THE UNIVERSITY OF SOUTHAMPTON

Polymer-Supported Reducing and Oxidising Reagents

by

Patrick Lecarpentier

Doctor of Philosophy

School of Chemistry

Faculty of Science

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PREFACE

The research described in this thesis was carried out under the supervision of Dr. B. Linclau at the University of Southampton in the Combinatorial Center of Excellence between November 2001 and February 2005. No part of this thesis has been previously submitted at this or any other University.

UNIVERSITY OF SOUTHAMPTON

ABSTRACT

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Polymer-supported reagents have the potential to yield very clean product with no purification needed. Solid-supported silane reagents were studied for the reduction of ester to the corresponding aldehyde or ketone. A commercially PS-DES resin was tested in the catch and release reduction of ester. A new silane resin was successfully synthesised in two steps. Unfortunately, an efficient procedure could not be found to perform the first part of the reduction, the hydrosilylation.

A protocol for the Tamao-Fleming oxidation was then devised with the new silane resin as its main reagent. Again the hydrosilylation of alkene seemed to be the limiting step.

Several polymer-bound IBX derivatives were then synthesised. The oxidation of alcohols proved to be successful despite a modest loading of the first IBX resin. Finally, an efficient three step synthesis of an IBX amide resin with a good loading and reactivity comparable to IBX was devised. A very good method to remove all trace of tetrabutylammonium species from the IBX resins was discovered.

ACKNOWLEDGMENTS

I am very indebted to my supervisor Dr. Linclau who always supported me during my PhD with a lot of enthusiasm, along with eternal patience; for these virtues I wish to thank him sincerely. I also would like to thank all the member of the Combinatorial Centre of Excellence in which I was included. It was composed of people from different nationality, which brought a particular atmosphere with lots of exchanges not only in chemistry but also in foreign language knowledge. I would particularly like to thank Dr. Crosignani whose advises helped me in the lab.

To my family who always supported and encouraged me, I dedicate this work.

Table of Contents.

ABBREVIATIONS

Ar	Aryl
br	Broad
Bu	Butyl
CI	Chemical impact
d	Doublet
δ	Chemical shift (ppm)
DIC	*N,N'*-Diisopropylcarbodiimide
DMA	*N,N'*-Dimethylacetamide
DMAP	4-*N,N'*-Dimethylaminopyridine
DMF	*N,N'*-Dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethylsulfoxide
DVB	Divinylbenzene
EI	Electron ionisation
equiv	Equivalents
ES	Electrospray
Et	Ethyl
FT-IR	Fourier transform infra-red spectroscopy
h	Hour
HPLC	High performance liquid chromatography
HOBt	1-Hydroxybenzotriazole
IBX	*o*-Iodoxybenzoic acid
J	Scalar coupling constant
LDA	Lithium diisopropylamide
m	Multiplet (NMR) or medium (IR)
m-CPBA	*Meta*-chloroperbenzoic acid
Me	Methyl
min	Minute
MP	Melting point
MS	Mass spectrometry
μw	Microwave irradiation
NMP	1-Methyl-2-pyrrolidinone

NMR	Nuclear magnetic resonance spectroscopy
PEG	Polyethylene glycol
PEGA	Polyethylene glycol acrylamide
ppm	Parts per million
Pr	Propyl
PS	Polystyrene
PASP	Polymer-assisted solution phase chemistry
q	Quartet
rt	Room temperature
s	Singlet (NMR) or strong (IR)
SPOS	Solid-phase organic synthesis
t	Triplet
TBAF	Tetra-*n*-butylammonium fluoride
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
UV	Ultraviolet
ν	Frequency (cm^{-1})
w	Weak

1 Introduction

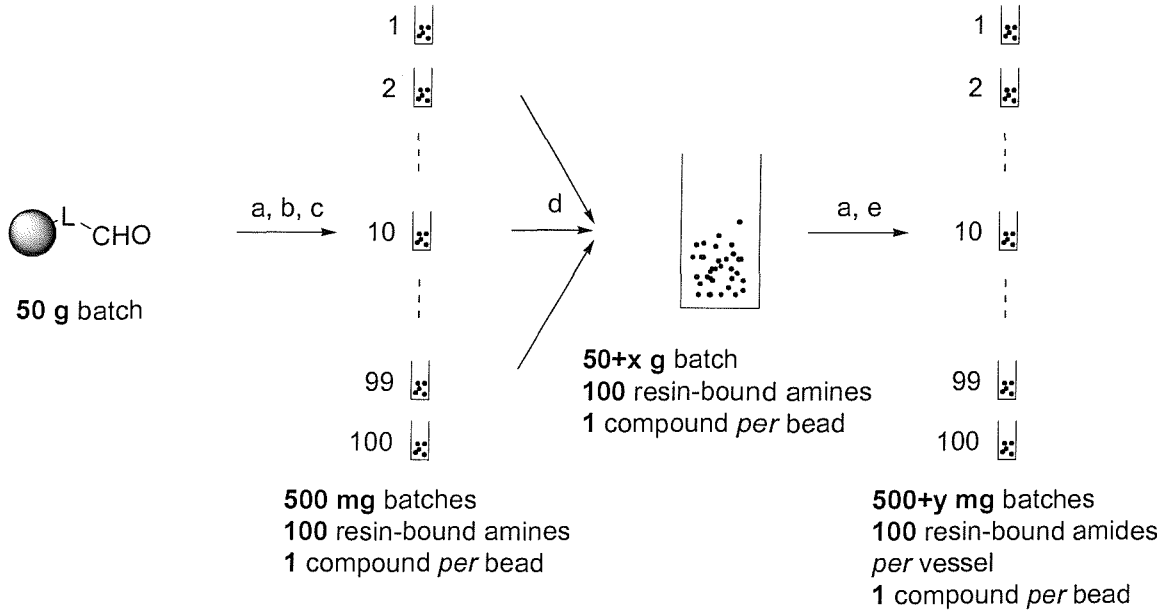
1.1 Solid-phase synthesis

1.1.1 Introduction

The solid-phase synthesis is a method to synthesise molecules on a solid-support, thus facilitating the purification. The release of the desired compound is achieved through a cleavage step. There are numerous advantages like the possibility to drive any reaction to completion by using large excess of reagent. This excess can later be easily removed by a simple washing procedure as the product is linked to the solid-support. This is the second main advantage, a very easy workup. This straightforward purification allows for an easy automation of the reaction, thus enabling the possibility to synthesise libraries of compounds very quickly.[1, 2] This technique is also known as "combinatorial chemistry".[3] This automation is particularly advantageous when used on linear syntheses such as multiple peptide coupling with iterative steps.

Various techniques were investigated to fully exploit the possibility opened by the use of solid-supports.[4] The split and mix methodology was developed for the synthesis of large libraries in a very short time and use each beads as microreactors to synthesise one compound per bead.[5-7] In Scheme 1.1 the synthesis of a 10,000 amides library by split and mix is described. Firstly, the resin (50 g) is divided between 100 vessels (500 mg) and in each vessel a different solid-supported amine is prepared through step a, b and c. Then the 100 resin aliquots are mixed together (50 g, step d). This 50 g of resin is then divided again in 100 portions of 500 mg and each vessel contain all the 100 amines but each bead is loaded with only a single compound as the loading of the amines was performed in separate vessels. A different acylating agent is then added to each vessel (step e) giving 100 amides per vessel and in total 10,000 amides with only 1 amide on each bead.

The mix and split process can be repeated several time to further increase the number of synthesised compounds thus creating a big library very quickly and can be fully automated.



Scheme 1.1. Principle of the split and mix for the synthesis of a 10,000 amides library

However, there are also multiple drawbacks with solid-phase synthesis such as the high cost of most solid-supports and the difficulties to monitor on-bead synthesis with only IR or UV analysis as rapid tool. The adaptation from solution-phase to solid-phase synthesis typically needs modification of the procedure to cope with the restriction of the solid-support such as solvent compatibility or heterogeneous conditions. Moreover, while the separation between the solid-supported product and the excess of reagents is simple, when completion is not reached unreacted starting material is left on the bead. Adding a capping step prevent further reaction of these functional groups but the number of step of the synthesis augment. The reaction performed on solid-phase must be complete without the formation of a side product otherwise the cleavage step release a mixture a product instead of the pure desired compound. Finally, the solid-support can be conceived as a kind of protecting group thus the chemistry applied must be orthogonal to prevent the cleavage of the growing molecule.

To overcome some of the drawbacks enumerated, the solid-supported species can be used as a reagent instead of being the support for the growing molecule. An excess of the supported reagent can be introduced and removed by filtration once the reaction is completed. When the solid-supported molecule is used as a scavenger, the unreacted starting material of a reaction or the impurities synthesised during a reaction can be removed. The solid-supported functionality can be added to catch the desired compound from a mixture then

released after more transformation if necessary. With these methods the reaction is performed in solution phase keeping the advantages such as fast reaction monitoring (TLC for example) and easier compound characterisation while still possessing an easy workup and the possibility of automation. These techniques will be discussed in the following sections.

1.1.2 Overview of resin-types

Several types of support can be found in solid-supported chemistry. One of the most widely used is the polymer support. It is obtained by polymerisation of a monomer and controlled by the addition of a cross-linker to give consistency to the polymer. The ratio of cross-linker will also give different properties to the support. Polystyrene beads were the first type developed in 1963 by Merrifield[8] using chloromethyl as functional group. This can be achieved by the polymerisation of styrene and divinylbenzene (DVB) as cross-linker, followed by chloromethylation.

Now, Merrifield resins are generally produced through the alkylation of polystyrene with chloromethyl methyl ether in the presence of a Lewis acid catalyst. However, during this process, additional cross-linking can take place. Moreover, the substitution with choromethyl can occur in *ortho*, *meta*, *para* or even a mix of these positions. The addition of 4-chloromethyl styrene as a co-polymer gives a more consistent loading between batches with a well-defined substitution position.

The loading corresponds to the number of millimole of desired functional group *per* gram of resin. It is the physical parameter that characterise a resin as it can be measured by physical analysis like elemental analysis of a typical atom, the chlorine in the Merrifield resin for example. When the loading is high, more products will be synthesised with a defined quantity of resin. However, due to kinetic problems with the increase of the steric hindrance created by newly formed molecules, the reaction time to reach complete conversion of the immobilised functional group will increase with the actual loading.

Typically, adding 1 or 2 % of DVB gives the resin enough physical resistance while retaining the ability to swell with the solvent, thus opening the inside of the bead to the various reactants. Unfortunately, very polar solvents make the resin shrink, leaving only the

external sites open for any reaction. The nature of the functional groups attached to the bead can change its swelling properties. Furthermore, during chemical reactions, as the functionality are changed, the swelling properties may vary, thus the choice of the reaction solvent is very important.[9]

When using more than 5 % of DVB, the structure of the beads obtained is more rigid and only limited swelling can occur, therefore blocking the access to the internal part of the beads. To by-pass this limitation, the formation of cavities inside the resin is necessary. A co-solvent in which the growing polymer is not soluble is added during the formation of the resin, usually toluene or hexane. This co-solvent will be trapped inside the beads and form pockets. As the beads do not swell, these cavities allow a much higher surface area, thus enabling a higher loading. However, the size of the pores limits the possible reaction to small molecules and decreases even more the kinetic of the various reactions performed.[10] This type of support is called macroporous resin.

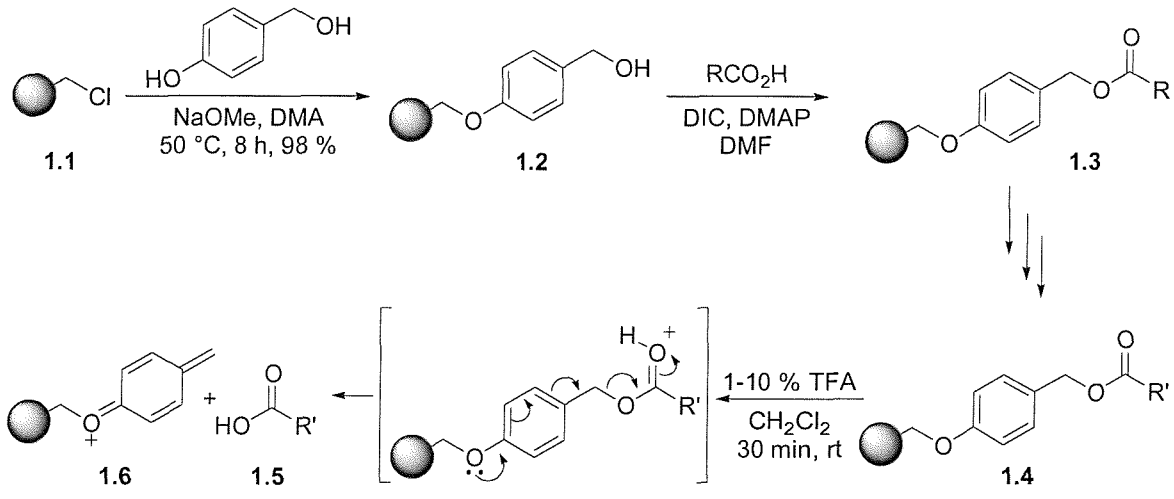
If no cross-linker is used, a soluble polymer is formed. This type is soluble in solvents like THF or dichloromethane and then cancels the drawbacks carried by the heterogeneous mixture. The resin is recovered generally when adding diethyl ether or hexane as it then precipitates. However, the physical integrity of the polymer threads can be broken more easily and the recovery can prove problematic if insoluble particles are formed during the reaction.

Poly(ethylene glycol) (PEG) can be grafted on the polystyrene bead. This will allow the use of a wider range of solvents. Moreover, this type of resin provides an environment having similarities with a solution-phase reaction due to the limited solubility of the PEG. However, the addition of PEG to polystyrene beads reduces its loading with the increase of the resin backbone mass. Poly(ethylene glycol) acrylamide (PEGA) resin possesses the same advantages as PEG polystyrene beads but with a higher swelling in polar solvents, giving a better solvatation. Both last resins can be used in continuous flow peptide synthesis and also in solid supported organic synthesis (SPOS).

Various other supports have been tested like paper, cellulose, glass, polyethylene powder and polyacrylamide sheets.

While attaching the resin to the molecule can be very easy, the releasing step can prove really problematic. To counter-balance this drawback, linkers can be introduced between the solid-support and the reactive substrate. These linkers must be selectively cleavable, thus allowing, after a synthetic sequence, to release effectively the desired compound from the bead into the solution. These linkers must be very resistant to a wide range of reactive conditions, then quantitatively cleavable using mild conditions.

The first examples of linkers were designed for peptide synthesis as the first application of SPOS was polypeptide synthesis. In 1973, Wang illustrated the concept using an acid-labile hydroxymethylphenoxyacetyl linker **1.2**.[11] After immobilisation of the linker, a carboxylic acid is introduced by the mean of a carbodiimide coupling (Scheme 1.2). Following subsequent transformation of the substrate, the cleavage is performed typically using a 1 to 10 % diluted solution of TFA in dichloromethane.



Scheme 1.2. Use and cleavage of the Wang linker

Along with the carboxylic acid **1.5**, the supported by-product **1.6** can further react with nucleophilic groups. To prevent this side reaction, which may result in loss of product, nucleophilic scavengers such as water, thioanisole or triethylsilane can be added.

While the first generation of linkers specifically designed for SPOS was intended for the synthesis of peptides, the scope was limited. Peptides have limited utility as bioavailable therapeutic agents. An acidic functionality was required for the attachment to the molecule, which was then regenerated after cleavage. This restricted dramatically the scope of possible use with molecules other than peptide. The solid-supported synthesis of 1,4-

benzodiazepine derivatives described by Ellman opened the way for a broader use of linkers.[12] The attachment to the solid-support was made through an hydroxy or a carboxylic acid functionality using an acid cleavable linker, [4-(hydroxymethyl) phenoxylacetic acid. This type of linker was named "traceless linkers" as once cleaved from the solid-support, no indication of the site where the molecule was bound to the resin is apparent.[13] Hundreds of linkers have been developed to cope with the widest possible range of reagents and syntheses.[14]

1.2 Polymer-assisted solution phase chemistry (PASP)

Polymer supported reagents and catalysts are reactive functionalities linked to a solid-support to avoid any purification step at the end of the reaction.[15-17] Many reagents, which are used in solution phase, can be immobilised on support. This causes a straightforward adaptation of the existing reaction scheme to the solid phase chemistry, thus enabling a gain in time due to the already known chemistry path. Moreover, this gain is further increased by the easy separation after reaction.

Both supported reagents or catalysts can be immobilized through three main methods:

a) Entrapment, with the capture within the polystyrene network of a catalyst.
b) Ion pairing where a cation or anion is bound to its counter ion, which is attached to the solid support.
c) Covalent binding.

With a broader applicability, the two last methods are the most commonly used.

The three methods are subjected to the possibility of leeching, where the captured reagent or catalyst is released from the support. The study by Drian[18] of a polymer supported palladium catalyst showed a loss between 0.60 an 0.65 % during a typical reaction. However, the entrapment is more prone to leeching as no covalent bond is formed between the reagent and the support.

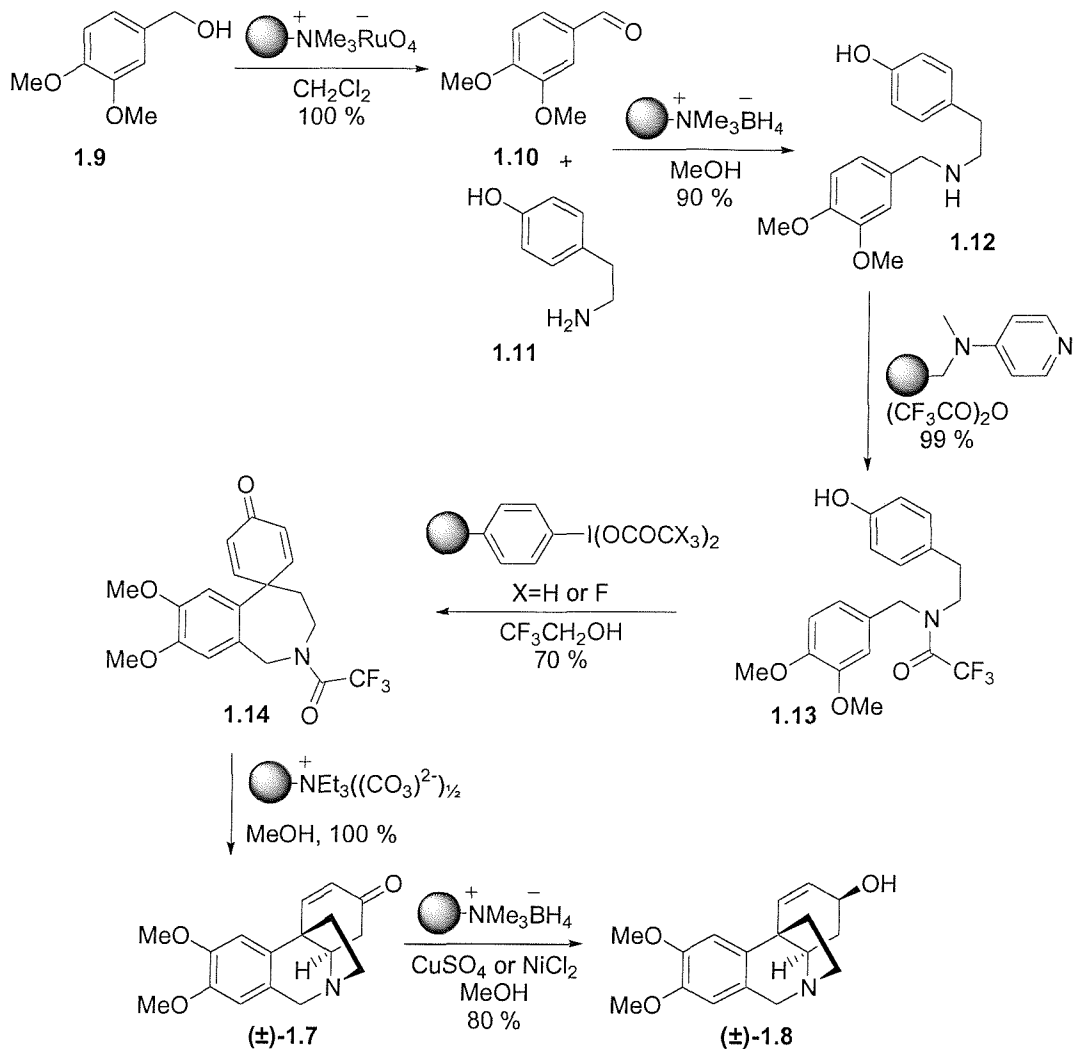
As compared to solid phase organic synthesis which limited the ability to effectively analyse the on-bead product using FT-IR, gel-phase NMR or microanalysis, a synthetic

scheme via polymer immobilised reagents always give a product that can be characterised by any traditional methods. The reaction is still performed in solution phase.

Another improvement is the possibility to perform experiments with an excess of supported reagents to drive to completion the most sluggish reactions. Despite slower kinetics due to the heterogeneous nature of the reagents, the very large excess of the reactive supported species can overcome the reactivity gradients traditionally existing in large arrays of differently substituted starting materials. With an excess of supported reagents, the complete on-bead conversion is not required thus the reaction kinetic increases, as the less reactive sites of the bead are not necessary.

An example by Ley *et al.*[19] illustrates clearly the use of such polymer-supported reagents in a multi-step synthesis of the alkaloids (±)-oxomaritidine **1.7** and (±)-epimaritidine **1.8** with respectively a sequence of five- and six-step reactions, using solely polymer-supported reagents as shown in Scheme 1.3.

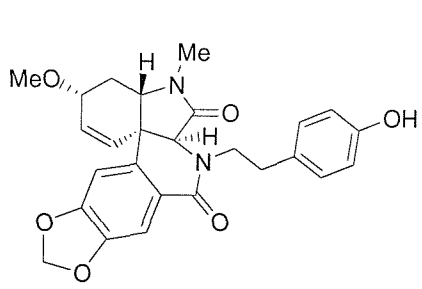
The first step consisted in the oxidation of the alcohol **1.9** to the aldehyde **1.10** using a polymer supported perruthenate reagent[20] developed in 1997. A reductive amination between primary amine **1.11** and aldehyde **1.10** involving a supported borohydride reagent[21] generated the norbelladine derivative **1.12** which under treatment with trifluoroacetic anhydride and supported aminomethyl pyridine[22] gave the amide **1.13**. Polymer supported (diacetoxyiodo)benzene[23] in trifluoroethanol allowed the intramolecular phenolic oxidative cyclisation of **1.13** to **1.14** in 70 % yield with no other products detected. After adding the polymer-supported carbonate to **1.14**, the deprotection followed by intramolecular 1,4-addition gave the desired (±)-oxomaritidine **1.7**, which upon reduction of the carbonyl group using polymer-supported borohydride and a metallic catalyst yielded (±)-epimaritidine **1.8**.



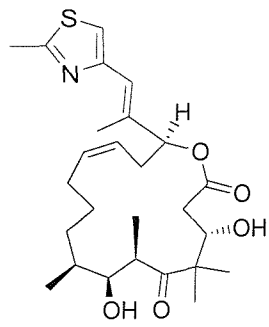
Scheme 1.3. Synthesis of (±)-oxomaritidine **1.7** and (±)-epimaritidine **1.8** using polymer-bound reagents

As exemplified in Scheme 1.3, the attachment to the support can be either covalent or ionic which enable a wider range of possible reagents. This synthesis gives a clear advantage of the solid phase synthesis with good to excellent yield for each step with work-up consisting in filtration followed by evaporation of the solvent. Ley specialised in total synthesis of natural compound using solid-supported reagents and catalysts. The total synthesis of the Amaryllidaceae alkaloid (+)-Plicamine **1.15** (Figure 1.1) and its unnatural enantiomer uses thirteen immobilised systems as a combination of supported reagents and scavengers without resorting to conventional chromatographic methods.[24] For the synthesis of Epothilone C **1.16**, one of the most challenging target synthesised with only solid-supported chemistry, 29 steps combining the use of supported reagents and supported scavengers were

necessary. The overall yield and high selectivity is comparable with the previous conventional syntheses.[25, 26]



1.15

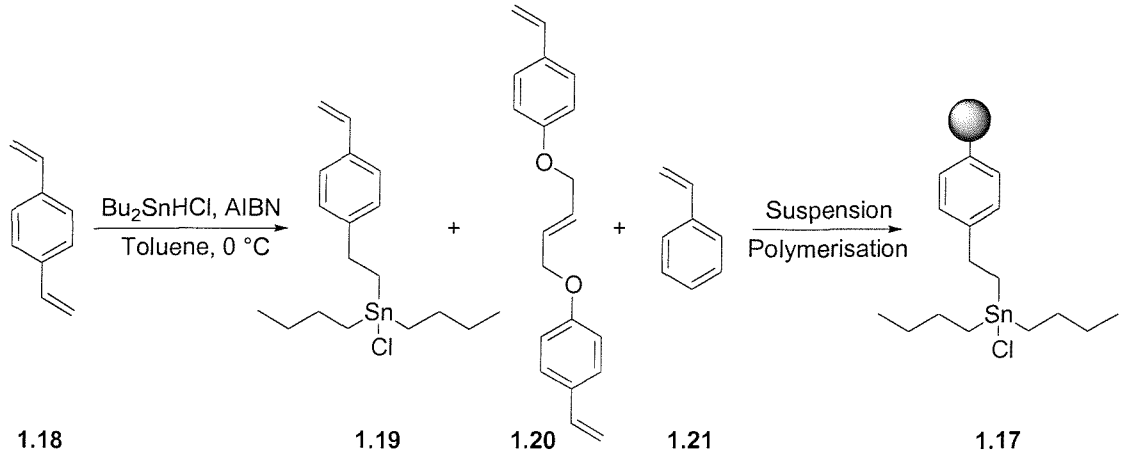


1.16

Figure 1.1. (+)-Plicamine **1.15** and Epothilone C **1.16**

The recovery of a catalyst can be transformed in a trivial filtration very easily performed when the catalyst is linked to a solid-support. Upon a simple wash, the catalyst is immediately available for further reactions.[15, 27, 28] This procedure is mostly advantageous for transition metal catalysts, which are very expensive and highly toxic. Moreover, as the catalyst can be recovered, higher concentrations can be used to drive the reactions to completion.

For example tin is very difficult to remove, highly toxic and traces can often still be detected even after several column chromatography purifications. Grafting a tin derivative to a solid-support prevent tin from forming complexes with the desired product thus virtually eliminating its toxicity. In 1998, Deleuze[29] describe a macroporous polymer-supported organotin hydride catalyst **1.17** with a reactivity comparable with soluble tributyltin chloride in the catalytic dehalogenation of 1-bromoadamantane using $NaBH_4$ as a hydride reservoir with a 10 % molar ratio of the tin supported catalyst with respect to 1-bromoadamantane (Scheme 1.4).

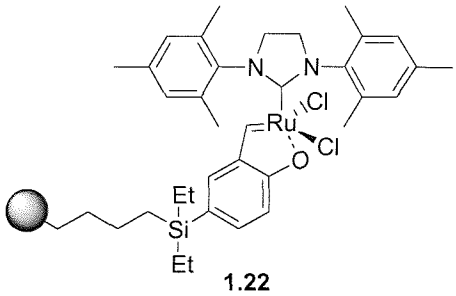


Scheme 1.4. Preparation of macroporous polymer-supported organotin hydride

In this synthesis, (*E*)-1,4-*bis*-(4-vinylphenoxy) but-2-ene **1.20** was preferred to DVB as cross-linker as it increased the swelling ability of the final polymer in a wider range of solvent. Furthermore, the reactivity of the various resin prepared with **1.20** was superior to those prepared with DVB. However, in the reduction of 1-bromoadamantane, while using a 20 % DVB cross-linked resin, the conversion was still complete after 10 runs while after 6 runs, whatever the level of cross-linking with **1.20**, the yield fell to less than 60 % with resins **1.17**. These types of resin did not necessitate any regeneration step between each use.

Metathesis is another area that had undergone a huge development in the past decade. The aim is to immobilise the ruthenium on a solid-support to prevent the formation of undesired ruthenium by-products. Grela *et al.*[30] developed the polymer-bound ruthenium carbene **1.22** using butyldiethylsilyl polystyrene as support (Figure 1.2). The use of a silyl linker enables a direct determination of the loading of the resin by cleavage followed by spectroscopic ruthenium measurement in solution (determined from the inductively coupled plasma mass spectrometry (ICP-MS) analysis of Ru). Furthermore, the distance between the ruthenium and the polymer matrix results in a better recyclability and improved reactivity.

The reaction kinetic was reported as slower than the solution phase equivalent (using a bromine instead of the silicon) with a reaction time increasing by 2 fold. The products were analyzed after a simple filtration and confirmed as pure.



1.22

Figure 1.2. Polystyrene diethylsilyl supported ruthenium carbene

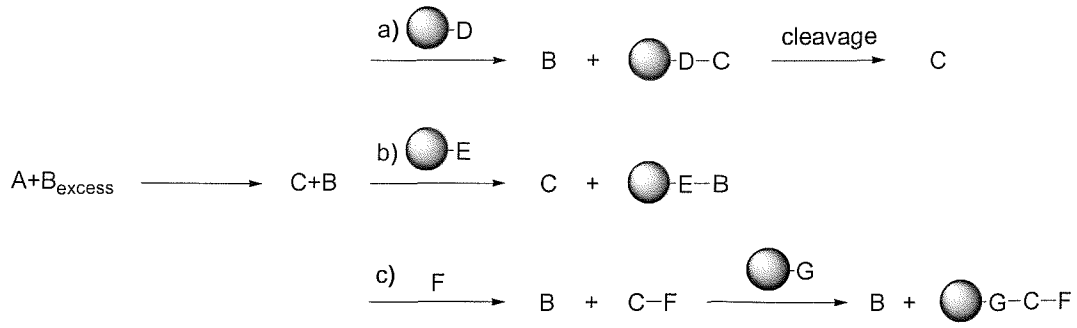
Up to six cycles of metathesis could be performed without loss in the conversion yield but slight loss of reactivity was described which was compensated by longer reaction time. The supported catalyst did not lose activity after 3 months of storage in the air at room temperature and could even be used with non-degassed dichloromethane. However, with non-degassed solvents, the catalyst could only be re-used up to three times before complete loss of reactivity.

1.3 Polymer-bound scavengers

While solid-supported chemistry allows the synthesis of pure products, the longer reaction time can prove to be an obstacle for the obtainment of unstable compounds. One solution is to perform the reaction in solution phase and then use a polymer-supported reagent to remove some product as demonstrated in Scheme 1.5.[31, 32] In this case, neither the reactants nor the reagents are immobilised. This method can be an alternative to a column chromatography when large array of chemical compound have been synthesised and are contaminated by the same type of impurity.

There are some requirements to be able to use a scavenging reaction. Firstly, the reaction must be complete and clean with no more side products related to the transformation. Then, a fast action is necessary to prevent degradation of the target and the pure product should be obtained after a simple filtration and evaporation.

There are several possibilities for scavenging application (Scheme 1.5)



Scheme 1.5. Principle of the scavenging technique for the purification

The method a) is the product scavenging enabling an immediate isolation of the product **C** after cleavage. When the reaction is completed, the addition of a polymer-supported reagent **D** will scavenge the required reaction product **C**. After the usual filtration and washing procedure, this compound will be released upon cleavage and recovered in pure form without any modification of its structure. This purification principle was first described by Siegel *et al.*.[33]

Method b) consist in the elimination of the excess reagent **B**. Using this technique, the reaction speed can be increased and complete transformation obtained when using an excess of the reagent. In the end, one of the reagents will be completely consumed and the remaining of the excess starting material **B** will be the designated target for the purification thus the choice of the resin necessary for the separation is greatly facilitated.

Method c) correspond to the use of tagging or sequestration enabling reagents. This method can be used when no resin is suitable to scavenge the target **C** or if the scavenging reaction is really slow. The product **C** reacts with a new reagent **F** whereas the excess of reagent **B** is unreactive. The new molecule **C-F** is then immobilised. If the cost of a polymer-support scavenger is too high, modifying the target can allow the use of a less expensive scavenger.

A vast possible choice of these supported scavengers can be found in the literature[16, 34] and here are a few examples in Table 1.1.

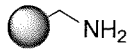
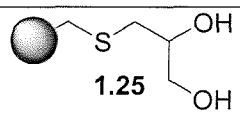
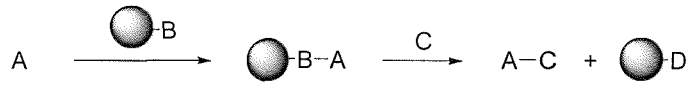
 **1.23**	Used with HCl, acid anhydride and carboxylic acid.
 **1.24**	Scavanges amine and can be used for catch and release.
 **1.25**	Immobilises aldehydes or ketones, can be released with *p*-TSA.
 **1.26**	For amines.

Table 1.1 Various polymer supported scavengers and their target

1.4 Catch and release

The catch and release[35] methodology derived from the product scavenger technique. As previously described, a product, which can come from a mixture, is attached to the solid-support and through this, lead to a reactive intermediate (Scheme 1.6). After filtration, adding a second reagent induces a reaction modifying the substrate and causing the cleavage from the resin. Obviously, while linked to the support, several steps can be performed before release is executed.

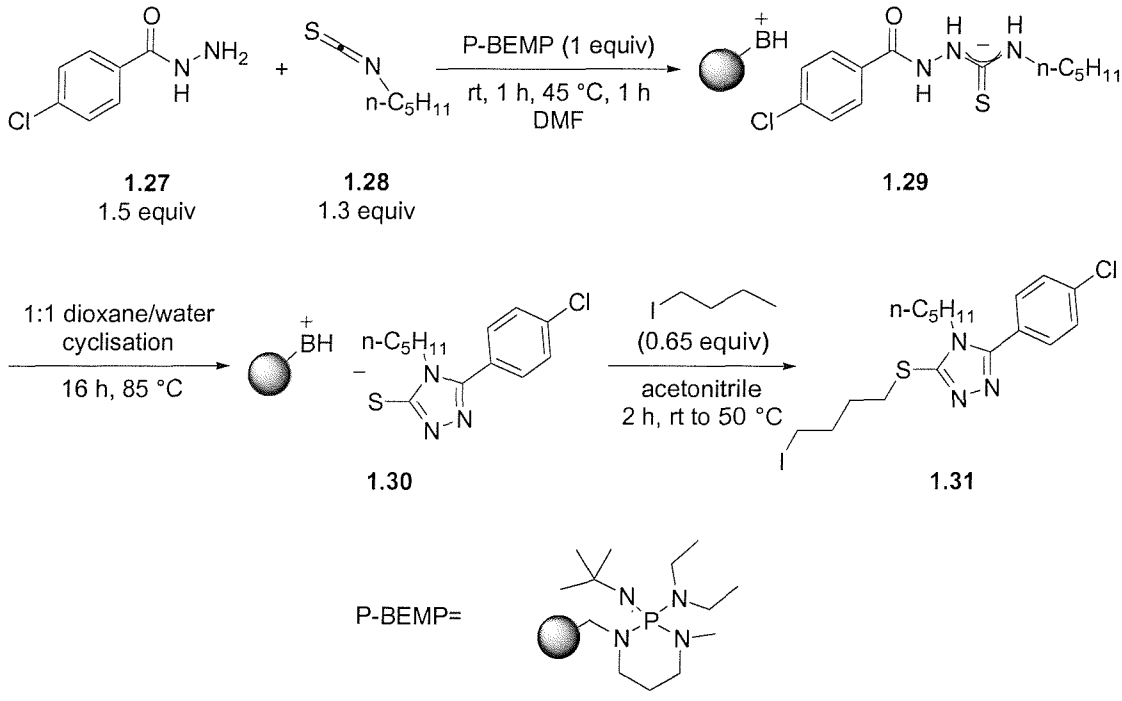


Scheme 1.6. Catch and release principle

With this method, the purification of reacted and unreacted product from the support is automatic. Furthermore, during the release step, if a limited amount of reagent is introduced, there will be complete transformation and a pure product is obtained. The catch and release procedure combines the advantages of polymer-bound scavengers and on-bead synthesis.

A good example is given by Graybill[36] with a synthesis of 3-thio-1,2,4-triazole (Scheme 1.7) with the immobilisation of intermediate **1.29** followed by the cyclisation to form the triazole **1.30**. The releasing step correspond to the alkylation of the sulfur giving **1.31** in a

93 % yield and 100 % purity. P-BEMP is a strongly basic, non-nucleophilic reagent making it the reagent of choice for deprotonation and *N*-alkylation of weakly acidic heterocycles.[37]



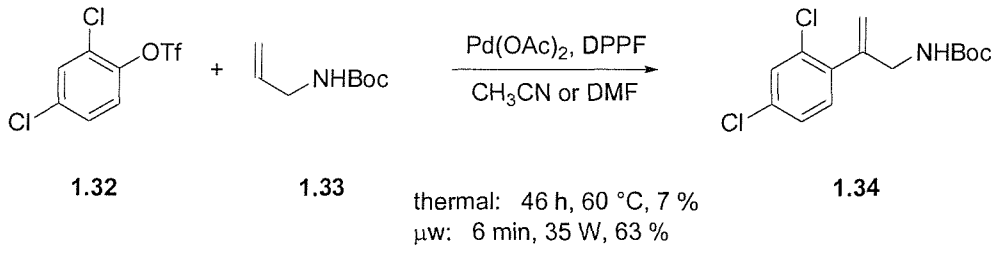
Scheme 1.7. Catch and release preparation of 3-thio-1,2,4-triazole

1.5 Microwave irradiation

Discovered 60 years ago by Spencer while working on radars, the microwave irradiation[38, 39] was only applied for chemistry purpose in 1986 when two different groups first published articles on the subject.[40, 41] Microwave irradiation allowed the acceleration of organic reactions. Two schools of thought exist to explain this phenomenon. For the first, as the heat source is equally located within the reaction mixture, the effect is only thermal. There is no "hot wall" effect thus preventing a possible degradation of either the products or the reagents. Moreover, when used in conjunction with a sealed vessel, temperatures higher than the boiling point of the solvent can be achieved. The increase in reaction speed is only due to the higher temperature. The second explanation deals with the presence of non-thermal effect to explain the acceleration.[42]

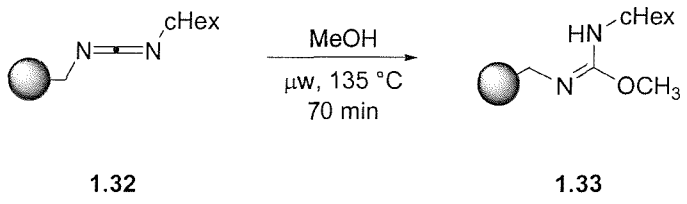
The interaction of the radiation with molecules is purely due to the presence of a dipolar moment. Thus the more polar solvents are the best to convert the microwave irradiation to heat.

While speeding up the rate of numerous reactions, an improvement in the yield can be observed with some reactions when submitted to microwave irradiation. Hallberg described a Heck reaction with a very poor 7 % yield under thermal condition (Scheme 1.8).[43] When microwave irradiation was applied, the desired product was obtained in a 63 % yield, 9 fold the original result while the reaction time was reduced dramatically.



Scheme 1.8. Increased speed and yield using microwave irradiation

As the reaction rate in solid-phase chemistry is slowed down, microwave irradiation proved to be efficient to speed up the reaction time as predicted by Caddick.[44] In 1992, Yu *et al.* demonstrated an enhancement in peptide coupling efficiency with microwave irradiation.[45] The coupling between an HMP-Gly resin and various activated amino acids was complete after only 6 min at 55 °C. Under thermal condition, only 60 to 70 % yield was obtained after 6 min. No racemization occurred during the microwave irradiation. A heptapeptide and a decapeptide were synthesised both thermally and with microwave irradiation. The non-microwaved assisted synthesis showed an average coupling yield of 80 % for each step. The microwave synthesis yielded 99 to 100 % yield for each step with a 4 min reaction time per step.



Scheme 1.9. Synthesis of a polymer-supported *O*-methyl isourea under microwave irradiation with methanol as solvent

An interesting effect caused by microwave irradiation is to change the properties of a solvent when high temperatures are employed. This case is perfectly illustrated with methanol, a very poor swelling solvent for polymer-supported reagents. Linclau developed the synthesis of a polymer supported *O*-methyl isourea by simply submitting a polymer-supported carbodiimide in dry methanol to microwave irradiation (Scheme 1.9).[46]

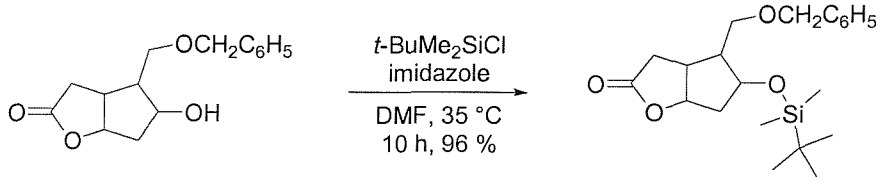
2 Solid-supported silanes for the conversion of esters to aldehydes

2.1 Introduction

2.1.1 Protecting groups

In the periodic table of element, silicon is just below carbon. This position gives similarities in their properties such as a valency of four and a tetrahedral conformation in molecules. The Si-C bond is strong enough to resist a vast range of synthetic transformation but is very weak towards particular conditions. With a lower electronegativity of the silicon compared to the carbon, the Si-C bond is polarised thus reactive to nucleophiles. Fluoride ion readily attacks silicon but is a poor nucleophile for carbon. The Si-F bond is one of the strongest single bonds known with a bon energy of 582 kJ/mol.

Silyl ethers are vastly used in organic chemistry as protecting group.[47] Silyl protecting groups are very useful for alcohols. A typical procedure for the synthesis of a silyl ether involves a base, often imidazole as exemplified in a synthesis by Corey and his group (Scheme 2.1).[48] The silyl ether protection is an almost quantitative reaction, a fundamental requirement for a protecting group.

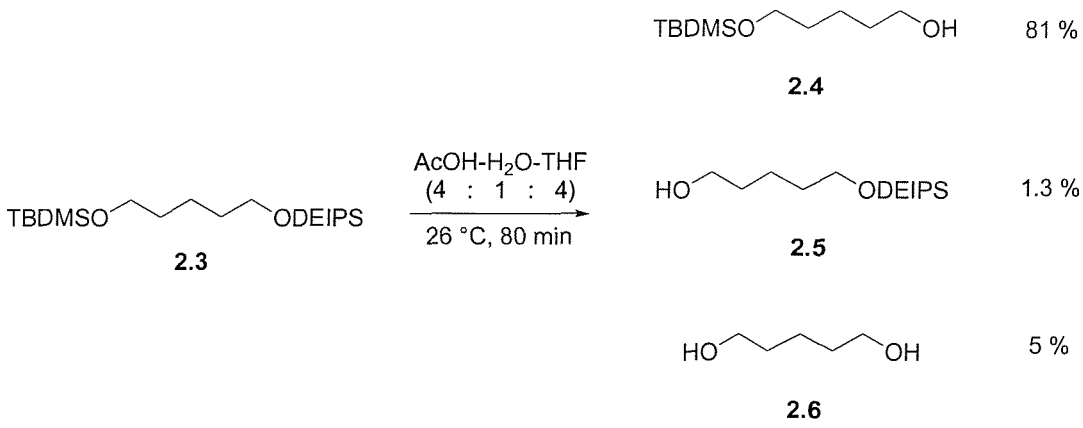


2.1 **2.2**

Scheme 2.1. Protection of a secondary alcohol as a *t*-butyldimethyl silyl ether

The *t*-butyldimethyl silyl ether (TBDMS) is one of the most stable and most popular silyl protecting group due to the steric hindrance introduced by the *t*-butyl group. TBDMS ethers survives aqueous work-up and silica-gel purification. Electron-withdrawing substituents on the silicon atom increase the susceptibility towards base hydrolysis of the silyl protecting group while decreasing its sensitivity towards acid hydrolysis. Phenolic silyl ether are more easily cleaved by base and allyl silyl ether are more affected by acidic conditions.[47] Modifying the substituents of the silicon atom affect the stability of the silyl ether allowing a differentiation between several different silyl protecting groups. Mild acidic conditions

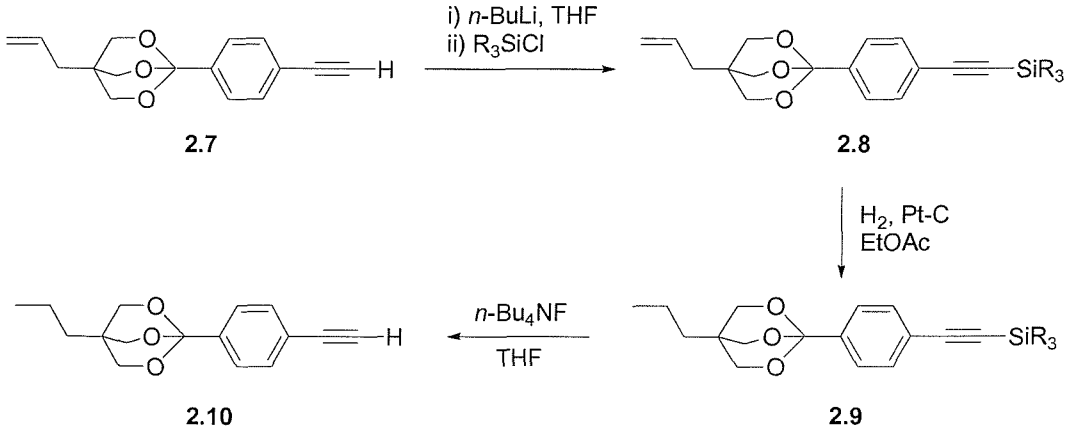
such as AcOH/H_2O/THF can also perform this selective deprotection as shown by Tatsuta with a deprotection of diethylisopropylsilyl (DEIPS) in presence of *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl or triethylsilyl ether groups (Scheme 2.2).[49]



Scheme 2.2. Deprotection of DEIPS in presences of TBDMS

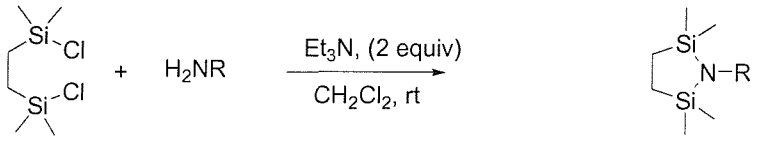
The popularity of silyl protecting groups comes from the very easy deprotection obtained when using fluoride anion. The deprotection with fluoride is quantitative due to the high affinity of Si for fluoride ion. Tetrabutyl ammonium fluoride (TBAF) is a mild reagent which is often used for this purpose.[50, 51]

The silyl functionality can act as a protecting group for a terminal alkyne. Palmer showed the selective hydrogenation of a double bond without reducing the alkyne functionality (Scheme 2.3) followed by an easy deprotection with TBAF.[52]



Scheme 2.3. Protection of a terminal alkyne

The protection of a primary amine by a silyl group was demonstrated by Magnus for the synthesis of alkylated amino-acid derivative.[53] For primary amines with a pKa in the range 10-11, triethylamine is sufficient as a base (Scheme 2.4). For less basic amine (pKa : 4-5), *n*-Butyl lithium was necessary. The deprotection was achieved with 10 % aqueous potassium hydroxide in methanol at reflux for 24 h.



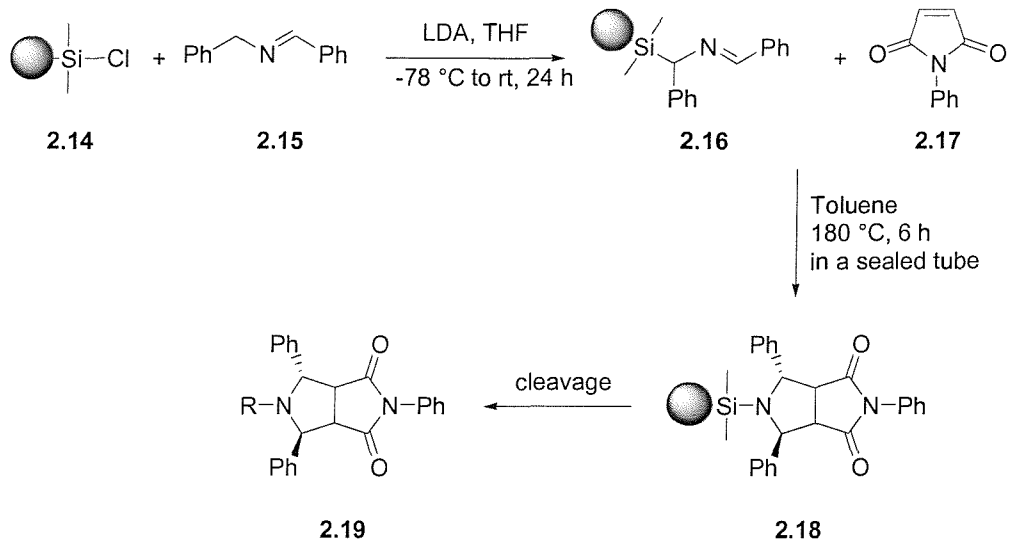
2.11 **2.12** **2.13**

Scheme 2.4. Protection of a primary amine

2.1.2 Silicon based groups in solid-phase chemistry

In solid-phase chemistry, silicon based groups are used as a linker[54-56] due to its facile and selective deprotection conditions. The cleavage can be performed with fluoride ion, which allow the use of other protecting groups on the molecule linked to the solid-support. A good use of a traceless synthesis of pyrrolidines derivatives was performed by Komatsu.[57] Firstly, a commercially available dimethyl silane resin was converted to the corresponding highly reactive and less stable dimethyl chlorosilane resin **2.14**. Adding *N*-benzylidene-*N*-benzylamine **2.15** and LDA afforded the polymer-bound silylimine **2.16** (Scheme 2.5). Upon reaction with phenylmaleimide **2.17** in toluene at 180 °C for 6 h in a sealed tube, the supported pyrrolidine **2.18** was formed through a 1,2 silatropic shift and a 1,3-dipolar cycloaddition. Depending of the conditions of the cleavage step, a substituent could be introduced on the nitrogen atom of **2.19**. The Si-N bond of the solid-supported intermediate **2.18** was reported as stable toward moisture whereas the solution phase corresponding product was not.

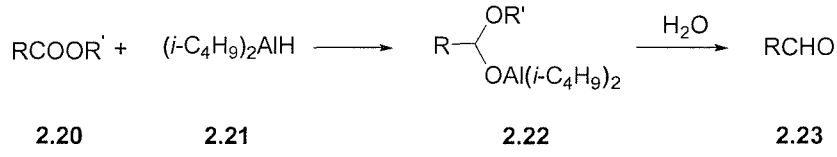
The highest yields after cleavage were obtained when using acids (HCl or TFA) with 90 % yield. Other nucleophiles were tested and benzoyl chloride gave a 70 % yield. Other dipolarophiles than **2.17** were also successfully investigated.



Scheme 2.5. Solid-supported silane as traceless linker

2.1.3 Silicon mediated reduction of carbonyl groups

Converting an ester group to the corresponding aldehyde derivative represents an important transformation in organic synthesis. This transformation can be achieved through several methods but most of them proceed in several steps. First the ester is fully reduced to the alcohol then an oxidation affords the desired aldehyde. The one-step conversion is obtained with diisobutylaluminium hydride (DIBALH) **2.21** (Scheme 2.6).[58] However this reaction must be performed at very low temperature (-70 °C) and the aldehyde is often obtained as a mixture with the corresponding alcohol derivative. This transformation is based on the stability of the tetrahedral intermediate **2.22**.

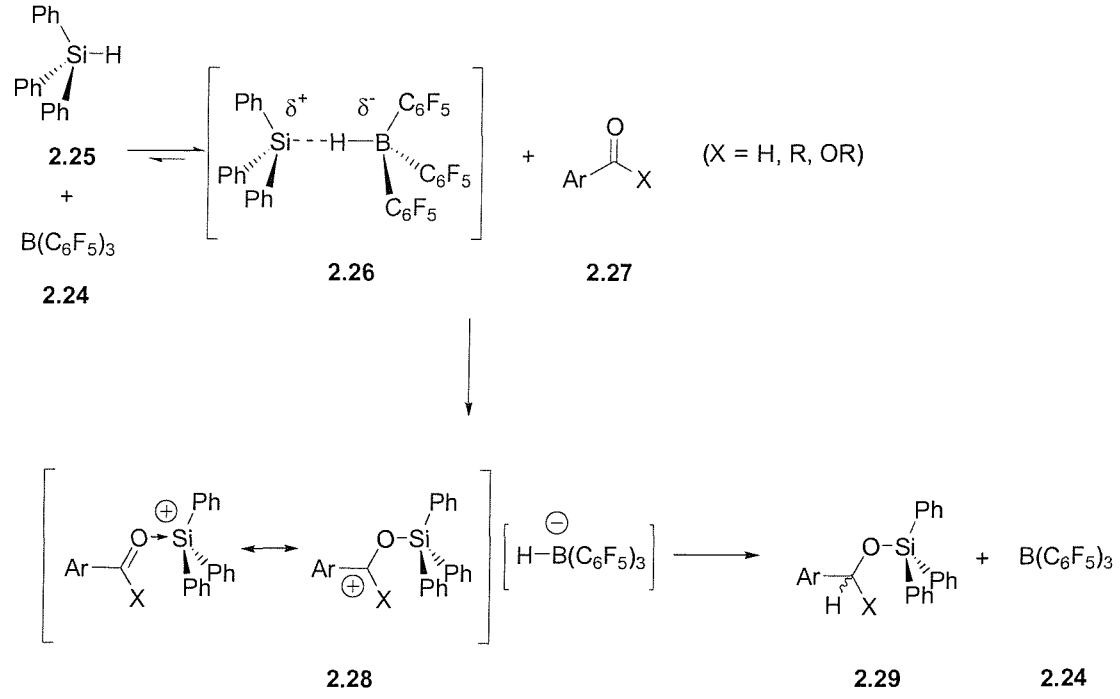


Scheme 2.6. DIBALH reduction of ester to aldehyde

The reduction of a carbonyl compound can be achieved with the use of a silane while using a metallic catalyst. R_3SiH compounds were reported as reducing reagents through the hydrosilylation process.[59, 60] Rhodium or ruthenium complexes were early described as

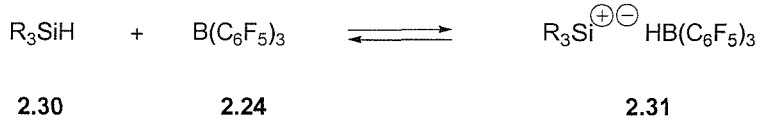
potent catalyst towards the reduction of carbonyl compounds.[61] Acyl chlorides were converted into aldehydes through the use of hypervalent silicon hydrides.[62]

The reduction of carbonyl compounds using silane was performed by Piers with tris(pentafluorophenyl)borane **2.24** as catalyst.[63-65] Good results were obtained with only 1 to 4 mol % of catalyst for aldehydes or ketones. The resulting silyl ethers were obtained in a 75-96 % yield. Instead of a borane activation of the carbonyl function, mechanistic studies demonstrated an unusual silane activation mechanism as shown in Scheme 2.7. The first step was an hydride abstraction from the silane **2.25** by $B(C_6F_5)_3$ **2.24**. Then the silicon center was nucleophilically attacked by the carbonyl substrate **2.27** to give the intermediate **2.28**. The borohydride $[HB(C_6F_5)_3]^-$ attacked then the silylium activated ketone to release the silyl ether **2.29** and regenerate the catalyst **2.24**.



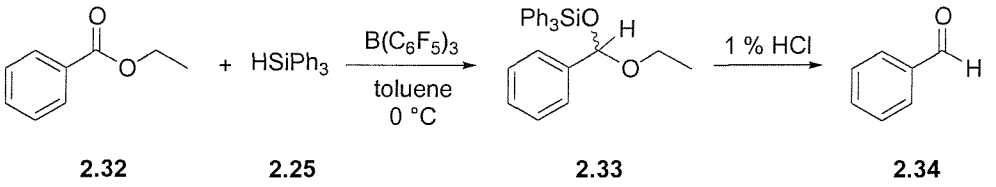
Scheme 2.7. Mechanism of the $B(C_6F_5)_3$ mediated hydrosilylation of carbonyl compounds

The formation of the reactive complex **2.31** between the silane and $B(C_6F_5)_3$ was well documented by Piers (eq. 2.1).[64, 65]



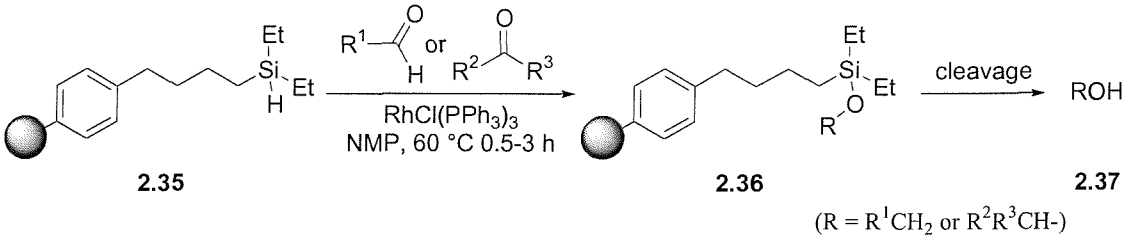
Eq. 2.1. Hydride abstraction from R_3SiH by $H(C_6F_5)_3$

The concept was also validated for the reduction of esters with an 80 % conversion of ethyl benzoate **2.32** to benzaldehyde **2.34** (Scheme 2.8). Only 1 equiv of silane **2.25** was necessary for this reaction.



Scheme 2.8. Hydrosilylation of ethyl benzoate using $B(C_6F_5)_3$ as catalyst

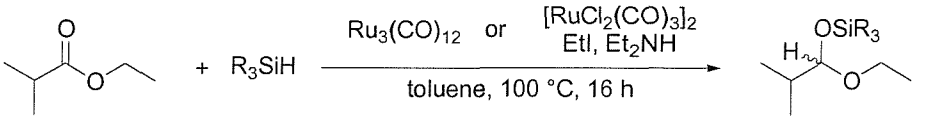
Porco Jr. developed a catch and release approach for the reduction of aldehydes and ketones using the Wilkinson's catalyst and the polymer-bound butyl diethyl silane **2.35** (PS-DES) (Scheme 2.9).[66] The first step was the hydrosilylation using the supported silane to obtain the solid-supported silyl acetals **2.36**. The alcohols **2.37** were obtained after treatment with HF/pyridine in THF or a mixture AcOH/THF/H_2O (6:6:1).[47]



Scheme 2.9. Solid-supported hydrosilylation of ketones and aldehydes using the Wilkinson's catalyst

NMP (1-methyl-2-pyrrolidinone) was added as a coordinative catalyst of the silicon to increase the hydrosilylation rate and prevent the deposition of metallic rhodium on the resin beads. Two equiv of the carbonyl derivative and 4 mol % of the Wilkinson's catalyst were necessary to obtain good results. 4-Bromobenzaldehyde was transformed in a 65 % yield to the 4-bromobenzylalcohol after 30 min while cyclohexanone gave a 61 % yield of cyclohexanol after 3 h.

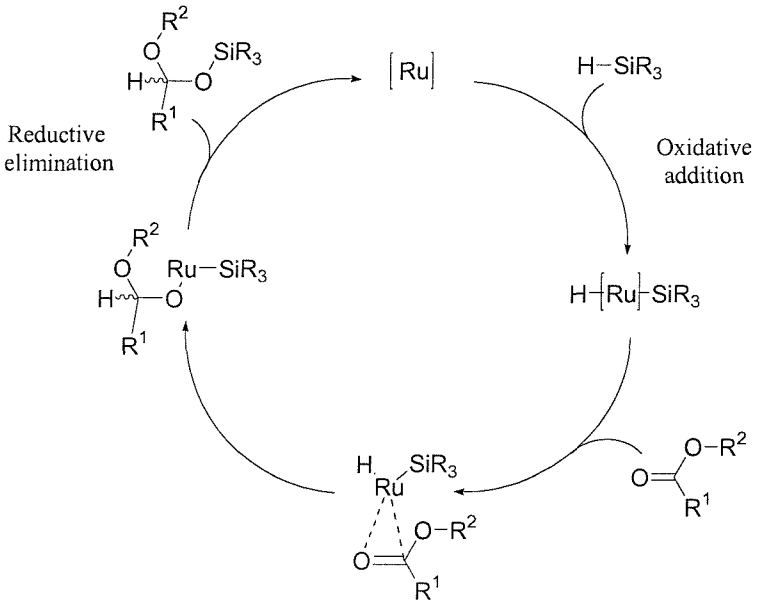
In 2001, Fuchikami applied $Ru_3(CO)_{12}$ and $[RuCl_2(CO)_3]_2$ as catalyst for the hydrosilylation of esters.[67] Both gave good results when using 1.5 equiv of the silane with the possibility to isolate the silyl acetal (Scheme 2.10). A simple treatment with 1 N HCl in THF at room temperature afforded the corresponding aldehyde.



2.38 **2.39** **2.40**

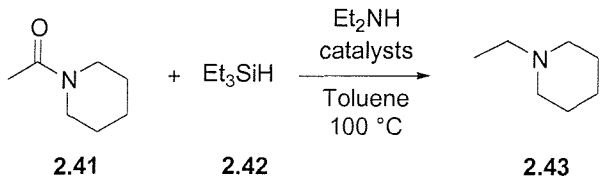
Scheme 2.10. Hydrosilylation of ethyl 2-methylpropionate

The ruthenium catalysed hydrosilylation proceeded through a Chalk-Harrod mechanism (Scheme 2.11).[68] The first step was an oxidative addition of Si-H to the metal followed by the reductive elimination giving the silyl acetal.



Scheme 2.11. Mechanism of the ruthenium catalysed hydrosilylation

Fuchikami also described the reduction of amides to amines using triethyl silane[69] with a variety of transition-metal complexes halides and amines as co-catalyst as shown in Scheme 2.12. Primary, secondary and tertiary amides were converted in good yields from 77 % to 99 % with a minimum of 3 equiv of Et_3SiH **2.42**.

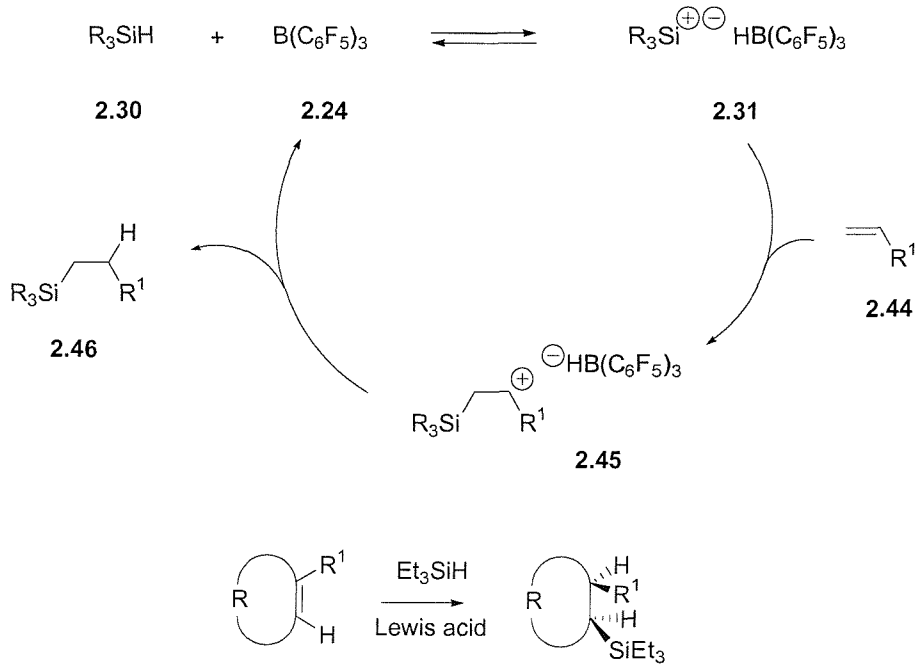


Scheme 2.12. Reduction from amide to amine with triethyl silane

2.1.4 Alkene hydrosilylation

The hydrosilylation of alkene with $B(C_6F_5)_3$ **2.24** and various silanes was developed by Gevorgyan.[70] The efficiency of **2.24** was proved in the hydrosilylation of C-C double bonds with high yield superior to 85 % over 13 examples composed of both acyclic and cyclic compounds.

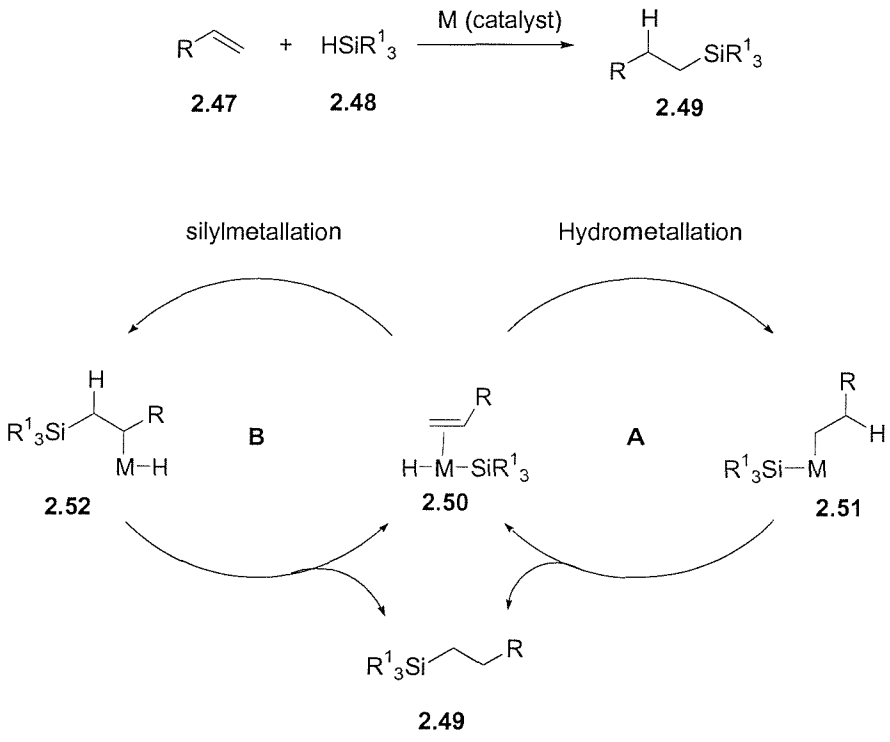
It was proved that this catalysed hydrosilylation protocol operates via *trans* stereochemistry of addition, with the hydride attacking from the less sterically hindered face as showed in Scheme 2.13.[71] The mechanism is similar to the hydrosilylation of carbonyl compounds



Scheme 2.13. Mechanism of the $B(C_6F_5)_3$-catalysed hydrosilylation of alkenes

The hydrosilylation of olefins catalyzed by transition-metal complexes could proceed through two mechanisms. The hydrosilylation of alkenes catalyzed by $H_2PtCl_6 \cdot 6H_2O$ in isopropanol is assumed to proceed by the Chalk-Harrod mechanism (Scheme 2.14, cycle A).[68] Oxidative addition of a hydrosilane **2.48** gives complex **2.50**, which is coordinated with the alkene substrate. The migratory insertion of the alkene into the M-H bond gives the alkyl-silyl species **2.51** and could be called hydrometallation. The hydrosilylation product **2.49** is then obtained after the reductive elimination of the alkyl and silyl ligands from **2.51**.

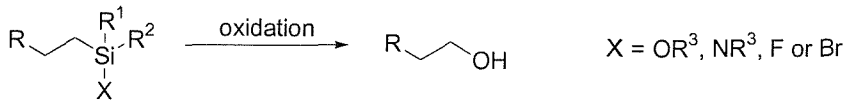
When using rhodium (I) or cobalt (III) catalyst, cycle B is preferred with the alkene insertion into the M-Si bond (silylmetallation). [72-75] The reductive elimination completes the hydrosilylation to afford **2.49**.



Scheme 2.14. Mechanism of transition-metal catalysed hydrosilylation of alkenes

2.1.5 Tamao-Fleming oxidation

The C-Si groups could be considered as C-OH precursors. An activated C-Si bond can be cleaved in a Baeyer-Villiger-type oxidation using peroxide, peracid or amine oxide as oxidants.[76] This reaction is named the Tamao-Fleming oxidation (Scheme 2.15).[77]

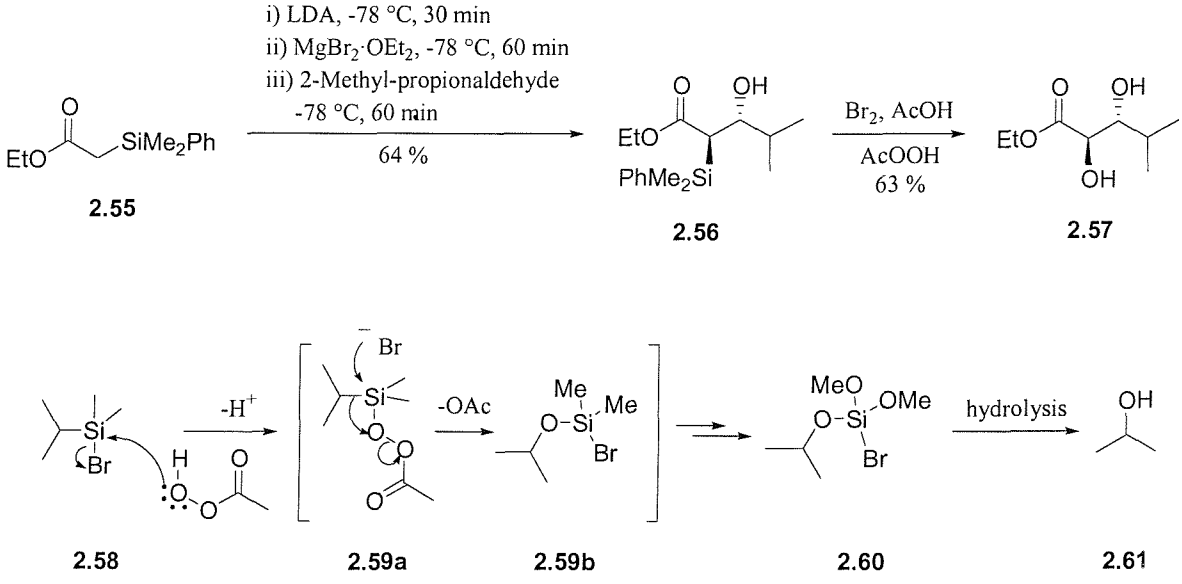


2.53 **2.54**

Scheme 2.15. Principle of the Tamao-Fleming oxidation

While the trialkyl silyl groups are cleaved with great difficulty, the presence of one electronegative atom (F, O, N) on the silicon favorises the processing of the oxidation to obtain the alcohol. Me_2PhSi is frequently used because the phenyl group can be removed by protonolysis or brominolysis to give an SiR_2-OH or SiR_2-Br group, which is subject to oxidation. Mader and Edel used this property for polyol preparation (Scheme 2.16).[78]

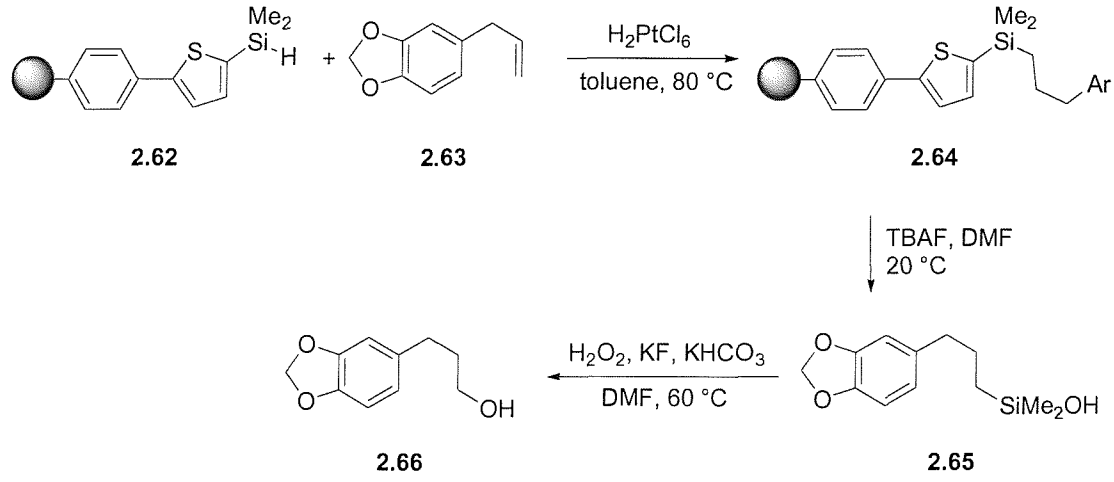
Ethyl(dimethylphenylsilyl)acetate **2.55** was treated with LDA to form the enolate then followed by the counterion exchange with $MgBr_2 \cdot OEt_2$ and finally addition of the aldehyde to yield the aldol condensation product **2.56** in a 64 % yield. After brominolysis of the Si-Ph bond, the oxidation gave the diol **2.57** in a 63 % yield. A nucleophilic attack of the peracid at the silicon center of **2.58** and the loss of the nucleofugal group (bromine here) produce the silyl peroxide **2.59a**. A migration analogous to the mechanism of the Baeyer-Villiger reaction occurs leading to **2.59b**. The transformation of the C-Si bond into a C-O bond takes place stereospecifically with retention of configuration at the carbon center.[79, 80]



2.58 **2.59a** **2.59b** **2.60** **2.61**

Scheme 2.16. Tamao-Fleming oxidation and mechanism of the oxidation

Deleuze and Landais reported the first example of a solid-supported silane resin used in a Tamao-Fleming oxidation sequence (Scheme 2.17).[81] Various soluble and insoluble resins based on a thiophene ring like **2.62** were synthesised. The thiophene was introduced to facilitate the silylation when synthesising the resin and then to allow the cleavage of the product from the resin under mild nucleophilic conditions (TBAF). A platinum mediated hydrosilylation of safrole **2.63** afforded the polymer-bound intermediate **2.64**. Upon cleavage with TBAF, silanol **2.65** was released and the subsequent Tamao-Fleming oxidation gave alcohol **2.66** in a 39 % yield. Only the hydrosilylation was performed on the solid-support.



2.62 **2.63** **2.64**

2.66 **2.65**

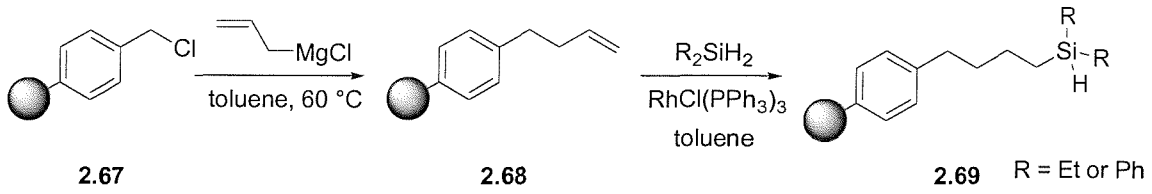
Scheme 2.17. Tamao-Fleming oxidation using a solid-supported silane

2.1.6 Solid-supported silanes

The solid-supported silanes were mostly used as linker for traceless solid-phase synthesis. Ellman described the key impact of a linker in solid-phase chemistry with an ideal linker stable to all the reactions conditions used in the synthesis and quantitatively cleaved under conditions that do not affect the target molecule.[82] The silicon-aryl bond would be easily cleavable by fluoride ion[83] and no trace of the linker would be detectable on the target molecule.

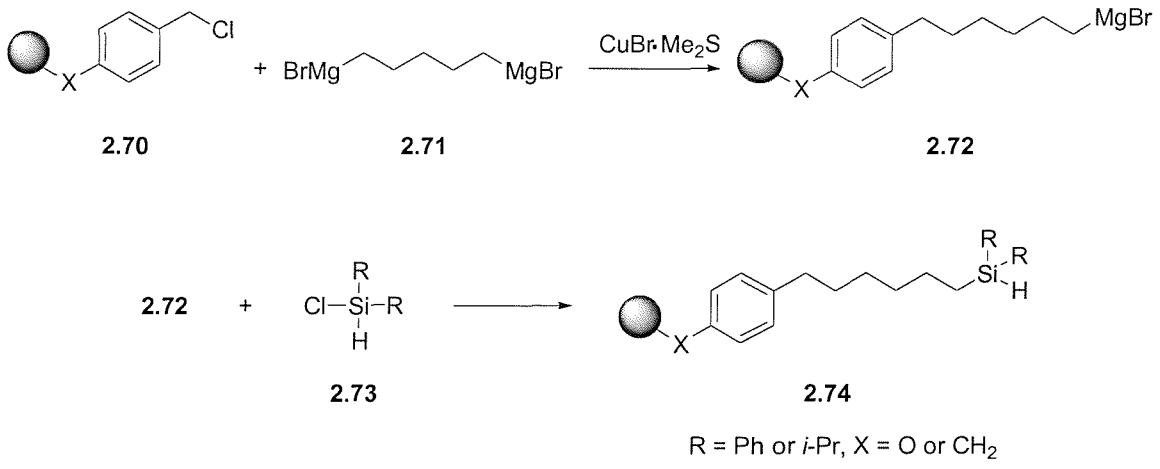
Hu and Porco devised a two steps synthesis of a supported silane as shown in Scheme 2.18.[84] The synthesis was aimed at the development of a stable and storable silane resin, with a potential for direct attachment without transformation to the more reactive silyl

chloride. Allylmagnesium chloride was added to a Merrifield resin **2.67** to give resin **2.68**. The final polymer-bound silane **2.69** was obtained after hydrosilylation of the double bound with various disubstituted silanes. Primary alcohols were successfully attached to the resin **2.69**. The conversion to a silyl chloride resin was also performed and the attachment of aromatic, allylic or alkenyl compounds was successful.



Scheme 2.18. Polymer-supported trialkylsilane

Doi performed a similar approach through the use of a di-grignard reagent (Scheme 2.19).[85] The steric hindrance of the polymer support **2.70** favoured a monoalkylation of the di-grignard reagent **2.71**. After a simple filtration to remove the excess of **2.71**, resin **2.72** was treated with various chlorodialkylsilanes **2.73** to yield the polymer-supported silane **2.74**.

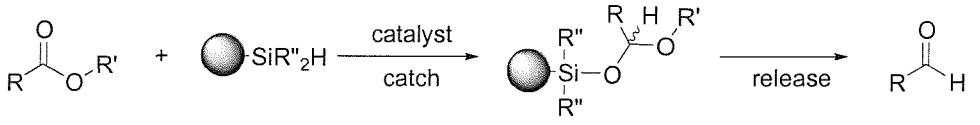


Scheme 2.19. Polymer-supported trialkylsilane

The attachment of various alcohols to the resin **2.74** was successfully investigated by following four methods: chlorosilane formation, silyl triflate formation, dehydrosilation with Wilkinson catalyst and dehydrosilation with $B(C_6F_5)_3$.

2.2 Project aim

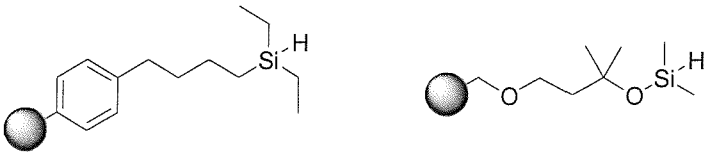
Due to the addition of an excess of the silane in some of these methods in solution phase and incomplete conversion of the starting material, a purification step is needed to obtain the aldehyde, which can prove to be difficult. Using the hydrosilylation of ester **2.75** with a solid-supported silane **2.76** would give an opportunity to exploit a catch and release protocol and then obtain the desired product **2.78** only (Scheme 2.20). Even if the hydrosilylation reaction is not complete, the washing of the resin **2.77** will remove all traces of starting material. Then a cleavage step will release the aldehyde.



2.75 **2.76** **2.77** **2.78**

Scheme 2.20. Principle of the catch and release hydrosilylation of ester

We decided to apply the solid-supported hydrosilylation to the conversion from the ester to the aldehyde using the commercially available polymer-supported butyl diethylsilane **2.35**. A new silane resin **2.79** shown in Figure 2.1 was also devised based on the work of Meloni concerning the synthesis of a new silyl linker.[86] The resin was tested for the hydrosilylation of esters.



2.35 **2.79**

Figure 2.1. Proposed solid-supported silanes

Moreover, microwave irradiation was tested in order to accelerate the hydrosilylation rate which could prove very slow on solid support as shown by the extended time needed by Porco when passing from aldehyde to ketone[66] as well as the 16 h needed in solution phase when ruthenium catalysts were concerned.[67]

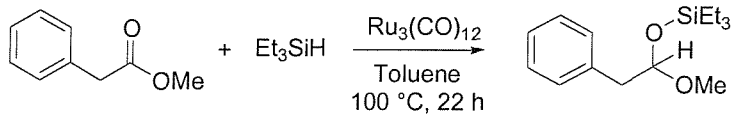
2.3 Results and discussion

2.3.1 Solution phase

2.3.1.1 $Ru_3(CO)_{12}$

Prior to the solid-supported application, a solution phase study was planed with the various catalyst selected. The ruthenium catalyst discussed by Fuchikami,[67] on which our strategy was based, was tested with esters (Scheme 2.21). Fuchikama converted the methyl phenyl acetate **2.80** to the alkyl silyl acetal **2.81** after reaction with the triethyl silane **2.42** with a good 81 % conversion.

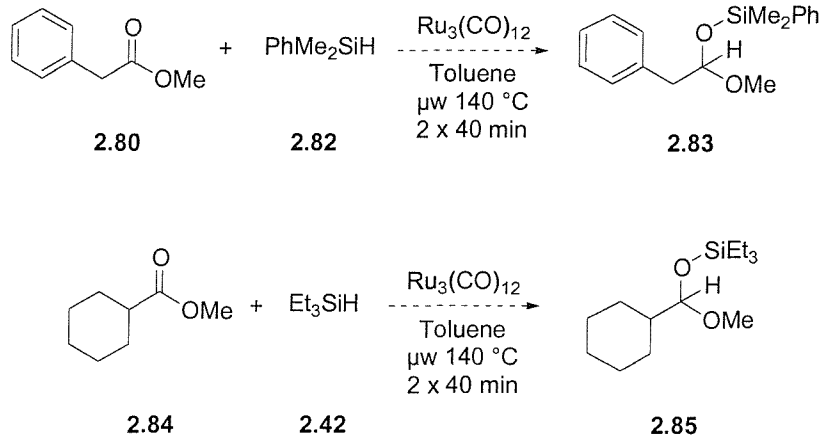
While trying to reproduce the same reaction we were unable to isolate the silyl acetal **2.81**. The same reaction was tested with other substrates (methyl-4-bromobenzoate, methyl-4-nitrobenzoate, 4-bromo benzaldehyde and 4-nitro benzaldehyde) but no significant amount of the hydrosilylation product could be isolated even with the more reactive aldehydes. The quality of the catalyst used was suspected and a new catalyst was ordered and the silyl acetal **2.81** was obtained in a lower yield than the japanese group with only 49 % yield. The ratio was 1.5 equiv of silane as compared to the ester and 1 % in ruthenium.



2.80 **2.42** **2.81**

Scheme 2.21. Hydrosilylation with triruthenium dodecacarbonyl

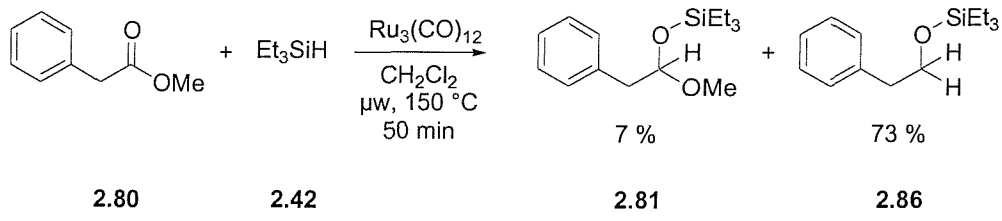
While using microwave irradiation, the same experiment was realised at 140 °C for twice 40 minutes. A comparable yield of 43 % was achieved. When phenyl dimethyl silane **2.82** was used instead of triethyl silane **2.42** (Scheme 2.22), the resulting silyl acetal **2.83** was too unstable to be isolated using column chromatography. With cyclohexylcarboxylic acid methyl ester **2.84** and triethyl silane **2.42**, no silyl acetal **2.85** could be detected after purification.

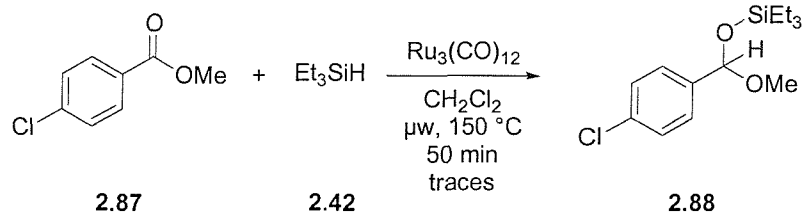


Scheme 2.22. Hydrosilylation with triruthenium dodecacarbonyl

Under microwave irradiation toluene was a poor solvent with a very low absorbing capacity. Dichloromethane overcame this limitation but led to another problem with the appearance of the over reduced silyl ether **2.86** as the main product with a 73 % yield while **2.81** was obtained with only 7 % yield (Scheme 2.23). Moreover a pressure of 15 bars was detected during the reaction with the safety limit fixed at 20 bars. With methyl 4-chlorobenzoate **2.87** as substrate, ester **2.87** was recovered after reaction with only traces of the corresponding silyl acetal **2.88** detected after purification (Scheme 2.23). No silyl ether could be observed.

A precedent was found in the literature for the direct conversion of ester **2.80** to the silyl ether **2.86** using $[(IPr)_2Cu]BF_4$ as a catalyst and 2 equiv of Et_3SiH in THF (IPr= *N,N'*-bis-(2,6-diisopropylphenyl)imidazol-2-ylidene).[87] Compound **2.86** was obtained in a 69 % yield

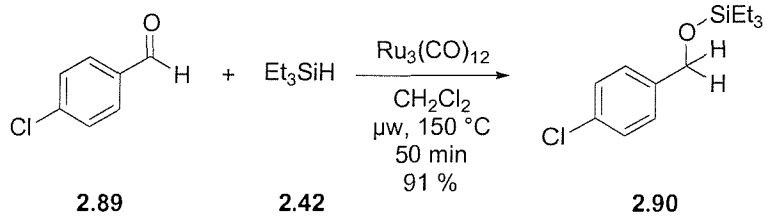




Scheme 2.23. Hydrosilylation of esters in dichloromethane under microwave irradiation

The change from toluene to dichloromethane was also necessary to ensure a good swelling of the polystyrene resin. In toluene, there was a very low swelling while dichloromethane gave an excellent swelling allowing an increased reaction surface and the availability of all the silane linked to the resin.

When 4-chlorobenzaldehyde **2.89** was treated under the same conditions (Scheme 2.24), a 91 % yield in the silyl ether **2.90** was obtained. The same 91 % yield was obtained by Nolan *et al.* with $[(IPr)_2Cu]BF_4$ as a catalyst.[87]



2.89 **2.42** **2.90**

Scheme 2.24. Hydrosilylation in dichloromethane under microwave irradiation

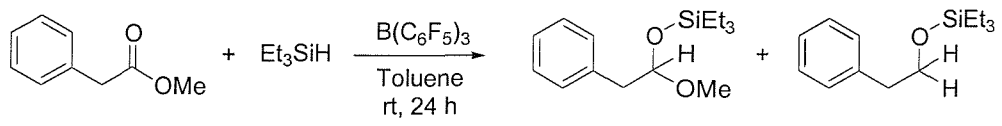
These results showed that $Ru_3(CO)_{12}$ had a limited reactivity towards the hydrosilylation of esters. However the direct conversion from ester **2.80** to silyl ether **2.86** was discovered as a side reaction but the same transformation could not be repeated when methyl 4-chlorobenzoate **2.87** was used as substrate.

Another problem with metallic catalyst, specific to microwave irradiation is the necessity to completely solvate the catalyst. In one experiment, some metal complex was not solvated, leading to a hot spot on the glass wall of the microwave vial. The wall of the vial melted and the high pressure caused the explosion in the microwave cavity.

2.3.1.2 $B(C_6F_5)_3$

Another catalyst was able to perform this reaction, tris(pentafluorophenyl)borane $B(C_6F_5)_3$.[63] The reaction was performed at room temperature in 20 minutes and was even reported at 0 °C. Triethylsilane **2.42** was still chosen as a model of the polystyrene diethyl silane (PS DES) **2.35**. The reactions were performed with a ratio 1:1:0.033 between the ester, the silane and the boron catalyst.

The first hydrosilylation of methyl phenyl acetate **2.80** with this borane catalyst gave **2.81** in 88 % yield after 24 h in toluene with no trace of **2.86** (Scheme 2.25). A high conversion was achieved after 1 h but some starting material was still detected so the reaction was let longer to try to reach completion. At the same time, the reaction was performed under microwave irradiation for 20 minutes at 100 °C in toluene with a 63 % yield observed.



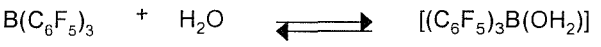
Scheme 2.25. Hydrosilylation with $B(C_6F_5)_3$ as catalyst

Again in order to use the PS DES resin **2.35**, a solvent swelling well the resin was needed, which was not the case with toluene. Hence dichloromethane or a mixture of dichloromethane and toluene were studied as solvent. Unfortunately, the yield of **2.81** decreased dramatically with a first experiment giving 43 % yield then only 22 % yield when the reaction was repeated a week later. The original conditions in toluene were then repeated with only a 37 % yield of **2.81** after 24 h proving the degradation of the boron catalyst.

A second sample of the borane that was rigorously kept under inert atmosphere showed the same reactivity profile. The first hydrosilylation of **2.80** with toluene as solvent at rt yielded 63 % of **2.81**. When a mixture of toluene and dichloromethane was tested as solvent, only 33 % of **2.81** were isolated. Finally, repeating the first experiment only yielded 12, 10 and finally 7 % of the silylated product **2.81**. $B(C_6F_5)_3$ was a very good catalyst toward the hydrosilylation of esters but proved to sensitive thus preventing the a repetition of the results.

A new batch of $B(C_6F_5)_3$ was purchased from a different supplier as a solution ~3% in isoparafine. The experiment described in Scheme 2.25 was repeated with the new borane leading only to a 32 % yield of **2.81** with only dichloromethane as solvent. The hydrosilylation of phenyl-acetaldehyde was also performed with this $B(C_6F_5)_3$ in dichloromethane with a 72 % yield of the silyl ether as a result.

Along with the decrease of the yield, we also started to see the silyl ether **2.86**. This might be the result of an acidic hydrolysis of the silyl acetal **2.81** followed by the hydrosilylation of the newly formed aldehyde, which is more reactive than the ester.
Tris(pentafluorophenyl) borane was found to react in presence of water to give a Brønsted acid (Eq. 2.1).[88]



Eq 2.1. Reaction with water of $B(C_6F_5)_3$

The reactivity of the borane catalyst has been tested on the hydrosilylation of some aldehydes. 4-Bromo benzaldehyde **2.91**, cyclohexanecarbaldehyde **2.92** and phenyl-acetaldehyde **2.93** were converted to the corresponding silyl ether with good yields (71 %, 86 % and 53% respectively) after 2 to 3 h at room temperature with dichloromethane as solvent. Nolan with his borane catalyst obtained 93 % for the conversion of 4-bromo benzaldehyde **2.91**, and 70 % for the conversion of cyclohexanecarbaldehyde **2.92**.[87] Phenylacetaldehyde **2.93** was also treated with toluene as solvent and an improved 84 % yield in silyl ether **2.86** was achieved. Those results were obtained with the catalyst giving only a 7 % yield of silyl acetal **2.81**.

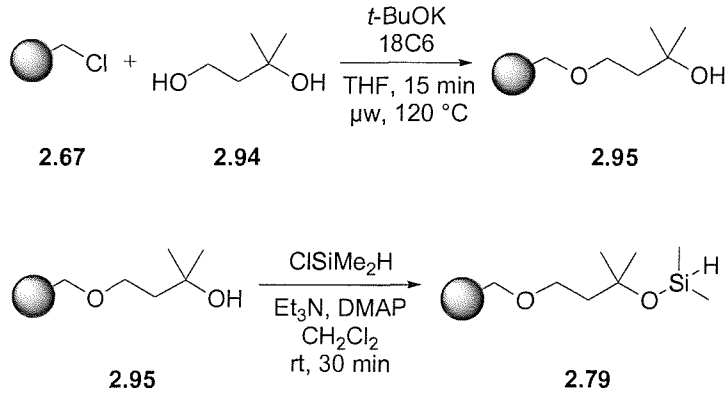
$B(C_6F_5)_3$ proved to be very potent for the hydrosilylation of ester but also very sensitive to external conditions. Despite being kept in a glove box under neutral atmosphere and the various solvents being freshly distilled, the reactivity decreased quickly. However, the same catalyst was still efficient with aldehyde.

2.3.2 Solid phase

2.3.2.1 Synthesis of a new resin

A new silane resin was developed based on a silyl linker described by Meloni.[86] Starting with the Merrifield resin **2.67** (1.6 $mmol \cdot g^{-1}$), 3-methyl-1,3-butanediol **2.94** was immobilised through a Williamson reaction using potassium *t*-butoxide under microwave irradiation (Scheme 2.26).[89] The reaction was followed by IR analysis through the disappearance of the C-Cl band and the appearance of the C-OH band (3460 cm^{-1}). The

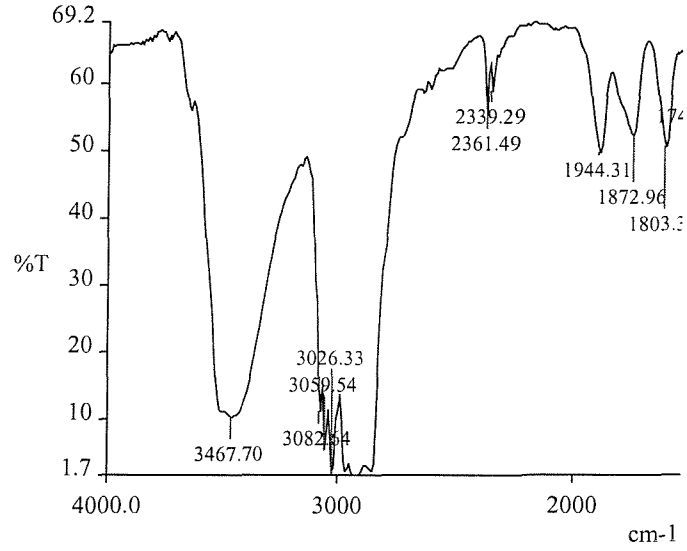
reaction was performed on 2.5 g of resin divided in ten batches of 0.25 g each in order to fit in the microwave vials and gave 2.87 g of the OH resin **2.95** with a loading of 1.3 mmol·g^{-1} (theoretical loading: 1.44 mmol·g^{-1}). Then chlorodimethyl silane was added to afford the silane resin **2.79**.



2.67 **2.94** **2.95** **2.95** **2.79**

Scheme 2.26. Synthesis of the new supported silane

This time the progress of the silylation was monitored though the loss of the OH band (3467 cm^{-1}) (Figure 2.2 top spectra) and the appearance of the Si-H band at 2110 cm^{-1} (Figure 2.2 bottom spectra). A loading of 1.1 mmol·g^{-1} (determined by Si elemental analysis) was achieved with a theoretical loading of 1.21 mmol·g^{-1}.



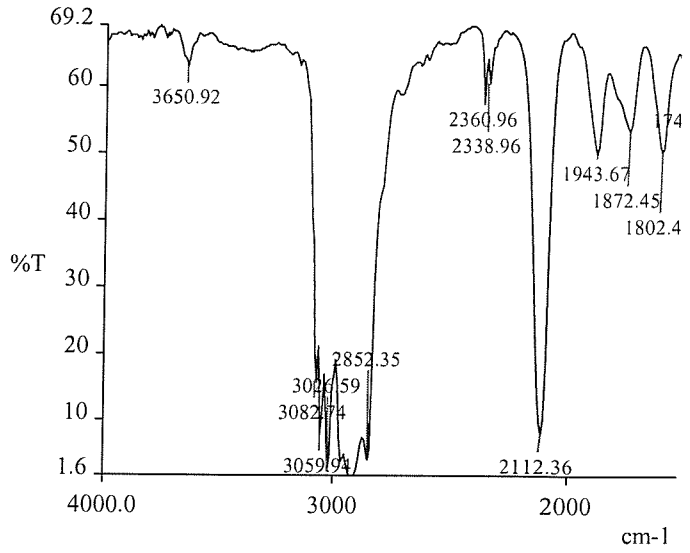


Figure 2.2. Disappearance of the OH peak (3460 cm^{-1}) and new Si-H peak (2110 cm^{-1})

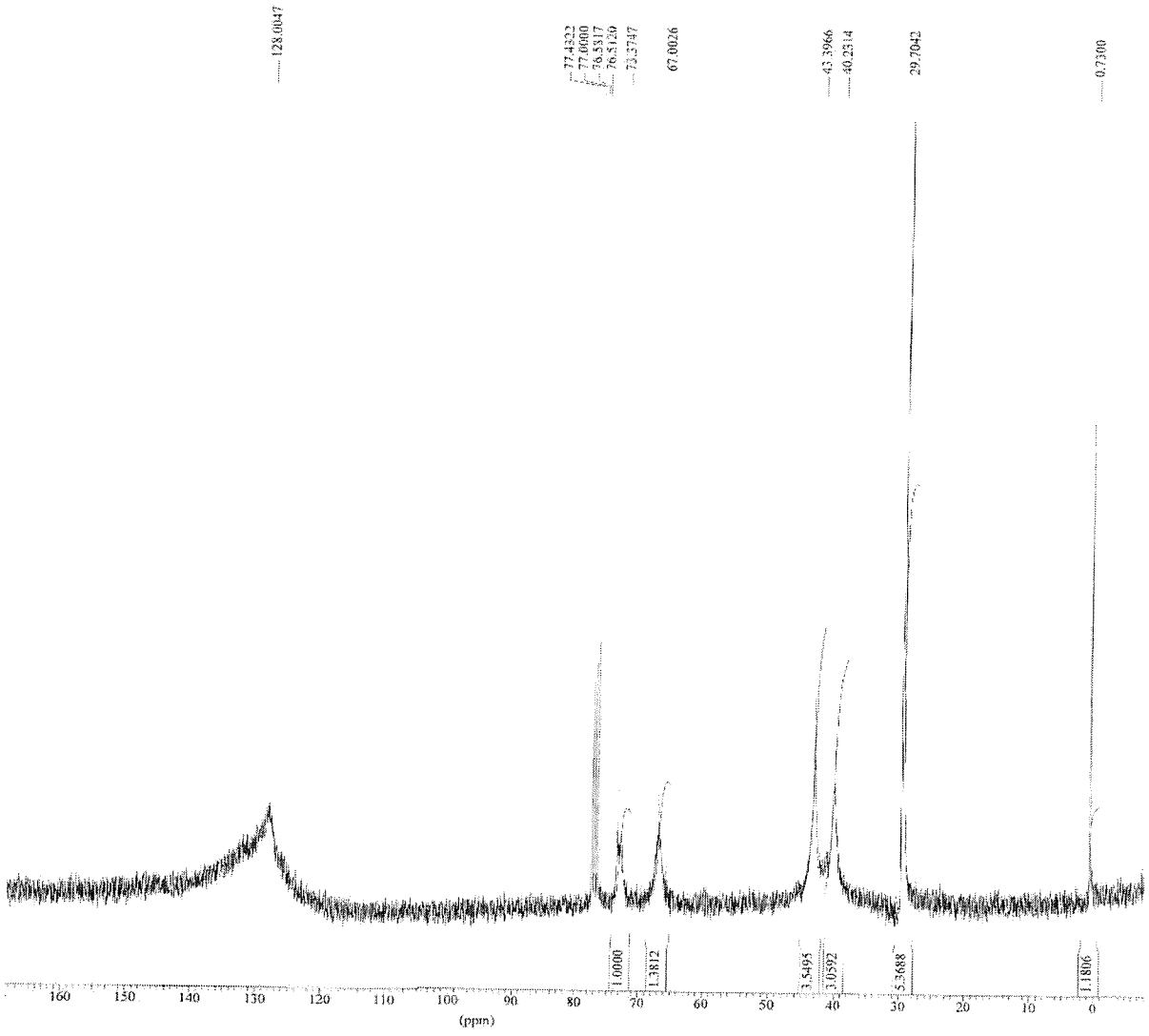


Figure 2.3. ^{13}C NMR of the solid-supported silane resin **2.79**

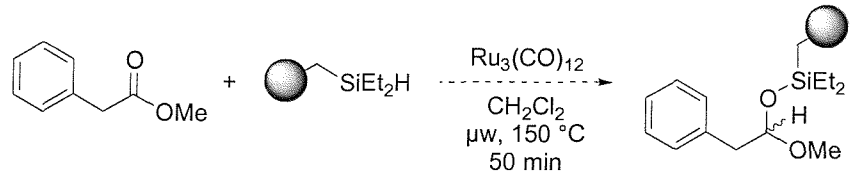
The gel-phase ^{13}C NMR of the silane resin is shown in Figure 2.3. The CH_3 on the silicon atom are clearly visible at 0.7 ppm. At 30 ppm are the two methyl groups near the oxygen atom. At 40 and 43 ppm are the two CH_2 of the 3-carbon chain.

The addition of the hetero-atom will modify the electronic nature of the silicon. With this effect, the sensitivity to nucleophilic reagents will increase thus facilitating the cleavage step.

2.3.2.2 Hydrosilylation

2.3.2.2.1 Using the commercial PS-DES resin

As described by Porco for the hydrosilylation of aldehydes and ketones,[66] the commercially available PS-DES **2.35** was one of the resins tested. Despite the modest results obtained in solution phase, the hydrosilylation of ester was performed with various catalyst starting with $Ru_3(CO)_{12}$ (Scheme 2.27). The reaction was monitored by IR analysis following the disappearance of the Si-H band. After the irradiation, the Si-H band completely disappeared but no new band could be detected. As a simple way to determine if the reaction was successful a cleavage using TBAF was performed but HPLC analysis detected no aldehyde.



2.80 **2.35** **2.96**

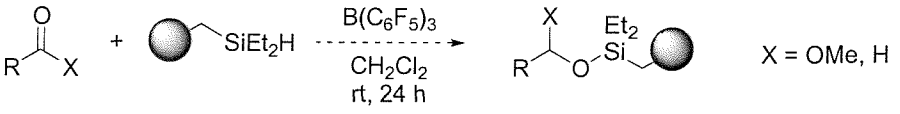
Scheme 2.27. Hydrosilylation of ester using a solid supported silane and $Ru_3(CO)_{12}$

The same reaction was performed with phenylacetaldehyde **2.93**. The Si-H band disappeared but after a cleavage step, no alcohol could be detected by HPLC. Similar results were obtained with methyl 4-chlorobenzoate **2.87** and methyl 4-nitrobenzoate **2.97** with no trace of the alcohol after the cleavage step. In order to promote the swelling of the resin, those reactions were performed in a mixture of dichloromethane / toluene in various proportions.

NMP was also used as solvent and the hydrosilylation of methyl 4-chlorobenzoate **2.87** was performed at 100 °C for 24 to 36 h or under microwave irradiation at 140 °C for 50 min. In both cases, the Si-H band disappeared in IR analysis but no aldehyde could be detected after cleavage.

A second ruthenium catalyst, $[RuCl_2(CO)_3]_2$ described by Fuchikami[67] with EtI and $NHEt_2$ as co-catalyst and NMP as solvent was also tested with resin **2.35**. The hydrosilylation of a very activated ester, methyl-4-nitrobenzoate **2.97** under microwave irradiation (45 minutes, 140 °C in toluene or NMP) or thermal condition (24 h, 100 °C in NMP) was performed. After washing the resin, no aldehyde could be detected after a cleavage step while the Si-H band disappeared in IR analysis.

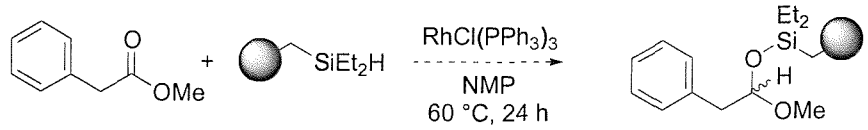
When $B(C_6F_5)_3$ was tested with the PS-DES resin under thermal (rt, 24 h) or microwave conditions (100 °C, 40 min) in dichloromethane as solvent (Scheme 2.28), only the disappearance of the Si-H band was observed and no desired product could be detected after the cleavage step. The hydrosilylation was performed on 4-bromobenzaldehyde **2.89**, methyl phenylacetate **2.80**, phenylacetaldehyde **2.93** and methyl-4-bromobenzoate **2.100**.



2.98 **2.35** **2.99**

Scheme 2.28. Hydrosilylation using solid supported diethyl silane and $B(C_6F_5)_3$

Using Porco[66] method (which was developed for the hydrosilylation of aldehydes) with the Wilkinson's catalyst $RhCl(PPh_3)_3$ and PS-DES **2.35** with ester (Scheme 2.29) only confirmed the previous results with no desired aldehyde obtained after a cleavage step. Methyl phenylacetate **2.80**, methyl 4-chlorobenzoate **2.87** and cyclohexylcarboxylic acid methyl ester were used as substrate in NMP as solvent under thermal condition or microwave irradiation with only the disappearance of the Si-H band in IR analysis as outcome.



2.80 **2.35** **2.96**

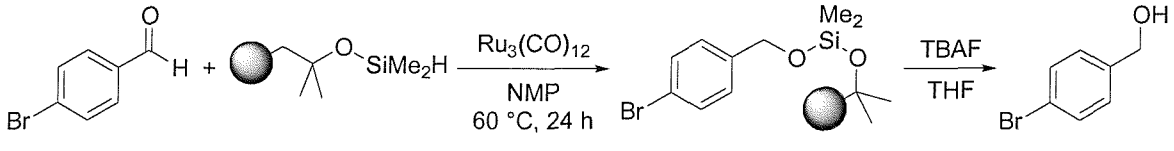
Scheme 2.29. Hydrosilylation using solid supported diethyl silane and the Wilkinson's catalyst

2.3.2.2.2 Using a new silane resin

The new supported silane **2.79** previously prepared was tested for the hydrosilylation of methyl-4-chlorobenzoate **2.87** using $[RuCl_2(CO)_3]_2$ as catalyst, with EtI and $NHEt_2$ as co-catalyst and NMP or toluene as solvent. The reactions were performed at 60 °C for 24 h or under microwave irradiation at 140 °C for 45 min. As with the previous resin, the Si-H band disappeared but no aldehyde could be detected by HPLC.

With $Ru_3(CO)_{12}$ as catalyst, the hydrosilylation of methyl-4-chlorobenzoate **2.87** was performed in NMP or toluene at 100 °C for 24 h or under microwave irradiation at 140 °C for 45 min. A reaction at reflux in dichloromethane for 24 h was also tested. Again, no trace of aldehyde was detected by HPLC.

When the hydrosilylation of the 4-bromobenzaldehyde **2.91** was tested with resin **2.79** and $Ru_3(CO)_{12}$ as catalyst (Scheme 2.30), traces of 4-bromobenzylalcohol **2.99** where detected by HPLC after cleavage but no product was isolated.



2.91 **2.79** **2.101** **2.102**

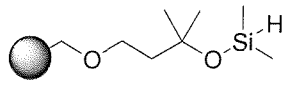
Scheme 2.30. Hydrosilylation of 4-bromobenzaldehyde using the new solid supported silane and $Ru_3(CO)_{12}$

Most of the experiments for the hydrosilylation of carbonyl compounds were repeated at least twice. In some case, new starting materials were purchased and the reactions repeated. However, seeing the poor results, the ester hydrosilylation project was cancelled.

2.4 Alkene hydrosilylation / Tamao-Fleming oxidation

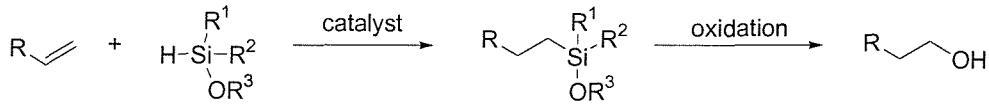
2.4.1 Project aim

The nature of the silane resin **2.79**, synthesized for the hydrosilylation of ester project, (Figure 2.4) gave us the opportunity to experiment the Tamao-Fleming oxidation, which could be performed after an alkene hydrosilylation. A catch and release procedure would be used. After hydrosilylation of an alkene **2.103** with the supported silane **2.104** to obtain the silyl ether **2.105**, the treatment with hydrogen peroxide, *m*-CPBA or peracetic acid should lead to the alcohol **2.106** (Scheme 2.31). This reaction has been intensively investigated in solution phase[76] but never on solid phase.



2.79

Figure 2.4. New solid-supported silane



2.103 **2.104** **2.105** **2.106**

solid-support in R^1, R^2 or R^3

Scheme 2.31. Principle of the double bond hydrosilylation followed by a Tamao-Fleming oxidation

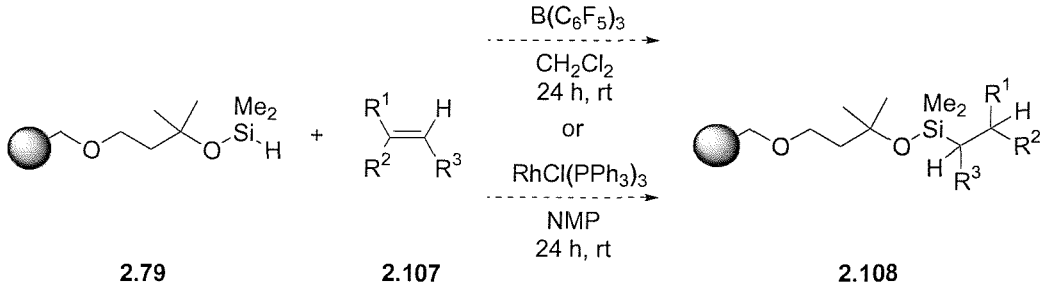
The transposition of the hydrosilylation to solid-phase chemistry with a supported silane as basis will help drive the reaction to completion by using an excess of silane and then an easy purification prior to the Tamao-Fleming oxidation.

2.4.2 Results and discussion

The Hydrosilylation of alkene was tested using the silane resin **2.79** and $B(C_6F_5)_3$ as catalyst in dichloromethane, following the conditions described by Gevorgyan (Scheme 2.32).[70] Cyclohexene **2.109**, 4-chlorostyrene **2.110**, allylbenzene **2.111** and α-methyl styrene **2.112** were chosen for their good reactivity observed by Gevorgyan. Large excess of the alkenes were added to the supported silane **2.79** with 1 to 2 % mol of the borane catalyst. After 24 h at room temperature, the various resins were analysed by IR analysis, showing the disappearance of the Si-H band at 2100 cm^{-1}.

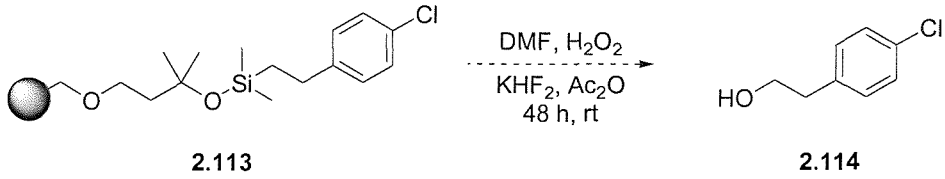
The hydrosilylation step was also performed using the Wilkinson's catalyst in NMP at 60 °C (Scheme 2.32). The same alkenes were investigated with 1 to 3 % mol of the rhodium catalyst. Here again, the IR analysis showed the disappearance of the Si-H band.

Gel-phase ^{13}C NMR of the resins were performed after the hydrosilylation but the spectra were similar to the one of the starting resin **2.79**. Particularly in the case of the cyclohexene **2.109**, no new peak for the $-CH_2-$ of the 6-carbon ring could be detected.



Scheme 2.32. Hydrosilylation of alkene

As a verification, an oxidation was performed as shown in Scheme 2.33 following conditions described by Tamao.[90] Acidic conditions were chosen as it was reported to be more efficient with a *t*-butoxy substituent on the silane.



Scheme 2.33. Oxidation of the silane using Tamao protocol

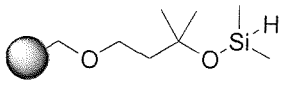
After work-up, no trace of the alcohol could be detected by NMR analysis.

2.5 Conclusions

The hydrosilylation of esters was performed in solution phase using triruthenium dodecacarbonyl and tris(pentafluorophenyl) borane as catalyst. With $Ru_3(CO)_{12}$ the desired silyl acetal (49 %) could be isolated when the reaction was performed in toluene at 100 °C. When using microwave irradiation, a similar yield (43 %) could be observed. When dichloromethane was introduced as solvent under microwave irradiation, the over-reduced silyl ether was detected as the main product in some reaction (73 %). With $B(C_6F_5)_3$ as catalyst, a very good yield in silyl acetal was achieved (81 %) but the catalyst proved very sensitive and the yield in silyl acetal decreased after each reaction even when the catalyst was kept under inert atmosphere. This same borane catalyst was still effective toward the aldehyde and ketone hydrosilylation giving the desired silyl ethers in good to very good yields.

The hydrosilylation of esters was tested using a solid-supported silane. A commercially available diethyl silane resin was investigated. The hydrosilylation using various catalyst proved difficult and no satisfactory results could be obtained. A new silane resin **2.79** was successfully synthesised and tested on the hydrosilylation of ester (Figure 2.5). Again, only poor results were achieved.

The presence of the oxygen atom as substituant on the silane of the resin **2.79** indicated a possibility to use this solid-supported silane for the Tamao-Fleming oxidation. However, the hydrosilylation of the various alkenes proved to be the limiting step with no evidence of the immobilisation of the alkene on the resin.



2.79

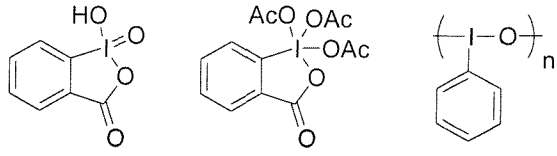
Figure 2.5. New silane resin **2.79**

3 A solid-supported hypervalent iodine reagent

3.1 Introduction on hypervalent iodine

Hypervalent iodine has been studied as soon as 1893 in organic chemistry for its oxidising properties especially *o*-iodoxybenzoic acid **3.1** (1-hydroxy-(1*H*)-benzo-1,2-iodoxol-3-one 1-oxide, IBX, Figure 3.1).[91] Hypervalent iodine relates to the oxidation state of the iodine atom, which is different to -1. It deals with iodine (III) and iodine (V). Iodine (V) compounds have been left aside due to their poor solubility in most organic solvent until the eighties with the development of the Dess-Martin periodinane[92] (DMP; 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one) **3.2** as a soluble version of IBX (Figure 3.1). Moreover, most iodine (V) compounds are reported to be explosive.[93]

Iodine (III) products were also reported as oxidant or oxygenating agents. While taking advantage of the strong leaving group ability of the –IAr fragment in iodonium salts, diverse reactivity can be achieved such as carbene or nitrene precursor. They can be used for the formation of carbon-carbon bond as well as carbon-heteroatom and heteroatom-heteroatom bonds.[94]



3.1 **3.2** **3.3**

Figure 3.1. IBX, DMP and iodosylbenzene

3.1.1 Iodine (III) compounds

As reported by Stang,[95] iodine (III) species share similar chemicals properties and reactivity with mercury (II), thalium (III) and lead (IV). But while those three heavy metals are toxic and not environmental friendly, iodine is the complete opposite.

Iodosylarene ArIO is reported to be a strong oxidising reagent.[96] However, iodosylbenzene **3.3** (Figure 3.1) suffered from low solubility due to the polymeric structure it exhibited with intermolecular iodine-oxygen bonds. To carry out reactions, a catalyst must be added such

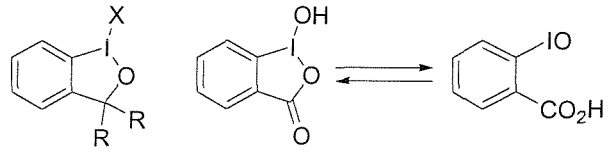
as a Lewis acid, bromide anion[97] or a transition-metal complex.[98] While added to a hydroxylic solvent, the monomeric species is released by preventing the intermolecular bonds. In 1981, Moriarty *et al.*[99] associated iodosylbenzene with the synthesis of α-hydroxydimethylacetals when used in combination with MeOH and KOH.

Iodine (III) compounds can also be fluorinating or chlorinating reagents with $ArIX_2$ as a general formula, with X=F or Cl. With X=Br, only unstable compounds that cannot be isolated are synthesised.[95, 96]

The most studied members of the iodine (III) organic derivatives are the [bis(acyloxy)iodo]arenes, $ArI(O_2CR)_2$. They are commonly used oxidising reagents and some like (diacetoxyiodo)benzene (DIB) and [bis(trifluoroacetoxy)iodo]benzene (BTI) are commercially available. These two molecules have a very low reactivity towards alcohols. However, when used in combination with the addition of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxyl), primary alcohols are oxidised to aldehydes[100] or carboxylic acids[101] according to the experimental conditions. It exhibit a high chemoselectivity for primary alcohol while in presence of secondary alcohol or other potentially oxidizable functional groups.

Analogous derivatives of strong acids $ArIX_2$ (X = RSO_3, ClO_4, NO_3, etc...) are instable and must be generally synthesised in situ. They are mostly used as starting materials for the synthesis of iodine (III) compounds.

Heterocyclic iodine (III) derivatives exhibit a higher stability than the acyclic derivatives. They generally derive from benzodioxole **3.4** (Figure 3.2) and the most investigated heterocyclic iodine (III) is 1-hydroxy-1,2-benzodioxol-3(1H)-one **3.5** which is the tautomeric form of 2-iodosylbenzoic acid **3.6** (Figure 3.2). While **3.5** is commercially available, **3.6** is not stable. The carboxylic acid form of heterocyclic iodine (III) derivatives can be isolated when substituted in the *para* position with an alkyl chain.



3.4 **3.5** **3.6**

Figure 3.2. Heterocyclic iodine (III) derivatives

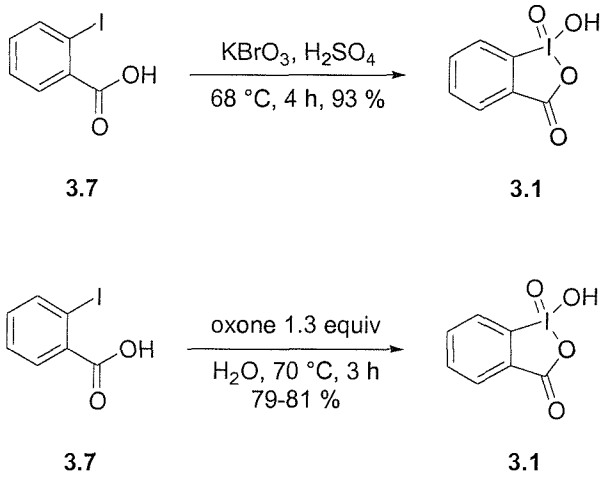
3.5 is used to perform catalytic cleavage of toxic phosphates and reactive esters.[102] When **3.5** is treated with *tert*-butyl hydroperoxide in the presence of BF_3·etherate,[103] the subsequent peroxide **7** is a strong oxidizing reagent toward ethers, organic sulfides, amides and phenols.

3.1.2 Iodine (V) compounds

While known as long as the iodine (III) compounds, iodine (V) chemistry is less developed. This is mostly due to its reported explosive properties and insolubility in most organic solvents.

Noncyclic iodylarenes are not stable except for the aryl-substituted ones. The most studied is iodylbenzene $PhIO_2$ which can perform oxidation from alcohols to ketones,[104] and from phosphorus compounds to phosphonium oxide.[105]

The most widely studied iodine (V) compounds are the heterocyclic derivatives such as benziodoxole oxides with IBX **3.1** and DMP **3.2** as the most important representatives. **3.1** was typically obtained by oxidizing 2-iodobenzoic acid with potassium bromate in sulphuric acid[92] but an improved synthesis was developed by Santagostino *et al.* using oxone in water[106] (Scheme 3.1). This procedure would prevent the contamination of the IBX by bromate or other impurities probably responsible for the explosive properties of the IBX synthesised by the former method.[107]

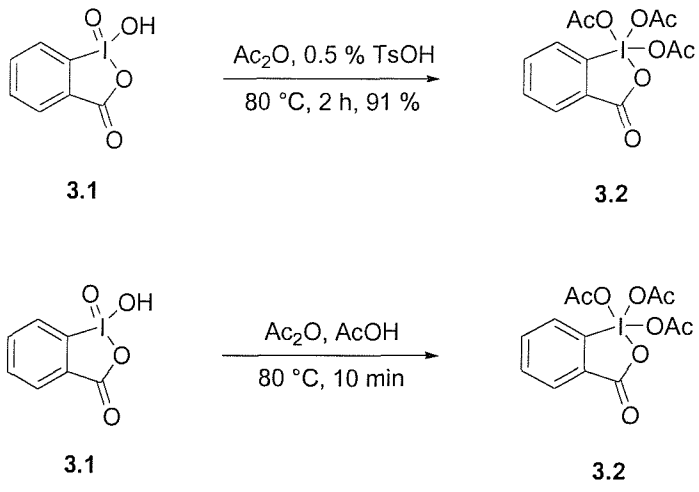


Scheme 3.1. Syntheses of IBX **3.1**

The use of IBX was limited due to its poor solubility in most organic solvents but in 1994, Santagostino[108] conveniently demonstrated the practical usefulness of IBX as a mild, selective oxidant when used in DMSO as solvent. Further work mainly by Nicolaou and co-workers contributed to establish **3.1** as a versatile reagent capable of a range of transformations.[109-112]

Despite very good results obtained with the use of DMSO, the limitation to this solvent and the reportedly explosive character of IBX resulted in a variety of research efforts in order to overcome one or both of these problems.

The discovery by Dess and Martin in 1983 of the DMP **3.2** was the first successful attempt to obtain a soluble derivative of IBX (Scheme 3.2).[92] Its mild reaction conditions, convenience of use and high chemoselectivity contributed to its wide use in the synthesis of biologically important natural products.[113] A variation of the synthesis of the Dess-Martin periodinane **3.2** was performed by Evans *et al.* in which **3.1** was treated in acetic anhydride and acetic acid at 80 °C until dissolution was complete (10 min in average).[114]



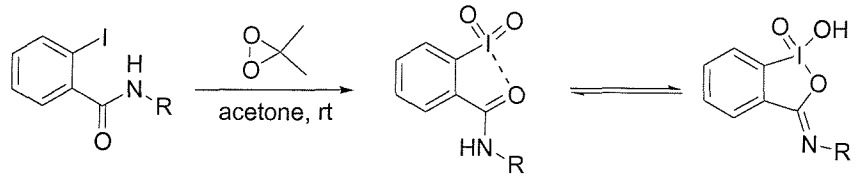
Scheme 3.2. Syntheses of the Dess-Martin periodinane **3.2**

One original discovery was the report by Finney of the ability of IBX **3.1** to perform oxidation in various solvents when heated to reflux temperature.[115] In that case, after reaction, the product could be easily isolated after a simple filtration as the excess of IBX and its various by-products were insoluble after cooling to room temperature. However, this method could be too harsh for sensitive substrates.

Another method developed by Liu and co-workers used the ability of ionic liquids to efficiently solubilize IBX.[116] The carbonyl product was then isolated by extraction and the IBX could be recovered and regenerated.

Modifying the skeleton of IBX also improved its solubility. The introduction of various substituents on the aromatic ring improved the solubility and allowed reaction in water or water-THF solution.[117] The transformation to various benziodazole by Zhdankin allowed performing reactions in non-polar solvents.[118]

One of the latest derivatives of IBX introduced by Zhdankin in 2003 was the synthesis of an IBX amide **3.7** (Scheme 3.3) which has increased solubility in solution and the same oxidative activity as **3.1**.[119]



3.8 **3.7**

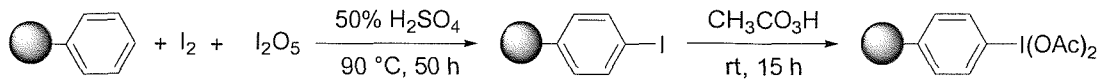
Scheme 3.3. Synthesis of IBX amide by Zhdankin

3.1.3 Polymer-bound hypervalent iodine compounds

3.1.3.1 Syntheses of polymer-bond DIB and BTI

To successfully prevent the explosive properties of most hypervalent iodine compounds, various polymer-supported derivatives have been studied. This technique allowed the easy recovery of the reagent and in most case its regeneration.

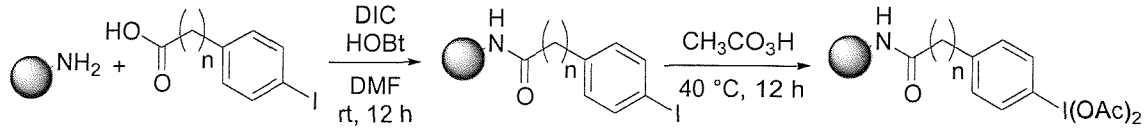
Several solid-supported [bis(acyloxy)iodo]arenes were developed in different groups. Togo and co-workers[120] prepared an insoluble poly[styrene(iodosodiacetate)] **3.9** in two steps with a loading between 2.96 and 3.50 mmol·g^{-1} while Wang and Chen worked on a soluble version of **3.9** starting from linear polystyrene.[121] The same resin was also synthesised with 2 % cross-linked polystyrene as support (Scheme 3.4).[122] After iodination of the polystyrene support with iodine **3.10** and iodine pentoxide **3.11**, **3.9** was obtained by treatment with peracetic acid.



3.10 **3.11** **3.12** **3.13** **3.9**

Scheme 3.4. Synthesis of the solid-supported DIB

Giannis[123] reported a solid-supported BTI **3.14**, starting with commercially available aminomethylated polystyrene **3.15** (Scheme 3.5). After coupling with 4-iodobenzoic acid or 4-iodophenylacetic acid **3.16** affording **3.17**, oxidation by treatment with peracetic acid gave **3.14**. As with the previous polymer-bound DIB **3.9**, resin **3.14** could be regenerated several times without loss of activity.



3.15 **3.16** **3.17** **3.14**

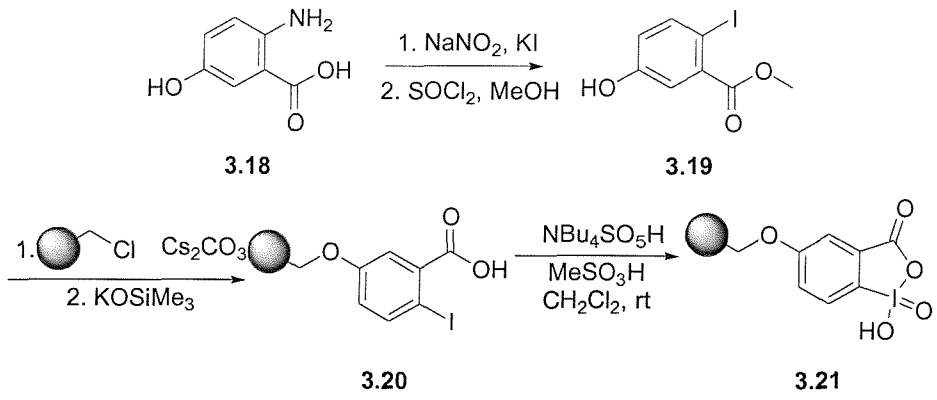
Scheme 3.5. Synthesis of the polymer-bound BTI

3.1.3.2 Existing solid-supported IBX resins

One of the most important characteristics of hypervalent iodine compounds is their oxidative activity towards alcohols. The two main iodine (V) compounds used were IBX **3.1** and DMP **3.2**. Various groups have reported on the immobilisation of IBX onto solid and soluble supports, leading to a non-explosive IBX variant compatible for use with solvents like THF and dichloromethane.

The first strategy was developed around 2-amino-5-hydroxy benzoic acid **3.18** and was shared by three groups.[124-126] The aim was to link a 2-iodobenzoic acid moiety onto a variety of resins. The Rademann[124] and Giannis[125] syntheses were devised separately but led to a common scheme. The Rademann synthesis is shown as a representative example (Scheme 3.6). The first step was a diazotation of **3.18**, followed by a Sandmeyer type reaction leading to the iodination and finally the protection of the carboxylic acid as a

methyl ester gave **3.19**. Attachment to a Merrifield resin[8] was obtained via a Williamson reaction then saponification using potassium trimethyl silanoxide in THF gave a solid-supported 2-iodobenzoic acid **3.20**. Subsequent oxidation by treatment with tetrabutylammonium oxone in addition with methanesulfonic acid yielded the polymer-bound IBX **3.21**.



Scheme 3.6. Solid-supported IBX from Rademann

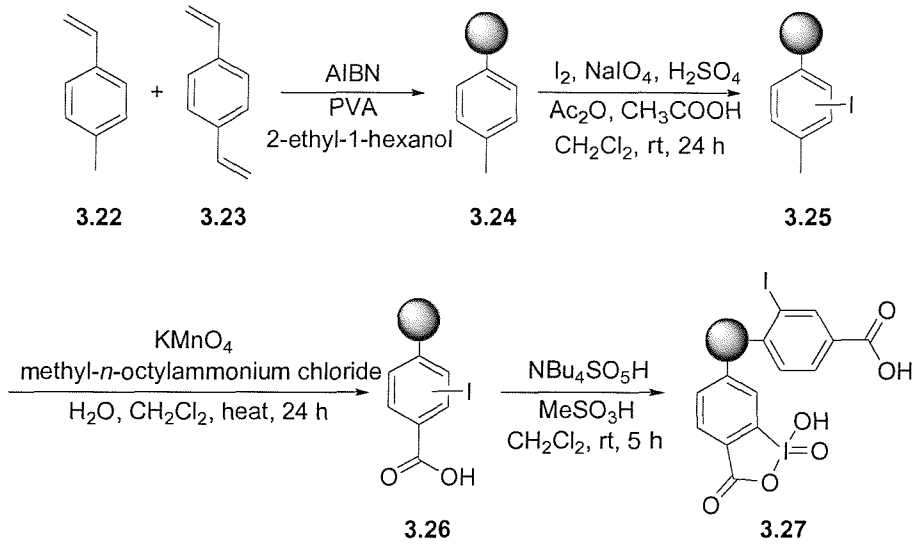
A loading of 0.8 mmol·g^{-1} was reported, with at least 1.75 equiv of the resin required for complete oxidation. Oxidations of alcohols were typically performed in dichloromethane. The commercial IBX resin is based on this procedure but two to four equiv are required to carry out complete oxidation (as reported in the Novabiochem catalogue).

The major modification in the synthesis from Giannis[125] was the use of aminopropyl silicagel as solid-support to afford a supported reagent having a loading in the range of 0.3–0.4 mmol·g^{-1}. 1.2 equiv were necessary for the oxidation of alcohols to the corresponding carbonyl compounds in THF.

Janda and co-workers[126] adapted this procedure to perform a set of soluble and insoluble supported IBX. The soluble non-crosslinked polystyrene-supported reagent was reported exhibiting the higher reactivity. Based on the loading of the pre-oxidised resin **3.20** (0.3-0.9 mmol·g^{-1}), 2 equiv were required for oxidation and the reaction was achieved in dichloromethane. A higher reactivity was reported for the soluble non-crosslinked polystyrene supported reagent but it exhibited the lowest loading (0.3 mmol·g^{-1}).

Hence, starting from **3.18**, IBX resins were synthesised in five steps. Sutherland[127] used a fundamentally different approach and relied on the introduction of the iodobenzoic acid moiety directly on the resin backbone (Scheme 3.7). Copolymerisation of *p*-methylstyrene

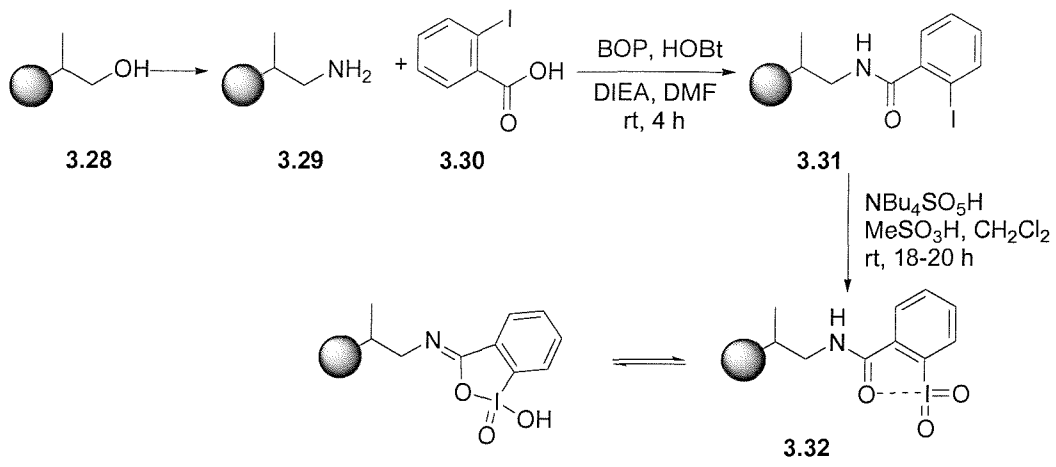
3.22 and divinylbenzene **3.23** led to a macroporous resin **3.24**. The aromatic ring was subsequently iodinated to afford compound **3.25** and the methyl group subjected to oxidation to give the carboxylic acid **3.26**. The resulting resin was treated under the same oxidation conditions described earlier and a supported IBX reagent with a loading between 0.2 and 0.5 mmol·g^{-1} was obtained. This range for the loading was the result of the regioselectivity of the iodination with the possibility of an *ortho*-or *meta*-iodination. Only the *ortho*-iodination was reactive toward the oxidation. With this reagent, 2 equiv of resin **3.27** were required for the oxidation reaction preformed in dichloromethane.



Scheme 3.7. Sutherland synthesis

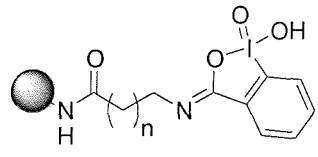
The last IBX resin designed by Lee[128] was based on the Zhdankin IBX amide[119] (Scheme 3.8). BTCore EM OH beads[129] **3.28** were converted to aminoalkyl polystyrene resin **3.29** using a Mitsunobu reaction followed by a Staudinger reaction.[130] Then, 2-iodobenzoic acid **3.30** was coupled through a peptide coupling reaction using BOP, HOBt and DIEA to afford the supported 2-iodobenzoic acid resin **3.31**, which was oxidised to the immobilised IBX amide **3.32**.

A loading of 0.98 mmol·g^{-1} was achieved and 2 equiv of resin were necessary for the total conversion of an alcohol to the corresponding carbonyl compound. An IBX ester resin was also synthesised by direct coupling of the 2-iodobenzoic acid **3.30** upon resin **3.28**. This resin was reported having the same oxidative properties as the IBX amide but with a lower reactivity.



Scheme 3.8. Lee synthesis

Recently, Lee proved the importance of a spacer in a polymer-supported IBX amide resin **3.33** (Figure 3.3).[131] The conversion rate was increased with the introduction of the spacer and a 4-carbon spacer was the best solution when long alkyl chain were oxidised with an increase of the conversion yield from 17 % to 60 % after 12 h with 1 equiv of IBX amide resin. With a longer spacer (9 carbon atoms) the rate decreased. The adjunction of an additive, trifluoroacetic acid (TFA), $BF_3{\cdot}EtO_2$ or tetraethylammonium bromide (TEAB) was also discussed. With $BF_3{\cdot}EtO_2$, the reaction rate was increased and complete conversion of benzyl alcohol could be obtained in only 5 minutes.



3.33 n = 1, 4 or 9

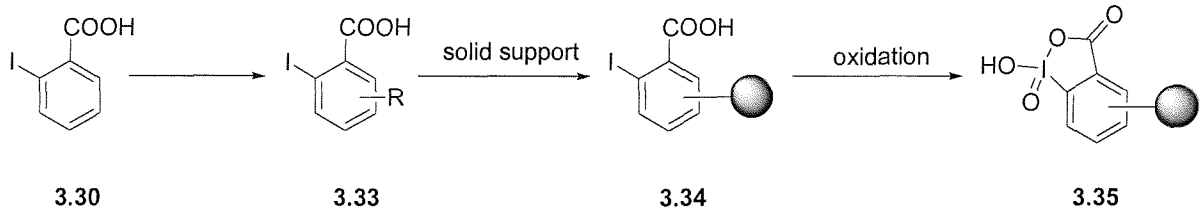
Figure 3.3. Lee's IBX amide resin with a spacer

3.2 Results and discussion

3.2.1 Solid-supported IBX

3.2.1.1 Project aims

This project was started when the only available syntheses of supported IBX where based on the 2-amino-5-hydroxy benzoic acid **3.18**. At this time, there were some difficulties to procure **3.18** and Lee's IBX amide synthesis had not been published. We decided to focus our investigations toward an IBX resin on a convenient preparation from easily obtainable and cheap commercial starting materials. Initially an approach was designed using the readily available inexpensive 2-iodobenzoic acid **3.30** as shown in Scheme 3.9. A linker would be introduced onto the aromatic ring followed by the immobilisation on solid-support. A final oxidation step would attain the desired solid-supported IBX **3.35**.



3.30 **3.33** **3.34** **3.35**

Scheme 3.9. General strategy for the synthesis of an immobilised IBX

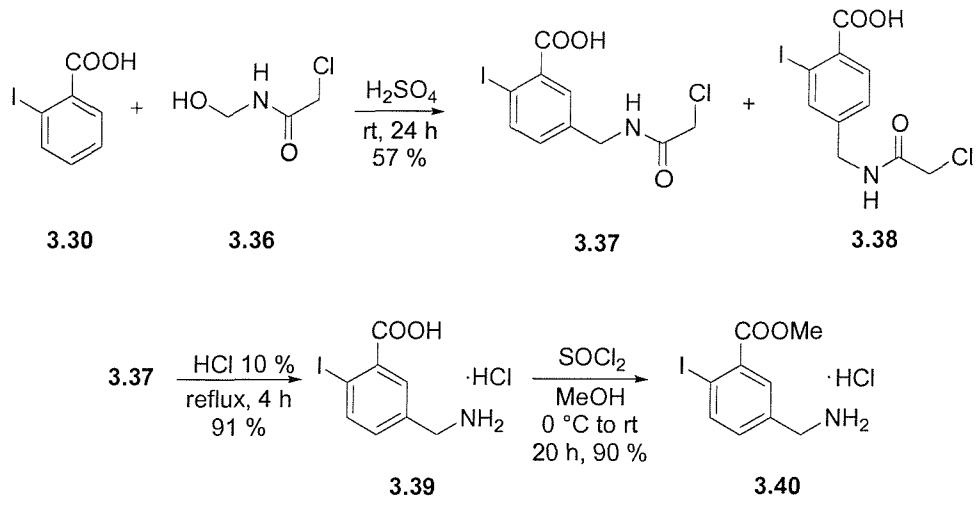
3.2.1.2 Synthesis of the intermediate **3.34**

A synthesis of immobilised IBX starting from **3.30** is compromised by the low reactivity of 2-iodobenzoic acid towards Friedel-Crafts type reactions to install an alkyl linker substituent. Though the alkoxy based linker of Rademann, Janda and Giannis ultimately proved of little consequence in terms of electronic influence to the reactivity of the IBX resins, our initial aim was to connect 2-iodobenzoic acid **3.30** to a support via an alkyl substituent.

Some research had been performed earlier in our laboratory for this kind of reaction and a solution was found in a former work from Fumagalli.[132] The Friedel-Crafts alkylation of **3.30** with the reactive (chloroacetylamino)methanol **3.36** was described (Scheme 3.10). The

result of this reaction allowed us to introduce the desired linker onto 2-iodobenzoic acid **3.30**. Two regioisomeric products **3.37** and **3.38** (7:3 ratio) were obtained in 97 % combined yield. The synthesis was difficult to scale-up due to the formation of a gum in the first stage of the reaction. Working on larger scale caused an extended time necessary for the dissolution of the solid residue.

Although both isomers could equally function as suitable precursors for immobilised IBX, separation of the two regioisomers was carried out, for the sake of straightforward characterisation. Hence, **3.37** and **3.38** were separated by a simple crystallisation from 70 % ethanol, giving pure **3.37** in a 57 % yield.



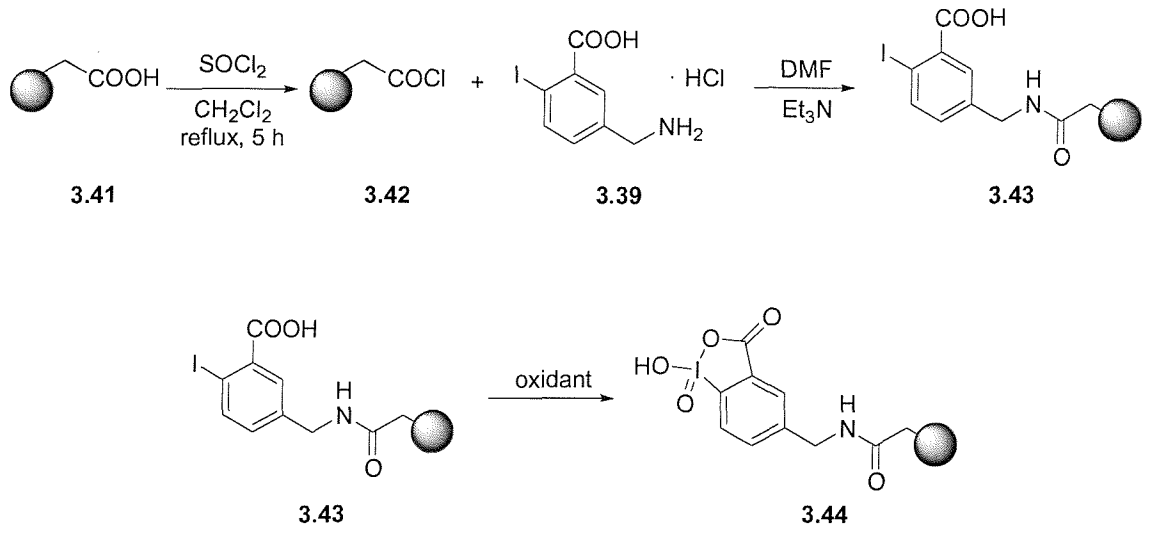
Scheme 3.10. Preparation of precursor **3.40**

Subsequent amide hydrolysis using a 10 % aqueous hydrochloric acid solution at reflux led to the amino acid **3.39** which was protected as the corresponding methyl ester **3.40** using thionyl chloride in methanol. This three step sequence routinely afforded **3.40** in a 47 % overall yield on 32 g scale starting from **3.30**.

3.2.1.3 Synthesis of the solid-supported IBX

In order to extend the solvent range of the previously developed solid-supported IBX and to obtain a very high loading, macroporous carboxylic acid resin IRC-50 (10 $mmol \cdot g^{-1}$) was first investigated as support. This inexpensive carboxylic acid resin **3.41** was first treated with thionyl chloride in dichloromethane as described in Scheme 3.11. The resulting acyl

chloride resin **3.42** was then added to **3.39** in presence of triethylamine in DMF to yield **3.43**.

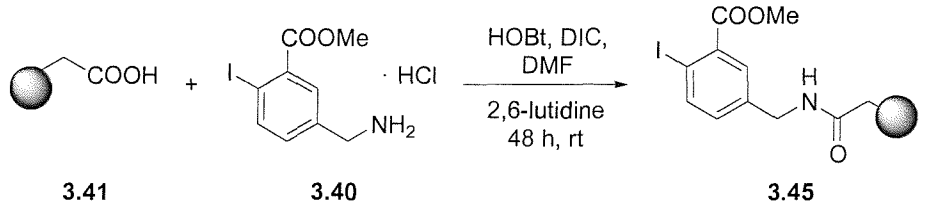


Scheme 3.11. Macroporous support

Any attempt to monitor the reaction by IR was hindered by the strong carboxylic acid band. But a small C-I band attested of a limited success of the coupling. As a test, **3.43** was oxidized either using the previously describe method with tetrabutylammonium oxone[133] in dichloromethane or adapting the oxidation procedure developed by Frigerio *et al.*[106] with oxone in water. Here again, no easy monitoring procedure was available and the resulting resin **3.44** was subjected to a test oxidation. Considering the loading of the resin as being 1.00 mmol·g^{-1}, 1 equiv of 4-bromobenzyl alcohol was added to **3.44** in dichloromethane. After an extended reaction time, only traces of 4-bromobenzaldehyde could be detected, attesting of the low reactivity of this solid-supported IBX and/or incomplete oxidation to iodine (V).

When the IRC-50 carboxylic acid resin **3.41** was coupled with the ester **3.40** through peptide coupling reaction (Scheme 3.12), the resulting supported ester intermediate **3.45** exhibited a loading of 1.81 mmol·g^{-1} as found by elemental analysis of iodine (with a theoretical loading of 2.4 mmol·g^{-1}). However a limited deprotection of the methyl ester could be achieved with various deprotection methods such $KOSiMe_3$ in THF as in the Rademann synthesis,[124] saponification using NaOH or KOH as aqueous solution in DMF (even when heating up to 80 °C). Another macroporous carboxylic acid resin IRC-86 was then tested. After coupling, the obtained loading was 1.13 mmol·g^{-1} (1.79 mmol·g^{-1}

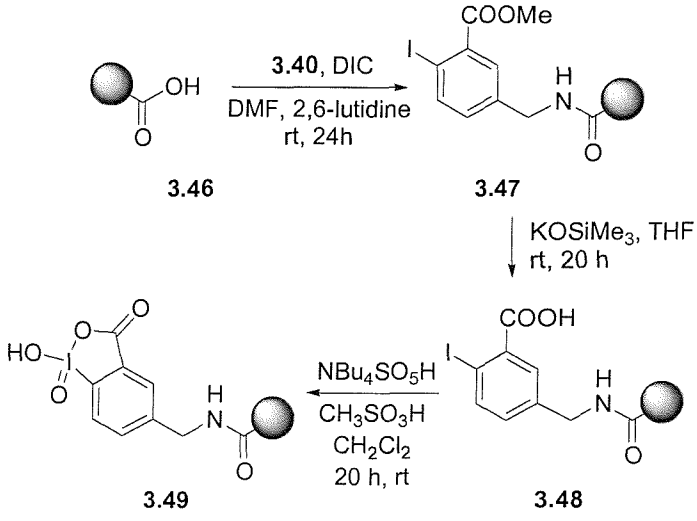
expected) and the deprotection step was again incomplete even while repeating the procedure several times. In any event, oxidation with tetrabutylammonium oxone resulted in a resin with no activity.



3.41 **3.40** **3.45**

Scheme 3.12. Macroporous support with ester intermediate

Then, a commercially available polystyrene carboxylic acid resin **3.46** (2.1 mmol·g^{-1}) was tested (Scheme 3.13). The transformation to the acyl chloride resin led to a mixture of anhydride and acyl chloride functionalities (as observed by IR analysis) and the following coupling with **3.39** was never complete. Thus, a peptide coupling between **3.46** and the ester intermediate **3.40** was achieved after addition of DIC and 2,6-lutidine. Dimethylformamide was used as solvent due to the very low solubility of **3.40** in other solvents. Following the amide band appearance allowed to easily monitor the coupling progress. Iodine elemental analysis revealed a loading of 1.10 mmol·g^{-1} (compared to the theoretical loading of 1.33 mmol·g^{-1}). Subsequent deprotection of the ester moiety under the Rademann condition went smoothly to yield **3.48**, although complete deprotection was never achieved as detected by IR analysis. The use of microwave irradiation was investigated as a possible way to drive the reaction towards completion but was unsuccessful.



3.46 **3.47** **3.49** **3.48**

Scheme 3.13. Preparation of polymer supported IBX **3.49**

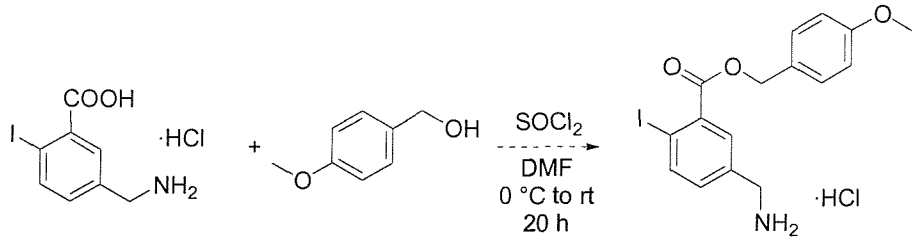
As the amount of remaining ester was negligible, resin **3.48** was oxidized with tetrabutylammonium oxone and methanesulfonic acid to afford the IBX resin **3.49**. The loading was not determined by elemental analysis due to the possibility of non-oxidized or partially oxidized iodine. The evaluation was performed by subjection of the resin to a known excess of 4-bromobenzyl alcohol. After filtration and isolation of the mixture of alcohol and aldehyde, the ratio was determined by ^{1}H NMR via comparison of the integration of the aldehyde proton and the benzylic protons of the remaining alcohol. Hence, the resulting value is referred to as the apparent loading, and is thus related to the reactivity of the resin and not exclusively to the physical loading of the IBX moiety on the polymer. In the event, an apparent loading of 0.20-0.25 mmol·g^{-1} was determined for **3.49**. Ten equiv of tetrabutylammonium oxone at room temperature over 20 h appeared to be the optimum conditions for the transformation to **3.49**. After subjection of the resin to 4-bromobenzyl alcohol, a reoxidation using tetrabutylammonium oxone and methanesulfonic acid only led to a lower apparent loading of the reoxidized IBX resin.

The direct transformation from the ester protected **3.47** to an IBX ester was also investigated and after test, an apparent loading of only 0.07 mmol·g^{-1} maximum was found.

3.2.1.4 Investigation of other protecting groups

The deprotection of the methyl ester from **3.47** was a challenging problem with an incomplete step in the synthesis lowering the loading of the final IBX resin. The procedure described by Rademann[124] using $KOSiMe_3$ in THF was incomplete. The saponification using an aqueous solution of potassium hydroxide in tetrahydrofuran or dimethylformamide at room temperature or even at reflux gave an even lower deprotection level.

Other protecting groups for the carboxylic acid **3.39** were then investigated. The first strategy was to replace the methyl ester by 4-methoxybenzyl alcohol **3.50** following the same procedure as with methanol (Scheme 3.14). The 4-methoxybenzyl ester would be easily removed with a treatment with TFA. Due to the low solubility of **3.39** the reaction was performed in DMF with a huge excess of **3.50**.

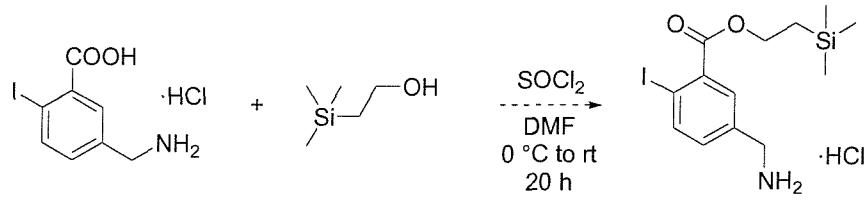


3.39 **3.50** **3.51**

Scheme 3.14. Protection of the carboxylic acid with 4-methoxybenzyl alcohol **3.50**

After purification, only traces of **3.51** were observed by ^{1}H NMR and another protecting group was then considered.

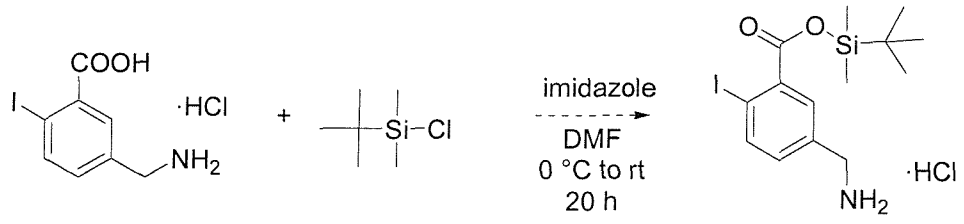
Using a silyl protecting group would allow a very easy deprotection step using TBAF as reagent. Trimethylsilyl ethanol **3.52** and *t-b*utyldimethyl chlorosilane **3.53** were investigated. Again, the procedure using thionyl chloride was used with trimethylsilyl ethanol **3.52** in DMF as solvent (Scheme 3.15). Again, after several attempts a gum was formed in the mixture and only traces of **3.54** were detected.



3.39 **3.52** **3.54**

Scheme 3.15. Protection of the carboxylic acid with trimethylsilyl ethanol **3.52**

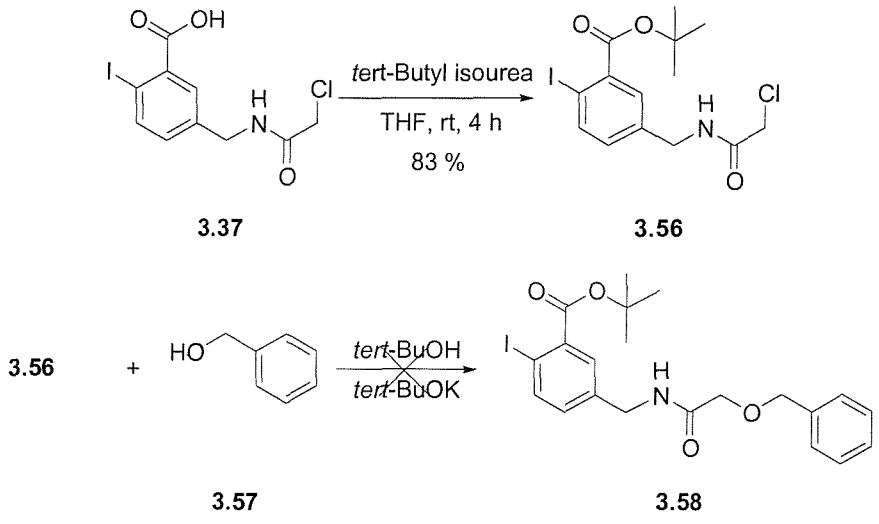
With the use of TBDMSCl **3.53** the possible formation of both the silyl ester and the silyl-protected amine had to be considered. However, the silyl amine would be less stable and should be deprotected under aqueous workup without touching the silyl ester. After reaction in DMF with a large excess of imidazole (10 equiv) and aqueous workup (Scheme 3.16), only traces of a silyl compound could be detected by ^{1}H NMR. Unfortunately the compound could not be purified and whether it was the silyl ester or the silyl amine could not be determined.



3.39 **3.53** **3.55**

Scheme 3.16. Protection of the carboxylic acid with *tert-b*utyldimethyl chlorosilane **3.53**

Another route was then investigated as shown in Scheme 3.17. The 2-iodobenzoic acid derivative **3.37** was treated with *t*-butyl isourea in THF to obtain the *t*-butyl protected ester **3.56**. Unfortunately, the chlorine displacement was unsuccessful while performed with benzyl alcohol **3.57** as a solution phase model.



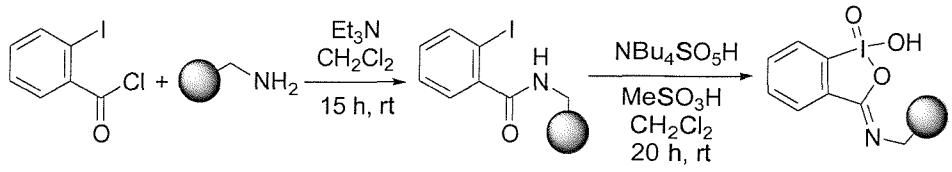
Scheme 3.17. Alternative routes

3.2.2 Solid-supported IBX amide

3.2.2.1 Using aminomethyl resin

Although the above-described approach starting from 2-iodobenzoic acid was successful, in total six steps were needed to obtain the resin **3.48** with a maximum loading of 0.25 $mmol \cdot g^{-1}$. A much shorter synthesis was realised based on the Zhdankin IBX amide oxidant.[119] The synthesis to the polymer-supported equivalent was straightforward and

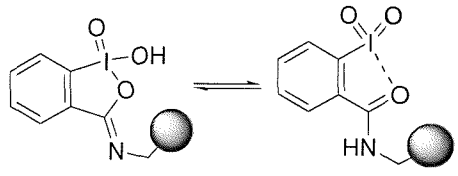
could be completed in only two steps as shown in Scheme 3.18. The cheap and commercially available 2-iodobenzoyl chloride **3.59** was simply coupled with a commercial aminomethyl polystyrene resin **3.60** (2.7 mmol·g^{-1}) affording the amide precursor **3.61**. Subsequent oxidation using tetrabutylammonium oxone and methanesulfonic acid gave the supported IBX amide **3.62**.



3.59 **3.60** **3.61** **3.62**

Scheme 3.18. Simplest version of the supported amide IBX

IR analysis effectively showed us a shift of the amide band from 1650 cm^{-1} to 1610 cm^{-1}. Figure 3.3 was the IR spectra of the amide resin **3.61** and clearly showed a strong peak of the amide moiety at 1650 cm^{-1} while Figure 3.4 showed a very strong peak at 1610 cm^{-1}. This was due to the modification of the environment of the amide functionality with an intramolecular weak bond between the oxygen atom of the amide carbonyl and the iodine as described in Scheme 3.19.



3.62

Scheme 3.19 Modification of the environment of the amide after oxidation to the amide IBX resin

However after testing with 4-bromobenzyl alcohol, an apparent loading of lower than 0.03 mmol·g^{-1} was the result. The explanation could be the bulk introduced with the polystyrene polymer, which could prevent the alcohol from accessing the IBX derivative moiety. Another explanation could be the oxidation to iodine (III) only. As a mean to check if a steric hindrance was the problem with this resin, inserting a spacer was investigated.

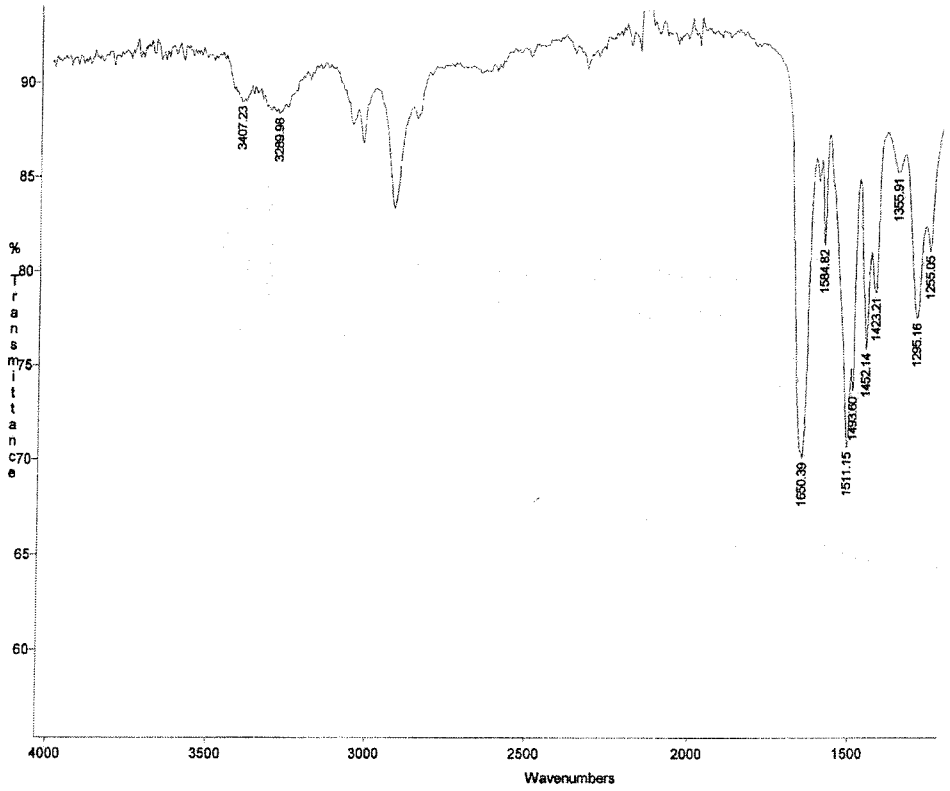


Figure 3.3. IR of resin **3.61,** amide peak at 1650 cm^{-1}

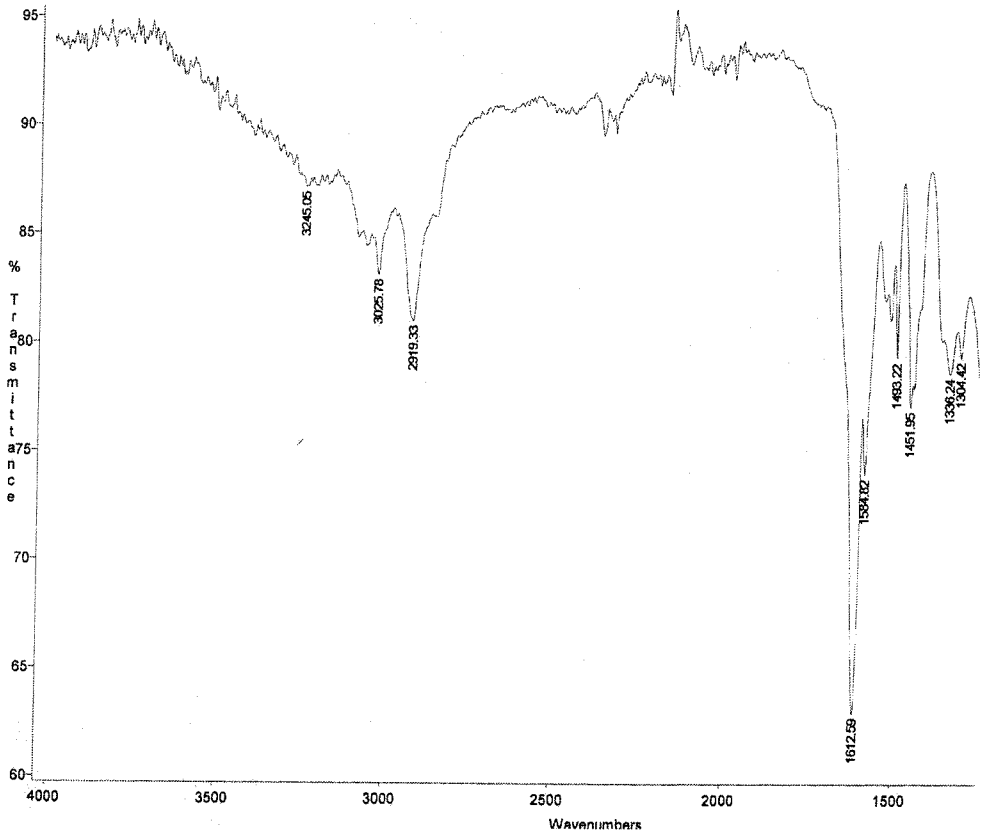
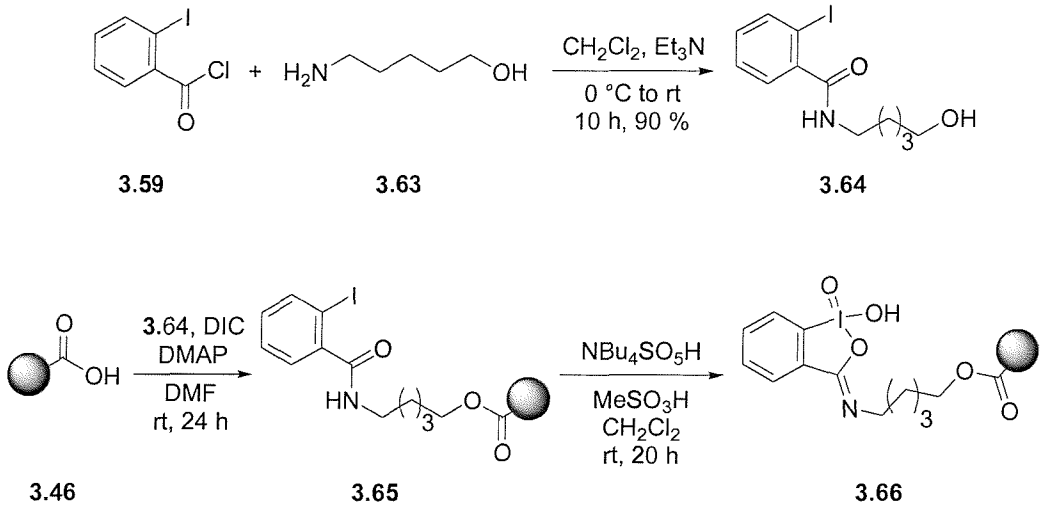


Figure 3.4. IR of IBX amide resin **3.62**, Shift of the amide peak to 1613 cm^{-1}

3.2.2.2 5 Carbon-spacer

It was then decided to insert 5-amino-1-pentanol **3.63** as a spacer as described in Scheme 3.20. The reaction between acyl chloride **3.59** and amino alcohol **3.63** was very straightforward using a modified literature procedure,[134] with an easy product isolation as **3.64** precipitated from the reaction mixture. This amide **3.64** was then coupled with a carboxylic acid resin **3.46** using DIC and DMAP to afford the 2-iodobenzamide derivative resin **3.65**. Again, the completion was checked by IR analysis with the disappearance of the carboxylic acid band and the formation of the ester band at 1705 cm^{-1}.

Oxidation following the usual procedure with tetrabutylammonium oxone gave **3.66**. The oxidation to hypervalent iodine was monitored through IR analysis by following the shift of the amide band from 1645 to 1595 cm^{-1}.



Scheme 3.20. Synthesis of the 5-carbon spacer ester bound amide IBX

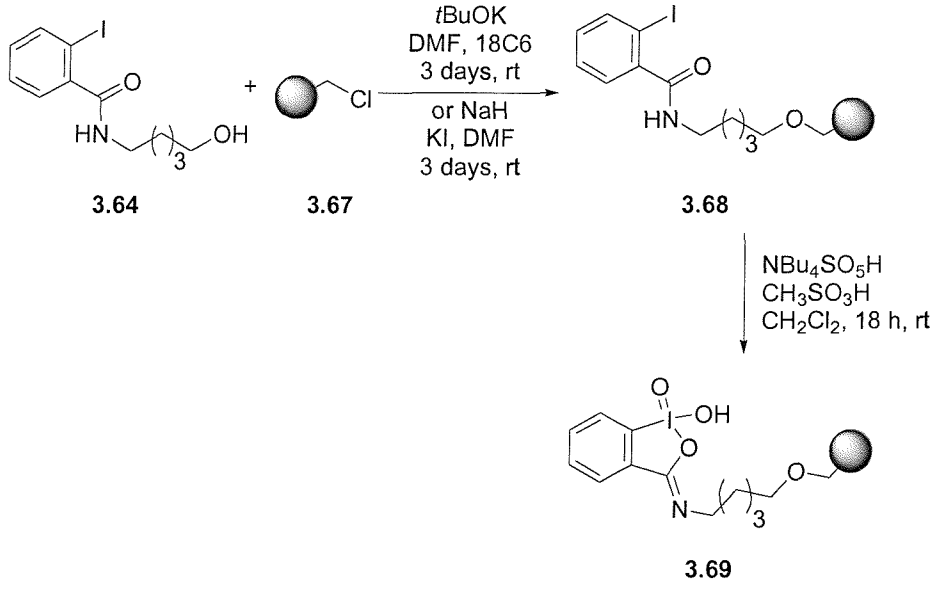
This polymer bound amide IBX **3.66** was synthesised starting from two carboxylic acid resins with a loading of 1.4 and 2.1 $mmol \cdot g^{-1}$. However, both resins gave an apparent loading of 0.23-0.28 $mmol \cdot g^{-1}$, estimated after oxidation of an excess of 4-bromobenzyl alcohol. The theoretical loadings were respectively 0.93 and 1.19 $mmol \cdot g^{-1}$ and such a difference could prove that more than 1 equiv of the IBX amide resin was necessary to perform the oxidation. This result was in the same range as the IBX resin **3.49** previously synthesized.

The supported reagent had been recycled up to two times following the same procedure with tetrabutylammonium oxone, however with a noticeable loss of reactivity as shown in Table 3.1. After the first reoxidations, half of the activity had already disappeared.

	Initial loading	1st reoxidation	2nd reoxidation
Apparent loading ($mmol \cdot g^{-1}$)	0.23	0.13	0.09

Table 3.1. Recycling of the IBX resin **3.66**

Though the apparent loading was acceptable, the carboxylic acid resin **3.46** used was very expensive (5 g for £120.00), and an alternative approach based on the more affordable Merrifield resin (25 g for £60) was investigated. Hence, attaching the IBX amide precursor **3.64** to Merrifield resin **3.67** using a Williamson reaction with potassium *tert*-butoxide as base afforded resin **3.68** (Scheme 3.21). Subsequent oxidation following standard procedure yielded **3.69** as demonstrated by IR analysis with a shift of the amide band from 1640 cm^{-1} to 1595 cm^{-1}. To test the probable relation between the loading and the oxidative activity of the resin, three different loadings of Merrifield resin were investigated.



Scheme 3.21. Synthesis of the 5-carbon spacer ether bound IBX amide

With a low loading Merrifield resin (0.97 $mmol \cdot g^{-1}$), the coupling was carried out at room temperature or using microwave irradiation. In both cases, the apparent loading of the

supported reagent **3.69** after oxidation was between 0.18 and 0.26 mmol·g^{-1} (with a corresponding theoretical loading of 0.73 mmol·g^{-1}).

Using a Merrifield resin with a loading of 1.60 mmol·g^{-1}, an apparent loading of the supported IBX amide **3.69** of 0.20-0.28 mmol·g^{-1} was achieved after coupling and oxidation at room temperature (theoretical loading of 1.05 mmol·g^{-1}). Surprisingly, this result was in the same range as obtained with the low loading resin.

Next, a very high loading Merrifield resin (3.99 mmol·g^{-1}) was evaluated. The IR analysis showed complete conversion for the attachment of **3.64** in the Williamson reaction after an extended reaction time (5 days). However, after conversion of **3.68** to **3.69**, only limited activity of the resulting IBX resin was detected (with an apparent loading of 0.12 mmol·g^{-1} as the best result). Consequently, a resin with a loading between 1.0 and 1.6 mmol·g^{-1} was used for the further synthesis of the IBX amide polymer-supported reagent.

However, with this IBX amide resin **3.69** in the synthesis of which potassium *tert*-butoxide was used, it was sometimes necessary to oxidise the same batch twice in order to obtain a complete shift of the amide band in IR. Moreover, some batches prove to exhibit no oxidising properties at all. We also observed a new band at 1725 cm^{-1}, which might indicate oxidation of the benzylic position of the Merrifield resin giving an ester linkage. Furthermore, after tetrabutylammonium oxone treatment, resin clustering could sometimes be observed, which dramatically reduced the reactivity of the obtained IBX resin.

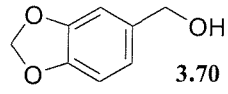
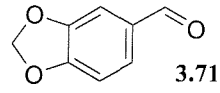
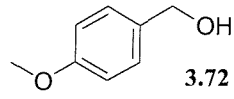
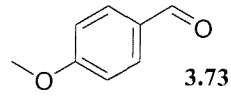
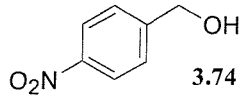
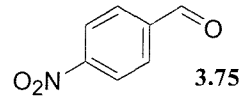
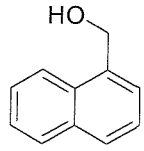
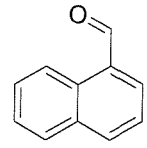
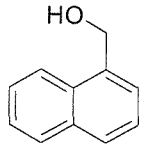
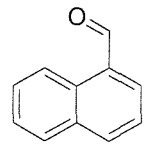
However, somewhat surprisingly, most of these practical problems could be avoided by using sodium hydride instead of potassium *tert*-butoxide for the Williamson reaction. In addition, the amount of tetrabutylammonium oxone necessary for the complete oxidation turned out to be lower: only 5 equiv (as compared to the theoretical loading) of tetrabutylammonium oxone were required while up to 20 equiv were needed to oxidise the previously synthesised resin. Subsequent determination of the loading with 4-bromobenzyl alcohol resulted in an apparent loading between 0.49 mmol·g^{-1} and 0.55 mmol·g^{-1} (starting with a Merrifield resin of 1.3 mmol·g^{-1}; theoretical loading of 0.94 mmol·g^{-1}).

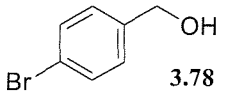
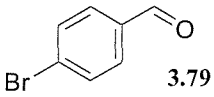
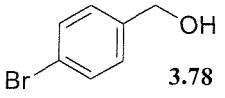
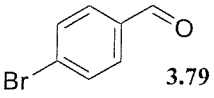
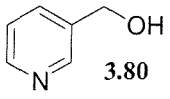
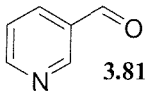
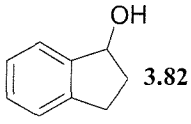
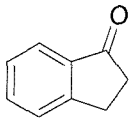
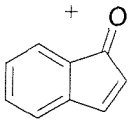
A modification in the treatment of the resin after the reaction was also decided. Instead of drying the resin at 40°C under vacuum, it was now dried at room temperature under vacuum. We could observe a slight increase of loading when following this procedure

showing some instability toward temperature of this IBX amide resin. After drying, the resin was kept in the fridge as a test showed a loss in apparent loading after two weeks at room temperature (from 0.49 to 0.30 $mmol \cdot g^{-1}$).

This supported reagent was then evaluated for the oxidation of various alcohols to the corresponding carbonyl compound as depicted in Table 3.2.

Benzylic primary alcohols were quantitatively converted to the aldehydes (Entries 1 to 6 and 8) and the reaction time was between 3 and 18 hours using 1.2 equiv of resin in dichloromethane at room temperature. Trace amounts of the carboxylic acid over-oxidation product were detected (^{1}H NMR) in only very few cases. When 1.1 equiv of **3.69** was used, oxidation of 4-bromobenzyl alcohol **3.78** only proceeded with 95 % conversion (Entry 7). With indan-1-ol **3.82** (Entry 9) less than 1 % of the over-oxidation conjugated product **3.84** was detected. Using naphthalene-1-methanol **3.76** (Entry 4), the reaction was not complete after 6 hours (monitored by TLC) and completion was finally reached after 18 hours. Adding 1.5 equiv of resin reduced the reaction time to 2.5 h (Entry 5).

Entry	Alcohols	Products	% Conversion[a]	Equiv of resin	Time
1	 **3.70**	 **3.71**	>95	1.2	3 h
2	 **3.72**	 **3.73**	>95[b]	1.2	3 h
3	 **3.74**	 **3.75**	>95	1.2	18 h
4	 **3.76**	 **3.77**	>95	1.2	18 h
5	 **3.76**	 **3.77**	>95	1.5	2.5 h

6	 **3.78**	 **3.79**	>95	1.2	3 h
7	 **3.78**	 **3.79**	95[c]	1.1	18 h
8	 **3.80**	 **3.81**	>95[b]	1.2	18 h
9	 **3.82**	 **3.83** +  **3.84**	95[b] <1	1.2	18 h

a) Conversion yield determined by ^{1}H NMR. When quoted >95 %, no trace of the starting material was observed b) Obtained with a reoxidised resin. c) The remaining is the starting material.

Table 3.2. Benzylic alcohols oxidation using 1.2 equiv of IBX resin **3.69** at room temperature in dichloromethane

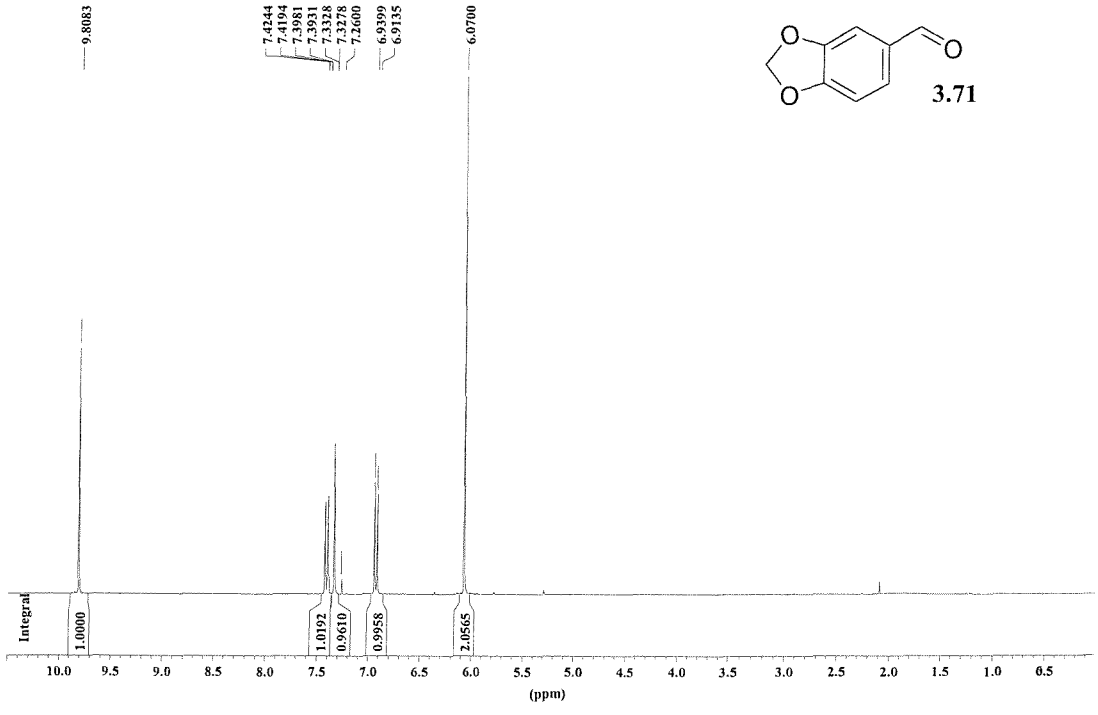
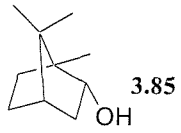
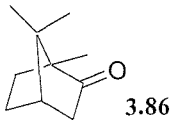
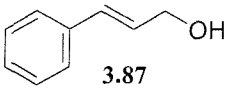
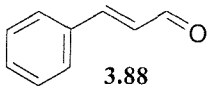
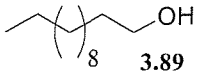
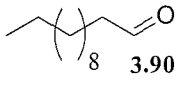
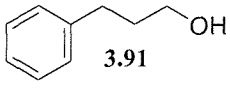
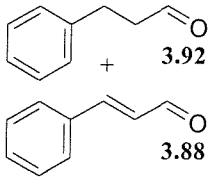
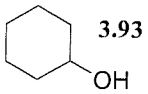
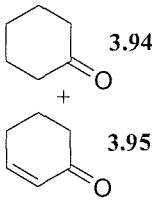
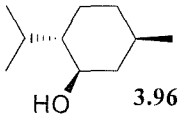
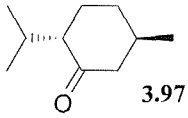
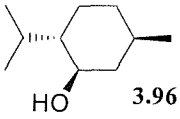
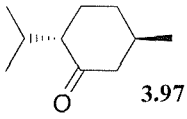
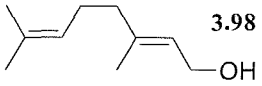
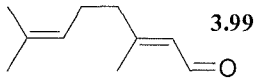
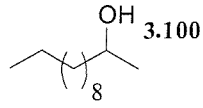
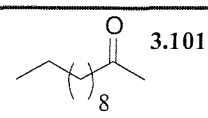
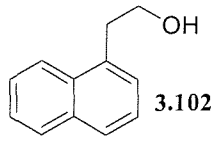
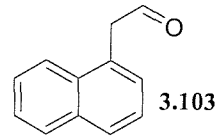
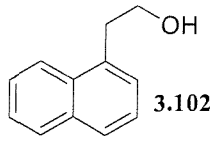
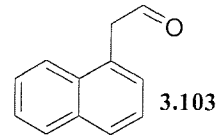


Figure 3.5. ^{1}H NMR of Benzo[1,3]dioxole-5-carbaldehyde **3.71**

The ^{1}H NMR spectra displayed in Figure 3.5 was taken directly after oxidation of piperonyl alcohol **3.70** without any purification just filtration and evaporation of the dichloromethane. It was a typical ^{1}H NMR obtained after the oxidation reaction with the IBX resin **3.69**, very clean.

Other alcohols were also successfully converted to the corresponding aldehyde as shown in Table 3.3. Secondary cyclic alcohols were also efficiently converted to the ketones (Entries 1 and 5 to 7). However, 2 equiv of the polymer-bound IBX resin **3.69** were necessary to attain a very good conversion of menthol **3.96** (Entry 6 and 7). Cinnamyl alcohol **3.87** was easily converted to the cinnamaldehyde **3.88** in 4 h (Entry 2).

Entry	Alcohols	Products	% Conversion[a]	Equiv of resin	Time
1	 **3.85**	 **3.86**	>95	1.2	18 h
2	 **3.87**	 **3.88**	>95	1.2	4 h
3	 **3.89**	 **3.90**	>95	1.2	18 h
4	 **3.91**	 **3.92** + **3.88**	95[b,c] 2[b,c]	1.2	18 h
5	 **3.93**	 **3.94** + **3.95**	82[c] 10[c]	1.2	18 h
6	 **3.96**	 **3.97**	70[b,c]	1.2	18 h
7	 **3.96**	 **3.97**	95[b,c]	2	18 h
8	 **3.98**	 **3.99**	>95[b] (E:Z 94:6)	1.2	18 h

9	 **3.100**	 **3.101**	85[b,c]	1.2	18 h
10	 **3.102**	 **3.103**	94[b,c]	1.2	18 h
11	 **3.102**	 **3.103**	95[b,c]	1.5	18 h

a) Conversion yield determined by ^{1}H NMR. When quoted >95 %, no trace of the starting material was observed b) Obtained with a reoxidised resin. c) The remaining is the starting material.

Table 3.3. Other alcohols oxidation using 1.2 equiv of IBX resin **3.69** at room temperature in dichloromethane

Aliphatic primary alcohols were quantitatively oxidised after an extended reaction time of 18 hours (Entries 3 and 4). But with hydrocinnamyl alcohol **3.91** and cyclohexanol **3.93** (Entries 4 and 5) the over-oxidation products cinnamaldehyde **3.88** and cyclohexenone **3.95** were detected. Furthermore, **3.93** was not completely oxidised with 1.2 equiv of polymer-bound IBX. The secondary acyclic alcohol dodecan-2-ol **3.90** (Entry 9) was converted in a good 85 % into the corresponding ketone. Geraniol **3.98** was completely oxidized to **3.99** with an E/Z ratio of 94/6 The conversion of **3.102** (Entry 10 and 11) did not reach completion and the remaining starting material could be recovered even while using 1.5 equiv of resin.

The polymer bound IBX **3.69** could be reoxidised up to three times before showing a substantial loss of reactivity and starting to form the resin clusters as previously described (Table 3.4). Only 2.5 equiv (relative to the theoretical loading of 0.9 mmol·g^{-1}) of tetrabutylammonium oxone were necessary for the reoxidation. When using only 2 equiv of tetrabutylammonium oxone, slightly lower loading could be observed (0.49 instead of 0.51 mmol·g^{-1} for the first reoxidation).

Oxidation	Initial	First reoxidation	Second	Third
Apparent loading ($mmol \cdot g^{-1}$)	0.54	0.51	0.49	0.35

Table 3.4. Recycling of the IBX amide resin **3.69**

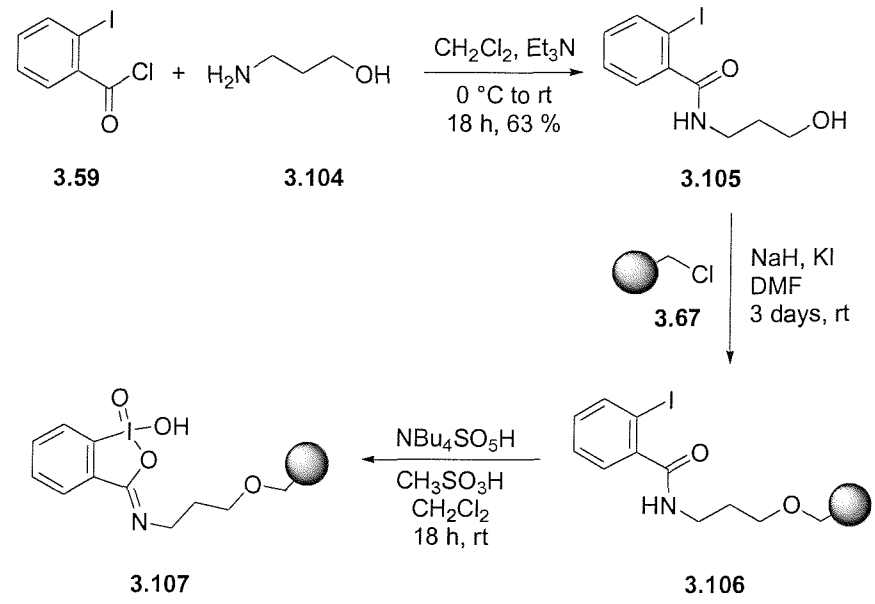
The oxidation reactions were simply worked-up by filtration, followed by evaporation of the filtrate. In some cases, an impurity was observed which appeared to be tetrabutylammonium species. While the impurity was not visible by HPLC analysis (UV detection), it was clearly visible from the NMR spectra. Apparently, the employed washing procedure after the oxidative step failed to remove all tetrabutylammonium species. Even with extended washing following a sequence using CH_2Cl_2 / CH_2Cl_2 + Et_2O (1:1) / Et_2O up to seven times, as reported for the Rademann IBX resin,[124] failed to completely remove the impurity. It was finally found that washing the resin with a diluted solution of acetic acid in dichloromethane (1.75 M) followed by dichloromethane and diethyl ether rinsing, with the sequence repeated twice, was effective in removing all traces of tetrabutylammonium, without loss of reactivity.

3.2.2.3 3 Carbon-spacer

Resin **3.69** was obtained with a maximum apparent loading of 0.55 $mmol \cdot g^{-1}$, which is significantly lower than the theoretical loading of 0.94 $mmol \cdot g^{-1}$. As the IBX moiety itself is not solvated by the reaction solvent dichloromethane, it is likely that minimal surface contact between the IBX and the solvent is a favoured situation, and that the IBX moiety is therefore in close contact with the polystyrene backbone. A long linker between the backbone and the IBX moiety would facilitate this situation.

Hence based on this rationale, we aimed to investigate a shorter spacer. The IBX precursor **3.105** (Scheme 3.22) was synthesised using the method previously described for the five-carbon precursor **3.64**. The amide coupling did however not proceed as smoothly compared to the synthesis of **3.64**, and the double addition product with formation of the amide and ester could be isolated. A 63 % yield of **3.105** was obtained after purification by column chromatography (literature yield: 67%).[134] The synthesis to the amide IBX resin **3.107** was

completed using the procedure developed for the five-carbon linker IBX resin **3.69** and a 1.4 mmol·g^{-1} Merrifield resin. To our delight, determination of the apparent loading of **3.107** using 4-bromobenzyl alcohol indicated that a significantly increased loading of 0.63 mmol·g^{-1} was obtained (with a theoretical loading of 1.02 mmol·g^{-1}).

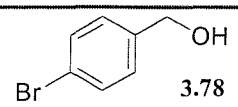
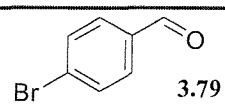
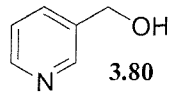
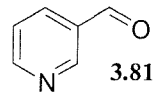
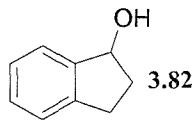
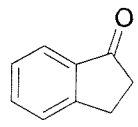
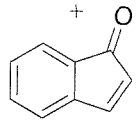


3.59 **3.104** **3.105** **3.67** **3.107** **3.106**

Scheme 3.22. Synthesis of the three-carbon spacer ether bound amide IBX

Screening this resin for oxidation of benzylic alcohols (Table 3.5) showed that the obtained results paralleled those achieved with the five-carbon spacer IBX resin, with complete conversions obtained using only 1.2 equiv of resin for most reactions.

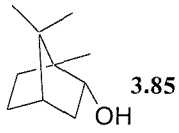
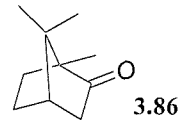
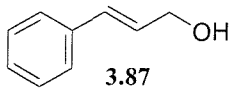
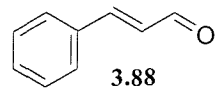
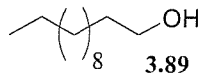
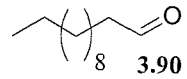
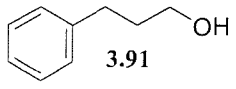
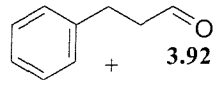
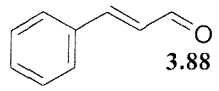
Entry	Alcohols	Products	% Conversion[a]	Equiv of resin	Time
1	**3.70**	**3.71**	>95	1.2	3 h
2	**3.72**	**3.73**	>95[b]	1.2	3 h
3	**3.76**	**3.77**	>95[b]	1.2	18 h

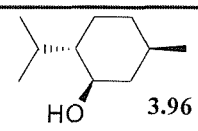
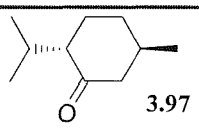
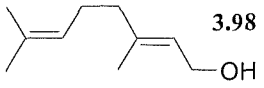
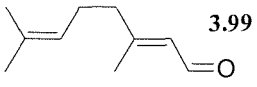
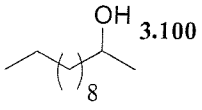
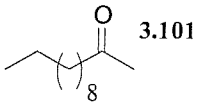
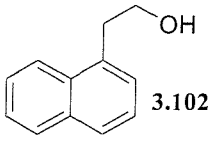
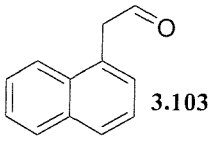
4	 **3.78**	 **3.79**	>95	1.2	3 h
5	 **3.80**	 **3.81**	>95[b]	1.2	18 h
6	 **3.82**	 **3.83** +  **3.84**	95[b] 1	1.2	18 h

a) Conversion yield determined by ^{1}H NMR. When quoted >95 %, no trace of the starting material was observed b) Obtained with a reoxidised resin.

Table 3.5. Benzylic alcohols oxidation using 1.2 equiv of IBX amide resin **3.107** at room temperature in dichloromethane

For the other alcohols, the results were similar (Table 3.6). However, oxidation of menthol **3.96** resulted in a lower yield than with the five-carbon IBX amide resin (Entry 5). Using 2 equiv of IBX amide resin, dodecan-2-ol **3.100** reached a very good 95 % conversion (Entry 7).

Entry	Alcohols	Products	% Conversion[a]	Equiv of resin	Time
1	 **3.85**	 **3.86**	>95[b]	1.2	18 h
2	 **3.87**	 **3.88**	>95	1.2	4 h
2	 **3.89**	 **3.90**	>95	1.2	18 h
4	 **3.91**	 **3.92** +  **3.88**	93[c] 2[c]	1.2	18 h

5	 **3.96**	 **3.97**	71[c]	2.0	18 h
6	 **3.98**	 **3.99**	>95 (E:Z 95:5)	1.3	18 h
7	 **3.100**	 **3.101**	95[b,c]	2.0	18 h
8	 **3.102**	 **3.103**	95[b,c]	1.5	18 h

a) Conversion yield determined by ^{1}H NMR. When quoted >95 %, no trace of the starting material was observed b) Obtained with a reoxidised resin.

Table 3.6. Other alcohols oxidation using 1.2 equiv of IBX amide resin **3.107** at room temperature in dichloromethane

The recycling of the resin proved also possible. Up to three reoxidations were performed with a slight decrease of the loading at each step (Table 3.7). Again, only 2.5 equiv of tetrabutylammonium oxone were required for reoxidation. However, while the loading was always higher than the five-carbon IBX resin, this polymer-bound IBX amide showed a tendency to adhere to the wall of the flask. This characteristic was not observed previously.

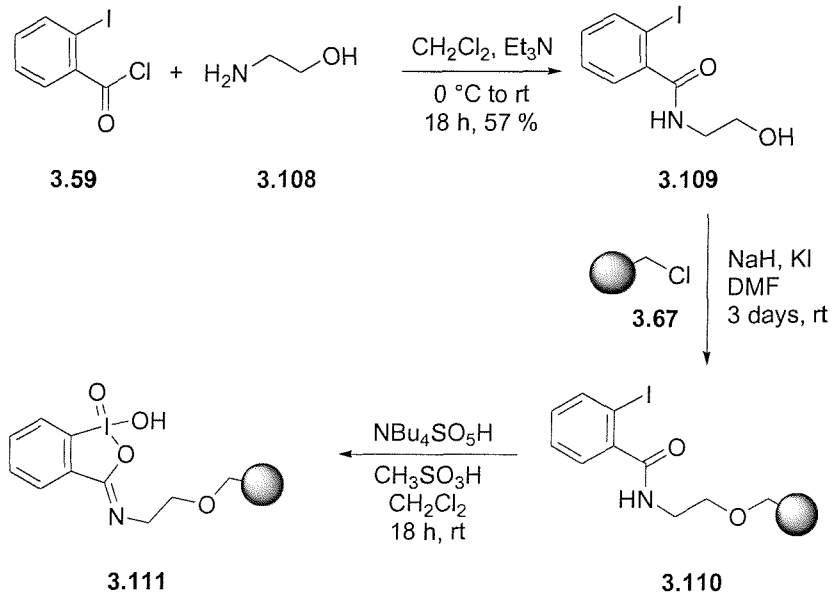
Oxidation	Initial	First reoxidation	Second	Third
Apparent loading (mmol·g^{-1})	0.63	0.60	0.57	0.45

Table 3.7. Apparent loadings after reoxidation of the three-carbon linker IBX amide resin

3.2.2.4 2 Carbon spacer

As reducing the length of the spacer from a five to a three-carbon chain increased the apparent loading of the IBX amide resin, a two-carbon chain was also introduced to check the impact of an even shorter spacer. The synthesis followed the procedure developed for

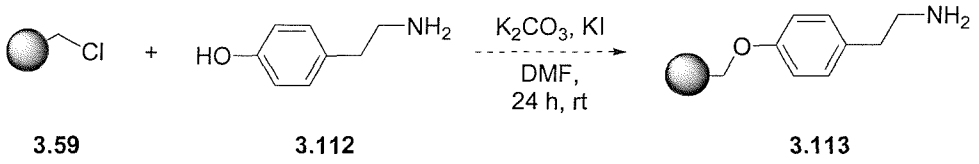
the other IBX amide resin (Scheme 3.23). Intermediate **3.109** was obtained in only 57 % yield due to the presence of the double addition product with the formation of amide and ester functional groups. Upon hydrolysis of the ester, **3.109** could be retrieve from this by-product. IBX amide resin **3.111** was then synthesized without further complication. However, the apparent loading detected was 0.49 $mmol \cdot g^{-1}$, lower than the previous resins, showing the steric effect of the solid-support and no further study was performed.



Scheme 3.23. Synthesis of the two-carbon spacer ether bound amide IBX

3.2.2.5 Tyramine as spacer

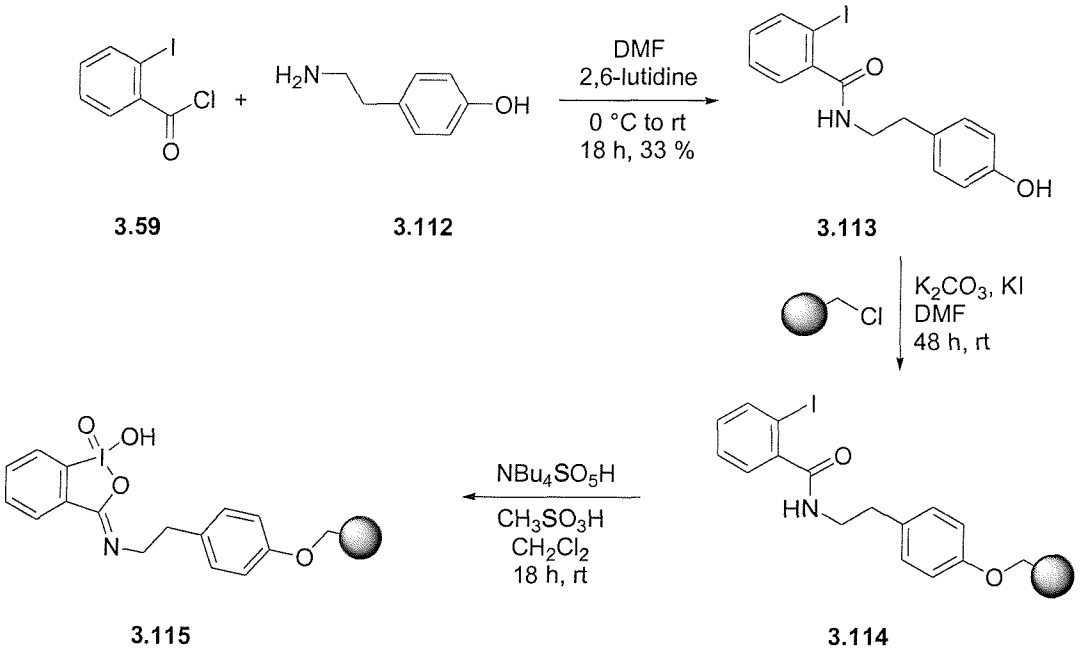
Tyramine was also tested as a more rigid spacer but the linkage to the resin proved more problematic. Firstly, the direct linkage between the tyramine **3.112** and the Merrifield resin **3.59** was tested (Scheme 3.24). The resulting resin **3.113** was submitted to a Kaiser test to show the presence of a free NH_2 group but a very weak response was obtained showing that only a few free NH_2 groups were available on the resin. After amide coupling and oxidation with tetrabutylammonium oxone, the obtained IBX amide resin showed very limited oxidative activity with only traces of the converted aldehyde.



3.59 **3.112** **3.113**

Scheme 3.24. Coupling of tyramine **3.112** and Merrifield resin **3.59**

A second route was then investigated starting with the coupling between 2-iodobenzoyl chloride **3.59** and tyramine **3.112** as shown in Scheme 3.25. The resulting amide **3.113** was obtained in a low yield of 33 % with non-optimised conditions. The linkage to the Merrifield resin was performed in DMF due to the low solubility of **3.113** and gave resin **3.114**. The subsequent oxidation with tetrabutylammonium oxone yielded the IBX amide resin **3.115**. The IR analysis confirmed the shifting of the amide peak from 1655 cm^{-1} to 1606 cm^{-1}.



3.59 **3.112** **3.113**

3.115 **3.114**

Scheme 3.25. Second route to the IBX amide resin **3.115**

Resin **3.115** was then tested using 4-bromobenzyl alcohol in dichloromethane. Only a very limited oxidative activity was detected with only traces of the converted aldehyde.

3.3 Conclusions

A series of IBX resins were prepared from a variety of resins, using commercially available and inexpensive iodobenzoic acid or the corresponding -equally inexpensive- acyl chloride. Ultimately, a straightforward three-step synthesis using Merrifield resin yielded IBX-resin **3.107**, having an apparent loading of 0.63 $mmol \cdot g^{-1}$.[135] Oxidation of a range of alcohols to the corresponding carbonyl compound proved very straightforward using 1.2 equiv of the resin. Recycling of the resin was also possible with minimal loss of activity after two reoxidations.

An efficient and practical washing procedure to completely remove all quaternary ammonium salts from the IBX-resin was also developed. It allowed a very quick washing of the resins with less solvent. Studies to extend the use of this procedure to other tetrabutylammonium species on other support showed a good but incomplete washing of the impurities.

The apparent loading of the three-carbon spacer IBX amide resin is among the highest reported for IBX resins, and its ease of preparation from Merrifield resin makes it a convenient reagent to use for alcohol oxidations. While the reactivity of the three-carbon spacer IBX amide resin **3.107**, and the five-carbon spacer resin **3.69** appear equally good, resin **3.107** is recommended for use because of the higher loading. On the other hand, the synthesis of the five-carbon IBX amide resin **3.69** is the simplest with no purification steps necessary while a column chromatography was needed for **3.107**.

4 Experimental

4.1 General

Reagents were purchased from Aldrich, Fluka and Acros and used without further purification. Solvent were distilled prior to use Anhydrous THF was distilled from sodium-benzophenone and CH_2Cl_2 was distilled from calcium hydride prior to use. Toluene and DMF were bought anhydrous from Aldrich in 100 mL bottle.

Microwave reactions are performed in a Smith Synthesizer™ microwave oven from Biotage.

^{1}H- and ^{13}C-NMR spectra were recorded using a BRUKER AC300, BRUKER AV300 or BRUKER DPX400 spectrometers.

NMR: s = singlet, d = doublet, t = triplet, q = quartet, dd = double doublet, dt = double triplet, m = multiplet, br = broad.

IR spectra were obtained on a Satellite FTIR from Thermo Mattson (MKII Golden Gate, single reflection ATR system from Specac)

IR: s = strong, m = medium, w = weak, br = broad.

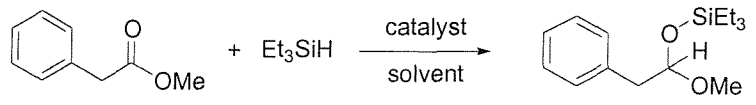
Column chromatographies were carried out on silica (model: gel 40-63 UM).

Merrifield resin (chloromethyl PS-DVB) was purchased from Novabiochem (loading 1.6 to 1.3 $mmol \cdot g^{-1}$ depending of the batch), Carboxylic acid resins (2.1 to 1.4 $mmol \cdot g^{-1}$ depending of the batch) were donated by Novabiochem.

Whenever possible, the identity of the products has been established by comparison of the spectral data with literature precedents or by direct comparison with authentic sample.

4.2 Experimental for Chapter 2

Synthesis of triethyl-(1-methoxy-2-phenyl-ethoxy)-silane 2.81



2.80 **2.42** **2.81**

With $B(C_6F_5)_3$ as catalyst:

To methyl phenylacetate **2.80** (0.15 mL, 1.0 mmol) and tris(pentafluorophenyl)borane (7.1 mg, 0.015 mmol) in dry toluene (1.5 mL), triethylsilane **2.42** (0.16 mL, 1.0 mmol) was added slowly. The mixture was stirred at rt for 3 h then filtered through silica and concentrated under vacuum. Purification by column chromatography (hexane/ethyl acetate 97:3) to yield **2.81** as a colourless oil (234 mg, 88%).

With $Ru_3(CO)_{12}$ as catalyst:

To methyl phenylacetate **2.80** (0.58 mL, 4.0 mmol) and triruthenium dodecacarbonyl (8.5 mg, 0.013 mmol) in dry toluene (6.0 mL), triethylsilane **2.42** (0.96 mL, 6.0 mmol) was added slowly. The mixture was stirred at 100 °C for 22 h then filtered through silica and concentrated under vacuum. Purification by column chromatography (hexane/ethyl acetate 97:3) to yield **2.81** as a colourless oil (516 mg, 49 %).

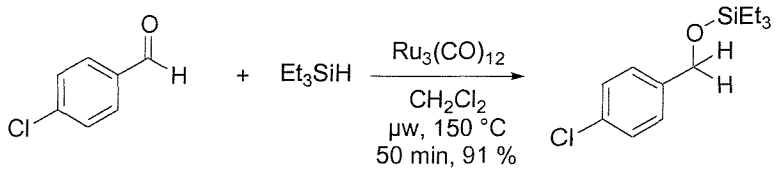
IR: (film) ν_{max} / (cm^{-1}): 2952 (b), 2875 (b), 1129 (s), 1058 (s).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H(ppm): 7.16 (5H, m, PhH), 4.77 (1H, dd, J = 6.0, 4.5 Hz, O-CH-O), 3.25 (3H, s, O-CH_3), 2.80 (2H, m, CH_2-Ph), 0.86 (9H, t, J = 8.0 Hz, $C\underline{H}_3$-CH_2-Si), 0.50 (6H, q, J = 8.0 Hz, CH_3-$C\underline{H}_2$-Si).

^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ_c(ppm): 137.7 (Ph^1), 130.1 ($Ph^{3,5}$), 128.6 ($Ph^{2,6}$), 126.7 (Ph^4), 100.2 (O-$\underline{C}$H-O), 54.2 (O-$\underline{C}H_3$), 44.5 (Ph-$\underline{C}H_2$), 7.1 ($\underline{C}H_3$-CH_2-Si), 5.4 (CH_3-$\underline{C}H_2$-Si).

HRMS (CI) for $C_{15}H_{27}O_2Si$ $(M + H)^+$: calcd 267.1780, found 267.1783.

Synthesis of triethyl-(4-chloro-benzyloxy)-silane 2.90



2.89 **2.42** **2.90**

To 4-chlorobenzaldehyde **2.89** (285.0 mg, 2.0 mmol) and triruthenium dodecacarbonyl (5.4 mg, 0.025 mmol) in dry CH_2Cl_2 (3.0 mL), triethylsilane **2.42** (0.96 mL, 6.0 mmol) was added slowly. The mixture was stirred under microwave irradiation at 150 °C for 50 min then filtered through silica and concentrated under vacuum. Purification by column chromatography (hexane/ethyl acetate 97:3) to yield **2.90** as a colourless oil (469 mg, 91 %).

IR: (film) ν_{max} / (cm^{-1}): 2954 (s), 2875 (s), 1084 (s).

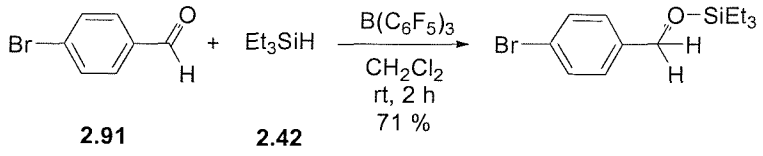
^{1}H NMR (400 MHz, $CDCl_3$): δ_H(ppm): 7.27-7.12 (4H, m, Ar), 4.62 (2H, s, Ar-C$\underline{H}_2$-O), 0.87 (9H, t, J = 8.0 Hz, C$\underline{H}_3$-CH_2-O), 0.55 (6H, q, J = 8.0 Hz, CH_3-C$\underline{H}_2$-O).

^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ_c(ppm): 138.9 (Ar^4-CH_2), 131.6 (Ar^1-Cl), 127.4 ($Ar^{2,6}$), 126.5 ($Ar^{3,5}$), 63.1 (Ar-$\underline{C}H_2$-O), 5.8 ($\underline{C}H_3$-CH_2-O), 3.5 (CH_3-$\underline{C}H_2$-O).

HRMS (CI) for $C_{13}H_{22}ClOSi$ $(M + H)^+$: calcd 257.1128, found 257.1135.

Data conform to literature.[87]

Synthesis of triethyl-(4-bromo-benzyloxy)-silane



2.91 **2.42**

To 4-bromobenzaldehyde **2.80** (185.0 mg, 1.0 mmol) and tris(pentafluorophenyl)borane (12.4 mg, 0.025 mmol) in dry CH_2Cl_2 (2.0 mL), triethylsilane **2.42** (0.16 mL, 1.0 mmol) was added slowly. The mixture was stirred at rt for 2 h then filtered through silica and concentrated under vacuum. Purification by column chromatography (hexane/ethyl acetate 97:3) to yield triethyl-(4-bromo-benzyloxy)-silane as a colourless oil (215 mg, 71 %).

IR: (film) ν_{max} / (cm^{-1}): 2953 (s), 2875 (s), 1083 (s).

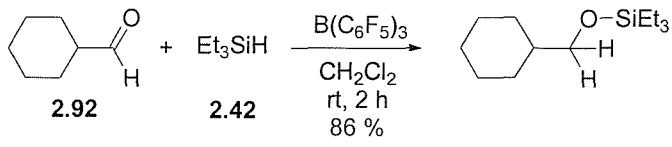
^{1}H NMR (300 MHz, $CDCl_3$): δ_H(ppm): 7.48 (2H, d, J = 7.7 Hz, Ar), 7.22 (2 H, d, J = 7.7 Hz, Ar), 4.68 (2H, s, Ar -C<u>H</u>$_2$-O), 0.98 (9H, t, J = 8.0 Hz, C<u>H</u>$_3$-CH$_2$-O); 0.65 (6H, q, J = 8.0 Hz, CH$_3$-C<u>H</u>$_2$-O).

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ_c(ppm): 143.6 (Ar ^{4}-CH_2), 137.3 (Ar ^{2,6}), 131.4 (Ar ^{3,5}), 128.0 (Ar ^{1}-Br), 64.2 (Ar -<u>C</u>H$_2$-O), 6.9 (<u>C</u>H$_3$-CH$_2$-O), 4.6 (CH$_3$-<u>C</u>H$_2$-O).

HRMS (CI) for $C_{13}H_{22}BrOSi$ $(M + H)^+$: calcd 301.0623, found 301.0630.

Data conform to literature.[136]

Synthesis of triethyl-(2-cyclohexane-methoxy)-silane



2.92 **2.42**

To cyclohexane carboxylate **2.92** (0.121 mL, 1.0 mmol) and tris(pentafluorophenyl)borane (23.6 mg, 0.045 mmol) in dry CH_2Cl_2 (2.0 mL), triethylsilane **2.42** (0.16 mL, 1.0 mmol) was added slowly. The mixture was stirred at rt for 2 h then filtered through silica and concentrated under vacuum. Purification by column chromatography (hexane/ethyl acetate 97:3) to yield triethyl-(2-cyclohexane-methoxy)-silane as a colourless oil (196 mg, 86 %).

IR: (film) ν_{max} / (cm^{-1}): 2952 (s), 2920 (b), 2876 (s), 1083 (s).

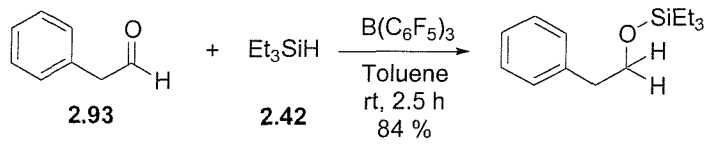
^{1}H NMR (300 MHz, $CDCl_3$): δ_H(ppm): 3.40 (2H, d, J = 6.6 Hz, C^1H-$C\underline{H}_2$-O), 1.78-1.70 (4H, m, $C^2\underline{H}_2$-C^1H-$C^6\underline{H}_2$), 1.52-1.40 (1H, m, C^6H_2-$C^1\underline{H}$-C^2H_2), 1.26-1.13 (4H, m, $C^3\underline{H}_2$-C^4H_2-$C^5\underline{H}_2$), 0.97 (9H, t, J = 8.1 Hz, $C\underline{H}_3$-CH_2-O), 0.98-0.85 (2H, m, C^3H_2-$C^4\underline{H}_2$-C^5H_2), 0.60 (6H, q, J = 8.1 Hz, CH_3-$C\underline{H}_2$-O).

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ_c(ppm): 68.8 ($\underline{C}H_2$-O), 40.7 (C^6H_2-$\underline{C}^1H$-C^2H_2), 30.0 ($\underline{C}^2H_2$-C^1H-$\underline{C}^6H_2$), 26.9 (C^3H_2-$\underline{C}^4H_2$-C^5H_2), 26.1 ($\underline{C}^3H_2$-C^4H_2-$\underline{C}^5H_2$), 7.0 ($\underline{C}H_3$-CH_2-O), 4.5 (CH_3-$\underline{C}H_2$-O).

HRMS (CI) for $C_{13}H_{28}OSi$ $(M + H)^+$: calcd 229.1988, found 229.1990.

Data conform to literature.[87]

Synthesis of triethyl-(2-phenyl-ethoxy)-silane



To phenylacetaldehyde **2.93** (0.117 mL, 1.0 mmol) and tris(pentafluorophenyl)borane (16.6 mg, 0.03 mmol) in dry toluene (2.0 mL), triethylsilane **2.42** (0.16 mL, 1.0 mmol) was added slowly. The mixture was stirred at rt for 2.5 h then filtered through silica and concentrated under vacuum. Purification by column chromatography (hexane/ethyl acetate 97:3) to yield triethyl-(2-phenyl-ethoxy)-silane as a colourless oil (199 mg, 84 %).

IR: (film) ν_{max} / (cm^{-1}): 2952 (s), 2875 (s), 1081 (s).

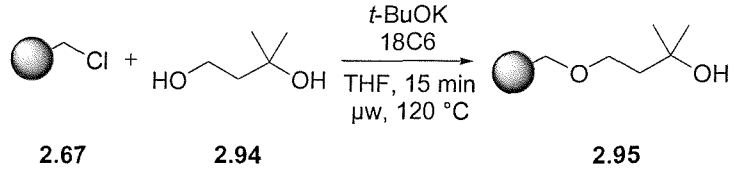
^{1}H NMR (400 MHz, $CDCl_3$): δ_H(ppm): 7.25-7.16 (5H, m, Ph), 3.73 (2H, t, J = 7.5 Hz, C$\underline{H}_2$-O), 2.77 (2H, t, J = 7.5 Hz, Ph-C$\underline{H}_2$), 0.86 (9H, t, J = 8.0, C$\underline{H}_3$-CH_2-Si), 0.50 (6H, q, J = 8.0 Hz, CH_3-C$\underline{H}_2$-Si).

^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ_c(ppm): 136.4 (Ph^1), 129.5 (Ph^{2,6}), 128.7 (Ph^{3,5}), 126.6 (Ph^4), 64.7 ($\underline{C}H_2$-O), 40.1 (Ph-$\underline{C}H_2$), 7.1 ($\underline{C}H_3$-CH_2-Si), 4.8 (CH_3-$\underline{C}H_2$-Si).

HRMS (CI) for $C_{14}H_{25}OSi$ $(M + H)^+$: calcd 237.1675, found 237.1669.

Data conform to literature.[87]

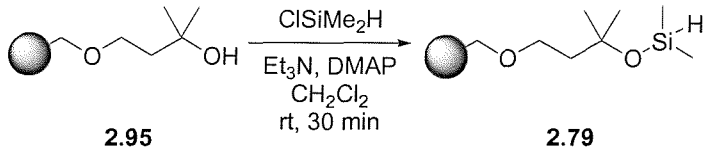
Synthesis of hydroxy resin 2.95



To an ice cooled solution of 3-methyl-1,3-butanediol **2.94** (1.28 ml, 12 mmol) in dry THF (30 mL) a solution of potassium *t*-butoxide was added (via canula) (12 mL, 12 mmol, solution 1.0 M in dry THF) with 18-crown-6 (0.32 mg, 1.2 mmol). The reaction was stirred 1 h at 0 °C and 3 h at rt. Then the solution was transferred via syringe into ten microwave flasks each containing 250 mg of the Merrifield resin **2.67** (preswollen in dry THF for 2 h). The vials were then placed under microwave irradiation at 120 °C during 15 min. The resin was washed thoroughly with THF (5 x 2 mL), DMF (5 x 2 mL), 1:1 DMF/H_2O (5 x 2 mL), DMF (5 x 2 mL), THF (5 x 2 mL), CH_2Cl_2 (5 x 2 mL), and dried under vacuum (40 °C) for 24 h. after combining the ten resins, 2.87 g of resin **2.95** were obtained.

IR FTIR microscope (cm^{-1}): 3467 (br), 1602 (s) 1365 (s), 1152 (br), 1093 (br).

Synthesis of dimethylsilane resin 2.79



2.95 **2.79**

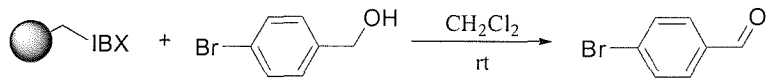
The resin **2.95** (2.87 g) was rinsed shortly with dry CH_2Cl_2 then the solvent was removed. Freshly distilled DCM was added (40 mL), followed by dry triethylamine (1.4 mL, 10 mmol), chlorodimethylsilane (0.71 mL, 6.4 mmol) and 4-dimethylaminopyridine (0.30 g, 2.45 mmol). The reaction was stirred 30 min at rt then the resin was rinsed quickly with dry CH_2Cl_2 (3 x 5 mL) and dried under vacuum (40 °C). 3.03 g of **2.79** were obtained.

IR FTIR microscope (cm^{-1}): 3650 (w), 3300 (w), 2112 (s), 1602 (s), 1365 (s), 1252 (s), 1030 (br).

^{13}C-NMR (75.5 MHz; $CDCl_3$) δ_C(ppm): 73.0 ($\underline{C}H_2$-O-CH_2), 67.1 (CH_2-$\underline{C}(CH_3)_2$-O), 43.4 (CH_2-O-$\underline{C}H_2$), 40.2 (O-CH_2-$\underline{C}H_2$-C), 29.7 ($\underline{C}H_3$-CO-$\underline{C}H_3$), 0.7 ($\underline{C}H_3$-Si).

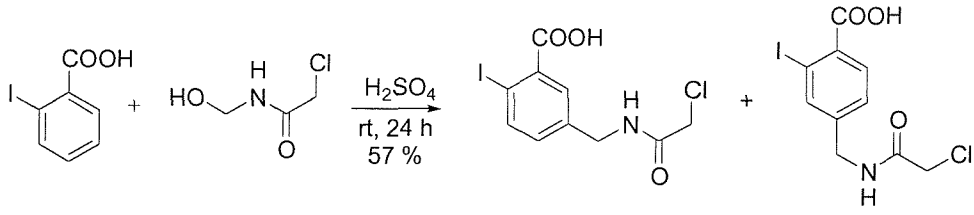
4.3 Experimental for Chapter 3

Standard procedure for testing the activity of the various IBX resin



To the resin in CH_2Cl_2 (1 mL for 100 mg), 2 to 3 equiv of 4-bromobenzaldehyde (estimated amount with a resin loading estimated as 1 $mmol \cdot g^{-1}$) were added. The mixture was stirred 15 h at rt, then filtered and washed with CH_2Cl_2. The solvent was evaporated under vacuum and the solid obtained analysed by ^1H NMR. The ratio between the aldehyde and the remaining alcohol gave the apparent loading of the resin.

Synthesis of 5-[(2-Chloroacetylamino)methyl]-2-iodobenzoic acid 3.37



3.30 **3.36** **3.37** **3.38**

2-Iodobenzoic acid **3.30** (32.00 g, 129.0 mmol) was dissolved in concentrated H_2SO_4 (200 mL). (Chloroacetylamino)methanol **3.36** (24.00 g, 194.2 mmol) was then added and stirring was continued 24 hours. The solution was then carefully poured into crushed ice (480 g) and the mixture was stirred 3 h (it could form a gum). The supernatant liquid was decanted and the solid residue was dissolved in a 10 % $NaHCO_3$ (aq) solution (640 mL). The clear solution was acidified with 37 % HCl until pH 3. The white precipitate was then filtered and

dried to give 44.69 g of a mixture of **3.37** and **3.38** (theoretical: 45.61 g). The crude product was then recrystallised from the minimum of 70 % ethanol to give the pure isomer **3.37** (25.98 g, 57 % yield).

Mp: 168-170 °C

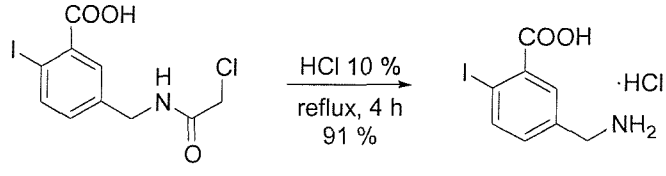
IR: (film) ν_{max} / (cm^{-1}): 3308 (s), 1702 (s) 1641 (s), 1543 (s), 1260 (s), 1014 (m).

^{1}H-NMR (400 MHz; CD_3OD) δ_H(ppm): 7.95 (1H, d, J = 8.0 Hz, ArH^3), 7.73 (1H, d, J = 2.0 Hz, ArH^6), 7.14 (1H, dd, J = 8.0 Hz, J = 2.5 Hz, ArH^4), 4.40 (2H, s, -N-CH_2-Ar), 4.10 (2H, s, CO-CH_2-Cl).

^{13}C-NMR+DEPT (100 MHz, CD_3OD) δ_C(ppm): 170.0 (COOH), 169.5 (CONH), 142.4 (ArC^5), 140.1 (ArC^1), 138.1 (ArC^3), 132.6 (ArC^4), 130.7 (ArC^6), 92.5 (ArC^2), 43.5 (CH_2), 43.1 (CH_2).

Results conform to those found previously in the laboratory, unpublished.

Synthesis of 5-Aminomethyl-2-iodobenzoic acid hydrochloride 3.39



3.37 **3.39**

5-[(2-Chloroacetylamino)methyl]-2-iodobenzoic acid **3.37** (25.98 g, 73.48 mmol) was placed in a 500 mL round bottom flask and HCl 10 % (250 mL) was added. The solution was heated at reflux for 4 h or until transparent, followed by cooling to 0 °C overnight and filtration. The white precipitate was then dried under vacuum and 20.92 g of the hydrochloride salt of **3.39** was obtained (91 %) as a white powder.

MP: over 250 °C (hydrochloride salt).

IR: (film) ν_{max} / (cm^{-1}): 3515 (m), 3360 (m), 2863 (br), 1697 (s), 1380 (s), 1237 (s), 1205 (s), 1013 (m).

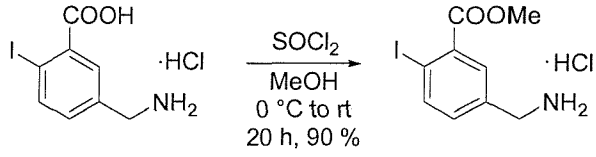
^{1}H-NMR (400 MHz, CD_3OD) δ_H(ppm): 8.09 (1H, d, J = 8.0 Hz, ArH^3), 7.91 (1H, d, J = 2.5 Hz, ArH^6), 7.31 (1H, dd, J = 8.0 Hz, J = 2.0 Hz, ArH^4), 4.14 (2H, s, -N-C$\underline{H}_2$-Ar).

^{13}C-NMR+DEPT (100 MHz, CD_3OD) δ_C(ppm): 169.4 (COOH), 143.2 (ArC^5), 138.8 (ArC^1), 134.7 (ArC^3), 133.8 (ArC^4), 132.1 (ArC^6), 95.1 (Ar$\underline{C}^2$), 43.4 ($\underline{C}H_2$).

MS (ES+): 260.9 (100 %) [M-NH_3], 278 (41 %) [M+H].

HRMS calcd for $C_8H_8INO_2$: 276.9600 found 276.9605.

Synthesis of 5-Aminomethyl-2-iodobenzoic acid methyl ester 3.40



3.39 **3.40**

To thionyl chloride (4.7 mL, 63.8 mmol) in dry MeOH (10 mL) at 0 °C under nitrogen, 5-aminomethyl-2-iodobenzoic acid hydrochloride **3.39** (2.01 g, 6.41 mmol) in dry MeOH (30 mL) was added dropwise via syringe. The solution was stirred for 1 h at 0 °C, and subsequently for 20 h at rt. The solution was then filtered and the white precipitate dried. The filtrate was concentrated under vacuum to half-volume, and the resulting precipitate was filtered and combined with the previous solid. After drying, 1.60 g of **3.40** was obtained as a white solid (90 %).

MP: over 250 °C

IR: (film) ν_{max} / (cm^{-1}): 3002 (br), 1729 (s), 1013 (s).

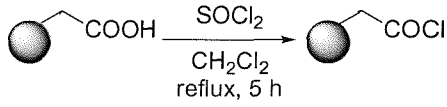
^{1}H-NMR (300 MHz, DMSO) δ_H(ppm): 8.57 (3H, s, $^+NH_3$), 8.05 (1H, d, J = 8.1 Hz, ArH^3), 7.85 (1H, d, J = 1.5 Hz, ArH^6), 7.42 (1H, dd, J = 8.1 Hz, J = 2.2 Hz, ArH^4), 4.02 (2H, s, -N-C$\underline{H_2}$-Ar), 3.86 (3H, s, O-Me).

^{13}C-NMR+DEPT (75 MHz, DMSO) δ_C(ppm): 166.9 (COOH), 140.8 (ArC^5), 135.9 (ArC^1), 134.5 (ArC^3), 133.6 (ArC^4), 130.9 (ArC^6), 94.4 (ArC^2), 52.7 (CH_3), 41.2 (CH_2).

MS (Es+): 275.0 (100 %) [(M-HCl)-NH_3]; 292.0 (21 %) [(M-HCl)+H].

HRMS calcd for $C_9H_{10}INO_2$: 290.9756 found 290.9747.

Synthesis of acyl chloride resin 3.42.

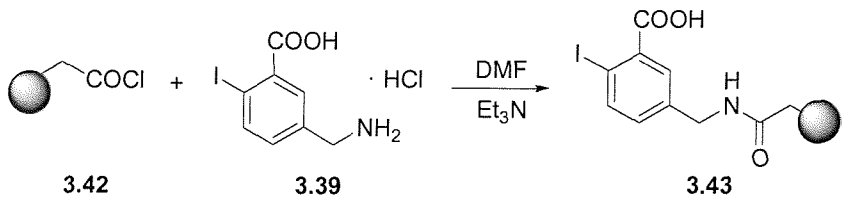


3.41 **3.42**

To amberlite IRC-50, carboxylic acid resin **3.41** (1.0 g) in dry CH_2Cl_2 (3 mL) was added thionyl chloride (4 mL, 54.8 mmol). The mixture was stirred at reflux for 5 hours. The resin was then washed with dry CH_2Cl_2 (3×5 mL) and dried in the vacuum oven (40 °C).

IR (cm^{-1}): 1800 (m); 1700 (br), 1169 (s).

Synthesis of polymer-supported iodo benzoic acid 3.43 (macroporous resin)

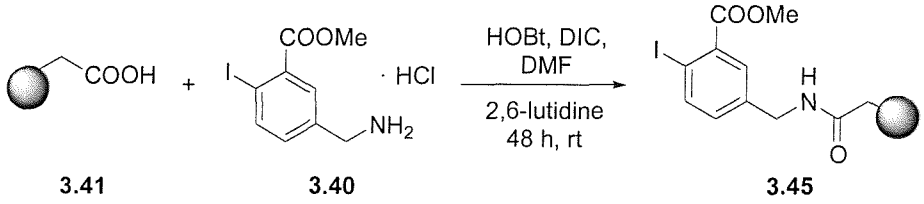


3.42 3.39 3.43

To 305 mg of acyl chloride resin **3.42** in 5 mL of dry DMF, 849 mg of 5-aminomethyl-2-iodo-benzoic acid **3.39** (8.95 mmol) and 1.64 mL of triethylamine were added. The mixture was stirred at rt 24 h. The resin was then washed with CH_2Cl_2 (3×5 mL), THF (3×5 mL), HCl 1N (3×5 mL), water (3×5mL), THF (3×5 mL) and CH_2Cl_2 (3×5 mL) and dried under vacuum (40 °C). The filtration might be very difficult for the first wash.

IR (cm^{-1}): 3300 (br), 1689 (s), 1636 (w), 1160 (s), 1014 (m).

Synthesis of polymer-supported 5-aminomethyl-2-iodo-benzoic acid methyl ester 3.45 (macroporous resin)



3.41 3.40 3.45

With Amberlite IRC-50:

To wet Amberlite IRC-50 resin **3.41** (205.5 mg, loading 10 $mmol \cdot g^{-1}$ dry) in 5 mL of DMF, DIC (0.80 mL, 5.13 mmol), HOBt (693 mg, 5.13 mmol) and 2,6-lutidine (1.8 mL, 15.45 mmol) were added. After stirring 15 min., **3.40** (1.697 g, 5.18 mmol) in 35 mL of DMF was

added. The flask was placed on a shaker for 48 h at rt. The resin was then washed with DMF (3×5 mL), THF (3×5 mL), MeOH (3×5 mL), CH_2Cl_2 (3×5 mL) and dry under vacuum (40 °C). 276 mg of resin **3.45** was obtained.

IR (cm^{-1}): 1800 (m); 1755 (br), 1724 (br), 1664 (br), 1513 (m)

Iodine elemental analysis: 1.81 $mmol \cdot g^{-1}$ (theoretical maximum loading: 2.34 $mmol \cdot g^{-1}$).

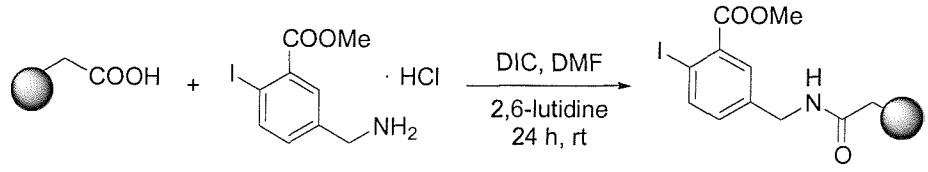
With Amberlite IRC-86:

To wet Amberlite IRC-86 resin **3.41** (764.4 mg, loading 4.37 $mmol \cdot g^{-1}$ dry) in 5 mL of DMF, DIC (1.05 mL, 6.71 mmol), HOBt (911 mg, 6.74 mmol) and 2,6-lutidine (2.34 mL, 20.09 mmol) were added. After stirring 15 min., **3.40** (2.192 g, 6.69 mmol) in 40 mL of DMF was added. The flask was placed on a shaker for 48 h days at rt. The resin was then washed with DMF (3×5 mL), THF (3×5 mL), MeOH (3×5 mL), CH_2Cl_2 (3×5 mL) and dry under vacuum (40 °C). 877 mg of resin **3.45** was obtained.

IR (cm^{-1}): 1725 (m), 1654 (br), 1526 (m)

Iodine elemental analysis: 1.14 $mmol \cdot g^{-1}$ (theoretical maximum loading: 1.79 $mmol \cdot g^{-1}$).

Synthesis of polymer-supported 5-aminomethyl-2-iodobenzoic acid methyl ester 3.47



3.46 **3.40** **3.47**

To a carboxylic acid resin **3.46** (309 mg, 0.65 mmol, loading 2.1 $mmol \cdot g^{-1}$) in dry DMF (2 mL), 2,6-lutidine (0.22 mL, 1.88 mmol) and diisopropylcarbodiimide (0.15 mL, 0.96 mmol)

were added. After stirring 15 minutes, **3.40** (424 mg, 1.29 mmol) in dry DMF (6 mL) was added. The flask was placed on a shaker for 24 h at rt. The resin was then washed with DMF (3×2 mL), THF (3×2 mL), MeOH (3×2 mL), CH_2Cl_2 (3×2 mL) and dried under vacuum (40 °C). 397 mg of resin **3.47** was obtained.

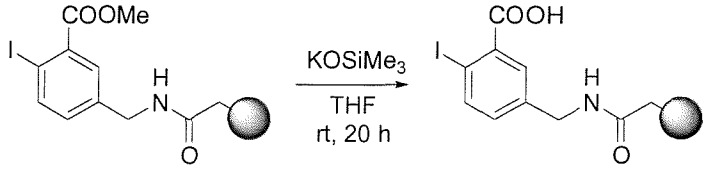
IR (cm^{-1}): 1703 (m), 1641 (s), 1015 (m).

Elemental analysis:

With 2.1 $mmol \cdot g^{-1}$ carboxypolystyrene resin: iodide loading = 1.10 $mmol \cdot g^{-1}$ [1.33 $mmol \cdot g^{-1}$].

With 1.4 $mmol \cdot g^{-1}$ carboxypolystyrene resin: iodide loading = 0.65 $mmol \cdot g^{-1}$ [1.01 $mmol \cdot g^{-1}$].

Synthesis of polymer-bound 5-aminomethyl-2-iodobenzoic acid 3.48

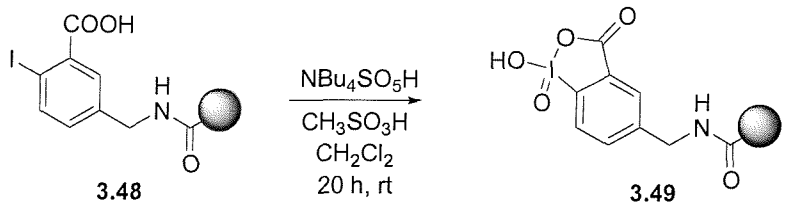


3.47 **3.48**

To **3.47** (97 mg) a solution of potassium trimethylsilanolate (465 mg, 3.62 mmol) in dry THF (3 mL) was added. The flask was shaken at rt for 20 h then the resin was washed with THF (3×1 mL), MeOH (3×1 mL), CH_2Cl_2 (3×1 mL), Et_2O (3×1 mL). Then 4 mL of THF and 1 mL of acetic acid were added and the resin was shaken 16 h and washed with THF (3×1 mL), CH_2Cl_2 (3×1 mL) Et_2O (3×1 mL) and dried under vacuum (40 °C).

IR (cm^{-1}): 3336 (br), 1640 (s), 1601 (s), 1376 (s), 1013 (m).

Synthesis of solid supported IBX 3.49

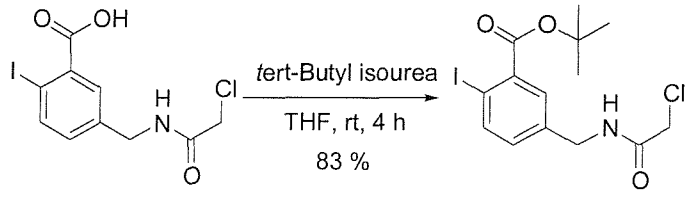


3.48 3.49

To the resin **3.48** was added tetrabutylammonium oxone (458 mg, 1.29 mmol), methanesulfonic acid (0.1 mL, 1.54) and CH_2Cl_2 (2 mL). The mixture was shaken 20 h at rt then the resin was washed with CH_2Cl_2 (5×2 mL) and Et_2O (5×2 mL). It could be dried under vacuum (40 °C) or used immediately for oxidation.

IR (cm^{-1}): 3300 (br), 1644 (br), 1608 (m), 1177 (br), 1031 (br).

Synthesis of 5-[(2-chloro-acetylamino)-methyl]-2-iodo-benzoic acid tert-butyl ester 3.56



3.37 3.56

5-[(2-Chloro-acetylamino)-methyl]-2-iodo-benzoic acid **3.37** (356.1 mg, 1.01 mmol) was placed in 3.5 ml of THF and *O-tert*-butyl-*N,N'*-diisopropylisourea (919 mg, 4.58 mmol) was added. The solution was stirred at rt for 4 h. The mixture was filtered to remove the urea formed and then purified by column chromatography (Hexane/AcOEt, 50/50) to yield 342.8 mg of **3.56** as a white solid (83 %).

MP: 63-65 °C (after recristallisation in CH_2Cl_2).

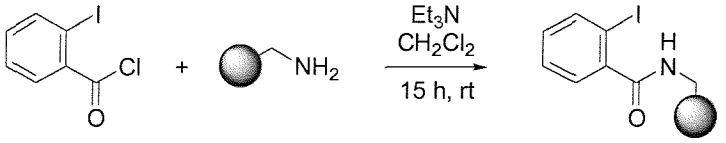
IR: (film) ν_{max} / (cm^{-1}): 3273 (m) NH, 1713 (s) ester, 1648 (s) amide, 1572 (m) amide, 1014 (m) iodine.

^{1}H-NMR (300 MHz; DMSO) δ_H(ppm): 8.81 (1H, t, J = 5.9 Hz, NH); 7.89 (1H, d, J = 8.1 Hz, ArH^3); 7.47 (1H, d, J = 2.2 Hz, ArH^6); 7.12 (1H, dd, J = 8.1 Hz, J = 2.2 Hz, ArH^4); 4.28 (2H, d, J = 5.9 Hz, -N-CH_2-Ar); 4.12 (2H, s, CH_2Cl); 1.56 (9H, s, ^{t}Bu).

^{13}C-NMR+DEPT (75 MHz, DMSO) δ_C(ppm): 164.9 (COOH), 164.7 (CONH), 138.8 (ArC^5), 138.1 (ArC^1), 136.6 (ArC^3), 129.8 (ArC^4), 127.1 (ArC^6), 89.9 (ArC^2),80.9 (C-$(CH_3)_3$), 41.2 (Cl-CH_2), 40.3 (N-CH_2), 26.3 (C-$(CH_3)_3$).

MS (Es+): 431.8 (100%) [M+Na]; 353.6 (35%) [M+H-^{t}Bu].

Synthesis of the polymer supported 2-iodo-*N*-methyl-benzamide 3.61

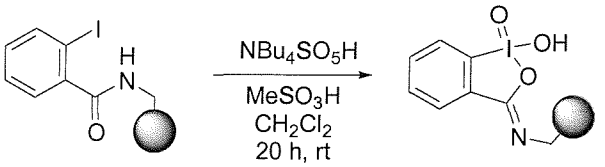


3.59 **3.60** **3.61**

To aminomethyl resin **3.60** (1.01 g, 2.73 mmol) in CH_2Cl_2 (10 mL) and Et_3N (0.49 mL, 3.5 mmol), 2-iodobenzoyl chloride **3.59** (1.09 g, 4.10 mmol) in CH_2Cl_2 (5 mL) was added. The mixture was stirred 15 h at rt then filtered and washed with CH_2Cl_2 (5×5 mL). 1.71 g of resin **3.61** was obtained after drying in vacuum oven (40 °C).

IR (cm^{-1}): 3290 (w), 1650 (br), 1511 (s), 1016 (m).

Synthesis of the polymer supported amide IBX 3.62

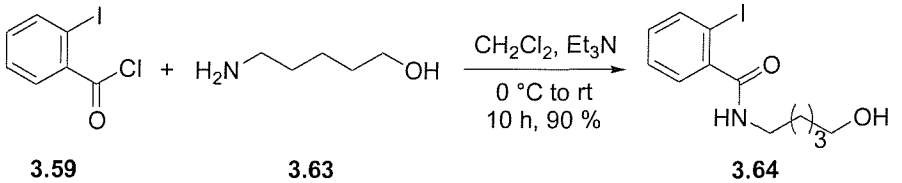


3.61 **3.62**

To resin **3.61** (147 mg) in CH_2Cl_2 (1 mL), tetrabutylammonium oxone (1.02 g, 2.87 mmol) and methanesulfonic acid (0.2 mL, 3.08 mmol) were added. The mixture was stirred for 20 h at rt then filtered and washed with CH_2Cl_2/DMF (50:50) (2×2 mL), CH_2Cl_2 (2×2 mL), CH_2Cl_2/Et_2O (50:50) (2×2 mL), Et_2O (2×2 mL), CH_2Cl_2 (2×2 mL), CH_2Cl_2/Et_2O (50:50) (2×2 mL), Et_2O (2×2 mL). 163 mg of **3.62** was obtained after drying in vacuum oven (40 °C).

IR (cm^{-1}): 3245 (br), 1612 (s), 1154 (s), 1030 (s).

Synthesis of the *N*-(5-hydroxy-pentyl)-2-iodo-benzamide 3.64



3.59 **3.63** **3.64**

To a solution of 5-amino-1-pentanol **3.63** (4.1 mL, 37.6 mmol) and Et_3N (8 mL, 56.9 mmol) in CH_2Cl_2 (100 mL) at 0 °C, a solution of CH_2Cl_2 (40 mL) containing 2-iodobenzoyl chloride **3.59** (10.10 g, 37.9 mmol) was added dropwise over 30 min via cannula. The mixture was stirred 1 h at 0 °C then allowed to reach rt and stirred for 10 h. The solution was cooled in a fridge and the white precipitate was filtered then dried to yield 8.99 g of

3.64 as a white solid. The filtrate was evaporated and the obtained solid was recrystallised in ethanol, giving 2.81 g of **3.64** as a white solid which was combined with the first solid giving a yield of 90 %.

MP: 110-114 °C.

IR: (film) ν_{max} / (cm^{-1}): 3241 (br), 1621 (s), 1048 (s).

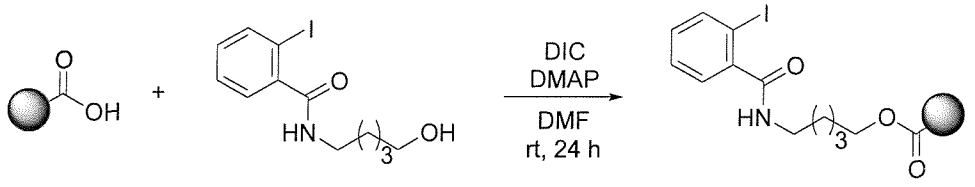
^{1}H-NMR (300 MHz, DMSO) δ_H(ppm): 8.29 (1H, t, J = 6.6 Hz, NH), 7.86 (1H, dd, J = 7.7 Hz, J = 0.7 Hz, ArH^3), 7.42 (1H, td, J = 6.6 Hz, J = 0.9 Hz, ArH^5), 7.23 (1H, dd, J = 7.5 Hz, J = 1.8 Hz, ArH^6), 7.15 (1H, td, J = 7.5 Hz, J = 1.8 Hz, ArH^4), 4.33 (1H, t, J = 5.4 Hz, OH), 3.40 (2H, q, J = 6 Hz, CH_2-O), 3.19 (2H, q, J = 6.6 Hz, CH_2-N), 1.54-1.33 (6H, m, $C\underline{H}_2$-$C\underline{H}_2$-$C\underline{H}_2$-CH_2-O).

^{13}C-NMR+DEPT (75 MHz, DMSO) δ_C(ppm): 168.7 (C=O), 143.4 (ArC^1), 138.9 (ArC^3), 130.5 (ArC^4), 127.9 (ArC^6), 127.8 (ArC^5), 93.4 (ArC^2), 60.6 (CH_2-O), 38.9 (CH_2-N), 32.2 ($\underline{C}H_2$-CH_2-O), 28.7 ($\underline{C}H_2$-CH_2-N), 22.9 ($\underline{C}H_2$-CH_2-CH_2-O).

MS (ES+): 688.9 (100 %) [$(2M+Na)^+$], 356.1 (25 %) [$(M+Na)^+$], 397.1 (20 %) [$(M+Na+CH_3CN)^+$], 334.1 (5 %) [$(M+H)^+$], 1021.7 (3 %) [$(3M+Na)^+$].

HRMS calcd for $C_{12}H_{16}INO_2$: 333.0226 found 333.0215.

Synthesis of the polymer supported ester bound precursor of amide IBX 3.65

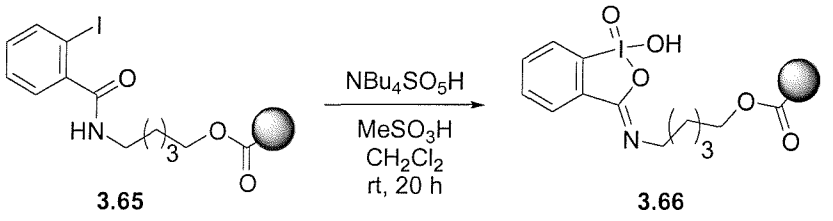


3.46 **3.64** **3.65**

To a carboxylic acid resin **3.46** (2.06 g, 2.89 mmol, loading 1.4 mmol g^{-1}) in DMF (20 mL), **3.64** (1.80 g, 5.4 mmol), DIC (0.9 mL, 5.8 mmol) and DMAP (35 mg, 0.29 mmol) were added. The mixture was stirred for 24 h at rt then filtered and washed with DMF (3×5 mL), MeOH (3×5 mL), DMF (3×5 mL), CH_2Cl_2 (3×5 mL) and Et_2O (3×5 mL). 2.75 g of resin **3.65** was obtained after drying in vacuum oven (40 °C).

IR (cm^{-1}): 3295 (w), 1703 (w), 1648 (s), 1273 (s), 1017 (m).

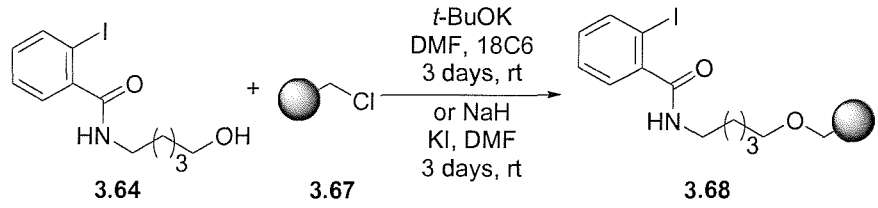
Synthesis of the polymer supported ester bound amide IBX 3.66



To resin **3.65** (1.52 g) in of CH_2Cl_2 (10 mL), tetrabutylammonium oxone (6.31 g, 17.7 mmol) and methanesulfonic acid (1.16 mL, 17.8 mmol) were added. The mixture was stirred for 20 h at rt then filtered and washed with CH_2Cl_2/DMF (50:50) (2×2 mL), CH_2Cl_2 (2×2 mL), CH_2Cl_2/Et_2O (50:50) (2×2 mL), Et_2O (2×2 mL), CH_2Cl_2 (2×2 mL), CH_2Cl_2/Et_2O (50:50) (2×2 mL), Et_2O (2×2 mL). 1.72 g of the resin **3.66** was obtained after drying in vacuum oven (40 °C).

IR (cm^{-1}): 3231 (w), 1708 (m), 1619 (s), 1038 (m).

Synthesis of the polymer supported ether bound precursor of amide IBX 3.68



3.64 **3.67** **3.68**

Procedure using *t*BuOK:

To **3.64** (1.40 g, 4.2 mmol) in dry DMF (15 mL), 18-crown-6 (125 mg, 0.47 mmol) and potassium *tert*-butoxide (1 M in *tert*-butanol) (4.2 mL, 4.2 mmol) were added. The mixture was stirred 3 h at rt then added to the Merrifield resin **3.67** (1.44 g, 1.9 mmol, loading 1.3 $mmol \cdot g^{-1}$) pre-swollen in dry DMF (10 mL). The mixture was stirred 3 days at rt, then filtered and washed with DMF (3×5 mL), MeOH (3×5 mL), DMF (3×5 mL), CH_2Cl_2 (3×5 mL), and Et_2O (3×5 mL). 1.60 g of resin **3.68** was obtained after drying in vacuum oven (40 °C).

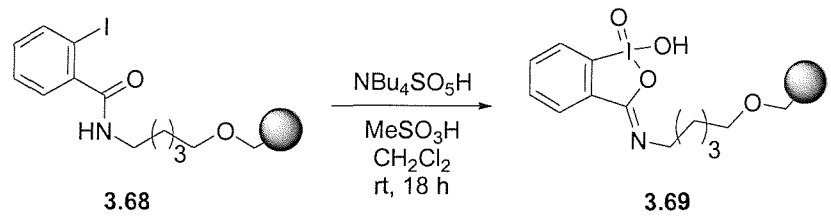
IR (cm^{-1}): 1641 (m), 1028 (w).

Procedure using NaH:

To the Merrifield resin **3.67** (4.28 g, 5.56 mmol, loading 1.3 $mmol \cdot g^{-1}$) in of dry DMF (50 mL), **3.64** (5.55 g, 16.65 mmol), NaH (60 % suspension in oil, 1.33 g, 33.25 mmol) and potassium iodide (111 mg, 0.67 mmol) were added. The mixture was stirred 3 days at rt, then filtered and washed with DMF (3×30 mL), MeOH (3×30 mL), DMF (3×30 mL), CH_2Cl_2 (3×30 mL), and Et_2O (3×30 mL). 5.714 g of resin **3.68** were obtained after drying in vacuum oven (40 °C).

IR (cm^{-1}): 1638 (m), 1018 (w).

Synthesis of the polymer supported ether bound amide IBX 3.69

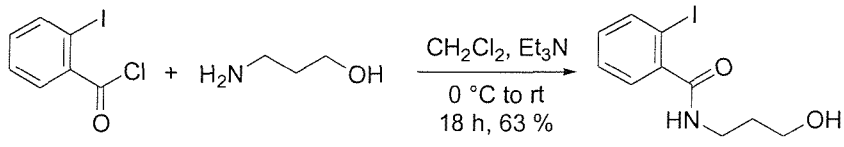


3.68 **3.69**

To 5.52 g of resin **3.68** in CH_2Cl_2 (55 mL), tetrabutylammonium oxone (8.87 g, 25.0 mmol) and methanesulfonic acid (1.62 mL, 25.0 mmol) were added. The mixture was stirred for 18 h at rt then filtered and washed with CH_2Cl_2 (2×30 mL), CH_2Cl_2/acetic acid (90:10) (30 mL), CH_2Cl_2 (2×30 mL), CH_2Cl_2/Et_2O (50:50) (30 mL), Et_2O (30 mL). The washing procedure was repeated once and 5.83 g of the resin **3.69** was obtained after drying under vacuum at rt. The resin was kept in a fridge to prevent a loss of loading.

IR (cm^{-1}): 1723 (w), 1600 (m), 1028 (m).

Synthesis of *N*-(3-hydroxy-propyl)-2-iodo-benzamide 3.105



3.59 **3.104** **3.105**

To 3-amino-1-propanol **3.104** (1.18 mL, 15.5 mmol) and Et_3N (3.24 mL, 23.2 mmol) in CH_2Cl_2 (37 mL) at 0 °C, a solution of CH_2Cl_2 (8 mL) containing 2-iodobenzoyl chloride **3.59** (4.13 g, 15.5 mmol) was added dropwise over 30 minutes via cannula. The mixture was stirred 1 h at 0 °C then allowed to reach rt and stirred for 18 h. After acid/base work-up,

the solvent was evaporated under reduced pressure. The oil obtained was purified by column chromatography (100 % ethyl acetate) to yield 2.97 g of **3.105** as a syrup (63 %).

IR: (film) ν_{max} / (cm^{-1}): 3276 (br), 1630 (s), 1014 (s).

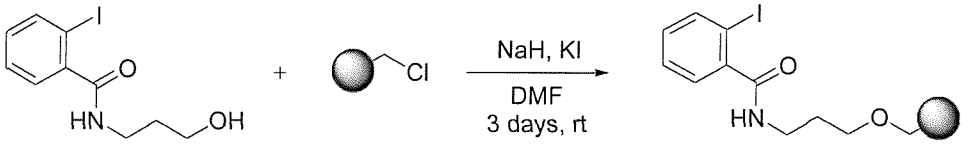
^{1}H-NMR (300 MHz, DMSO) δ_H(ppm): 8.29 (1H, t, J = 5.2 Hz, NH), 7.86 (1H, dd, J = 7.9 Hz, J = 0.8 Hz, ArH^3), 7.42 (1H, td, J = 7.5 Hz, J = 1.0 Hz, ArH^5), 7.29 (1H, dd, J = 7.6 Hz, J = 1.6 Hz, ArH^6), 7.15 (1H, td, J = 7.7 Hz, J = 1.7 Hz, ArH^4), 4.42 (1H, t, J = 5.2 Hz, OH), 4.50 (2H, q, J = 6.3 Hz, CH_2-O), 3.26 (2H, q, J = 6.6 Hz, CH_2-N), 1.68 (2H, m, $C\underline{H}_2$-CH_2-O).

^{13}C-NMR+DEPT (75 MHz, DMSO) δ_C(ppm): 168.8 (C=O), 143.3 (ArC^1), 139.0 (ArC^3), 130.5 (ArC^4), 127.9 (ArC^6), 127.8 (ArC^5), 93.4 (ArC^2), 58.6 (CH_2-O), 36.3 (CH_2-N), 32.2 ($\underline{C}H_2$-CH_2-O).

MS (ES+): 305.9 (100 %) [$(M+H)^+$], 327.9 (90 %) [$(M+Na)^+$], 632.9 (55 %) [$(2M+Na)^+$].

Data conform to literature.[134]

Synthesis of polymer supported ether bound precursor of amide IBX 3.106



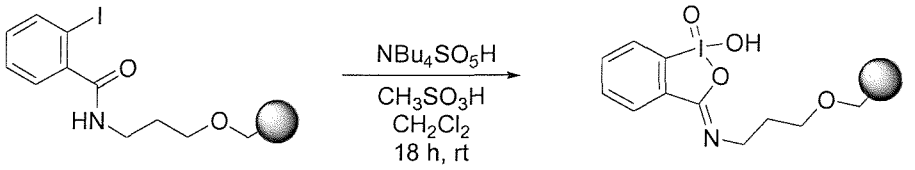
3.99 **3.61** **3.100**

To the Merrifield resin **3.67** (1.02 g, 1.32 mmol, loading 1.3 mmol·g^{-1}) in dry DMF (10 mL), **3.105** (1.22 g, 1.58 mmol), NaH (60 % suspension in oil, 325 mg, 8.12 mmol) and potassium iodide (20.5 mg, 0.12 mmol) were added. The mixture was stirred 3 days at rt then filtered and washed with DMF (3×5 mL), MeOH (3×5 mL), DMF (3×5 mL), CH_2Cl_2

(3×5 mL), and Et_2O (3×5 mL). 1.083 g of resin **3.106** was obtained after drying in vacuum oven (40 °C).

IR (cm^{-1}): 1629 (m), 1017 (w).

Synthesis of polymer supported ether bound amide IBX 3.107

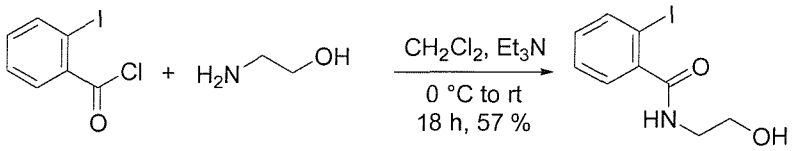


3.106 **3.107**

To 0.823 g of resin **3.106** in CH_2Cl_2 (8.2 mL), tetrabutylammonium oxone (1.695 g, 4.8 mmol) and methanesulfonic acid (0.31 mL, 4.8 mmol) were added. The mixture was stirred for 18 h at rt then filtered and washed with CH_2Cl_2 (2×10 mL), CH_2Cl_2/acetic acid (90:10) (10 mL), CH_2Cl_2 (2×10 mL), CH_2Cl_2/Et_2O (50:50) (10 mL), Et_2O (10 mL), repeated once. 0.886 g of the resin **3.107** was obtained after drying under vacuum at rt. The resin was kept in a fridge to prevent a loss of loading.

IR (cm^{-1}): 1723 (w), 1600 (m), 1028 (m), 755 (s).

Synthesis of *N*-(2-hydroxy-ethyl)-2-iodo-benzamide 3.109



3.59 **3.108** **3.109**

To 2-amino-1-ethanol **3.108** (0.5 mL, 8.3 mmol) and Et_3N (1.73 mL, 12.4 mmol) in CH_2Cl_2 (20 mL) at 0 °C, a solution of CH_2Cl_2 (5 mL) containing 2-iodobenzoyl chloride **3.59** (2.0 g, 7.5 mmol) was added dropwise over 30 minutes via cannula. The mixture was stirred 1 h at 0 °C then allowed to reach rt and stirred for 18 h. After acid/base work-up, the solvent was evaporated under reduced pressure. The oil obtained was purified by column chromatography (100 % ethyl acetate) to yield 1.25 g of **3.109** as a colourless oil (57 %).

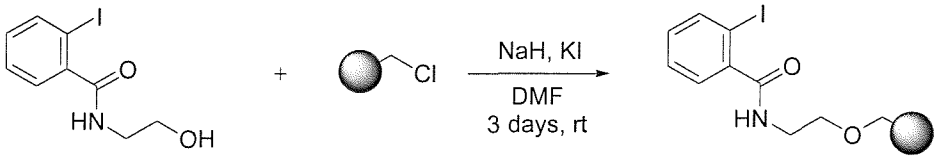
IR: (film) ν_{max} / (cm^{-1}): 3265 (br), 1635 (s), 1034 (s).

^{1}H-NMR (300 MHz, DMSO) δ_H(ppm): 8.29 (1H, t, J = 5.2 Hz, NH), 7.86 (1H, dd, J = 7.7 Hz, J = 0.9 Hz, ArH^3), 7.42 (1H, td, J = 7.5 Hz, J = 1.0 Hz, ArH^5), 7.27 (1H, dd, J = 7.6 Hz, J = 1.7 Hz, ArH^6), 7.15 (1H, td, J = 7.7 Hz, J = 1.8 Hz, ArH^4), 4.51 (1H, t, J = 5.2 Hz, OH), 4.30 (2H, q, J = 6.3 Hz, CH_2-O), 3.28 (2H, q, J = 6.6 Hz, CH_2-N).

^{13}C-NMR+DEPT (75 MHz, DMSO) δ_C(ppm): 168.8 (C=O), 143.3 (ArC^1), 139.0 (ArC^3), 130.5 (ArC^4), 127.9 (ArC^6), 127.8 (ArC^5), 93.4 (ArC^2), 58.6 (CH_2-O), 36.3 (CH_2-N), 32.2 ($\underline{C}H_2$-CH_2-O).

MS (ES+): 291.9 (100 %) [$(M+H)^+$], 323.9 (80 %) [$(M+Na)^+$], 604.9 (35 %) [$(2M+Na)^+$].

Synthesis of polymer supported ether bound precursor of amide IBX 3.110



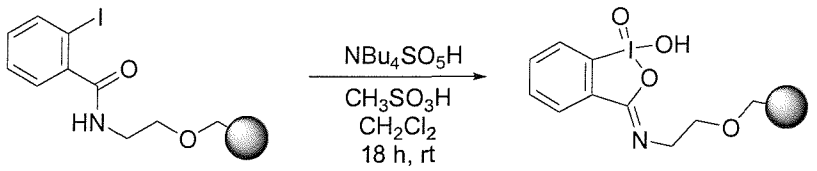
3.109 **3.67** **3.110**

To the Merrifield resin **3.67** (1.37 g, 1.92 mmol, loading 1.4 mmol·g^{-1}) in dry DMF (11 mL), **3.109** (1.11 g, 3.81 mmol), NaH (60 % suspension in oil, 320 mg, 8.0 mmol) and

potassium iodide (70.0 mg, 0.42 mmol) were added. The mixture was stirred 3 days at rt then filtered and washed with DMF (3×5 mL), MeOH (3×5 mL), DMF (3×5 mL), CH_2Cl_2 (3×5 mL), and Et_2O (3×5 mL). 1.67 g of resin **3.110** was obtained after drying in vacuum oven (40 °C).

IR (cm^{-1}): 1635 (m), 1013 (w).

Synthesis of polymer supported ester bound amide IBX 3.111

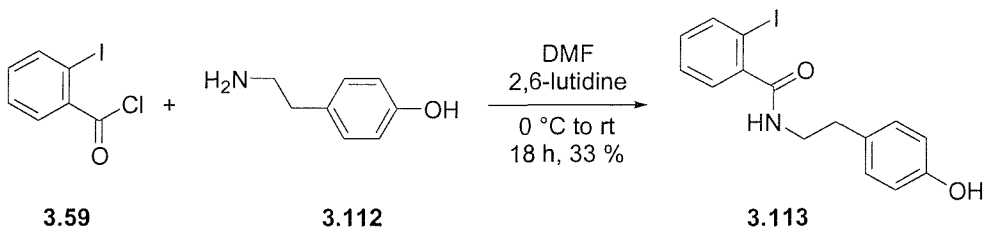


3.110 **3.111**

To 1.293 g of resin **3.110** in CH_2Cl_2 (10.0 mL), tetrabutylammonium oxone (2.417 g, 7.2 mmol) and methanesulfonic acid (0.46 mL, 7.2 mmol) were added. The mixture was stirred for 18 h at rt then filtered and washed with CH_2Cl_2 (2×10 mL), CH_2Cl_2/acetic acid (90:10) (10 mL), CH_2Cl_2 (2×10 mL), CH_2Cl_2/Et_2O (50:50) (10 mL), Et_2O (10 mL), repeated once. 1.374 g of the resin **3.111** was obtained after drying under vacuum at rt. The resin was kept in a fridge to prevent a loss of loading.

IR (cm^{-1}): 1710 (w), 1605 (m), 1025 (m).

Synthesis of *N*-[2-(4-hydroxy-phenyl)-ethyl]-2-iodobenzamide 3.113



3.59 **3.112** **3.113**

To tyramine **3.112** (2.01 g, 14.7 mmol) and 2,6-lutidine (2.56 mL, 22.0 mmol) in DMF (40 mL) at 0 °C, a solution of DMF (10 mL) containing 2-iodobenzoyl chloride **3.59** (4.69 g, 17.6 mmol) was added dropwise over 30 minutes via cannula. The mixture was stirred 1 h at 0 °C then allowed to reach rt and stirred for 18 h. After acid/base work-up, the solvent was evaporated under reduced pressure. The oil obtained was purified by column chromatography (100 % ethyl acetate) to yield 1.76 g of **3.113** as a colourless oil (57 %).

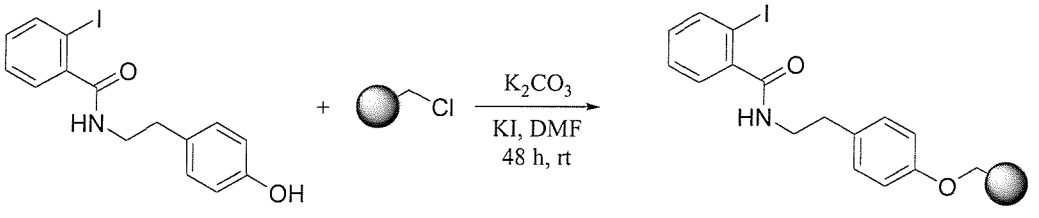
IR: (film) ν_{max} / (cm^{-1}): 3272 (br), 1625 (s), 1024 (s).

^{1}H-NMR (300 MHz, DMSO) δ_H(ppm): 8.29 (1H, t, J = 5.2 Hz, NH), 7.86 (1H, dd, J = 7.9 Hz, J = 0.8 Hz, ArH^3), 7.42 (1H, td, J = 7.5 Hz, J = 0.8 Hz, ArH^5), 7.24 (1H, dd, J = 7.5 Hz, J = 1.5 Hz, ArH^6), 7.15 (1H, td, J = 7.9 Hz, J = 1.9 Hz, ArH^4), 7.05 (2H, d, J = 8.3 Hz, Ar-OH), 6.69 (2H, d, J = 8.6 Hz, Ar-OH), 3.42-3.29 (2H, m, $C\underline{H}_2$-N) 2.73 (2H, t, J = 6.4 Hz, Ar-$C\underline{H}_2$).

^{13}C-NMR+DEPT (75 MHz, DMSO) δ_C(ppm): 168.7 (C=O), 153.6 ($\underline{C}$-OH), 143.3 (ArC^1), 139.0 (ArC^3),134.5 ($\underline{C}$-CH2-CH2-N) 130.4 (ArC^4), 129.1 ($\underline{C}$H-C(CH_2)-$\underline{C}$H), 127.9 (ArC^6), 127.8 (ArC^5),115.3 ($\underline{C}$H-C(OH)-$\underline{C}$H), 93.4 (ArC^2), 42.5 (CH_2-N), 35.3 (C-$\underline{C}$H2-CH2-N).

MS (ES-): 365.9 (100 %) [$(M-H)^-$], 732.9 (45 %) [$(2M-H)^-$].

Synthesis of tyramine-linked supported 2-iodobenzamide 3.114

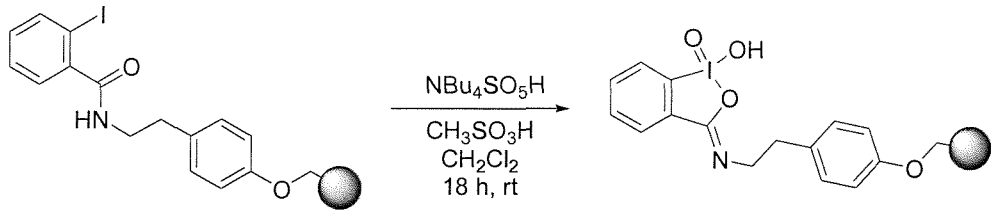


3.113 **3.67** **3.114**

To the Merrifield resin **3.67** (3.85 g, 5.39 mmol, loading 1.4 $mmol \cdot g^{-1}$) in dry DMF (40 mL), **3.113** (3.95 g, 12.9 mmol), K_2CO_3 anhydrous (7.50 g, 54.3 mmol) and potassium iodide (90.0 mg, 0.54 mmol) were added. The mixture was stirred 48 h at rt then filtered and washed with DMF (3×5 mL), MeOH (3×5 mL), DMF (3×5 mL), CH_2Cl_2 (3×5 mL), and Et_2O (3×5 mL). 5.52 g of resin **3.114** was obtained after drying in vacuum oven (40 °C).

IR (cm^{-1}): 1665 (m), 1017 (w).

Synthesis of tyramine linked IBX amide resin 3.115



3.114 **3.115**

To 1.27 g of resin **3.114** in CH_2Cl_2 (14.0 mL), tetrabutylammonium oxone (2.25 g, 6.32 mmol) and methanesulfonic acid (0.41 mL, 6.35 mmol) were added. The mixture was stirred for 18 h at rt then filtered and washed with CH_2Cl_2 (2×10 mL), CH_2Cl_2/acetic acid (90:10) (10 mL), CH_2Cl_2 (2×10 mL), CH_2Cl_2/Et_2O (50:50) (10 mL), Et_2O (10 mL), repeated once. 1.32 g of the resin **3.115** was obtained after drying under vacuum at rt.

IR (cm^{-1}): 1724 (w), 1606 (m), 1175 (m), 1030 (m).

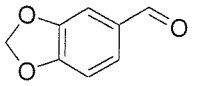
Standard procedure for the oxidation of alcohols

To 1.2 equiv of IBX resin in CH_2Cl_2 (1 mL for 100 mg), 1 equiv of alcohol was added. The mixture was stirred until complete conversion of the alcohol to the corresponding carbonyl compound (followed by TLC) or for a maximum of 18 h then filtered. The resin was

washed twice with CH_2Cl_2 and the filtrate was concentrated under reduced pressure then analysed by NMR.

All the NMR spectra of the reported aldehydes and ketones were conform to the commercially available products NMR found on the Sigma-Aldrich website.

Benzo[1,3]dioxole-5-carbaldehyde 3.71

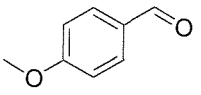


^{1}H-NMR (300 MHz, $CDCl_3$) δ_H(ppm): 9.81 (1H, s), 7.41 (1H, dd, J = 7.9 Hz, J = 1.6 Hz), 7.33 (1H, d, J = 1.6 Hz), 6.93 (1H, d, J = 7.9 Hz), 6.07 (2H, s).

^{13}C-NMR+DEPT (75 MHz, $CDCl_3$) δ_C(ppm): 190.4, 153.3, 148.9, 132.1, 128.8, 108.5, 107.1, 102.2.

Data conform to literature.[137]

4-Methoxybenzaldehyde 3.73

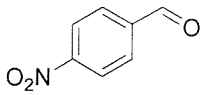


^{1}H-NMR (300 MHz, $CDCl_3$) δ_H(ppm): 9.89 (1H, s), 7.84 (2H, d, J = 8.7 Hz), 7.01 (2H, d, J = 8.7 Hz), 3.89 (3H, s).

^{13}C-NMR+DEPT (75 MHz, $CDCl_3$) δ_C(ppm): 190.9, 164.8, 132.1, 130.2, 114.5, 55.7.

Data conform to literature.[138]

4-Nitrobenzaldehyde 3.75

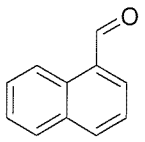


^{1}H-NMR (300 MHz, $CDCl_3$) δ_H(ppm): 10.16 (1H, s), 8.40 (2H, d, J = 8.6 Hz), 8.08 (2H, d, J = 8.6 Hz).

^{13}C-NMR+DEPT (75 MHz, $CDCl_3$) δ_C(ppm): 190.2, 140.1, 130.5, 124.3.

Data conform to literature.[137]

Naphthaline-1-carbaldehyde 3.77

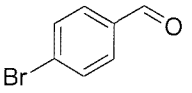


^{1}H-NMR (300 MHz, $CDCl_3$) δ_H(ppm): 10.41 (1H, s), 9.26 (1H, d, J = 8.7 Hz), 8.10 (1H, d, J = 8.6 Hz), 8.00 (1H, dd, J = 6.8 Hz, J = 1.5 Hz), 7.93 (1H, d, J = 8.3 Hz), 7.73-7.57 (3H, m).

^{13}C-NMR+DEPT (75 MHz, $CDCl_3$) δ_C(ppm): 193.6, 136.7, 135.4, 133.9, 131.6, 130.7, 129.2, 128.6, 127.1, 125.0.

Data conform to literature.

4-Bromobenzaldehyde 3.79

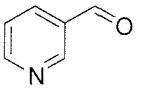


^{1}H-NMR (300 MHz, $CDCl_3$) δ_H(ppm): 9.98 (1H, s), 7.75 (2H, d, J = 8.5 Hz), 7.69 (2H, d, J = 8.5 Hz).

^{13}C-NMR+DEPT (75 MHz, $CDCl_3$) δ_C(ppm): 191.2, 135.3, 132.6, 131.1, 129.9.

Data conform to literature.[138]

Pyridine-3-carbaldehyde 3.81

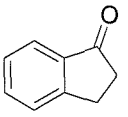


^{1}H-NMR (300 MHz, $CDCl_3$) δ_H(ppm): 10.13 (1H, s), 9.09 (1H, d, J = 1.3 Hz), 8.86 (1H, dd, J = 4.8 Hz, J = 1.5 Hz), 8.19 (1H, dt, J = 7.9 Hz, J = 1.9 Hz), 7.50 (1H, dd, J = 7.8 Hz, J = 4.8 Hz).

^{13}C-NMR+DEPT (75 MHz, $CDCl_3$) δ_C(ppm): 190.6, 154.7, 152.0, 135.9, 124.1, 53.4

Data conform to literature.[139]

Indan-1-one 3.83

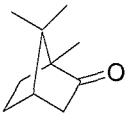


^{1}H-NMR (300 MHz, $CDCl_3$) δ_H(ppm): 7.76 (1H, d, J = 7.6 Hz), 7.58 (1H, t, J = 7.6 Hz), 7.48 (1H, d, J = 7.6 Hz), 7.36 (1H, t, J = 7.6 Hz), 3.15 (2H, t, J = 5.7 Hz), 2.67-2.71 (2H, m).

^{13}C-NMR+DEPT (75 MHz, $CDCl_3$) δ_C(ppm): 207.1, 155.2, 137.2, 134.6, 127.3, 126.9, 123.7, 36.2, 25.9.

Data conform to literature.[140]

(±)-Camphor 3.86

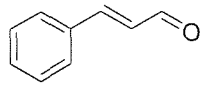


^{1}H-NMR (300 MHz, $CDCl_3$) δ_H(ppm): 2.34 (1H, ddd, J = 18.2 Hz, J = 4.1 Hz, J = 3.8 Hz), 2.08 (1H, t, J = 4.4 Hz), 1.99-1.89 (1H, m), 1.48 (1H, d, J = 18.2 Hz), 1.72-1.6 (1H, m), 1.45-1.29 (2H, m), 0.95 (3H, s), 0.91 (3H, s), 0.83 (3H, s).

^{13}C-NMR+DEPT (75 MHz, $CDCl_3$) δ_C(ppm): 219.8, 57.8, 46.9, 43.5, 43.2, 30.1, 27.2, 19.9, 19.3, 9.4.

Data conform to literature.[141]

(E)-3-Phenylpropenal 3.88

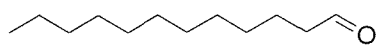


^{1}H-NMR (300 MHz, $CDCl_3$) δ_H(ppm): 9.71 (1H, d, J = 7.7 Hz), 7.59-7.43 (6H, m), 6.73 (1H, dd, J = 15.9 Hz, J = 7.6 Hz).

^{13}C-NMR+DEPT (75 MHz, $CDCl_3$) δ_C(ppm): 193.8, 152.9, 134.2, 131.4, 129.2, 128.8, 128.6.

Data conform to literature.[137]

Dodecanal 3.90

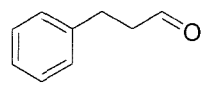


^{1}H-NMR (300 MHz, $CDCl_3$) δ_H(ppm): 9.76 (1H, t, J = 1.8 Hz), 2.41 (2H, dt, J = 7.3 Hz, J = 1.8 Hz), 1.68-1.58 (2H, m), 1.4-1.2 (16H, m), 0.88 (3H, t, J = 6.9 Hz).

^{13}C-NMR+DEPT (75 MHz, $CDCl_3$) δ_C(ppm): 203.1, 44.1, 32.0, 29.7, 29.6, 29.5, 29.5, 29.3, 22.8, 22.3, 14.2.

Data conform to literature.[142]

3-Phenylpropanal 3.92

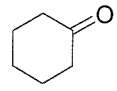


^{1}H-NMR (300 MHz, $CDCl_3$) δ_H(ppm): 9.83 (1H, t, J = 1.4 Hz), 7.32-7.19 (5H, m), 2.97 (2H, t, J = 7.6 Hz), 2.81-2.76 (2H, m).

^{13}C-NMR+DEPT (75 MHz, $CDCl_3$) δ_C(ppm): 201.7, 140.5, 128.8, 128.4, 126.5, 45.4, 28.3.

Data conform to literature.[137]

Cyclohexanone 3.94

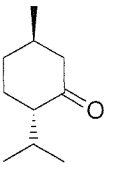


^{1}H-NMR (300 MHz, $CDCl_3$) δ_H(ppm): 2.33 (4H, t, J = 6.5 Hz), 1.90-1.82 (4H, m), 1.75-1.68 (2H, m).

^{13}C-NMR+DEPT (75 MHz, $CDCl_3$) δ_C(ppm): 212.3, 42.1, 27.2, 25.1.

Data conform to literature.[143]

2-Isopropyl-5-methylcyclohexanone 3.96

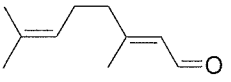


^{1}H-NMR (400 MHz, $CDCl_3$) δ_H(ppm): 2.37-2.33 (1H, m), 2.18-1.81 (6H, m), 1.46-1.29 (2H, m), 1.01 (3H, d, J = 6.5 Hz), 0.91 (3H, d, J = 7.0 Hz), 0.85 (3H, d, J = 6.5 Hz).

^{13}C-NMR+DEPT (100 MHz, $CDCl_3$) δ_C(ppm): 212.6, 56.1, 51.0, 35.6, 34.1, 28.0, 26.1, 22.4, 21.4, 18.9.

Data conform to literature.[137]

3,7-Dimethyl-octa-2,6-dienal 3.99

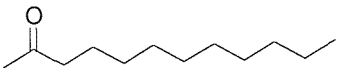


^{1}H-NMR (300 MHz, $CDCl_3$) δ_H(ppm): 9.99 (1H, d, J = 8.1 Hz), 5.88 (1H, d, J = 8.0 Hz), 5.08-5.06 (1H, m), 2.25-2.16 (4H, m), 2.16 (3H, s), 1.68 (3H, s), 1.60 (3H, s).

^{13}C-NMR+DEPT (75 MHz, $CDCl_3$) δ_C(ppm): 191.3, 163.8, 132.9, 127.4, 122.6, 40.6, 25.7, 25.6, 17.7, 17.6.

Data conform to literature.[144]

Dodecan-2-one 3.101

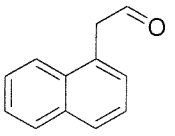


^{1}H-NMR (300 MHz, $CDCl_3$) δ_H(ppm): 2.41 (2H, t, J = 7.5 Hz), 2.12 (3H, s), 1.59-1.54 (2H, m), 1.30-1.20 (14 H, br s), 0.87 (3 H, t, J = 6.5 Hz).

^{13}C-NMR+DEPT (75 MHz, $CDCl_3$) δ_C(ppm): 209.4, 43.8, 31.9, 29.8, 29.6, 29.5, 29.4, 29.3, 29.2, 23.9, 22.7, 14.1.

Data conform to literature.[145]

Naphthalen-1-yl-acetaldehyde 3.103



^{1}H-NMR (300 MHz, $CDCl_3$) δ_H(ppm): 9.79 (1H, t, J = 2.3 Hz), 7.92-7.83 (3H, m), 7.58-7.40 (4H, m), 4.11 (2H, d, J = 2.4 Hz).

^{13}C-NMR+DEPT (75 MHz, $CDCl_3$) δ_C(ppm): 199.7, 134.1, 132.5, 129.1, 128.6, 128.5, 126.9, 126.2, 125.8, 123.7, 48.5.

Data conform to literature.[143]

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