the polymer support without using magic angle spinning techniques. The purification of the reaction mixture is easily achieved by precipitation and solid-phase extraction of the PEG derivative.

1.2.2. Linkers

The term linker refers to a handle to attach a small molecule onto the polymeric resin.[47a] It needs to be stable to the reaction conditions used during the solid phase synthesis, but it should be selectively cleavable at the end of the synthesis to release the small molecule into solution. Many commercially available linkers (e.g. ester, amide) owe their existence to

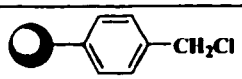
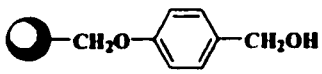
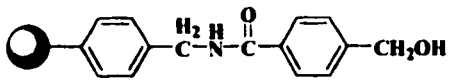
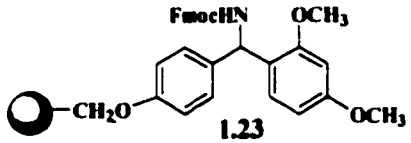
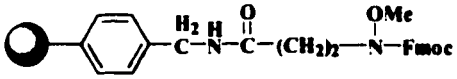
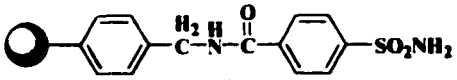
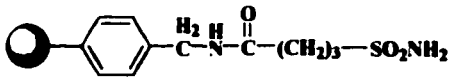
the field of solid-phase peptide synthesis.[75] The synthesis of oligosaccharides on solid supports have afforded methodologies for anchoring alcohols via an ether linkage.[76] However, the rapid expansion of solid-phase organic chemistry has created a need to broaden the range of linkers in order to introduce new chemical diversity and to accomodate new synthetic methods.[77]

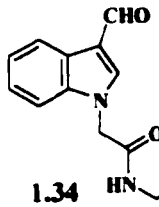
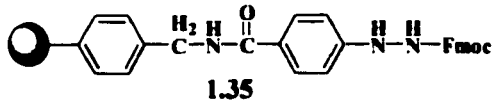
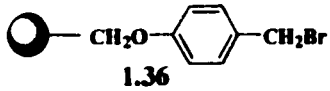
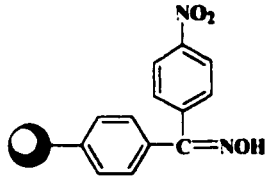
There are many different ways of classifying linkers. Dörner and co-workers[78] differentiate in their classification the linkers that are functionalised and derivatised as protecting groups and the linkers that are functionalised and derivatised as reagents.

The linkers of the first category are bound to the starting material and are regenerated upon release of the final product. The major functionalities anchored to the resins acting as protecting groups are carboxylic acids,[79] alcohols,[80] amines,[81] hydrazides,[82] thiols,[83] and aldehydes[84] for which the attachment and cleavage conditions depend on the nature of the resin.

The linkers of the second category act in a different manner. When the final product is cleaved from the solid support, the functional group released FG' is different from the one of the starting material FG. Many cleavage conditions can be used in parallel yielding different functionalities of the same library introducing more molecular diversity during the final step of a solid-phase synthesis. The major linkers participating in functional-group transformation during the cleavage step are listed in **Table 1.1**.

Table 1.1. Linkers acting as reagents

Entry	Resin	Attached group	Leaving group	Cleavage conditions	Ref
1	 1.2 Merrifield	RCO_2H	RCH_2OH	$LiBH_4$	86
2		RCO_2H	RCH_2OH	DIBAL	87
3		RCO_2H	RCO_2Me	NaOMe	122a
4		RCO_2H	RCO_2Me	$C_2H_5CO_2Me$ / $Ti(OEt)_4$	88
5	 1.22 Wang	RCO_2H	RCH_2OH	DIBAL	89
6		RCO_2H	$RCONR^1R^2$	R^1R^2NH / $AlCl_3$ / DCM	90
7	 1.30 HMBA AM	RCO_2H	R^1CONHR^2	R^2NH_2	91
8		RCO_2H	RCH_2OH	$NaBH_4$ / EtOH	87
9		RCO_2H	RCO_2Me	MeOH / TEA	92
10		RCO_2H	$RCONHNH_2$	NH_2NH_2 / $CHCl_3$ / MeOH	93
11	 1.23 Rink Amide	RCO_2H	R^1CONH_2	TFA	107
12	 1.31 Weinreb AM	RCO_2H	R^1COR^2	R^2MgX	94
13		RCO_2H	RCHO	LAH, DIBAL	95
14	 1.32 4-Sulfamylbenzoyl AM	RCO_2H	$RCONHR^1$	i) CH_2N_2 ii) R^1NH_2	96
15	 1.33 4-Sulfamylbutyryl AM	RCO_2H	$RCONHR^1$	i) ICH_2CN ii) R^1NH_2	97

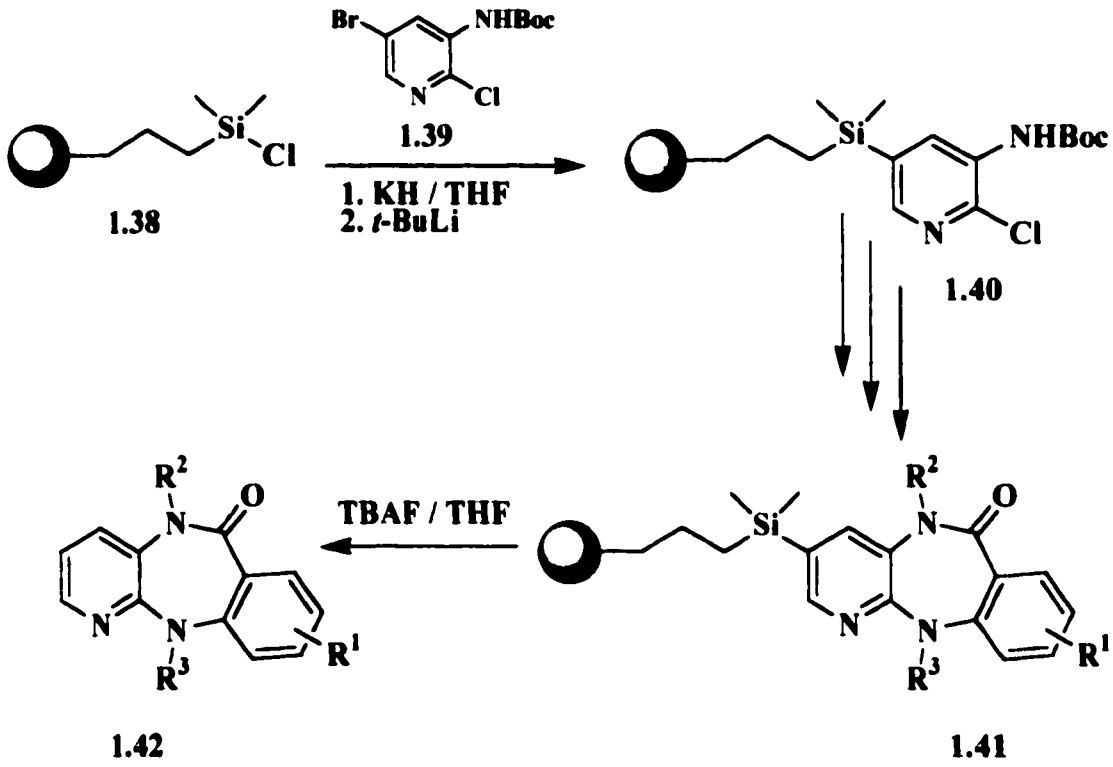
Entry	Resin	Attached group	Leaving group	Cleavage conditions	Ref
16	 1.34 Indole-3-carboxaldehyde	RNH_2	$R^2SO_2NHR^1$	i) R^2SO_2Cl ii) TFA / DCM	98
17		RNH_2	R^2CONHR^1	i) R^2COA^a ii) TFA / DCM	98
18		RNH_2	$R^1NHC{=}NHNH_2$	i) $(BOCNH_2)CS$ / DIC ii) TFA / DCM	98
19	 1.35 Fmoc-4-hydrazinobenzoyl	RCO_2H	R^1CO_2Me	i) Cu(II) acetate ii) MeoH / pyr	99
20	 1.36 4-(Bromomethyl)phenoxy methyl polystyrene	RNH_2	$RNHSO_2R^1$	i) R^1SO_2Cl ii) TFA	100
21	 1.37 Oxime	R^2NCO	$R^1NHCONHR^2$	R^1NH_2	101

[a] A represents an activating group

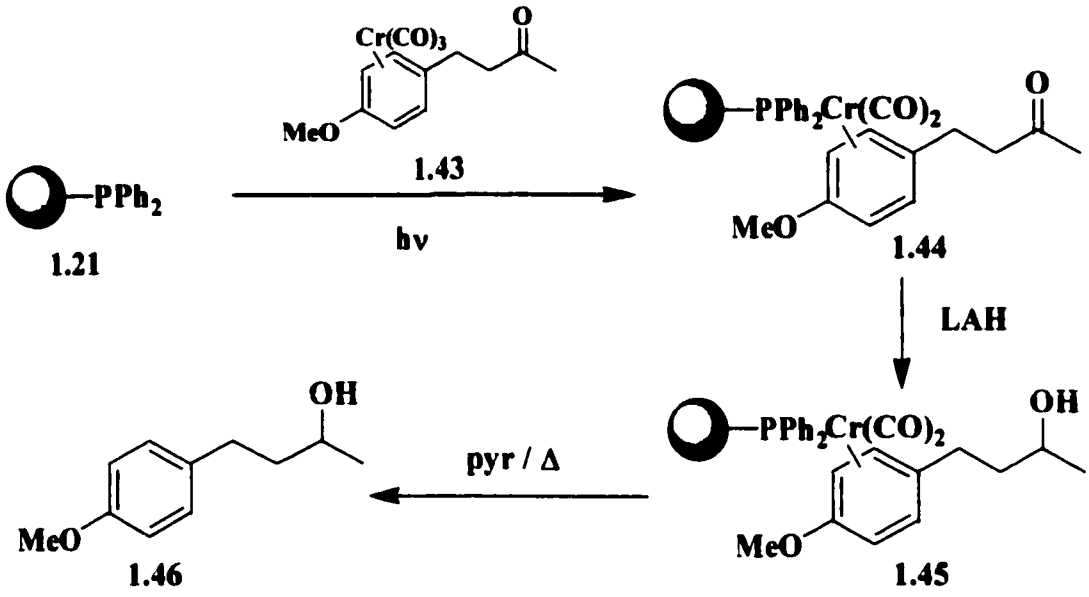
In this category, the safety catch linkers are found (entries 14 and 15). A safety catch linker involves a functional group that is unreactive during the synthesis but activated by chemical transformation immediately prior to cleavage. They are particularly promising since they are compatible with many reaction conditions in the non-activated state. Ellman used the acylsulfonamide linker first described by Kenner[101] (entry 14); the activation is achieved by N-methylation of the sulfonamide nitrogen with diazomethane leading to a secondary sulfonamide that can be cleaved by nucleophilic attack of an amine. Ellman's sulfamylbutyryl

linker (entry 15) is another typical example. The N-acylsulfonamide is not susceptible to nucleophilic attack unless activated by treatment with iodoacetonitrile.

Much emphasis has been put on the development of traceless linkers,[42h] which leave no traces of their original points of attachment in the target products upon cleavage. The arylsilyl linkers in which a C-H bond can be formed upon cleavage of a C-Si bond were extensively used (**Scheme 1.11.**);[102] other types of traceless linkers[103] were reported, such as the chromium carbonyl complexes (**Scheme 1.12.**).[104]



Scheme 1.11. Arylsilyl traceless linker.



Scheme 1.12. Chromium carbonyl complexes as traceless linker.

1.2.3. Analytical Techniques

The growing interest in combinatorial chemistry has, of necessity, led to the evolution of new associated purification and analytical techniques.[105] Monitoring a solid phase reaction and characterising and quantifying a compound still bound to a polymer support are more difficult tasks than in classical solution phase chemistry. Chromatographic methods such as TLC, HPLC cannot be used when the molecule is tethered to the solid support and spectroscopic methods such as NMR of bound products also pose problems.

A non-destructive method such as FTIR spectroscopy of resins is a powerful qualitative as well as quantitative characterisation tool. Typically, the polymer beads are ground with IR-quality KBr and FTIR spectra of the KBr pellets are run. Generally very good

FTIR spectra are obtained from KBr discs using PS-DVB supports; however absorption bands from PEG-PS-DVB resins are typically of much lower intensity and are generally less useful.[106] By difference between the FTIR reference spectrum of the non-functionalised resin and the FTIR spectrum of the resin after reaction, the bands of the new FGs introduced may be identified.[107] Quantitative data can be obtained by calibrating measurements on several loaded resins.[108] For example, the absorption band of the H-C-Cl stretching vibration (1250 cm^{-1}) can be used to determine the yield of the coupling of carboxylic acids to Merrifield resin. A calibration curve can be constructed: log(absorption) vs chlorine content for different loaded resins and the completeness of the reaction can be verified. Of the recent more sophisticated methods such as photoacoustic FTIR spectroscopy,[109] or internal reflection FTIR spectroscopy,[110] single-bead FTIR spectroscopy represents a tremendous improvement since it allows a real-time monitoring of organic synthesis on solid support owing to its speed and sensitivity.[111]

Major developments have occurred in the area of gel-phase and solid-state NMR to allow them to become reliable methods for monitoring reactions performed on solid support. Gel phase NMR was first used for the characterisation of solid-supported biopolymers,[112] its use for monitoring solid phase organic synthesis was first reported in 1993.[26a] To perform gel phase NMR spectroscopy,[113] the resin sample is transferred to an ordinary NMR tube and allowed to swell. After the sample is degassed, the NMR spectrum can be measured under the conditions typically used for dissolved samples. Fully solvated PS-DVB or PEG-PS-DVB resins give good ^{13}C NMR spectra under standard acquisition conditions. ^{1}H NMR spectra generally cannot be interpreted due to the strong line broadening.[114] High-resolution ^{1}H NMR spectra can be obtained with MAS (Magic Angle Spinning),[115] a method in which the line broadening is suppressed and, even with short acquisition times, the signal-to-noise ratio is

improved considerably. However, the ^{1}H coupling patterns can be resolved only when the solid support used is PEG-PS-DVB.

Elemental analysis of products linked to a solid support did not prove to be a reliable method. The inaccuracy of the results can be explained by the low loading of the substrates on the support and the reproducibility of C, H, N, halogen analysis is too poor to quantify small variations so that the results obtained generally deviate severely from the actual yields of cleaved products.

Titration of functional groups such as acid, base, phenol, chlorine released in solution can be performed. For instance, the titration of the amount of chlorine in Merrifield resin can be achieved by displacement of the chlorine by a tertiary amine, followed by Volhard determination of the liberated chloride.[116]

Colourimetric tests have been developed to detect characteristic functionalities still bound on the polymer support, such as the ninhydrin test[117] for support bound amines.

MS has also been explored for evaluating solid phase synthesis.[118] A single bead contains about 100 pmol of compound, which is sufficient to run a mass spectrum. Fitzgerald and co-workers[119] have demonstrated the application of photolytic cleavage and matrix-assisted laser desorption/ionisation (MALDI) mass spectrometry in the direct analysis of molecules bound on solid supports. A very small quantity of matrix was photolysed and ionised at the same time with an UV laser, the mass spectrum was recorded and the resin could be recovered from the sample.

The above analytical methods used on the polymer bound products are routinely quantified and confirmed by traditional determination of loading by analysis of the isolated product from the cleavage of a known aliquot of resin. It constitutes the most rigorous method

to evaluate a polymer-supported synthesis. HPLC and GC analysis are performed on volumetric solutions of the recovered products and, by comparison of known standards, the loadings of the resins are calculated. Internal standard NMR spectroscopy of the cleaved products (comparing the integration of selected signals to that of the signal of reference (e.g. hexamethyldisiloxane) introduced in the NMR solution) can be carried out. This method represents a major improvement since it may be applied to any compound and does not require comparison to known standards of the recovered products after cleavage.[120]

Since the various analytical methods are automated (NMR, HPLC, GC), the analysis of large numbers of nominally discrete components is not problematic. The new challenge has then moved from collecting analytical data to interpreting such large amounts of data.

It must be stressed that usually all the reactions reported are performed on a scale of 150-200 mg of beads for a loading of 0.7 mmole / g allowing the isolation of at least 20 mg of crude product. The yields reported can refer to the weight of the crude products corrected by the purity evaluated by NMR or to isolated yields of products purified by column chromatography.

1.3. The Transition Metal Catalysed Cross Coupling Reaction on Solid Support

1.3.1. Introduction

The needs to obtain large libraries of compounds for drug discovery have driven most pharmaceutical companies to develop solid phase chemistry by adapting known solution phase

reactions to the solid phase. Due to the power of transition metal catalysed reactions for the synthesis of clinically useful compounds[121] by achieving high-yielding carbon - carbon bond formation in solution, polymer supported Suzuki-Miyaura,[122] Stille,[123] Negishi,[124] Heck,[125] and Sonogashira[126] cross coupling reactions have evolved rapidly. The Buchwald-Hartwig coupling to achieve C-N bond formation[127] has also been transfered to the solid phase.[128] However, combined D*o*M-cross coupling methodologies on polymer support was not reported and we wished to contribute to the rapidly advancing area of solution phase to polymer support conversion by developing new polymer supported methods. Our experience in the solution chemistry of the Directed *ortho* Metalation (D*o*M) reaction[129] and in the combined D*o*M-transition metal catalysed cross coupling strategy accumulated over a twenty year period,[130] and continuously evolving,[131] place our laboratories in an advantageous position to define the required polymer support chemistry and contribute to the generation of combinatorial libraries of polysubstituted aromatic and heteroaromatic compounds using these methodologies.

1.3.2. The Transition Metal Catalysed Cross Coupling Reaction

The transition metal catalysed cross coupling reaction represents a relatively recent and powerful tool for the formation of new carbon-carbon or carbon-heteroatom bonds. The most common transition metal catalysts are the nickel triad (Ni, Pd, Pt) metals; however, other metals such as cobalt, manganese, chromium, silver, iron and copper have been used.[132] It catalyses the formation of the new bond between two different coupling partners an organometallic species R-Met and an electrophile R'-LG (**Scheme 1.13.**).



R = aryl, alkyl, alkenyl, alkynyl, acyl, heteroatom

R' = aryl, alkyl, alkenyl, alkynyl, acyl

Scheme 1.13. Cross coupling reactions: general process.

The most common metals are boron, tin, zinc and magnesium. Belatskaya[133] carried a comparative study of the effect of the organometallic species on various cross coupling reactions with aryl and acyl halides. Simple coupling partners were employed and the coupling of the organic partners were compared against each other under identical reaction conditions. The leaving group is primarily a halogen (Br, I); however oxygen-based (OTf, OR) or sulphur-based leaving groups have also been employed (**Table 1.2.**).

Table 1.2. The transition metal cross coupling grid.

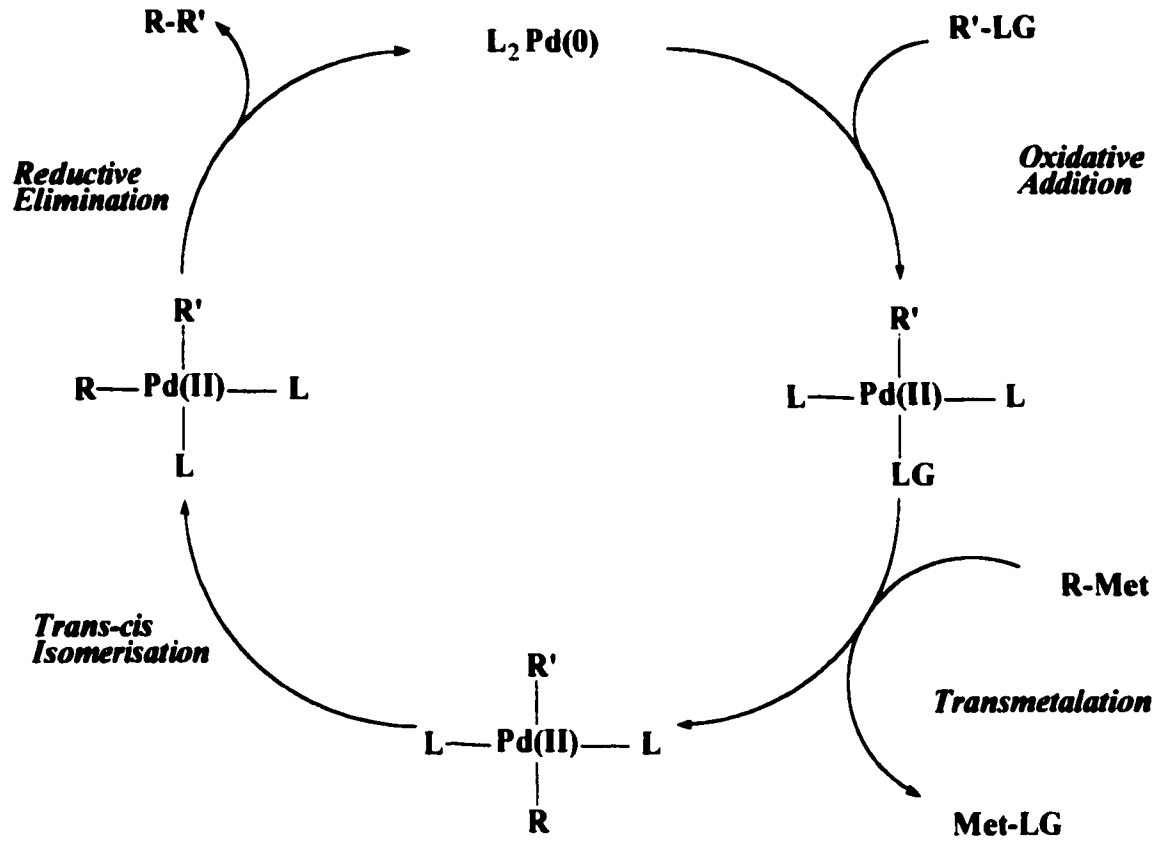
LG	*Cat for Met*[a]								
	MgX 134	ZnX 135	$B(OH)_2$ 136	SnR_3 137	AlR_2	HgX	Cu	Li	SiR_3
Cl	Ni/Pd 138	Ni	Ni/Pd 139						
Br	Ni/Pd	Ni/Pd	Pd	Pd					
I	Ni/Pd	Ni/Pd	Pd	Pd	Pd 140	Pd 141	Pd 142	Pd 143	Pd 144
OTf	Ni 145	Ni/Pd 145a,146	Pd 147	Pd					Pd 148
$OCONR_2$	Ni 145b								
OMe	Ni 145ab	Ni 145a							
$OP(O)(OEt)_2$	Ni 149								
SH	Ni								
SR	Ni 150	Ni 151							
SOR	Ni								
SO_2R	Ni								
$SCONR_2$	Ni 150								

[a] References under various metal entries

In 1941, Kharash and Fields discovered the Co and Ni catalysed homocoupling reaction of aryl Grignards to biaryls.[152] This discovery was compromised by many side reactions and therefore remained dormant for 30 years until Tamura and Kochi studied the mechanisms of silver and iron catalysed couplings.[153] In 1972, the groups of Corriu[134a] and of Kumada[134b] published independently the cross coupling reaction of aryl and vinyl halides with Grignards under Ni catalysis and showed that these high yielding reactions could be carried out under mild conditions. The ready availability of Grignard reagents has favoured the

development of the reaction; however, the nucleophilic character of the Grignards limits the use of many functional groups.[154] The arylzinc-aryl halide Pd and Ni cross coupling followed shortly from Negishi.[155] The main advantages of this coupling process are the possibility of using inexpensive reagents and carrying out the reaction under mild conditions. The functional group compatibility is better than in the case of the Corriu-Kumada-Tamao coupling but the reaction requires anhydrous conditions.[156] In the same period, an initial report by Kosugi and Migita[137b] on the coupling of stannanes with organo halides under Pd (0) catalysis suggested this protocol as an alternative to the Corriu-Kumada-Tamao and Negishi reactions. Stille broadened considerably the scope of this coupling reaction and its synthetic utility by diversifying the cross coupling partners possibly suitable for this reaction to aryl and benzyl halides,[137a] acid chlorides,[157] vinyl triflates,[158] vinyltins,[159] and aryl triflates.[160] The Stille cross coupling reaction gained the favour of organic chemists at an impressive pace.[161] In 1979, Suzuki and Miyaura reported the coupling of vinylboranes with organohalides[162] and subsequently in 1981 a truly novel cross coupling reaction that now bears their names: the arylboronic acid–aryl halide cross coupling reaction under Pd catalysis.[163] Since this first publication, the Suzuki-Miyaura cross coupling reaction has been widely studied and has been applied to numerous synthetic problems.[164] In 1982, the cross coupling reaction vinylsilane – aryl halide was reported.[165] Although Hiyama has extensively studied the arylsilane – aryl halide reaction, it remains nevertheless underdeveloped.[166]

The currently accepted mechanism for the Pd catalysed cross coupling reaction involves three basic steps.[132b] **(Scheme 1.14.)**



Scheme 1.14. A general catalytic pathway for Pd catalysed reactions.

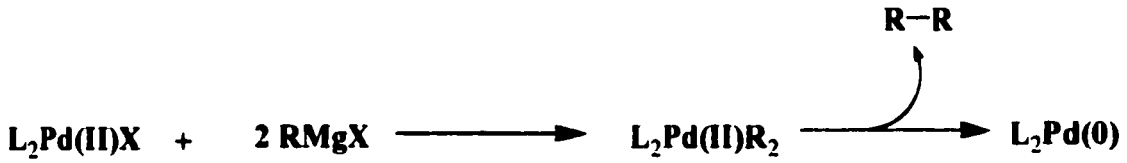
The first step is the oxidative addition[167] of the zero-valent catalyst ($L_2Pd(0)$) to the electrophile R'-LG providing the Pd(II) species ($L_2Pd(R')LG$). This species undergoes transmetalation with the organometallic coupling partner R-Met to provide the diorganopalladium complex (L_2PdRR'). For reductive elimination to take place, the organic groups attached to the Pd catalyst must shift from the most stable *trans* configuration to the *cis* configuration. The reductive elimination[168] step affords the cross-coupled product and regenerates the catalyst.

In the case of saturated metal - ligand complex, dissociation may occur before the oxidative addition step providing more reactive unsaturated metal - ligand complexes.[169] **Scheme 1.15.** shows the case of the dissociation of d^{10} metals from the Ni triad – ligand complexes. The saturated ML_4 (18 e^-) is in equilibrium with the unsaturated complexes ML_3 (16 e^-) or ML_2 (14 e^-).

$$ML_4 \rightleftharpoons ML_3 \rightleftharpoons ML_2$$

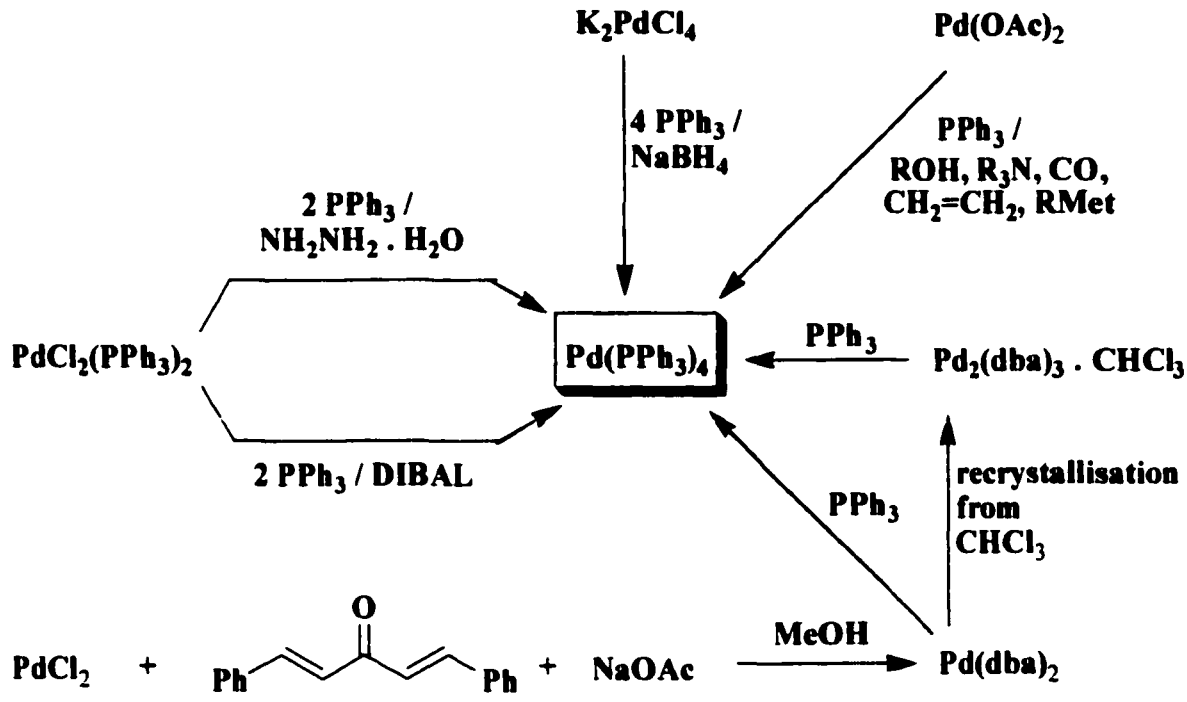
Scheme 1.15. Metal – ligand dissociation.

The zero-valent catalyst may be introduced in the reaction mixture in the proper oxidation state (e.g. $Pd(PPh_3)_4$) or may be generated *in situ* from a catalyst precursor Pd(II) (**Scheme 1.16.**). The organometallic species (e.g. RMgX) adds to the Pd(II) species. By reductive elimination of the intermediate formed the required Pd(0) species is formed.



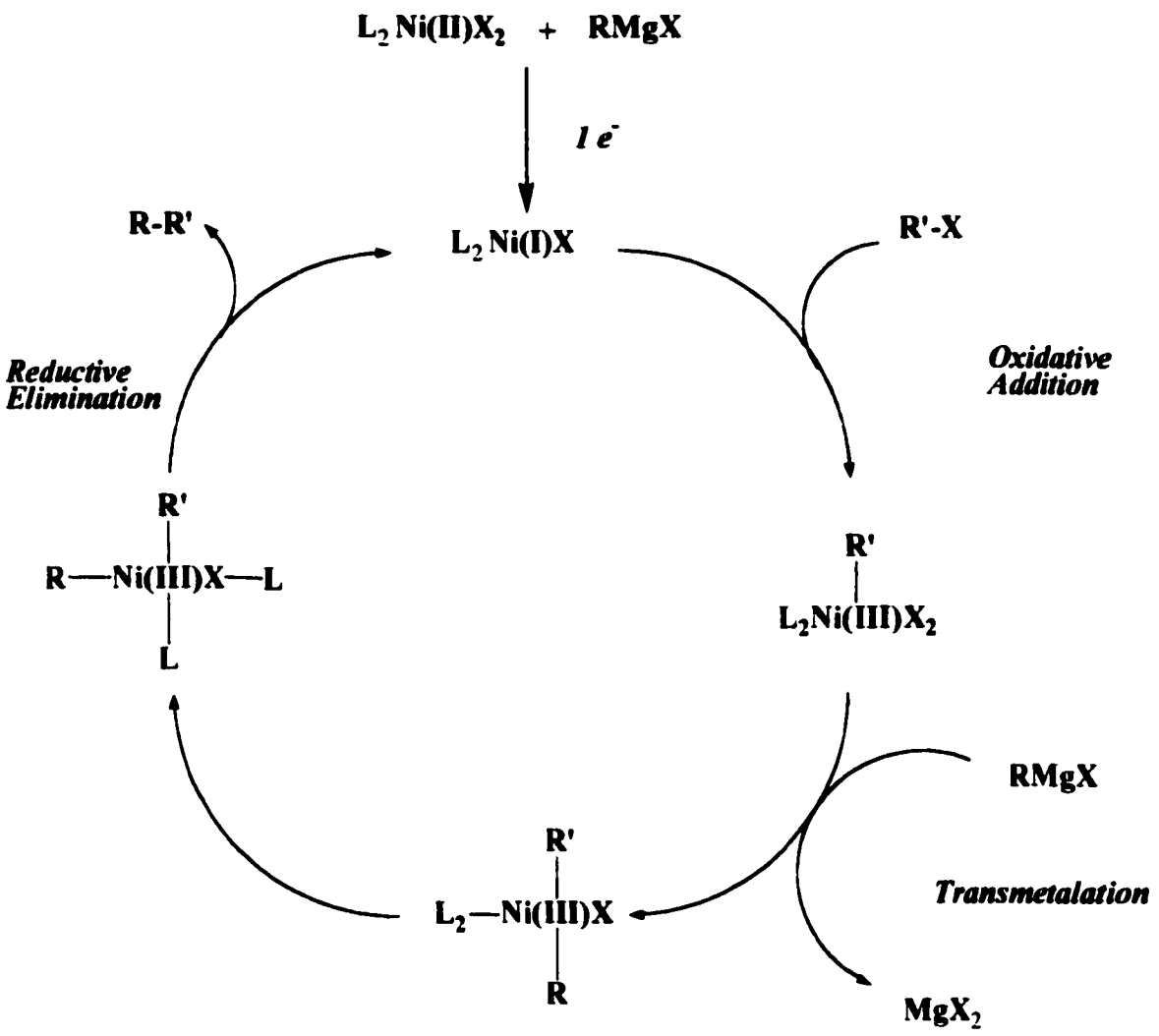
Scheme 1.16. In situ generation of zero-valent catalyst.

Besides being potentially reduced by organometallics, the Pd(II) species may also be reduced by alcohols, amines, carbon monoxide, olefins, and phosphines to afford Pd(0). A very large number of Pd catalysts ($Pd(PPh_3)_4$, $Pd(dba)_2$ / $Pd_2(dba)_3.CH_3Cl$ plus phosphine) or Pd catalysts precursors have been used. The most common are summarised in **Scheme 1.17.**



Scheme 1.17. Pd(0) precursors.

Another catalytic cycle has been proposed by Kochi and Tsou for some Ni catalysed reactions.[170] The catalyst $L_2Ni(I)X$ is generated *in situ* from $L_2Ni(II)X_2$ by prior reaction with the organometallic species (**Scheme 1.18.**).

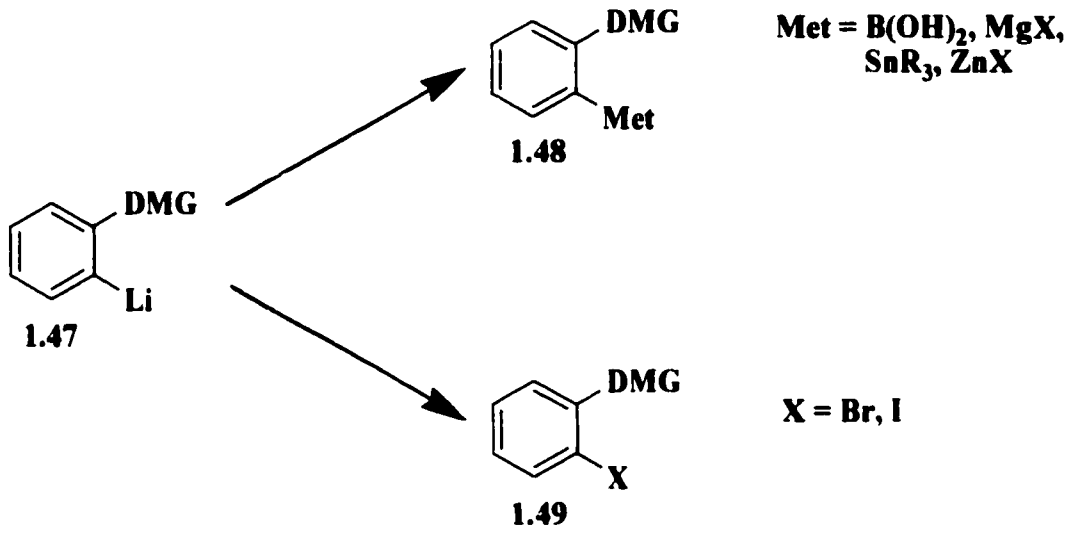


Scheme 1.18. An alternative catalytic cycle for some Ni catalysed reactions.

1.3.3. The Directed *ortho* Metalation – Cross Coupling Connection

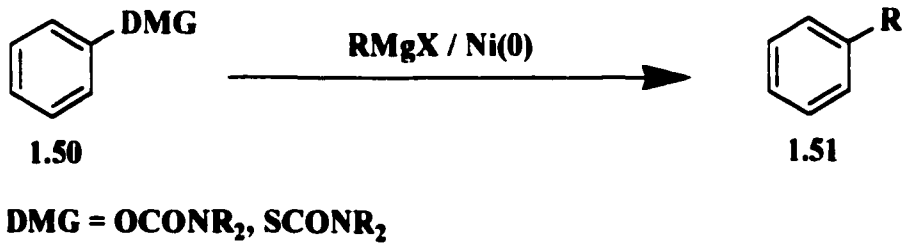
To enhance the utility of DoM in synthetic organic chemistry, Snieckus developed and demonstrated the usefulness of linking DoM to cross coupling methodologies.[129c]

DoM represents a powerful means to prepare *ortho* functionalised metallic species **1.48** and thus organometallic partners for the cross coupling reactions. The organohalide partners **1.49** may also be prepared regiospecifically *via* DoM (**Scheme 1.19.**).



Scheme 1.19. Preparation of cross coupling partners via DoM.

O-Carbamate and *S*-thiocarbamate **1.50** were the most recently discovered leaving groups for the cross coupling process (**Scheme 1.20.**).

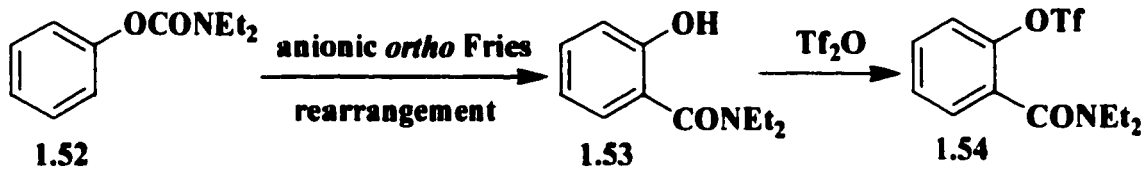


Scheme 1.20. Cross coupling reaction with aryl DMG partners.

Kocienski[171] and Sengupta[172] demonstrated that vinyl-*O*-carbamates undergo Ni (0) mediated cross coupling reaction with Grignard reagents. This result was followed by the report of Sengupta and Leite,[145b] who showed that the Corriu-Kumada-Tamao reaction could also be carried out with aryl-*O*-carbamate derivatives.

Beaulieu[150b] and Puumala[151] in our laboratories have shown that *S*-arylthiocarbamates may be coupled with Grignard reagents under Ni catalysis.

Ortho substituted triflates were also prepared successfully by means of the anionic *ortho* Fries rearrangement[173] allowing another link between D*o*M and cross coupling reactions (**Scheme 1.21.**).



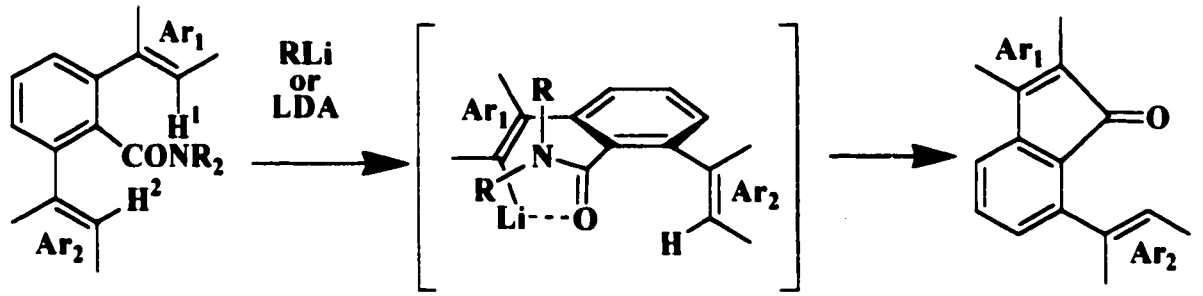
1.52 **1.53** **1.54**

Scheme 1.21. Preparation of *ortho* substituted triflates.

The tandem D*o*M – cross coupling reaction has thus considerably increased the scope of the cross coupling reaction by allowing the synthesis of unsymmetrical biaryls, heterobiaryls and terphenyls with unusual substitution patterns and high functional group diversity. As a consequence, this strategy has been applied extensively in the synthesis of natural and unnatural products as well as pharmaceuticals.[174]

1.3.4. The Directed Remote Metalation - Cross Coupling Connection

The directed remote metalation (DReM) refers to the metalation in a remote site, namely the metalation on the second ring of a 2-DMG-subsituted biaryl. The examination of the close proximity of H_1 and H_2 to the tertiary amide group in the X-ray crystallographic structure of *m*-terphenyl **1.55** [130a] suggested that the Complex Induced Proximity Effect (CIPE) [175] may play a key role for the regiospecific remote metalation. It was found, in fact, that these significant effects of co-ordination between the tertiary amide DMG and LDA or *t*-BuLi contributed to the enhancement of the acidity at remote (thermodynamically unacidic) sites. Following this initial discovery by Sharp,[176] Fu and Zhao[177] developed short routes to a variety of substituted fluorenones **1.57** based on the DreM - cyclisation sequence (**Scheme 1.22.**)

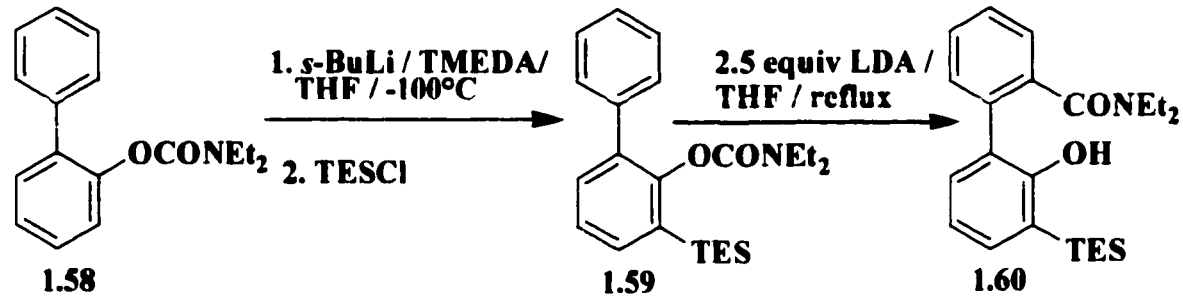


1.55 **1.56** **1.57**

Scheme 1.22. Route to fluorenones by DReM.

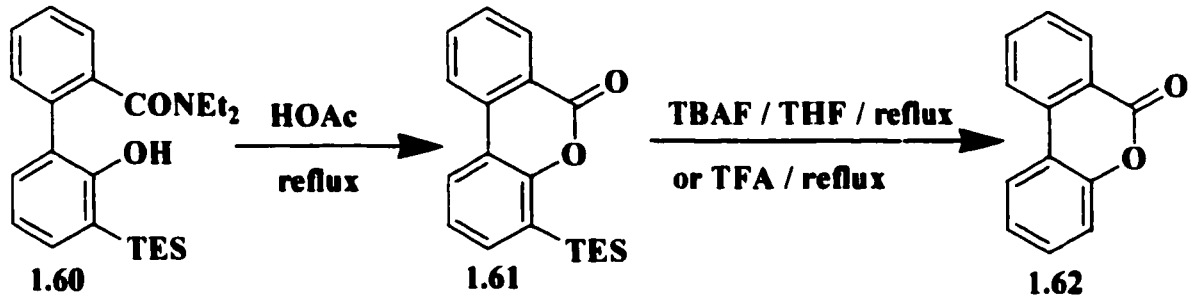
As a logical extension of the biaryl amide DReM concept, the corresponding reaction of biaryl-*O*-carbamates **1.58** was developed by Wang (**Scheme 1.23.**).[178] The biaryl *O*-carbamate obtained by the tandem DoM - cross coupling was subjected to *s*-BuLi/TMEDA

deprotonation at –100°C to avoid the facile anionic *ortho*-Fries rearrangement to salicylamides which had been reported by Sibi.[173] At this temperature, triethylsilylation proceeds well to give the biaryl TES-*O*-carbamate **1.59**. After treatment by LDA at reflux, the ring to ring carboxamide migration occurs leading to the 2-amido-2'-hydroxy biaryl **1.60** in good yields.



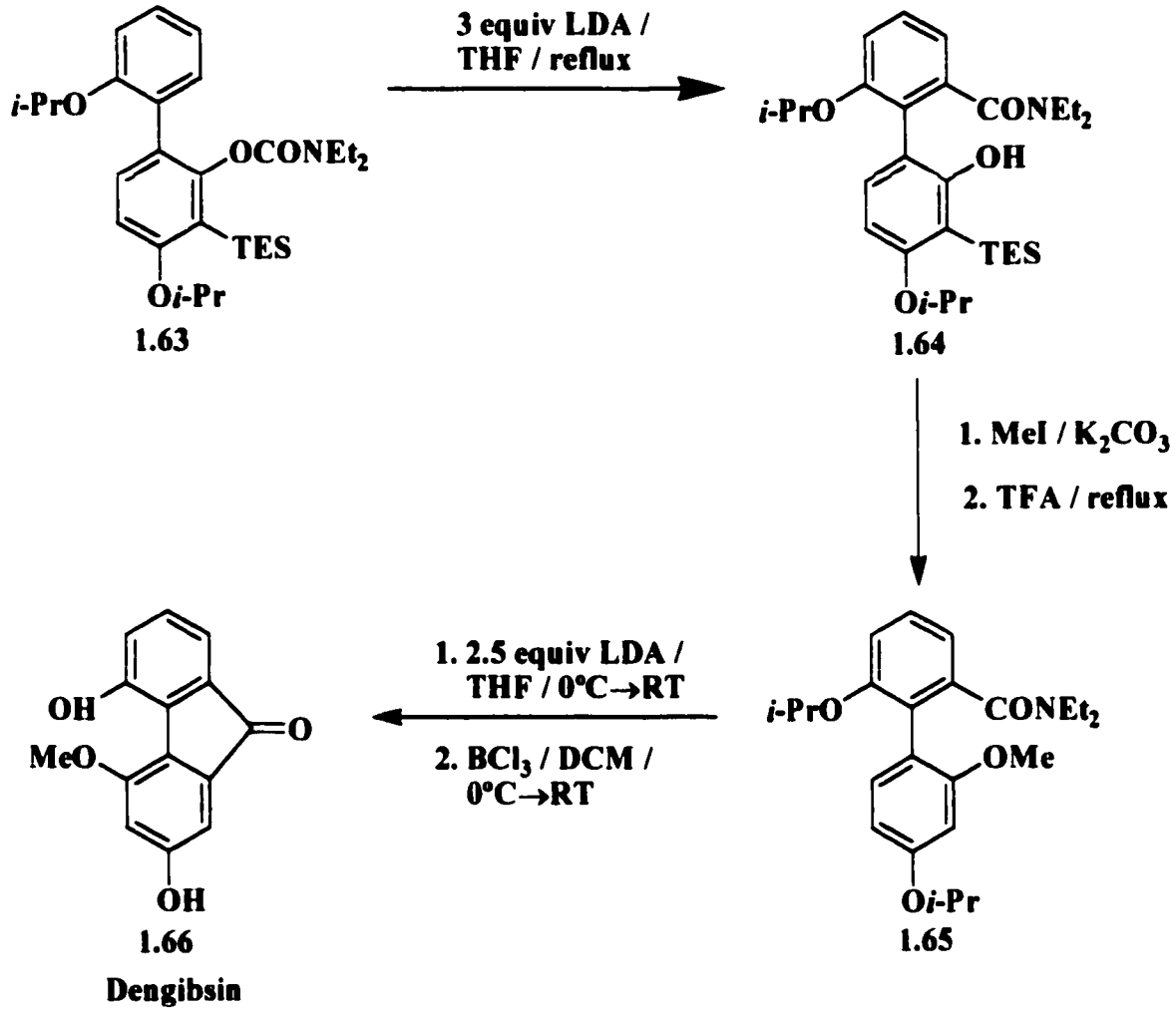
Scheme 1.23. DReM of biaryl-*O*-carbamate.

The resulting phenolic biaryl benzamide **1.60** was transformed into dibenzo[*b,d*]pyranone **1.62** under acid catalysis. The TES protecting group can be removed using TBAF or TFA (**Scheme 1.24.**)



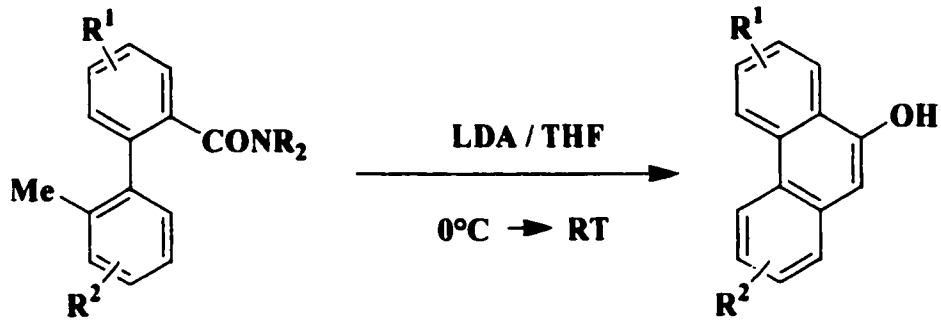
Scheme 1.24. Preparation of dibenzo[*b,d*]pyranone using the DReM concept.

Another application of the phenolic biaryl benzamides obtained by DReM involves the preparation of fluorenones and especially Dengibsin **1.66**, a fluorenone isolated from the Indian orchid *Dendrobium gibsonii* (**Scheme 1.25.**).[178b]



Scheme 1.25. Preparation of Dengibsin by the DReM concept.

The synthesis of phenanthrols **1.68** was achieved using the sequence cross coupling – carbamoyl transfer – phenol protection – cyclisation under LDA on the appropriately substituted tolyl system (**Scheme 1.26.**).[179]

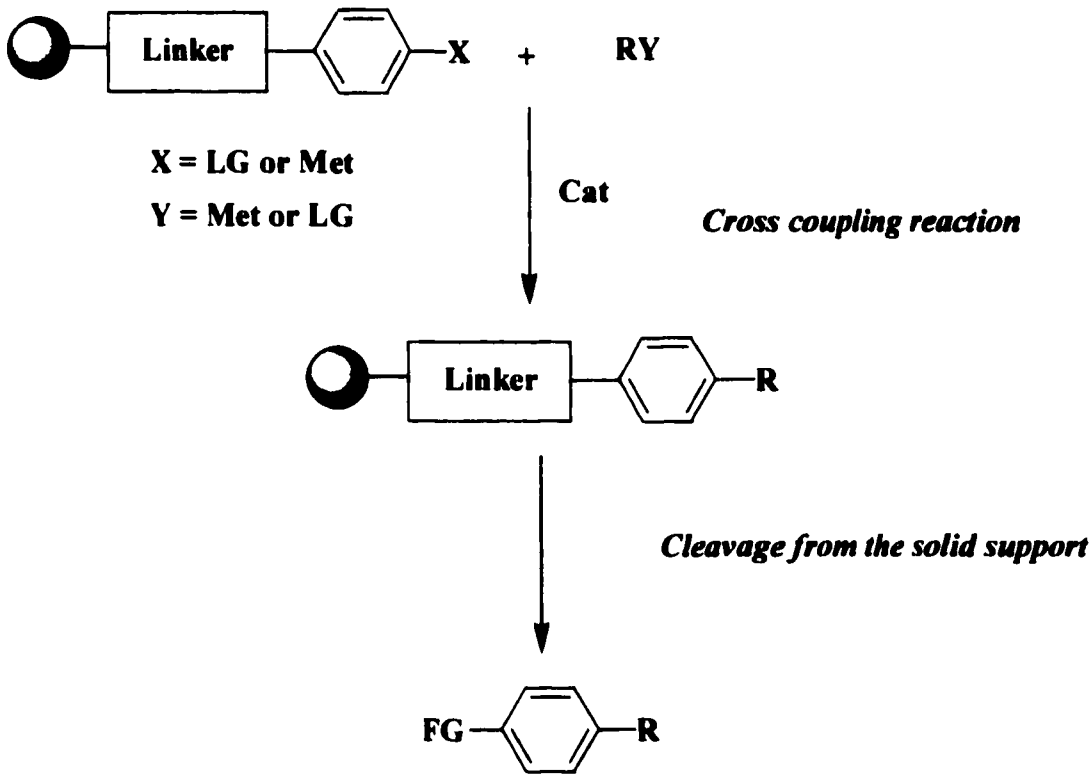


1.67 1.68

Scheme 1.26. Synthesis of phenanthrols by the DReM concept.

1.3.5. Transfer of the Transition Metal Catalysed Cross Coupling Reaction to Solid Support

The general routes that can be envisaged for transition metal catalysed cross coupling reactions on solid support are summarised in **Scheme 1.27.** The basic approach can be conceived in two ways. A solid phase aryl electrophile (X = LG) can be treated with an organometallic species (Y = Met) in solution under transition metal catalysis to give the bound cross coupled products and, after cleavage, the desired cross coupled product is obtained. One can also conceive the reverse approach in which a solid-phase organometallic species (X = Met) is treated with an electrophile in solution (Y = LG).



Scheme 1.27. Cross coupling reactions on solid support. General process.

1.4. The Stille Cross Coupling Reaction on Solid Support

1.4.1. Introduction

Considerable emphasis has been placed on the transition metal catalysed cross coupling reaction and in particular on the Stille cross coupling reaction, which is reflected in the intense activity to effect solution phase to solid support translations.[123] The reasons for this reaction to become so popular to combinatorial chemists are numerous. The stability to oxygen and moisture and the ready availability of the stannanes (commercially available or

easily prepared) are attractive features as well as the high yields due to the facility with which the tin reagents transmetalate to palladium. The excellent functional group compatibility and the mild reaction conditions offer the potential of an easy access to a high degree of structural diversity. Finally, through the Stille reaction one can prepare important classes of potentially bioactive molecules such as biphenyl derivatives. Biphenyls are present in many important natural products that exhibit both antitumor and antiviral activity as well as in unnatural products acting as angiotensin II receptor antagonists or possessing tubilin binding properties and estrogenic activity.[180] The inherent toxicity of the stannanes and the difficulty in removing tin by-products, which are major drawbacks of this reaction in solution, are not such important issues due to the very small quantity necessary to carry on solid phase chemistry.

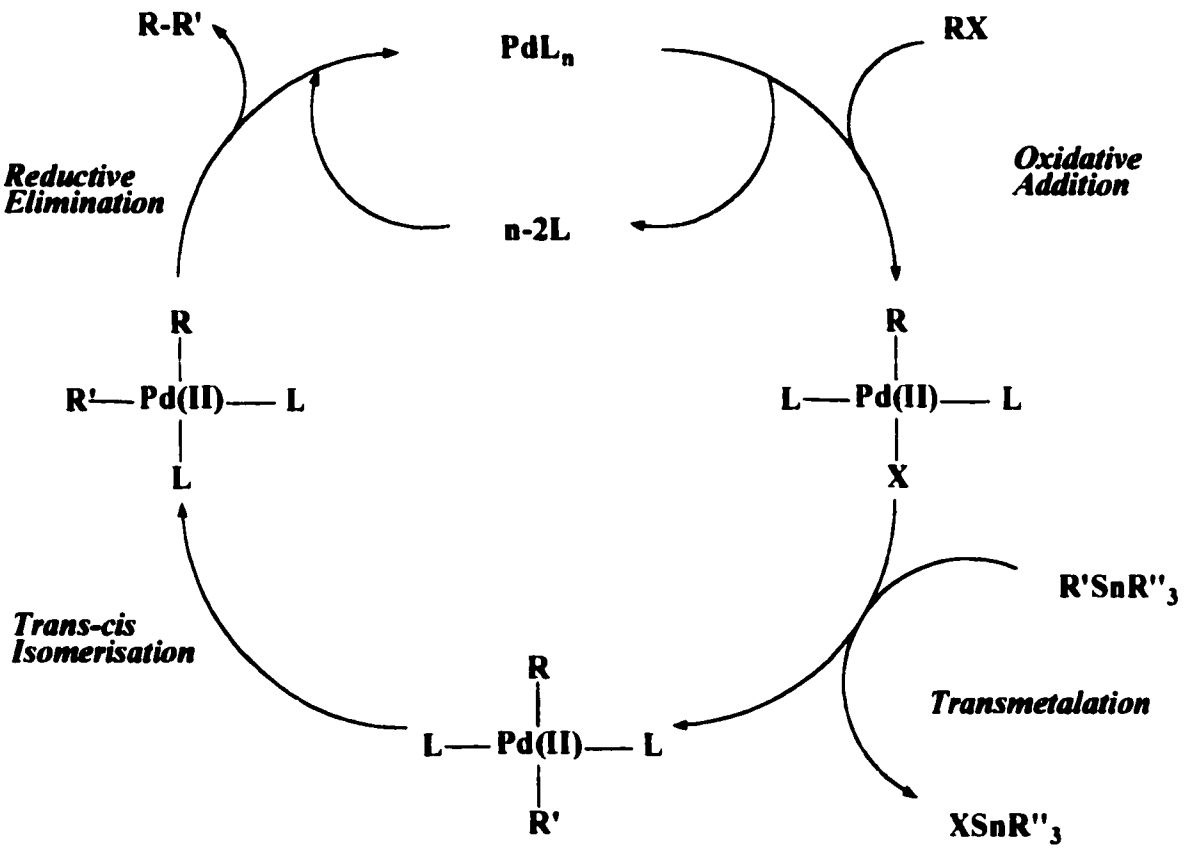
1.4.2. Main features of the Stille Cross Coupling Reaction

The palladium catalysed cross coupling reaction of an organostannane with an unsaturated bromide, iodide or triflate,[181] named the Stille cross coupling reaction, has become a most valuable and versatile route to new carbon – carbon bonds.[182] Various functional groups, including the ester, nitrile, ketone, and aldehyde functionalities are tolerated by this reaction, thereby eliminating the need for protection/deprotection strategies, a feature that makes this coupling method advantageous over other cross couplings methods.

A wide variety of organic electrophiles and organotins can be used. Benzyl halides, allyl halides, vinyl halides and triflates, aryl halides and triflates and heteroaryl halides and triflates are suitable electrophiles. The aryl – aryl coupling has also been extended to novel coupling partners such as aryl fluorosulfonates,[183] and aryl *p*-fluorophenylsulfonates.[184] These

reagents represent less expensive alternatives to triflates and the yields of cross coupling reactions with these reagents were found to be comparable with that for the corresponding aryl triflates. It has been shown that a wide range of stannanes such as alkyl, vinyl, allyl, alkynyl, aryl and heteroaryl tin reagents may be used. Only one group from the tetraorganotin is transferred at an appreciable rate. When unsymmetrical organotin compounds are employed, phenyl and vinyl are transferred in preference to methyl and butyl respectively. The reaction requires a highly polar and aprotic solvent such as HMPA, NMP, DMF, or DMSO.[158] The reaction is catalysed by Pd(0) complexes such as $Pd(PPh_3)_4$, $Pd_2(dba)_3$. $Pd(OAc)_2$, $Pd(PPh_3)_2Cl_2$, $Pd(CH_3CN)Cl_2$ have also been used since these catalysts are reduced to the zero oxidation state by the organostannes. For the reactions involving triflates, the best catalytic system found consists of $Pd(PPh_3)_2Cl_2$ / PPh_3 / LiCl / refluxing DMF.[185] Although Stille rationalised the acceleration of the cross coupling of organotriflates in the presence of LiCl by assuming that LiCl accelerates the transmetalation step by replacing an inert Pd-O bond into an active Pd-Cl bond,[160b] this interpretation does not meet general agreement.[161i,182b]

The general catalytic cycle for the Stille cross coupling reaction involves three basic steps: oxidative addition of the Pd(0) species to the organohalide or triflate, transmetalation from palladium to tin and reductive elimination to the cross coupled product and regeneration of the Pd(0) catalyst. The formation of trioorganotin halide provides the driving force for the reaction (**Scheme 1.28.**).

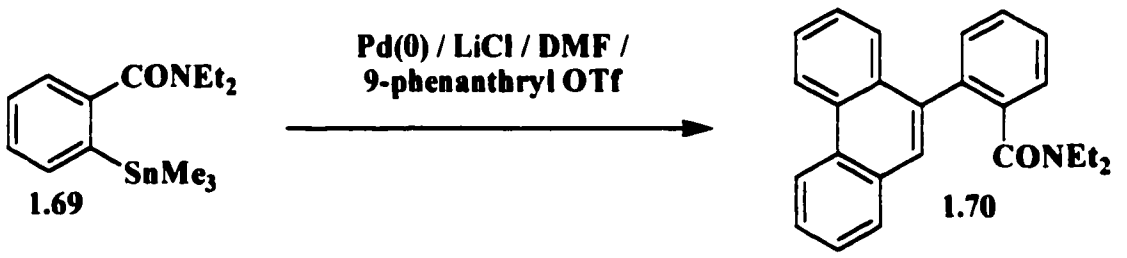


Scheme 1.28. A general catalytic pathway for the Stille cross coupling reaction.

Farina[186] discovered a large ligand effect in the Stille cross coupling reaction and developed mild conditions, which allow large rate enhancements of > 10^3 over the original Stille conditions (triphenylphosphine based-catalyst). The rate determining step in the catalytic cycle is the transmetalation and it proceeds via ligand dissociation and formation of a Pd-stannane π complex. The key role of the ligand is to facilitate the dissociation from Pd(II) and this is what ligands of low donicity such as triphenylarsine or tri(2-furyl)phosphine do

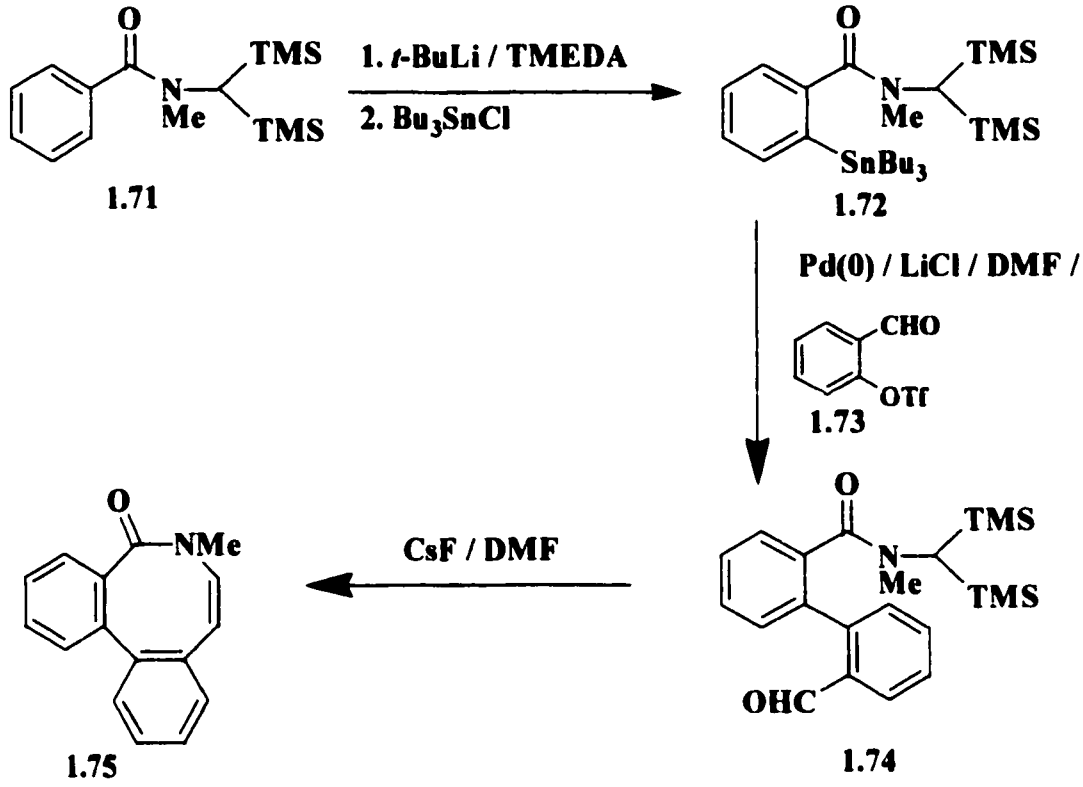
more readily than triphenylphosphine. Catalysts employing triphenylarsine promote higher rates but they are less stable than the one based on tri(2-furyl)phosphine.

Ortho-stannylated benzamides[187] and *O*-arylcarbamates,[188] readily obtained by D*o*M processes represent examples of synthetic link between D*o*M and Stille cross coupling reaction. *Ortho*-stannylated benzamide **1.69** was cross coupled with 9-phenanthryl triflate in 76% (**Scheme 1.29.**).[179a]



Scheme 1.29. D*o*M-Stille cross coupling connection.

The synthesis of the dibenzazocinone **1.75** [187b] was achieved by the sequence lithiation – stannylation – Stille cross coupling – intramolecular Peterson olefination (**Scheme 1.30.**).

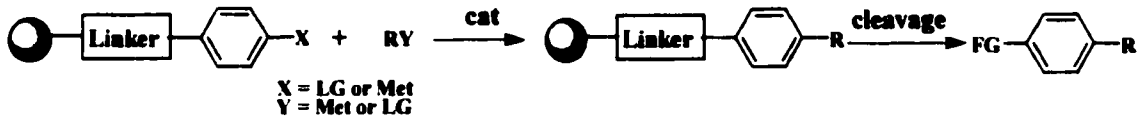


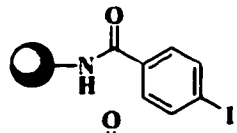
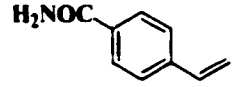
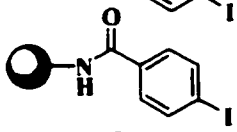
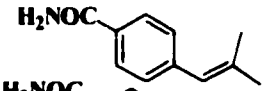
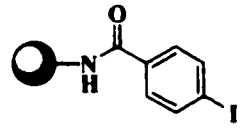
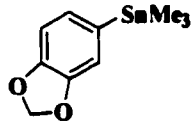
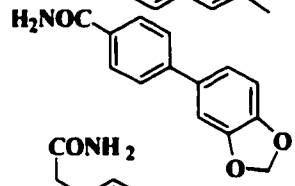
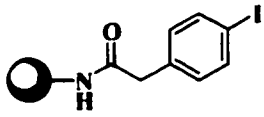
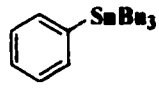
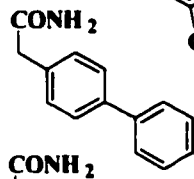
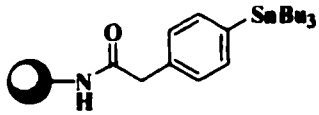
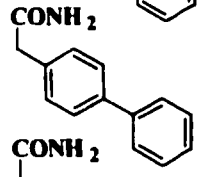
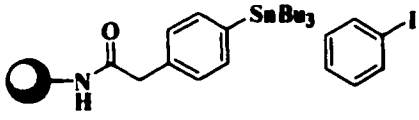
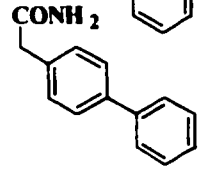
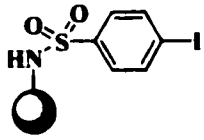
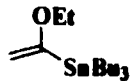
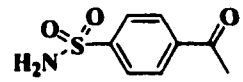
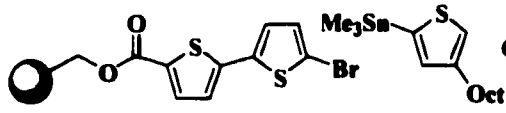
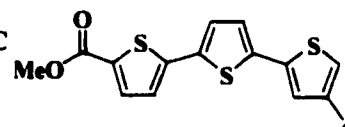
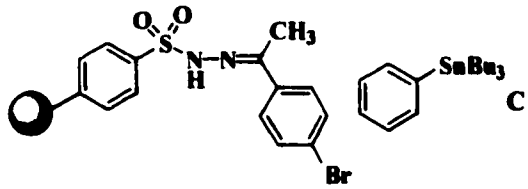
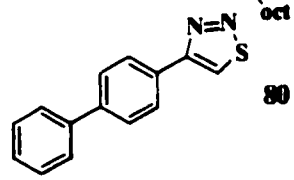
Scheme 1.30. Synthesis of the dibenzazocinone using the tandem D*o*M-Stille cross coupling reaction.

1.4.3. The Stille Cross Coupling Reaction on Solid Support

Most of the published work employing Stille cross coupling reactions on solid support has focused on one-step syntheses leading to simple biaryls or vinyl-aryl compounds (**Table 1.3.**).

Table 1.3. Stille cross coupling reactions on solid support.



Entry	Linker–X	RY	cat[a]	FG–R	Yield (Purity)(%)	Resin	Ref
1			A		89 (>90)	Rink Amide	123a
2			A		85 (>90)	Rink Amide	123a
3			A		90 (<90)	Rink Amide	123a
4			B		33 (>90)	Rink Amide	123c
5			B		3 (-[b])	Rink Amide	123c
6			B		15 (-[b])	Rink Amide	123c
7			A		-[c] (78)	Rink Amide	123d
8			C		-[c] (95)	chloro-methylated macroporous	123i
9			C		80 (87)	PS sulfonyl-hydrazine	123j

[a]cat: A: Pd_2dba_3 / $AsPh_3$; B: Pd_2dba_3 / LiCl /TFP; C: $Pd(PPh_3)_2Cl_2$. [b]Purity not reported. [c]Yield not reported.

Deshpande[123a] examined the Stille cross coupling reaction between polymer bound iodides and vinyl / aryl stannanes in the synthesis of 4-substituted benzamides (entry 1,2,3). 4-Iodobenzoic acid was coupled to deprotected Fmoc Rink amide resin and Stille cross coupling reactions were performed according to the conditions devised by Farina using Pd_2dba_3 as catalyst and $AsPh_3$ as ligand. Cleavage from the support using TFA in DCM provided the cross coupled products in high purities and yields. Even difficult couplings with a hindered stannane (entry 2) and an aryl stannane (entry 3) were reported to proceed in good yields.

Sucholeiki[123c] also reported the formation of biphenyls via Stille cross coupling reaction on solid support. Treating the polymer bound 4-iodophenylacetic acid with trialkylphenylstannanes under the conditions devised by Farina provided the cross coupled product which, upon mild acid catalysed amide hydrolysis, gave the unbound 4-biphenylacetamide in poor yield (entry 4). However, this approach resulted in higher yields than those obtained using tributylphenyltin attached to the Rink amide resin and aryl triflate and iodide in solution. The results corroborate that an iodine leaving group is more reactive than a triflate (entry 5 and 6).

Spear and co-workers[123d] reported that a variety of sulfonyl chlorides undergo smooth reaction with Rink amide resin to form a sulfonamide linker. In order to test this linker under a variety of reaction conditions, they carried out Stille (entry 7) and Heck reactions. In the case of Stille cross coupling, the bound iodo derivatives were treated with 1-(ethoxyvinyl)tributyltin in the presence of Pd_2dba_3 and $AsPh_3$. Upon cleavage by TFA in

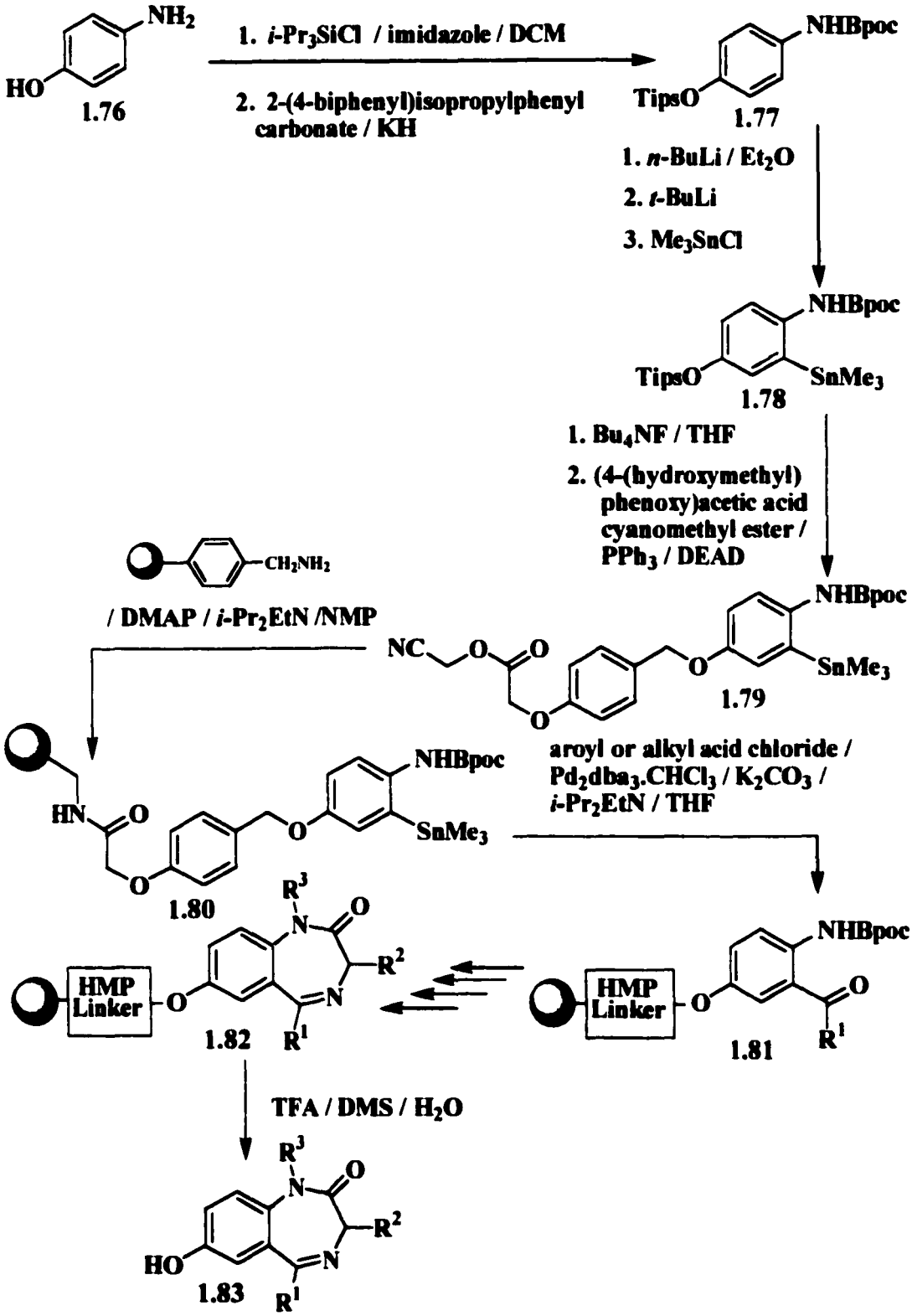
DCM, 4-acetylbenzenesulfonamide was obtained in 78% purity determined by HPLC, the initially formed enol ether being hydrolysed during the cleavage.

Malenfant and Fréchet[123i] reported the first solid phase synthesis of oligothiophenes (entry 8) using an alternative sequence of bromination by NBS and Stille coupling reactions. This work provides an efficient, high-yielding synthesis of oligothiophenes from the dimer to the pentamer with excellent purities. The pentamer was isolated in 90% yield and high purity as assessed by HPLC, ^{1}H NMR, and elemental analysis.

Porco and coworkers[123j] reported the parallel synthesis of a variety of 1.2,3-thiadiazoles employing Stille cross coupling reaction under $Pd(PPh_3)_2Cl_2$ or Pd $(PPh_3)_4$ (10 mol%) catalysis. A gel type polystyrene-sulfonyl-hydrazide resin[189] commercially available from Argonaut serves as a linker for carbonyl derivatives. Support-bound sulfonylhydrazone generated from 4-bromoacetophenone was treated with tributylphenyltin (entry 9). After cyclative cleavage under Hurd-Mori conditions[190] with thionyl chloride, 1,2,3-thiadiazoles were obtained in 80% yield.

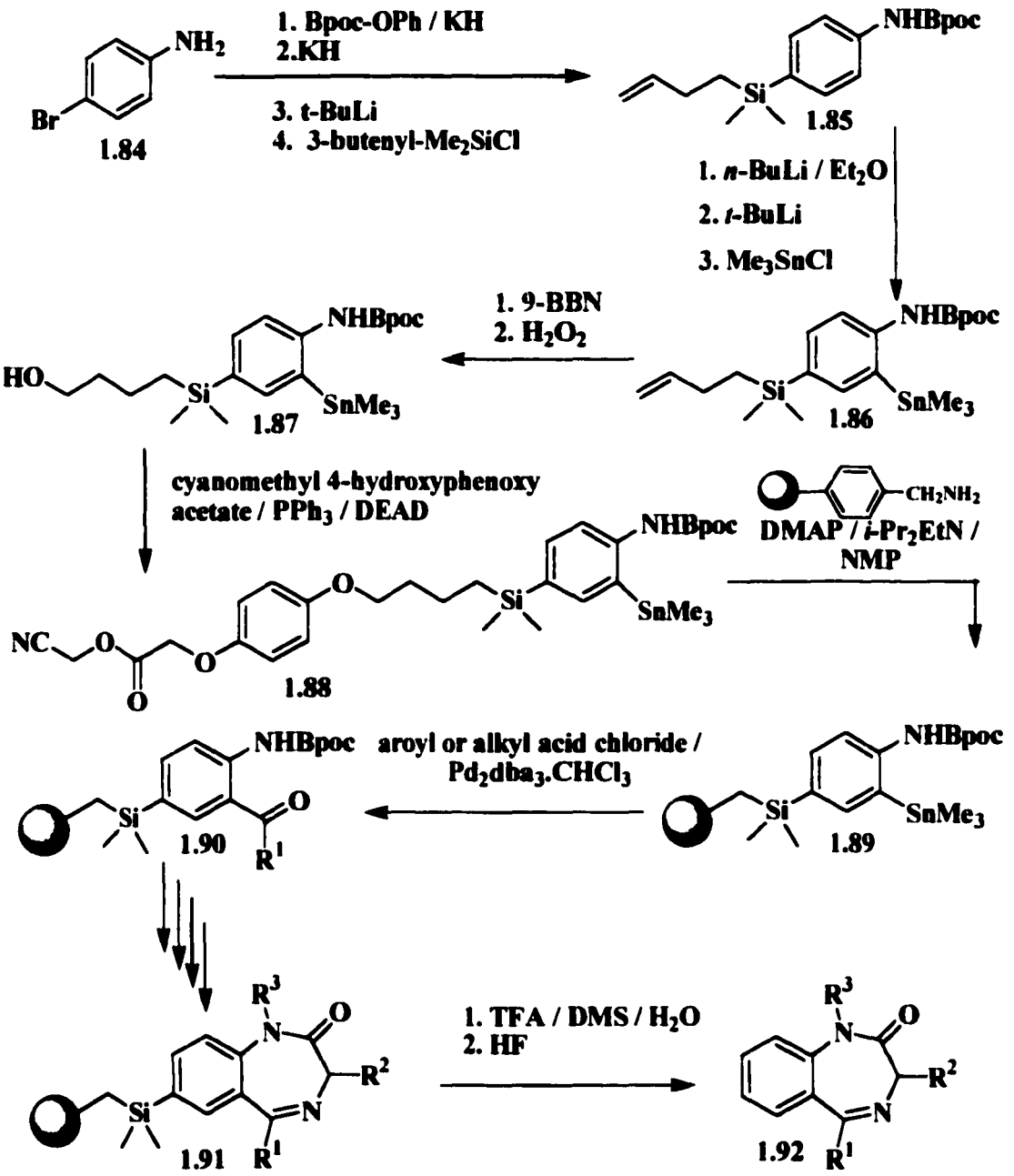
Shortly after the study of Deshpande, Ellman reported the use of the polymer supported Stille cross coupling reaction in his synthesis of libraries of 1,4-benzodiazepine derivatives **(Scheme 1.31.)**.[123c] 2-Aminoaryl ketone constitutes one of the building blocks of the 1,4-benzodiazepine derivatives. Since only a few 2-aminoaryl ketones are commercially available, Ellman developed an approach using Stille cross coupling reaction between a support-bound stannane **1.80** and a variety of aromatic and aliphatic acid chlorides to provide rapid access to hundreds of diverse 2-aminoaryl ketone derivatives **1.81** which, in turn,

enhances the range of diverse 1,4-benzodiazepine derivatives **1.83** synthesised. The 2-aminoarylstannane **1.78** was prepared in solution starting from 4-aminophenol **1.76**. The protection of the alcohol functionality by TipsCl was followed by the protection of the free amine as NHBpoc affording **1.77**. NHBpoc is stable to basic and Stille conditions and is cleavable under mild acidic conditions, to which the linker is stable. D*o*M of the *N*-Bpoc protected substrate **1.77** followed by quench with trimethyltin chloride afforded the tin species **1.78**. After deprotection of the phenol, Mitsunobu reaction with (4-(hydroxymethyl)phenoxy)acetic acid cyanomethyl ester afforded the precursor **1.79** of the HMP linkage. **1.79** was coupled to aminomethylated polystyrene resin in NMP in the presence of *i*-Pr_2EtN as base and DMAP as catalyst. The support bound stannane **1.80** was subjected to Stille cross coupling reaction with a variety of aroyl and alkyl chlorides with the ligandless catalyst $Pd_2dba_3.CHCl_3$ in THF at rt. K_2CO_3 and *i*-Pr_2EtN were added as acid scavengers to minimise protodestannylation and carbamate deprotection. After deprotection of the Bpoc group, the previously published procedure[24,40] of the synthesis of 1,4-benzodiazepine was followed. The benzodiazepine derivatives **1.83** were ultimately obtained by cleavage of the HMP linker using TFA, DMS and water. The yields of the 1,4-benzodiazepine derivatives **1.83** determined by mass balance of purified material based upon initial aminomethyl loading level of the solid support were between 52% and 82%.



Scheme 1.31. Solid phase synthesis of structurally diverse 1,4-benzodiazepines using the Stille cross coupling reaction.[123c]

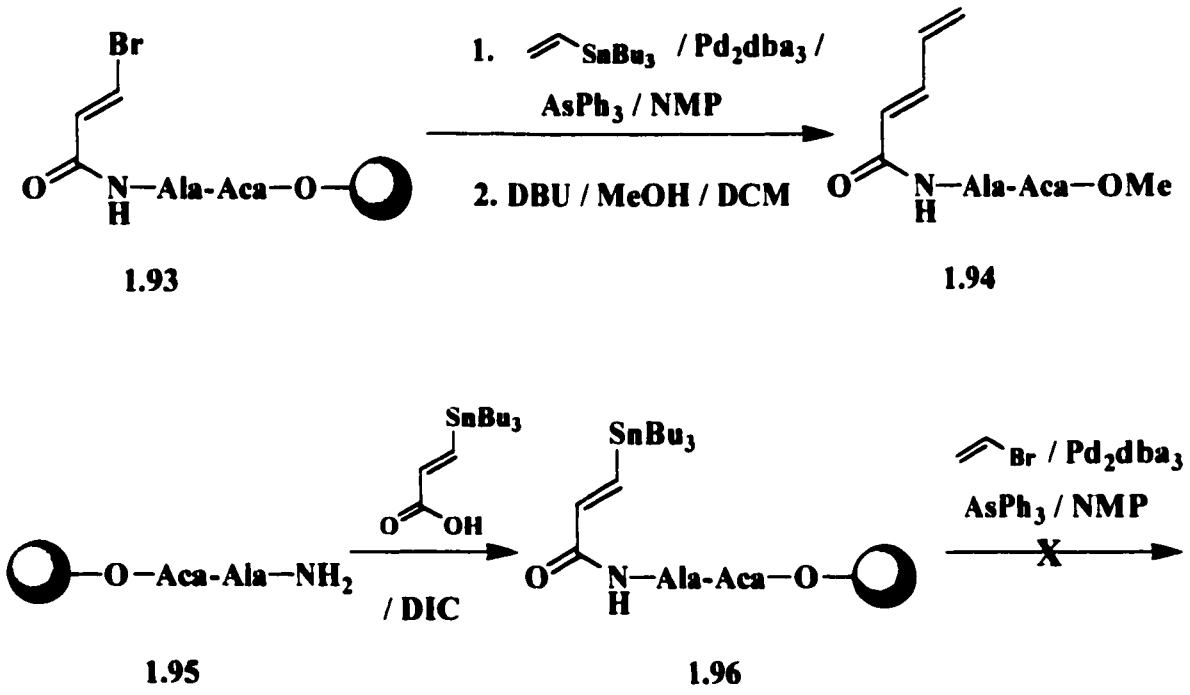
Shortly after, Ellman[191] published the solid phase synthesis of 1,4-benzodiazepine derivatives **1.92** with a silicon-based traceless linker using the Stille cross coupling reaction (**Scheme 1.32.**). The functionalised silicon-containing stannane **1.86** was prepared from 4-bromoaniline **1.84**. The free amino group was protected with Bpoc group. The protected arylsilane **1.85** was obtained by lithium halogen-exchange and quenched with 3-butenylchlorodimethylsilane. KH was previously added to deprotonate the carbamate. D*o*M of *N*-Bpoc protected substrate **1.85** followed by quench with trimethyltin chloride afforded the tin species **1.86**. Hydroboration of **1.86** provided the primary alcohol **1.87**, which was subjected to Mitsunobu conditions to afford the precursor **1.88** for the linkage process. The coupling was effected in a similar manner to that used in the previous synthetic route developed by Ellman to an (aminomethyl)polystyrene.[123c] The support-bound stannane **1.89** was subjected to Stille cross coupling reaction with a variety of aroyl and alkyl chlorides with the ligandless catalyst $Pd_2dba_3.CHCl_3$ in THF at rt. The 1,4-benzodiazepine derivatives **1.92** were obtained by cleavage of the [4-(hydroxymethyl)phenoxy]acetic acid side chain with TFA / DMS / H_2O, followed by cleavage of the aryl-silicon bound of the traceless linker with anhydrous HF. Good purity of the crude products was observed, > 85% by ^1H NMR , and the isolated yields after purification ranged from 50% to 68% for four representative compounds, based on the initial aminomethyl loading of the polystyrene resin.



Scheme 1.32. Solid phase synthesis of 1,4-benzodiazepines using a traceless linker.[191]

Blaskovich and Kahn [123h] reported the first use of the Stille cross coupling reaction for the preparation of functionalised dienes on PEG-monomethyl ether resin (**Scheme 1.33.**). The

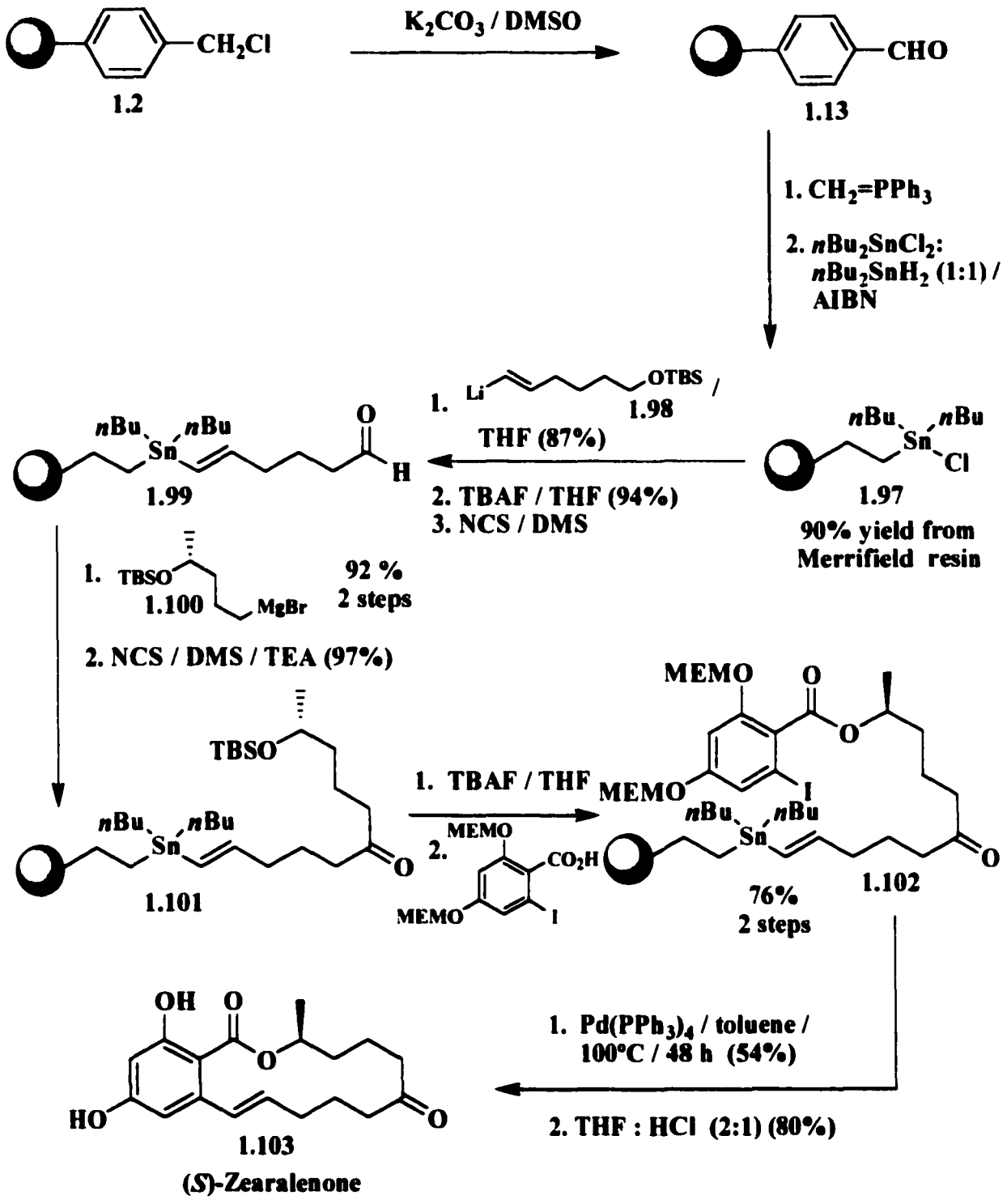
polymer bound bromoacrylic acid derivative **1.93** was treated with tributylvinylstannane under the modified Farina conditions.[186c] A variety of substituted alkenylstannanes (*E*) and (*Z*) were also treated with the polymer bound bromide. It was found that the (*E*)-alkenylstannanes gave good yields and stereoselectivity as opposed to the (*Z*)-alkenylstannanes, which underwent reaction sluggishly. The extended linker Ala-Aca was chosen to possibly allow enzymatic assay of the final product directly on the resin. The possibility of reversing the coupling partners was also studied. However, the PEG-linked stannane **1.96** was treated in the same conditions with a variety of alkenylbromides without success.



Scheme 1.33. Solid phase synthesis of dienes using the Stille cross coupling reaction.[123h]

The total synthesis of natural products on solid phase is an emerging area.[192] Nicolaou[123g] achieved the synthesis of the macrocycle (*S*)-zearalenone **1.103** in 12 steps on

solid support starting from Merrifield resin **1.2** with an overall yield of 22% (**Scheme 1.34.**). A new cleavage tactic involving Stille cross coupling reaction was developed to release the macrocyclic system. (*S*)-zearalenone **1.103** is a biological active product that was already synthesised in solution by a similar strategy by Stille and Hegedus in 1991.[193] The preparation of resin (polystyrene-di-*n*-butyltin chloride) **1.97** is achieved in 90% overall yield by oxidation of Merrifield resin **1.2** with K_2CO_3 in DMSO,[38] followed by olefination of the formyl resin **1.13** and, finally, reaction of the polystyrene vinyl resin intermediate with an equimolar amount of $n Bu_2SnCl_2$ and $n Bu_2SnH_2$ forming in situ $n Bu_2SnHCl$ in the presence of AIBN. Polystyrene-di-*n*-butyltin chloride **1.97** was further functionalised by reaction with the lithium reagent **1.98**, by desilylation and oxidation of the alcohol to the aldehyde. Nucleophilic addition of the Grignard reagent **1.100** to the aldehyde is followed by Corey-Kim oxidation. After deprotection of the alcohol and Mitsunobu esterification, the bifunctional substrate iodide-stannane **1.102** was obtained. The cyclorelease was carried out under $Pd(PPh_3)_4$ in toluene with a 54% yield. Finally (*S*)-zearalenone **1.103** was obtained after deprotection under acidic conditions of the two alcohols functionalities.



Scheme 1.34. Synthesis of the natural product (*S*)-zearalenone on solid support.[123g]

1.4.4. Results and Discussion

1.4.4.1. Objectives

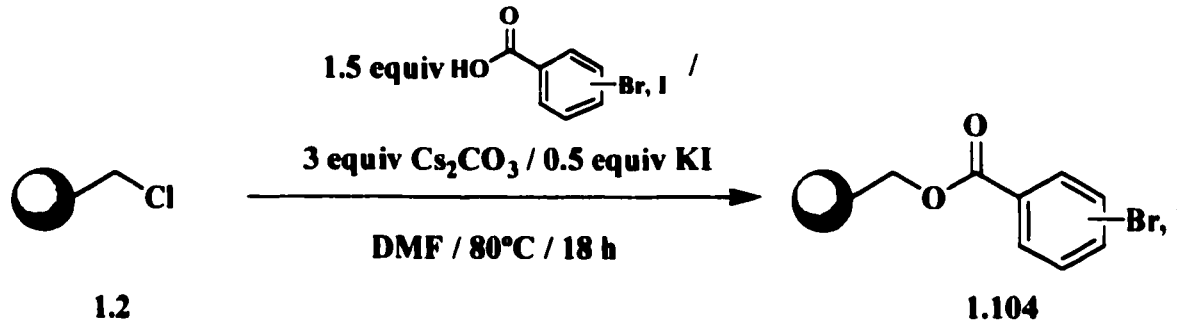
While the area of SPOS was emerging, the adaptation of the transition metal catalysed cross coupling reactions to the solid phase became a major issue. Given the previous work in our laboratories on these reactions in solution phase and our wish to contribute to the new area of SPOS, we considered that an investigation of these methodologies on solid support would be in order. In this thesis, the goals were to study the translation of these methods to the solid phase and to demonstrate their synthetic values in connection with D*o*M and DReM, connections as yet unknown in SPOS, which can offer additional synthetic advantage and diversity in comparison to previous results.[123] The work in the field of the SPOS in our laboratories started by an investigation of the Stille cross coupling reaction on solid support using an ester linker for the generation of arrays of functionalised biaryl, heterobiaryl and styryl derivatives.

1.4.4.2. The Ester Linker

The attachment of an *N*-protected amino acid to a chloromethylated resin via a benzyl ester linkage is a standard procedure of the solid phase peptide synthesis.[194] The esterification is generally achieved by reaction between Merrifield resin and the cesium salt of the appropriate carboxylic acid. The large cesium cation makes the salt more lipophilic and therefore more compatible with the resin. In addition, the reaction is carried out in a polar

solvent such as DMF to increase the extent of dissociation of the salt of the carboxylic acid. A high degree of dissociation is very desirable since the carboxylate rather than the ion pair is the nucleophile that displaces the iodide. KI is introduced to contribute to the replacement of the chlorine by iodine to form a better leaving group (Finkelstein reaction). Alternative methods of esterification of Merrifield resin involving the use of Me_4N salts,[195] sodium salts[59c] in THF with Bu_4NF catalysis,[87] and zinc salts in ethanol[196] have also been described.

1% cross-linked and 2% cross-linked Merrifield resins **1.2** were functionalised according to the previously optimised conditions (**Scheme 1.35.**) with the cesium salts of halobenzoic acids in the presence of KI in DMF.[122a,197] Better loadings in halobenzoic acids were obtained when 1% cross-linked Merrifield resin was employed. The functionalisation step was readily monitored by FTIR spectroscopy as the CH_2Cl peak at 1265 cm^{-1} disappeared while a new peak at 1710 cm^{-1} corresponding to the bound benzoate functionality of resin **1.104** appeared.

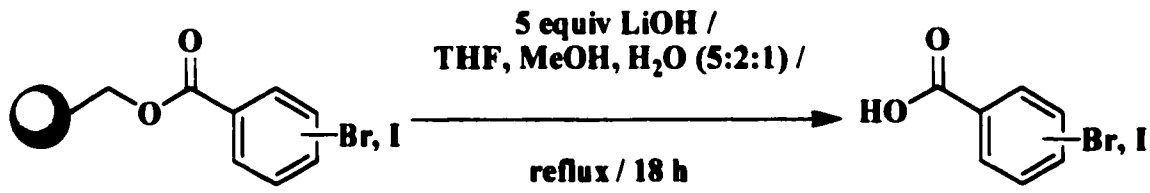


Scheme 1.35. Attachment of halobenzoic acids to Merrifield resin.

Ester cleavage by transesterification with sodium methoxide / methanol in THF according to the Frenette and Friesen method[122a] proved to be temperamental in our hands. Methyl benzoates contaminated with varying amounts of the corresponding acids, presumably

formed by hydroxide hydrolysis due to the retention of water within the polymer structure, were obtained. Fréchet and Malenfant[123i] also found that the cleavage of the ester linker using sodium methoxide in THF affords a mixture of the methyl ester and a lesser amount of the sodium carboxylate product. In order to obtain only ester derivatives as cleaved products, they treated the cleavage product mixture (ester and carboxylate) with methyl iodide under phase transfer conditions with 18-crown-6 to ensure conversion of the sodium carboxylate fraction to its methyl ester derivative.

With the aim of providing a solid support method that produces pure materials suitable for direct bioscreening regimens, we tested various cleavage conditions. The extent of the cleavage was monitored by FTIR spectrometry of the resin after it had been submitted to the cleavage conditions, washed and dried. For all the following cleavage conditions, the ester absorption band was still present in the IR spectrum. Cleavage to the amide with Et_2NH / *n*-BuLi, basic hydrolysis with KO^{t}Bu, and with LiOH in the presence of Bu_4NHSO_4 did not give satisfying results. Finally, hydrolysis to the benzoic acids **1.105** using LiOH / H_2O / MeOH / THF was found to give highest yields and reproducible reactions (**Scheme 1.36.**).



1.104 **1.105**

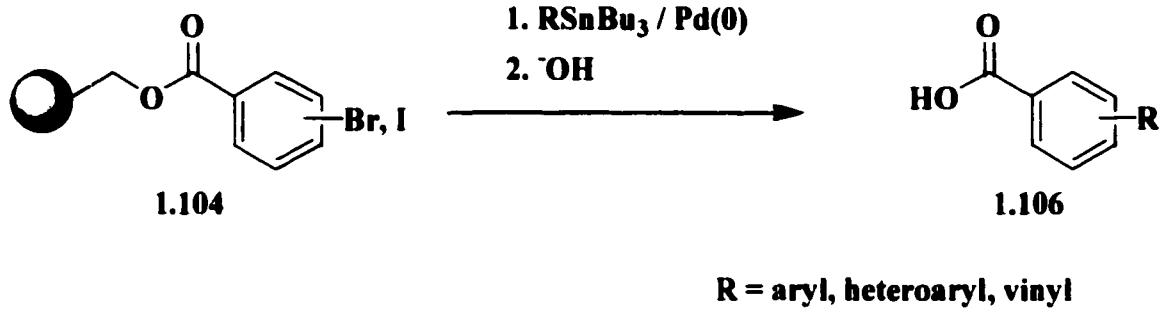
Scheme 1.36. Conditions developed for the cleavage of the ester linker.

The solvent mixture used meets two requirements: it dissolves LiOH and properly swells the resin. The loading in benzoic acids were found to be in the range of 0.8 mmol /g meaning that at least 80% of the reaction sites were functionalised.

These new conditions developed for the cleavage of the ester linker to carboxylic acids represent a major improvement to the existing methods using harsh conditions, usually liquid HF or TFMSA.[194]

1.4.4.3. The Stille Cross Coupling Reaction on Solid Support Using an Ester Linker

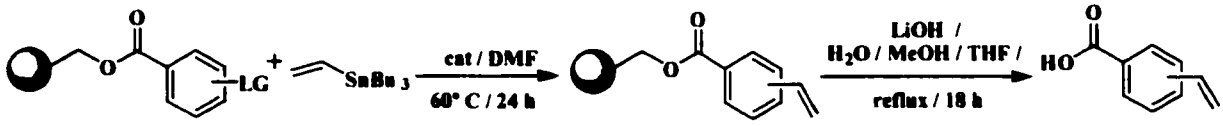
Our general approach to the Stille cross coupling reactions on solid support using an ester linker is summarised on **Scheme 1.37.** A variety of halobenzoic acids were loaded onto Merrifield resin **1.2** through the ester linkage. The solid phase aryl electrophiles **1.104** were subsequently treated with a wide range of organostannanes in solution under Pd (0) catalysis to give the bound cross-coupled products. After applying the basic cleavage conditions, developed as described above, arrays of functionalised styryl, biaryl, heteroaryl derivatives **1.106** were released. The reactions were carried out under argon and in DMF, a solvent suitable for the Stille cross coupling reaction and allowing good swelling of the PS-DVB matrix. Excess organostannanes (3 equiv) was used. $Pd(PPh_3)_4$ was always tried first as the source of the Pd(0) catalyst.

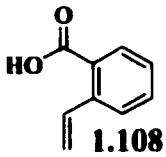
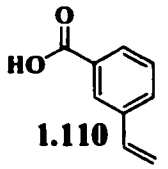
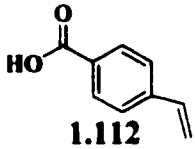
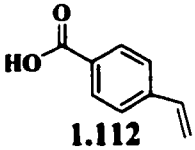


Scheme 1.37. Stille cross coupling reactions on solid support using an ester linker.

2-, 3-, 4- Iodobenzoic acids and 4- bromobenzoic acid were loaded onto Merrifield resin **1.2**. The polymer bound halides were treated with commercially available tributylvinyltin (**Table 1.4.**). Within the exception of entry 1, good yields and excellent purity of styryl carboxylic acids were obtained. In the case of the polymer bound 2-iodobenzoic acid **1.107**, the purity of the product obtained **1.108** using $Pd(PPh_3)_4$ as catalyst was only 56%. It was increased to 84% by switching the Pd catalyst to Pd_2dba_3 using TFP as a ligand according to the conditions devised by Farina (entry 1).

Table 1.4. Synthesis of styryl carboxylic acids by Stille cross coupling reactions on solid support.

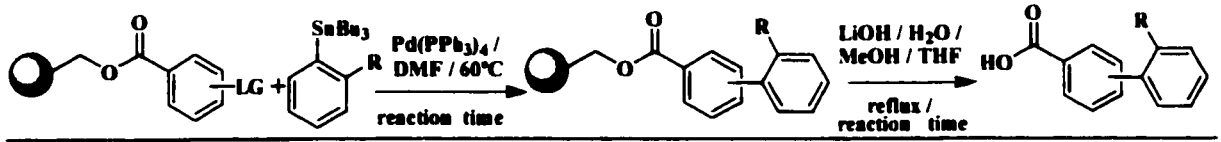


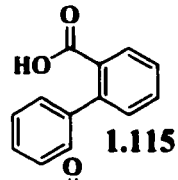
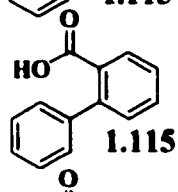
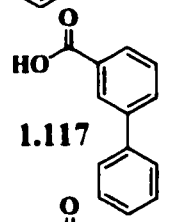
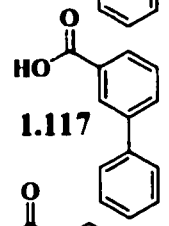
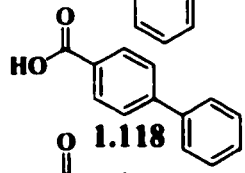
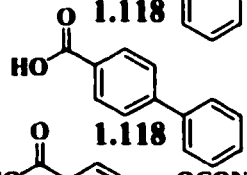
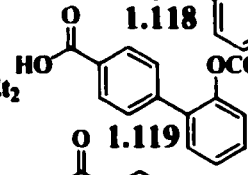
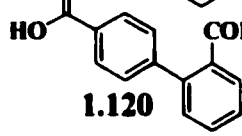
Entry	LG	cat	Product	Reaction Composition (%)[a]			Yield (%)[b]
				Product	SM	De-Halo SM	
1	*o*-I **1.107**	Pd_2dba_3 / TFP	 **1.108**	84	11	1	71
2	*m*-I **1.109**	$Pd(PPh_3)_4$	 **1.110**	96	0	1	87
3	*p*-Br **1.111**	$Pd(PPh_3)_4$	 **1.112**	96	0	1	88
4	*p*-I **1.113**	$Pd(PPh_3)_4$	 **1.112**	98	0	1	>95

[a] Reaction composition determined by HPLC and ^1H NMR. [b] Isolated yields determined after column chromatography.

The Stille cross coupling reactions were also carried out between the solid support-attached halo benzoic acids and tributylarylstannanes to form biaryl carboxylic acids (**Table 1.5.**).

Table 1.5. Synthesis of biaryl carboxylic acids by Stille cross coupling reactions on solid support.

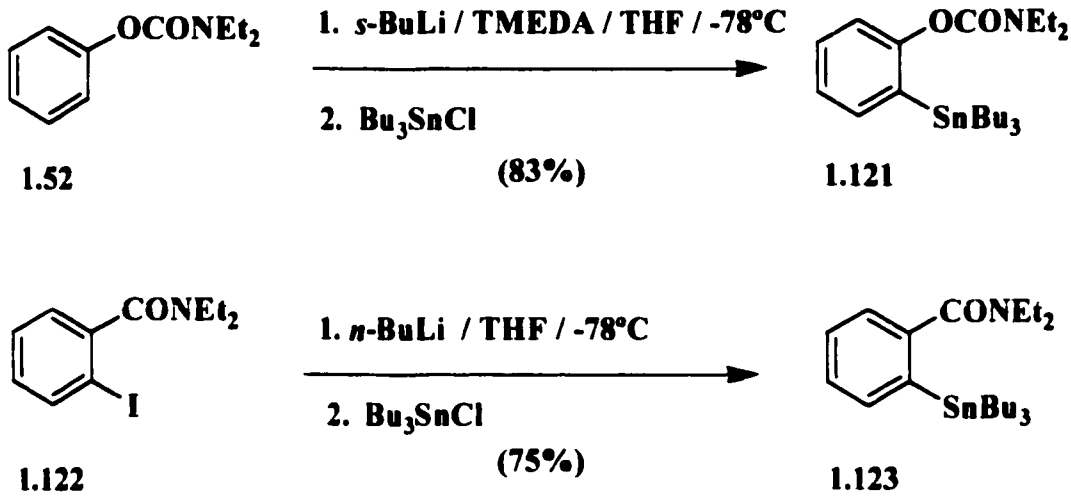


Entry	LG	R	Product	Reaction time (h)[a] Cross coupling	Cleavage	Reaction Composition (%)[b] Product	SM	Yield(%)[c]
1	*o*-Br 1.114	H	 1.115	24	42	94	4	>95
2	*o*-I 1.107	H	 1.115	24	42	90	7	88
3	*m*-Br 1.116	H	 1.117	24	18	95	4	94
4	*m*-I 1.109	H	 1.117	24	18	96	0	91
5	*p*-Br 1.111	H	 1.118	24	18	93	0	93
6	*p*-I 1.113	H	 1.118	24	42	97	0	>95
7	*p*-I 1.113	$OCONEt_2$	 1.119	48	18	95	0	78
8	*p*-I 1.113	$CONEt_2$	 1.120	48	18	95	0	80

[a]Optimised reaction time. [b] Reaction composition determined by HPLC and ^{1}H NMR. [c] Isolated yields determined after column chromatography.

As gleaned from the table, in the absence of steric influences excellent yields and purities of biaryl carboxylic acids were obtained. In the 2-substituted cases (entries 1 and 2), remaining starting material was observed. Longer LiOH hydrolysis times were necessary to achieve good yields of the ortho-coupled derivatives, presumably owing to steric effects and /or to the alteration of the resin by ortho-substitution, which would obstruct the penetration of the hydroxide. In contrast to solution phase Stille cross coupling reactions, no general trends of ArI > ArBr higher yield and rate effects was observed. Echavarren and Stille found the reactivity of the Stille cross coupling reaction in solution to be I > Br > OTf when $Pd(PPh_3)_4$ was used as a catalyst.[160a] When $PdCl_2(PPh_3)_2$ was used, the order of reactivity was found to be I > OTf > Br. The high reactivity of the polymer bound bromides might be attributed to the presence of the ester linker acting as an EWG. In fact, the coupling reaction of bromoaromatics containing EWG occurs at faster rate than the corresponding cross coupling reaction with bromoaromatics containing EDG groups. The EWGs contribute to stabilise the palladium intermediate formed after the oxidative addition.

Once suitable reaction conditions were established for the cross coupling with tributylphenyltin (entries 1-6), links between the Stille cross coupling and DoM were examined (entries 7 and 8). *Ortho*-stannylated carbamate **1.121** and benzamide **1.123** were prepared respectively by DoM and metal halogen exchange followed by stannylation (**Scheme 1.38.**). These were treated with the polymer bound 4-iodobenzoic acid **1.113**. The cross-coupled products **1.119** and **1.120** were obtained in excellent purities and good yields, when longer reaction times were applied.

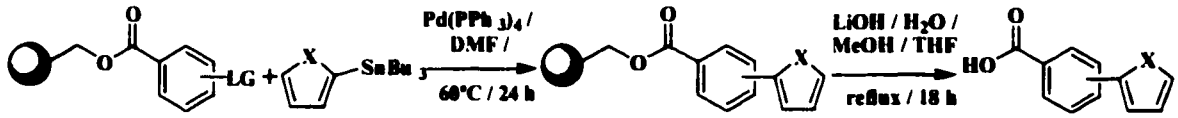


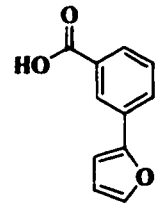
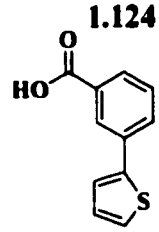
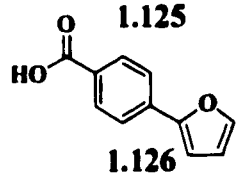
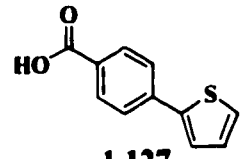
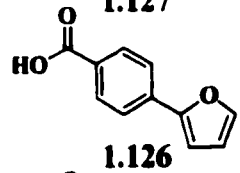
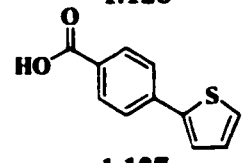
Scheme 1.38. Preparation of *ortho*-stannylated carbamate and benzamide.

The derived products obtained **1.119** and **1.120** are candidates for solution phase DreM reaction leading to fluorenones[198] and for the sequence directed remote metalation – carbamoyl migration – cyclisation leading to dibenzopyranones[178b] respectively as already reported.

The possibility of producing monoheterobiaryl carboxylic acids from the Stille cross coupling reaction on solid support was also investigated by treating the bound halo benzoic acids with 2-tributylstannylfuran and 2-tributylstannylthiophene[199] (**Table 1.6.**). High yields and purities were achieved. There was no trend noticed that iodo derivatives were more reactive than the bromo ones. However, in all cases, it was observed that the Stille cross coupling reactions with 2-tributylstannylthiophene (entries 2,4 and 6) gave better results than the ones with 2-tributylstannylfuran (entries 1,3 and 5).

Table 1.6. Synthesis of heterobiaryl carboxylic acids using heteroaromatic stannanes by Stille cross coupling reactions on solid support.

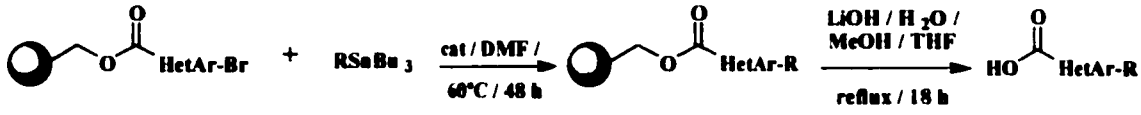


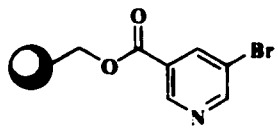
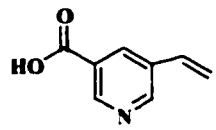
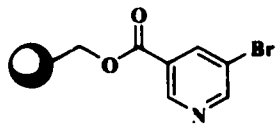
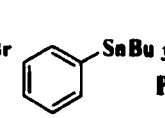
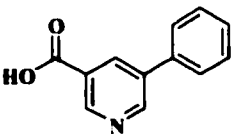
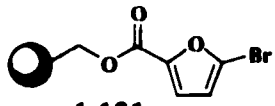
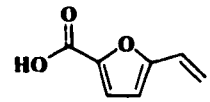
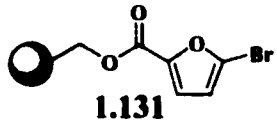
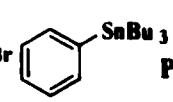
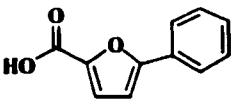
Entry	LG	X	Product	Reaction Composition (%)[a] Product	SM	Yield(%)[b]
1	*m*-I 1.109	O	 1.124	96	0	86
2	*m*-I 1.109	S	 1.125	98	0	89
3	*p*-Br 1.111	O	 1.126	96	0	84
4	*p*-Br 1.111	S	 1.127	98	0	91
5	*p*-I 1.113	O	 1.126	86	0	80
6	*p*-I 1.113	S	 1.127	95	0	93

[a]Reaction composition determined by HPLC and ^{1}H NMR. [b]Isolated yields determined after column chromatography.

Another approach to heteroaryl carboxylic acids was also examined (**Table 1.7.**). Heterocyclic bromides: 5-bromonicotinic acid and 5-bromo-2-furoic acid were loaded onto Merrifield resin **1.2** and subjected to cross coupling reactions.

Table 1.7. Synthesis of heterobiaryl / styryl carboxylic acids using heteroaromatic bromides by Stille cross coupling reactions on solid support.



Entry	HetAr-Br	$RSnBu_3$	cat	Product	Reaction Composition (%)[a] Product	SM	De-Halo SM	Yield (%)[b]
1	 **1.128**		Pd_2dba_3 / TFP	 **1.129**	48	3	47	-[c]
2	 **1.128**		$Pd(PPh_3)_4$	 **1.130**	96	1	2	89
3	 **1.131**		Pd_2dba_3 / TFP	 **1.132**	68	2	11	-[c]
4	 **1.131**		$Pd(PPh_3)_4$	 **1.133**	75	2	15	68

[a]Reaction composition determined by HPLC and ^1H NMR. [b]Isolated yields determined after column chromatography. [c]Isolated yields not determined.

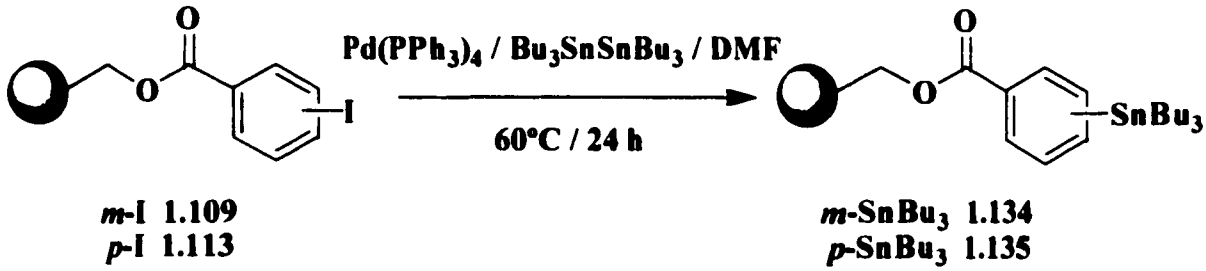
On the one hand, successful cross coupling reactions were achieved with tributylphenyltin (entries 2 and 4), although longer reaction times were required. On the other hand, Stille cross coupling reactions with tributylvinyltin (entries 1 and 3) did not show successful results, even after switching the Pd catalyst from $Pd(PPh_3)_4$ to Pd_2dba_3 with TFP as ligand. In the case of the reaction between the polymer bound bromonicotinic acid **1.128** and tributylvinyltin, an equal amount of nicotinic acid (entry 1) was obtained.

Attempts to cross couple solid support-bound 4-bromocinnamate **1.140**, 3,5-dibromobenzoic acid **1.141** as well as 3-bromo, 4-methoxybenzoic acid **1.142** under the standard conditions with tributylphenyltin and tributylvinyltin led to complex mixtures and therefore these reactions were deemed to be of little synthetic utility.

The Stille cross coupling reaction of polymer bound iodo and bromo benzoic acid with allyltributyltin failed, leading to the recovery of the starting material. Usually allyltributyltin undergoes also solution phase coupling in lower yields.[160a]

To improve the scope of the methodology, the inversion of the cross coupling partners was tested. Beside the fact that a larger number of bromides and iodides compared to stannanes are commercially available, the major advantages of having the tin reagents on the polymer as opposed to the aryl electrophiles are those of economy and toxicity. When the stannane species is on the solid support, it becomes the limiting reagent and, instead of using excess of tin reagents, excess of electrophile is used which is less expensive and less toxic. Another potential advantage is that, when inverting the cross coupling partners, it may be possible to quantify the resin bound aryltin substitution level by gel-phase tin NMR.

A number of reactions have been reported in solution phase synthesis in which hexamethyl- or hexabutyl-ditin are used to transfer an organotin species to an organic substrate. It represents an extremely useful alternative to the standard syntheses involving reactions of a Grignard or organolithium with an organic halide but involves release of a ½ equiv of Sn into waste products.[200] Although this method has been extensively studied in solution, it had not, to our knowledge, been used on polymer support. We applied the solution phase reaction conditions for the preparation of polymer-bound arylstannanes **1.134** and **1.135**.[201] **1.134** and **1.135** were thus prepared, from polymer-bound 3-iodobenzoic acid **1.109** and 4-iodobenzoic acid **1.113** respectively, by treatment with hexabutylditin under $Pd(PPh_3)_4$ (10 mol%) catalysis. (**Scheme 1.39.**).



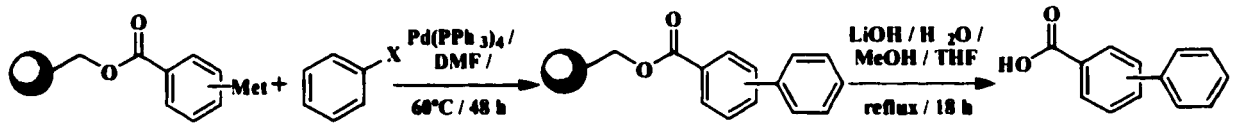
m-I **1.109**
p-I **1.113**

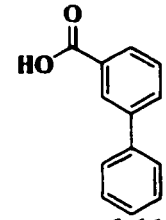
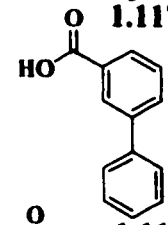
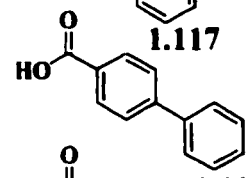
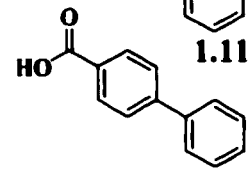
m-$SnBu_3$ **1.134**
p-$SnBu_3$ **1.135**

Scheme 1.39. Preparation of polymer-bound arylstannanes.

The polymer-bound arylstannanes **1.134** and **1.135** were cross coupled with iodobenzene and bromobenzene under $Pd(PPh_3)_4$ (10 mol%) catalysis. After cleavage, low purities by HPLC (between 35 and 75%) were observed (**Table 1.8.**).

Table 1.8. Synthesis of biaryl carboxylic acids using polymer-bound arylstannanes by Stille cross coupling reactions on solid support.

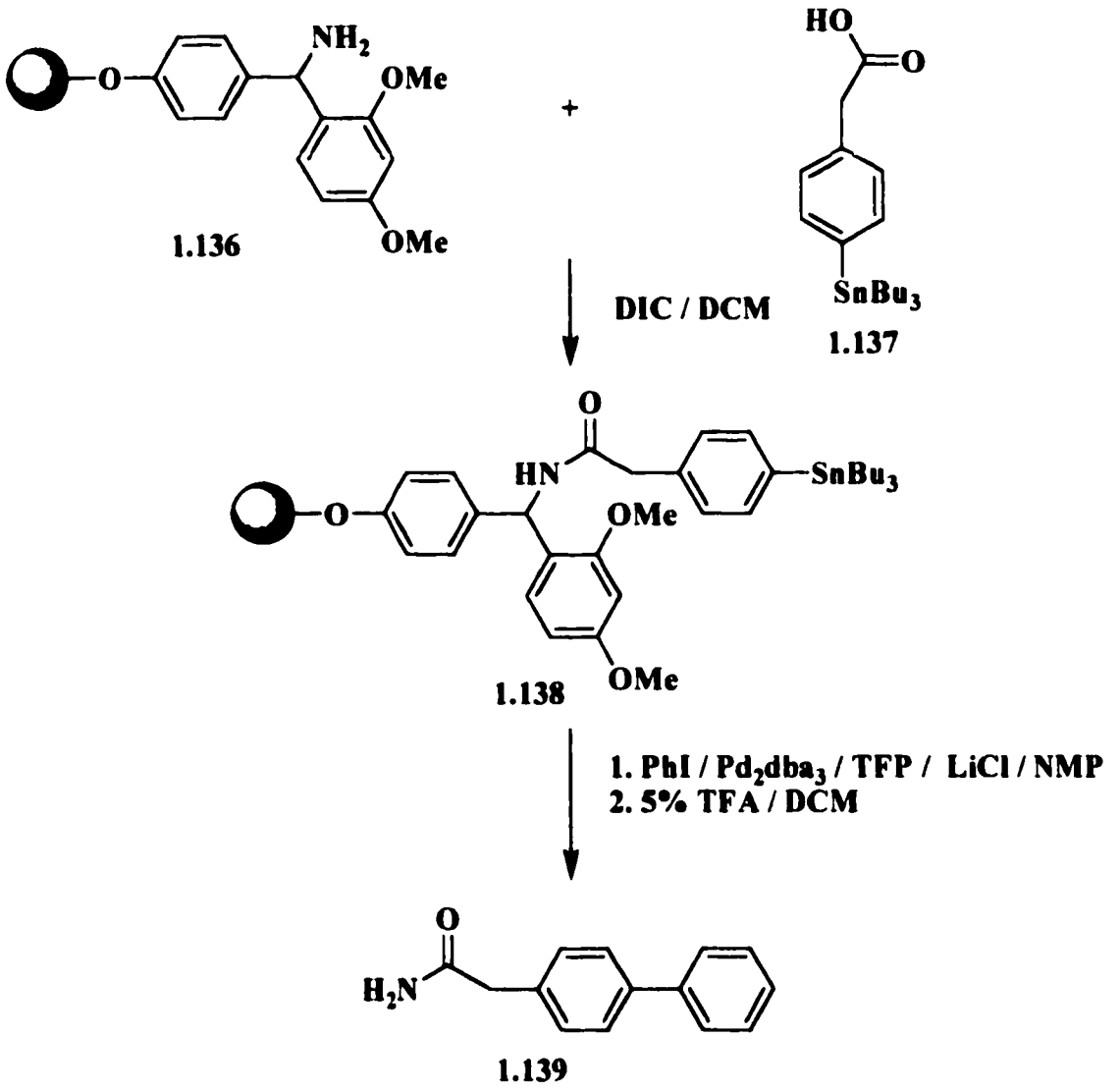


Entry	Met	X	Product	Purity (%)[a]
1	*m*-SnBu$_3$ **1.134**	Br	 **1.117**	35
2	*m*-SnBu$_3$ **1.134**	I	 **1.117**	66
3	*p*-SnBu$_3$ **1.135**	Br	 **1.118**	74
4	*p*-SnBu$_3$ **1.135**	I	 **1.118**	52

[a]Purity determined by HPLC.

The results indicate that the synthetic utility was compromised by the inversion of the cross coupling partners although the comparison may be inappropriate since two cross coupling reactions were involved in this sequence.

Sucholeiki[123c] attached a preformed tributylphenyltin derivative **1.137** to the resin and carried out the Stille cross coupling reaction of **1.138** with iodobenzene (**Scheme 1.40.**) and also observed lower yield (15 %) than when the cross coupling partners were inverted (33%).



Scheme 1.40. Preparation of biaryls on solid support via Stille cross coupling reaction with polymer-bound stannane.[123c]

He assumed that the resin bound tin changes the expansion and contraction properties of the cross-linked polystyrene which would result in the restriction of the access of the reagents to the interior of the support. This rationalisation was used for the lower biaryl coupling yields when coupling iodobenzene to a support containing tributylphenyltin in comparison to the reverse situation.

1.4.4.4. Conclusion

Stille cross coupling reactions on solid support using an ester linker have been achieved leading to biaryl, heterobiaryl, and styryl carboxylic acids in high yield and purities. Furthermore, connection of this process to solution phase DoM and DReM processes is indicated. The application of this methodology to diverse library synthesis may be anticipated.

1.5. Experimental

1.5.1. General Procedures

Melting points were determined using a Büchi model SMP-20 instrument or a Fisher-Johns hot stage melting point apparatus and are uncorrected. Infrared spectra were recorded on either a BOMEM MB-100 or a Perkin Elmer 1600 FTIR infrared spectrometer as thin films or in KBr pellet form. ^{1}H NMR and ^{13}C NMR spectra were recorded on either a Bruker AM-250, AC-200 or AC-300 MHz spectrometer in chloroform-d_1 with tetramethylsilane as an

internal standard unless otherwise stated. NMR spectral data are reported in the following order: chemical shifts, multiplicity, coupling constants in Hertz and number of protons. Mass spectral data (MS) were determined by Laboratory Services Division, University of Guelph, Guelph, Ontario on either a high-resolution Varian MAT-CH7 or a VG 70 / 70SE double focusing mass spectrometer at 70 eV unless otherwise stated. Elemental Analyses were performed by MHW laboratories, Phoenix, Arizona. Thin Layer Chromatography (TLC) was performed using Merck 60F-254 precoated silica sheets. Flash Chromatography[202] was carried out using EM Science gel 60, particle size 0.040 - 0.063 mm (230 - 400 mesh ASTM) purchased from VWR Scientific of Canada Ltd. Hexane and ethyl acetate were used as mobile phase in flash chromatography unless otherwise stated and were distilled prior to use.

The reaction compositions were determined using a Waters HPLC system consisting of a 600E multi-solvent delivery system, a Waters 486 UV detector (λ = 254 nm), a Waters 746 integrator / recorder. Waters reverse phase (C-18, Novapak) 8 x 100 mm radial compression module (RCM) columns were used with a methanol / (KOAc / EtOAc) buffer mobile phase.

All dry solvents and reagents used were purified according to Perrin.[203] Tetrahydrofuran, dimethoxyethane and diethyl ether were freshly distilled from sodium benzophenone ketyl under nitrogen prior to use. Toluene was freshly distilled from sodium metal under nitrogen prior to use. *N,N,N',N'*-Tetramethylethylenediamine (TMEDA) was dried and distilled over CaH_2 before use and stored under argon. *n*-Butyllithium was kindly supplied by FMC Corporation, Lithco Division, as a solution in hexane. *s*-Butyllithium and *t*-butyllthium were purchased from Aldrich Chemical Company as solutions in cyclohexane and pentane, respectively. All alkyllithiums were stored in resealable containers and titrated

regularly against 1,10-phenanthroline / *n*-butanol.[204] Cs_2CO_3 was generously donated by Chemetall Gesellschaft. $Pd(PPh_3)_4$ was prepared following a literature procedure[205] and stored in a freezer. All other commercial reagents were purchased from Aldrich Chemical Company, Lancaster Synthesis Ltd. or Fluka Chemie A.G.

All reactions were carried out in oven-dried glassware under inert atmosphere (Ar. N_2) unless otherwise specified, using syringe-septum cap techniques. The -78°C temperature designated is approximate as achieved by a dry ice–acetone bath. Allowing a reaction to proceed overnight implies a period of 16-18 h.

1.5.2. Standard Methods

Procedure A. Attachment of halobenzoic acids to Merrifield resin

1% cross-linked resin

In a SPOS flask fitted with an overhead stirrer, the Merrifield resin **1.2** (1% cross-linked, loading 1 mmole / g, 3 g, 3 mmole) was swollen for 30 min in anhydrous DMF (30 mL). Cesium carbonate (9 mmole), potassium iodide (1.5 mmole) and halobenzoic acid (4.5 mmole) were added. The mixture was stirred at 80°C overnight. The reaction mixture was cooled to rt and the resin was collected by filtration and washed twice with DMF, twice with DMF:H_2O (1:1), four times with H_2O, three times with methanol, twice with CH_2Cl_2 and dried overnight in an Abderhalden apparatus. The resin obtained was analysed by FTIR.

2% cross-linked resin

In a SPOS flask fitted with an overhead stirrer, the Merrifield resin **1.2** (2% cross-linked, loading 2 mmole / g, 1.5 g, 3 mmole) was swollen for 30 min in anhydrous DMF (15 mL). Cesium carbonate (9 mmole), potassium iodide (1.5 mmole) and halobenzoic acid (4.5 mmole) were added. The mixture was stirred at 80°C overnight. The reaction mixture was cooled to rt and the resin was collected by filtration and washed twice with DMF, twice with DMF:H_2O (1:1), four times with H_2O, three times with methanol, twice with CH_2Cl_2 and dried overnight in an Abderhalden apparatus. The resin obtained was analysed by FTIR.

Procedure B. Determination of the loading capacity of resin-bound halobenzoic acids.

1% cross-linked resin

Resin-bound halobenzoic acid (1% cross-linked, theoretical loading 1 mmole / g, 0.15 g) was swollen in THF (2.5 mL) for 30 min, a solution of lithium hydroxide monohydrate (0.75 mmole) in MeOH:H_2O (2:1, 1.5 mL) was added and the mixture was refluxed overnight. After cooling to rt, a solution of 1 M HCl (3 mL) was added and the whole was stirred (10 min) and subjected to filtration (fritted glass funnel). The resin was successively washed three times with THF, three times with THF:1 M HCl (1:1) and three times with ether, and the filtrate was repeatedly extracted with EtOAc. The combined organic extract was washed with water and brine, dried (Na_2SO_4), and evaporated to dryness. The residue was purified on silica gel to give the halobenzoic acid. The extent of the cleavage was established by monitoring the ester carbonyl absorption in the IR spectrum.

2% cross-linked resin

Resin-bound halobenzoic acid (2% cross-linked, theoretical loading 2 mmole / g, 0.15 g) was swollen in THF (2.5 mL) for 30 min, a solution of lithium hydroxide monohydrate (1.5 mmole) in MeOH:H_2O (2:1, 1.5 mL) was added and the mixture was refluxed overnight. After cooling to rt, a solution of 1 M HCl (6 mL) was added and the whole was stirred (10 min) and subjected to filtration (fritted glass funnel). The resin was successively washed three times with THF, three times with THF:1 M HCl (1:1) and three times with ether, and the filtrate was repeatedly extracted with EtOAc. The combined organic extract was washed with water and brine, dried (Na_2SO_4), and evaporated to dryness. The residue was purified on silica gel to give the halobenzoic acid. The extent of the cleavage was established by monitoring the ester carbonyl absorption in the IR spectrum.

Procedure C. Stille cross coupling reaction of resin-bound halobenzoic acids with organostannanes

1% cross-linked resin

Resin-bound halobenzoic acid (1% cross-linked, theoretical loading 0.8 mmole / g, 0.15 g) was swollen in anhydrous DMF (5 mL) and the system was flushed with argon (30 min). $Pd(PPh_3)_4$ (0.006 mmole) was added and the reaction mixture was stirred for 10 min at rt. Organostannane (0.36 mmole) was added and the reaction mixture was stirred at 60°C for 24 h. The reaction mixture was cooled to rt, treated with aq. satd. NH_4Cl solution (5 mL) and stirred for 10 min. The resin was removed by filtration (fritted glass funnel) and washed successively once with DMF, twice with DMF:H_2O (1:1), twice with 0.3 M HCl, three times

with H_2O, once with DMF, twice with EtOAc, twice with EtOAc:MeOH (1:1) and three times with MeOH, and dried overnight in an Abderhalden apparatus.

2% cross-linked resin

Resin-bound halobenzoic acid (2% cross-linked, theoretical loading 1.5 mmole / g, 0.10 g) was swollen in anhydrous DMF (3.3 mL) and the system was flushed with argon (30 min). $Pd(PPh_3)_4$ (0.0075 mmole) was added and the reaction mixture was stirred for 10 min at rt. Organostannane (0.45 mmole) was added and the reaction mixture was stirred at 60°C for 24 h. The reaction mixture was cooled to rt, treated with aq. satd. NH_4Cl solution (6 mL) and stirred for 10 min. The resin was removed by filtration (fritted glass funnel) and washed successively once with DMF, twice with DMF:H_2O (1:1), twice with 0.3 M HCl, three times with H_2O, once with DMF, twice with EtOAc, twice with EtOAc:MeOH (1:1) and three times with MeOH, and dried overnight in an Abderhalden apparatus.

Procedure D. Cleavage of the cross-coupled product from the solid support

1% cross linked-resin

Resin-bound styryl, biaryl or heterobiaryl carboxylic acid (1% cross-linked, theoretical loading 0.8 mmole / g, 0.125 g) was swollen in THF (2.1 mL) for 30 min, a solution of lithium hydroxide monohydrate (0.5 mmole) in MeOH:H_2O (2:1, 1 mL) was added and the mixture was refluxed overnight. After cooling to rt, a solution of 1 M HCl (2 mL) was added and the whole was stirred (10 min) and subjected to filtration (fritted glass funnel). The resin was successively washed three times with THF, three times with THF:1 M HCl (1:1) and three times with ether, and the filtrate was repeatedly extracted with EtOAc. The combined organic

extract was washed with water and brine, dried (Na_2SO_4), and evaporated to dryness. The reaction composition of the crude was analysed by HPLC prior to purification on silica gel to give the cross-coupled product. The extent of the cleavage was established by monitoring the ester carbonyl absorption in the IR spectrum.

2% cross-linked resin

Resin-bound styryl, biaryl or heterobiaryl carboxylic acid (2% cross-linked, theoretical loading 1.5 mmole / g, 0.10 g) was swollen in THF (1.7 mL) for 30 min, a solution of lithium hydroxide monohydrate (0.75 mmole) in MeOH:H_2O (2:1, 1 mL) was added and the mixture was refluxed overnight. After cooling to rt, a solution of 1 M HCl (3 mL) was added and the whole was stirred (10 min) and subjected to filtration (fritted glass funnel). The resin was successively washed three times with THF, three times with THF:1 M HCl (1:1) and three times with ether, and the filtrate was repeatedly extracted with EtOAc. The combined organic extract was washed with water and brine, dried (Na_2SO_4), and evaporated to dryness. The reaction composition of the crude was analysed by HPLC prior to purification on silica gel to give the cross-coupled product. The extent of the cleavage was established by monitoring the ester carbonyl absorption in the IR spectrum.

Procedure E. Preparation of resin-bound (tributylstannyl)benzoic acid

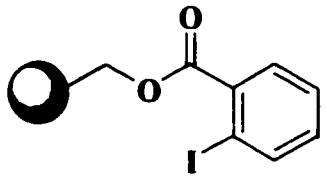
Resin-bound iodobenzoic acid (1% cross-linked, theoretical loading 0.8 mmole / g, 0.375 g) was swollen in anhydrous DMF (12.5 mL) and the system flushed with argon (30 min). $Pd(PPh_3)_4$ (0.021 mmol) was added and the reaction mixture was stirred (15 min). Bis(tributyltin) (0.45 mmole) was added and the reaction mixture was stirred at 60°C for 24h.

The reaction mixture was cooled to rt, treated with aq. satd. NH_4Cl solution (12.5 mL) and stirred for 10 min. The resin was removed by filtration (fritted glass funnel) and washed successively once with DMF, twice with DMF:H_2O (1:1), twice with 0.3 M HCl, three times with H_2O, once with DMF, twice with EtOAc, twice with EtOAc:MeOH (1:1) and three times with MeOH, and dried overnight in an Abderhalden apparatus. The resin-bound aryl stannane was used directly in the cross coupling without being cleaved to determine its loading.

Procedure F. Stille cross coupling reaction of resin-bound (tributylstannyl)benzoic acid with organohalide

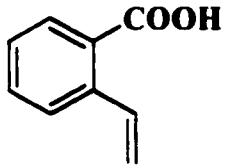
Resin-bound (tributylstannyl)benzoic acid (1% cross-linked, loading max 0.8 mmole / g, 0.162 g) was swollen in anhydrous DMF (5.4 mL) and the system was flushed with argon (30 min). $Pd(PPh_3)_4$ (0.013 mmole) was added and the reaction mixture was stirred for 10 min at rt. Freshly distilled halobenzene (0.26 mmole) was added and the reaction mixture was stirred at 60°C for 48 h. The reaction mixture was cooled to rt, treated with aq. satd. NH_4Cl solution (5.5 mL) and stirred for 10 min. The resin was removed by filtration (fritted glass funnel) and washed successively once with DMF, twice with DMF:H_2O (1:1), twice with 0.3 M HCl, three times with H_2O, once with DMF, twice with EtOAc, twice with EtOAc:MeOH (1:1) and three times with MeOH, and dried overnight in an Abderhalden apparatus. The cleavage of the cross-coupled product was done according to general Procedure D. The reaction composition of the resulting crude was analysed by HPLC.

Resin-bound 2-iodobenzoic acid (1.107)



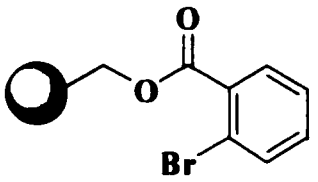
According to General Procedure A, the Merrifield resin **1.2** (2% cross-linked, loading 2 mmole / g, 1.5 g, 3 mmole) was swollen in anhydrous DMF (15 mL) and treated with cesium carbonate (2.93 g, 9 mmole), potassium iodide (0.25 g, 1.5 mmole) and 2-iodobenzoic acid 98 % (1.139 g, 4.5 mmole). The resulting resin was collected by filtration, washed and dried to afford **1.107**, IR (KBr) 1712 cm^{-1} (ester band). The loading capacity of **1.107** was determined according to General Procedure B. **1.107** (0.152 g) was swollen in THF (2.5 mL) and treated with a solution of lithium hydroxide monohydrate (0.063 g, 1.5 mmole) in MeOH:H_2O (2:1, 1.5 mL). After acidification, filtration and washing, the filtrate was worked-up and purified on silica gel (80:19.5:0.5 hexane:EtOAc:AcOH) to give 2-iodobenzoic acid (0.0517 g) showing a loading of **1.107** of 1.37 mmole / g.

2-Vinylbenzoic acid (1.108)



Resin-bound 2-iodobenzoic acid **1.107** (2% cross-linked, loading 1.37 mmole / g, 0.146 g, 0.20 mmole) was swollen in anhydrous DMF (5 mL) and the system was flushed with argon (30 min). Tri-2-furylphosphine (0.0047g, 0.020 mmole) and Pd_2dba_3 (0.0092 g, 0.010 mmole) were added and the reaction mixture was stirred for 10 min at rt. Tributyl(vinyl)tin 97% (0.196 g, 0.18 mL, 0.60 mmole) was added and the reaction mixture was stirred at 60°C for 24 h. The reaction mixture was cooled to rt, treated with aq. satd. NH_4Cl solution (8.3 mL) and stirred for 10 min. The resin was removed by filtration (fritted glass funnel) and washed successively once with DMF, twice with DMF:H_2O (1:1), twice with 0.3 M HCl, three times with H_2O, once with

DMF, twice with EtOAc, twice with EtOAc:MeOH (1:1) and three times with MeOH, and dried overnight in an Abderhalden apparatus. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.107 g) was swollen in THF (1.8 mL) and treated with a solution of lithium hydroxide monohydrate (0.031 g, 0.733 mmole) in MeOH:H_2O (2:1, 1.1 mL). After acidification, filtration and washing, the filtrate was worked-up. The crude obtained was analysed by HPLC and purified on silica gel (80:19.5:0.5 hexane:EtOAc:AcOH) to give 2-vinylbenzoic acid **1.108** (0.0154 g, loading: 0.972 mmole / g, 71%) as a colourless solid : Beilstein Registry # [1931493]; mp 93-95 °C (Lit.[206] mp 94-95 °C (EtOH/H_2O)); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.05 (d, J = 8.0 Hz, 1H), 7.63-7.33 (m, 4H), 5.67 (d, J = 17.2 Hz, 1H), 5.38 (d, J = 10.6 Hz, 1H).

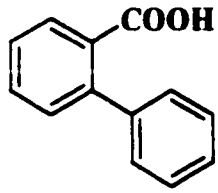


Resin-bound 2-bromobenzoic acid (1.114)

According to General Procedure A, the Merrifield resin **1.2** (2% cross-linked, loading 2 mmole /g, 1.5 g, 3 mmole) was swollen in anhydrous DMF (15 mL) and treated with cesium carbonate (2.93 g, 9 mmole), potassium iodide (0.25 g, 1.5 mmole) and 2-bromobenzoic acid 97% (0.933 g, 4.5 mmole). The resulting resin was collected by filtration, washed and dried to afford **1.114**, IR (KBr) 1724 cm^{-1} (ester band). The loading capacity of **1.114** was determined according to General Procedure B. **1.114** (0.102 g) was swollen in THF (1.7 mL) and treated with a solution of lithium hydroxide monohydrate (0.043 g, 1.02 mmole) in MeOH:H_2O (2:1, 1.0 mL). After acidification, filtration and washing, the filtrate was worked-up and purified on

silica gel (80:19.5:0.5 hexane:EtOAc:AcOH) to give 2-bromobenzoic acid (0.0304 g) showing a loading of **1.114** of 1.48 mmole / g.

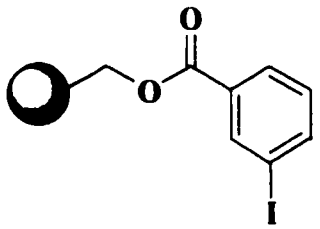
Biphenyl-2-carboxylic acid (1.115)



According to General Procedure C, resin-bound 2-bromobenzoic acid **1.114** (2% cross-linked, loading 1.48 mmole / g, 0.101 g, 0.150 mmole) was swollen in anhydrous DMF (3.7 mL) and coupled with tributylphenyltin 97% (0.170 g, 0.15 mL, 0.45 mmole) in the presence of $Pd(PPh_3)_4$ (0.0087 g, 0.0075 mmole). After 24 h, the reaction mixture was cooled to rt. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.0908 g) was swollen in THF (1.5 mL) and treated with a solution of lithium hydroxide monohydrate (0.028 g, 0.67 mmole) in MeOH:H_2O (2:1, 0.9 mL) for 42 h. After acidification, filtration and washing, the filtrate was worked-up. The crude obtained was analysed by HPLC and purified on silica gel (90:9.5:0.5 hexane:EtOAc:AcOH) to give biphenyl-2-carboxylic acid **1.115** (0.0254 g, loading: 1.41 mmole / g, >95%) as a yellow solid : Beilstein Registry # [974075]; mp 110-112 °C (Lit.[207] mp 111-111.5°C (hexane/acetone 9:1); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.95 (d, J = 8.0 Hz, 1H), 7.59 (m, 1H), 7.45-7.35 (m, 7H); MS (EI (70 eV)) m/z (rel intensity) 198 (M^+, 100); HRMS *m/e* calcd for $C_{13}H_{10}O_2$: 198.0681, found 198.0681.

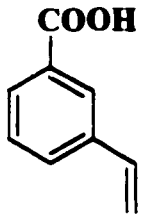
According to General Procedure C, resin-bound 2-iodobenzoic acid **1.107** (2% cross-linked, loading 1.37 mmole / g, 0.109 g, 0.149 mmole) was swollen in anhydrous DMF (3.6 mL) and

coupled with tributylphenyltin 97% (0.170 g, 0.15 mL, 0.45 mmole) in the presence of $Pd(PPh_3)_4$ (0.0087 g, 0.0075 mmole). After 24 h, the reaction mixture was cooled to rt. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.0898 g) was swollen in THF (1.5 mL) and treated with a solution of lithium hydroxide monohydrate (0.026 g, 0.61 mmole) in MeOH:H_2O (2:1, 0.9 mL) for 42h. After acidification, filtration and washing, the filtrate was worked-up. The crude obtained was analysed by HPLC and purified on silica gel (90:9.5:0.5 hexane:EtOAc:AcOH) to give biphenyl-2-carboxylic acid **1.115** (0.0215 g, loading: 1.21 mmole / g, 88%) as a yellow solid.



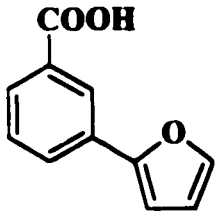
Resin-bound 3-iodobenzoic acid (1.109)

According to General Procedure A, the Merrifield resin **1.2** (1% cross-linked, loading 1 mmole / g, 3.07 g, 3.07 mmole) was swollen in anhydrous DMF (30 mL) and treated with cesium carbonate (3.01 g, 9.21 mmole), potassium iodide (0.26 g, 1.54 mmole) and 3-iodobenzoic acid 98% (1.17 g, 4.6 mmole). The resulting resin was collected by filtration, washed and dried to afford **1.109**, IR (KBr) 1719 cm^{-1} (ester band). The loading capacity of resin **1.109** was determined according to General Procedure B. **1.109** (0.153 g) was swollen in THF (2.5 mL) and treated with a solution of lithium hydroxide monohydrate (0.032 g, 0.77 mmole) in MeOH:H_2O (2:1, 1.5 mL). After acidification, filtration and washing, the filtrate was worked-up and purified on silica gel (80:19.5:0.5 hexane:EtOAc:AcOH) to give 3-iodobenzoic acid (0.0310 g) showing a loading of **1.109** of 0.82 mmole / g.



3-Vinylbenzoic acid (1.110)

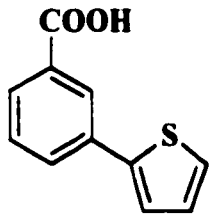
According to General Procedure C, resin-bound 3-iodobenzoic acid **1.109** (1% cross-linked, loading 0.82 mmole / g, 0.146 g, 0.12 mmole) was swollen in anhydrous DMF (5 mL) and coupled with tributyl(vinyl)tin 97% (0.118 g, 0.109 mL, 0.36 mmole) in the presence of $Pd(PPh_3)_4$ (0.0069 g, 0.006 mmole). After 24 h, the reaction mixture was cooled to rt. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.123 g) was swollen in THF (2.1 mL) and treated with a solution of lithium hydroxide monohydrate (0.021 g, 0.504 mmole) in MeOH:H_2O (2:1, 1.2 mL) overnight. After acidification, filtration and washing, the filtrate was worked-up. The crude obtained was analysed by HPLC and purified on silica gel (95:4.5:0.5 hexane:EtOAc:AcOH) to give 3-vinylbenzoic acid **1.110** (0.0129 g, loading: 0.71 mmole / g, 87%) as a colourless solid : Beilstein Registry # [1931138]; mp 93-95 °C (Lit.[208] mp 92-94 °C (water)); ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.62 (m, 2H), 6.76 (dd, J = 17.5, 11.0 Hz, 1H), 5.85 (d, J = 17.5 Hz, 1H), 5.35 (d, J = 11.0 Hz, 1H).



3-(2-Furanyl)benzoic acid (1.124)

According to General Procedure C, resin-bound 3-iodobenzoic acid **1.109** (1% cross-linked, loading 0.82 mmole / g, 0.146 g, 0.12 mmole) was swollen in anhydrous DMF (4.9 mL) and coupled with 2-(tributylstannyl)furan 97% (0.132 g, 0.12 mL, 0.36 mmole) in the presence of $Pd(PPh_3)_4$

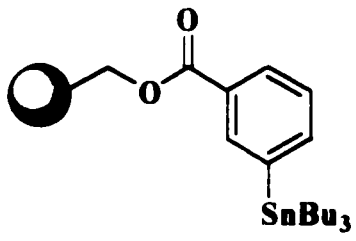
(0.0069 g, 0.006 mmole). After 24 h, the reaction mixture was cooled to rt and acidified. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.130 g) was swollen in THF (2.2 mL) and treated with a solution of lithium hydroxide monohydrate (0.022 g, 0.53 mmole) in MeOH:H_2O (2:1, 1.3 mL) overnight. After acidification, filtration and washing, the filtrate was worked-up. The crude was analysed by HPLC and purified on silica gel (90:9.5:0.5 hexane:EtOAc:AcOH) to give 3-(2-furanyl)benzoic acid **1.124** (0.0171 g, loading: 0.70 mmole / g, 86%) as colourless solid :Beilstein Registry # [1368131]; mp 154-156 °C (Lit.[209] mp 158 °C (water:EtOH(1 :1)); ^{1}H NMR (200 MHz, $CDCl_3$) δ 11.65 (bs, 1H), 8.39 (s, 1H), 7.99 (d, J = 7.3 Hz, 1H), 7.86 (d, J = 7.9 Hz, 1H), 7.42 (m, 2H), 6.75 (m, 1H), 6.50 (m, 1H); MS (EI (70 eV)) m/z (rel intensity) 188 (M^+, 100) ; HRMS *m/e* calcd for $C_{11}H_8O_3$: 188.0473, found 188.0468.



3-(2-Thienyl)benzoic acid (1.125)

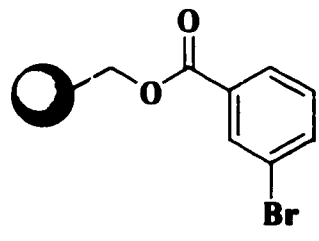
According to General Procedure C, resin-bound 3-iodobenzoic acid **1.109** (1% cross-linked, loading 0.82 mmole / g, 0.146 g, 0.12 mmole) was swollen in anhydrous DMF (4.9 mL) and coupled with 2-(tributylstannyl)thiophene 95% (0.141 g, 0.12 mL, 0.36 mmole) in the presence of $Pd(PPh_3)_4$ (0.0069 g, 0.006 mmole). After 24 h, the reaction mixture was cooled to rt. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.127 g) was swollen in THF (2.1 mL) and treated with a solution of lithium hydroxide monohydrate (0.022 g, 0.52 mmole) in

MeOH:H_2O (2:1, 1.3 mL) overnight. After acidification, filtration and washing, the filtrate was worked-up. The crude obtained was analysed by HPLC and purified on silica gel (98:1.5:0.5 hexane:EtOAc:AcOH) to give 3-(2-thienyl)benzoic acid **1.125** (0.0189 g, loading: 0.73 mmole / g, 89%) as a colourless solid : Beilstein Registry # [1309222]; mp 171-172 °C (Lit.[210] mp 173-175 °C (EtOAc)); ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.11 (d, J = 7.3 Hz, 1H), 8.01 (d, J = 7.7 Hz, 1H), 7.53-7.38 (m, 2H), 7.33 (d, J = 5.5 Hz, 1H), 7.11 (m, 1H); MS (EI (70 eV)) m/z (rel intensity) 204 (M^+, 4), 146 (24), 144 (38), 123 (22), 121 (73), 119 (100); HRMS *m/e* calcd for $C_{11}H_8O_2S$: 204.0245, found 204.0246.



Resin-bound 3-(tributylstannyl)benzoic acid (1.134)

According to General Procedure E, resin-bound 3-iodobenzoic acid **1.109** (1% cross-linked, loading 0.82 mmole / g, 0.366 g, 0.30 mmol) was swollen in anhydrous DMF (12.2 mL) and coupled with bis(tributyltin) 95% (0.275 g, 0.24 mL, 0.45 mmole) in the presence of $Pd(PPh_3)_4$ (0.024 g, 0.021 mmole). After 24h, the reaction mixture was cooled to rt and acidified. The resin was removed by filtration, washed and dried.

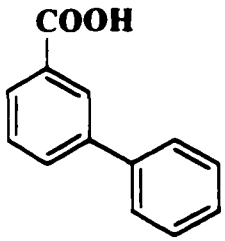


Resin-bound 3-bromobenzoic acid (1.116)

According to General Procedure A, the Merrifield resin **1.2** (1% cross-linked, loading 1 mmole / g, 1.5 g, 1.5 mmole) was swollen in anhydrous DMF (15 mL) and treated with cesium

carbonate (1.47 g, 4.5 mmole), potassium iodide (0.125 g, 0.75 mmole) and 3-bromobenzoic acid 99% (0.457 g, 2.25 mmole). The resulting resin was collected by filtration, washed and dried to afford **1.116**, IR (KBr) 1713 cm^{-1} (ester band). The loading capacity of **1.116** was determined according to General Procedure B. **1.116** (0.200 g) was swollen in THF (3.3 mL) and treated with a solution of lithium hydroxide monohydrate (0.042 g, 1.00 mmole) in MeOH:H_2O (2:1, 2 mL). After acidification, filtration and washing, the filtrate was worked-up and purified on silica gel (80:19.5:0.5 hexane:EtOAc:AcOH) to give 3-bromobenzoic acid (0.0346 g) showing a loading of **1.116** of 0.86 mmole / g.

Biphenyl-3-carboxylic acid (1.117)



According to General Procedure C, resin-bound 3-bromobenzoic acid **1.116** (1% cross-linked, loading 0.86 mmole / g, 0.139 g, 0.12 mmole) was swollen in anhydrous DMF (4.6 mL) and coupled with tributylphenyltin 97% (0.136 g, 0.12 mL, 0.36 mmole) in the presence of $Pd(PPh_3)_4$ (0.0069 g, 0.006 mmole). After 24 h, the reaction mixture was cooled to rt. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.125 g) was swollen in THF (2.1 mL) and treated with a solution of lithium hydroxide monohydrate (0.023 g, 0.54 mmole) in MeOH:H_2O (2:1, 1.2 mL) overnight. After acidification, filtration and washing, the filtrate was worked-up and analysed by HPLC and purified on silica gel (98:1.5:0.5 hexane:EtOAc:AcOH) to give biphenyl-3-carboxylic acid **1.117** (0.0201 g, loading: 0.81 mmole / g, 94%) as a colourless solid : Beilstein Registry # [1868625]; mp 161-164 °C (Lit.[211,212] mp 162-163 °C (EtOH)); ^1H NMR (200 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.08 (dd, J =

7.3, 1 Hz, 1H), 7.84 (dd, J = 7.0, 1.4 Hz, 1 H), 7.66-7.34 (m, 6H); MS (EI (70 eV)) m/z (rel intensity) 198 (M^+, 100); HRMS *m/e* calcd for $C_{13}H_{10}O_2$: 198.0681, found 198.0687.

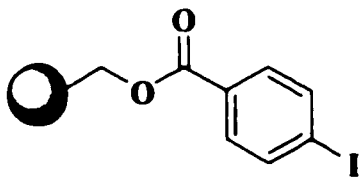
According to General Procedure C, resin-bound 3-iodobenzoic acid **1.109** (1% cross-linked, loading 0.82 mmole / g, 0.146 g, 0.12 mmole) was swollen in anhydrous DMF (4.9 mL) and coupled with tributylphenyltin 97% (0.136 g, 0.12 mL, 0.36 mmole) in the presence of $Pd(PPh_3)_4$ (0.0069 g, 0.006 mmole). After 24 h, the reaction mixture was cooled to rt. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.124 g) was swollen in THF (2.1 mL) and treated with a solution of lithium hydroxide monohydrate (0.021 g, 0.51 mmole) in MeOH:H_2O (2:1, 1.2 mL) overnight. After acidification, filtration and washing, the filtrate was worked-up. The crude obtained was analysed by HPLC and purified on silica gel (98:1.5:0.5 hexane:EtOAc:AcOH) to give biphenyl-3-carboxylic acid **1.117** (0.0185 g, loading: 0.75 mmole / g, 91%) as a colourless solid.

According to General Procedure F, resin-bound 3-(tributylstannyl)benzoic acid **1.134** (1% cross-linked, loading max 0.82 mmole / g, 0.1611 g, 0.132 mmole) was swollen in anhydrous DMF (5.4 mL) and coupled with freshly distilled bromobenzene (0.0415 g, 0.028 mL, 0.264 mmole) in the presence of $Pd(PPh_3)_4$ (0.0153 g, 0.0132 mmole). After 48 h, the reaction mixture was cooled to rt. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.139 g) was swollen in THF (2.3 mL) and treated with a solution of lithium hydroxide monohydrate (0.024 g, 0.57 mmole) in MeOH:H_2O (2:1, 1.4 mL) overnight. After

acidification, filtration and washing, the filtrate was worked-up. The crude obtained was analysed by HPLC showing a purity in biphenyl-3-carboxylic acid **1.117** of 35%.

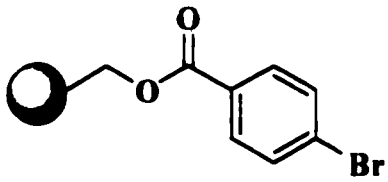
According to General Procedure F, resin-bound 3-(tributylstannyl)benzoic acid **1.134** (1% cross-linked, loading max 0.82 mmole / g, 0.1611 g, 0.132 mmole) was swollen in anhydrous DMF (5.4 mL) and coupled with freshly distilled iodobenzene (0.054 g, 0.029 mL, 0.264 mmole) in the presence of $Pd(PPh_3)_4$ (0.0152 g, 0.0132 mmole). After 48 h, the reaction mixture was cooled to rt. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.143 g) was swollen in THF (2.4 mL) and treated with a solution of lithium hydroxide monohydrate (0.024 g, 0.59 mmole) in MeOH:H_2O (2:1, 1.4 mL) overnight. After acidification, filtration and washing, the filtrate was worked-up. The crude obtained was analysed by HPLC showing a purity in biphenyl-3-carboxylic acid **1.117** of 66%.

Resin-bound 4-iodobenzoic acid (1.113)



According to General Procedure A, the Merrifield resin **1.2** (1% cross-linked, loading 1 mmole / g, 2.00 g, 2.0 mmole) was swollen in anhydrous DMF (20 mL) and treated with cesium carbonate (1.95 g, 6.0 mmole), potassium iodide (0.17 g, 1.0 mmole) and 4-iodobenzoic acid 98% (0.76 g, 3 mmole). The resulting resin was collected by filtration, washed and dried to afford **1.113**, IR (KBr) 1720 cm^{-1} (ester band). The loading capacity of **1.113** was determined according to General Procedure B. **1.113** (0.135 g) was swollen in THF (2.3 mL) and treated with a solution of lithium hydroxide monohydrate (0.028 g, 0.675 mmole) in MeOH:H_2O (2:1,

1.4 mL). After acidification, filtration and washing, the filtrate was worked-up and purified on silica gel (80:19.5:0.5 hexane:EtOAc:AcOH) to give 4-iodobenzoic acid (0.0261 g) showing a loading of **1.113** of 0.78 mmole / g.



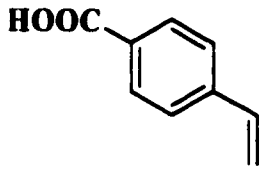
Resin-bound 4-bromobenzoic acid (Resin 1.111)

According to General Procedure A, the Merrifield resin **1.2** (2% cross-linked, loading 2 mmole / g, 1.5 g, 3 mmole) was swollen in anhydrous DMF (15 mL) and treated with cesium carbonate (2.93 g, 9 mmole), potassium iodide (0.25 g, 1.5 mmole) and 4-bromobenzoic acid 98% (0.923 g, 4.5 mmole). The resulting resin was collected by filtration, washed and dried to afford **1.111**, IR (KBr) 1718 cm^{-1} (ester band). The loading capacity of **1.111** was determined according to General Procedure B. **1.111** (0.096 g) was swollen in THF (1.6 mL) and treated with a solution of lithium hydroxide monohydrate (0.040 g, 0.96 mmole) in MeOH:H_2O (2:1, 1.0 mL). After acidification, filtration and washing, the filtrate was worked-up and purified on silica gel (80:19.5:0.5 hexane:EtOAc:AcOH) to give 4-bromobenzoic acid (0.0284 g) showing a loading of **1.111** of 1.47 mmole / g.

According to General Procedure A, the Merrifield resin **1.2** (1% cross-linked, loading 1 mmole / g, 3.0 g, 3 mmole) was swollen in anhydrous DMF (30 mL) and treated with cesium carbonate (2.93 g, 9 mmole), potassium iodide (0.25 g, 1.5 mmole) and 4-bromobenzoic acid 98% (0.923 g, 4.5 mmole). The resulting resin was collected by filtration, washed and dried to afford **1.111**, IR (KBr) 1718 cm^{-1} (ester band). The loading capacity of **1.111** was determined according to General Procedure B. **1.111** (0.639 g) was swollen in THF (10.7 mL) and treated

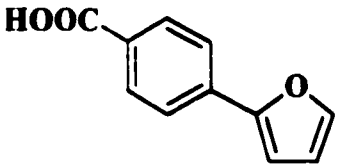
with a solution of lithium hydroxide monohydrate (0.134 g, 3.2 mmole) in MeOH:H_2O (2:1, 6.4 mL). After acidification, filtration and washing, the filtrate was worked-up and purified on silica gel (80:19.5:0.5 hexane:EtOAc:AcOH) to give 4-bromobenzoic acid (0.1168 g) showing a loading of **1.111** of 0.91 mmole / g.

4-Vinylbenzoic acid (1.112)



According to General Procedure C, resin-bound 4-bromobenzoic acid **1.111** (2% cross-linked, loading 1.47 mmole / g, 0.102 g, 0.150 mmole) was swollen in anhydrous DMF (3.4 mL) and coupled with tributyl(vinyl)tin 97% (0.147 g, 0.14 mL, 0.45 mmole) in the presence of $Pd(PPh_3)_4$ (0.0087 g, 0.0075 mmole). After 24 h, the reaction mixture was cooled to rt. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.0891 g) was swollen in THF (1.5 mL) and treated with a solution of lithium hydroxide monohydrate (0.027 g, 0.66 mmole) in MeOH:H_2O (2:1, 0.9 mL) overnight. After acidification, filtration and washing, the filtrate was worked-up. The crude obtained was analysed by HPLC and purified on silica gel (90:9.5:0.5 hexane:EtOAc:AcOH) to give 4-vinylbenzoic acid **1.112** (0.0170 g, loading: 1.29 mmole / g, 88%) as a colourless solid : Beilstein Registry # [2041130] mp 142-145 °C (Lit.[208] mp 144°C (water)); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.09 (d, J = 8.2 Hz, 2H), 7.43 (d, J = 8.5 Hz, 2H), 6.79 (dd, J = 17.6, 10.9 Hz, 1H), 5.89 (d, J = 17.6 Hz, 1H), 5.42 (d, J = 10.9 Hz, 1H); MS (EI (70 eV)) m/z (rel intensity) 148 (M^+, 24), 131 (22), 103 (16), 89 (28), 88 (51), 86 (79), 84 (100); HRMS *m/e* calcd for $C_9H_8O_2$: 148.0524, found 148.0528.

According to General Procedure C, resin-bound 4-iodobenzoic acid **1.113** (1% cross-linked, loading 0.78 mmole / g, 0.154 g, 0.12 mmole) was swollen in anhydrous DMF (5.1 mL) and coupled with tributyl(vinyl)tin 97% (0.118 g, 0.109 mL, 0.36 mmole) in the presence of $Pd(PPh_3)_4$ (0.0069 g, 0.006 mmole). After 24 h, the reaction mixture was cooled to rt. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.132 g) was swollen in THF (2.2 mL) for 30 min and treated with a solution of lithium hydroxide monohydrate (0.022 g, 0.515 mmole) in MeOH:H_2O (2:1, 1.3 mL) overnight. After acidification, filtration and washing, the filtrate was worked-up. The crude obtained was analysed by HPLC and purified on silica gel (90:9.5:0.5 hexane:EtOAc:AcOH) to give 4-vinylbenzoic acid **1.112** (0.0147 g, loading: 0.75 mmole / g, >95%) as a colourless solid.

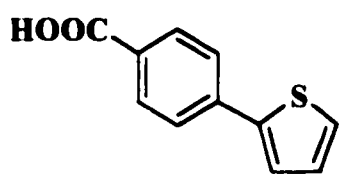


4-(2-Furanyl)benzoic acid (1.126)

According to General Procedure C, resin-bound 4-bromobenzoic acid **1.111** (2% cross-linked, loading 1.47 mmole / g, 0.102 g, 0.150 mmole) was swollen in anhydrous DMF (3.4 mL) and coupled with 2-(tributylstannyl)furan 97% (0.166g, 0.147 mL, 0.45 mmole) in the presence of $Pd(PPh_3)_4$ (0.0086 g, 0.0075 mmole). After 24 h, the reaction mixture was cooled to rt. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.084 g) was swollen in THF (1.4 mL) and treated with a solution of lithium hydroxide monohydrate (0.026 g, 0.62 mmole) in MeOH:H_2O (2:1, 0.8 mL) overnight. After acidification, filtration and washing, the filtrate was worked-up. The crude obtained was

analysed by HPLC and purified on silica gel (85:14.5:0.5 hexane:EtOAc:AcOH) to give 4-(2-furanyl) benzoic acid **1.126** (0.0195 g, loading: 1.23 mmole / g, 84%) as a colourless solid : Beilstein Registry # [1309230]; mp 221-223 °C (water:EtOH (1 : 1)) (Lit.[213,214] mp 226 °C); ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.12 (d, J = 8.3 Hz, 2H), 7.76 (d, J = 8.3 Hz, 2H), 7.54 (d, J = 1.8 Hz, 1H), 6.82 (d, J = 3.2 Hz, 1H), 6.52 (dd, J = 3.2, 1.8 Hz, 1H); MS (EI (70 eV)) m/z (rel intensity) 188 (M^+, 1), 170 (5), 135 (17), 133 (18), 121 (31), 119 (35), 99 (55), 98 (17), 97 (100); HRMS *m/e* calcd for $C_{11}H_8O_3$: 188.0473, found 188.0471.

According to General Procedure C, resin-bound 4-iodobenzoic acid **1.113** (1% cross-linked, loading 0.78 mmole / g, 0.154 g, 0.12 mmole) was swollen in anhydrous DMF (5.1 mL) and coupled with 2-(tributylstannyl)furan 97% (0.132 g, 0.12 mL, 0.36 mmole) in the presence of $Pd(PPh_3)_4$ (0.0069 g, 0.006 mmole). After 24 h, the reaction mixture was cooled to rt. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.134 g) was swollen in THF (2.2 mL) and treated with a solution of lithium hydroxide monohydrate (0.022 g, 0.523 mmole) in MeOH:H_2O (2:1, 1.3 mL) overnight. After acidification, filtration and washing, the filtrate was worked-up. The crude obtained was analysed by HPLC and purified on silica gel (85:14.5:0.5 hexane:EtOAc:AcOH) to give 4-(2-furanyl)benzoic acid **1.126** (0.0158 g, loading: 0.625 mmole / g, 80%) as a colourless solid.

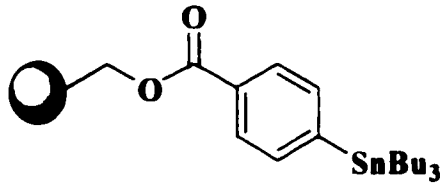


4-(2-Thienyl) benzoic acid (1.127)

According to General Procedure C, resin-bound 4-bromobenzoic acid **1.111** (2% cross-linked, loading 1.47 mmole / g, 0.102 g, 0.150 mmole) was swollen in anhydrous DMF (3.4 mL) and coupled with 2-(tributylstannyl)thiophene 95% (0.177g, 0.15 mL, 0.45 mmole) in the presence of $Pd(PPh_3)_4$ (0.0086 g, 0.0075 mmole). After 24 h, the reaction mixture was cooled to rt. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.089 g) was swollen in THF (1.5 mL) and treated with a solution of lithium hydroxide monohydrate (0.027 g, 0.66 mmole) in MeOH:H_2O (2:1, 0.9 mL) overnight. After acidification, filtration and washing, the filtrate was worked-up. The crude obtained was analysed by HPLC and purified on silica gel (95:4.5:0.5 hexane:EtOAc:AcOH) to give 4-(2-thienyl) benzoic acid **1.127** (0.0244 g, loading: 1.34 mmole / g, 91%) as a colourless solid : Beilstein Registry # [1309231]; mp 244-247 °C (Lit.[210] mp 247-249 °C (EtOAc)); ^{1}H NMR (250 MHz, DMSO-d_6) δ 13.01 (bs, 1H), 7.96 (d, J = 8.6 Hz, 2H), 7.85 (d, J = 8.6 Hz, 2H), 7.78-7.61 (m, 2H), 7.16 (dd, J = 4.9, 3.5 Hz, 1H); MS (EI (70 eV)) m/z (rel intensity) 204 (M^+, 100); HRMS *m/e* calcd for $C_{11}H_8O_2S$: 204.0245, found 204.0247.

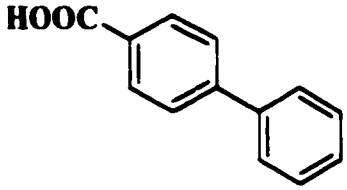
According to General Procedure C, resin-bound 4-iodobenzoic acid **1.113** (1% cross-linked, loading 0.78 mmole / g, 0.154 g, 0.12 mmole) was swollen in anhydrous DMF (5.1 mL) and coupled with 2-(tributylstannyl)thiophene 95% (0.141 g, 0.12 mL, 0.36 mmole) in the presence of $Pd(PPh_3)_4$ (0.0069 g, 0.006 mmole). After 24 h, the reaction mixture was cooled to rt. The resin was removed by filtration, washed and dried. The cleavage from the solid

support was done according to General Procedure D. The resulting resin (0.132 g) was swollen in THF (2.2 mL) and treated with a solution of lithium hydroxide monohydrate (0.022 g, 0.52 mmole) in MeOH:H_2O (2:1, 1.3 mL) overnight. After acidification, filtration and washing, the filtrate was worked-up. The crude obtained was analysed by HPLC and purified on silica gel (95:4.5:0.5 hexane:EtOAc:AcOH) to give 4-(2-thienyl)benzoic acid **1.127** (0.0196 g, loading: 0.726 mmole / g, 93%) as a colourless solid.



Resin-bound 4-(tributylstannyl)benzoic acid (1.135)

According to General Procedure E, resin-bound 4-iodobenzoic acid **1.113** (1% cross-linked, loading 0.78 mmole / g, 0.385 g, 0.30 mmol) was swollen in anhydrous DMF (12.8 mL) and coupled with bis(tributyltin) 95% (0.275 g, 0.24 mL, 0.45 mmole) in the presence of $Pd(PPh_3)_4$ (0.024 g, 0.021 mmol). After 24h, the reaction mixture was cooled to rt and acidified. The resin was removed by filtration, washed and dried.



Biphenyl-4-carboxylic acid (1.118)

According to General Procedure C, resin-bound 4-bromobenzoic acid **1.111** (1% cross-linked, loading 0.91 mmole / g, 0.132 g, 0.12 mmole) was swollen in anhydrous DMF (4.4 mL) and treated with tributylphenyltin 97% (0.136 g, 0.12 mL, 0.36 mmole) in the presence of $Pd(PPh_3)_4$ (0.0069 g, 0.006 mmole). After 24 h, the reaction mixture was cooled to rt. The resin was removed by filtration, washed and dried. The cleavage from the solid

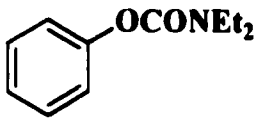
support was done according to General Procedure D. The resulting resin (0.110 g) was swollen in THF (1.8 mL) and treated with a solution of lithium hydroxide monohydrate (0.021 g, 0.50 mmole) in MeOH:H_2O (2:1, 1.1 mL) overnight. After acidification, filtration and washing, the filtrate was worked-up. The crude obtained was analysed by HPLC and purified on silica gel (95:4.5:0.5 hexane:EtOAc:AcOH) to give biphenyl-4-carboxylic acid **1.118** (0.0186 g, loading: 0.85 mmole / g, 93%) as a colourless solid : Beilstein Registry # [973519]; mp 220-221 °C (Lit.[215] mp 218-220 °C (EtOH)); ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.12 (d, J = 8.4 Hz, 2H), 7.67-7.62 (m, 4H), 7.50-7.31 (m, 3H); MS (EI (70 eV)) m/z (rel intensity) 198 (M^+, 100); HRMS *m/e* calcd for $C_{13}H_{10}O_2$: 198.0681, found 198.0688.

According to General Procedure C, resin-bound 4-iodobenzoic acid **1.113** (1% cross-linked, loading 0.78 mmole / g, 0.193 g, 0.151 mmole) was swollen in anhydrous DMF (6.4 mL) and coupled with tributylphenyltin 97% (0.171 g, 0.152 mL, 0.45 mmole) in the presence of $Pd(PPh_3)_4$ (0.0087 g, 0.0076 mmole). After 24 h, the reaction mixture was cooled to rt. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.170 g) was swollen in THF (2.8 mL) and treated with a solution of lithium hydroxide monohydrate (0.028 g, 0.67 mmole) in MeOH:H_2O (2:1, 1.7 mL) overnight. After acidification, filtration and washing, the filtrate was worked-up. The crude obtained was analysed by HPLC and purified on silica gel (95:4.5:0.5 hexane:EtOAc:AcOH) to give biphenyl-4-carboxylic acid **1.118** (0.0256 g, loading: 0.76 mmole / g, >95%) as a colourless solid.

According to General Procedure F, resin-bound 4-(tributylstannyl)benzoic acid **1.135** (1% cross-linked, loading max 0.78 mmole / g, 0.168 g, 0.131 mmole) was swollen in anhydrous DMF (5.6 mL) and coupled with freshly distilled bromobenzene (0.0411 g, 0.028 mL, 0.262 mmole) in the presence of $Pd(PPh_3)_4$ (0.0151 g, 0.0131 mmole). After 48 h, the reaction mixture was cooled to rt. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.138 g) was swollen in THF (2.3 mL) and treated with a solution of lithium hydroxide monohydrate (0.023 g, 0.538 mmole) in MeOH:H_2O (2:1, 1.4 mL) overnight. After acidification, filtration and washing, the filtrate was worked-up. The crude obtained was analysed by HPLC showing a purity in biphenyl-4-carboxylic acid **1.118** of 74%.

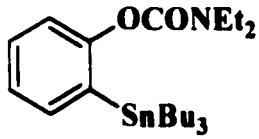
According to General Procedure F, resin-bound 4-(tributylstannyl)benzoic acid **1.135** (1% cross-linked, loading max 0.78 mmole / g, 0.169 g, 0.132 mmole) was swollen in anhydrous DMF (5.6 mL) and coupled with freshly distilled iodobenzene (0.054 g, 0.029 mL, 0.264 mmole) in the presence of $Pd(PPh_3)_4$ (0.0153 g, 0.0132 mmole). After 48 h, the reaction mixture was cooled to rt. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.130 g) was swollen in THF (2.2 mL) and treated with a solution of lithium hydroxide monohydrate (0.021 g, 0.51 mmole) in MeOH:H_2O (2:1, 1.3 mL) overnight. After acidification, filtration and washing, the filtrate was worked-up. The crude obtained was analysed by HPLC showing a purity in biphenyl-4-carboxylic acid **1.118** of 52%.

Diethyl-carbamic acid phenyl ester (1.52)



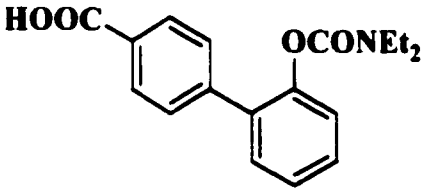
To a stirred suspension of hexane-washed NaH (1.8 g, 60 wt% in oil, 45 mmole) and diethylcarbamoyl chloride (8.39 g, 7.84 mL, 60 mmole) in THF (75 mL) was added dropwise over a period of 20 min at 0°C a solution of phenol (2.82 g, 30 mmole) in THF (25 mL). After stirring overnight at rt, the reaction mixture was quenched with aq aq.satd.NH4Cl and extracted with ether (3x). The combined organic extract was washed with water (2x), brine (2x), dried over Na_2SO_4 and evaporated under vacuum to give a yellow oil which was purified via flash chromatography (4:1 hexane:EtOAc) to give diethyl-carbamic acid phenyl ester **1.52** as a colourless oil (3.420 g, 59%) : Beilstein Registry # [1951039]; IR (neat) ν (max) 1714 cm^{-1}; ^1H NMR[216] (250 MHz, $CDCl_3$) δ 7.40-7.09 (m, 5H), 3.41 (q, J = 6.7 Hz, 4H), 1.23 (t, J = 6.6 Hz, 6H) ; MS (EI (70 eV)) m/z (rel intensity) 193 (M^+, 100).

2-*N,N*-Diethylcarbamoyl tributylstannyl benzene (1.121)



To a solution of diethyl-carbamic acid phenyl ester **1.52** (0.518 g, 2.69 mmole) in anhydrous THF (27 mL) flushed with argon was added at rt TMEDA (0.34 g, 0.45 mL, 2.96 mmole). The reaction mixture was cooled to –78°C and *s*-BuLi (2.96 mL, 1.0 M, 2.96 mmole) was added dropwise over a period of 10 min and stirred for 15 min at –78°C. Tributyltin chloride (0.973 g, 0.81 mL, 2.96 mmole) was added dropwise over a period of 10 min at –78°C. The reaction mixture was stirred 30 min at –78°C and was allowed to warm to rt and stirred 1 h at rt. The reaction mixture was quenched with aq aq. satd. NH_4Cl and extracted with ethyl acetate (3x). The combined organic extract was washed

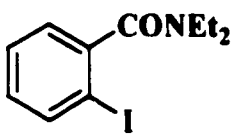
with water (2x), brine (2x), dried over Na_2SO_4 and evaporated under vacuum to give a yellow oil which was purified on silica gel (95:5 hexane:EtOAc) to give 2-*N,N*-diethylcarbamoyl tributylstannyl benzene **1.121** (1.075 g, 83%) as a colourless oil : IR (neat) 2958, 2920, 1720, 1615, 1582, 1461, 1414, 1378, 1267, 1188, 1153, 1062, 960,870, 752 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.44-7.12 (m, 4H), 3.57-3.35 (m, 4H), 1.55-0.84 (m, 33H) ; ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 156.6, 154.4, 139.7, 136.7, 129.2, 124.8, 121.4, 41.8, 41.5, 28.9, 27.2, 13.5, 9.6 ; MS (CI) m/z (rel intensity) 484 (M^++1, 7), 426 (33), 425 (13), 424 (25), 423 (10), 422 (14), 291 (9), 194 (28), 119 (8), 100 (42), 95 (10), 72 (10), 71 (11), 69 (14), 61 (15), 57 (100) ; HRMS (EI (70 eV)) *m/e* calcd for $C_{23}H_{41}NO_2{}^{120}Sn$: 483.2159, found 483.2150.



4-(2-*N,N*-Diethylcarbamoylphenyl)benzoic acid (1.119)

According to General Procedure C, resin-bound 4-iodobenzoic acid **1.113** (1% cross-linked, loading 0.78 mmole / g, 0.141 g, 0.11 mmole) was swollen in anhydrous DMF (4.7 mL) and coupled with 2-N,N'-diethylcarbamoyl tributylstannyl benzene **1.121** in the presence of $Pd(PPh_3)_4$ (0.0064 g, 0.0055 mmole). After 48 h, the reaction mixture was cooled to rt. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.129 g) was swollen in THF (2.2 mL) and treated with a solution of lithium hydroxide monohydrate (0.021 g, 0.50 mmole) in MeOH:H_2O (2:1, 1.3 mL) overnight. After acidification, filtration and washing, the filtrate was worked-up. The crude obtained was analysed by HPLC and purified on silica gel (75:24.5:0.5

hexane:EtOAc:AcOH) to give 4-(2-*N,N'*-diethylcarbamoylphenyl)benzoic acid **1.119** (0.0246 g, loading: 0.61 mmole / g, 78%) as a colourless solid : mp 176-178 °C (EtOH); IR (DMSO) 3438, 2963, 1704, 1419, 1267, 1200, 1157, 1103, 1027 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 12.97 (bs, 1H), 7.98 (d, J = 8.3 Hz, 2H), 7.50 (d, J = 8.3 Hz, 2H), 7.45-7.19 (m, 4H), 3.19 (m, 4H), 0.95 (m, 6H) ; ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 167.1, 153.0, 148.2, 141.8, 133.6, 130.2, 128.7, 129.2, 129.1, 128.9, 125.8, 123.6, 41.4, 41.2, 13.9, 12.9 ; m/z (rel intensity) 313 (M^+, 21), 269 (13), 214 (22), 196 (30), 169 (22), 139 (22), 115 (16), 100 (100); HRMS (EI (70 eV)) *m/e* calcd for $C_{18}H_{19}NO_4$: 313.1314, found 313.1320.

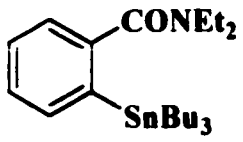


N,N-Diethyl-2-iodobenzamide (1.122)

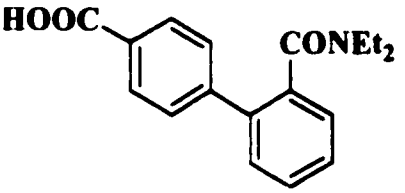
To 2-iodobenzoic acid 98% (7.59 g, 0.03 mol) was added dropwise at 0 °C thionyl chloride (42.9 g, 26.3 mL, 0.36 mol) over a period of 30 min. The reaction mixture was heated at reflux overnight. The reaction mixture was cooled to rt and the excess thionyl chloride was removed under vacuum. The residue was dissolved in THF (25 mL) and cooled to 0°C To this solution was added dropwise a solution of diethylamine (15.36 g, 21.7 mL, 0.21 mol) in THF (0.15 mL) over a period of 15 min. The reaction mixture was allowed to warm to rt overnight and was concentrated under vacuum. The brown residue was dissolved in ether. This solution was successively washed with water (1×), 10% HCl (2×), water (1×), aq satd. $NaHCO_3$ (3×), water (2×), brine (1×), dried over Na_2SO_4 and evaporated under vacuum. The residue was purified on silica gel (3:1 hexane:EtOAc) to give *N,N*-diethyl-2-iodobenzoamide **1.122** (6.548 g, 72%) as a colourless oil : Beilstein Registry # [4408101]; ^1H NMR [217](250 MHz, $CDCl_3$) δ 7.82 (d, J = 8.2 Hz, 1H), 7.38 (d, J = 7.6 Hz, 1H), 7.21 (dd, J = 8.1, 7.8 Hz, 1H), 7.04 (dd, J = 8.3, 7.7 Hz, 1H), 3.86-

3.11 (m, 4H), 1.29 (t, J = 7.2 Hz, 3H), 1.07 (t, J = 7.0 Hz, 3H) ; ^{13}C NMR (50.3MHz, $CDCl_3$) δ 170.8, 144.1, 138.2, 130.2, 127.2, 126.4, 97.3, 42.8, 40.3, 13.8, 13.6.

***N,N*-Diethyl 2-tributylstannylbenzamide (1.123)**

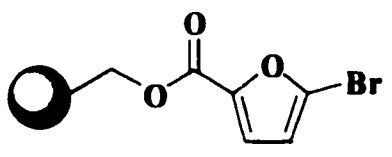


A solution of N,N-diethyl-2-iodobenzamide **1.122** (0.824 g, 2.72 mmole) in anhydrous THF (27 mL) was flushed with argon and cooled to –78°C. *n*-BuLi (1.97 mL, 1.52 M, 2.99 mmole) was added dropwise over a period of 10 min and stirred for 15 min at –78°C. Tributyltin chloride (0.973 g, 0.81 mL, 2.99 mmole) was added dropwise over a period of 10 min at –78°C. The reaction mixture was stirred 1 h at –78°C and was allowed to warm to rt overnight. The reaction mixture was quenched with aq aq. satd. NH_4Cl and extracted with ethyl acetate (3x). The combined organic extract was washed with water (2x), brine (2x), dried over Na_2SO_4 and evaporated under vacuum to give a yellow oil. The residue was purified on silica gel (9:1 hexane:EtOAc) to give *N,N*-diethyl-2-tributylstannyl benzamide **1.123** (0.95 g, 75%) as a colourless oil : IR (neat) 2956, 2916, 1626, 1456, 1422, 1376, 1285, 1220, 1097, 1064, 872, 790, 740, 661 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.56-7.24 (m, 4H), 3.54-3.26 (m, 4H), 1.57-0.83 (m, 33H) ; ^{13}C NMR (50.3MHz, $CDCl_3$) δ 172.9, 143.6, 142.3, 137.2, 128.2, 127.0 125.7, 43.6, 39.2 29.0, 27.4, 13.7, 10.2 ; MS (CI) m/z (rel intensity) 468 (M^++1, 8), 414 (16), 412 (15), 411 (21), 410 (98), 409 (41), 408 (75), 407 (31), 406 (42), 178 (34), 119 (10), 117 (10), 107 (14), 100 (12), 89 (57), 71 (14), 69 (14), 61 (87), 59 (26), 57 (100); HRMS *m/e* calcd for $C_{23}H_{41}NO^{120}Sn$ + H : 468.2288, found 468.2278.



4-(2-*N,N*-Diethylcarboxamidophenyl)benzoic acid (1.120)

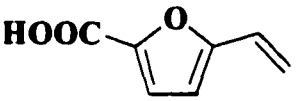
According to General Procedure C, resin-bound 4-iodobenzoic acid **1.113** (1% cross-linked, loading 0.78 mmole / g, 0.141 g, 0.11 mmole) was swollen in anhydrous DMF (4.7 mL) and coupled with N,N-diethyl 2-tributylstannylbenzamide **1.123** (0.154 g, 0.33 mmole) in the presence of $Pd(PPh_3)_4$ (0.0064 g, 0.0055 mmole). After 48 h, the reaction mixture was cooled to rt. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.128 g) was swollen in THF (2.1 mL) and treated with a solution of lithium hydroxide monohydrate (0.021 g, 0.50 mmole) in MeOH:H_2O (2:1, 1.3 mL) overnight. After acidification, filtration and washing, the filtrate was worked-up. The crude obtained was analysed by HPLC and purified on silica gel (85:14.5:0.5 hexane:EtOAc:AcOH) to give 4-(2-*N,N*-diethylcarboxamidophenyl)benzoic acid **1.120** (0.0236 g, loading: 0.62 mmole / g, 80%) as a colourless solid : ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.12 (d, J = 8.5 Hz, 2H), 7.61 (d, J = 8.5 Hz, 2H), 7.52-7.39 (m, 4H), 3.73 (m, 1H), 2.96 (m, 2H), 2.71 (m, 1H), 0.92 (t, J = 7.1 Hz, 3H), 0.77 (t, J = 7.1 Hz, 3H). This compound was mislaid.



Resin-bound 5-bromo-2-furoic acid (1.131)

According to General Procedure A, the Merrifield resin **1.2** (1% cross-linked, loading 1 mmole / g, 2.0 g, 2.0 mmole) was swollen in anhydrous DMF (20 mL) and treated with cesium carbonate (1.95 g, 6 mmole),

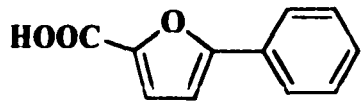
potassium iodide (0.17 g, 1.0 mmole) and 5-bromo-2-furoic acid 98% (0.59 g, 3 mmole). The resulting resin was collected by filtration, washed and dried to afford **1.131**, IR (KBr) 1719 cm^{-1} (ester band). The loading capacity of **1.131** was determined according to General Procedure B. **1.131** (0.403 g) was swollen in THF (6.7 mL) and treated with a solution of lithium hydroxide monohydrate (0.084 g, 2.0 mmole) in MeOH:H_2O (2:1, 4.0 mL). After acidification, filtration and washing, the filtrate was worked-up and purified on silica gel (80:19.5:0.5 hexane:EtOAc:AcOH) to give 5-bromo-2-furoic acid (0.0561 g) showing a loading of **1.131** of 0.73 mmole / g.



5-Vinylfuran-2-carboxylic acid (1.132)

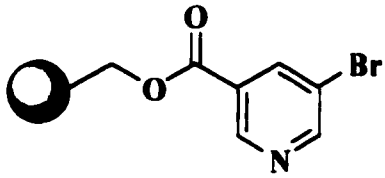
Resin-bound 5-bromo-2-furoic acid **1.131** (1% cross-linked, loading 0.73 mmole / g, 0.205 g, 0.150 mmole) was swollen in anhydrous DMF (6.8 mL) and the system was flushed with argon (30 min). Tri-2-furylphosphine (0.0035 g, 0.015 mmole) and Pd_2dba_3 (0.0069 g, 0.0075 mmole) were added and the reaction mixture was stirred for 10 min at rt. Tributyl(vinyl)tin 97% (0.147 g, 0.136 mL, 0.45 mmole) was added and the reaction mixture was stirred at 60°C for 48 h. The reaction mixture was cooled to rt, treated with aq. satd. NH_4Cl solution (6.3 mL) and stirred for 10 min. The resin was removed by filtration (fritted glass funnel) and washed successively once with DMF, twice with DMF:H_2O (1:1), twice with 0.3 M HCl, three times with H_2O, once with DMF, twice with EtOAc, twice with EtOAc:MeOH (1:1) and three times with MeOH, and dried overnight in an Abderhalden apparatus. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.178 g) was swollen in THF (3.0 mL) and treated with a solution of lithium hydroxide monohydrate (0.027 g, 0.65

mmole) in MeOH:H_2O (2:1, 1.8 mL). After acidification, filtration and washing, the filtrate was worked-up. The crude obtained was analysed by HPLC and mislaid.



5-Phenylfuran-2-carboxylic acid (1.133)

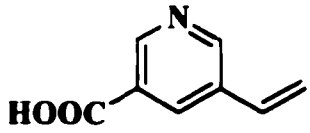
According to General Procedure C, resin-bound 5-bromo-2-furoic acid **1.131** (1% cross-linked, loading 0.73 mmole / g, 0.205 g, 0.150 mmole) was swollen in anhydrous DMF (6.8 mL) and coupled with tributylphenyltin 97% (0.170 g, 0.151 mL, 0.45 mmole) in the presence of $Pd(PPh_3)_4$ (0.0087 g, 0.0075 mmole). After 48 h, the reaction mixture was cooled to rt. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.188 g) was swollen in THF (3.1 mL) and treated with a solution of lithium hydroxide monohydrate (0.029 g, 0.68 mmole) in MeOH:H_2O (2:1, 1.9 mL) overnight. After acidification, filtration and washing, the filtrate was worked-up. The crude obtained was analysed by HPLC and purified on silica gel (90:9.5:0.5 hexane:EtOAc:AcOH) to give 5-phenylfuran-2-carboxylic acid **1.133** (0.0177 g, loading: 0.50 mmole / g, 68%) as a colourless solid : Beilstein Registry # [135286]; mp 147-149 °C (Lit.[218] mp 150-150.5 °C ($CHCl_3$)); ^{1}H NMR (250 MHz, DMSO-d_6) δ 12.5 (bs, 1H), 7.80 (d, J = 6.7 Hz, 2H), 7.49-7.35 (m, 3H), 7.26 (d, J = 3.7 Hz, 1H), 7.01 (d, J = 3.7 Hz, 1H); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 159.2, 156.2, 144.1, 129.1, 128.7, 128.6, 124.2, 119.4, 107.3 ; MS (EI (70 eV)) m/z (rel intensity) 188 (M^+, 100); HRMS *m/e* calcd for $C_{11}H_8O_3$: 188.0473, found 188.0474.



Resin-bound 5-bromonicotinic acid (1.128)

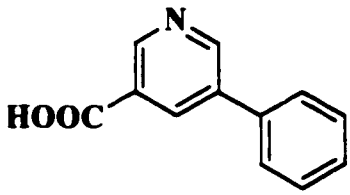
According to General Procedure A, the Merrifield resin **1.2** (1% cross-linked, loading 1 mmole / g, 2.0 g, 2.0 mmole) was swollen in anhydrous DMF (20 mL) and treated with cesium carbonate (1.95 g, 6 mmole), potassium iodide (0.17 g, 1.0 mmole) and 5-bromonicotinic acid 98% (0.62 g, 3 mmole). The resulting resin was collected by filtration, washed and dried to afford **1.128**, IR (KBr) 1726 cm^{-1} (ester band). The loading capacity of **1.128** was determined according to General Procedure B. **1.128** (0.428 g) was swollen in THF (7.1 mL) and treated with a solution of lithium hydroxide monohydrate (0.09 g, 2.14 mmole) in MeOH:H_2O (2:1, 4.3 mL). After acidification, filtration and washing, the filtrate was worked-up and purified on silica gel (80:19.5:0.5 hexane:EtOAc:AcOH) to give 5-bromonicotinic acid (0.0657 g) showing a loading of **1.128** of 0.76 mmole / g.

5-Vinylnicotinic acid (1.129)



Resin-bound 5-bromonicotinic acid **1.128** (1% cross-linked, loading 0.76 mmole / g, 0.197 g, 0.150 mmole) was swollen in anhydrous DMF (5 mL) and the system was flushed with argon (30 min). Tri-2-furylphosphine (0.0035 g, 0.015 mmole) and Pd_2dba_3 (0.0069 g, 0.0075 mmole) were added and the reaction mixture was stirred for 10 min at rt. Tributyl(vinyl)tin 97% (0.147 g, 0.136 mL, 0.45 mmole) was added and the reaction mixture was stirred at 60°C for 48 h. The reaction mixture was cooled to rt, treated with aq. satd. NH_4Cl solution (6.3 mL)

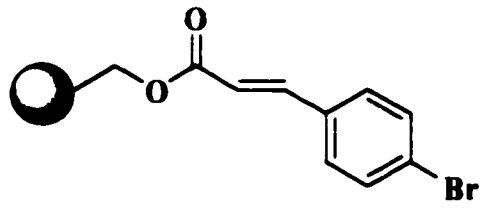
and stirred for 10 min. The resin was removed by filtration (fritted glass funnel) and washed successively once with DMF, twice with DMF:H_2O (1:1), twice with 0.3 M HCl, three times with H_2O, once with DMF, twice with EtOAc, twice with EtOAc:MeOH (1:1) and three times with MeOH, and dried overnight in an Abderhalden apparatus. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.166 g) was swollen in THF (2.8 mL) and treated with a solution of lithium hydroxide monohydrate (0.026 g, 0.63 mmole) in MeOH:H_2O (2:1, 1.7 mL). After acidification, filtration and washing, the filtrate was worked-up. The crude obtained was analysed by HPLC and mislaid.



5-Phenylnicotinic acid (1.130)

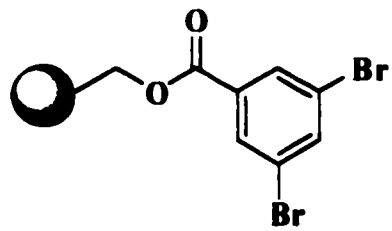
According to General Procedure C, resin-bound 5-bromonicotinic acid **1.128** (1% cross-linked, loading 0.76 mmole / g, 0.197 g, 0.150 mmole) was swollen in anhydrous DMF (6.6 mL) and coupled with tributylphenyltin 97% (0.170 g, 0.151 mL, 0.45 mmole) in the presence of $Pd(PPh_3)_4$ (0.0087 g, 0.0075 mmole). After 48 h, the reaction mixture was cooled to rt. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.178 g) was swollen in THF (3.0 mL) and treated with a solution of lithium hydroxide monohydrate (0.029 g, 0.68 mmole) in MeOH:H_2O (2:1, 1.8 mL) overnight. After acidification, filtration and washing, the filtrate was worked-up. The crude obtained was analysed by HPLC and purified on silica gel (95:4.5:0.5 hexane:EtOAc:AcOH) to give 5-phenylnicotinic acid (0.0241 g, loading: 0.68 mmole / g, 89%) as a colourless solid : Beilstein Registry # [138591]; mp 258-261 °C (Lit.[219] mp 260-263 °C (EtOH)); ^1H NMR (250 MHz, DMSO-d_6) δ 9.03 (d, J = 1.8 Hz,

1H), 8.97 (d, J = 2.2 Hz, 1H), 8.42 (dd, J = 2.2, 1.8 Hz, 1H), 7.67-7.61 (m, 2H), 7.50-7.35 (m, 3H); MS (EI (70 eV)) m/z (rel intensity) 199 (M^+, 100) ; HRMS *m/e* calcd for $C_{12}H_9NO_2$: 199.0633, found 199.0634.



Resin-bound 4-bromocinnamic acid (1.140)

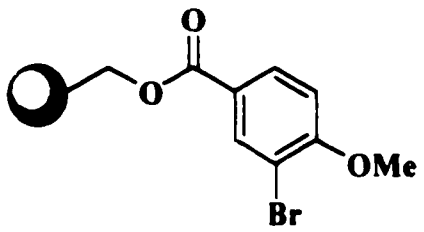
According to General Procedure A, the Merrifield resin **1.2** (1% cross-linked, loading 1 mmole / g, 1.5 g, 1.5 mmole) was swollen in anhydrous DMF (15 mL) and treated with cesium carbonate (1.47 g, 4.5 mmole), potassium iodide (0.125 g, 0.75 mmole) and 4-bromocinnamic acid 98% (0.52 g, 2.25 mmole). The resulting resin was collected by filtration, washed and dried to afford **1.140**, IR (KBr) 1714 cm^{-1} (ester band). The loading capacity of **1.140** was determined according to General Procedure B. **1.140** (0.120 g) was swollen in THF (2.0 mL) and treated with a solution of lithium hydroxide monohydrate (0.025 g, 0.6 mmole) in MeOH:H_2O (2:1, 1.2 mL). After acidification, filtration and washing, the filtrate was worked-up and purified on silica gel (80:19.5:0.5 hexane:EtOAc:AcOH) to give 4-bromocinnamic acid (0.0221 g) showing a loading of **1.140** of 0.81 mmole / g.



Resin-bound 3,5-dibromobenzoic acid (1.141)

According to General Procedure A, the Merrifield resin **1.2** (1% cross-linked, loading 1 mmole / g, 1.5 g, 1.5 mmole) was swollen in anhydrous DMF (15 mL) and treated with

cesium carbonate (1.47 g, 4.5 mmole), potassium iodide (0.125 g, 0.75 mmole) and 3,5-dibromobenzoic acid 97% (0.65 g, 2.25 mmole). The resulting resin was collected by filtration, washed and dried to afford **1.141**, IR (KBr) 1726 cm^{-1} (ester band). The loading capacity of **1.141** was determined according to General Procedure B. **1.141** (0.205 g) was swollen in THF (3.4 mL) treated with a solution of lithium hydroxide monohydrate (0.043 g, 1.02 mmole) in MeOH:H_2O (2:1, 2.1 mL). After acidification, filtration and washing, the filtrate was worked-up and purified on silica gel (80:19.5:0.5 hexane:EtOAc:AcOH) to give 3,5-dibromobenzoic acid (0.0448 g) showing a loading of **1.141** of 0.78 mmole / g.



Resin-bound 3-bromo-4-methoxy-benzoic acid (1.142)

According to General Procedure A, the Merrifield resin **1.2** (2% cross-linked, loading 2 mmole / g, 1.5 g, 3 mmole) was swollen in anhydrous DMF (15 mL) and treated with cesium carbonate (2.93 g, 9 mmole), potassium iodide (0.25 g, 1.5 mmole) and 3-bromo-4-methoxy-benzoic acid 98% (1.06 g, 4.5 mmole). The resulting resin was collected by filtration, washed and dried to afford **1.142**, IR (KBr) 1703 cm^{-1} (ester band). The loading capacity of **1.142** was determined according to General Procedure B. **1.142** (0.150 g) was swollen in THF (2.5 mL) and treated with a solution of lithium hydroxide monohydrate (0.063 g, 1.50 mmole) in MeOH:H_2O (2:1, 1.5 mL). After acidification, filtration and washing, the filtrate was worked-up and purified on silica gel (80:19.5:0.5 hexane:EtOAc:AcOH) to give 3-bromo-4-methoxy-benzoic acid (0.0437 g) showing a loading of **1.142** of 1.26 mmole / g.

Chapter 2

2. The Suzuki-Miyaura Cross Coupling Reaction on Solid Support

2.1. Introduction

Following the work on the Stille cross coupling reactions on solid support using an ester linker, the corresponding Suzuki-Miyaura reaction on solid support using the original Leznoff linker methodology was studied.

This cross coupling method is extensively employed in natural product synthesis and in medicinal chemistry, particularly in the large scale industrial synthesis of the angiotensin II receptor antagonist Losartan by Merck and Dupont-Merck[220] and is gaining more and more interest among combinatorial chemists.

The Leznoff acetal linker allows the release of biaryl and heterobiaryl aldehydes, a hitherto difficult to access class of molecules using the currently available linker technologies.

2.2. The Suzuki-Miyaura Cross Coupling Reaction

2.2.1. Main Features

In 1968, Davidson and Triggs[221] first reported a biaryl synthesis from phenylboronic acid and a stoichiometric amount of sodium palladate. However, it was not until 1979 that Suzuki and Miyaura, in a series of papers,[162] first demonstrated that organic boron derivatives partake in coupling reactions with organic halides under Pd catalysis. Progress in the area led

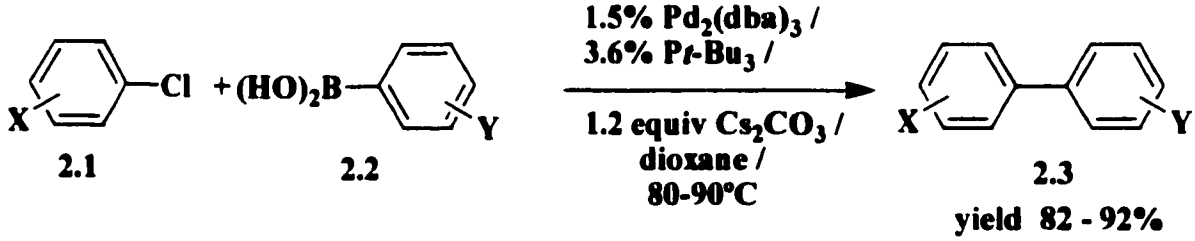
to the discovery that aryl boronic acids undergo a facile and efficient palladium catalysed cross coupling reaction with aryl bromides, iodides and triflates.[222] The general process is depicted in **Scheme 2.1.**

$$Ar{-}X \;+\; Ar'{-}B(OH)_2 \xrightarrow{\text{base / } PdL_n} Ar{-}Ar' \;+\; MX \;+\; B(OH)_3$$

Scheme 2.1. The Suzuki-Miyaura cross coupling reaction.

In a study of the order of reactivity of the LG partner in the Suzuki-Miyaura cross coupling reaction, Fu[147b] found the reactivity to be I > OTf > Br when $Pd(PPh_3)_4$ was used as the catalyst. Suzuki also studied the reactivity of triflates and halides and found I > Br > OTf when the cross coupling was done with 9-octyl-9-BBN in the presence of $Pd(PPh_3)_4$ and K_3PO_4.[223]

Recently, the conditions of the Suzuki-Miyaura cross coupling have been fine tuned by Littke and Fu[139f] to allow the reaction to be carried out with a wide range of aryl chlorides from electron-poor, to electron rich, and hindered ones (**Scheme 2.2.**).



Scheme 2.2. Suzuki-Miyaura cross coupling reaction with aryl chlorides.

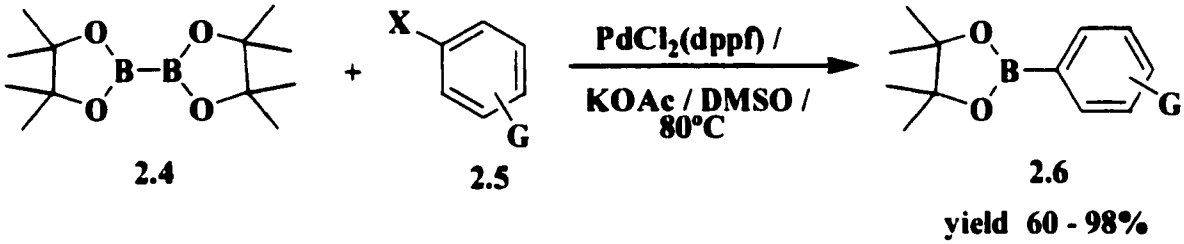
The cross coupling of aryl chlorides is disfavoured due to the difficult oxidative insertion of palladium into the C-Cl bond.[224] Its major interest remains in the fact that aryl chlorides are less expensive and more available than aryl bromides and iodides.

The reaction requires a base, which may be Na_2CO_3,[163] K_2CO_3,[225] Cs_2CO_3,[226] Tl_2CO_3,[227] $NaHCO_3$,[228] TlOH,[229] $Ba(OH)_2$,[164g] K_3PO_4,[230,147b] CsF,[231] and Et_3N[232] in order to generate the borate species as the actual organometallic species that undergoes transmetalation. The bases can be used as aqueous solution along with benzene, toluene, DME, THF, diethyl ether, acetone, EtOH or as suspension in dioxane, DMF, DME, EtOH or toluene. Benzene and toluene were the initial solvents used for the Suzuki-Miyaura cross coupling reaction.[163] DME was suggested by Gronowitz[233] to suppress competitive deboronation.

By far, the most extensively used Pd catalyst for the Suzuki-Miyaura cross coupling reaction is $Pd(PPh_3)_4$. However, a very wide range of palladium (0) catalysts or precursors has been used, such as $PdCl_2(PPh_3)_2$ and $Pd(OAc)_2$ plus phosphine or other phosphine ligands.[234] Phosphine-based catalysts are usually used since they are stable on prolonged heating; however, extremely high coupling reaction rates can be achieved with phosphine free palladium catalysts.[235] Pd / C was also demonstrated as an alternative catalyst for the coupling of aryl boronic acids and aryl halides and triflates.[236, 164l]

The organic boron derivatives may be arylboronic acids, aryl borates[227, 229b] or aryl boranes.[237] Treatment by trialkylborates of the aryl lithium or magnesium derivatives leads to the organoboron compounds.[238] The boronate esters obtained may be hydrolysed to the

boronic acids, used directly in the cross coupling reaction or transesterified with other alcohols to form stable boronate esters, which can be purified by column chromatography and stored. The preparation of boronate esters circumvent the inherent problems of the isolation and the purification of boronic acids, which can be difficult to isolate due to their high water solubility, cannot be chromatographed, and may be difficult to recrystallise. Miyaura introduced an alternative strategy for the formation of boronate esters **2.6** *via* the palladium catalysed reaction of pinacol ester of diboronic acid[239] **2.4** with aryl halide **2.5** (**Scheme 2.3.**).[240] This mild method, which does not require the use of strong base, can be employed with aryl halides containing base sensitive functionalities (such as aldehyde, nitrile, nitro and ester groups). Although the pinacol ester of diboronic acid is difficult to make and expensive to buy, it has been successfully employed in solution chemistry for the one pot synthesis of unsymmetrical biaryls[241] and on solid phase[242] as will be further described.



2.4 **2.5** **2.6**

yield 60 - 98%

Scheme 2.3. Preparation of boronate esters.

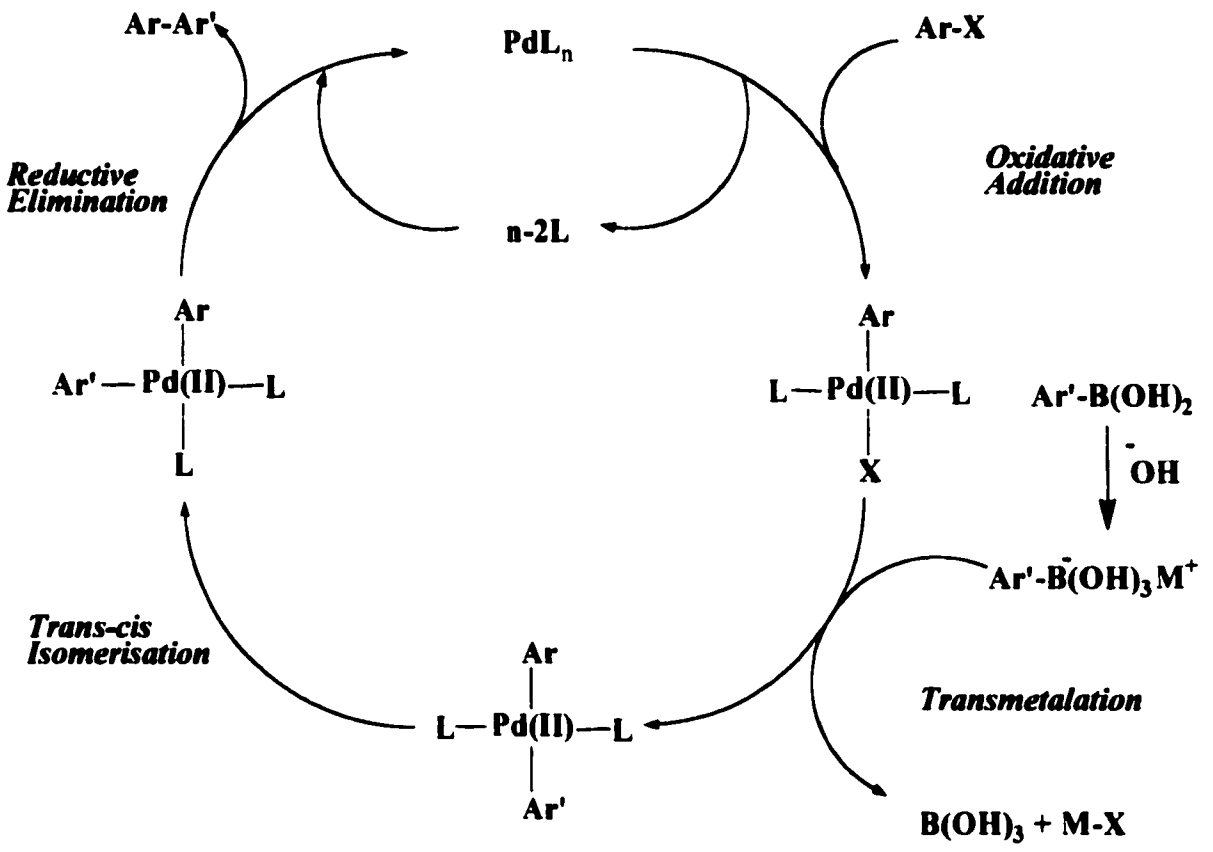
Many functional groups (e.g. aldehyde, amino, carbonyl, cyano, ester, and nitro) tolerate the mild reaction conditions of the Suzuki-Miyaura cross coupling reaction.

2.2.2. Mechanism

The Suzuki-Miyaura cross coupling reaction between arylboronic acids and aryl halides follows a catalytic cycle similar to most other transition metal catalysed cross coupling reactions. The mechanism proceeds by oxidative addition of the aryl halide to the Pd(0) catalyst, transmetalation of boron for palladium to form a diarylpalladium (II) species, and reductive elimination of the biaryl regenerating the catalyst.

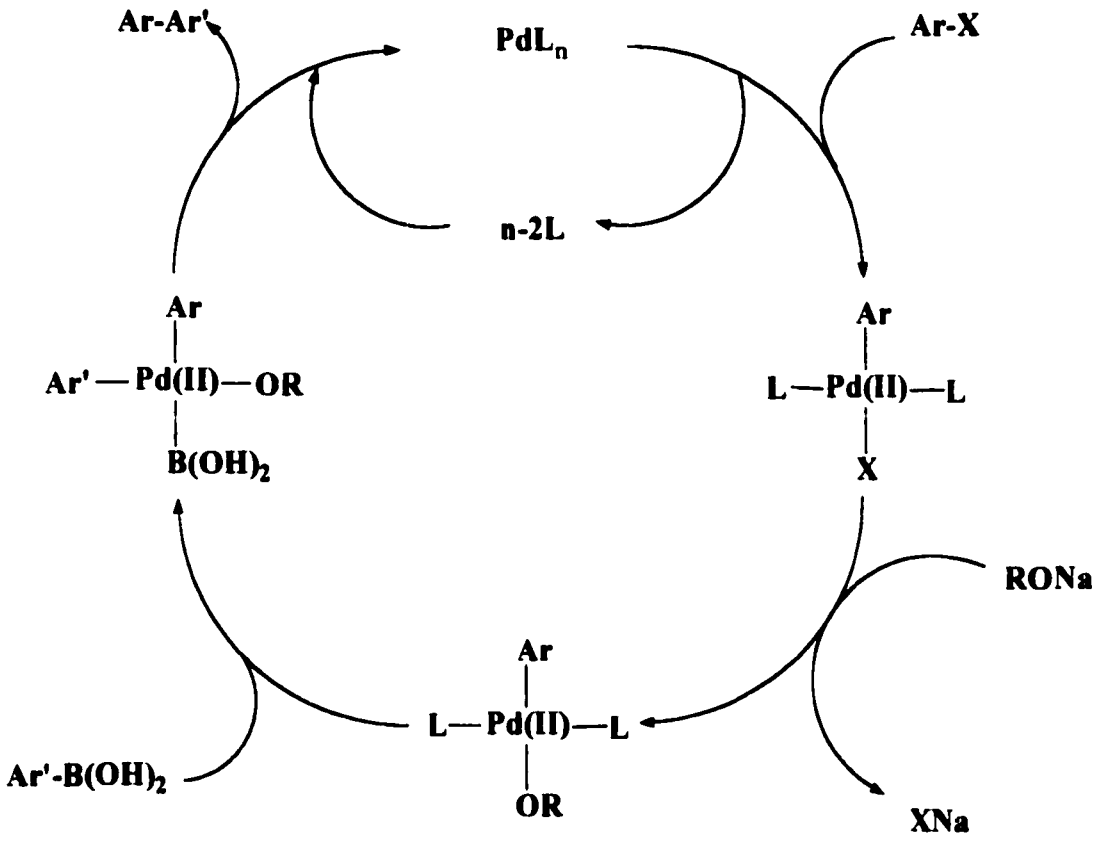
In contrast to the coupling induced by other metals such as Mg, Zn, and Sn a base is required. Several rationalisations have been suggested and various routes for the transmetallation step of organoboron with palladium halides have been proposed.[222,243]

For instance, it has been proposed that the low nucleophilicity of the organic group on the boron might be enhanced by the reaction of the arylboronic acid with the base to form a $[ArB(OH)_3]^-$ species (**Scheme 2.4.**). Even if there is no evidence that the boronate anions are involved in the transmetallation to Pd (II) halides, it was observed that the cross coupling reaction of arylboronic acids with aryl halides at $pH > pK_A$ was faster suggesting that the formation of $ArB(OH)_3^-$ occurs.



Scheme 2.4. Proposed mechanism 1 of the Suzuki-Miyaura cross coupling reaction.

An alternative explanation consists in assuming that the base is involved in the exchange to hydroxide or alkoxide of the halide attached to the Pd catalyst upon the oxidative addition (**Scheme 2.5.**). The (alkoxo)palladium intermediate would be involved in the transmetallation step. This alternative mechanism was proposed knowing that the halogen ligand on an organopalladium (II) halide is readily displaced by an alkoxy, hydroxy or acetoxy anion to provide Pd-OR complexes.

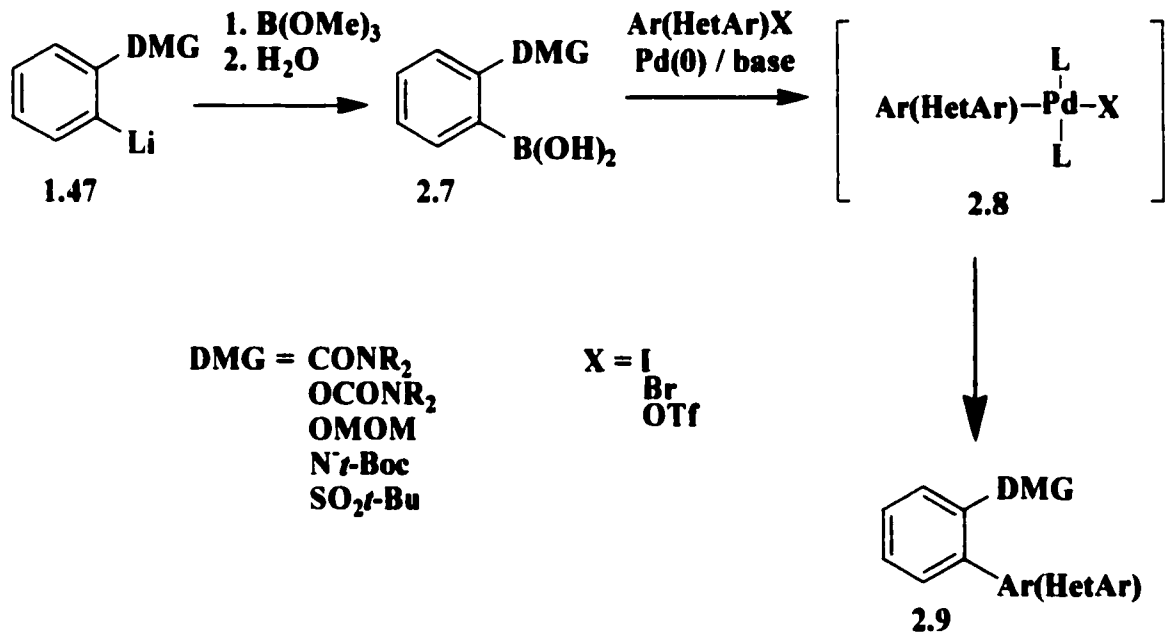


Scheme 2.5. Proposed mechanism 2 of the Suzuki-Miyaura cross coupling reaction.

Electrospray ionisation mass spectrometry was employed to study the Suzuki-Miyaura cross coupling reaction. The intermediates $ArPd(OR)L_2$ were not detected[244] and no definite mechanism of the Suzuki-Miyaura cross coupling reaction has been yet widely accepted. However, according to Suzuki the formation of alkoxo-, hydroxo- or acetoxo palladium (II) intermediates should be considered to be one of the crucial transmetallation processes.[222]

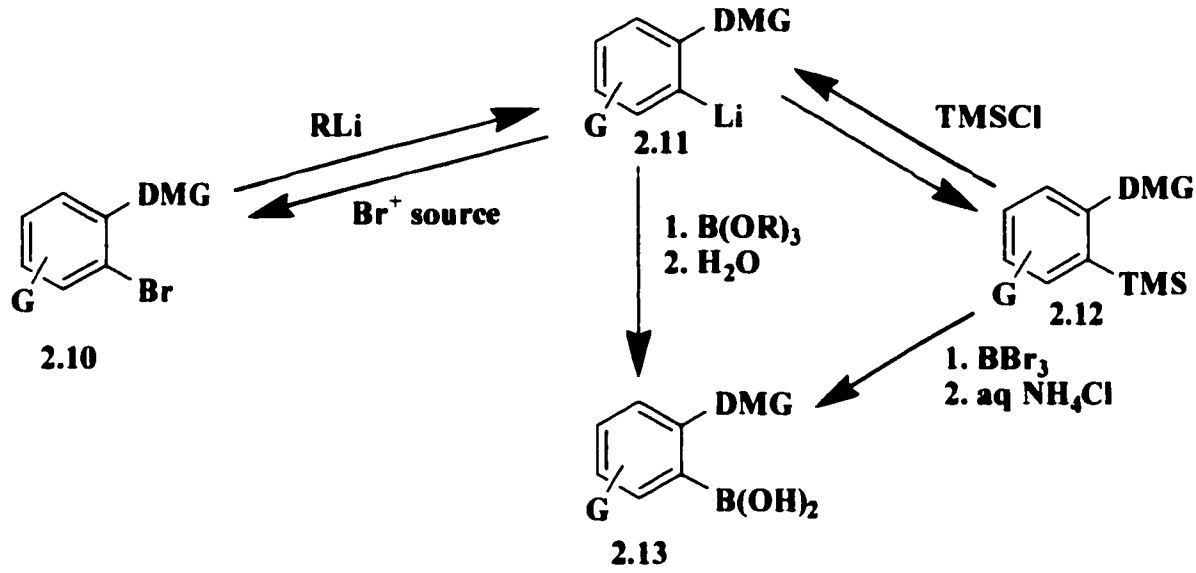
2.2.3. The Directed *ortho* Metalation – Suzuki-Miyaura Cross Coupling Connection

DoM represents a powerful means to prepare regiospecifically polysubstituted aromatic boronic acids. By treating *ortho*-lithiated DMG aromatics **1.47** with trimethyl borate followed by hydrolysis, the corresponding *ortho*-DMG substituted boronic acids **2.7** were obtained and used as substrates for cross coupling with aryl halide and triflate partners to give a variety of biaryls and heterobiaryls **2.9** (**Scheme 2.6.**).[130g, 228]



Scheme 2.6. Preparation of *ortho*-DMG substituted boronic acids via DoM and their application.

In addition to the original DoM-mediated route to *o*rtho-DMG substituted aryl boronic acids, two alternative routes were developed (**Scheme 2.7.**).



Scheme 2.7. Preparation of *ortho*-DMG substituted boronic acids *via* metal-halogen exchange and *ipso*-borodesilylation.

The *ortho*-lithiated species **2.11** may be converted into the *ortho*-TMS derivatives **2.12**, which may be subsequently *ipso*-borodesilylated with BBr_3 to the boronic acids derivatives **2.13**, which were at times obtained cleaner and in higher yields than via the direct route.[179a] The other alternative involves the metal-halogen exchange of aryl bromide derivatives **2.10** followed by trialkylborate quench and acidic work-up.

2.3. The Suzuki-Miyaura Cross Coupling Reaction on Solid Support

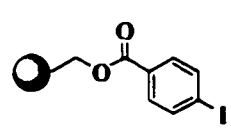
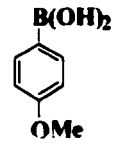
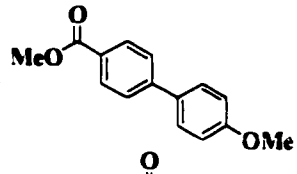
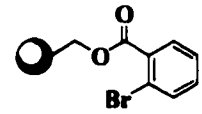
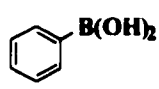
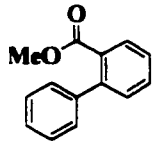
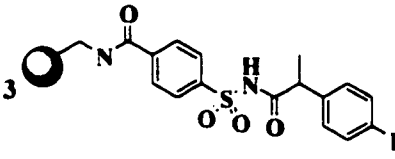
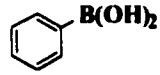
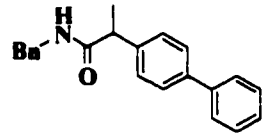
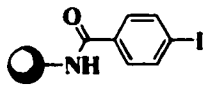
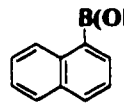
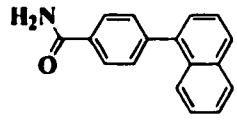
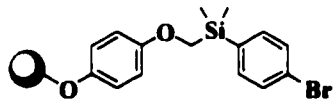
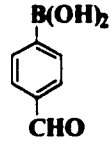
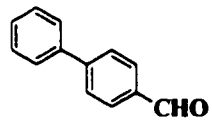
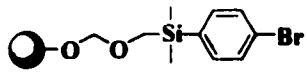
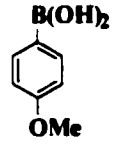
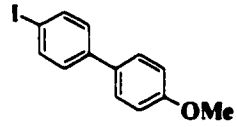
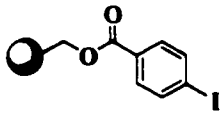
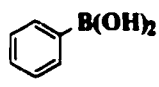
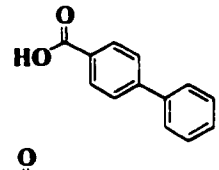
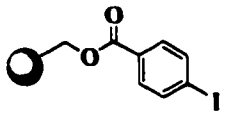
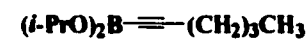
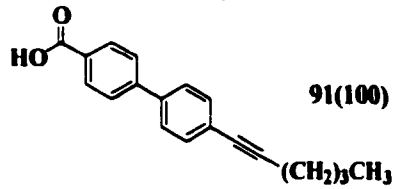
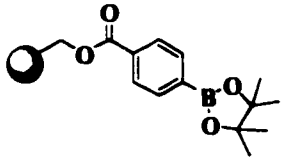
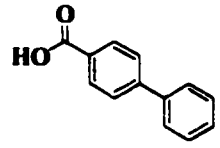
The mildness, the high generality of the Suzuki-Miyaura cross coupling reaction due to its tolerance of a wide scope of functionalities and its high yields make it suitable for combinatorial chemistry.[122] **Table 2.1.** summarises the reports of several groups of the Suzuki-Miyaura reaction on polymer support.

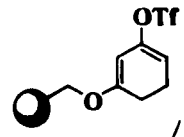
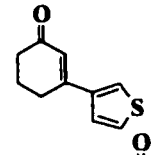
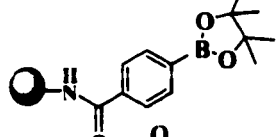
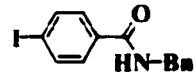
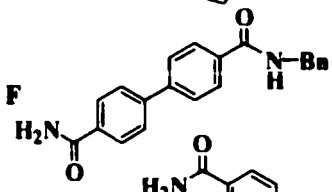
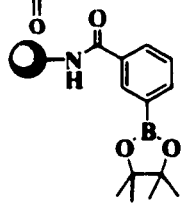
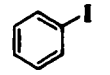
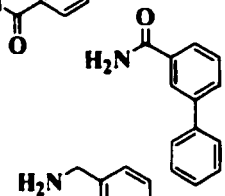
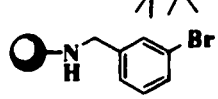
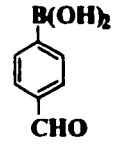
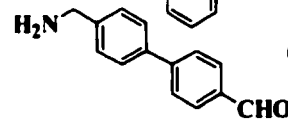
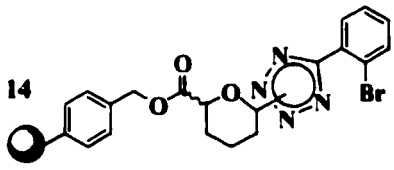
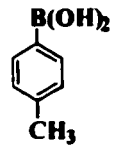
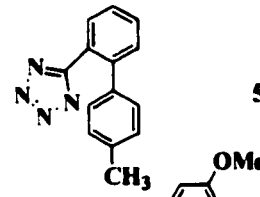
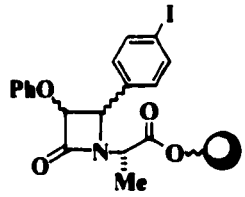
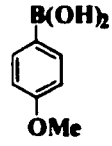
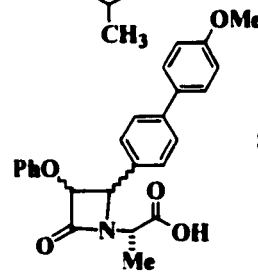
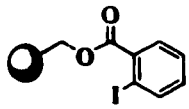
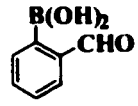
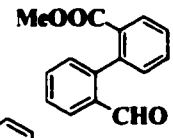
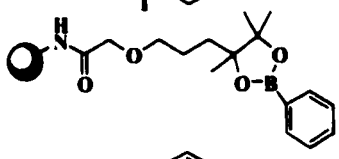
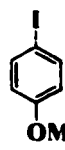
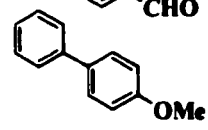
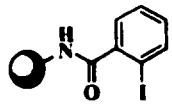
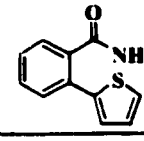
As seen from the Table, the preparation of simple biphenyl compounds represents a large part of the work already achieved in this area.

Considerable effort has been placed in the optimisation of the reaction conditions of the cross coupling reaction, and in exploring new linkers suitable for this chemistry in order to generalise the synthesis of libraries of diverse biphenyl derivatives. However, the power of this attractive method to form carbon-carbon bond on solid support is starting to be extended to the preparation of libraries of more elaborated derivatives of biologically active molecules such as biphenyltetrazoles,[122k] 4-arylazetindin-2-ones,[122n] tropanes[122g] and tamoxifens[242].

Table 2.1. Suzuki-Miyaura cross coupling reactions on solid support.



Entry		R'Y	cat / base[a]	FG-R-R'	Yield(Purity)(%)	Resin	Ref
1			A		>95(>99)	Merrifield	122a
2			A		>95(>99)	Merrifield	122a
3			A		95(>95)	amino methylene	96
4			A		99(-[b])	Rink amido TentaGel	122f
5					70(-[b])	Merrifield	122c
6			B		98(-[b])	Wang	122e
7			C		72(100)	Wang	122h
8			D		91(100)	Wang	122h
9			E		-[c](60)	Wang	122h

Entry	Linker—R—X	R'Y	cat / base[a]	FG–R–R'	Yield(Purity)(%)	Resin	Ref
10			A		42(>95)	hydroxy-methyl-polystyrene	122m
11			F		95(-[b])	Rink amide	122i
12			G		95(-[b])	Rink amide	122j
13			E		60(-[b])	Rink chloride	83
14			A		57(-[b])	Merrifield	122k
15			H		80(-[b])	Wang	122n
16			A		80(>95)	PEG	249
17			I		85(>95)	Rink amide	122r
18			J		95(100)	ArgoGel	122d

[a]cat / base: A: $Pd(PPh_3)_4$ / Na_2CO_3; B: $Pd(PPh_3)_4$ / TEA; C: $Pd_2(dba)_3$ / K_2CO_3; D: $PdCl_2(dppf)$ / K_2CO_3; E: $Pd(PPh_3)_4$ / K_2CO_3; F: $Pd(PPh_3)_4$ / KOH; G: $Pd(PPh_3)_4$ / K_3PO_4; H: $PdCl_2(dppf)$ / TEA; I: $PdCl_2(binap)$ / K_3PO_4; J: $PdCl_2(PPh_3)_2$ / Na_2CO_3. [b]Purity not reported. [c]Yield not reported.

Frenette and Friesen (entry 1 and 2) were the first to report a systematic study of the Suzuki-Miyaura cross coupling reaction on solid support.[122a] A number of benzoic acids were loaded on commercially available Merrifield resin by esterification. The coupling reactions were performed with a variety of palladium catalysts and boronic acids to produce biphenyl ester derivatives, which were released from the support by transesterification using catalytic amount of sodium methoxide in MeOH and THF. The optimal cross coupling conditions were found to be 5 mol % $Pd(PPh_3)_4$ in DME with 2M Na_2CO_3 as a base. Polymer bound bromobenzoic acids were found to be as efficient coupling partners as the polymer bound iodobenzoic acids and even polymer bound-2-bromobenzoic acid coupled in excellent yields with phenylboronic acid (entry 2) . A wide range of boronic acids from electron rich to electron deficient appeared to be suitable substrates. The isolated yields were generally higher than 95%.

Shortly after, Backes and Ellman[96] used an acylsulfonamide linker developed by Kenner[245] for solid phase peptide synthesis to carry out the Suzuki-Miyaura cross coupling reaction on solid support (entry 3). Using this method, they prepared substituted arylacetic acid derivatives, an important class of cyclooxygenase inhibitors. The cross coupling was performed under standard reaction conditions: $Pd(PPh_3)_4$, 2M Na_2CO_3, THF, reflux. DME was not a satisfactory solvent due to the precipitation of Pd(0) which complicated the cleavage steps involving diazomethane and benzylamine by decomposing diazomethane. The reaction times varied from 24 to 40 h to ensure complete conversion to the cross-coupled product. Alkyl 9-BBN derivatives and various aryl boronic acids gave high yields (>90%) of products.

In 1996, Lahred and co-workers[122f] described the use of microwave irradiation to enhance dramatically the rate of the Suzuki-Miyaura cross coupling reaction on polymer support. Reaction times of 3.8 min were sufficient to achieve the cross coupling reactions between 4-iodo and 4-bromobenzoic acids linked to Rink amide Tentagel resin with a variety of organoboronic acids (entry 4). Excellent conversions were obtained and minimal decomposition of the solid support was observed. Slightly better results were obtained with the polymer bound iodobenzoic acids versus the polymer bound bromobenzoic acids.

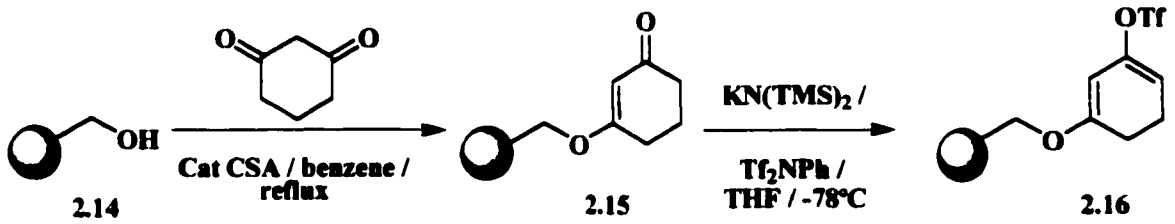
The synthesis of 4-formyl biphenyl in 70% yield (entry 5) has been accomplished *via* the Suzuki-Miyaura cross coupling reaction between 4-formylboronic acid and polystyrene-bound aryl bromide.[122c] A novel traceless arylsilane linker was developed leaving an unsubstituted aryl ring upon cleavage with either TFA or CsF in DMF or with HF. The introduction of the aldehyde functional group was carried out to allow further functionalisation of the resin bound biphenyl aldehyde with benzylamine.

With the aim of introducing functional diversity at the cleavage step, Young and co-workers studied a new silicon based linker.[122e] The arylsilane linker developed can be converted, upon cleavage with a variety of electrophiles (H^+, I^+, Br^+, Cl^+, Ac^+, NO_2^+...), to a large number of functionalities. This new silicon based linking technology was applied for the synthesis of biaryls *via* the Suzuki-Miyaura cross coupling reaction (entry 6). Although standard aqueous conditions were tested ($Pd(PPh_3)_4$, 2M Na_2CO_3, DME, reflux), the coupling reactions were mainly performed under anhydrous conditions[232a] ($Pd(PPh_3)_4$, TEA, DMF, reflux) giving, upon electrophilic cleavages using ICl or Br_2/pyr, biaryls in excellent isolated yields. The aqueous conditions gave better results only in the case of the coupling with the

highly electron deficient 3-nitrophenylboronic acid. In this case, the cross coupled product was obtained in 82% instead of 33% yield when the anhydrous conditions were employed. The protiodesilylation with TFA afforded biphenyls in moderate yields, probably due to the difficulty in isolating them (they are volatile and sublime at rt).

To further enhance the utility of the Suzuki-Miyaura cross coupling methodology for combinatorial chemistry, a study on its generality on solid-phase was undertaken by Guiles and co-workers (entry 7, 8, 9).[122h] Commercially available Wang and SASRIN resins were functionalised by esterification with 2-,3- and 4- iodobenzoic acid. The cleavage of the ester linker was achieved by TFA. The investigation began with a study of the effects of numerous catalysts on the coupling with phenylboronic acid at rt. $Pd_2(dba)_3$ and $Pd(PPh_3)_4$ were found to give high conversions in the meta and para cases while $PdCl_2(dppf)$ and $NiCl_2(dppp)$ catalysts were totally ineffective. The coupling of the bound 2-iodobenzoic acid proceeded only to 57% conversion probably due to steric hindrance. Under similar reaction conditions, no coupling of the bound bromobenzoic acid was observed. Having optimised the conditions of the Suzuki-Miyaura cross coupling reaction with phenylboronic acid, the scope of the coupling process was investigated. A wide array of boronic coupling partners (heteroaryl, alkyl, alkenyl, alkynyl (entry 8)) was employed and a study of the Pd catalyst was again undertaken. It appeared that the best Pd catalyst to be used is a function of the boronic coupling partners. The coupling was also attempted with polymer-bound boronic acid reagent (entry 9), prepared by attaching phenyldioxaneborinane[246] to Wang resin. Lower yields of biphenyls were obtained even after increasing the reaction time. Unreacted boronate was still observed.

Fraley and Rubino[116k] were the first to report the Suzuki-Miyaura cross coupling reaction between a resin-bound vinyl triflate and a wide array of boronic acids (entry 10). Yields in the order of 40% were achieved while purities higher than 95% were obtained by using standard Suzuki-Miyaura cross coupling conditions. The vinyl triflate resin **2.16** was prepared by treating hydroxymethyl polystyrene resin **2.14** with 1,3-cyclohexanedione in the presence of catalytic amount of camphorsulfonic acid, followed by the treatment of the resin bound ester with potassium hexamethyldisilazide and trapping of the enolate with *N*-phenyltrifluoromethanesulfonimide according to the procedure of Mc Murry[247] (**Scheme 2.8.**). The enone derivatives were cleaved from the solid support using diluted TFA in acetone.



Scheme 2.8. Preparation of vinyl triflate resin.

Brown and Armstrong[122i] studied the Suzuki-Miyaura reaction between the polymer bound aryl boronate and a free iodide (entry 11). They followed the Suzuki-Miyaura procedure, treating the polymer bound iodobenzamide with the pinacol ester diboron under Pt catalysis to prepare the polymer bound aryl boronate, that was subsequently coupled to *N*-benzyl-4-iodobenzamide in >95% yield.

Shortly after, Piettre and Baltzer[122j] prepared 2-, 3-, and 4- polymer bound boronates of arylbenzamides from the polymer bound halobenzamides using Miyaura conditions (pinacol

ester of diboron, $PdCl_2(dppf)$, KOAc) (entry 12) since the classical methodology to prepare boronic acids[232a] failed when adapted on the solid phase. They carried out an extensive study of the Suzuki-Miyaura cross coupling reactions of theses substrates with bromo and aryl halides and demonstrated that the limited number of commercially available boronic acids could be circumvented by carrying out successfully the Suzuki-Miyaura cross coupling reaction in a reverse manner by having the boronic acid reagent on the polymer instead of free in solution (entry 12). The best reaction conditions for the Suzuki-Miyaura cross coupling reaction were found to be $Pd(PPh_3)_4$, K_3PO_4, DMF, 80°C. In the absence of steric hindrance or poor solubility of the reactants, high isolated yields of biaryls were obtained.

Garipati[83] showed an example of the Suzuki-Miyaura cross coupling reaction on Rink chloride resin functionalised by bromobenzylamine (entry 13). Polymer bound bromobenzylamine was treated with 4-formylboronic acid under Pd catalysis leading, after cleavage with TFA, to the cross coupled product in 60% yield.

Various biphenyltetrazole derivatives have been prepared by Yoo and co-workers[122k] on solid support using the Suzuki-Miyaura cross coupling reaction in connection with a research program on the development of Angiotensin II receptor antagonists (entry 14). The choice of the dihydropyran carboxylic acid linker was dictated by the need of not only attaching the tetrazole unit to the resin but also protecting the tetrazole group. The palladium catalysed cross coupling reaction was carried out between the polymer bound bromotetrazole and arylboronic acids using the standard Suzuki-Miyaura conditions. Good overall yields of the biphenyl tetrazole derivatives were obtained after cleavage with dilute HCl in MeOH.

Noteworthy is the use of the Suzuki-Miyaura cross coupling reaction on solid support by Ruhland and co-workers[122n] to produce combinatorial libraries of 4-biarylazetidin-2-ones that represent a novel class of β-lactams (entry 15). After a study of the reaction conditions, it was found that $PdCl_2$(dppf), TEA, DMF and 65°C gave the most satisfactory results with bound iodo as well as with bromo derivatives. The large P-Pd-P bite angle in $PdCl_2$(dppf) has been shown to favour the reductive elimination step.[248] Efficient cross coupling reactions of the iodophenyl β-lactam with a large variety of heterocyclic boronates and aryl boronates bearing EDGs or EWGs were performed (isolated yields 65%-83%). The reverse coupling of polymer bound arylboronic acid prepared by attachment of preformed boronic acid in solution to the resin gave satisfactory preliminary results.

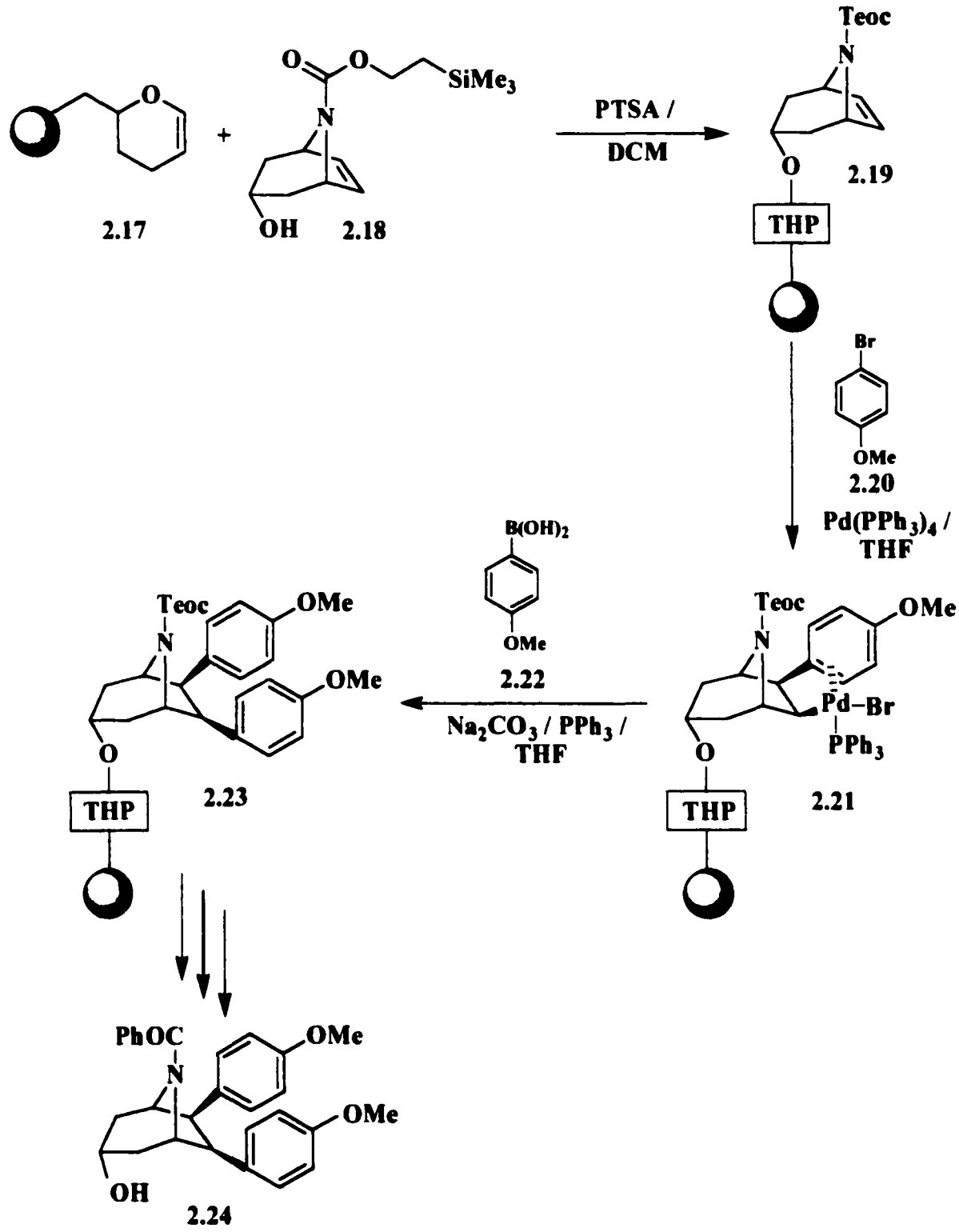
Blettner and co-workers[249] have described the synthesis of biaryls and heterobiaryls *via* the Suzuki-Miyaura cross coupling reaction using PEG as the polymer support (entry 16). Sterically hindered polymer bound aryl iodides, sterically hindered boronic acids as well as heteroaryl bromide and heteroarylboronic acids were employed leading to good yields of biaryls and heterobiaryls after cleavage as methyl esters using TEA in MeOH (yields 52% to 98%). However it was found that in general, and not only in the case of sterically hindered cases, higher temperatures (110°C) and longer reaction times were necessary to achieve good conversion into the cross coupled products compared to non-polymer supported solution chemistry.

Burgess and Li[122r] developed a new boronic acid linker strategy that leads to the direct release of biaryls after Suzuki cross coupling reaction (entry 17). The resin bound boronate

ester prepared from Rink amide resin was treated with 5 equivalents of 4-iodomethoxybenzene in the presence of $PdCl_2$(binap) 5 mol % and 2M K_3PO_4. These conditions were found to give the highest yield. The purpose to develop such a linker was to find a method to prepare on solid support macrocycles containing the biaryl moiety. The last step of the synthesis involving the Suzuki cross coupling reaction performs simultaneously the macrocyclisation and the resin cleavage.

The Suzuki cross coupling reactions on solid support were performed on an automated workstation by Porco and co-workers from Argonaut[122d] (entry 18). To demonstrate the capabilities of the Nautilus^{TM} 2400 system to achieve in an automated manner reactions under inert atmosphere and to optimise the reaction times, the Suzuki cross coupling reactions of resin bound iodobenzamides were performed with boronic acids, such as 2-thienylboronic acid and 2-tolylboronic acid in the presence of $PdCl_2(PPh_3)_2$ and Na_2CO_3. The results indicated full conversion of the resin bound aryl iodide to cross coupled products in high chemical yield and purity in only one hour.

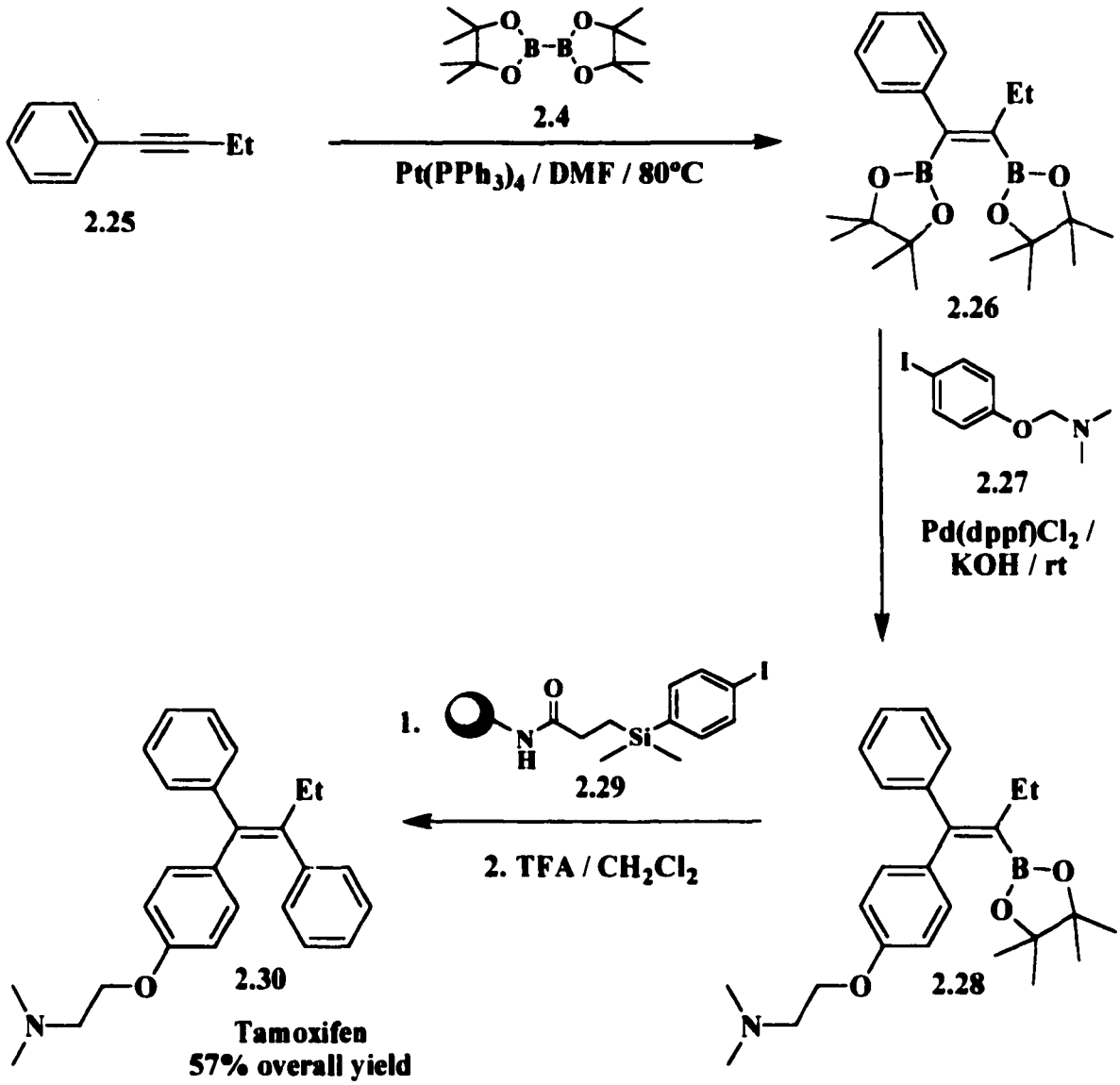
In the general effort to apply Suzuki-Miyaura cross coupling reaction on solid support for the synthesis of pharmacologically active molecules, Koh and Ellman[122g] reported the synthesis of tropane derivatives[250] (**Scheme 2.9.**). The tropane scaffold derived from 3-α-hydroxy-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate[251] was attached to the dihydropyran functionalised polystyrene support.



Scheme 2.9. Synthesis of a tropane derivative on solid support *via* Suzuki-Miyaura cross coupling reaction.[122g]

Palladium mediated addition of aryl bromide **2.20** to the olefin functionality of **2.19** afforded the polymer bound palladium intermediate **2.21**, which, after isolation, was submitted to the Suzuki-Miyaura cross coupling reaction (2M Na_2CO_3, PPh_3 in THF), using various aryl boronic acids in excess. PPh_3 was added to prevent the formation of palladium black after the reductive elimination step by complexing Pd(0). After deprotection of the Teoc group, acylation of the secondary amine and cleavage with TFA, the tropane derivatives **2.24** were obtained in good overall yields (50-73%).

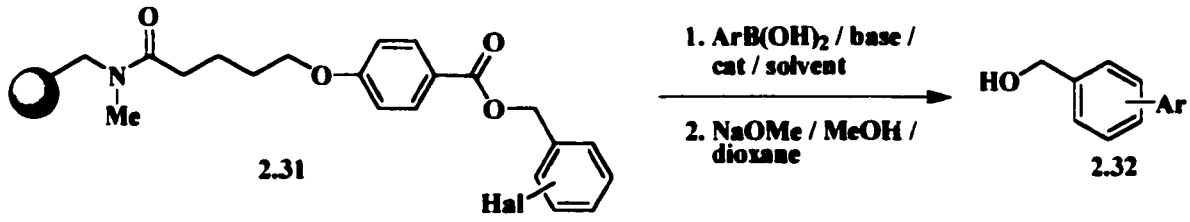
The synthesis of Tamoxifen **2.30**, used in the treatment of breast cancer, was achieved on solid support by Brown and Amstrong[242] by application of the tandem Suzuki-Miyaura cross coupling reaction - resin capture technique[252] (**Scheme 2.10.**). Following the conditions developed by Suzuki and Miyaura,[253,254] a variety of unsymmetrical alkynes were diborated. The crude bis(boryl)alkenes, obtained with high stereoselectivity, were subjected to the solution phase Suzuki-Miyaura cross coupling reaction with an excess of aryl halide in the presence of $PdCl_2(PPh_3)_2$ and KOH at rt. Once the bis(boryl)alkene borane was consumed, the resin bound aryl iodide was introduced in the mixture of the two possible stereoisomers (for simplicity, only one of the two possible stereoisomers is shown on Scheme 2.10.) to initiate a second Suzuki-Miyaura reaction on solid support without further addition of palladium catalyst. The capture on the resin allows the separation of the by-products by simple filtration. Tamoxifen was released from the polymer support by cleavage with TFA of the silicon based traceless linker in 57% overall yield. Twenty-four other Tamoxifen derivatives were also prepared in parallel following the same route, the molecular diversity was introduced by varying all four substituents of the ethylene core.



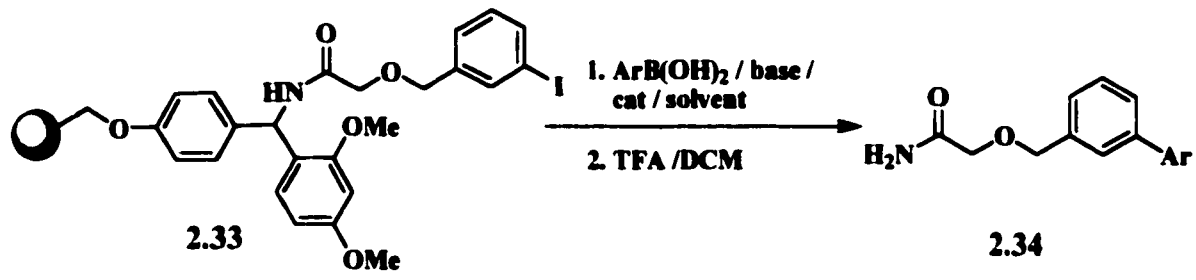
Scheme 2.10. Synthesis of Tamoxifen *via* the tandem Suzuki-Miyaura cross coupling – resin capture technique.[242]

The resin capture technique has offered some advantages over a single phase synthesis. No optimisation of the diboration on solid support is necessary and no side products build up on the resin. However, once the intermediate is captured on the resin, this reaction effectively has purified the solution product. The advantages of solid phase synthesis are realised after the resin capture (i.e. easy isolation by filtration and purification by washing).

De Mesmaeker and co-workers[122o] carried out an extensive study on the scope and limitations of the Suzuki-Miyaura cross coupling reaction of bound aryl halides linked on PS–DVB via a base labile linker (**Scheme 2.11.**) as well as an acid labile Rink linker (**Scheme 2.12.**).



Scheme 2.11. Suzuki-Miyaura cross coupling reactions with a base labile linker.[122o]

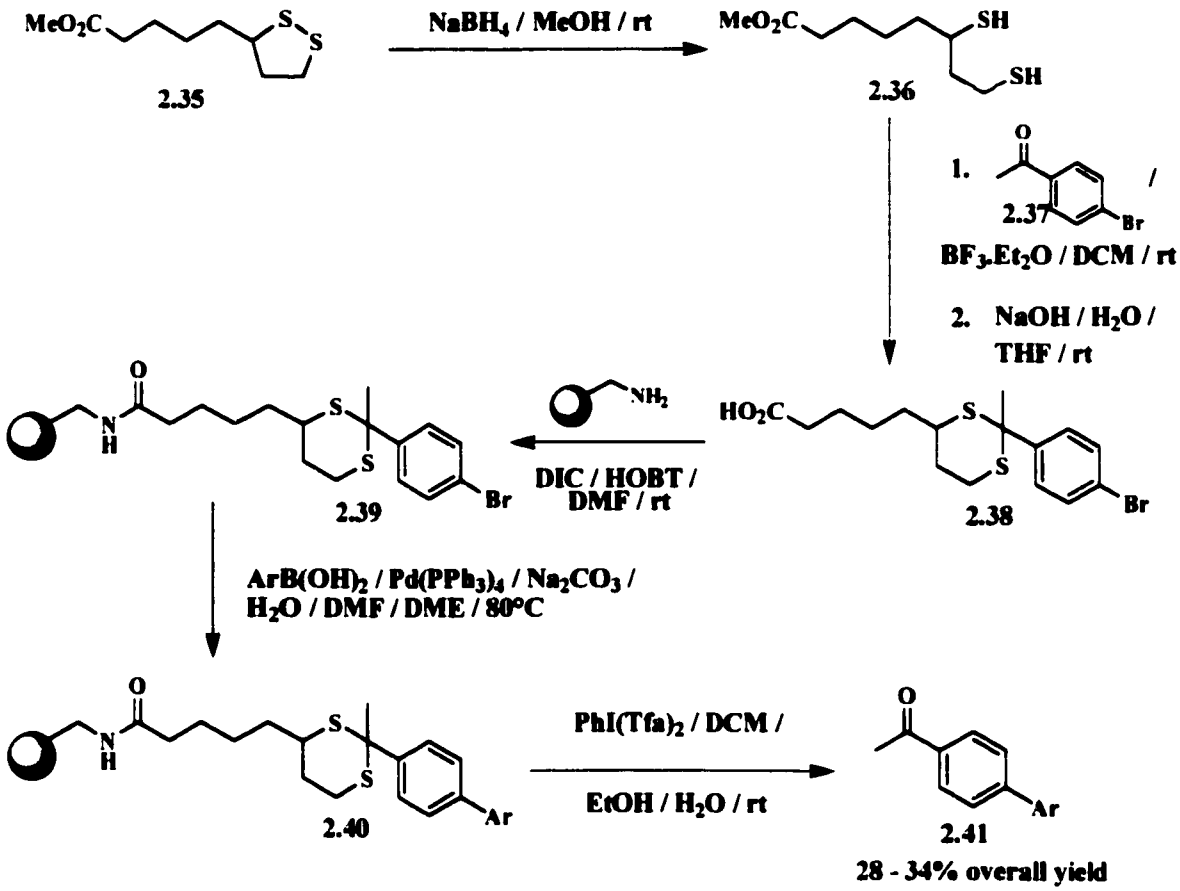


Scheme 2.12. Suzuki-Miyaura cross coupling reactions with the acid labile Rink linker.[122o]

General trends for the most generally favourable reaction conditions for the Suzuki-Miyaura cross coupling reaction on solid support were deduced from this study. Similarly to the reaction in solution phase, the conditions for every single case on solid support may be fine-tuned. In general, aryl iodides were found to give better results than aryl bromides in the absence of EWGs. The study of the catalyst showed that 10 mol % $Pd(OAc)_2$ allowed the formation of cleaner products than 10 mol % $Pd(PPh_3)_4$. The most favourable base was found to be K_2CO_3 in comparison with K_3PO_4 and KF. Dioxane was the solvent of choice. The reaction times were also optimised and 24 h was recommended to get complete conversion. The purpose of this type of study is to allow the production of as many compounds as possible under the same reaction conditions which is the aim of combinatorial chemistry.

Huwe and Künzer[122q] described the use of a novel thioacetal linker allowing the immobilisation of ketones to synthetise 4-acetylbiphenyls **2.41** on a solid support via the Suzuki-Miyaura cross coupling reaction (**Scheme 2.13.**). This report illustrates the need to develop new linkers to release functionalities rarely obtained using the traditional solid phase peptide synthesis linkers as well as the continuous expansion of the study of ways to produce the biaryl moiety. The thioacetal linker was prepared from the commercially available (±) α-lipoic acid. Its methyl ester **2.35** was reduced using $NaBH_4$; the dithiol **2.36** obtained was subsequently treated with 4-bromoacetophenone **2.37** in the presence of BF_3 leading to the formation of the thioacetal moiety. After saponification of the ester group with NaOH, the carboxylic acid **2.38** was attached to commercially available aminomethyl polystyrene resin through an amide bond. The polymer bound aryl bromide **2.39** was subjected to Suzuki-Miyaura cross coupling reaction with four different arylboronic acids in the presence of

$Pd(PPh_3)_4$ and Na_2CO_3. After cleavage of the thioacetal linker with [bis(trifluoroacetoxy)iodo]benzene, the 4-acetylbiphenyls **2.41** were obtained in 28-34% overall yield.



Scheme 2.13. Suzuki-Miyaura cross coupling reaction on solid support using a novel thioacetal linker.[122q]

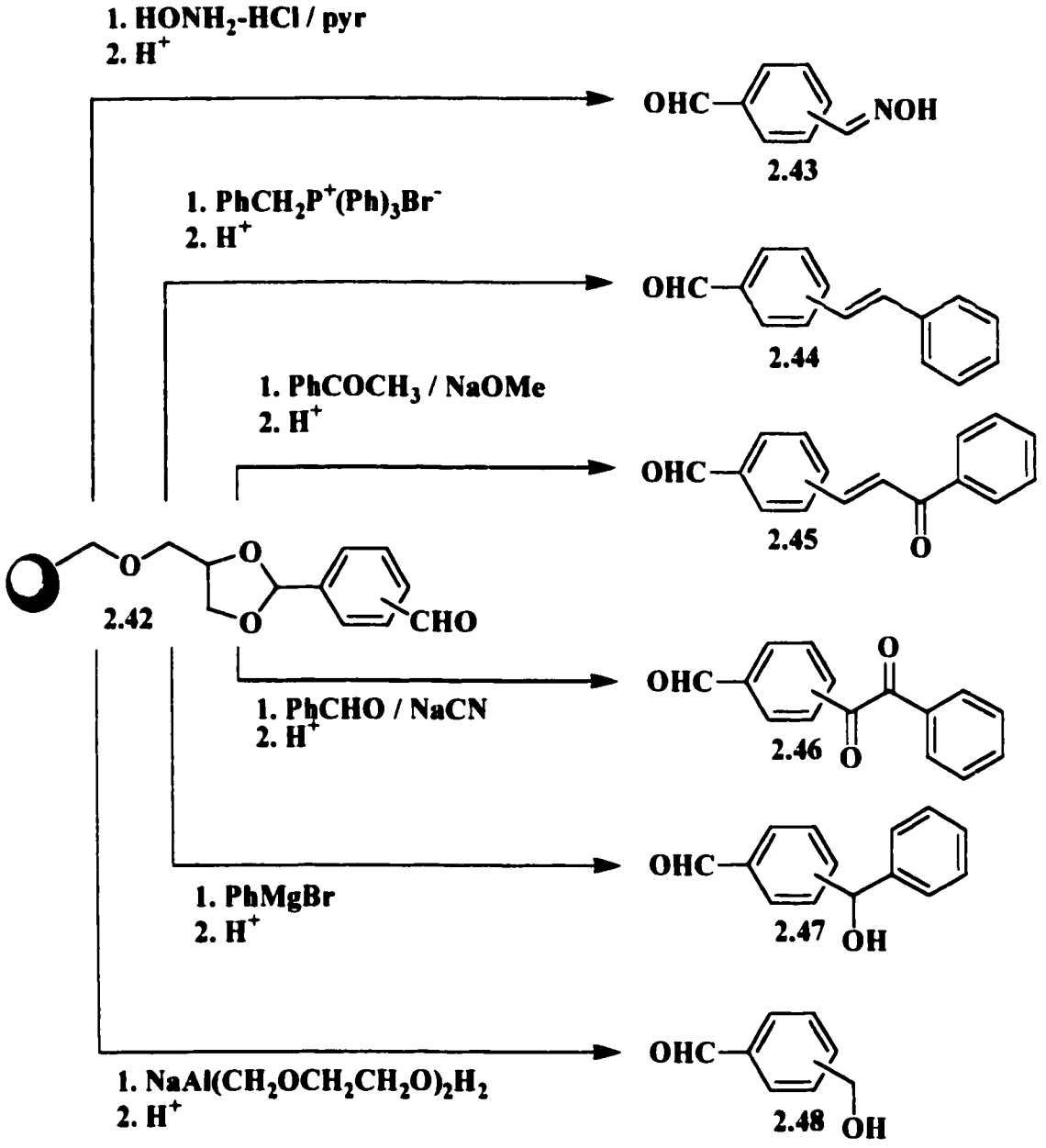
2.4. Results and Discussion

2.4.1. The Leznoff Acetal Linker

The choice of the acetal linker was dictated by the possibility of releasing biaryl aldehydes, a class of molecules difficult to obtain using the current available linkers. The further possible functionalisation in solution of the cleaved aldehydes by reductive amination with libraries of amines appeared as an attractive feature to generate molecular diversity.

The acetal linker was developed by Leznoff[84a] in 1973 to achieve the monoprotection of symmetrical bialdehydes (isophthalaldehyde and terephthalaldehyde).

Unusual structures containing free formyl groups were prepared using the solid attached free aldehydes (**Scheme 2.14.**). Thus, the free aldehyde functionality was treated with hydroxylamine to give mono-oximes upon cleavage from the solid support. Wittig reaction, crossed aldol condensation, benzoin condensation, Grignard reaction and reduction with metal hydride were also performed on the monoprotected dialdehyde. In all of these reactions, it was found that the yield of all products obtained from polymer bound isophthalaldehyde were slightly but consistently lower than the ones from polymer bound terephthalaldehyde, suggesting that steric hindrance plays a non negligible role in the polymer supported reactions using the acetal linker. In the case of the benzoin condensation, formylbenzils **2.46** were isolated, presumably after oxidation of the benzoins.



Scheme 2.14. Selective chemical reactions on one aldehyde group of symmetrical dialdehydes using solid support "protection".[84a]

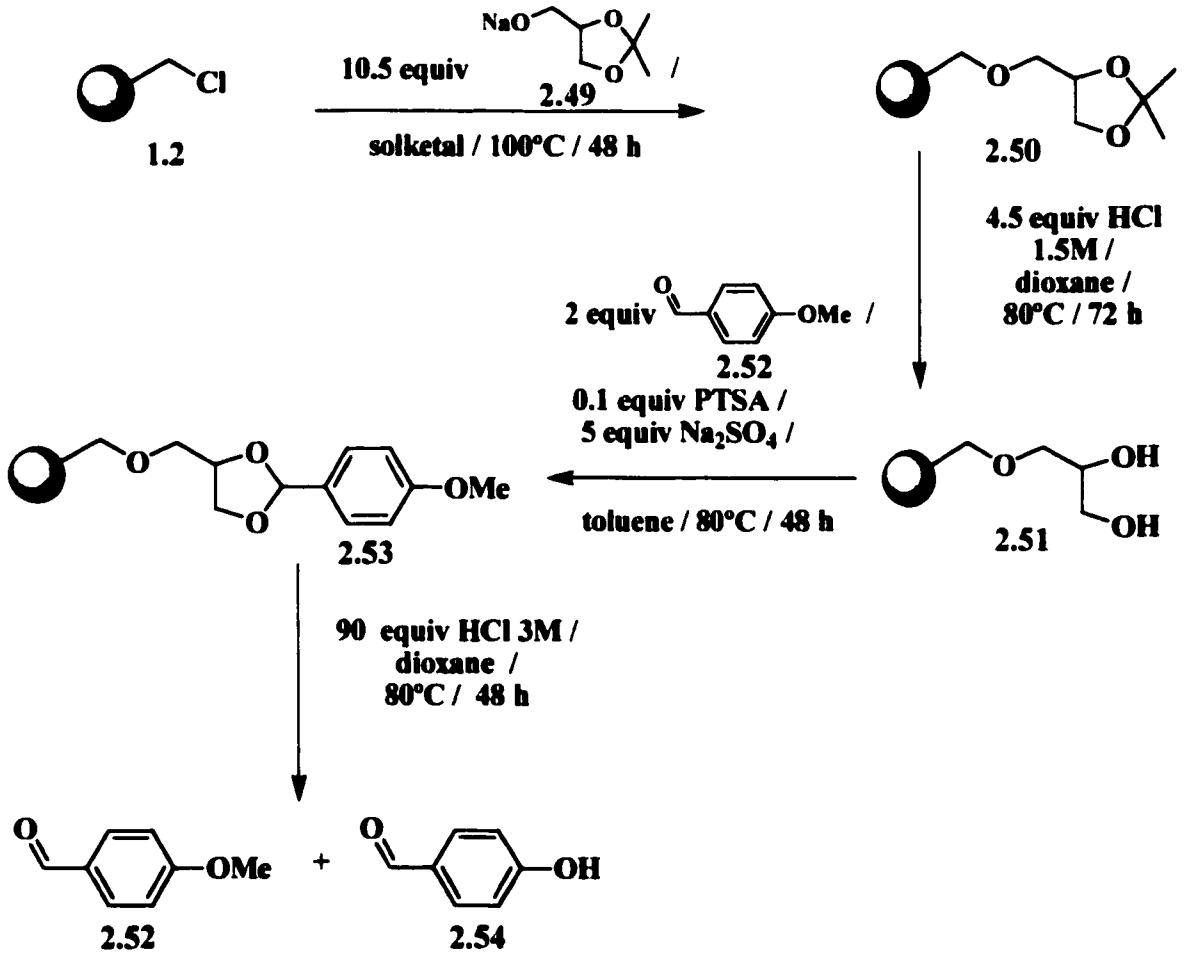
In 1977, Leznoff[255] demonstrated that the polymer 1,2-diol could also be functionalised by a completely conjugated symmetrical dialdehyde and, through this polymer supported monoprotection, the total synthesis of unsymmetrical carotenoids was achieved.

Finally in 1983, Leznoff[256] published optimised reaction conditions for the preparation of the acetal linker and applied them to the monoprotection of diketones. To our knowledge, this linker has not been used since this work for other applications.

One limitation of the acetal linker is that the reactions of the polymer bound substrates as well as the washing of the resin to remove excess reagents should be carried under basic conditions. This feature of the acetal linker does not present problems for carrying out the Suzuki-Miyaura cross coupling reaction.

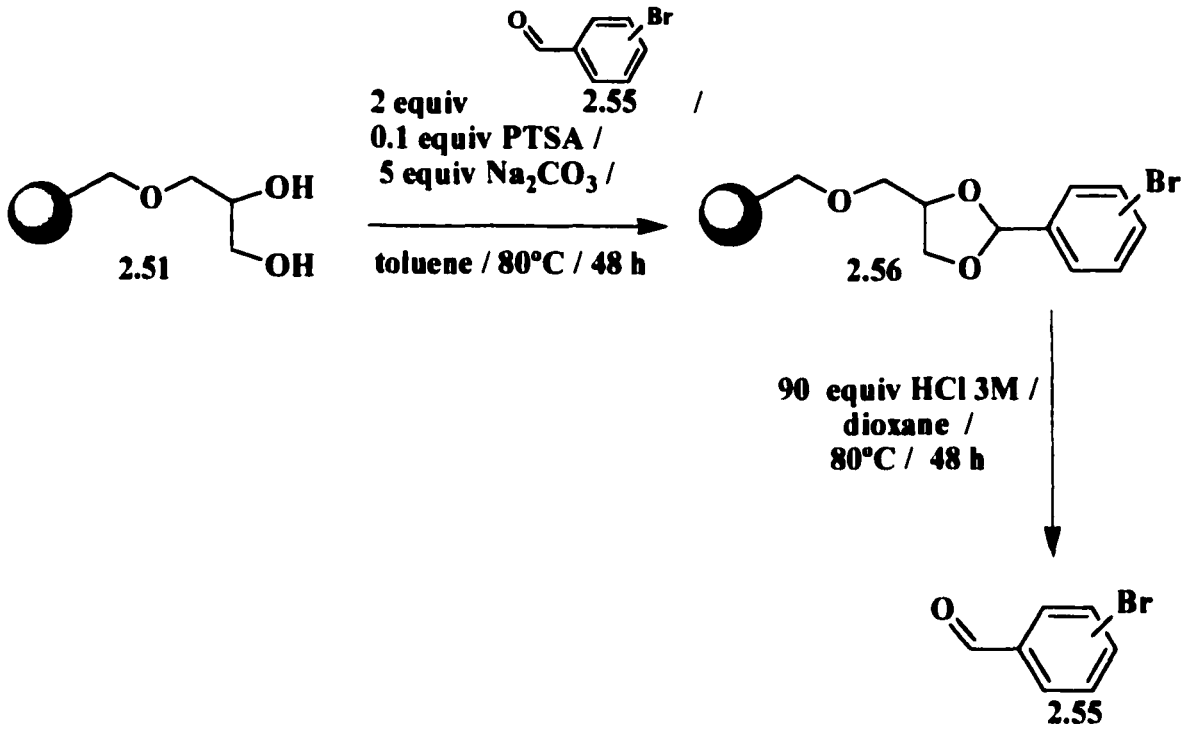
Following the optimised Leznoff protocol, the commercially available Merrifield resin **1.2** (1% cross-linked polystyrene beads with a loading of 1 mmol of $-CH_2Cl$ groups per gram of resin) was treated with the sodium alkoxide of solketal **2.49** (prepared by treatment of solketal with sodium metal), excess solketal being used as solvent to give the protected diol **2.50** (**Scheme 2.15.**). The loading level of the resin was found to be 0.95 mmol / g by determining the amount of residual chlorine.[257] For this purpose, a portion of resin was heated in pyridine to displace chlorine. The titration of the chlorine was performed by Volhard analysis. The diol functionality was treated with dilute acid in aqueous dioxane to unmask the diol linker enabling aldehydes to be loaded onto the solid support. 4-Methoxybenzaldehyde **2.52** was chosen as a test substance for attachment and removal because of its facile NMR detection (MeO signal). The attachment was carried out in the presence of a catalytic amount

of PTSA and sodium sulphate was used to absorb the liberated water. To calculate the loading of aldehyde on the resin, the functionalised resin was subjected to acidic cleavage in aqueous dioxane with dilute HCl to give, after washing of the polymer 4-methoxybenzaldehyde **2.52** and a small amount of the 4-hydroxybenzaldehyde **2.54** resulting from methyl ether deprotection during cleavage. Calculated loading of 4-methoxybenzaldehyde of 0.73 mmol/g was achieved.



Scheme 2.15. Functionalisation of Merrifield resin *via* the Leznoff acetal linker.

With this experience in hand, similar attachment and removal experiments were carried out on 2-, 3-, and 4-bromobenzaldehyde **2.55** (**Scheme 2.16.**) and loadings in the region of 0.6 mmol/g were calculated. The cleavage method proved to be very reliable even if prolonged reaction times were necessary.

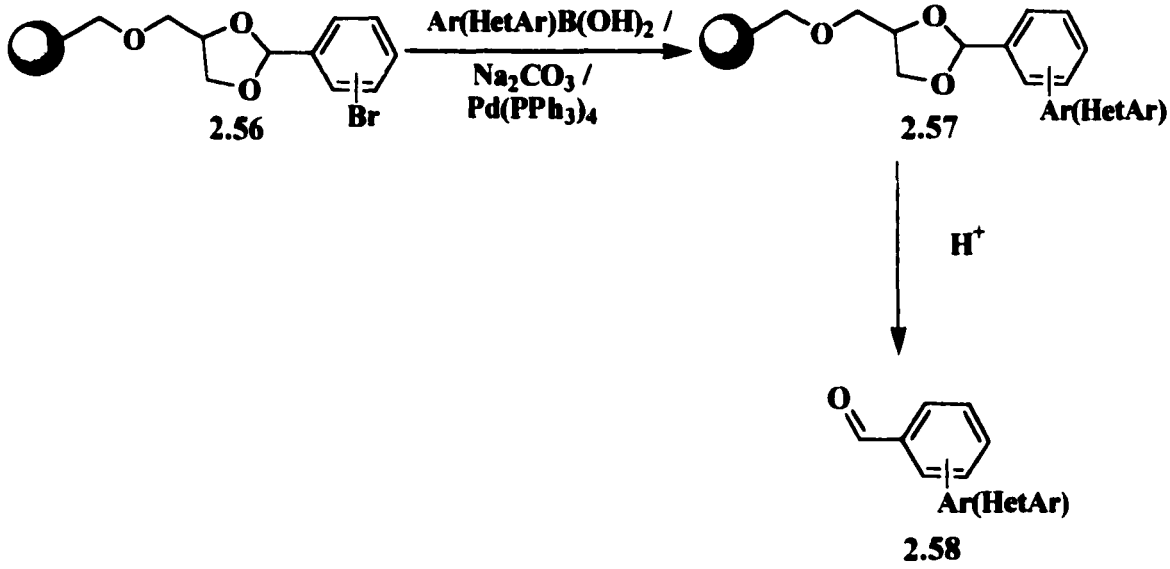


Scheme 2.16. Functionalisation of Merrifield resin by bromobenzaldehyde *via* the Leznoff acetal linker.

2.4.2. The Suzuki-Miyaura Cross Coupling Reaction on Solid Support Using the Leznoff Acetal Linker

The Leznoff–linked Merrifield resin bearing a bromobenzaldehyde acetal **2.56** was subjected to the Suzuki-Miyaura cross coupling reactions with aryl and heteroaryl boronic

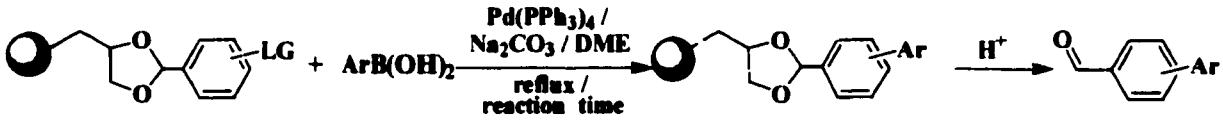
acids to give, after hydrolysis biaryls and heterobiaryls **2.58** (**Scheme 2.17.**). The cross coupling reactions were carried out using 5 mol% $Pd(PPh_3)_4$, Na_2CO_3 as the base and DME as the solvent.

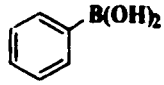
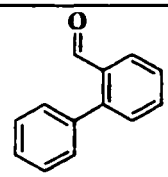
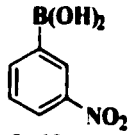
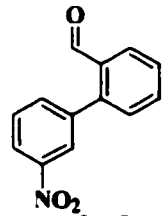
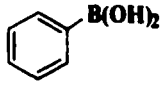
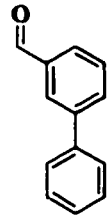
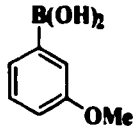
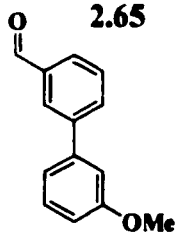
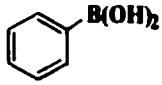
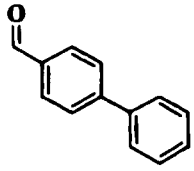


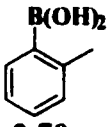
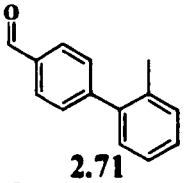
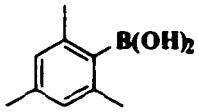
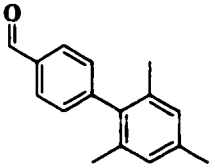
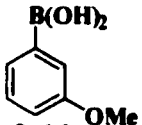
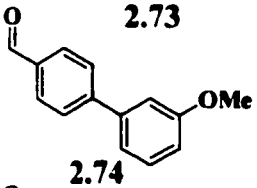
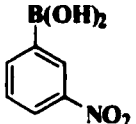
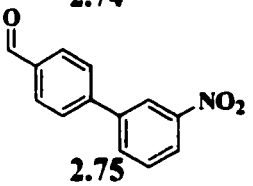
Scheme 2.17. Suzuki-Miyaura cross coupling reactions on solid support using the Leznoff acetal linker.

Upon the release from the solid support, biaryl aldehydes were prepared (**Table 2.2.**). In the absence of steric effects, excellent yields of the biaryl aldehydes were obtained. The problem of increasing steric demands could be circumvented in many cases by increasing the reaction times from 24 h to 48 h. However, in two cases, 2-tolylboronic acid **2.70** and mesitylboronic acid **2.72** (entries 6 and 7), even prolonged reaction times had minimal effects on the cross coupling reactions. The best results achieved were, respectively, 60% and 45%.

Table 2.2. Synthesis of biaryl aldehydes by Suzuki-Miyaura cross coupling reactions on solid support.



Entry	LG	$ArB(OH)_2$	Product	Reaction time (h)[a]	Yield(%)[b]
1	*o*-Br **2.59**	 **2.60**	 **2.61**	48	>95
2	*o*-Br **2.59**	 **2.62**	 **2.63**	48	87
3	*m*-Br **2.64**	 **2.60**	 **2.65**	24	>95
4	*m*-Br **2.64**	 **2.66**	 **2.67**	24	>95
5	*p*-Br **2.68**	 **2.60**	 **2.69**	24	>95

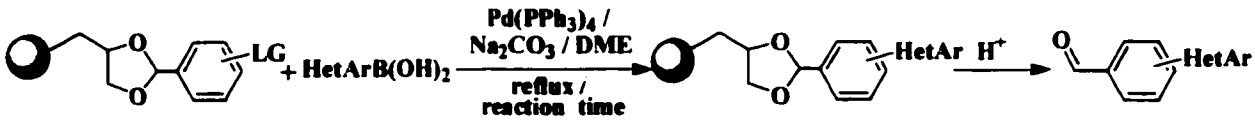
Entry	LG	$ArB(OH)_2$	Product	Reaction time (h)[a]	Yield(%)[b]
6	*p*-Br **2.68**	 **2.70**	 **2.71**	48	60 (SM : 30%)
7	*p*-Br **2.68**	 **2.72**	 **2.73**	48	45 (SM : 45%)
8	*p*-Br **2.68**	 **2.66**	 **2.74**	24	>95
9	*p*-Br **2.68**	 **2.62**	 **2.75**	24	77

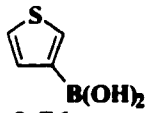
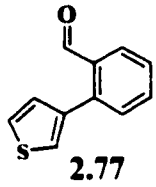
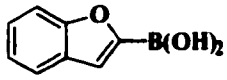
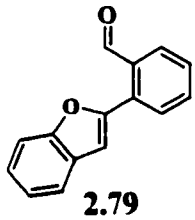
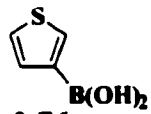
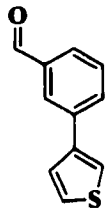
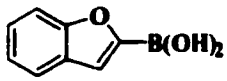
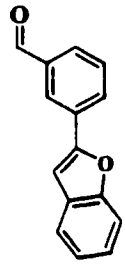
[a]Optimised reaction time. [b]Isolated yields determined after column chromatography.

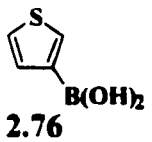
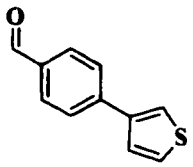
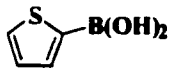
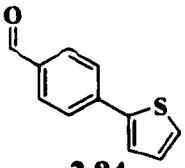
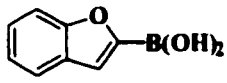
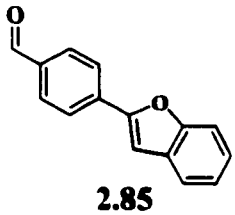
Although steric hindrance of aryl halides is not a major concern for the synthesis of substituted biaryls in solution, lower yields are observed when using *ortho*-disubstituted arylboronic acids. For example, cross coupling of mesitylboronic acid **2.72** with aryl halides is known to proceed slowly in solution due to steric hindrance during the transmetalation to Pd (II) halide.[232a]

In order to expand the scope of the Suzuki-Miyaura cross coupling reaction on solid support, heterobiaryl aldehydes were prepared using heteroaromatic boronic acids such as 2-thienylboronic acid **2.83** and 3-thienylboronic acid **2.76** and benzofuran-2-ylboranediol **2.78** (**Table 2.3.**).

Table 2.3. Synthesis of heterobiaryl aldehydes using heteroaomatic boronic acids by Suzuki-Miyaura cross coupling reactions on solid support.



Entry	LG	$HetArB(OH)_2$	Product	Reaction time (h)[a]	Yield(%)[b]
1	*o*-Br 2.59	 2.76	 2.77	48	>95
2	*o*-Br 2.59	 2.78	 2.79	48	64
3	*m*-Br 2.64	 2.76	 2.80	24	85
4	*m*-Br 2.64	 2.78	 2.81	48	95

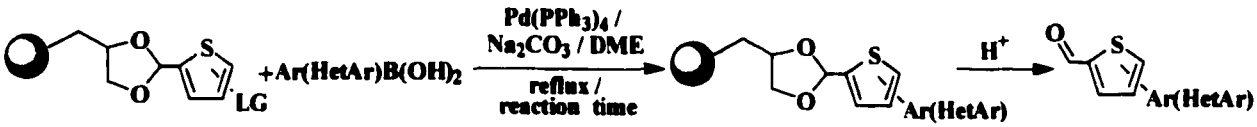
Entry	LG	HetArB(OH)$_2$	Product	Reaction time (h)[a]	Yield(%)[b]
5	*p*-Br **2.68**	 **2.76**	 **2.82**	24	>95
6	*p*-Br **2.68**	 **2.83**	 **2.84**	24	65 SM : 30%
7	*p*-Br **2.68**	 **2.78**	 **2.85**	24	>95

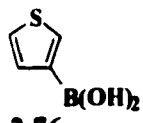
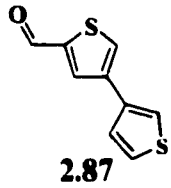
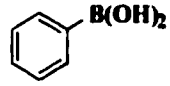
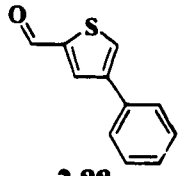
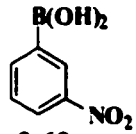
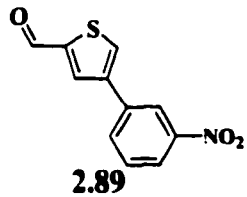
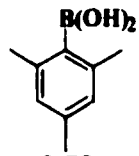
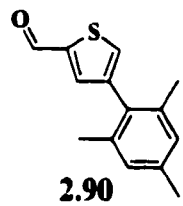
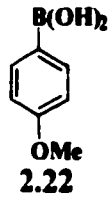
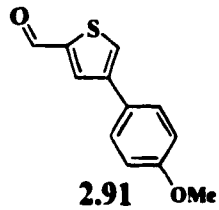
[a]Optimised reaction time. [b]Isolated yields determined after column chromatography.

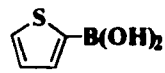
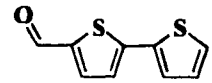
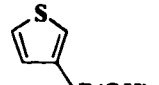
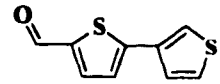
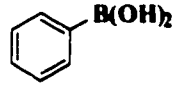
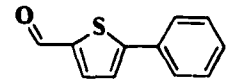
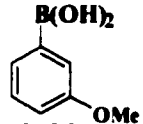
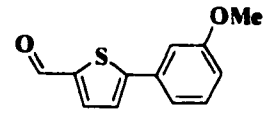
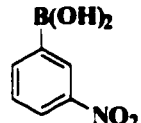
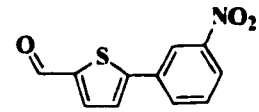
Steric hindrance was the main difficulty to circumvent. Very good conversion especially with 3-thienylboronic acid was obtained.

The synthesis of heterobiaryl aldehydes was also performed by using heterocyclic bromides directly attached to the polymer : 4-bromo-thiophene-2-carbaldehyde and 5-bromo-thiophene-2-carbaldehyde (**Table 2.4.**). The cross coupling reaction was carried out with a wide range of boronic acids (aryl and heteroaryl). Bithiophenylcarboxaldehydes were prepared in high yields by coupling with thienylboronic acids **2.76** and **2.83** (entries 1, 6, and 7). Successful results were obtained with the highly hindered mesitylboronic acid **2.72** (entry 4).

Table 2.4. Synthesis of heterobiaryl aldehydes using heteroaromatic bromides by Suzuki-Miyaura cross coupling reactions on solid support.



Entry	LG	Ar(HetAr)B(OH)$_2$	Product	Reaction time (h)[a]	Yield (%)[b]
1	4-Br 2.86	 2.76	 2.87	24	>95
2	4-Br 2.86	 2.60	 2.88	24	>95
3	4-Br 2.86	 2.62	 2.89	48	83
4	4-Br 2.86	 2.72	 2.90	48	81
5	4-Br 2.86	 2.22	 2.91	48	90

Entry	LG	Ar(HetAr)B(OH)$_2$	Product	Reaction time (h)[a]	Yield (%)[b]
6	5-Br 2.92	 2.83	 2.93	48	>95
7	5-Br 2.92	 2.76	 2.94	24	92
8	5-Br 2.92	 2.60	 2.95	24	91
9	5-Br 2.92	 2.66	 2.96	24	>95
10	5-Br 2.92	 2.62	 2.97	48	74

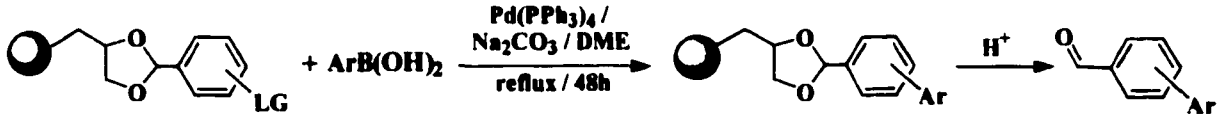
[a]Optimised reaction time. [b]Isolated yields determined after column chromatography.

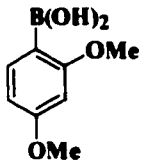
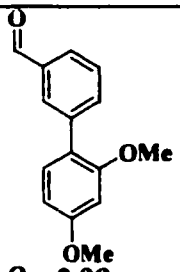
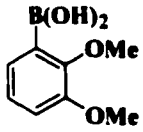
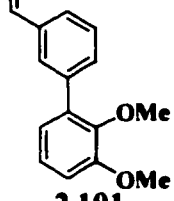
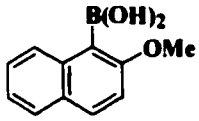
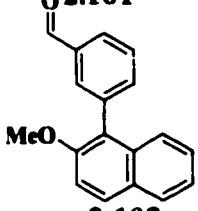
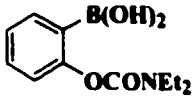
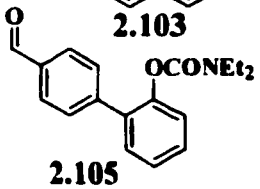
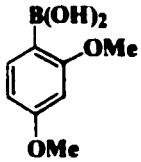
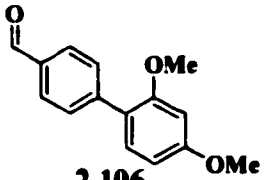
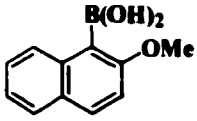
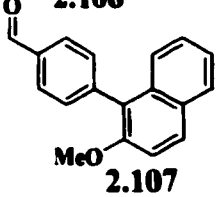
Lower yields were obtained with 3-nitrophenylboronic acid **2.62** (entries 3 and 10), which may be explained by the EWG effect of the nitro functionality disfavouring cross coupling. At the opposite end, high yields were obtained with boronic acids functionalised with the methoxy EDG (entries 5 and 9).

To demonstrate the *ortho*-metalation-polymer support cross coupling links, boronic acids bearing DMGs, prepared *via* D*o*M or metal halogen exchange were used as cross coupling partners affording cross coupled products in excellent yields under slightly longer reaction times (**Table 2.5.**). The variety of boronic acids was large: monofunctionalised (entry 4), bifunctionalised (entries 1, 2 and 5) phenylboronic acids, as well as a naphthyl boronic acid derivative (entries 3 and 6) participated in the reaction.

The *o*-functionalised biaryls released have the potential to be further derivatised by D*o*M leading to highly substituted compounds. DReM reaction may also be feasible leading to heterocycles.

Table 2.5. Synthesis of biaryl aldehydes using *ortho*-DMG boronic acids by Suzuki-Miyaura cross coupling reactions on solid support.



Entry	LG	$ArB(OH)_2$	Product	Yield(%)[a]
1	*m*-Br **2.64**	 **2.98**	 **2.99**	>95
2	*m*-Br **2.64**	 **2.100**	 **2.101**	>95
3	*m*-Br **2.64**	 **2.102**	 **2.103**	78
4	*p*-Br **2.68**	 **2.104**	 **2.105**	>95
5	*p*-Br **2.68**	 **2.98**	 **2.106**	>95
6	*p*-Br **2.68**	 **2.102**	 **2.107**	91

[a]Isolated yields determined after column chromatography.

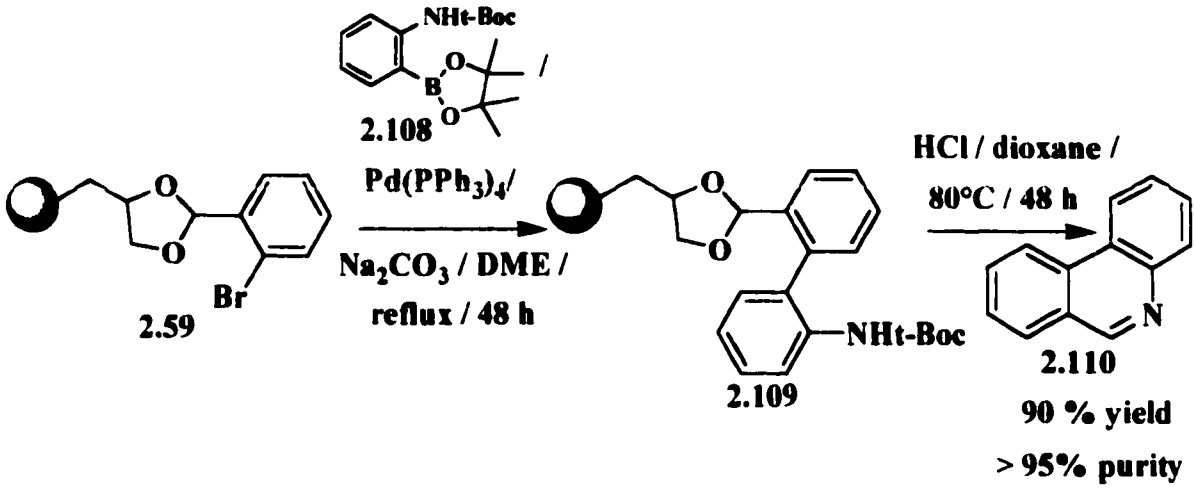
The demonstration of the synthetic utility for the formation of heterocycles by virtue of the solid support Suzuki-Miyaura-DoM connection was established in two prototype cases. Two classes of molecules, the phenanthridines and the dibenzopyranones, which had never been prepared on solid support to our knowledge, may thus be accessed by this methodology.

Phenanthridine and dibenzopyranone ring systems are present in biologically active molecules. Phenanthridines are present as subunits in several classes of alkaloids and have pharmacological properties.[258] The dibenzo[*b,d*]pyran-6-one ring system is found in some oxygenated natural products such as castoreum,[259] autumnariol,[260] and altenuisol.[261] The biological activity of the dibenzopyranone derivatives is quite diverse, having been reported to show general cytoxicity[262] as well as antibiotic and antitumor effects.[263]

In 1979, Gschwend[264] reported the first nitrogen-based DMG, *N*-pivaloyl (NHCO*t*Bu) DMG, which has, more recently, been used for the synthesis of substituted pyridines[265] and quinolines.[266] The more useful nitrogen-based NH*t*-Boc amino DMG was discovered by Muchowski in 1980.[267] The facile removal of the *t*-Boc group[268] allows the preparation of ortho functionalised anilines and the D*o*M strategy has been applied for the synthesis of biologically active products.[269]

Thus cross coupling of solid support-tethered 2-bromobenzaldehyde **2.59** with the boronate ester of *N*Boc aniline **2.108** resulted, upon cleavage, in cyclisation to phenanthridine **2.110** in excellent combined yield (90%, two steps) and purity (95%) (**Scheme 2.18.**). This

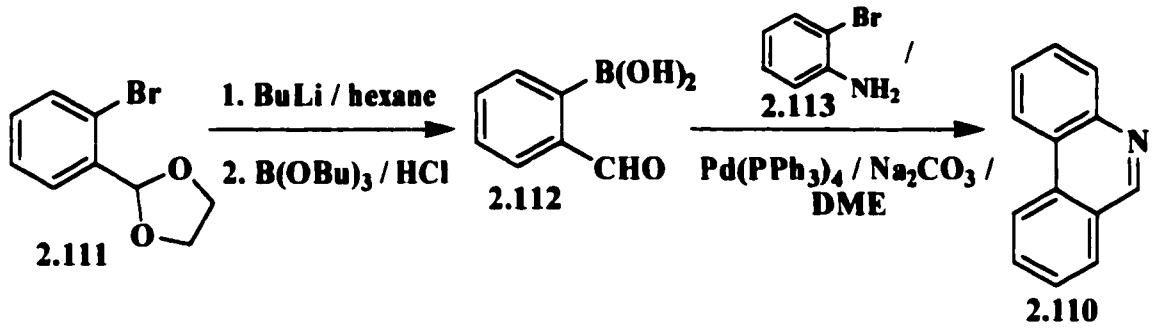
result, based on the versatile cross coupling on solid support - DoM promises broad scope for the rapid access of libraries of phenanthridines with a variety of substitution patterns.



Scheme 2.18. Synthesis of phenanthridine *via* the Suzuki-Miyaura cross coupling reaction on solid support.

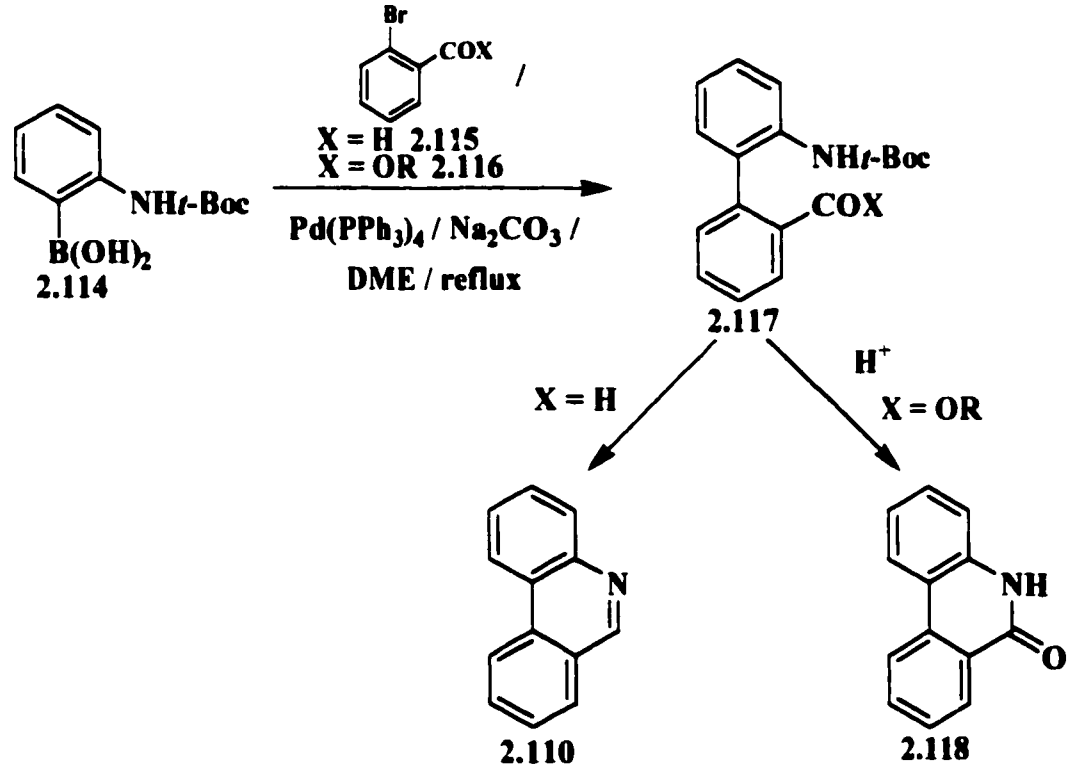
Many strategies had been developed for the synthesis of phenanthridines in solution phase such as benzyne-mediated condensation of *o*-haloanilines,[270] directed-metalation based cyclisation of 2-substituted biphenyls,[271] and radical-cyclisation of biphenylimines.[272]

In 1986, Gronowitz[273] reported the synthesis of phenanthridine **2.110** using the Suzuki-Miyaura cross coupling reaction of 2-formylbenzeneboronic acid **2.112** prepared by metal halogen exchange of the acetal of 2-bromobenzaldehyde **2.111** and 2-bromoaniline **2.113** (**Scheme 2.19.**).



Scheme 2.19. Synthesis of phenanthridine using the Suzuki-Miyaura cross coupling reaction.

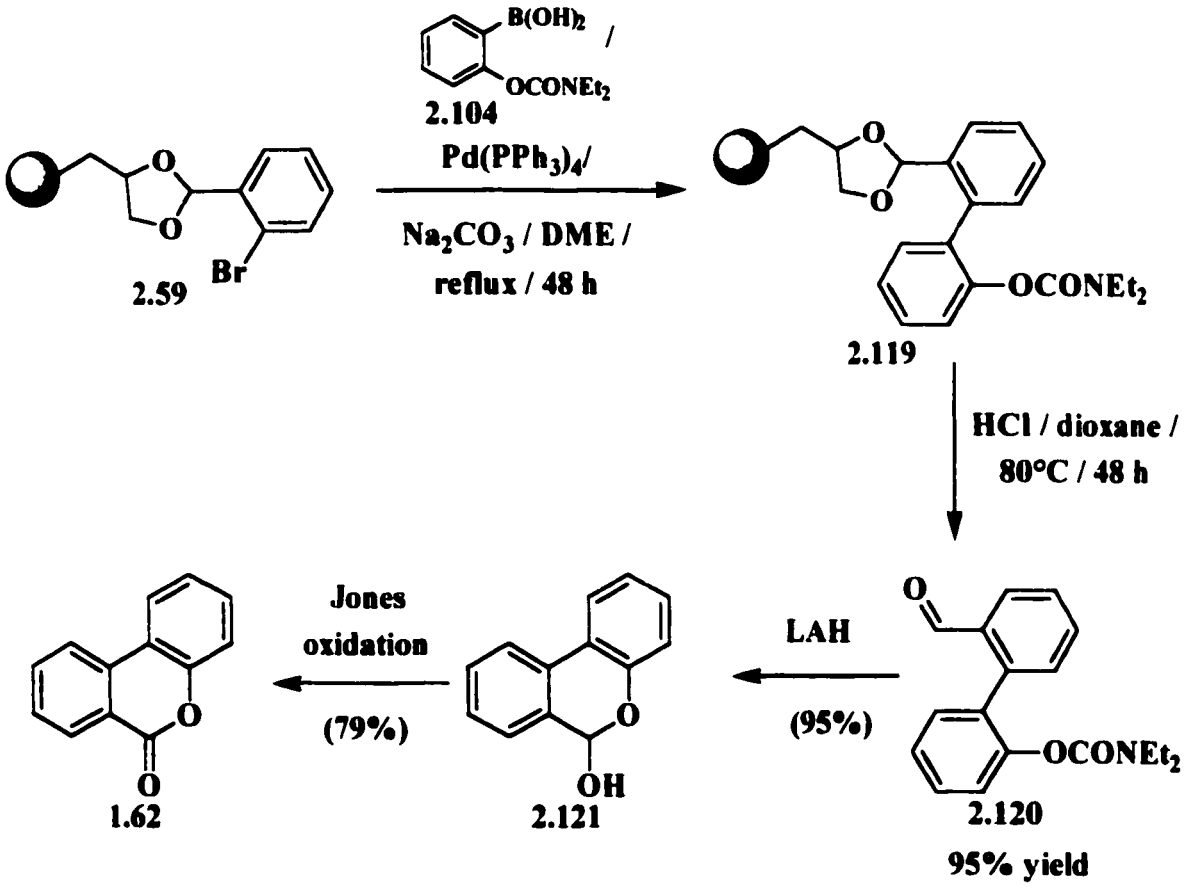
Our strategy on solid support is analogous to the one developed by Siddiqui[274] for the solution phase synthesis of phenanthridines **2.110** and phenanthridinones **2.118** (**Scheme 2.20.**).



Scheme 2.20. Synthesis of phenanthridines and phenanthridinones using the solution phase Suzuki-Miyaura cross coupling reaction.

o-NH*t*-Boc boronic acid **2.114** was subjected to the coupling reaction with 2-bromobenzaldehyde (X = H) **2.115** and 2-bromophenylester (X = OR) **2.116** followed by either spontaneous (X = H) or acid-catalysed (X = OR) cyclisation. In the case of phenanthridine **2.110**, Siddiqui obtained a yield of 77%.

To follow the work in solution phase accomplished in our laboratories by Sharp[228] in 1985 and by Alo and coworkers[275] in 1991, we wished to develop a solid phase strategy for the synthesis of 6*H*-dibenzo[*b,d*]pyran-6-one (**Scheme 2.21.**).



Scheme 2.21. Synthesis of 6*H*-dibenzo[*b,d*]pyran-6-one *via* the Suzuki-Miyaura cross coupling reaction on solid support.

Our approach first involved the solid phase Suzuki-Miyaura cross coupling reaction between the polymer-bound 2-bromobenzaldehyde **2.59** and 2-*N,N*-diethylcarbamoylphenylboronic acid **2.104**. Treatment of the cross coupled product released in solution **2.120** with LAH lead to dibenzopyranol **2.121**. Finally, Jones oxidation furnished 6*H*-dibenzo[*b,d*] pyran-6-one **1.62** in good yield.

2.4.3. Conclusion

The Suzuki-Miyaura cross coupling reactions leading to biaryl and heterobiaryl aldehydes, a hitherto difficult to access class of molecules using currently available linker technologies, was performed successfully on solid support using the Leznoff acetal linker. A general set of conditions that allows for complete conversion over a wide range of substrates was found. Furthermore, connection of this process to solution phase D*o*M strategy has been demonstrated. The application of this methodology to diverse libraries of biaryls, phenanthridines and dibenzopyranones may be anticipated.

2.5. Experimental

2.5.1. Standard Methods

Procedure A. Attachment of halobenzaldehydes to resin-bound 3-benzyloxypropan-1,2-diol.

Resin-bound 3-benzyloxypropan-1.2-diol **2.51** (theoretical loading 0.915 mmol/g, 2.73 g, 2.5 mmole) was swollen in anhydrous toluene (50 mL) for 30 min in a dry SPOS flask fitted with an overhead stirrer. Bromobenzaldehyde (5 mmole) and *p*-toluenesulfonic acid monohydrate (0.25 mmole) were added. To the mixture was added anhydrous Na_2SO_4 (12.5 mmole) to absorb liberated water and the mixture was stirred at 80° C for 48 h under exclusion of moisture ($CaCl_2$ drying tube). The resin was collected by filtration, neutralised with anhydrous pyridine (to prevent cleavage of the aldehyde from the polymer by hydrolysis of the acetal linkage) and filtered. The resin was washed twice with pyridine-water (1:1), ten times with water (to remove Na_2SO_4), three times with EtOH, three times with anhydrous ether and dried overnight in an Abderhalden apparatus.

Procedure B. Determination of the loading capacity of resin-bound bromobenzaldehydes.

Resin-bound bromobenzaldehyde (theoretical maximal loading 0.920 mmole / g, 0.20 g) was swollen in dioxane (5.5 mL) for 30 min, a solution of 3 M hydrochloric acid (5.5 mL) was added and the mixture was stirred at 80° C for 48 h. The reaction mixture was cooled to rt and

subjected to filtration (fritted glass funnel). The resin was successively washed three times with water, three times with water:MeOH (1:1), three times with MeOH, and three times with DCM, and the filtrate was repeatedly extracted with DCM. The combined organic extract was washed with water and brine, dried (Na_2SO_4), and evaporated to dryness. The residue was purified on silica gel to give bromobenzaldehyde.

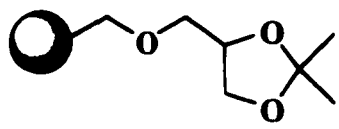
Procedure C. Suzuki cross coupling reaction of resin-bound halobenzaldehydes with boronic acids.

Resin-bound bromobenzaldehyde (theoretical loading 0.5 mmole / g, 0.20 g, 0.10 mmole) was swollen in anhydrous DME (6.5 mL) and the system was flushed with argon (30 min). $Pd(PPh_3)_4$ (0.005 mmole) was added and the reaction mixture was stirred for 10 min at rt and treated with degassed Na_2CO_3 solution (2 M aqueous, 0.4 mL) and stirred for 10 min. Boronic acid (0.30 mmole) was added, the reaction mixture was flushed with argon (15 min) and heated to reflux. The reaction mixture was cooled to rt and treated with aq. satd. NH_4Cl solution (5 mL) and further stirred for 10 min. The resin was removed by filtration (fritted glass funnel) and washed successively once with DME, twice with DME:H_2O (1:1), twice with 0.3 M HCl, three times with H_2O, once with DME, twice with EtOAc, twice with EtOAc: MeOH (1:1), and three times with MeOH, and dried overnight in an Abderhalden apparatus.

Procedure D. Cleavage of the cross-coupled product from the solid support.

Resin-bound biaryl or heterobiaryl aldehyde (theoretical loading max 0.5 mmole / g, 0.18 g) was swollen in dioxane (2.8 mL) for 30 min, a solution of 3 M hydrochloric acid (2.8 mL) was

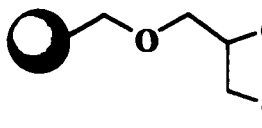
added and the mixture was stirred at 80° C for 48 h. The reaction mixture was cooled to rt and subjected to filtration (fritted glass funnel). The resin was successively washed three times with water, three times with water:MeOH (1:1), three times with MeOH, and three times with DCM. The filtrate was repeatedly extracted with DCM. The combined organic extract was washed with water and brine, dried (Na_2SO_4), and evaporated to dryness. The reaction composition was analysed by GC. The residue was purified on silica gel to give the cross-coupled product.



Resin-bound 1-O-benzyl-2,3-isopropylidene glycerol (2.50)

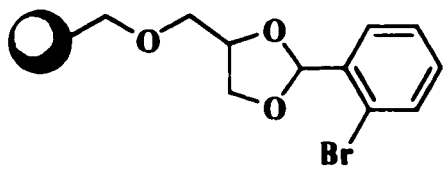
To cold (0°C) 2,2-dimethyl-1,3-dioxolane-4-methanol (Solketal) 98% (50 mL, 53.15 g, 394.1 mmole) purged with argon sodium metal (1.2 g, 52.2 mmole) was added slowly over 3h. The reaction was allowed to stir 48 h at rt under argon until all the sodium had dissolved. In a SPOS flask fitted with an overhead stirrer and an argon inlet the Merrifield resin **1.2** (1% cross-linked, loading 1 mmole / g, 5 g, 5 mmole) was added followed by the freshly prepared sodium alkoxide of Solketal. The mixture was stirred at rt overnight and at 80°C for 48 h. The reaction mixture was cooled to rt and the resin was collected by filtration and washed three times with dioxane, six times with water, three times with EtOH-water (1:1), three times with EtOH, and three times with anhydrous ether, and dried overnight in an Abderhalden apparatus. A modified Volhard analysis[116] of **2.50** showed 0.085 mmole of residual chloride per g of resin. IR (KBr) 1067 cm^{-1} (C-O-C).

Resin-bound 3-benzyloxypropan-1,2-diol (2.51)



Resin-bound 1-O-benzyl-2,3-isopropylidene glycerol **2.50** (loading 0.915 mmol/g, 4.94 g, 4.52 mmole) was swollen in dioxane (13.6 mL) for 30 min in a SPOS flask fitted with an overhead stirrer. A solution of 1.5 M hydrochloric acid (13.6 mL, 20.4 mmole) was added and the mixture was stirred at 80° C for 72 h. The reaction mixture was cooled to rt and the resin **2.51** was collected by filtration and washed six times with water, once with acetone, three times with EtOH, and three times with anhydrous ether and dried overnight in an Abderhalden apparatus. IR (KBr) 3416 (OH), 1067 cm^{-1} (C-O-C).

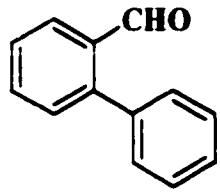
Resin-bound 2-bromobenzaldehyde (2.59)



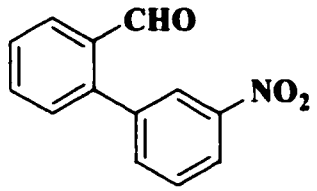
According to General Procedure A, resin-bound 3-benzyloxypropan-1,2-diol **2.51** (loading 0.915 mmol/g max, 2.73 g, 2.5 mmole max) was swollen in anhydrous toluene (50 mL) and treated with freshly distilled 2-bromobenzaldehyde (0.925 g, 0.58 mL, 5 mmole), *p*-toluenesulfonic acid monohydrate (0.048 g, 0.25 mmole) and anhydrous Na_2SO_4 (1.775 g, 12.5 mmole). After 48 h at 80°C, the reaction mixture was cooled to rt and the resulting resin was collected by filtration, neutralised with anhydrous pyridine, washed and dried to afford **2.59**. The loading capacity of **2.59** was determined according to General Procedure B. **2.59** (0.205 g) was swollen in dioxane (5.6 mL) and treated with a solution of 3 M hydrochloric acid (5.6 mL) for 48 h at 80°C. After filtration of the reaction mixture and washing of the resin, the filtrate was worked-up and the residue obtained purified on silica gel

(5:1 hexane:EtOAc) to give 2-bromobenzaldehyde (0.0125 g) showing a loading of **2.59** of 0.33 mmol/g.

Biphenyl-2-carbaldehyde (2.60)

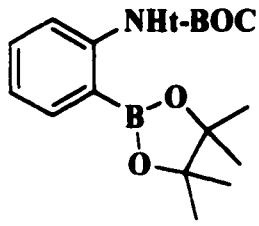


According to General Procedure C, resin-bound 2-bromobenzaldehyde **2.59** (1% cross-linked, loading 0.315 mmol/g, 0.317 g, 0.10 mmole) was swollen in anhydrous DME (10.6 mL) and coupled with phenylboronic acid 97% **2.60** (0.038 g, 0.3 mmole) in the presence of $Pd(PPh_3)_4$ (0.0058 g, 0.005 mmole) and Na_2CO_3 solution (2 M aqueous, 0.4 mL). After 48 h, the reaction mixture was cooled to rt and treated with aq. satd. NH_4Cl solution (5 mL) and further stirred for 10 min. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.2855 g) was swollen in dioxane (2.7 mL) for 30 min and treated with a solution of 3 M HCl (2.7 mL) for 48 h at 80°C. After filtration of the reaction mixture and washing of the resin, the filtrate was worked-up and the residue obtained purified on silica gel (5:1 hexane:EtOAc) to give biphenyl-2-carbaldehyde **2.60** (0.0161 g, loading: 0.309 mmol/g, >95%) as a colourless oil : Beilstein Registry # [2081880] IR (neat) 2760, 1690 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.98 (s, 1H), 8.03 (d, J = 7.7 Hz, 1H), 7.68-7.38 (m, 8H). Spectral data are consistent with those reported.[276]



2-(3-Nitrophenyl)benzaldehyde (2.63)

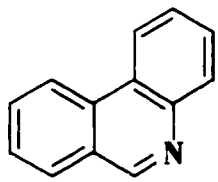
According to General Procedure C, resin-bound 2-bromobenzaldehyde **2.59** (1% cross-linked, loading 0.315 mmol/g, 0.317 g, 0.10 mmole) was swollen in anhydrous DME (10.6 mL) and coupled with 3-nitrophenylboronic acid 98% **2.62** (0.051 g, 0.3 mmole) in the presence of $Pd(PPh_3)_4$ (0.0058 g, 0.005 mmole) and Na_2CO_3 solution (2 M aqueous, 0.4 mL). After 48 h, the reaction mixture was cooled to rt and treated with aq. satd. NH_4Cl solution (5 mL) and further stirred for 10 min. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.298 g) was swollen in dioxane (2.8 mL) for 30 min and treated with a solution of 3 M HCl (2.8 mL) for 48 h at 80°C. After filtration of the reaction mixture and washing of the resin, the filtrate was worked-up and the residue obtained purified on silica gel (5:1 hexane:EtOAc) to give 2-(3-nitrophenyl)benzaldehyde **2.63** (0.0185 g, loading: 0.273 mmol/g, 87%) as a colourless solid : Beilstein Registry # [7992002] mp 111-113 °C (hexane); IR (DCM) 3057, 1694, 1533, 1424, 1352 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.90 (s, 1H), 8.27-7.37 (m, 8H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 191.0, 148.1, 139.6, 135.8, 133.9, 133.4, 130.8, 129.3, 128.9, 124.4, 122.9; MS (EI (70 eV)) m/z (rel intensity) 227 (M^+, 46), 226 (16), 210 (24), 181 (27), 180 (56), 153 (39), 152 (100); HRMS *m/e* calcd for $C_{13}H_9NO_3$: 227.0582, found 227.0578; Anal. Calcd for $C_{13}H_9NO_3$: C, 68.72 ; H, 3.99 ; N, 6.16. Found : C, 68.84; H, 4.20 ; N, 5.98.



Pinacol[*N*-(*tert*-butoxycarbonyl)-2-amino-1-phenyl]boronate (2.108)

Sample supplied by Stephen Houldsworth.[277] Colourless solid.: Beilstein Registry # [7218656]; IR (KBr) 3377, 2982, 1729, 1608, 1360, 1317, 1232, 1148cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.67 (bs, 1H), 8.17 (d, J = 8.5 Hz, 1H), 7.71 (dd, J = 7.3, 1.8 Hz, 1H), 7.41 (ddd, J = 7.3, 7.3, 1.8 Hz, 1H), 6.98 (ddd, J = 7.3, 7.3, 0.9 Hz, 1H), 1.53(s, 9H), 1.36(s, 12H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 153.1, 145.2, 136.1, 132.7, 121.5, 117.6, 84.1, 79.7, 28.3, 24.8 ; MS (FAB (glycerol)) m/z (rel intensity) 320 (M^++1, 17), 319 (M^+, 18), 263 (34), 246 (17), 220 (45), 185 (100) ; HRMS *m/e* calcd for $C_{17}H_{26}{}^{11}BNO_4$: 319.1955, found 319.1943. Spectral data are consistent with those reported.[278]

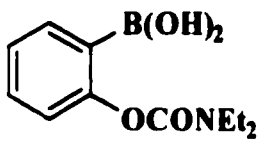
Phenanthridine (2.110)



According to General Procedure C, resin-bound 2-bromobenzaldehyde **2.59** (1% cross-linked, loading 0.315 mmol/g, 0.317 g, 0.10 mmole) was swollen in anhydrous DME (10.6 mL) and coupled with pinacol[N-(tert-butoxycarbonyl)-2-amino-1-phenyl]boronate **2.108** (0.096 g, 0.3 mmole) in the presence of $Pd(PPh_3)_4$ (0.0058 g, 0.005 mmole) and Na_2CO_3 solution (2 M aqueous, 0.4 mL). After 48 h, the reaction mixture was cooled to rt and treated with aq. satd. NH_4Cl solution (5 mL) and further stirred for 10 min. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.301 g) was swollen in dioxane (3.0 mL) for 30 min and treated with a solution of 3 M HCl (3.0 mL) for 48 h at 80°C. After filtration of the reaction mixture and washing of the

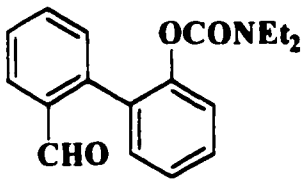
resin, the filtrate was worked-up and the residue obtained purified on silica gel (5:1 hexane:EtOAc) to give phenanthridine **2.110** (0.0154 g, loading: 0.285 mmol/g, 90 %) as a colourless solid : Beilstein Registry # [120204]; mp 104-105 °C (Lit.[274a] mp 107-108 °C (EtOH)); ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.36 (s, 1H), 8.66 (d, J = 7.6 Hz, 1H), 8.61 (d, J = 7.2 Hz, 1H), 8.34 (dd, J = 7.0, 1.9 Hz, 1H), 8.13 (dd, J = 7.9, 0.6 Hz, 1H), 8.00-7.69 (m, 4H); MS (FAB (glycerol)) m/z (rel intensity) 180 (M^++1, 100); HRMS *m/e* calcd for $C_{13}H_{10}N$: 180.0813, found 180.0810.

2-*N,N*-Diethylcarbamoylphenylboronic acid (2.104)



To a solution of diethyl-carbamic acid phenyl ester **1.52** (0.522 g, 2.7 mmole) in anhydrous THF (27 mL) was added at rt TMEDA (0.345 g, 0.45 mL, 2.97 mmole). The reaction mixture was cooled to –78°C and *s*-BuLi (2.52 mL, 1.18 M, 2.97 mmole) was added dropwise to the cooled solution over a period of 10 min and stirred for 15 min at -78°C. Trimethyl borate (1.21 mL, 1.12 g, 10.8 mmole) was added rapidly to the cooled solution. The reaction mixture was stirred 30 min at –78° and was allowed to warm to rt and stirred 1h at rt. H_2O (10 mL) was added and the reaction mixture was acidified to a pH ~6 with 1.5 M HCl. The solution was concentrated under vacuum and the residue extracted with ether (2 x 10 mL). The combined organic extract was washed with H_2O (1x), brine (1x), dried over Na_2SO_4 and evaporated to dryness to give a yellow solid. The residue was recrystallised from H_2O to give 2-*N,N*-diethylcarbamoylphenylboronic acid **2.104** (0.415 g, 65%) as a colourless solid : mp 117-119 °C (water); IR (KBr) 3054, 2985, 1709, 1646, 1428, 1266, 731 cm^{-1}; ^{1}H NMR (200 MHz,

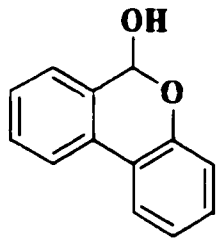
$CDCl_3$) δ 7.87-6.96 (m, 4H), 3.41 (bs, 1H), 3.28-3.24 (m, 4H), 1.60 (bs, 1H), 1.25-1.00 (m, 6H); ^{13}C NMR (75.5 MHz,$CDCl_3$) δ 155.2, 135.2, 130.1, 129.1, 124.9, 122.0, 119.2, 42.2, 41.7, 13.7, 13.1.



2-(2-*N,N*-Diethylcarbamoylphenyl)benzaldehyde (2.120)

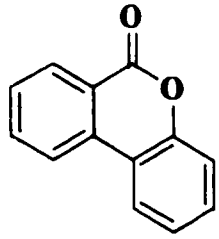
According to General Procedure C, resin-bound 2-bromobenzaldehyde **2.59** (1% cross-linked, loading 0.315 mmol/g, 1.212 g, 0.40 mmole) was swollen in anhydrous DME (40 mL) and coupled with 2-N,N-diethylcarbamoylphenylboronic acid **2.104** (0.284 g, 1.2 mmole) in the presence of $Pd(PPh_3)_4$ (0.0231 g, 0.020 mmole) and Na_2CO_3 solution (2 M aqueous, 1.6 mL). After 48 h, the reaction mixture was cooled to rt and treated with aq. satd. NH_4Cl solution (5 mL) and further stirred for 10 min. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (1.194 g) was swollen in dioxane (12 mL) for 30 min and treated with a solution of 3 M HCl (12 mL) for 48 h at 80°C. After filtration of the reaction mixture and washing of the resin, the filtrate was worked-up and the residue obtained purified on silica gel (5:1 hexane:EtOAc) to give 2-(2-*N,N*-diethylcarbamoylphenyl)benzaldehyde **2.120** (0.1125 g, loading: 0.317 mmol/g, >95%) as a yellow oil : IR (neat) 2973, 1716, 1710, 1597, 1472, 1274 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.78 (s, 1H), 7.93 (d, J = 7.7 Hz, 1H), 7.65-7.18 (m, 7H), 3.01 (m, 4H), 0.83 (m, 6H); ^{13}C NMR (50.3 MHz,$CDCl_3$) δ 192.2, 153.2, 133.9, 133.4, 131.2, 129.5, 128.0, 126.6, 125.4, 123.0. 41.9, 41.5, 13.6, 12.9; MS (CI) m/z (rel

intensity) 298 (M^++1, 14), 181 (77), 118 (9), 100 (100) ; HRMS *m/e* calcd for $C_{18}H_{19}NO_3$ + H : 298. 144319, found 298.143000.



6*H*-Dibenzo[*b,d*]pyran-6-ol (2.121)

Sample supplied by Stephen Houldsworth.[277] Colourless solid.: Beilstein Registry # [4420143] mp 88-90 °C (Lit. [279] mp 86-88°C (*n*-pentane / diisopropyl ether (9 :1)); ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.40 (d, J = 7.6 Hz, 1H), 8.09 (d, J = 7.9 Hz, 1H), 8.03 (d, J = 8.1 Hz, 1H),7.81 (t, J = 8.1 Hz, 1H), 7.54 (t, J = 7.7 Hz, 1H), 7.51-7.27 (m, 3H), 6.25 (m, 1H), 3.42 (bs, 1H) ; ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 151.2, 134.8, 134.7, 130.9, 130.5, 130.4, 128.8, 124.5, 122.7, 121.6, 118.0, 117.7, 113.5; MS (FAB (glycerol)) m/z (rel intensity) 198 (M^+, 25), 197 (100).

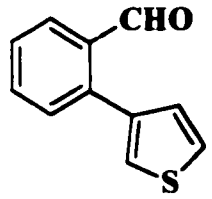


6*H*-Dibenzo[*b,d*]pyran-6-one (1.62)

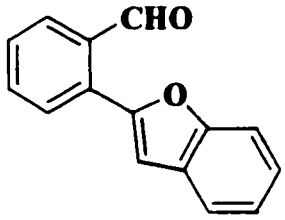
Jones[280] reagent was added dropwise to a solution of 6*H*-dibenzo[*b,d*]pyran-6-ol **2.121** (0.045 g, 0.23 mmole) in acetone (32 mL) until the orange colour of the reagent was maintained. After decomposition of the excess reagent by addition of isopropyl alcohol, the mixture was poured into water and repeatedly extracted with DCM. The combined organic extract was washed with water (2x), 1 M NaOH (2x), water (2x), brine (1x), dried over Na_2SO_4 and evaporated. The residue was purified on silica gel (9:1 hexane:EtOAc) to give 6*H*-dibenzo[*b,d*]pyran-6-one **1.62** as (0.036 g, 79%) as a colourless solid : Beilstein Registry # [140721]; mp 91-93 °C

(Lit.[281] mp 92-93 °C (MeOH)); IR ($CHCl_3$) 1733 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.35 (d, J = 7.7 Hz, 1H), 8.05 (d, J = 8.1 Hz, 1H), 7.95 (d, J = 8.1, 1H), 7.75 (t, J = 8.0 Hz, 1H), 7.52 (t, J = 7.7, 1H), 7.42-7.28 (m, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 170.4, 161.1, 151.3, 134.8, 130.6, 130.4, 128.8, 124.5, 122.7, 121.6, 121.2, 117.8, 117.7.

2-(3-Thienyl)benzaldehyde (2.77)



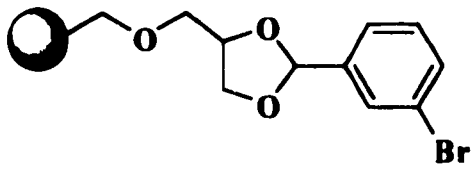
According to General Procedure C, resin-bound 2-bromobenzaldehyde **2.59** (1% cross-linked, loading 0.315 mmol/g, 0.317 g, 0.10 mmole) was swollen in anhydrous DME (10.6 mL) and coupled with 3-thiopheneboronic acid 95% **2.76** (0.040 g, 0.3 mmole) in the presence of $Pd(PPh_3)_4$ (0.0058 g, 0.005 mmole) and Na_2CO_3 solution (2 M aqueous, 0.4 mL). After 48 h, the reaction mixture was cooled to rt and treated with aq. satd. NH_4Cl solution (5 mL) and further stirred for 10 min. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.302 g) was swollen in dioxane (2.9 mL) for 30 min and treated with a solution of 3 M HCl (2.9 mL) for 48 h at 80°C. After filtration of the reaction mixture and washing of the resin, the filtrate was worked-up and the residue obtained purified on silica gel (9:1 hexane:EtOAc) to give 2-(3-thienyl)benzaldehyde **2.77** (0.0171 g, loading: 0.30 mmol/g, >95%) as a yellow oil : Beilstein Registry # [5502986]; IR (neat) 1690 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 10.07 (s, 1H), 7.98 (m, 1H), 7.70-7.14 (m, 6H); MS (EI (70 eV)) m/z (rel intensity) 188 (M^+, 66), 160 (94), 149 (26), 128 (24), 115 (100) ; HRMS *m/e* calcd for $C_{11}H_8OS$: 188.0296, found 188.0293. Spectral data are consistent with those reported.[282]



2-(2-Benzofuranyl)benzaldehyde (2.79)

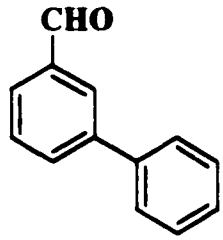
According to General Procedure C, resin-bound 2-bromobenzaldehyde **2.59** (1% cross-linked, loading 0.33 mmol/g, 0.303 g, 0.10 mmole) was swollen in anhydrous DME (10 mL) and coupled with benzofuran-2-yl-boranediol **2.78** (0.049 g, 0.3 mmole) in the presence of $Pd(PPh_3)_4$ (0.0058 g, 0.005 mmole) and Na_2CO_3 solution (2 M aqueous, 0.4 mL). After 48 h, the reaction mixture was cooled to rt and treated with aq. satd. NH_4Cl solution (5 mL) and further stirred for 10 min. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.289 g) was swollen in dioxane (2.9 mL) for 30 min and treated with a solution of 3 M HCl (2.9 mL) for 48 h at 80°C. After filtration of the reaction mixture and washing of the resin, the filtrate was worked-up and the residue obtained purified on silica gel (9:1 hexane:EtOAc) to give 2-(2-benzofuranyl)benzaldehyde **2.79** (0.0135 g, loading: 0.21 mmol/g, 64%) as a yellow oil : IR (neat) 3055, 2986, 1692, 1599, 1432, 1265, 895 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.39 (s, 1H), 7.96 (d, J = 7.9 Hz, 1H), 7.76 (d, J = 7.9 Hz, 1H), 7.62-7.42 (m, 4H), 7.30-7.17 (m, 2H), 6.90 (s, 1H) ; ^{13}C NMR (75.5 MHz $CDCl_3$) δ 192.0, 155.5, 152.9, 133.0, 128.8, 128.5, 128.6, 128.2, 125.2, 125.0, 123.4, 122.3, 121.4, 111.3, 107.8;MS (EI (70 eV)) m/z (rel intensity) 222 (M^+, 68), 195 (14), 194 (92), 166 (19), 165 (100) ; HRMS *m/e* calcd for $C_{15}H_{10}O_2$: 222.0681, found 222.0676.

Resin-bound 3-bromobenzaldehyde (2.64)



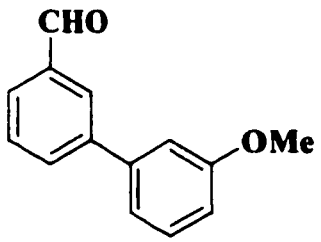
According to General Procedure A, resin-bound 3-benzyloxypropan-1,2-diol **2.51** (loading 0.919 mmol/g max. 3.26 g, 3 mmole max) was swollen in anhydrous toluene (60 mL) and treated with freshly distilled 3-bromobenzaldehyde (1.11 g, 0.70 mL, 6 mmole), *p*-toluenesulfonic acid monohydrate (0.057 g, 0.3 mmole) and anhydrous Na_2SO_4 (2.13 g, 15 mmole). After 48 h at 80°C, the reaction mixture was cooled to rt and the resulting resin was collected by filtration, neutralised with anhydrous pyridine, washed and dried to afford **2.64**. The loading capacity of **2.64** was determined according to General Procedure B. **2.64** (0.201 g) was swollen in dioxane (5.5 mL) and treated with a solution of 3 M hydrochloric acid (5.5 mL) for 48 h at 80°C. After filtration of the reaction mixture and washing of the resin, the filtrate was worked-up and the residue obtained purified on silica gel (5:1 hexane:EtOAc) to give 3-bromobenzaldehyde (0.0215 g) showing a loading of **2.64** of 0.58 mmol/g.

Biphenyl-3-carbaldehyde (2.65)



According to General Procedure C, resin-bound 3-bromobenzaldehyde **2.64** (1% cross-linked, loading 0.52 mmol/g, 0.191 g, 0.10 mmole) was swollen in anhydrous DME (6.4 mL) and coupled with phenylboronic acid 97% **2.60** (0.038 g, 0.30 mmole) in the presence of $Pd(PPh_3)_4$ (0.0058 g, 0.005 mmole) and Na_2CO_3 solution (2 M aqueous, 0.4 mL). After 24 h, the reaction mixture was cooled to rt and treated with aq. satd. NH_4Cl solution (5 mL) and further stirred for 10 min. The resin was removed by filtration, washed and dried. The cleavage from

the solid support was done according to General Procedure D. The resulting resin (0.180 g) was swollen in dioxane (2.8 mL) for 30 min and treated with a solution of 3 M HCl (2.8 mL) for 48 h at 80°C. After filtration of the reaction mixture and washing of the resin, the filtrate was worked-up and the residue obtained purified on silica gel (5:1 hexane:EtOAc) to give biphenyl-3-carbaldehyde **2.65** (0.0168 g, loading: 0.50 mmol/g, >95%) as a colourless oil : Beilstein Registry # [2435839]; IR (neat) 2880, 2740, 1700 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 10.02 (s, 1H), 8.05 (s, 1H), 7.69-7.25 (m, 8H). Spectral data are consistent with those reported.[283]

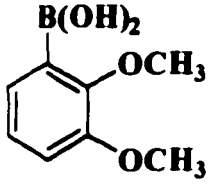


3-(3-Methoxyphenyl)benzaldehyde (2.67)

According to General Procedure C, resin-bound 3-bromobenzaldehyde **2.64** (1% cross-linked, loading 0.52 mmol/g, 0.192 g, 0.10 mmole) was swollen in anhydrous DME (6.4 mL) and coupled with 3-methoxyphenylboronic acid **2.66** (0.046 g, 0.30 mmole) in the presence of $Pd(PPh_3)_4$ (0.0058 g, 0.005 mmole) and Na_2CO_3 solution (2 M aqueous, 0.4 mL). After 24 h, the reaction mixture was cooled to rt and treated with aq. satd. NH_4Cl solution (5 mL) and further stirred for 10 min. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.168 g) was swollen in dioxane (2.6 mL) for 30 min and treated with a solution of 3 M HCl (2.6 mL) for 48 h at 80°C. After filtration of the reaction mixture and washing of the resin, the filtrate was worked-up and the residue obtained purified on silica gel (5:1 hexane:EtOAc) to give 3-(3-methoxyphenyl)benzaldehyde **2.67** (0.0181 g, loading: 0.51

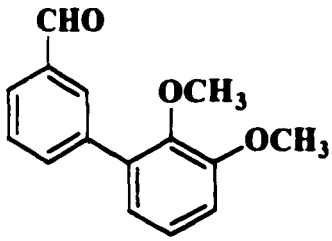
mmol/g, >95%) as a colourless oil : Beilstein Registry # [5514019]; IR (neat) 2952, 2730, 1698, 1596, 1217, 1158 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 10.13 (s, 1H), 8.15-6.88 (m, 8H), 3.85 (s, 3H). Spectral data are consistent with those reported.[284]

2,3-Dimethoxyphenylboronic acid (2.100)



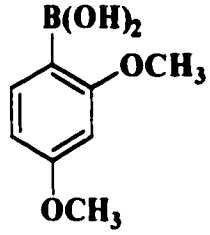
Sample supplied by Peter Riebel.[285] Colourless solid.: Beilstein Registry # [3051295]; mp 68-69 °C (water) (Lit. [286] mp 70°); IR ($CHCl_3$) 3354, 2942, 2837, 1583, 1467, 1352, 1265, 1211, 1162, 1109, 1077, 1032 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, J = 7.2 Hz, 1H), 7.14-6.97 (m, 4H), 3.92 (s, 3H), 3.85 (s, 3H) ; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 154.2, 151.4, 128.0, 127.4, 124.6, 115.7, 61.3, 55.6 ; MS (EI (70 eV)) m/z (rel intensity) 182 (M^+, 100) ; HRMS *m/e* calcd for $C_8H_{11}BO_4$: 182.0750, found 182.0748.

3-(2,3-Dimethoxyphenyl)benzaldehyde (2.101)



According to General Procedure C, resin-bound 3-bromobenzaldehyde **2.64** (1% cross-linked, loading 0.58 mmol/g, 0.259 g, 0.15 mmole) was swollen in anhydrous DME (8.6 mL) and coupled with 2,3-dimethoxyphenylboronic acid **2.100** (0.082 g, 0.45 mmole) in the presence of $Pd(PPh_3)_4$ (0.0086 g, 0.0075 mmole) and Na_2CO_3 solution (2 M aqueous, 0.6 mL). After 48 h, the reaction mixture was cooled to rt and treated with aq. satd. NH_4Cl solution (7.5 mL) and further stirred for 10 min. The resin was removed by filtration, washed and dried.

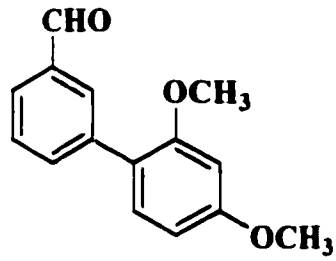
The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.247 g) was swollen in dioxane (4.3 mL) for 30 min and treated with a solution of 3 M HCl (4.3 mL) for 48 h at 80°C. After filtration of the reaction mixture and washing of the resin, the filtrate was worked-up and the residue obtained purified on silica gel (85:15 hexane:EtOAc) to give 3-(2,3-dimethoxyphenyl)benzaldehyde **2.101** (0.0332 g, loading: 0.56 mmol/g, >95%) as a yellow oil : IR (neat) 3056, 1698, 1585, 1473, 1422, 1318, 1266, 1169, 1115, 1038, 1005 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.91 (s, 1H), 7.93 (s, 1H), 7.72 (m, 2H), 7.43 (t, J = 7.5 Hz, 1H), 7.06-6.81 (m, 3H), 3.77 (s, 3H), 3.47 (s, 3H) ; ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 191.9, 152.9, 146.3, 138.9, 136.2, 135.0, 134.0, 130.4, 128.4, 127.7, 124.0, 122.0, 112.1, 60.2, 55.6 ; MS (EI (70 eV)) m/z (rel intensity) 242 (M^+, 27), 199 (13), 184 (9), 86 (70), 84 (100) ; HRMS *m/e* calcd for $C_{15}H_{14}O_3$: 242.0943, found 242.0935.



2,4-Dimethoxyphenylboronic acid (2.98)

A solution of 1-bromo-2,4-dimethoxybenzene (2.78 g, 1.84 mL, 12.8 mmole) in anhydrous THF (125 mL) was flushed with argon for 20 min. The solution was cooled to –78°C and *t*-BuLi (18.4 mL, 1.53 M, 28.16 mmole) added dropwise over 10 min. The clear yellow solution was stirred for 15 min followed by rapid addition of trimethyl borate (5.74 mL, 5.32 g, 51.2 mmole) at which time the solution became colourless. The flask was removed from the cooling bath and warmed to rt. Water (50 mL) was added and the reaction mixture was acidified to a pH ~6 with 1.5 M HCl. The solution was concentrated under vacuum and the residue extracted with ether (2 x 50 mL). The combined organic extract was washed with water (1x), brine (1x), dried over Na_2SO_4 and evaporated to dryness to give a grey solid. The residue was recrystallised from

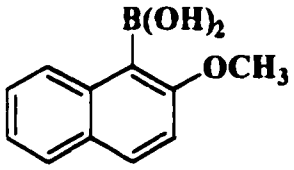
water to give 2,4-dimethoxyboronic acid **2.98** (1.65 g, 71%) as a colourless solid : Beilstein Registry # [4744213]; mp 109-118 °C (water) (Lit.[287] mp 112-119°C (water)); IR (KBr) 3328, 1605, 1569, 1451, 1343, 1285, 1143 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.80 (d, J = 8.2 Hz, 1H), 6.58 (dd, J = 8.2, 2.1 Hz, 1H), 6.51 (d, J = 2.1 Hz, 1H), 5.92 (brs, 2H), 3.93 (s, 3H), 3.85 (s, 3H).



3-(2,4-Dimethoxyphenyl)benzaldehyde (2.99)

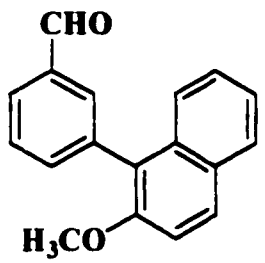
According to General Procedure C, resin-bound 3-bromobenzaldehyde **2.64** (1% cross-linked, loading 0.52 mmol/g, 0.231 g, 0.12 mmole) was swollen in anhydrous DME (7.7 mL) and coupled with 2,4-dimethoxyphenylboronic acid **2.98** (0.066 g, 0.36 mmole) in the presence of $Pd(PPh_3)_4$ (0.0069 g, 0.006 mmole) and Na_2CO_3 solution (2 M aqueous, 0.48 mL). After 48 h, the reaction mixture was cooled to rt and treated with aq. satd. NH_4Cl solution (6 mL) and further stirred for 10 min. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.209 g) was swollen in dioxane (3.3 mL) for 30 min and treated with a solution of 3 M HCl (3.3 mL) for 48 h at 80°C. After filtration of the reaction mixture and washing of the resin, the filtrate was worked-up and the residue obtained purified on silica gel (5:1 hexane:EtOAc) to give 3-(2,4-dimethoxyphenyl)benzaldehyde **2.99** (0.0253 g, loading: 0.50 mmol/g, >95%) as a colourless oil : IR (neat) 2996, 1696, 1602, 1511, 1463, 1265, 1208, 1162, 1032 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 10.00 (s, 1H), 7.98 (s, 1H), 7.73 (d, J = 8.0 Hz, 2H), 7.50 (dd, J = 8.0 Hz, 1H), 7.23 (d, J = 8.0 Hz, 1H), 6.54 (m,

2H), 3.82 (s, 3H), 3.77 (s, 3H) ; ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 192.3, 160.7, 157.3, 139.3, 136.2, 135.3, 131.1, 130.7, 128.4, 127.4, 121.8, 104.2, 98.8, 55.4, 55.2 ; MS (EI (70 eV)) 242 (M^+, 100); HRMS *m/e* calcd for $C_{15}H_{14}O_3$: 242.0943, found 242.0955.



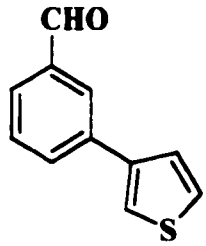
2-Methoxy-1-naphthyl-boronic acid (2.102)

A solution of 1-bromo-2-methoxynaphthalene (0.5 g, 2.11 mmole) in anhydrous THF (20 mL) was flushed with argon for 20 min. The solution was cooled to –78°C and *t*-BuLi (2.81 mL, 1.65 M, 4.64 mmole) added dropwise over 10 min. The clear brown solution was stirred for 15 min followed by rapid addition of trimethyl borate (0.95 mL, 0.88 g, 8.44 mmole) at which time the solution became yellow. The flask was removed from the cooling bath and warmed to rt. Water (10 mL) was added and the reaction mixture was acidified to a pH ~6 with 1.5 M HCl. The solution was concentrated under vacuum and the residue extracted with ether (2 x 10 mL). The combined organic extract was washed with water (1x), brine (1x), dried over Na_2SO_4 and evaporated to dryness to give a grey solid. The residue was recrystallised from water to give 2-methoxy-1-naphthyl-boronic acid **2.102** (0.273 g, 64%) as a colourless solid : Beilstein Registry # [3292263]; ^1H NMR (300 MHz, $CDCl_3$) δ 8.81 (d, J = 8.7 Hz, 1H), 7.92 (d, J = 9.2 Hz, 1H), 7.55-7.21 (m, 4H), 6.08 (bs, 2H), 4.01 (s, 3H); MS (CI) m/z (rel intensity) 203 (M^++1, 17), 187 (38), 160 (34), 159 (100); HRMS *m/e* calcd for $C_{11}H_{11}BO_3$ + H : 203.0879, found 203.0880. Spectral data are consistent with those reported.[288]



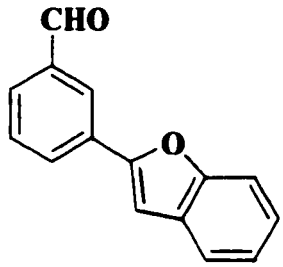
3-(2'-Methoxy-1-naphthyl)benzaldehyde (2.103)

According to General Procedure C, resin-bound 3-bromobenzaldehyde **2.64** (1% cross-linked, loading 0.58 mmol/g, 0.172 g, 0.10 mmole) was swollen in anhydrous DME (5.7 mL) and coupled with 2-methoxy-1-naphthyl-boronic acid **2.102** (0.061 g, 0.3 mmole) in the presence of $Pd(PPh_3)_4$ (0.0058 g, 0.005 mmole) and Na_2CO_3 solution (2 M aqueous, 0.4 mL). After 48 h, the reaction mixture was cooled to rt and treated with aq. satd. NH_4Cl solution (5 mL) and further stirred for 10 min. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.155 g) was swollen in dioxane (2.7 mL) for 30 min and treated with a solution of 3 M HCl (2.7 mL) for 48 h at 80°C. After filtration of the reaction mixture and washing of the resin, the filtrate was worked-up and the residue obtained purified on silica gel (95:5 hexane:EtOAc) to give 3-(2'-methoxy-1-naphthyl)benzaldehyde **2.103** (0.0183 g, loading: 0.45 mmol/g, 78%) as a yellow oil : IR (neat) 2957, 2923, 2845, 1704, 1600, 1471, 1383, 1268 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.91 (s, 1H), 7.83-7.73 (m, 3H), 7.72-7.65 (m, 1H), 7.52-7.46 (m, 2H), 7.32-7.26 (m, 1H), 7.24-7.17 (m, 3H), 3.67 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 192.2, 153.7, 137.5, 137.2, 136.5, 133.2, 132.7, 129.7, 128.8, 128.0, 126.6, 124.5, 123.6, 123.5, 113.4, 56.5; MS (EI (70 eV)) m/z (rel intensity) 262 (M^+, 100); HRMS *m/e* calcd for $C_{18}H_{14}O_2$: 262.0994, found 262.0992.



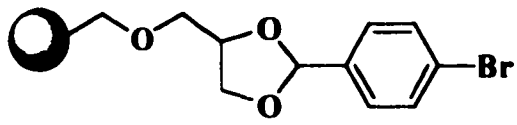
3-(3-Thienyl)benzaldehyde (2.80)

According to General Procedure C, resin-bound 3-bromobenzaldehyde **2.64** (1% cross-linked, loading 0.52 mmol/g, 0.192 g, 0.10 mmole) was swollen in anhydrous DME (6.4 mL) and coupled with 3-thiopheneboronic acid 95% **2.76** (0.040 g, 0.3 mmole) in the presence of $Pd(PPh_3)_4$ (0.0058 g, 0.005 mmole) and Na_2CO_3 solution (2 M aqueous, 0.4 mL). After 24 h, the reaction mixture was cooled to rt and treated with aq. satd. NH_4Cl solution (5 mL) and further stirred for 10 min. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.179 g) was swollen in dioxane (2.9 mL) for 30 min and treated with a solution of 3 M HCl (2.9 mL) for 48 h at 80°C. After filtration of the reaction mixture and washing of the resin, the filtrate was worked-up and the residue obtained purified on silica gel (9:1 hexane:EtOAc) to give 3-(3-thienyl)benzaldehyde **2.80** (0.0148 g, loading: 0.44 mmol/g, 85%) as a yellow solid : Beilstein Registry # [7987829] mp 47-48 °C (EtOH); IR ($CHCl_3$) 3053, 1694, 1604, 1596 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.96 (s, 1H), 8.00 (s, 1H), 7.75-7.70 (m, 2H), 7.55-7.22 (m, 4H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 192.0, 140.4, 136.5, 131.8, 129.2, 128.2, 126.8, 126.7, 126.6, 125.7, 121.1 ; MS (EI (70 eV)) m/z (rel intensity) 188 (M^+, 92), 187 (52), 159 (38), 158 (20), 115 (100) ; HRMS *m/e* calcd for $C_{11}H_8OS$: 188.0296, found 188.0298; Anal. Calcd for $C_{11}H_8OS$: C, 70.19 ; H, 4.28. Found : C, 70.39 ; H, 4.50.



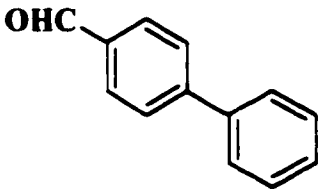
3-(2-Benzofuranyl)benzaldehyde (2.81)

According to General Procedure C, resin-bound 3-bromobenzaldehyde **2.64** (1% cross-linked, loading 0.58 mmol/g, 0.207 g, 0.12 mmole) was swollen in anhydrous DME (6.9 mL) and coupled with benzofuran-2-yl-boranediol **2.78** (0.058 g, 0.36 mmole) in the presence of $Pd(PPh_3)_4$ (0.0069 g, 0.006 mmole) and Na_2CO_3 solution (2 M aqueous, 0.48 mL). After 24 h, the reaction mixture was cooled to rt and treated with aq. satd. NH_4Cl solution (6 mL) and further stirred for 10 min. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.164 g) was swollen in dioxane (2.9 mL) for 30 min and treated with a solution of 3 M HCl (2.9 mL) for 48 h at 80°C. After filtration of the reaction mixture and washing of the resin, the filtrate was worked-up and the residue obtained purified on silica gel (9:1 hexane:EtOAc) to give 3-(2-benzofuranyl)benzaldehyde **2.81** (0.0200 g, loading: 0.55 mmol/g, 95%) as a yellow solid : mp 118-119 °C (hexane); IR (KBr) 2940, 1697, 1452, 1299, 1257, 1173, 909 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.99 (s, 1H), 8.24 (dd, J = 1.6, 1.1 Hz, 1H), 7.97 (ddd, J = 7.7, 1.6, 1.1 Hz, 1H), 7.76 (ddd, J = 7.7, 1.6, 1.1 Hz, 1H), 7.57-7.46 (m, 3H), 7.31-7.18 (m, 2H), 7.01 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 191.6, 154.9, 154.1, 136.8, 130.1, 129.3, 129.1, 128.7, 128.6, 125.7, 124.8, 123.1, 121.1, 111.1, 102.5; MS (EI (70 eV)) m/z (rel intensity) 222 (M^+, 100); HRMS *m/e* calcd for $C_{15}H_{10}O_2$: 222.0681, found 222.0678.



Resin-bound 4-bromobenzaldehyde (2.68)

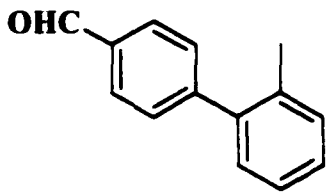
According to General Procedure A, resin-bound 3-benzyloxypropan-1,2-diol **2.51** (loading 0.919 mmol/g max, 2.18 g, 2 mmole max) was swollen in anhydrous toluene (40 mL) and treated with 4-bromobenzaldehyde 99% (0.75 g, 4 mmole), *p*-toluenesulfonic acid monohydrate (0.038 g, 0.2 mmole) and anhydrous Na_2SO_4 (1.42 g, 10 mmole). After 48 h at 80°C, the reaction mixture was cooled to rt and the resulting resin was collected by filtration, neutralised with anhydrous pyridine, washed and dried to afford **2.68**. The loading capacity of **2.68** was determined according to General Procedure B. **2.68** (0.201 g) was swollen in dioxane (5.5 mL) and treated with a solution of 3 M hydrochloric acid (5.5 mL) for 48 h at 80°C. After filtration of the reaction mixture and washing of the resin, the filtrate was worked-up and the residue obtained purified on silica gel (5:1 hexane:EtOAc) to give 4-bromobenzaldehyde (0.0247 g) showing a loading of **2.68** of 0.66 mmol/g.



Biphenyl-4-carbaldehyde (2.69)

According to General Procedure C, resin-bound 4-bromobenzaldehyde **2.68** (1% cross-linked, loading 0.60 mmol/g, 0.167 g, 0.10 mmole) was swollen in anhydrous DME (5.6 mL) and coupled with phenylboronic acid 97% **2.60** (0.038 g, 0.30 mmole) in the presence of $Pd(PPh_3)_4$ (0.0058 g, 0.005 mmole) and Na_2CO_3 solution (2 M aqueous, 0.4 mL). After 24 h, the reaction mixture was cooled to rt and treated with aq. satd. NH_4Cl solution (5 mL) and further stirred for 10 min. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.151 g) was

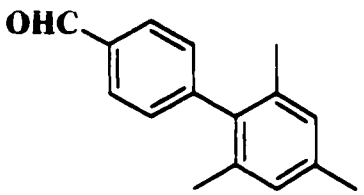
swollen in dioxane (2.7 mL) for 30 min and treated with a solution of 3 M HCl (2.7 mL) for 48 h at 80°C. After filtration of the reaction mixture and washing of the resin, the filtrate was worked-up and the residue obtained purified on silica gel (9:1 hexane:EtOAc) to give biphenyl-4-carbaldehyde **2.69** (0.0160 g, loading: 0.58 mmol/g, >95%) as a colourless solid : Beilstein Registry # [606693]; mp 58-60 °C (Lit. [289] mp 58-59.5 °C (cyclohexane)) ; IR (neat) 1700, 1599 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.97 (s, 1H), 7.93-7.23 (m,9H).



4-(2-Tolyl)benzaldehyde (2.71)

According to General Procedure C, resin-bound 4-bromobenzaldehyde **2.68** (1% cross-linked, loading 0.60 mmol/g, 0.167 g, 0.10 mmole) was swollen in anhydrous DME (5.6 mL) and coupled with tri-*o*-tolyl-cyclotriboroxane (0.035 g, 0.1 mmole) in the presence of $Pd(PPh_3)_4$ (0.0058 g, 0.005 mmole) and Na_2CO_3 solution (2 M aqueous, 0.4 mL). After 48 h, the reaction mixture was cooled to rt and treated with aq. satd. NH_4Cl solution (5 mL) and further stirred for 10 min. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.149 g) was swollen in dioxane (2.7 mL) for 30 min and treated with a solution of 3 M HCl (2.7 mL) for 48 h at 80°C. After filtration of the reaction mixture and washing of the resin, the filtrate was worked-up and the residue obtained purified on silica gel (9:1 hexane:EtOAc) to give 4-(2-tolyl)benzaldehyde **2.71** (0.0105 g, loading: 0.36 mmol/g, 60%) as a colourless solid : Beilstein Registry # [7988144] mp 56-57 °C (hexane); IR (DCM) 3048, 1701, 1605, 1265, 1210, 1168, 1006 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 10.0 (s, 1H), 7.88 (d, J = 8.2 Hz, 2H), 7.43 (d, J = 8.2 Hz, 2H),

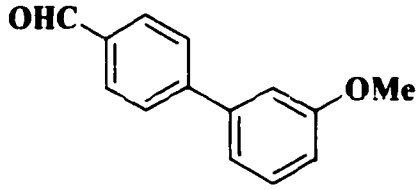
7.22 (m, 4H), 2.25 (s, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 191.5, 148.0, 140.3, 134.8, 130.4, 129.6, 129.3, 127.8, 125.7, 20.0; MS (EI (70 eV)) m/z (rel intensity) 196 (M^+, 100); HRMS *m/e* calcd for $C_{14}H_{12}O$: 196.0888, found 196.0892.



4-(2,4,6-Trimethylphenyl)benzaldehyde (2.73)

According to General Procedure C, resin-bound 4-bromobenzaldehyde **2.68** (1% cross-linked, loading 0.60 mmol/g, 0.166 g, 0.10 mmole) was swollen in anhydrous DME (5.5 mL) and coupled with mesitylboronic acid **2.72** (0.049 g, 0.30 mmole) in the presence of $Pd(PPh_3)_4$ (0.0058 g, 0.005 mmole) and Na_2CO_3 solution (2 M aqueous, 0.4 mL). After 48 h, the reaction mixture was cooled to rt and treated with aq. satd. NH_4Cl solution (5 mL) and further stirred for 10 min. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.150 g) was swollen in dioxane (2.7 mL) for 30 min and treated with a solution of 3 M HCl (2.7 mL) for 48 h at 80°C. After filtration of the reaction mixture and washing of the resin, the filtrate was worked-up and the residue obtained purified on silica gel (9:1 hexane:EtOAc) to give 4-(2,4,6-trimethylphenyl)benzaldehyde **2.73** (0.0091 g, loading: 0.27 mmol/g, 45%) as a colourless oil : IR (neat) 2924, 1701, 1606, 1462, 1382, 1303, 1208, 1167 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.01 (s, 1H), 7.91 (d, J = 8.1 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 6.94 (s, 2H), 2.32 (s, 3H), 1.98 (s, 6H); ^{13}C NMR (75.5 MHz,$CDCl_3$) δ 191.8, 147.9, 137.6, 137.1, 135.1, 134.8, 129.9, 129.8, 128.9, 128.1, 128.0, 127.9, 20.9, 20.6 ; MS

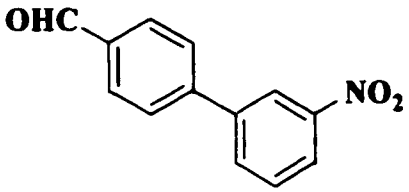
(EI (70 eV)) m/z (rel intensity) 224 (M^+, 100) ; HRMS *m/e* calcd for $C_{16}H_{16}O$: 224.1201, found 224.1197.



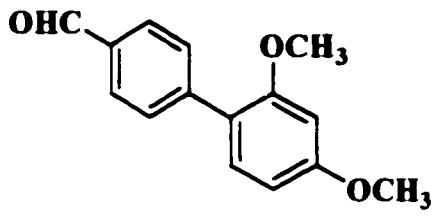
4-(3-Methoxyphenyl)benzaldehyde (2.74)

According to General Procedure C, resin-bound 4-bromobenzaldehyde **2.68** (1% cross-linked, loading 0.60 mmol/g, 0.167 g, 0.10 mmole) was swollen in anhydrous DME (5.6 mL) and coupled with 3-methoxyphenylboronic acid **2.66** (0.046 g, 0.3 mmole) in the presence of $Pd(PPh_3)_4$ (0.0058 g, 0.005 mmole) and Na_2CO_3 solution (2 M aqueous, 0.4 mL). After 24 h, the reaction mixture was cooled to rt and treated with aq. satd. NH_4Cl solution (5 mL) and further stirred for 10 min. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.159 g) was swollen in dioxane (2.9 mL) for 30 min and treated with a solution of 3 M HCl (2.9 mL) for 48 h at 80°C. After filtration of the reaction mixture and washing of the resin, the filtrate was worked-up and the residue obtained purified on silica gel (9:1 hexane:EtOAc) to give 4-(3-methoxyphenyl)benzaldehyde **2.74** (0.0196 g, loading: 0.58 mmol/g, >95%) as a yellow oil : Beilstein Registry # [7990167] IR (neat) 2950, 2834, 1697, 1602, 1567, 1474, 1299, 1217, 1173, 1053, 1028 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.86 (s, 1H), 7.74 (d, J = 8.2 Hz, 2H), 7.54 (d, J = 8.2 Hz, 2H), 7.25-6.77 (m, 4H), 3.69 (s, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 191.6, 159.9, 146.7, 140.9, 135.1, 130.0, 129.9, 127.4, 119.6, 113.6, 113.0, 55.1 ;MS (EI (70 eV)) m/z (rel intensity) 212 (M^+, 100) ; HRMS *m/e* calcd for $C_{14}H_{12}O_2$: 212.0820, found 212.0837.

4-(3-Nitrophenyl)benzaldehyde (2.75)

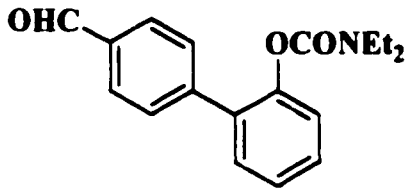


According to General Procedure C, resin-bound 4-bromobenzaldehyde **2.68** (1% cross-linked, loading 0.65 mmol/g, 0.1545 g, 0.10 mmole) was swollen in anhydrous DME (5.0 mL) and coupled with 3-nitrophenylboronic acid 98% **2.62** (0.051 g, 0.3 mmole) in the presence of $Pd(PPh_3)_4$ (0.0058 g, 0.005 mmole) and Na_2CO_3 solution (2 M aqueous, 0.4 mL). After 24 h, the reaction mixture was cooled to rt and treated with aq. satd. NH_4Cl solution (5 mL) and further stirred for 10 min. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.135 g) was swollen in dioxane (2.6 mL) for 30 min and treated with a solution of 3 M HCl (2.6 mL) for 48 h at 80°C. After filtration of the reaction mixture and washing of the resin, the filtrate was worked-up and the residue obtained purified on silica gel (5:1 hexane:EtOAc) to give 4-(3-nitrophenyl)benzaldehyde **2.75** (0.0153 g, loading: 0.50 mmol/g, 77%) as a colourless solid : mp 115-117 °C (hexane); IR (DCM) 3055, 2986, 1703, 1607, 1533, 1423, 1352, 1265 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.99 (s, 1H), 8.38 (t, J = 1.9 Hz, 1H), 8.16 (dd, J = 8.2, 1.1 Hz, 1H), 7.91 (d, J = 8.2 Hz, 2H), 7.86 (s, 1H), 7.70 (d, J = 8.2 Hz, 2H), 7.58 (t, J = 8.2 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 191.5, 148.7, 144.2, 141.2, 136.0, 133.1, 130.4, 130.0, 127.7, 123.0, 122.1; MS (EI (70 eV) m/z (rel intensity) 227 (M^+, 80), 226 (59), 199 (18), 180 (8), 153 (34), 152 (100); HRMS *m/e* calcd for $C_{13}H_9NO_3$: 227.0582, found 227.0581.



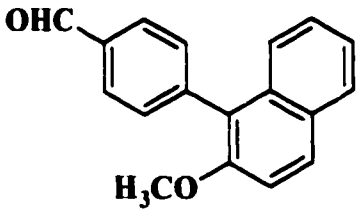
4-(2,4-Dimethoxyphenyl)benzaldehyde (2.106)

According to General Procedure C, resin-bound 4-bromobenzaldehyde **2.68** (1% cross-linked, loading 0.60 mmol/g, 0.200 g, 0.12 mmole) was swollen in anhydrous DME (6.7 mL) and coupled with 2,4-dimethoxyphenylboronic acid **2.98** (0.066 g, 0.36 mmole) in the presence of $Pd(PPh_3)_4$ (0.0069 g, 0.006 mmole) and Na_2CO_3 solution (2 M aqueous, 0.48 mL). After 48 h, the reaction mixture was cooled to rt and treated with aq. satd. NH_4Cl solution (6 mL) and further stirred for 10 min. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.187 g) was swollen in dioxane (3.4 mL) for 30 min and treated with a solution of 3 M HCl (3.4 mL) for 48 h at 80°C. After filtration of the reaction mixture and washing of the resin, the filtrate was worked-up and the residue obtained purified on silica gel (5:1 hexane:EtOAc) to give 4-(2,4-dimethoxyphenyl)benzaldehyde **2.106** (0.0263 g, loading: 0.58 mmol/g, >95%) as a colourless solid : mp 79-81°C (hexane); ^1H NMR (250 MHz, $CDCl_3$) δ 9.98 (s, 1H), 7.86 (d, J = 8.1 Hz, 2H), 7.71 (d, J = 8.1 Hz, 2H), 7.23 (d, J = 8.4 Hz, 1H), 6.61-6.49 (m, 2H), 3.82 (s, 3H), 3.78 (s, 3H) ; ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 192.0, 145.1, 134.4, 131.5, 129.2, 105.1, 98.8, 55.4, 55.3; MS (EI (70 eV)) m/z (rel intensity) 242 (M^+, 100) ; HRMS *m/e* calcd for $C_{15}H_{14}O_3$: 242.0943, found 242.0951.



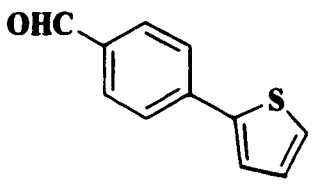
4-(2-*N,N*-Diethylcarbamoylphenyl)benzaldehyde (2.105)

According to General Procedure C, resin-bound 4-bromobenzaldehyde **2.68** (1% cross-linked, loading 0.65 mmol/g, 0.1545 g, 0.10 mmole) was swollen in anhydrous DME (5 mL) and coupled with *2*-N,N-diethylcarbamoylphenylboronic acid **2.104** in the presence of $Pd(PPh_3)_4$ (0.0058 g, 0.005 mmole) and Na_2CO_3 solution (2 M aqueous, 0.4 mL). After 48 h, the reaction mixture was cooled to rt and treated with aq. satd. NH_4Cl solution (5 mL) and further stirred for 10 min. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.1392 g) was swollen in dioxane (2.7 mL) for 30 min and treated with a solution of 3 M HCl (2.7 mL) for 48 h at 80°C. After filtration of the reaction mixture and washing of the resin, the filtrate was worked-up and the residue obtained purified on silica gel (5:1 hexane:EtOAc) to give 4-(2-*N,N*-diethylcarbamoylphenyl)benzaldehyde **2.105** (0.0257 g, loading: 0.62 mmol/g, >95%) as a colourless solid : mp 96-98 °C (hexane); IR (DCM) 2958, 1708, 1606, 1427, 1242, 1046, 1007 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.92 (s, 1H), 7.79 (d, J = 8.2 Hz, 2H), 7.47 (d, J = 8.2 Hz, 2H), 7.30-7.11 (m, 4H), 3.13 (m, 4H), 0.91 (m, 6H) ; ^{13}C NMR (75, 5 MHz, $CDCl_3$) δ 191.7, 153.5, 148.2, 144.2, 134.9, 133.5, 130.1, 129.4, 129.2, 129.0, 125.4, 123.2, 41.8, 41.4, 13.7, 12.9 ; MS (EI (70 eV)) m/z (rel intensity) 297 (M^+, 4), 169 (12), 152 (9), 139 (15), 115 (12), 100 (100); HRMS *m/e* calcd for $C_{18}H_{19}NO_3$: 297.1365, found 297.1361; Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71 ; H, 6.44 ; N, 4.71. Found : C, 72.94; H, 6.60 ; N, 4.51.



4-(2'-Methoxy-1-naphthyl)benzaldehyde (2.107)

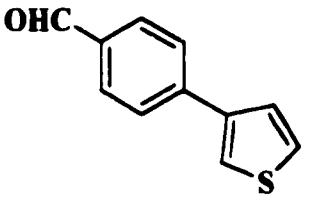
According to General Procedure C, resin-bound 4-bromobenzaldehyde **2.68** (1% cross-linked, loading 0.66 mmol/g, 0.151 g, 0.10 mmole) was swollen in anhydrous DME (5 mL) and coupled with 2-methoxy-1-naphthyl-boronic acid **2.102** (0.061 g, 0.3 mmole) in the presence of $Pd(PPh_3)_4$ (0.0058 g, 0.005 mmole) and Na_2CO_3 solution (2 M aqueous, 0.4 mL). After 48 h, the reaction mixture was cooled to rt and treated with aq. satd. NH_4Cl solution (5 mL) and further stirred for 10 min. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.140 g) was swollen in dioxane (2.8 mL) for 30 min and treated with a solution of 3 M HCl (2.8 mL) for 48 h at 80°C. After filtration of the reaction mixture and washing of the resin, the filtrate was worked-up and the residue obtained purified on silica gel (95:5 hexane:EtOAc) to give 4-(2'-methoxy-1-naphthyl)benzaldehyde **2.107** (0.0220 g, loading: 0.60 mmol/g, 91%) as a yellow oil : IR (neat) 2924, 2837, 1699, 1601, 1507, 1465, 1385, 1333, 1260, 1209, 1168, 1121, 1067 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.87 (s, 1H), 7.78 (d, J = 8.2 Hz, 2H), 7.69 (d, J = 8.8 Hz, 1H), 7.64 (m, 1H), 7.34 (d, J = 8.2 Hz, 2H), 7.26 (m, 1H), 7.16 (m, 3H), 3.61 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 191.7, 153.3, 143.2, 134.9, 132.7, 131.6, 129.7, 129.2, 129.1, 128.7, 127.8, 126.5, 124.3, 123.5, 113.1, 56.1; MS (EI (70 eV)) m/z (rel intensity) 262 (M^+, 100) ; HRMS *m/e* calcd for $C_{18}H_{14}O_2$: 262.0994, found 262.0996.



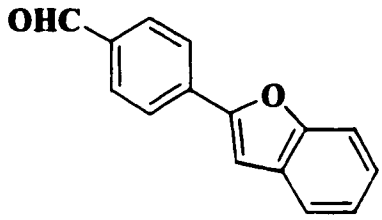
4-(2-Thienyl)benzaldehyde (2.84)

According to General Procedure C, resin-bound 4-bromobenzaldehyde **2.68** (1% cross-linked, loading 0.66 mmol/g, 0.151 g, 0.10 mmole) was swollen in anhydrous DME (5 mL) and coupled with 2-thiopheneboronic acid **2.83** (0.038 g, 0.3 mmole) in the presence of $Pd(PPh_3)_4$ (0.0058 g, 0.005 mmole) and Na_2CO_3 solution (2 M aqueous, 0.4 mL). After 24 h, the reaction mixture was cooled to rt and treated with aq. satd. NH_4Cl solution (5 mL) and further stirred for 10 min. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.139 g) was swollen in dioxane (2.8 mL) for 30 min and treated with a solution of 3 M HCl (2.8 mL) for 48 h at 80°C. After filtration of the reaction mixture and washing of the resin, the filtrate was worked-up and the residue obtained purified on silica gel (9:1 hexane:EtOAc) to give 4-(2-thienyl)benzaldehyde **2.84** (0.0112 g, loading: 0.43 mmol/g, 65%) as a colourless solid : Beilstein Registry # [4245000]; mp 66-68 °C (Lit. [290] mp 67-68 °C (2-propanol)) ; IR (KBr) 1690 cm^{-1} ; ^1H NMR (200 MHz, $CDCl_3$) δ 9.84 (s, 1H), 7.72 (d, J = 8.8 Hz, 2H), 7.58 (d, J = 8.2 Hz, 2H), 7.28 (m, 2H), 6.97 (dd, J = 5.1 Hz, 3.5 Hz, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 191.2, 142.5, 139.8, 134.9, 130.2, 128.3, 126.7, 125.8, 124.9 ; MS (EI (70 eV)) m/z (rel intensity) 188 (M^+, 100) ; HRMS *m/e* calcd for $C_{11}H_8OS$: 188.0296, found 188.0298.

4-(3-Thienyl)benzaldehyde (2.82)

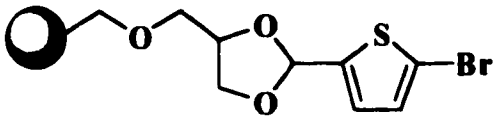


According to General Procedure C, resin-bound 4-bromobenzaldehyde **2.68** (1% cross-linked, loading 0.66 mmol/g, 0.154 g, 0.10 mmole) was swollen in anhydrous DME (5 mL) and coupled with 3-thiopheneboronic acid 95% **2.76** (0.040 g, 0.3 mmole) in the presence of $Pd(PPh_3)_4$ (0.0058 g, 0.005 mmole) and Na_2CO_3 solution (2 M aqueous, 0.4 mL). After 24 h, the reaction mixture was cooled to rt and treated with aq. satd. NH_4Cl solution (5 mL) and further stirred for 10 min. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.134 g) was swollen in dioxane (2.7 mL) for 30 min and treated with a solution of 3 M HCl (2.7 mL) for 48 h at 80°C. After filtration of the reaction mixture and washing of the resin, the filtrate was worked-up and the residue obtained purified on silica gel (95:5 hexane:EtOAc) to give 4-(3-thienyl)benzaldehyde **2.82** (0.0157 g, loading: 0.62 mmol/g, >95%) as a yellow solid : Beilstein Registry # [8036633]; mp 99-102 °C (EtOH); IR (DCM) 3055, 1697, 1604, 1424 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.98 (s, 1H), 7.87 (d, J = 8.2 Hz, 2H), 7.64 (d, J = 8.2 Hz, 2H), 7.57 (dd, J = 2.8 Hz, 1.0 Hz, 1H), 7.41 (m, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 191.5, 141.3, 140.7, 134.8, 130.2, 126.8, 126.6, 126.0, 122.4 ; MS (EI (70 eV)) m/z (rel intensity) 188 (M^+, 91), 187 (84), 160 (18), 159 (24), 158 (22), 116 (14), 115 (100) ; HRMS *m/e* calcd for $C_{11}H_8OS$: 188.0296, found 188.0293; Anal. Calcd for $C_{11}H_8OS$: C, 70.19 ; H, 4.28. Found : C, 70.10 ; H, 4.45. Spectral data are consistent with those reported.[291]



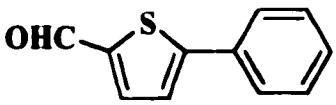
4-(2-Benzofuranyl)benzaldehyde (2.85)

According to General Procedure C, resin-bound 4-bromobenzaldehyde **2.68** (1% cross-linked, loading 0.66 mmol/g, 0.182 g, 0.12 mmole) was swollen in anhydrous DME (6 mL) and coupled with benzofuran-2-yl-boranediol **2.78** (0.058 g, 0.36 mmole) in the presence of $Pd(PPh_3)_4$ (0.0069 g, 0.006 mmole) and Na_2CO_3 solution (2 M aqueous, 0.48 mL). After 24 h, the reaction mixture was cooled to rt and treated with aq. satd. NH_4Cl solution (6 mL) and further stirred for 10 min. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.169 g) was swollen in dioxane (3.4 mL) for 30 min and treated with a solution of 3 M HCl (3.4 mL) for 48 h at 80°C. After filtration of the reaction mixture and washing of the resin, the filtrate was worked-up and the residue obtained purified on silica gel (9:1 hexane:EtOAc) to give 4-(2-benzofuranyl)benzaldehyde **2.85** (0.0238 g, loading: 0.63 mmol/g, >95%) as a yellow solid : mp 136-137 °C (hexane); IR (KBr) 2945, 1699, 1606, 1213, 1170, 908 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.89 (s, 1H), 7.81 (AA'XX' system, J = 8.8, 2.2 Hz, 4H), 7.51 (d, J = 7.1 Hz, 1H), 7.46 (d, J = 8.2 Hz, 1H), 7.28 (ddd, J = 5.5, 1.6 Hz, 1H), 7.20 (ddd, J = 5.3, 3.8 Hz, 1H), 7.02 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 191.1, 155.1, 135.6, 135.5, 129.9, 128.6, 125.2, 124.8, 123.1, 121.2, 111.2, 104.0 ; MS (EI (70 eV)) m/z (rel intensity) 222 (M^+, 100) ; HRMS *m/e* calcd for $C_{15}H_{10}O_2$: 222.0681, found 222.0673.



Resin-bound 5-bromo-thiophene-2-carbaldehyde (2.92)

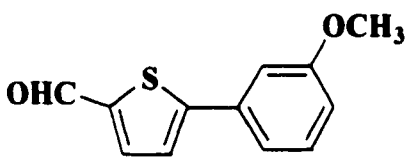
According to General Procedure A, resin-bound 3-benzyloxypropan-1,2-diol **2.51** (loading 0.922 mmol/g max, 2.17 g, 2 mmole max) was swollen in anhydrous toluene (40 mL) and treated with 5-bromo-thiophene-2-carbaldehyde 95% (0.804 g, 0.50 mL, 4 mmole), *p*-toluenesulfonic acid monohydrate (0.038 g, 0.2 mmole) and anhydrous Na_2SO_4 (1.42 g, 10 mmole). After 48 h at 80°C, the reaction mixture was cooled to rt and the resulting resin was collected by filtration, neutralised with anhydrous pyridine, washed and dried to afford **2.92**. The loading capacity of **2.92** was determined according to General Procedure B. **2.92** (0.248 g) was swollen in dioxane (6.8 mL) and treated with a solution of 3 M hydrochloric acid (6.8 mL) for 48 h at 80°C. After filtration of the reaction mixture and washing of the resin, the filtrate was worked-up and the residue obtained purified on silica gel (5:1 hexane:EtOAc) to give 5-bromo-thiophene-2-carbaldehyde (0.0337 g) showing a loading of **2.92** of 0.71 mmol/g.



5-Phenylthiophene-2-carbaldehyde (2.95)

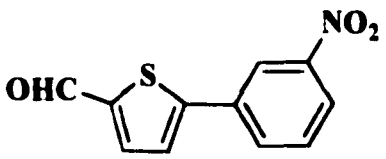
According to General Procedure C, resin-bound 5-bromo-thiophene-2-carbaldehyde **2.92** (1% cross-linked, loading 0.71 mmol/g, 0.141 g, 0.10 mmole) was swollen in anhydrous DME (4.7 mL) and coupled with phenylboronic acid 97% **2.60** (0.038 g, 0.30 mmole) in the presence of $Pd(PPh_3)_4$ (0.0058 g, 0.005 mmole) and Na_2CO_3 solution (2 M aqueous, 0.4 mL). After 24 h, the reaction mixture was cooled to rt and treated with aq. satd. NH_4Cl solution (5 mL) and further stirred for 10 min. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to

General Procedure D. The resulting resin (0.122 g) was swollen in dioxane (2.6 mL) for 30 min and treated with a solution of 3 M HCl (2.6 mL) for 48 h at 80°C. After filtration of the reaction mixture and washing of the resin, the filtrate was worked-up and the residue obtained purified on silica gel (95:5 hexane:EtOAc) to give 5-phenylthiophene-2-carbaldehyde **2.95** (0.0149 g, loading: 0.649 mmol/g, 91%) as a pale yellow solid : Beilstein Registry # [120734]; mp 91-93 °C (Lit.[292] mp 92-93°C (EtOH)); IR ($CHCl_3$) 2917, 1651, 1442, 1265, 1235 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.81 (s, 1H), 7.65 (d, J = 3.9 Hz, 1H), 7.62-7.34 (m, 5H), 7.31 (d, J = 3.9 Hz, 1H) ; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 182.8, 154.3, 142.4, 137.3, 133.0, 129.4, 129.2, 126.4, 124.1 ; MS (EI (70 eV)) m/z (rel intensity) 188 (M^+, 100) ; HRMS *m/e* calcd for $C_{11}H_8OS$: 188.0296, found 188.0290.



5-(3'-Methoxyphenyl)thiophene-2-carbaldehyde (2.96) According to General Procedure C, resin-bound 5-bromo-thiophene-2-carbaldehyde **2.92** (1% cross-linked, loading 0.71 mmol/g, 0.140 g, 0.10 mmole) was swollen in anhydrous DME (4.7 mL) and coupled with 3-methoxyphenylboronic acid **2.66** (0.046 g, 0.30 mmole) (0.038 g, 0.30 mmole) in the presence of $Pd(PPh_3)_4$ (0.0058 g, 0.005 mmole) and Na_2CO_3 solution (2 M aqueous, 0.4 mL). After 24 h, the reaction mixture was cooled to rt and treated with aq. satd. NH_4Cl solution (5 mL) and further stirred for 10 min. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.130 g) was swollen in dioxane (2.8 mL) for 30 min and treated with a solution of 3 M HCl (2.8 mL) for 48 h at 80°C. After filtration of the reaction mixture and

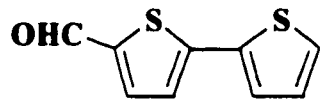
washing of the resin, the filtrate was worked-up and the residue obtained purified on silica gel (9:1 hexane:EtOAc) to give 5-(3'-methoxyphenyl)thiophene-2-carbaldehyde **2.96** (0.0193 g, loading: 0.68 mmol/g, >95%) as an orange oil : IR (neat) 2933, 1663, 1592, 1529, 1447, 1289, 1221, 1168, 1050 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.70 (s, 1H), 7.53 (d, J = 3.9 Hz, 1H), 7.20 (d, J = 4.4 Hz, 1H), 7.16-7.00 (m, 3H), 6.77 (d, J = 7.7 Hz, 1H), 3.67 (s, 3H) ; ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 182.5, 159.9, 153.7, 142.2, 137.1, 134.0, 130.0, 124.1, 118.6, 114.6, 111.8, 55.0 ; MS (EI (70 eV)) m/z (rel intensity) 218 (M^+, 27), 217 (17), 184 (9), 88 (13), 86 (75), 84 (100) ; HRMS *m/e* calcd for $C_{12}H_{10}O_2S$: 218.0401, found 218.0396.



5-(3'-Nitrophenyl)thiophene-2-carbaldehyde (2.97)

According to General Procedure C, resin-bound 5-bromo-thiophene-2-carbaldehyde **2.92** (1% cross-linked, loading 0.71 mmol/g, 0.141 g, 0.10 mmole) was swollen in anhydrous DME (4.7 mL) and coupled with 3-nitrophenylboronic acid 98% **2.62** (0.051 g, 0.30 mmole) (0.038 g, 0.30 mmole) in the presence of $Pd(PPh_3)_4$ (0.0058 g, 0.005 mmole) and Na_2CO_3 solution (2 M aqueous, 0.4 mL). After 24 h, the reaction mixture was cooled to rt and treated with aq. satd. NH_4Cl solution (5 mL) and further stirred for 10 min. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.133 g) was swollen in dioxane (2.8 mL) for 30 min and treated with a solution of 3 M HCl (2.8 mL) for 48 h at 80°C. After filtration of the reaction mixture and washing of the resin, the filtrate was worked-up and the residue obtained purified on silica gel (4:1 hexane:EtOAc) to give 5-(3'-nitrophenyl)thiophene-2-carbaldehyde **2.97** (0.0162 g,

loading: 0.523 mmol/g, 74%) as a yellow solid : Beilstein Registry # [1684241] mp 144-146 °C (Lit.[293] mp 147°C (hexane)); IR (DCM) 3096, 2955, 2921, 1660, 1527, 1346, 1228, 1049 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.86 (s, 1H), 8.43 (s, 1H), 8.16 (d, J = 8.2 Hz, 1H), 7.89 (d, J = 8.2 Hz, 1H), 7.73 (d, J = 4.4 Hz, 1H), 7.56 (t, J = 8.2 Hz, 1H), 7.46 (d, J = 3.8 Hz, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 182.6,143.9, 137.0, 132.0, 130.3, 128.8, 125.6, 123.6, 121.0 ; MS (EI (70 eV)) m/z (rel intensity) 233 (M^+, 100); HRMS *m/e* calcd for $C_{11}H_7NO_3S$: 233.0147, found 233.0151.

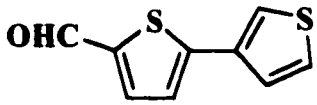


5-(2'-Thienyl)-2-thiophenecarbaldehyde (2.93)

According to General Procedure C, resin-bound 5-bromo-thiophene-2-carbaldehyde **2.92** (1% cross-linked, loading 0.71 mmol/g, 0.140 g, 0.10 mmole) was swollen in anhydrous DME (4.7 mL) and coupled with 2-thiopheneboronic acid **2.83** (0.038 g, 0.30 mmole) in the presence of $Pd(PPh_3)_4$ (0.0058 g, 0.005 mmole) and Na_2CO_3 solution (2 M aqueous, 0.4 mL). After 24 h, the reaction mixture was cooled to rt and treated with aq. satd. NH_4Cl solution (5 mL) and further stirred for 10 min. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.1231 g) was swollen in dioxane (2.6 mL) for 30 min and treated with a solution of 3 M HCl (2.6 mL) for 48 h at 80°C. After filtration of the reaction mixture and washing of the resin, the filtrate was worked-up and the residue obtained purified on silica gel (95:5 hexane:acetone) to give 5-(2'-thienyl)-2-thiophenecarbaldehyde **2.93** (0.0167 g, loading: 0.70 mmol/g, >95%) as a orange solid : Beilstein Registry # [128982] mp 55-56 °C (MeOH) (Lit.[294] mp 59°C (EtOH)); IR ($CHCl_3$) 3094, 2926, 2811, 1723, 1660,

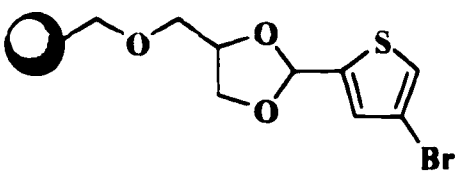
1508, 1447, 1417, 1222, 1050, 910 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.70 (s, 1H), 7.51 (d, J = 3.9 Hz, 1H), 7.21-7.18 (m, 2H), 7.08 (d, J = 3.9 Hz, 1H), 6.91 (t, J = 3.9 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 182.3, 146.8, 141.4, 137.2, 135.7, 128.1, 126.9, 125.9, 124.0; MS (EI (70 eV)) m/z (rel intensity) 194 (M^+, 100) ; HRMS *m/e* calcd for $C_9H_6OS_2$: 193.9860, found 193.9865.

5-(3'-Thienyl)-2-thiophenecarbaldehyde (2.94)



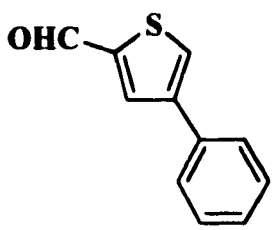
According to General Procedure C, resin-bound 5-bromo-thiophene-2-carbaldehyde **2.92** (1% cross-linked, loading 0.71 mmol/g, 0.139 g, 0.10 mmole) was swollen in anhydrous DME (4.6 mL) and coupled with 3-thiopheneboronic acid 95% **2.76** (0.040 g, 0.30 mmole) in the presence of $Pd(PPh_3)_4$ (0.0058 g, 0.005 mmole) and Na_2CO_3 solution (2 M aqueous, 0.4 mL). After 24 h, the reaction mixture was cooled to rt and treated with aq. satd. NH_4Cl solution (5 mL) and further stirred for 10 min. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.0945 g) was swollen in dioxane (2.0 mL) for 30 min and treated with a solution of 3 M HCl (2.0 mL) for 48 h at 80°C. After filtration of the reaction mixture and washing of the resin, the filtrate was worked-up and the residue obtained purified on silica gel (95:5 hexane:EtOAc) to give 5-(3'-thienyl)-2-thiophenecarbaldehyde **2.94** (0.0120 g, loading: 0.65 mmol/g, 92%) as a orange solid : mp 97-98 °C (EtOH); IR ($CHCl_3$) 3088, 2940, 1640, 1580, 1460, 1221, 1053 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.73 (s, 1H), 7.56 (d, J = 3.9 Hz, 1H), 7.44 (m, 1H), 7.25 (dd, J = 3.9, 3.3 Hz, 1H), 7.20 (d, J = 5.2 Hz, 1H), 7.13 (d, J = 3.3 Hz, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 182.5, 148.4,

141.4, 137.3, 134.3, 127.0, 125.7, 124.0, 122.5 ; MS (EI (70 eV)) m/z (rel intensity) 194 (M^+, 100) ; HRMS *m/e* calcd for $C_9H_6OS_2$: 193.9860, found 193.9862; Anal. Calcd for $C_9H_6OS_2$: C, 55.65 ; H, 3.11. Found : C, 56.00; H, 3.00.



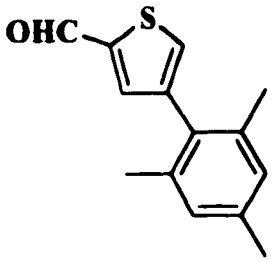
Resin-bound 4-bromo-thiophene-2-carbaldehyde (2.86)

According to General Procedure A, resin-bound 3-benzyloxypropan-1,2-diol **2.51** (loading 0.922 mmol/g max, 2.17 g, 2 mmole max) was swollen in anhydrous toluene (40 mL) and treated with 4-bromo-thiophene-2-carbaldehyde 90% (0.849 g, 4 mmole), *p*-toluenesulfonic acid monohydrate (0.038 g, 0.2 mmole) and anhydrous Na_2SO_4 (1.42 g, 10 mmole). After 48 h at 80°C, the reaction mixture was cooled to rt and the resulting resin was collected by filtration, neutralised with anhydrous pyridine, washed and dried to afford **2.86**. The loading capacity of **2.86** was determined according to General Procedure B. **2.86** (0.242 g) was swollen in dioxane (6.7 mL) and treated with a solution of 3 M hydrochloric acid (6.7 mL) for 48 h at 80°C. After filtration of the reaction mixture and washing of the resin, the filtrate was worked-up and the residue obtained purified on silica gel (5:1 hexane:EtOAc) to give 4-bromo-thiophene-2-carbaldehyde (0.0342 g) showing a loading of **2.86** of 0.74 mmol/g.



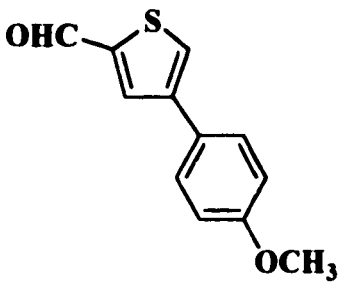
4-Phenylthiophene-2-carbaldehyde (2.88)

According to General Procedure C, resin-bound 4-bromo-thiophene-2-carbaldehyde **2.86** (1% cross-linked, loading 0.74 mmol/g, 0.136 g, 0.10 mmole) was swollen in anhydrous DME (4.5 mL) and coupled with phenylboronic acid 97% **2.60** (0.038 g, 0.30 mmole) in the presence of $Pd(PPh_3)_4$ (0.0058 g, 0.005 mmole) and Na_2CO_3 solution (2 M aqueous, 0.4 mL). After 24 h, the reaction mixture was cooled to rt and treated with aq. satd. NH_4Cl solution (5 mL) and further stirred for 10 min. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.0943 g) was swollen in dioxane (2.1 mL) for 30 min and treated with a solution of 3 M HCl (2.1 mL) for 48 h at 80°C. After filtration of the reaction mixture and washing of the resin, the filtrate was worked-up and the residue obtained purified on silica gel (9:1 hexane:EtOAc) to give 4-phenylthiophene-2-carbaldehyde **2.88** (0.0128 g, loading: 0.72 mmol/g, >95%) as a colourless solid : Beilstein Registry # [1282336] mp 65-67 °C (EtOH) (Lit.[295] mp 67.5-68.5°C); IR (DCM) 3055, 2986, 1674, 1427, 1264, 1175, 899 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.78 (s, 1H), 7.83 (d, J = 1.7 Hz, 1H), 7.64 (s, 1H), 7.44-7.19 (m, 5H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 182.7, 144.2, 143.3, 134.5, 134.1, 129.3, 128.9, 127.9, 126.1 ; MS (EI (70 eV)) m/z (rel intensity) 188 (M^+, 100) ; HRMS *m/e* calcd for $C_{11}H_8OS$: 188.0296, found 188.0294.



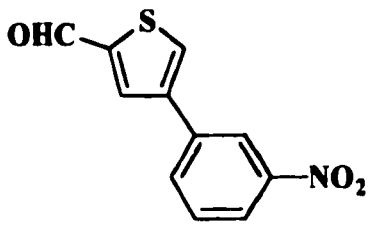
4-(2',4',6'-Trimethylphenyl)thiophene-2-carbaldehyde (2.90)

According to General Procedure C, resin-bound 4-bromo-thiophene-2-carbaldehyde **2.86** (1% cross-linked, loading 0.74 mmol/g, 0.1489 g, 0.11 mmole) was swollen in anhydrous DME (5 mL) and coupled with mesitylboronic acid **2.72** (0.054 g, 0.33 mmole) in the presence of $Pd(PPh_3)_4$ (0.0064 g, 0.0055 mmole) and Na_2CO_3 solution (2 M aqueous, 0.44 mL). After 48 h, the reaction mixture was cooled to rt and treated with aq. satd. NH_4Cl solution (5.5 mL) and further stirred for 10 min. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.127 g) was swollen in dioxane (2.8 mL) for 30 min and treated with a solution of 3 M HCl (2.8 mL) for 48 h at 80°C. After filtration of the reaction mixture and washing of the resin, the filtrate was worked-up and the residue obtained purified on silica gel (9:1 hexane:EtOAc) to give 4-(2',4',6'-trimethylphenyl)thiophene-2-carbaldehyde **2.90** (0.0175 g, loading: 0.60 mmol/g, 81%) as a yellow solid : mp 45-48 °C (hexane); IR ($CHCl_3$) 2918, 1673, 1446, 1175, 910 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.78 (s, 1H), 7.45 (s, 1H), 7.29 (s, 1H), 6.82 (s, 2H), 2.20 (s, 3H), 1.94 (s, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 182.6, 143.7, 142.1, 137.6, 136.4, 132.3, 131.9, 128.2, 29.5, 20.8, 20.5; MS (CI) m/z (rel intensity) 231 (M^++1, 100); HRMS *m/e* calcd for $C_{14}H_{14}OS$ + H: 231.084362, found 231.083523 ; Anal. Calcd for $C_{14}H_{14}OS$: C, 73.01; H, 6.13. Found : C, 73.03; H, 6.26.



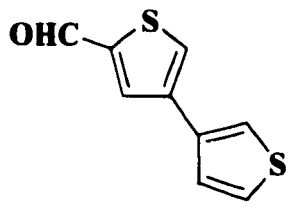
4-(4'-Methoxyphenyl)thiophene-2-carbaldehyde (2.91)

According to General Procedure C, resin-bound 4-bromo-thiophene-2-carbaldehyde **2.86** (1% cross-linked, loading 0.74 mmol/g, 0.1351 g, 0.10 mmole) was swollen in anhydrous DME (4.5 mL) and coupled with 4-methoxyphenylboronic acid 97% **2.22** (0.047 g, 0.30 mmole) in the presence of $Pd(PPh_3)_4$ (0.0058 g, 0.005 mmole) and Na_2CO_3 solution (2 M aqueous, 0.4 mL). After 24 h, the reaction mixture was cooled to rt and treated with aq. satd. NH_4Cl solution (5 mL) and further stirred for 10 min. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.110 g) was swollen in dioxane (2.5 mL) for 30 min and treated with a solution of 3 M HCl (2.5 mL) for 48 h at 80°C. After filtration of the reaction mixture and washing of the resin, the filtrate was worked-up and the residue obtained purified on silica gel (9:1 hexane:EtOAc) to give 4-(4'-methoxyphenyl)thiophene-2-carbaldehyde **2.91** (0.0160 g, loading: 0.67 mmol/g, 90%) as a yellow solid : mp 72-73 °C (hexane); IR ($CHCl_3$) 2835, 1671, 1610, 1547, 1512, 1434, 1365, 1287, 1249, 1177, 1051, 1031, 909 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.77(s, 1H), 7.79 (s, 1H), 7.56 (s, 1H), 7.34 (d, J = 8.2 Hz, 2H), 6.80 (d, J = 8.8 Hz, 2H), 3.68 (s, 3H) ; ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 182.7, 159.3, 144.1, 143.1, 134.3, 128.0, 127.2, 126.8, 114.2, 55.1 ; MS (CI) m/z (rel intensity) 219 (M^++1, 100); HRMS *m/e* calcd for $C_{12}H_{10}O_2S$ + H : 219.0479, found 219.0486; Anal. Calcd for $C_{12}H_{10}O_2S$: C, 66.03 ; H, 4.62. Found : C, 66.40; H, 4.93.



4-(3'-Nitrophenyl)thiophene-2-carbaldehyde (2.89)

According to General Procedure C, resin-bound 4-bromo-thiophene-2-carbaldehyde **2.86** (1% cross-linked, loading 0.74 mmol/g, 0.135 g, 0.10 mmole) was swollen in anhydrous DME (4.5 mL) and coupled with 3-nitrophenylboronic acid 98% **2.62** (0.052 g, 0.30 mmole) in the presence of $Pd(PPh_3)_4$ (0.0058 g, 0.005 mmole) and Na_2CO_3 solution (2 M aqueous, 0.4 mL). After 24 h, the reaction mixture was cooled to rt and treated with aq. satd. NH_4Cl solution (5 mL) and further stirred for 10 min. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.122 g) was swollen in dioxane (2.7 mL) for 30 min and treated with a solution of 3 M HCl (2.7 mL) for 48 h at 80°C. After filtration of the reaction mixture and washing of the resin, the filtrate was worked-up and the residue obtained purified on silica gel (95:5 hexane:EtOAc) to give 4-(3'-nitrophenyl)thiophene-2-carbaldehyde **2.89** (0.0175 g, loading: 0.614 mmol/g, 83%) as a pale yellow solid : mp 177-180 °C (hexane); IR ($CHCl_3$) 3151, 3086, 1673, 1643, 1597, 1527, 1350, 1208, 920 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.94 (s, 1H), 8.38 (s, 1H), 8.14 (d, J = 7.9 Hz, 1H), 8.02 (d, J = 2.0 Hz, 1H), 7.92 (s, 1H), 7.86 (d, J = 7.7 Hz, 1H), 7.57 (t, J = 7.9 Hz, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 184.2, 148.5, 144.3, 140.2, 136.2, 135.4, 132.5, 132.4, 130.6, 122.4, 120.4; MS (EI (70 eV)) m/z (rel intensity) 233 (M^+, 100); HRMS *m/e* calcd for $C_{11}H_7NO_3S$: 233.0147, found 233.0143.



4-(3'-Thienyl)-2-thiophenecarbaldehyde (2.87)

According to General Procedure C, resin-bound 4-bromo-thiophene-2-carbaldehyde **2.86** (1% cross-linked, loading 0.74 mmol/g, 0.150 g, 0.11 mmole) was swollen in anhydrous DME (5 mL) and coupled with 3-thiopheneboronic acid 95% **2.76** (0.045 g, 0.33 mmole) in the presence of $Pd(PPh_3)_4$ (0.0064 g, 0.0055 mmole) and Na_2CO_3 solution (2 M aqueous, 0.4 mL). After 24 h, the reaction mixture was cooled to rt and treated with aq. satd. NH_4Cl solution (5.5 mL) and further stirred for 10 min. The resin was removed by filtration, washed and dried. The cleavage from the solid support was done according to General Procedure D. The resulting resin (0.137 g) was swollen in dioxane (3 mL) for 30 min and treated with a solution of 3 M HCl (3 mL) for 48 h at 80°C. After filtration of the reaction mixture and washing of the resin, the filtrate was worked-up and the residue obtained purified on silica gel (95:5 hexane:EtOAc) to give 4-(3'-thienyl)-2-thiophenecarbaldehyde **2.87** (0.0193 g, loading: 0.73 mmol/g, >95%) as a yellow solid : mp 100-101 °C (MeOH); IR ($CHCl_3$) 3094, 2960, 2930, 2840, 1668, 1513, 1445, 1399, 1245, 1168, 1049, 908 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.80(s, 1H), 7.81 (s, 1H), 7.61 (s, 1H), 7.29-7.17 (m, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 182.8, 143.9, 138.3, 135.5, 134.5, 128.8, 126.6, 125.7, 120.7 ; MS (EI (70 eV)) m/z (rel intensity) 194 (M^+, 100) ; HRMS *m/e* calcd for $C_9H_6OS_2$: 193.9861, found 193.9868; Anal. Calcd for $C_9H_6OS_2$: C, 55.65 ; H, 3.11. Found : C, 55.80; H, 3.31.

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