UNIVERSITY OF SOUTHAMPTON

Studies on *O*-Alkylisoureas in Solution Phase and on Solid Support

by

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Doctor of Philosophy

Department of Chemistry

Faculty of Science

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PREFACE

The research described in this thesis was carried out under the supervision of Dr. Bruno Linclau at the University of Southampton between October 2000 and August 2003. No part of this thesis has been previously submitted at this or any other University.

UNIVERSITY OF SOUTHAMPTON

ABSTRACT

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The use of polymer-supported reagents is proving to be an ideal methodology for the clean and efficient preparation of chemical libraries. Polymer-supported reagents for the oxidation of alcohols and for the *O*-alkylation of carboxylic acids were studied.
Several polymer-supported sulfoxides were prepared in order to accomplish catch-and-release oxidations of primary and secondary alcohols. Unfortunately, an efficient protocol for the oxidations with purification of the intermediate polymer-supported sulfoxonium ion could not be achieved.
A protocol for the synthesis of polymer-supported *O*-alkylisoureas was developed, and the isoureas thus obtained proved to be excellent reagents for the *O*-alkylation of carboxylic acids. The usefulness of microwave irradiation to accelerate the esterification reactions was demonstrated. The use of polymer-supported isoureas as intermediates in a catch-and-release esterification procedure was also investigated.
Some novel reactions of *O*-alkylisoureas were investigated in solution phase. Alcohols could be *O*-benzylated using *O*-benzylisourea with Lewis acid catalysis. Isoureas were used as reactive intermediates for the cyclisation of β-hydroxyamides to form 2-oxazolines and of *N*-hydroxyalkylsulfonamides to form cyclic sulfonamides.
Finally, a new activation mechanism for the reactions of isoureas using acetyl halides has been discovered, and applied to an efficient one-pot conversion of alcohols into haloalkanes.

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Acknowledgements

I would like to thank all the members of both the CCE and the Linclau group, past and present, in particular Carol, Katerina, Marco, Max and Patrick for sharing these three years with me. Special thanks to Stifun Mittoo, the best post-doc I could hope to share a lab with.

Thanks to Joan Street and Neil Wells for the NMR spectroscopy and John Langley and Julie Herniman for the Mass Spectrometry.

Finally, I would like to thank Bruno Linclau for his constant attention and encouragement over these three years.

ABBREVIATIONS

aq	Aqueous
b.p.	Boiling point
Boc	*tert*-Butyloxycarbonyl
br	Broad
cat.	Catalytic
Cy	Cyclohexyl
d	Doublet
δ	Chemical shift (ppm)
DCE	Dichloroethane
DCM	Dichloromethane
DCC	*N,N'*-Dicyclohexylcarbodiimide
DIC	*N,N'*-Diisopropylcarbodiimide
DMAP	*N,N'*-Dimethylaminopyridine
DMF	*N,N'*-Dimethylformamide
DMSO	Dimethyl sulfoxide
DPPF	Diphenylphosphinoferrocene
DVB	Divinylbenzene
ε	Dielectric constant
e.e.	Enantiomeric excess
EI	Electron ionisation
equiv	Equivalents
ES	Electrospray
Fmoc	9-Fluorenylmethoxycarbonyl
FT-IR	Fourier transform infra-red spectroscopy
GC	Gas chromatography
GOESY	1D-Gradient nuclear Overhauser spectroscopy
HPLC	High performance liquid chromatography
HR	High resolution
J	Scalar coupling constant
L.A.	Lewis acid
λ	Wavelength (nm)

m	Multiplet (NMR) or medium (IR)
MALDI	Matrix assisted laser desorption ionisation
MAS	Magic angle spinning
min	Minute
m.p.	Melting point
MS	Mass spectrometry
μω	Microwave irradiation
m/z	Mass / charge ratio
NMP	1-Methyl-2-pyrrolidinone
NMR	Nuclear magnetic resonance spectroscopy
NOE	Nuclear Overhauser Effect
p	*para*
PEG	Polyethylene glycol
ppm	Parts per million
PS	Polystyrene
q	Quartet
R_F	Retention factor
RT	Room temperature
s	Singlet (NMR) or strong (IR)
SPOS	Solid-phase organic synthesis
t	Triplet
tan δ	Loss Tangent
tert	Tertiary
TEA	Triethylamine
TFA	Trifluoroacetic acid
TFE	Trifluoroethanol
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	*N,N,N',N'*-Tetramethylethylenediamine
TMS	Trimethylsilyl
UV/VIS	Ultraviolet/visible spectroscopy
ν	Frequency (cm^{-1})
w	Weak

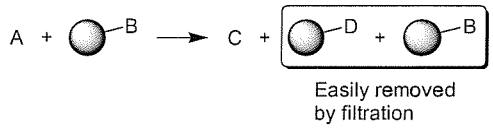
1. Introduction

1.1. Polymer-supported reagents

1.1.1. General concept

Supported reagents are defined as "reactive species that are associated with a support material" (Scheme 1.1).[1] The support can be either insoluble in all solvents (e.g. crosslinked polystyrene, silica, glass, zeolites etc.) or it can become insoluble upon addition of an appropriate solvent (e.g. polyethylene glycol of sufficient molecular weight, which is soluble in most solvents but becomes insoluble upon addition of diethyl ether).[2-4] The linkage of the reagent with the support can be either covalent or ionic. This approach is complementary to solid-phase organic synthesis (SPOS), in which it is the substrate that is linked to the insoluble matrix.

The concept of using reagents linked to insoluble matrices to facilitate removal of excess or spent reagent is not new. The first example was reported as early as 1946, although it is in the seventies that the first important results were obtained, thanks to the pioneering work by Frechet,[5] Cainelli,[6] Leznoff and Sherrington, among others.

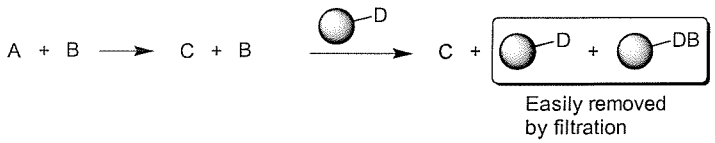


Scheme 1.1 Concept of the use of polymer-supported reagents.

Despite these interesting results, the field remained of limited interest to the synthetic community. These reagents were generally considered to have slow kinetics and to be too expensive for effective use in organic synthesis. However, this has changed during the last decade, and the reason is the advent of combinatorial chemistry. In the first place, the progress in the preparation of solid supports for solid-phase organic synthesis with better characteristics (higher loadings, uniform distribution of reactive sites, better reaction kinetics, lower cost) inevitably has had an impact on the area of polymer-supported reagents. Perhaps more importantly, the use of polymer-supported reagents is proving to be an ideal methodology for the clean and efficient preparation of smaller-sized chemical libraries. This has given a great impetus to research in this area. One of the main advantages of the use of polymer-supported reagents is the convenient use of an excess of

reagent to drive the reaction to completion. If enough reagent is used, the variation in reactivity in an array of differently substituted substrates should be overcome, so that the library can be treated with the same reaction conditions. Subsequently, both the excess of reagent and the spent reagent can be easily removed by simple filtration. The fact that the workup can be reduced to simple filtrations and resin-washing routines is extremely important: these operations are very easily automated on relatively simple robots. Since preparation of large libraries relies heavily on automation to increase the throughput, it is obvious that this represents an essential requisite for employing these reagents in combinatorial chemistry.

It is worth noting that the use of polymer-supported scavengers offers a perfectly complementary technique to the use of polymer-supported reagents, and in several cases the two have been successfully employed together.[7] In the example shown in Scheme 1.2, an immobilised scavenger removes the excess of unreacted reagent B, leaving pure C in solution after filtration (Scheme 1.2).

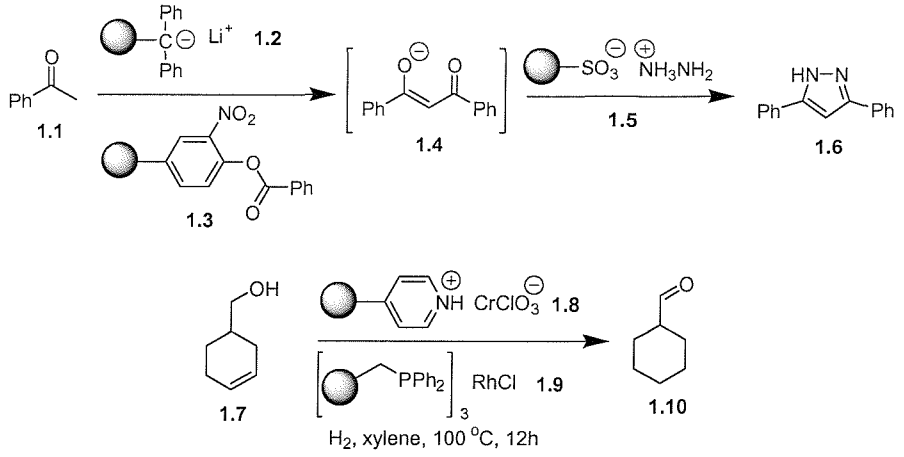


Scheme 1.2 Concept of the use of polymer-supported scavengers.

Compared to the other mainstream technique used for combinatorial chemistry, solid-phase organic synthesis, the use of polymer-supported reagents has a number of distinct advantages: as the substrate and product remain in solution, it is possible to follow the reaction progress with all the traditional analytical techniques (TLC, GC or GC-MS, HPLC or HPLC-MS, NMR etc.), while analysis of products which are attached to resins remains limited to few techniques, some of which require expensive and complex apparatus (e.g. gel-phase or MAS NMR, MALDI mass spectrometry), or is time consuming (cleavage off the resin of an analytical sample). Perhaps even more importantly, adaptation of literature conditions is often more straightforward from traditional solution-phase chemistry to the use of polymer-supported reagents than it is for SPOS, so that less time is spent optimising the conditions prior to the actual library synthesis.

In 1977, Cohen *et al.* described the first use of one of the most attractive features of polymer-supported reagents, namely what he described as the "wolf and lamb" principle:[8]

two (or more) resins bearing mutually incompatible functionalities can be used together, as the site isolation provided by the support ensures that no reaction can occur between the various reagents (Scheme 1.3).

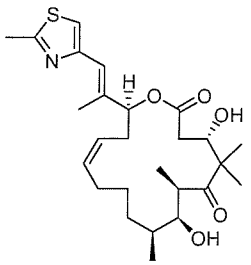


Scheme 1.3 Applications of the wolf-and-lamb principle.

This means that several steps can be accomplished in the same pot, reducing significantly the time needed as well as the amount of work-ups required.[9]

It is important to notice that the use of polymer-supported reagents is by no means limited to applications of library generation. Recently, a number of total syntheses of natural products have been reported using polymer-supported reagents and/or scavengers in some or in every step.[10,11] These examples demonstrate first of all that polymer-supported reagents are compatible with complex structures and show the same kind of chemoselectivities exhibited by their soluble counterparts. They also illustrate just how traditional chemistry can be translated to the use of these reagents. Even more importantly, they show that the advantages inherent to polymer-supported reagents (easy workups, no subsequent purifications, possibility for several steps to be accomplished together) can be useful not only to combinatorial chemists but also to the more widespread synthetic community.

Perhaps the most complex natural product prepared using this strategy is epothilone C (Figure 1.1).[12] The synthesis proposed by Ley comprises 29 overall step (17 steps for the longest linear sequence) and involved only one purification by flash chromatography, to eliminate an unwanted minor diastereoisomer, in the very last step.



1.11

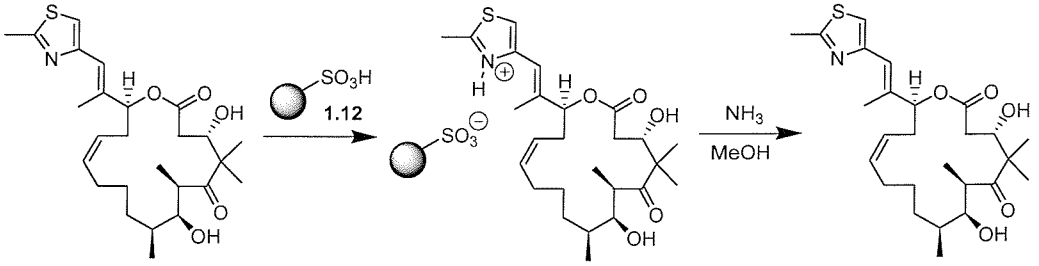
Figure 1.1 Epothilone C.

1.1.2 The catch-and-release principle

In his review on polymer-supported reagents and scavengers, Ley *et al.* define "catch and release" as:

> a technique used to selectively trap the desired product of a solution-phase reaction onto a functionalised support material. Following filtration (and washing) to remove solution-phase contaminants, the compound may then be released from the support. Also referred to as 'capture and release' and variants thereof.[1]

As an example, in the synthesis of epothilone C cited previously,[12] the final product was captured using a polymer-supported sulfonic acid (through protonation of the thiazole nitrogen, Scheme 1.4). Washing with DCM eliminates a number of impurities and a purer product can be released using a methanolic solution of ammonia.



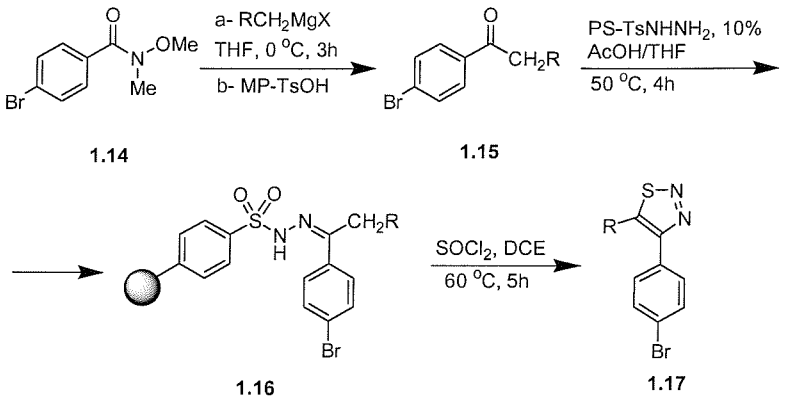
1.11 1.13 1.11

Scheme 1.4 Application of the catch-and-release principle to the synthesis of epothilone C.

In many respects, this approach is complementary to the use of scavengers, as it is the product of the reaction which is selectively trapped on the resin while the excess reagents are removed by filtration.[13-18] This is particularly important when the molecules which must be removed from the product do not bear suitable functional groups and cannot therefore be eliminated using scavengers.

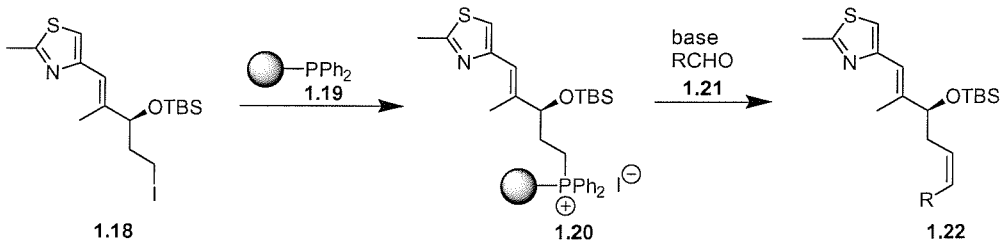
In some cases, the release from the resin can be achieved through a productive step instead of being just a "deprotection" step.[19,20] For example, Porco and co-workers described a

method to selectively "catch" onto the resin an array of ketones **1.15** synthesised in solution and then "release" them as the corresponding 1,2,3-thiadiazoles **1.17** using Hurd-Mori cyclisation (Scheme 1.5). Other reactions (such as Stille couplings) can be performed on the substrate while on the solid-support before the release step.[21]



Scheme 1.5 Application of the catch-and-release principle to the synthesis of a 1,2,3-thiadiazole library.

A similar approach was described by Ley (again in his synthesis of epothilone C) when using polymer-supported phosphine to perform a Wittig reaction (Scheme 1.6).[12] Washing the intermediate polymer-supported phosphonium salt allowed an easy removal of some impurities remaining from preceding steps.



Scheme 1.6 Catch-and-release Wittig reaction.

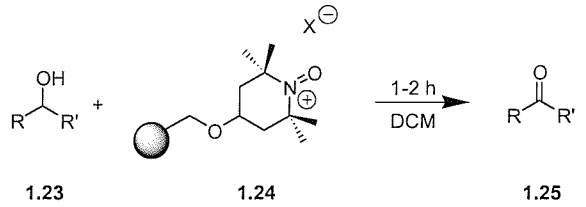
1.1.3. Polymer-supported oxidants: oxidation of alcohols to aldehydes and ketones

Several "oxidising resins" have already been described. A significant number of these are based on ion-exchange resins, with anionic oxidants bound to the resin via ionic bonds. Chromate,[6,22] permanganate,[23,24] bromate[25] and periodate[26] resins have been developed, with polymer-supports typically bearing either quaternary ammonium or pyridinium groups.

Polymer-supported perruthenate described by Ley deserves a particular mention for the excellent results obtained with this resin.[27] It is used in catalytic amount with a co-oxidant, molecular oxygen being the best option with respect to purification purposes.[28,29]

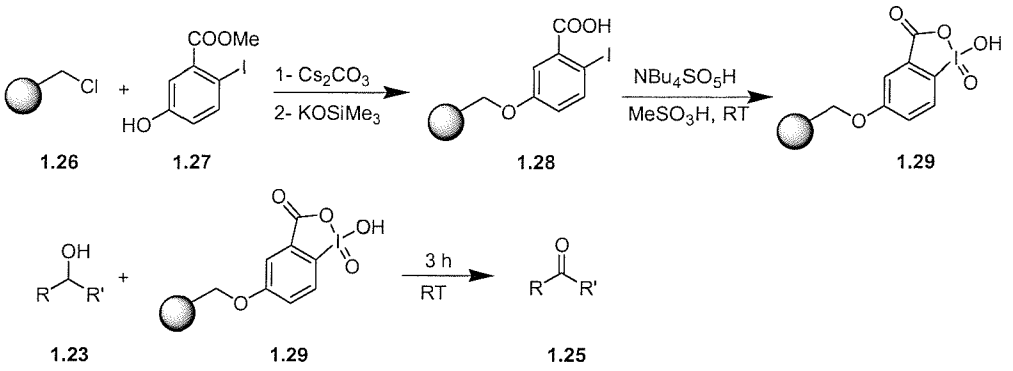
Other, non-ionic polymer-supported reagents have also been described.

Oxoammonium resin has been prepared by Rademann and used successfully in oxidation reactions (Scheme 1.7).[30]



Scheme 1.7 Oxidation of alcohols using oxoammonium resin.

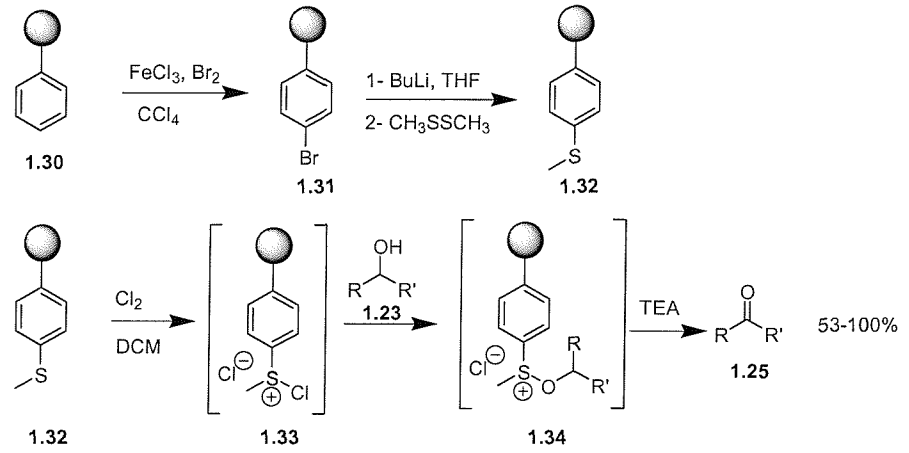
Several hypervalent iodine oxidants have been described. Three different versions of polymer-supported IBX have been reported in the last two years, on either polystyrene or silica support (Scheme 1.8).[31-33]



Scheme 1.8 Synthesis and use of polymer-supported IBX.

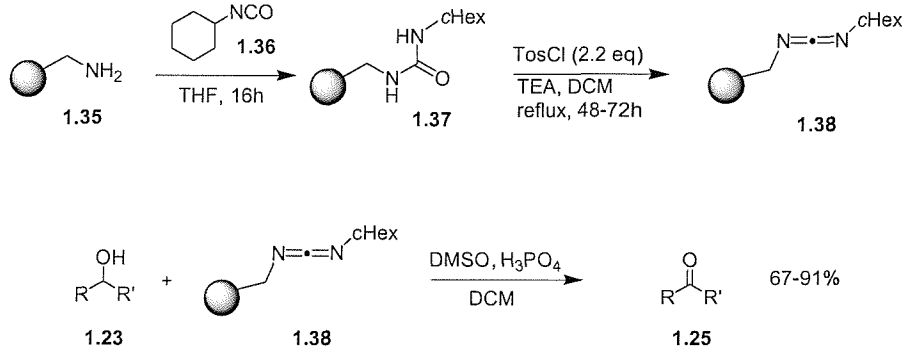
Polymer-supported iodoxy acetate is another member of this family which has been successfully employed.

Oxidations based on DMSO have also generated widespread interest for application with polymer-supported reactions. In 1975 Crosby[34] described the synthesis of a polymer supported sulfide and its use for oxidations of alcohols using chlorine or *N*-chlorosuccinimide as co-reagents (Scheme 1.9). Observed yields were not very good, especially for benzyl substrates, with extensive formation of the corresponding chlorides.



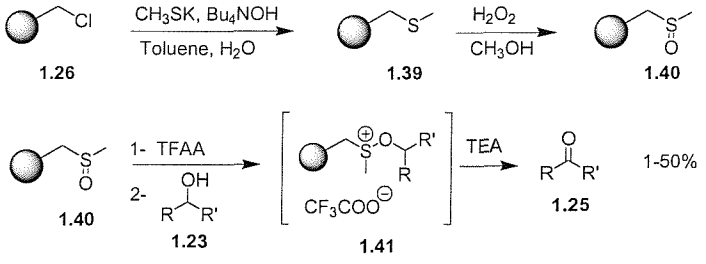
Scheme 1.9 Oxidations using polymer-supported sulfide.

In 1972 Weinshenker prepared a polymer-supported carbodiimide, which could be used in conjunction with DMSO for the Pfizner-Moffatt oxidation of alcohols (Scheme 1.10).[35,36]



Scheme 1.10 Preparation of polymer-supported carbodiimide and its use in Pfizner-Moffatt oxidations.

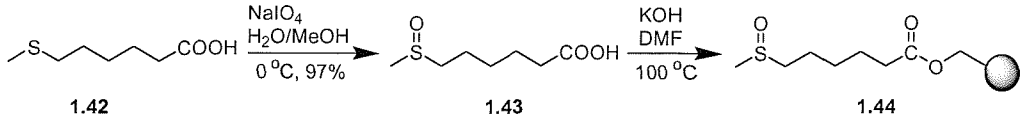
In 1985 Yaacoub synthesised a polymer supported sulfoxide,[37] and used it for oxidation of both alcohols[38] (using trifluoroacetic anhydride or DCC/H_3PO_4) and halides[37] (with $NaHCO_3$). Again, the yields were not comparable to those obtained in solution (Scheme 1.11).



Scheme 1.11 The first polymer-supported sulfoxide.

Finally, in 1998 Vederas linked 4-(methylsulfinyl)hexanoic acid to Merrifield resin and used it in conjunction with oxalyl chloride.[39] Oxidation of *endo*-borneol with this reagent can be accomplished with 96% yield in stoichiometric conditions, and in 100% yield if 0.5

equiv of alcohol are used. However, he reported that recycling of the reagent (by re-oxidation with $NaIO_4$) resulted in a large decrease in activity. The same author later claimed that a similar oxidant based on a polyethylene glycol (PEG) support could be used more effectively and reused several times without loss of activity (Scheme 1.12).[40]



1.42 1.43 1.44

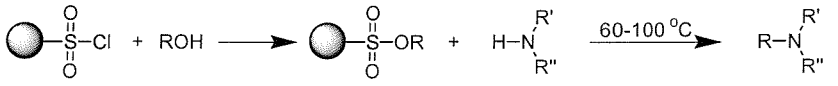
Scheme 1.12 Vederas' polymer-supported sulfoxide.

More recently, Cole demonstrated that a similar sulfoxide linked to a polystyrene backbone was recyclable without loss in activity using a different system for the reoxidation from sulfide to sulfoxide (*tert*-butyl hydroperoxide in the presence of catalytic *para*-toluenesulfonic acid).[41]

1.1.4 Polymer-supported alkylating resins for the conversion of carboxylic acids into esters

Various polymer-supported reagents have been employed over the years for the synthesis of esters from carboxylic acids. However, the reagents that were immobilised always consisted of catalysts or coupling reagents, and either an alcohol or alkyl halide was required to react with the carboxylic acid partner. An example is polymer-supported carbodiimide **1.38**, which has been used for the synthesis of esters or amides.

While alkylating resins were known (e.g. polymer-supported sulfonates), they were mainly used for reactions with amines under basic conditions (Scheme 1.13).[42]

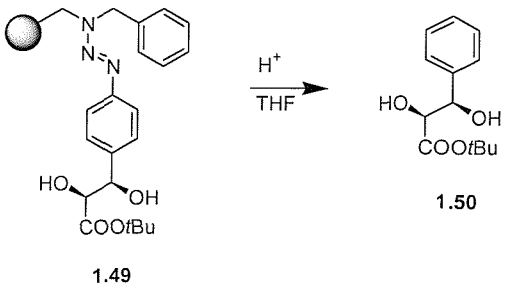


1.45 1.23 1.46 1.47 1.48

Scheme 1.13 Use of polymer-supported sulfonates as alkylating resins.

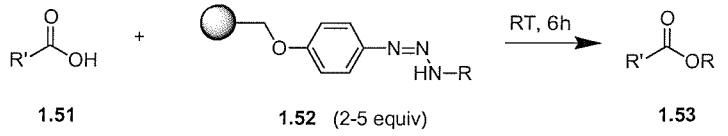
It was not until 2000 that the first polymer-supported reagents capable of alkylating a carboxylic acid without necessity of any other co-reagent appeared.

Polymer-supported triazenes were developed by Brase as "traceless" linkers for SPOS (Scheme 1.14).[43]



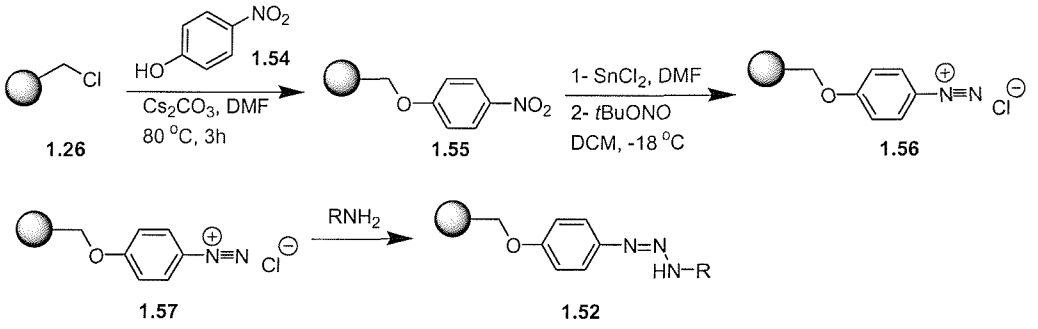
Scheme 1.14 Triazenes as traceless linkers.

In 2001 Brase[44] and Rademann[45] described independently the efficient reaction of triazenes with carboxylic acids, which produced carboxylic esters of excellent purity in high yields (Scheme 1.15). Several functional groups can be present on the carboxylic acid without affecting the reaction.



Scheme 1.15 Reaction of carboxylic acids with polymer-supported triazenes.

The triazene resins were easily prepared starting from Merrifield resin as shown in Scheme 1.16.[45]

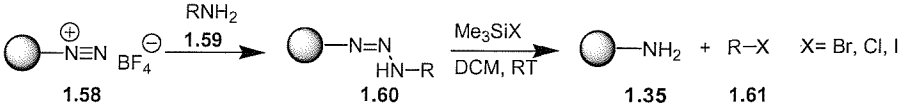


Scheme 1.16 Preparation of Rademann's triazene alkylating resins.

More recently, Struber has proposed an alternative synthesis of triazenes starting from unfunctionalised polystyrene resin and he has further demonstrated the scope of this type of polymer-supported reagents for the esterification of carboxylic acids.[46]

Other classes of compounds have been successfully alkylated using triazenes: sulfonic, phosphoric and phosphinic acids have been successfully converted into the corresponding esters using these reagents.[47,48] Interestingly, the conjugate anions of these species could be used if an acidic ion-exchange resin was added to act as the proton source.

Brase also discovered that triazene resins react with trimethylsilylchloride to form the corresponding chloroalkane. This has been developed into a "catch-and-release" synthesis of haloalkanes from the corresponding amines (Scheme 1.17).[44]



Scheme 1.17 Catch-and-release synthesis of haloalkanes *via* polymer-supported triazenes.

1.2. Microwave-assisted chemistry.

1.2.1. Microwave heating[49]

When a molecule possessing a dipole moment is irradiated with electromagnetic radiation, it will tend to rotate to align to the electric field. If the molecule is in the gas phase, it will be unhindered by other molecules and therefore will be able to reorient itself to the electric field easily. However, in liquid phase the presence of other molecules hinders this rotation. In this case, if the frequency of the radiation is high, the molecules do not have enough time to rotate and align to the rotating field. On the contrary, if the frequency is low the molecules will rotate in phase with the field, dispersing little energy. However, when the frequency of the radiation is in the microwave region (0.3 to 300 GHz), the molecules will have time to start rotating, but not enough to follow the field exactly. The phase difference between the field and the molecules causes energy to be lost in intermolecular collisions, generating heat (dipolar polarization mechanism, Figure 1.2).

If ions are present, heating is instead generated by translational movement of the ions caused by the electric field. This is defined as "conduction mechanism", and generates more heat than the dipolar polarization mechanism.

Figure 1.2 An oscillating electric field of appropriate wavelength causes polar molecules to oscillate, generating heat (reproduced from ref. 49 with permission).

Since 1954, the principle that microwave irradiation can be used to generate heat within substances has been used extensively, for example in microwave ovens, which permit

quick cooking of food. In 1984, over thirty years later, two groups independently reported how microwave irradiation could accelerate organic reactions.[50,51] Since then, several research groups have investigated the influence of microwave irradiation on a number of chemical systems. Despite the sometimes astonishing reduction in reaction times reported, this technique is only now becoming a useful and widespread synthetic tool. The reason for this is essentially technological: until a couple of years ago the only type of microwave reactor available were household microwave ovens. These systems have a number of disadvantages when used to accomplish chemical reactions.

Microwaves can rebound from the internal walls of the ovens. These reflections of the radiation eventually form a number of stationary waves (modes) within the reactor (Figure 1.3). Household ovens normally have between 3 and 6 modes present within the cavity. While this creates an adequately uniform heating profile for large samples (such as food items), the heating pattern is too inhomogeneous to give reproducible results in organic synthesis. The formation of so-called "hot and cold spots" can cause big differences in the behaviour of reactions depending on the exact position of the sample within the microwave cavity. Modern, dedicated microwave reactors use instead cavities designed to have only one mode, and therefore an uniform heating anywhere in the reaction vessel.

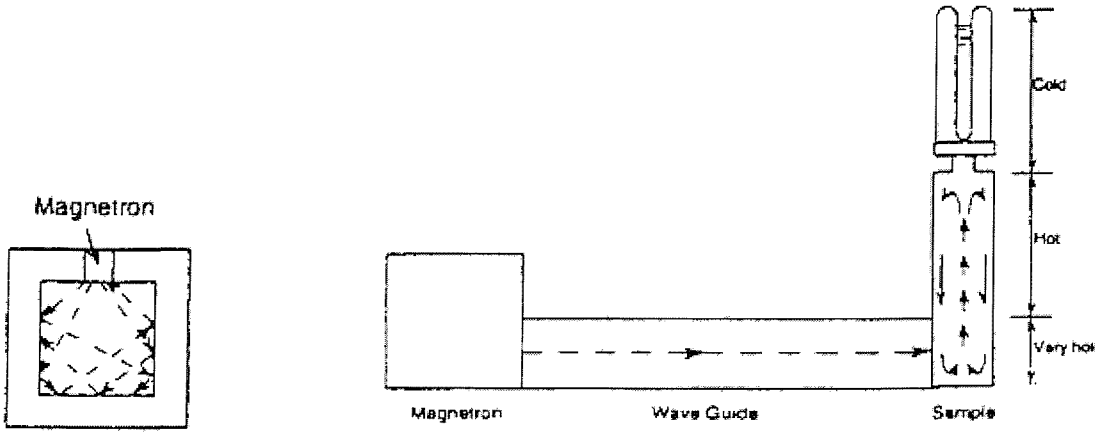
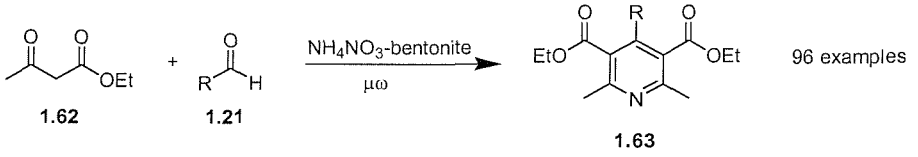


Figure 1.3 Differences between a domestic oven (left) and a monomodal system (right) (reproduced from ref. 49 with permission).

A second problem when using household microwave ovens is the lack of temperature control: household ovens have control over the output power of the irradiation, but given the differences in absorption behaviour between different solvents (*vide infra*), a given power can give rise to very different temperatures inside the reaction vessel. This not only causes reproducibility problems, but it can also be dangerous: the temperature inside the

vessel can reach a much higher value than the boiling point of the solvent. As many reactions are done in sealed tubes, lack of control over the actual temperature inside the vessel can lead to explosions. This is the reason why many of the reactions in the literature where household ovens were used were actually performed under solvent-free conditions, typically having the substrates absorbed on silica or other suitable supports (various types of clays, alumina).[52]



Scheme 1.18 Example of a solvent free microwave-assisted reaction.

In many of the most recent models of dedicated microwave reactors, a sensor measures the temperature at all times and relays the information to the control software, which adjusts the power provided in order to reach and then maintain the temperature set by the experimenter (Figure 1.4)

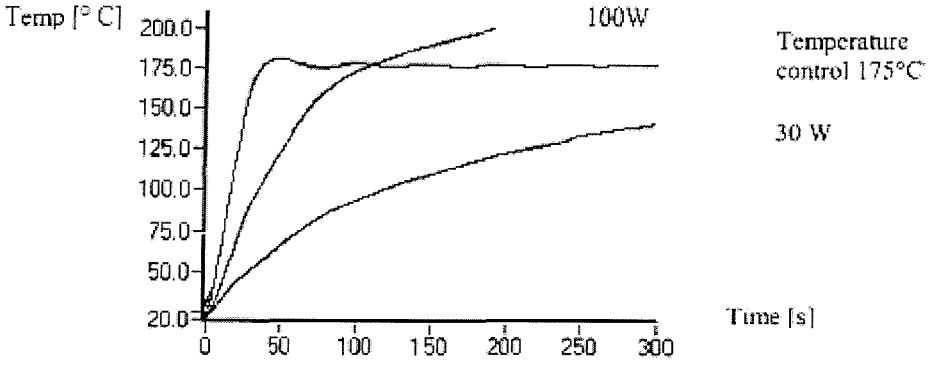


Figure 1.4 Different heating profiles of DMF in fixed power systems with output of 30 and 100 W respectively, and in a fixed temperature system, with selected temperature= 175 °C (reproduced from ref. 49 with permission).

The recent technological improvements in the construction of microwave reactors designed specifically for the needs of synthetic chemists have successfully tackled the problem of reproducibility and safety associated with microwave-assisted acceleration of organic reactions. This technique is therefore finding a more widespread use and will no doubt become a standard synthetic tool within the next few years.

All examples and discussions reported in the remainder of this chapter refer exclusively to experiments performed with monomodal systems (with either power or temperature control).

As microwave irradiation was becoming a useful technique for the acceleration of organic reactions, a number of hypotheses on the origin of this effect were brought forward. Two schools of thought still exist. The first maintains that the acceleration effect is purely thermal: the microwave irradiation serves only as a very efficient heating system. In a sealed vessel, temperatures higher than the boiling point of the solvent can be achieved, in very short times. As the heating is generated from within the solution, there is no "hot wall" effect, which could cause decomposition of either the products or the reagents. It is the higher temperature that increases the reaction speed. A second school advocates the presence of so-called non-thermal effects to explain the acceleration instead.[53]

At the moment, it seems the majority of authors tends to rule out the presence of non-thermal effects, at least when reactions are carried out in homogeneous phase.[54]

The energy of microwave irradiation must therefore be converted into heat. The efficiency of this process depends on the reaction mixture itself. To start, we will consider only the pure solvents. As mentioned before, the interaction of the radiation with the molecules is caused by the presence of a dipolar moment. It is therefore hardly surprising to notice that in a qualitative sense the more polar a solvent is, the better it converts microwave power to heat. This affects both the higher temperature achievable by that solvent at a fixed power, but also the time required to achieve it. When solvents possessing similar dielectric constants are compared (such as ethanol and acetone, Figure 1.5), a closer relationship exists between microwave absorption and a parameter called loss tangent (tan δ), which takes into account not only the dielectric constant but also the efficiency in transforming the energy absorbed into heat.

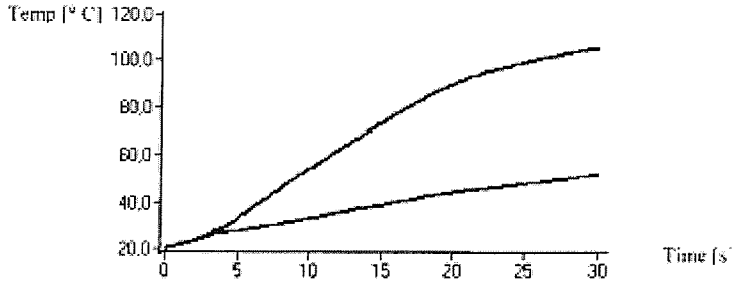


Figure 1.5 Heating profiles (fixed power, 150 W) of ethanol (top curve) and acetone (lower curve) (reproduced from ref. 49 with permission).

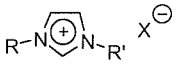
A list of solvents with their loss tangent values, as well as the temperature reached after 100 s of irradiation at 100 W is reported in Table 1.1.

Table 1.1 Solvents for microwave-assisted chemistry. Temperatures and pressures after 100 s at 100 W.

Solvent	Dielectric constant	Loss tangent	T (°C)	p (bar)
DCM	9.1	0.042	100	18
THF	7.6	0.047	110	3
Acetone	20.6	0.054	150	7
Methanol	32.7	0.659	145	17
Ethanol	24.6	0.941	155	13
Acetonitrile	36.0	0.062	180	13
DMF	36.7	0.161	250	4
DMSO	47.0	0.825	250	1
H_2O	80.4	0.123	165	10

As the acceleration of reactions is caused by the increase in temperature, it is therefore advantageous to use a solvent with high loss tangent (qualitatively, a more polar solvent). However, the situation changes if solutes are present: a poor microwave-absorbing solvent can be used if some of the other species in the solution can efficiently absorb the microwaves. So if a substrate or reagent is sufficiently polar and the reaction mixture is sufficiently concentrated, good temperature profiles can be obtained even with "poor" solvents such as DCM, THF or toluene.

An alternative is to use additives which can be used to serve as "antennas" to absorb the radiation. An example are the so-called ionic-liquids (Figure 1.6), typically imidazolium salts which are liquid at room temperature.[55,56] Being ionic, they absorb microwave radiation very well. They are generally inert, have very low vapour pressure and are usually easy to separate from the reaction mixture by extraction.



1.64

Figure 1.6 Ionic liquids based on the imidazolium core are frequently used to facilitate heating under microwave irradiation.

Another property of the solvent that needs to be taken into account is the vapour pressure. As reactions are carried out in a sealed vessel (able to withstand pressures of up to 20 bars), it is obvious that the maximum temperatures employable depend on the pressure the solvent would cause at that temperature. So for example heating DCM at 100 °C leads to a

pressure of 18 bar, while DMF at the same temperature only leads to negligible pressure. If the reagents and/or products of the reactions are volatile, that needs to be taken into account as well, especially in those cases when a gaseous by-product is formed as the sudden increase in pressure could cause explosion of the reaction vessel.

Finally, it must be emphasised that several physical and chemical properties of solvents change significantly with increased temperatures. Most importantly, the dielectric constant decreases with the increase in temperature: for example water has ε=78 at 25 °C but ε=20 at 300 °C (Figure 1.7).

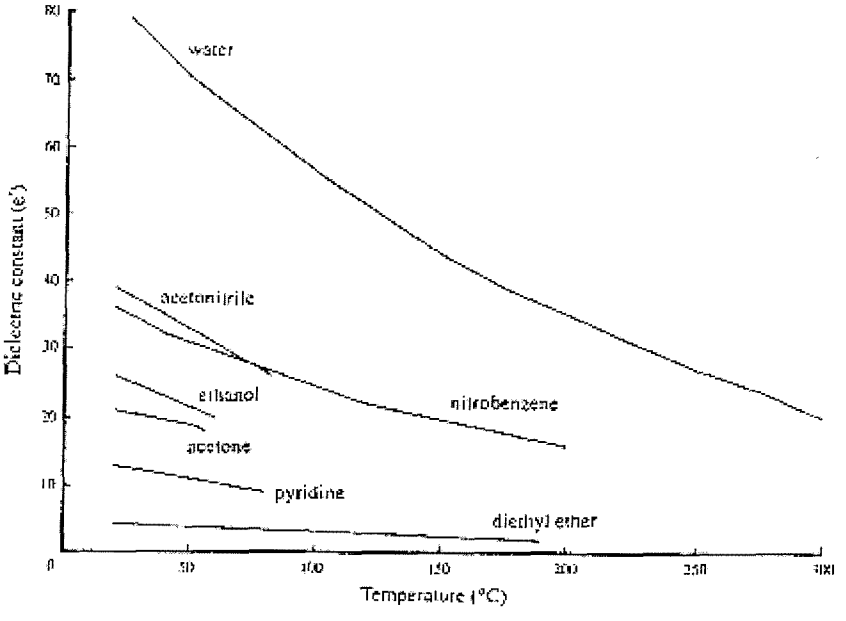
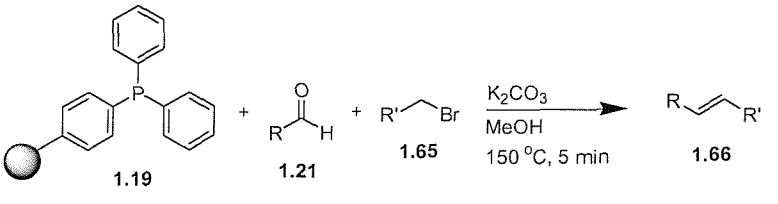


Figure 1.7 Effect of temperature on the dielectric constants of several common solvents (reproduced from ref. 49 with permission).

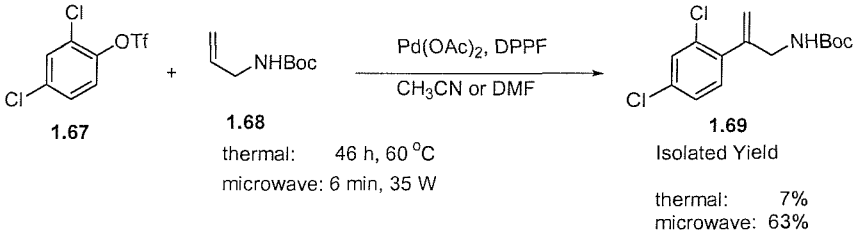
This characteristic has been exploited in synthesis. For example, methanol is known not to be a good solvent for swelling resins, because of its high polarity and for being a protic solvent. However, it can be used as solvent for reactions involving polymer-supported reagents at high temperatures, as demonstrated by Westman (Scheme 1.19).[57]



Scheme 1.19 Wittig reaction using polymer-supported phosphine in methanol.

1.2.2. Organic reactions under microwave irradiation

An enormous variety of reactions have been adapted for use with microwave heating: alkylations, oxidations, reductions, palladium-catalysed couplings, synthesis of heterocycles etc. Apart from the advantage of necessitating shorter reaction times, in a variety of cases reactions which could not be achieved with normal heating gave reasonable yields. For example, Hallberg showed how a Heck reaction which only gave 7% yield using thermal heating could give a yield of 63% under microwave irradiation (Scheme 1.20).[58]

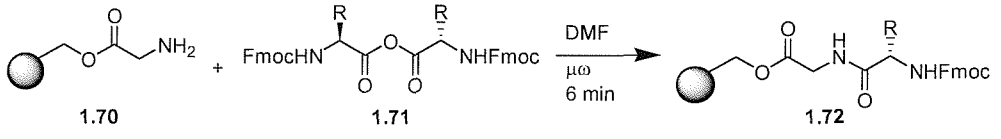


Scheme 1.20 Dramatic improvement of the yield using microwave-irradiation.

1.2.3. The use of resins with microwave-heating[59]

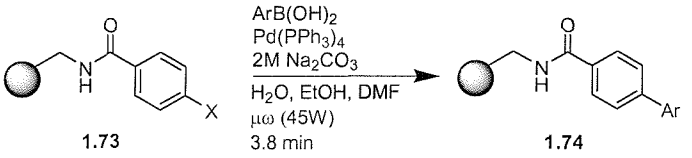
The ability of microwave flash heating to accelerate chemical reactions makes it a perfect tool to use in solid-phase organic chemistry. While reactions on polymer-support have a number of advantages, especially for the preparation of combinatorial libraries, they also normally exhibit slower kinetics than their solution-phase counterparts. Microwave flash heating has been successfully employed in a number of cases to significantly reduce reaction time. As there is no hot-wall effect, decomposition of the resin is normally limited even at high temperatures.

This combination of techniques was first applied in peptide synthesis, in order to reduce the time needed to cleave the amino acids from the support from 7 hours to just 7 minutes (in a household oven).[60] Four years later, the same group used microwave irradiation to accelerate peptide couplings as well.[61] The couplings using microwave assistance proceeded in higher yields and no racemisation was observed (Scheme 1.21).



Scheme 1.21 Microwave-accelerated peptide coupling using a symmetrical anhydride.

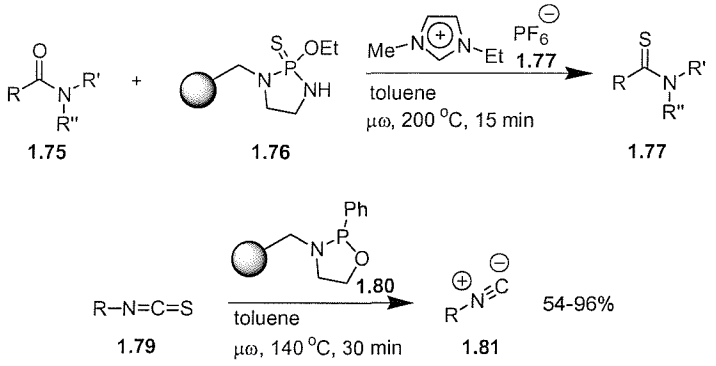
In 1996, Larhed pioneered the use of microwave-assisted chemistry for the synthesis of small organic molecules on solid-support, through Suzuki and Stille couplings (Scheme 1.22).[62]



Scheme 1.22 Microwave-assisted Suzuki couplings on solid-support.

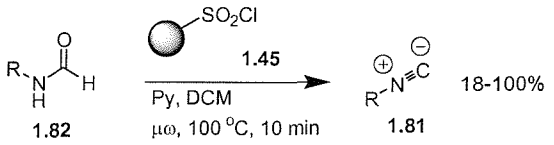
A few examples of the combination of microwave-assisted chemistry with the use of polymer-supported reagents have also appeared in the literature. As described earlier, Westman has used polymer-supported phosphines to perform Wittig reactions.[57]

Among the various polymer-supported reagents introduced by Ley, polymer-supported [1,3,2]oxazaphospholidine[63] (used for the conversion of isothiocyanates to isocyanides) and aminothiophosphate[64] (used for the conversion of carbonyl groups into thiocarbonyls) have been shown to give better results when used under microwave irradiation, as opposed to normal thermal heating, giving better yields and better purity profiles as fewer decomposition products are observed (Scheme 1.23).



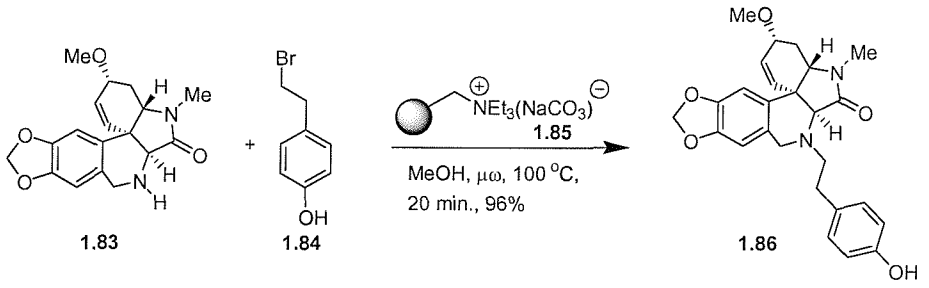
Scheme 1.23 Use of polymer-supported reagents in conjunction with microwave irradiation.

Recently, Bradley described a facile dehydration of formamides to give isocyanides using polymer-supported sulfonyl chloride under microwave irradiation (Scheme 1.24).[65]



Scheme 1.24 Facile synthesis of isocyanides using polymer-supported sulfonyl chloride.

During the course of two different total syntheses entirely performed using polymer-supported reagents and/or scavengers, Ley has used microwave heating to perform several difficult steps (Scheme 1.25).[10] The use of microwave heating with such complex substrates further demonstrates the utility of this technique.



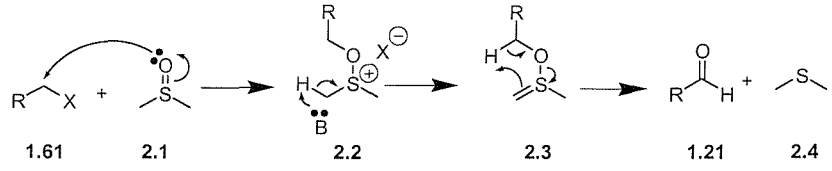
Scheme 1.25 Application of microwave-irradiation with polymer-supported reagents in the synthesis of (+)-plicamine. Excess alkyl bromide was scavenged using a polymer-supported thiol.

2. Catch-and-release oxidations using polymer-supported sulfoxides

2.1 Introduction

Dimethyl sulfoxide-based oxidations of alcohols or halides play an important role in organic synthesis, with the Swern oxidation being the most commonly used.[66,67]

The first discoveries of the oxidising properties of DMSO were made by Kornblum and Nace,[68,69] who reacted alkyl tosylates or iodides with DMSO at high temperature. Better yields were obtained in the presence of a base (typically $NaHCO_3$). The scope of this reaction was later widened, allowing for the oxidation of other halides, using either an excess of KI at high temperature or $AgNO_3$ at room temperature.[70] The mechanism proposed for this transformation is depicted in Scheme 2.1: the oxygen atom of the sulfoxide acts as a nucleophile, displacing the tosylate or iodide. The cationic species produced subsequently undergoes deprotonation to give intermediate **2.3**, which then collapses by a cyclic mechanism to give aldehyde **1.21**, with dimethylsulfide as by-product.

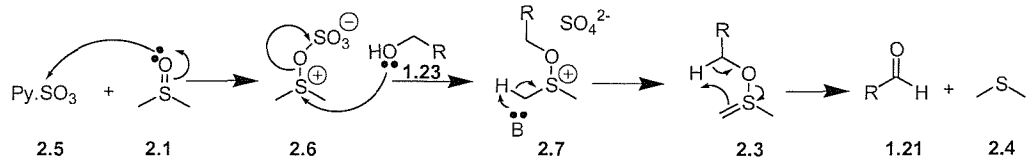


Scheme 2.1 Mechanism of the Kornblum oxidation of alkyl halides.

This mechanism has been investigated by Torsell.[71,72] He demonstrated that treating isolated sulfoxonium salts with a base lead to the same products that were obtained from Kornblum oxidation, which suggested that they can be an intermediate in the reaction. The cyclic mechanism for the elimination of dimethylsulfide was demonstrated through deuterium labelling experiments.

Of more general interest are the methods that allow the direct transformation of primary and secondary alcohols into the corresponding aldehydes or ketones. In this case, the dimethyl sulfoxide must be activated to make it reactive towards the alcohol. Several reagents can be used as activators. The first activator used was acetic anhydride, but trifluoroacetic anhydride,[73] SO_3.py[74] and especially oxalyl chloride[75] are now the most used. When SO_3.py is used the reaction is called Parikh-Doering oxidation and when oxalyl chloride is used the reaction is referred to as Swern oxidation.

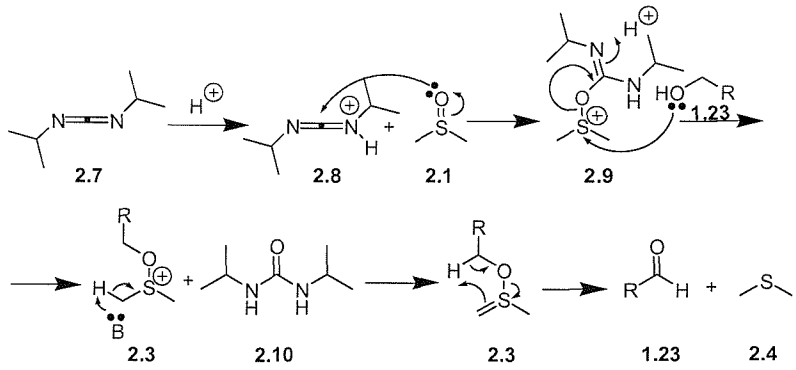
In all these cases the mechanism is very similar (Parikh-Doering mechanism is depicted in Scheme 2.2). The sulfoxide acts as a nucleophile on the electrophilic activator. The species which is formed reacts with the alcohol to form the sulfoxonium salt **2.7**. In presence of a base (typically TEA) this species reacts as shown before giving the desired carbonyl compound.



Scheme 2.2 Mechanism of the Parikh-Doering oxidation.

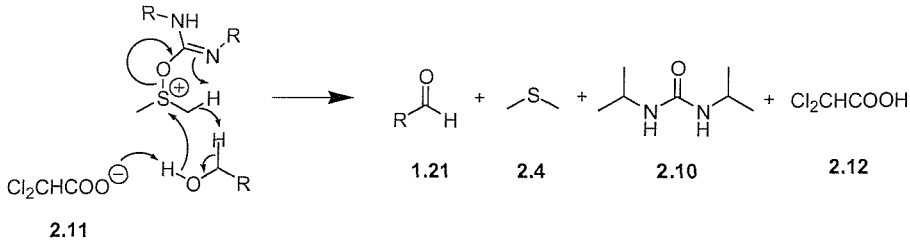
As the reaction of DMSO with some of the activators (namely oxalyl chloride and trifluoroacetic anhydride) is very violent, the reaction must be carried out at low temperatures (-60 °C to –78 °C). Only upon addition of the triethylamine, the temperature can be raised to room temperature for a brief time to allow the subsequent steps to the carbonyl product to take place.

Finally, in 1965 Pfitzner and Moffatt reported a substantially different procedure to carry out DMSO-based oxidations.[76,77] They discovered that if a carbodiimide and an acid of appropriate acidity were used in DMSO, alcohols could be oxidised to ketones and aldehydes. The same authors have proposed the mechanism depicted in Scheme 2.3.[78] As the reaction requires both acid and base catalysis, it is important that the pKa of the acid partner is within narrow boundaries.[77] In fact, while dichloroacetic acid gives excellent yields, both monochloroacetic acid and trichloroacetic acid fail to promote the oxidation, the former not being acidic enough to catalyse the first step, while the conjugate base of the latter is not basic enough to give the final deprotonation. In practice, either pyridinium trifluoroacetate or dichloroacetic acid are used.



Scheme 2.3 Mechanism of the Pfitzner-Moffatt oxidation.

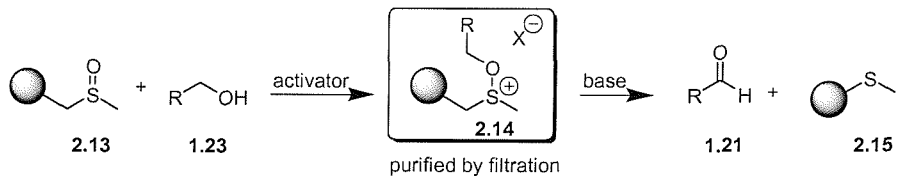
Torsell, on the basis of his studies on isolated sulfoxonium salts, has hypothesised a slightly different mechanism (Scheme 2.4).[71] He had demonstrated that the conditions of the Pfitzner-Moffatt reaction were not sufficiently basic to afford deprotonation of a discrete sulfoxonium ion, so he proposed that the abstraction of the hydrogen atom and alcohol attack occur simultaneously, the anionic leaving group acting as a base, without the formation of a discrete sulfoxonium species.



Scheme 2.4 Alternative mechanism proposed by Torsell for the Pfitzner-Moffatt oxidation.

2.2. Project aims

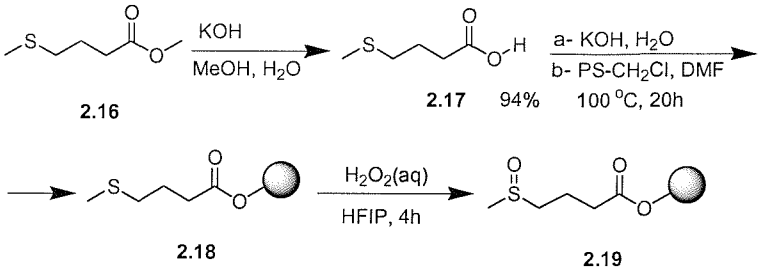
As mentioned in section 1.1.5, polymer-supported sulfoxides have already been used for the oxidation of alcohols.[38-41] Our objective was to use similar polymer-supported reagents to accomplish a catch-and-release oxidation process (Scheme 2.5). For this to be possible, isolation of the intermediate sulfoxonium ion **2.14** on the polymer-support was required. Filtration of the resin at this point would remove any unreacted alcohol as well as any eventual contaminant present in the starting material. Following this operation, the resin would be treated with a base to release the carbonyl compound. Any unreacted sulfoxonium ion would remain trapped on the resin. An attractive feature of this process would be the possibility to obtain products with high purity even if the yield of the reaction was low (as residual starting materials and intermediates would have been removed) and/or if the starting material was contaminated.



Scheme 2.5 Proposed strategy for the catch-and-release oxidation of alcohols using polymer-supported sulfoxides.

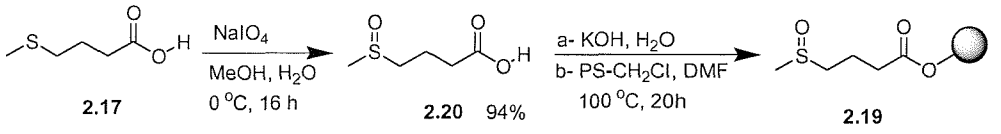
2.3. Synthesis of the solid supported sulfoxides.

The synthesis of solid supported sulfoxide **2.19** started from the commercially available methyl-4-(methylsulfanyl) butyrate **2.16**, which could be easily converted into the corresponding acid **2.17** by alkaline hydrolysis (Scheme 2.6). The acid was easily attached to Merrifield resin via reaction with the corresponding potassium salt (in DMF at 100 °C overnight). Selective oxidation of the sulfide **2.18** to the sulfoxide **2.19** was achieved using hydrogen peroxide in hexafluoroisopropanol (HFIP).[79] Elemental analysis of **2.19** gave a loading of 1.52 mmol/g, with 0.147 mmol/g of residual chlorine (yield 91%).



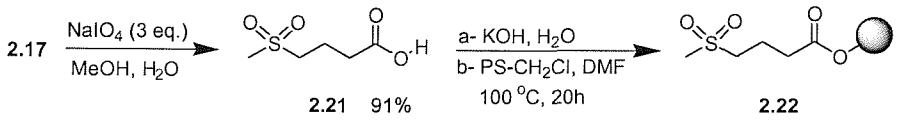
Scheme 2.6 Synthesis of polymer-supported sulfoxide.

To evaluate the efficiency of the oxidation step, a small sample of **2.19** was prepared by an alternative method following a strategy similar to that proposed by Vederas (Scheme 2.7).[39] Hence the thioether **2.17** was oxidised in solution with $NaIO_4$ in $MeOH/H_2O$ while carefully maintaining the temperature at 0 °C overnight and loading the product on the resin via the same methodology as employed earlier. Batches of **2.19** obtained with both methods show identical IR spectra.



Scheme 2.7 Alternative strategy for the synthesis of **2.19**.

The corresponding solid-supported sulfone **2.22** has also been prepared and linked to the resin as depicted in Scheme 2.8. Comparison of the IR and ^{13}C spectra of **2.19** and **2.22** confirmed the absence of overoxidation during the H_2O_2/HFIP oxidation.

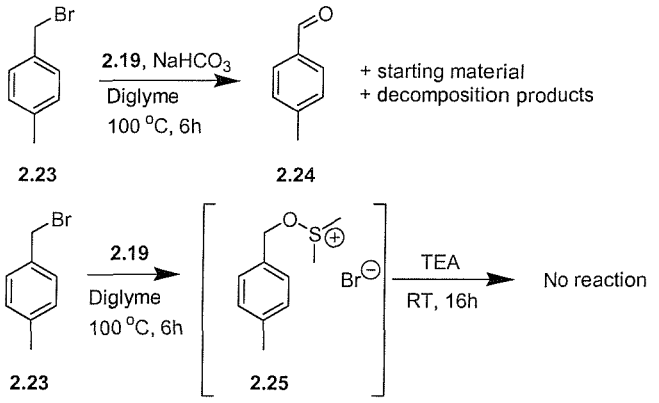


Scheme 2.8 Synthesis of a polymer-supported sulfone analogue.

2.4.Oxidations.

2.4.1. Kornblum oxidation[68]

Preliminary work in solution-phase was executed on the oxidation of benzyl bromides using the Kornblum reaction (Scheme 2.9).

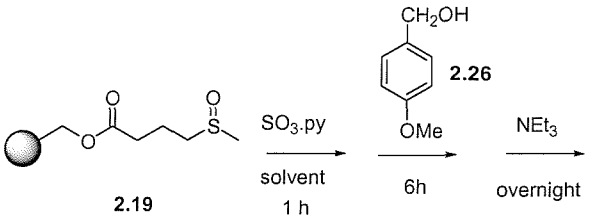


Scheme 2.9 Solution-phase model studies for the Kornblum oxidation.

The oxidations that have been reported required the presence of a base, typically $NaHCO_3$. In order to be suitable for the catch-and-release approach, it was essential that the intermediate sulfoxonium ion **2.25** could be formed quantitatively in the absence of base, and the reaction be completed with subsequent addition of a base to give the oxidised product. To discover if this was possible in the case of the Kornblum oxidation, *p*-methyl-benzyl-bromide **2.23** and the supported sulfoxide **2.19** were heated at 100 °C in diglyme with or without sodium bicarbonate. After this period, the reaction with base was quenched while TEA was added to the other reaction at room temperature. The crude products were then analysed by ^{1}H-NMR. The first reaction gave a substantial amount of aldehyde **2.24**. On the contrary, the second reaction showed no trace of aldehyde. This means that the presence of the base is necessary to drive the overall process to completion, suggesting that the formation of the key sulfoxonium ion intermediate is not irreversible (see also section 2.4.2 and Scheme 2.13, page 26). This obviously prevents any attempt to purify this intermediate by filtration, and so this method was abandoned, as a catch-and-release protocol would not be possible. Alternative approaches towards the formation of the crucial sulfoxonium ion were investigated, starting from alcohols as substrates.

2.4.2. Parikh-Doering oxidation[74]

As mentioned, oxidation of alcohols using DMSO requires an activator. The first activator that was selected was SO_3.py. It is an easy to handle solid, cheap and less hygroscopic and toxic than oxalyl chloride. The reaction using SO_3.py can operate at room temperature. However, SO_3.py is not soluble in DCM or THF, and since DMSO cannot be used, the first task was to search for a suitable solvent. DMF, NMP and nitromethane were evaluated. The general procedure used is outlined in Scheme 2.10.



Scheme 2.10 Attempted Parikh-Doering oxidations using polymer-supported sulfoxide.

The resin-bound sulfoxide was swollen in the solvent and reacted with the activator for 1 hour. The alcohol substrate **2.26** was then added, followed after 6 hours by excess triethylamine and left to react overnight before work-up.

In all the experiments, regardless of solvent and stoichiometric ratios employed, no trace of aldehyde was detected by NMR. Also the amount of the recovered alcohol was very low and in some cases no material was obtained at all. As an aqueous work-up was performed to eliminate the high-boiling solvents, the low recovery yields seemed to indicate that an ionic species was formed instead of the desired aldehyde. To avoid aqueous work-up, nitromethane was used as solvent, which could be evaporated under vacuum. Following this protocol, analysis of the crude mixture by ^{1}H-NMR revealed the presence of **2.27** which is indeed ionic, hence lost in the aqueous work-up.

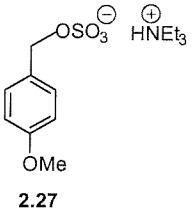
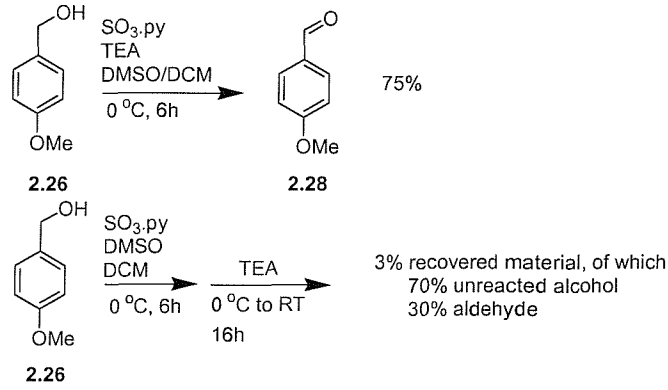


Figure 2.1

This structure has been confirmed by preparing **2.27** following a literature protocol for the synthesis of sulfates.[80]

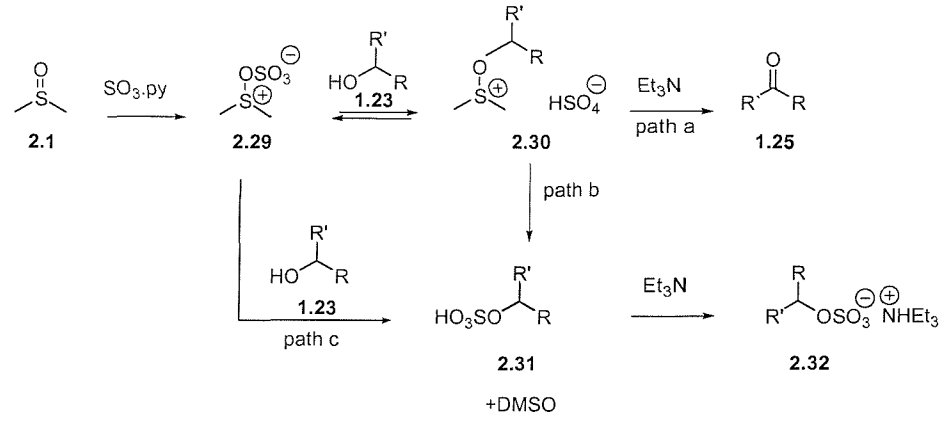
Following the unsuccessful experiments using the immobilised sulfoxide, some control experiments were performed in solution (Scheme 2.11).



Scheme 2.11 Solution-phase model studies for the Parikh-Doering oxidation.

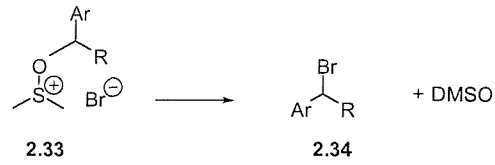
Two reactions were run, differing in the timing of the base addition: in the first reaction TEA was added at the beginning of the reaction, and anisaldehyde was obtained in good yield. However, when TEA was added after 6 h, only minute amounts of product were recovered. These observations could be explained as indicated in Scheme **2.12**. When the base was present from the beginning, the reaction was driven to completion because the intermediate sulfoxonium salt **2.30** was immediately and irreversibly transformed into the aldehyde (Scheme 2.12, path *a*). Otherwise, the sulfate **2.31** was formed (through either path *b* or *c*, Scheme 2.12), which could not undergo oxidation when finally TEA was added, and which was lost in water upon work-up, giving rise to the very low recovered yield.

As the base promoted elimination could not be separated from the formation of the sulfoxonium salt, this procedure was not suitable for a catch-and-release strategy.



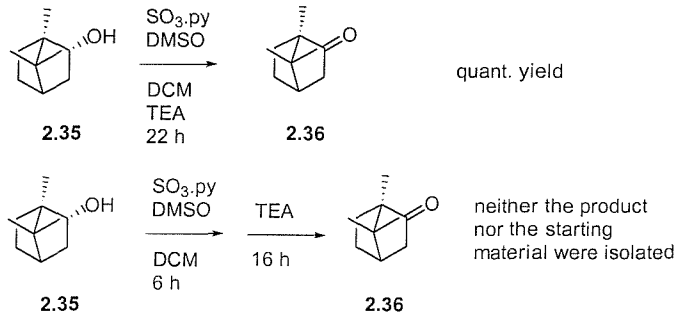
Scheme 2.12 Possible reaction paths in the Parikh-Doering reaction.

Nucleophilic substitutions on sulfoxonium salts by their counter ion (like the one depicted in Scheme 2.12, path b) had already been described for the synthesis of benzylic or allylic halides (Scheme 2.13).[81]



Scheme 2.13 Literature precedents for the nucleophilic substitution reaction on sulfoxonium ions.

It was decided to investigate this reaction using a non-activated, secondary alcohol. A parallel study similar to the one described for 4-methoxybenzyl alcohols was set up, using *endo*-borneol **2.35** as the substrate to be oxidised (Scheme 2.14).



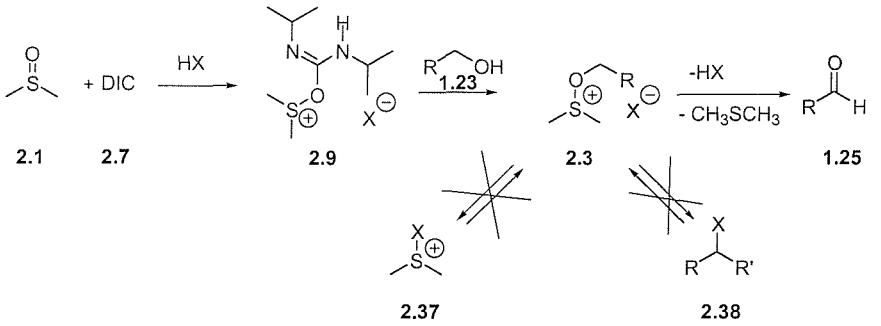
Scheme 2.14 Solution-phase model studies for the Parikh-Doering oxidation on a non-benzylic alcohol.

While the standard reaction gave quantitative yield, the reaction in which TEA was added in a second step gave, after aqueous work-up, only traces of either the starting material or the corresponding ketone **2.36**. Again, it was supposed that this was caused by the formation of the corresponding sulfate, although this product has not been isolated.

2.4.3. Pfitzner-Moffatt conditions[77]

In order to obtain a stable intermediate for our "catch-and-release" oxidation, it was decided to investigate an activation method for which a non-nucleophilic counter anion for the activated sulfoxonium ion **2.9** could be used . The use of a non-nucleophilic anion like BF_4^- should avoid the competitive formation of species like **2.32 or 2.34**. The only method for the activation of DMSO that allows such a counter anion is the use of a carbodiimide (typically DIC or DCC). In solution, this reaction is normally performed using a co-reagent that can act as both an acid and a base (typically dichloroacetic acid or pyridinium trifluoroacetate). For our purpose, it was again essential to demonstrate that it was possible

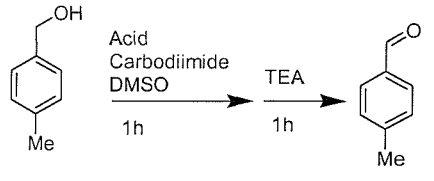
to separate the two steps of the oxidation, using first an acid that could catalyse the formation of the sulfoxonium salt, and then a base to promote the fragmentation of the sulfoxonium ion (Schemes 2.15). Because the two steps must be separated, the pKa of the acid must be low, so that the fragmentation does not take place before the addition of the base.



Scheme 2.15 Modified Pfitzner-Moffatt oxidation using a non-nucleophilic counter anion.

The first series of experiments (Table 2.1) revolved around the choice of the best acid to perform the first step and DMSO was used as solvent, thus being in great excess. As expected, the best acid was $HBF_4.Et_2O$: the yield of aldehyde **2.40** using 2 equivalents of acid and 3 equiv of DIC followed by an excess of TEA was satisfactory (70%, entry 7).

Table 2.1 Selection of the acid reactant for the modified Pfitzner-Moffatt oxidation.



Entry	Acid (equiv)	Carbodiimide (equiv)	TEA (equiv)	Yield[a]
1	Cl_3COOH (0.5)	DIC (3)	0	10%
2	Cl_3COOH (0.5)	DIC (3)	10	20%
3	Cl_3COOH (0.5)	DCC (3)	10	20%
4	$(PhO)_2P(=O)OH$ (0.5)	DCC (3)	10	25%
5	$(PhO)_2P(=O)OH$ (2)	DCC (5)	10	Complex mixture
6	$(PhO)_2P(=O)OH$ (4*0.5)	DIC (3)	20	60%
7	**$HBF_4.Et_2O$ (2)**	**DIC (3)**	**20**	**70%**
8	$HBF_4.Et_2O$ (2)	DIC (3)	0	0%

[a] Based on integration of the crude ^{1}H-NMR

No oxidation is observed without the addition of the base (entry 8). Also, reaction of alcohol **2.39** with DMSO and DIC in the presence of both TEA and HBF_4 in the usual ratios did not give any oxidation product. This demonstrated that tetrabutylammonium tetrafluoroborate could not promote the oxidation in the same way as dichloroacetic acid, and the formation of the sulfoxonium ion was indeed promoted by HBF_4.

A series of experiments was then run to evaluate the effects of the solvent, of the stoichiometric ratios and of the order of the additions.

The results are summarised in Table 2.2.

Table 2.2 Solution-phase model studies for the modified Parikh-Doering reaction.

Entry	Method (see text)	DIC (equiv)	HBF_4 (equiv)	DMSO (equiv)	Solvent	Conc. (M)	Yield[a]
1	A	3	2	1	DCM	0.28	15%
2	A	3	2	1	THF	0.28	5%
3	A	3	2	1	$MeNO_2$	0.28	--
4	A	3	3	2	DCM	0.28	25%
5	B	3	3	2	DCM	0.56	15%
6	B	3	3	4	DCM	0.28	<10%
7	B	1.5	1.5	2	DCM	2.24	<10%
8	D	1.5	1.5	2	DCM	0.56	<10%
9	D	1.5	1.5	2	DMF	0.56	<10%
10	**A**	**3**	**3**	**4**	**DCM**	**0.56**	**60%**
11	C	3	3	4	DCM	0.56	55%
12	B	1.5	1.5	2	DCM	0.56	<10%
13	B	3	3	4	DCM	0.56	<10%
14	A	3	3	4	DMF	0.56	Complex mixture
15	B	3	3	4	DMF	0.56	<10%
16	B	3	3	≈20	DMSO	0.56	20%
17	**A**	**3**	**2**	**≈20**	**DMSO**	**0.28**	**70%**

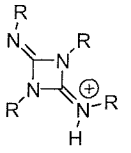
[a] Based on integration of the crude ^{1}H-NMR.

All the experiments have been run using 4-methyl-benzyl alcohol (1 equivalent) as the substrate. Several solvents were tried (DCM, THF, nitromethane, entries 1-3). Although the stoichiometric ratios were not optimal in this series of experiments, hence the bad yields, DCM seemed the best solvent and was used for most subsequent experiments. We have used four different orders for the addition of substrate, DMSO, carbodiimide and tetrafluoroboric acid, while TEA was always added at a later stage (see experimental section for details).

The first evidence gathered from this series of experiments was that the order of addition of the reagents was of capital importance. All the experiments in which the alcohol was added after DMSO, HBF_4 and carbodiimide were unsuccessful, regardless of the order in which the last two were added (methods B and D). On the contrary, the relative order of addition of the acid and the carbodiimide was not important (HBF_4 added before DIC in method C, the opposite in method A).

One possible explanation for the crucial importance of the order of addition was that the DMSO-carbodiimide complex **2.9** (Scheme 2.15) was not stable, even in the presence of a large excess of DMSO (compare entries 17 and 16). In this case the alcohol had to be present in the medium in order to trap **2.9** immediately when it was formed.

As for the stoichiometry, different factors could be observed: first of all using a DIC : acid ratio of >1 lowered the yields when compared to a 1:1 ratio. The presence of different isopropyl signals in the ^{1}H-NMR of the crude mixture suggested that different DIC adducts were formed, probably by nucleophilic addition of excess DIC to the protonated DIC, although the adducts have not been isolated and characterised. The formation of the dimeric species **2.41** has been demonstrated for the reaction of carbodiimides with tetrafluoroboric acid.[82] When the 1:1 DIC:HBF_4 ratio was employed, no neutral DIC was present to act as nucleophile, as HBF_4 is a very strong acid.



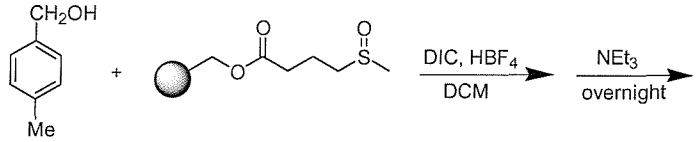
2.41

Figure 2.2 Carbodiimide dimer.

Another important factor was that the presence of an excess of DMSO compared to carbodiimide and acid greatly increased the yields. Probably this was due to the fact that

the protonated DIC had to be readily and completely trapped by the DMSO. Of course, the necessity to use a large amount of sulfoxide compared to the substrate alcohol became a problem when transferring this chemistry to the solid phase. Hence, the use of equal amounts of carbodiimide and acid and an excess of sulfoxide, adding the alcohol substrate before any other reagent was found to be the best method.

Having established the best conditions to use this system in solution, the oxidation was performed using the resin-bound sulfoxide **2.19** (Scheme 2.16). The same protocol that had been found to work best in solution was applied. The resin (2 equiv) was swollen in the solvent, then the alcohol (1 equiv) and DIC (1.5 equiv) were added, followed by the HBF_4 (1.5 equiv). In a second step, an excess of TEA was added. The results were very disappointing: no trace of oxidation product could be observed, and quite surprisingly the starting material was recovered unchanged. The only other by-product that could be detected was a small amount (ca. 7.5 mol %) of the corresponding symmetrical ether.

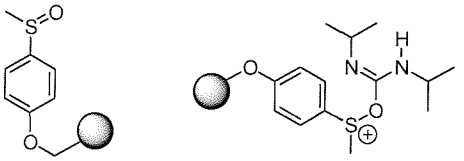


2.39 **2.19**

Scheme 2.16 Attempted oxidations using polymer-supported sulfoxide **2.19**.

One possible explanation for this behaviour was that the polymer-supported sulfoxide was not reacting fast enough with the protonated carbodiimide **2.8**. It is well known that reactions involving molecules on a polymer-support exhibit slower kinetics compared to their soluble analogues. In this case, the retarded intervention of the sulfoxide was causing the reaction to follow some alternative pathway which evidently did not involve the polymer-supported sulfoxide. This was confirmed by the fact that the polymer-bound sulfoxide appeared unchanged by IR analysis. The alternative pathway that was thought to be followed by the reaction has not been elucidated.

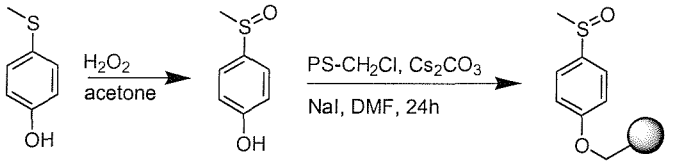
As a possible solution it was decided to prepare polymer-supported sulfoxide **2.42**, which could have interesting characteristics: the mesomeric effect of the *p*-alkoxyphenyl moiety could possibly render the sulfoxide both more reactive and its adducts with carbodiimides (**2.43**) more stable.



2.42 2.43

Figure 2.3 Alternative polymer-supported sulfoxide.

The synthesis of **2.42** was very straightforward (Scheme 2.17): the commercially available 4-methoxy-thiophenol **2.44** was quantitatively oxidised using H_2O_2 in acetone,[83] without overoxidation to sulfone. Sulfoxide **2.45** was then linked to the resin using cesium carbonate in DMF at 100 °C in the presence of sodium iodide.[84] The coupling worked smoothly and gel-phase ^{13}C-NMR showed complete substitution of the chlorine.



2.44 2.45 92% 2.42

Scheme 2.17 Synthesis of the alternative polymer-supported sulfoxide **2.42**.

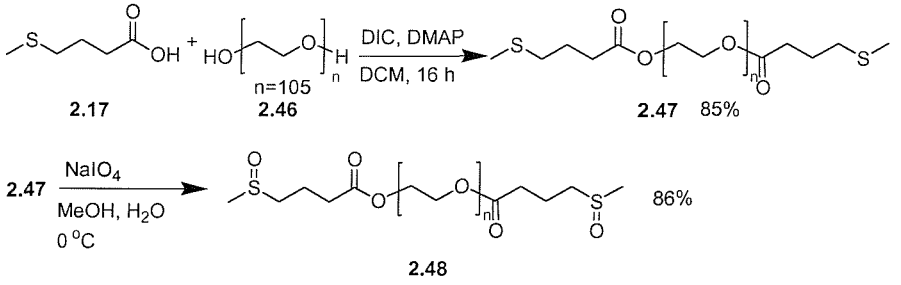
However, when the new resin was tested for the oxidation of *p*-methyl-benzyl alcohol no aldehyde was observed. The electron-donor effect does not seem to influence the reaction in any way.

As the use of a sulfoxide linked to a classical polystyrene polymer did not work out, it was decided to explore a different technique. The main point that had emerged so far was that in order for the reaction to proceed the sulfoxide was required to be in solution, but for the purification step it had to be on the solid-support. A possible solution to this dilemma was the use of poly(ethylene)glycol (PEG), as these polymers possess a very interesting property: they are soluble in many organic solvents (like DCM), but are highly insoluble in diethyl ether, provided that they have a high enough molecular weight.[85] In fact, Vederas described the use of a PEG-linked sulfoxide for Swern oxidations.[40]

Using a PEG-bound sulfoxide, it could be theoretically possible to perform the oxidation in solution (in DCM, which had already been assessed as the best solvent for this reaction), then by adding diethyl ether the PEG-bound intermediate should precipitate allowing for a purification step and finally be re-dissolved in DCM for the final step of the

oxidation. As a quick and quantitative precipitation was needed, a high molecular weight PEG was selected (4600 g/mol).

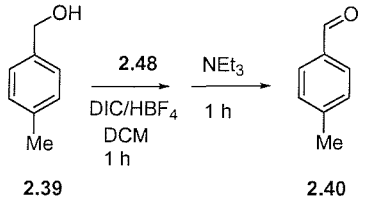
The synthesis of the PEG-linked sulfoxide **2.48** was performed using the same procedure described by Vederas (Scheme 2.18).[40]



Scheme 2.18 Synthesis of PEG-supported sulfoxide **2.48**.

The first attempts to use this reagent to perform the oxidation of *p*-methylbenzyl alcohol were very disappointing: in 3 experiments with different ratios of sulfoxide to DIC to HBF_4 the yields remained lower than 25% (Table 2.3, entries 1-3). Oxidations performed in presence of molecular sieves worked considerably better, giving yields in the range 47-53% (Table 2.3, entries 4-5), not too far from the results obtained using DMSO.

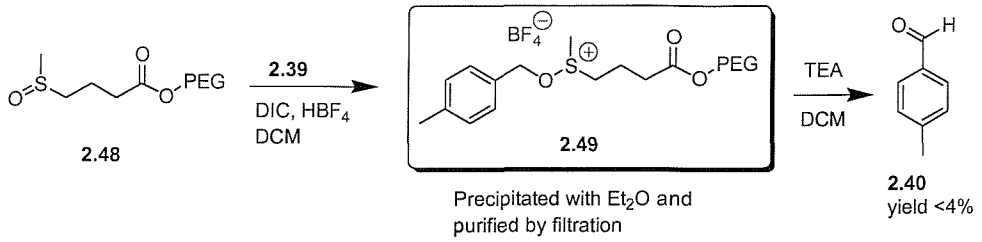
Table 2.3 Oxidation reactions using PEG-supported sulfoxide **2.48**.



Entry	DIC (equiv)	HBF_4 (equiv)	**2.48** (equiv)	**2.45** (%)
1	1.5	1.5	2	25
2	1.5	0.75	2	15
3	3	3	4	6
4	1.5	1.5	4	55[b]
5	1.5	1.5	2	50[b]

[a] Based on integration of the crude ^{1}H-NMR; [b] Reaction run in presence of 4Å mol. Sieves.

However, every attempt to perform the reaction using the catch-and-release procedure, precipitating and purifying intermediate **2.49** using Et_2O, has completely failed, and at best 4% of the desired product could be found after the second step (Scheme 2.19).



Scheme 2.19 Attempted catch-and-release oxidation of 4-methylbenzyl alcohol with isolation of the PEG-supported intermediate sulfoxonium ion.

2.5. Conclusions

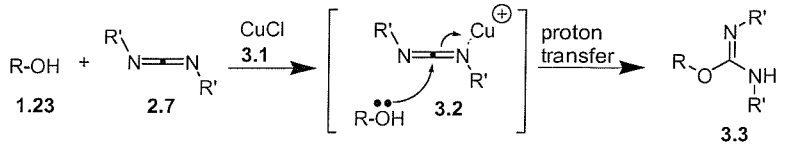
The main goal of this project, to develop a catch-and-release reaction for the oxidation of alcohols to carbonyls, has not been met. A number of the traditional methods employed to accomplish this reaction using dimethyl sulfoxide were demonstrated not to be suitable for a catch-and-release approach. A procedure suitable for the purpose was developed and proved to be moderately successful for the oxidation of alcohols using a PEG-supported sulfoxide. However, implementation of the catch-and-release methodology proved to be impossible.

3. Esterifications using polymer-supported *O*-alkylisoureas[86-88]

3.1 Introduction and project aims

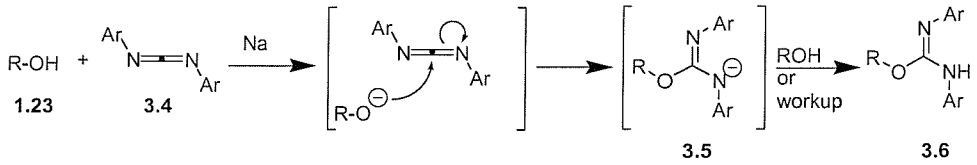
3.1.1. Formation of *O*-alkylisoureas

O-Alkyl-*N,N'*-disubstituted isoureas have been known for over 100 years.[89] The first synthesis was reported as early as 1899.[90] They are prepared by reaction of a carbodiimide with an alcohol, usually catalysed by a copper-based Lewis-acid, typically CuCl or $CuCl_2$. The metal ion coordinates the carbodiimide, hereby promoting a nucleophilic addition leading to the isourea (Scheme 3.1).[89]



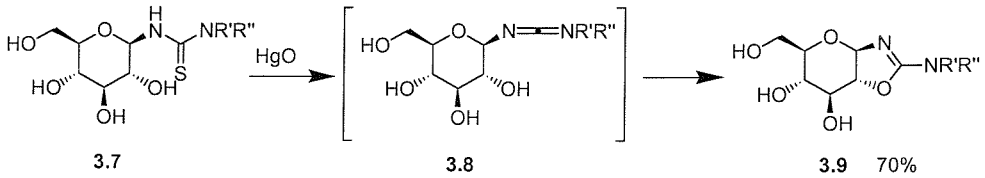
Scheme 3.1 Mechanism of the copper chloride-catalysed synthesis of *O*–alkylisoureas.

When both R'- substituents are aromatic, a base-catalysed preparation of isoureas is possible (Scheme 3.2).[91] The alcohol is deprotonated in the first step, followed by alkoxide attack on the carbodiimide, forming anion **3.5** which can either deprotonate another alcohol molecule or remain stable until acidic work-up. With dialkylcarbodiimides the electron-donating properties of the alkyl groups make this process unfavourable.



Scheme 3.2 Mechanism of the base-catalysed synthesis of *O*–alkylisoureas.

In some cases the reaction between alcohols and carbodiimides can proceed spontaneously when the reaction is intramolecular, as exemplified by the synthesis of tetrahydropyrano-[2,3-d]oxazoles **3.9** presented in Scheme 3.3.[92]

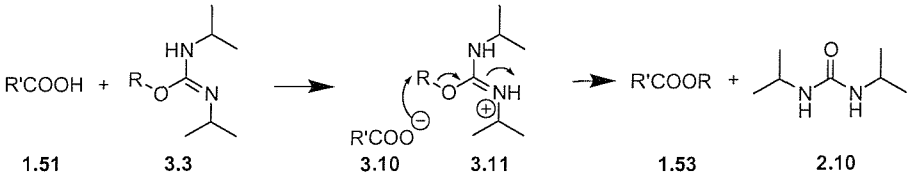


Scheme 3.3 Intramolecular additions of alcohols to carbodiimide can proceed in the absence of the copper catalyst

For most applications, DIC and DCC are used to prepare isoureas. Hence, for reasons of brevity, we will abbreviate *O*-alkyl-*N,N'*-disubstituted isoureas to *O*-alkylisoureas as the *N*-substitution consists of either isopropyl or cyclohexyl groups.

3.1.2. Reaction of *O*-alkylisoureas with protic species

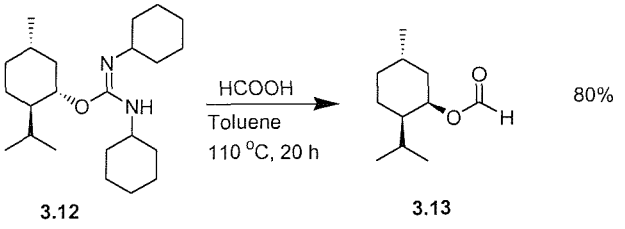
In 1967 Vowinkel discovered that *O*-alkylisoureas can react with carboxylic acids to give carboxylic esters with concomitant formation of dialkylurea.[93] The accepted mechanism is depicted in Scheme 3.4.[89]



Scheme 3.4 Mechanism of the reaction of *O*–alkylisoureas with carboxylic acids.

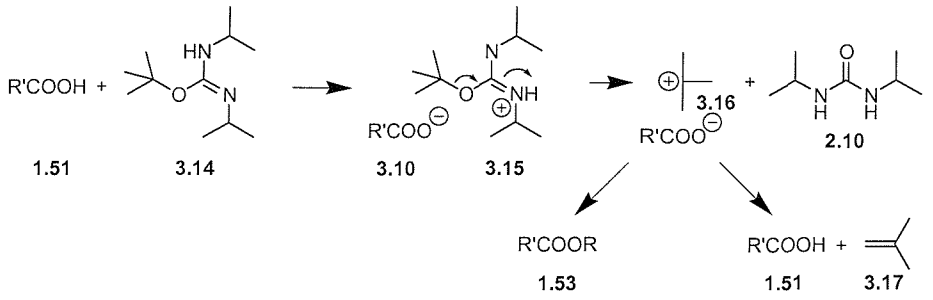
The first step is the protonation of the basic isourea by the acid. The isourea moiety is thus converted into a good leaving group, and can subsequently be substituted by the carboxylate anion formed in the first step. The driving force of the process is the formation of the stable urea product.

Support for this mechanism was provided by Kaulen, who demonstrated that the reactions of isoureas derived from secondary alcohols proceed with inversion of configuration, although whether this happens in a true S_N2 reaction or an S_N1 with an ion pair mechanism is not entirely clear (Scheme 3.5).[94]



Scheme 3.5 Esterification reactions with *O*-alkylisoureas proceed with inversion of configuration.

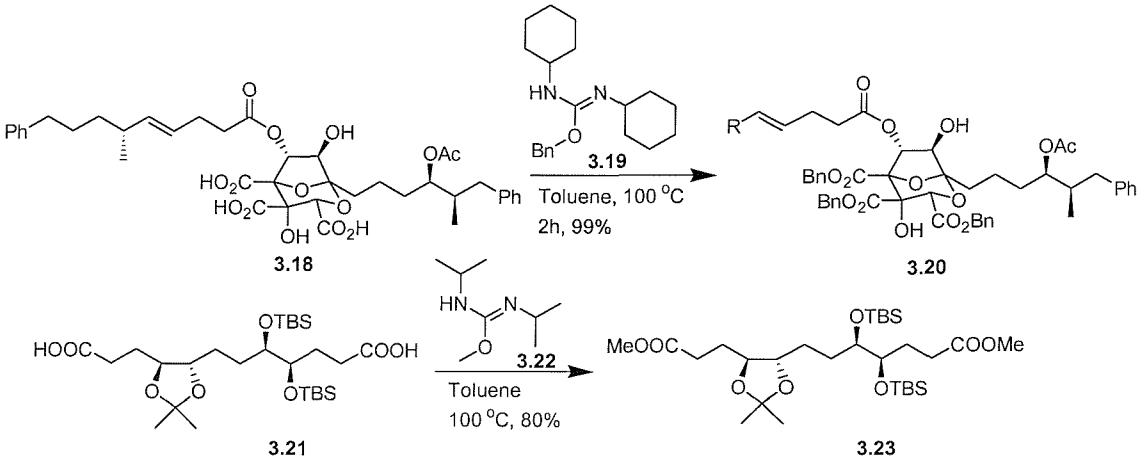
In the case of isoureas derived from tertiary substrates, the reaction is most likely to occur via an S_N1 mechanism. In this case, elimination (E1) is known to be a competing side-reaction, so that when tert-butyl esters are sought, an excess of isourea must be used to compensate for the decomposition of the isourea reagent (Scheme 3.6).



Scheme 3.6 Esterification reactions with *O-tert*-butylisoureas and competing elimination reaction.

Over the years, the use of isoureas in ester formation reaction has found widespread application, especially for the introduction of protecting groups for carboxylic acids. Various isoureas were used for this purpose such as *O*-methyl, benzyl, allyl, *p*-methoxybenzyl, *tert*-butyl and diphenylmethyl isourea, which were all prepared via copper catalysis from the corresponding alcohols and a carbodiimide.

The esterification reaction shows a remarkable chemoselectivity, since several functional groups can be present on the carboxylic acid without affecting the reaction: alcohols, phenols, protected amines and amides are among the groups that do not react under these reaction conditions. Hence, ester formation *via* isoureas has been used in natural product synthesis. For example, Nicolaou used isoureas to convert carboxylic acids into benzyl esters in his synthesis of zaragozic acid A without protecting the hydroxyl groups on the bicyclic core.[95] Sharpless has used *O*-methylisourea to prepare methyl esters in a synthesis of enantiomerically pure C12 building blocks used in acetogenin synthesis (Scheme 3.7).[96]

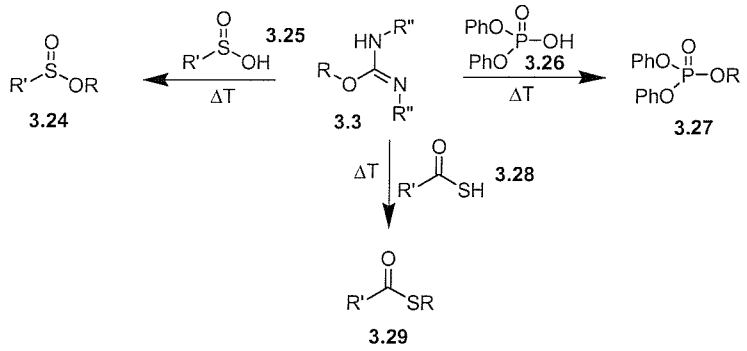


Scheme 3.7 Examples of the use of *O*-alkylisoureas in total synthesis.

Another reason for the popularity of these reagents is that, compared to other alkylating agents, they have a low toxicity (cf. for example *O*-methylisourea with methyl iodide or dimethyl sulfate) and reduced associated hazards (cf. diazomethane). Also, they are easy

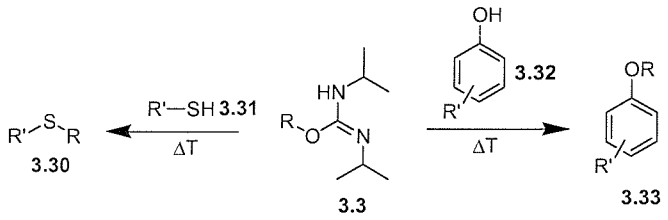
to handle (cf. isobutene) and the esterification reactions do not require anhydrous conditions.

Carboxylic acids are not the only species that can react with *O*-alkylisoureas. Reaction of isoureas with other acids such as dialkylphosphonic acids,[91] sulfinic acids[97] and thiocarboxylic acids[98] are reported to give the corresponding esters (Scheme 3.8).



Scheme 3.8 Reactions of *O*-alkylisoureas with phosphonic and sulfinic acids.

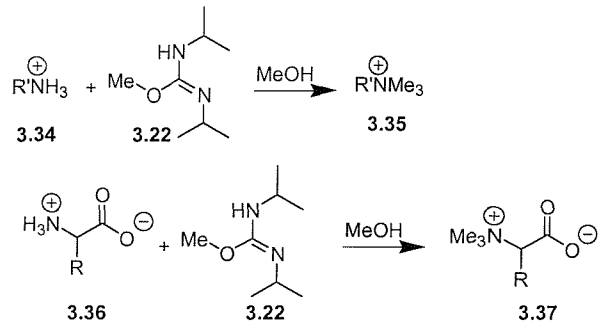
A few years after his discovery of the reaction of isoureas with carboxylic acids, Vowinkel discovered that phenols[99] and thiols[100] can react with isoureas as well (Scheme 3.9). However, their much reduced acidity compared to carboxylic acids means that the reaction requires much harsher conditions, typically heating a mixture of phenol or thiol and isourea without solvent for several hours at 100 °C or more. Less forcing conditions can be employed for aromatic thiols, due to their higher acidity.



Scheme 3.9 Reactions of *O*-alkylisoureas with thiols and phenols.

Amines can react with isoureas, but only in their protonated form (Scheme 3.10).[101] So for example reaction of benzylamine hydrochloride with 3 equivalents of *O*-methylisourea affords benzyl-trimethylammonium chloride. Unfortunately, it has not been proven possible to obtain controlled partial alkylation, and the reaction always proceeds to the ammonium salt. In the case of amino acids, the reaction with isoureas can either proceed through *O*- or *N*- alkylation, depending on the solvent. In protic solvents such as water or methanol the only products obtained are alkylated amino acid betaines. However, if the reaction is carried out in less polar solvents (such as THF), the reduced solvation of the

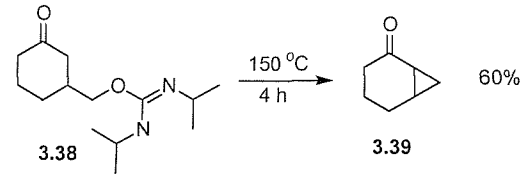
carboxylate group renders the latter more nucleophilic resulting in formation of mixtures of products.



Scheme 3.10 Reactions of *O*-alkylisoureas with amine hydrochlorides and amino acids.

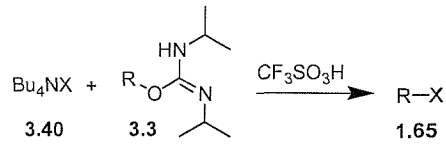
Among other nitrogen-containing molecules which have been shown to react with isoureas are phthalimides, pyrimidines and tetrazoles, although few examples have been reported.[102]

Also a few reactions with carbon nucleophiles have been successful, especially when an intramolecular reaction was possible (Scheme 3.11).[103]



Scheme 3.11 Cyclisation of γ-hydroxy-ketones.

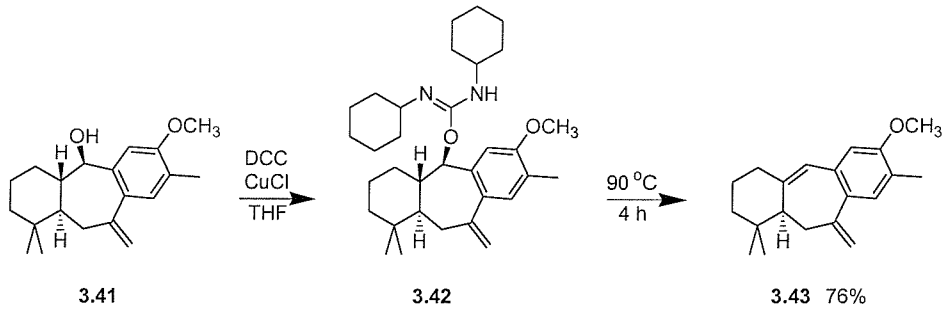
Finally, Golding reported how isoureas could be converted into haloalkanes by reaction with the appropriate tetrabutylammonium halide in the presence of 1 equivalent of triflic acid to protonate the isourea (Scheme 3.12).[104] Alkyl bromides and iodides could be obtained using this procedure, with excellent yields especially for allylic alcohols. However, when the reaction was performed on chiral alcohols extensive racemisation could be observed. Optical purity decreased with length of reaction, which is consistent with racemisation of the chiral alkyl bromide in the presence of excess bromide ions via Finkelstein reaction.



Scheme 3.12 Synthesis of haloalkanes using the Golding method.

3.1.3 Other reactions

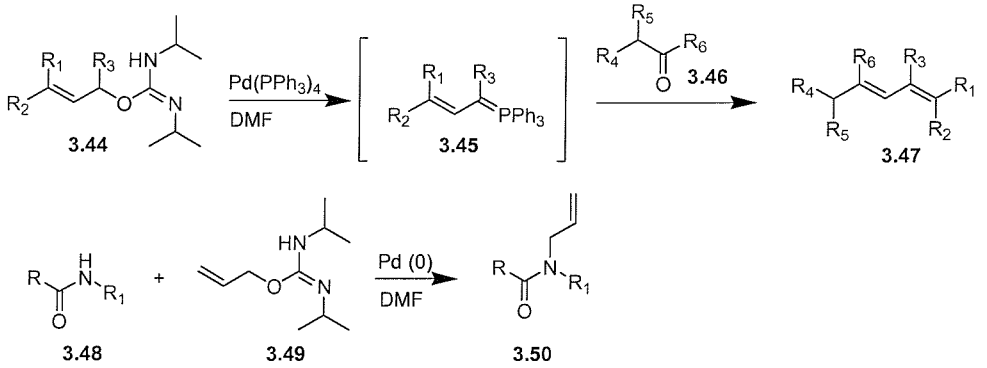
Tertiary, allylic or benzylic isoureas are reported to form alkenes quite easily upon heating (Scheme 3.13).[105] The reaction of isoureas derived from non-benzylic or allylic secondary alcohols proved to require very high temperatures and exhibited low selectivity when different regioisomeric alkenes could be formed.



3.41 3.42 3.43 76%

Scheme 3.13 Dehydration of a benzylic *O*-alkylisourea.

Finally, a few examples of reactions which did not require the presence of a proton source have recently been described. *O*-Allylisoureas can be used for the N-alkylation of amides under palladium catalysis with amides and with aldehydes.[106-108] The reaction with aldehydes gives dienes through a Wittig reaction of intermediate ylide **3.45**, while amides are *N*-alkylated (Scheme 3.14).

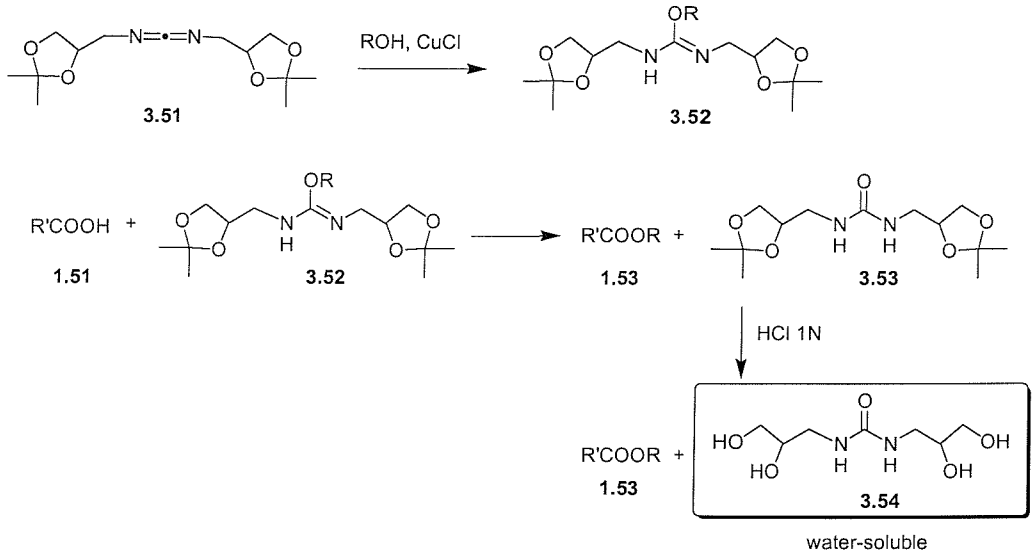


Scheme 3.14 Reactions of *O*-allylisoureas under palladium catalysis.

3.1.4 Project aims

Despite the obvious usefulness of isoureas, particularly in ester formation reactions, the process is made less attractive due to the need of removing the urea byproduct. Even if most of it can be removed by filtration due to its low solubility in most solvents, additional purification, typically column chromatography, must still be performed. This problem had been recognised in the past, and Rapoport had reported a solution in the form of phase-

tagged isoureas as shown in Scheme 3.15.[109] Carbodiimide **3.51** (which was developed for use in peptide synthesis), was first converted into the corresponding isourea using the traditional conditions. When it was made to react with a carboxylic acid, the urea byproduct as well as any unreacted isourea could be converted into water-soluble species by treatment with acid so that they could be removed by extraction.



Scheme 3.15 A phase-tagged *O*-alkylisourea: synthesis and application for ester synthesis.

However, though this method possesses some attractive features, it has still some drawbacks, especially for application in parallel synthesis: not all substrates could survive the acid hydrolysis which is necessary, water-soluble esters would be lost and finally the application of liquid-liquid extractions to robotised parallel synthesis is not as ideal compared to the use of filtration protocols.

Hence, there was clearly much room for improvement in this area and our first project was to develop a series of polymer-supported *O*-alkylisoureas and demonstrate their utility for the esterification of carboxylic acids in parallel synthesis.

3.2 Synthesis of polymer-supported carbodiimide resin

The typical synthesis of isoureas from carbodiimides and alcohols was an excellent starting point for our purposes. Not only does it allow for great potential diversity with respect to the alkyl groups to be transferred to the carboxylic acids, solid supported carbodiimides are also commercially available. Of the polymer-supported carbodiimides commercially available on the market, *N*-cyclohexyl-*N'*-methylpolystyrenecarbodiimide

1.38a was selected because it is available with a considerably higher loading than either **3.55** or **3.56**.

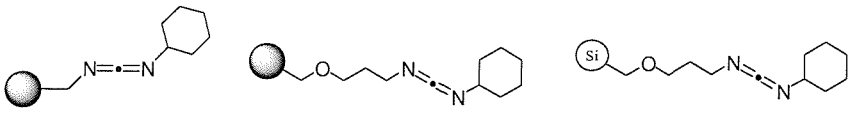
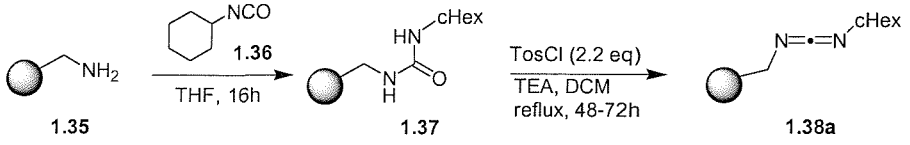


Figure 3.1 Commercially available polymer-supported carbodiimides.

Resin **1.38a** is prepared industrially in two steps from aminomethylpolystyrene.[35] In the first step reaction with cyclohexyl isocyanate affords urea **1.37**. The second step is a dehydration of the urea using tosyl chloride and TEA. The industrial preparation calls for the dehydration reaction to take place under rather harsh conditions to ensure complete conversion (Scheme 3.16).



Scheme 3.16 Industrial synthesis of commercial polymer-supported carbodiimide **1.38a**.

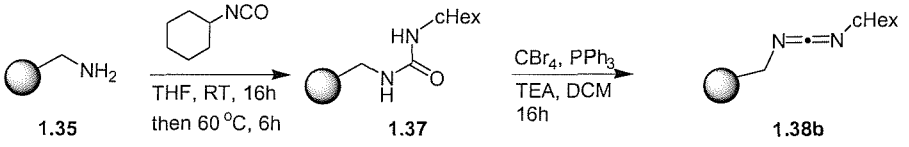
For reasons that will become clear later (chapter 3.4) it was decided to investigate an alternative synthesis for carbodiimide resin **1.38**. The urea formation was straightforward (using the literature protocols),[35] but the dehydration was not easily accomplished. A number of dehydration procedures which had been described as very successful for this reaction in solution phase were tested.[110,111] Quite surprisingly most of them failed completely (Table 3.5). Only methods based on the use of triphenilphosphine gave the desired carbodiimide (as analysed by IR).

Table 3.1 Dehydration of polymer-supported urea **1.37**

Dehydrating agent	Base	Formation of carbodiimide
$SOCl_2$	TEA	No
$SOCl_2$	DBU	No
PBr_3	TEA	No
PBr_3	DBU	No
$(PhO)P(O)Cl_2$	TEA	No
$Ph_3P.Br_2$	TEA	Yes
$CBr_4 + Ph_3P$	TEA	Yes

The use of $Ph_3P.Br_2$ gave very good conversions but proved to be difficult to reproduce. While these studies were in progress, the use of CBr_4 in conjunction with Ph_3P was described by Lange for dehydration of polymer-supported ureas to give carbodiimides.[112] Although no details were given (not even the number of equivalents used or the reaction time) it was decided to investigate this method and it was found that the dehydration could be accomplished using 3 equivalents of CBr_4 and 3 equivalents of Ph_3P (Scheme 3.17). Though Lange concluded that the best dehydration method involved the use of Burgess reagent, it was decided against using this method as its cost was too high for large-scale preparations.

The carbodiimide resin prepared via this alternative procedure will be referred to as **1.38b**.



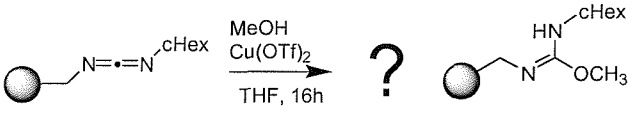
1.35 1.37 1.38b

Scheme 3.17 Modified synthesis of polymer-supported carbodiimide **1.38b.**

3.3 Synthesis of polymer-supported *O*-alkylisoureas

The first target was the simplest member of this family, *O*-methyl-*N*-cyclohexylcarbodiimide-*N'*-methylpolystyrene **3.57**.

Our initial attempts of reaction of methanol with resin **1.38** in the presence of copper salts (50-70 mol%) in THF gave confusing results (Scheme 3.18): while the carbodiimide band in the IR spectrum (2119 cm-1) of the resin clearly disappeared, the expected band around 1650 cm^{-1} was not really visible while unexpected strong bands at 1223, 1152 and 1027 cm^{-1} were present. Moreover, the resin thus prepared did not react with a carboxylic acid to form the expected ester. The facts that the resin was of green colour and that upon addition of a carboxylic acid the solution turned blue seemed to suggest that copper species were still present on the resin, which could be the origin of these anomalies.



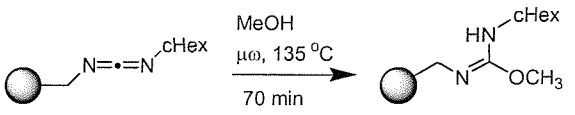
1.38 3.57

Scheme 3.18 Attempted synthesis of polymer-supported *O*-methylisourea.

It was decided that using a simplified procedure at this point, without the use of copper catalysis, would render the analysis of the product much easier. In 1899, Dains had demonstrated that isoureas could be formed simply by heating a mixture of neat carbodiimide and an alcohol, which, applied to the formation of immobilised polymer-supported *O*-methyl isourea, would require heating resin **1.38** in methanol as solvent.[90] However, a major obstacle was the well known inability of methanol to swell polystyrene-type resins, without which no reaction could be expected within the beads. The recent development of microwave technology gave an answer to that problem. As described in the introduction, in focused microwave ovens it is possible to reach high temperatures in a very homogeneous fashion in short times. At these high temperatures the polarity of a solvent decreases significantly, which allowed the use of methanol as solvent for solid-phase chemistry, as demonstrated by Westman.[57]

Hence, it was decided to investigate whether irradiation of resin **1.38** in methanol as the solvent could afford the desired isourea (Scheme 3.19). The reactions were carried out at the temperature of 135 °C as this was the highest temperature that could be consistently achieved without generating excessive pressure (the system has a maximum allowed pressure of 20 bars).

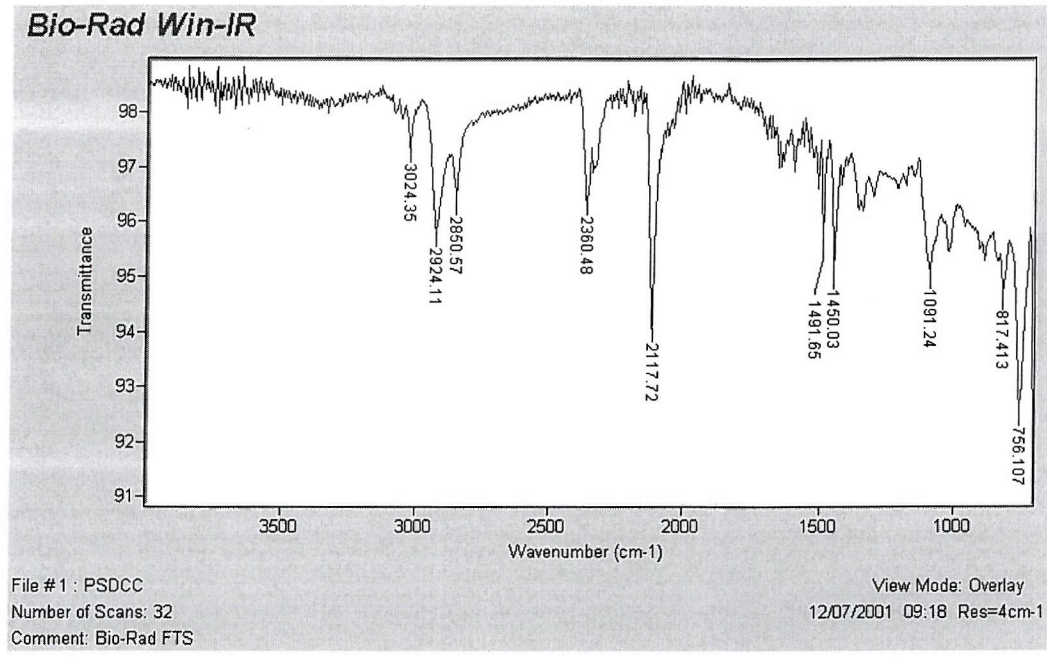
After a 30 minutes reaction, the IR of the resin revealed a significantly reduced carbodiimide band and the presence of two new bands at 1654 and 1329cm^{-1} which were easily attributed to the desired product by comparison with the IR spectrum of *O*-methylisourea. As the reaction temperature could not be further increased to achieve total conversion, the reaction times had to be increased. A series of experiments conducted with different reaction times showed that 70 minutes were necessary to achieve complete conversion.



1.38 **3.57**

Scheme 3.19 Microwave-assisted synthesis of polymer-supported *O*-methylisourea **3.57**.

As no other reagent apart from methanol was required, the purification of the resin was very straightforward, as opposed to the copper catalysed procedure: a simple filtration followed by washing twice with DCM and drying under vacuum for 4-6 hours afforded the product, with a theoretical loading of 1.75 mmol/g assuming complete conversion.



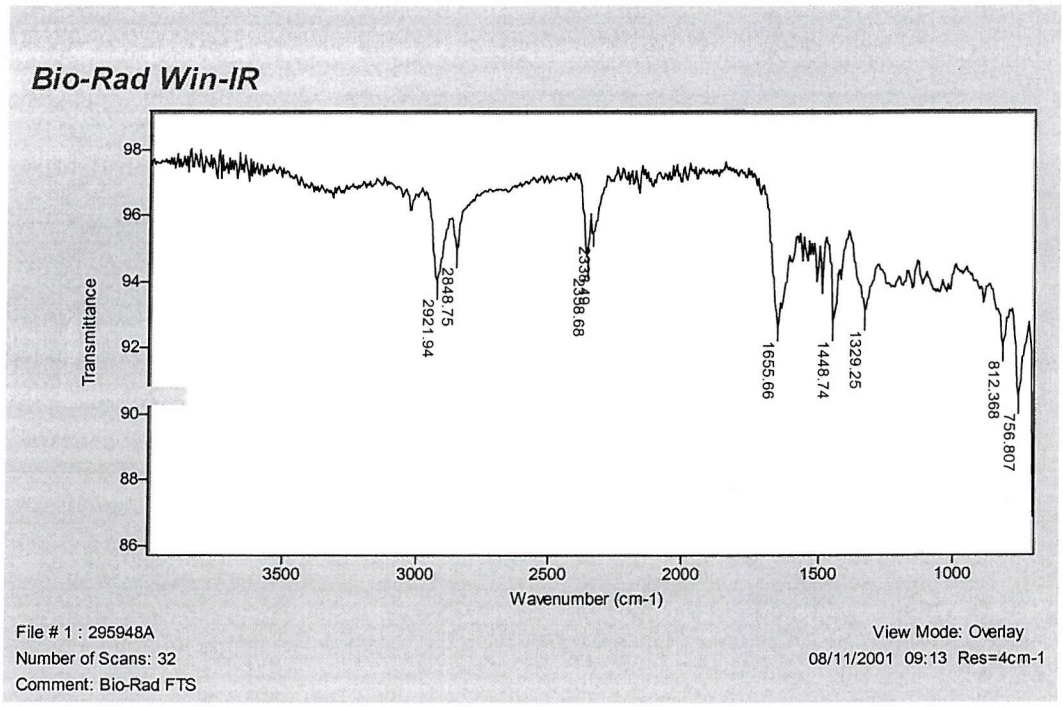
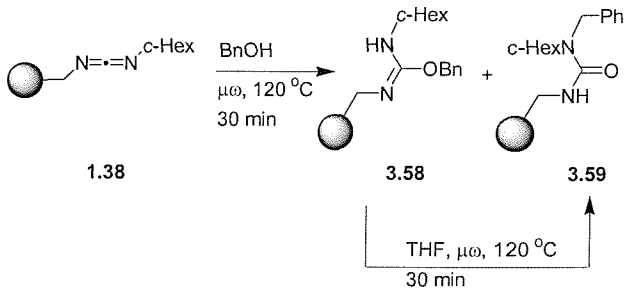


Figure 3.2 IR spectra of resins **1.38** (top) and **3.57** (bottom).

Subsequently the preparation of other polymer-supported *O*-alkylisoureas using the same methodology used for **3.57** was attempted. However, when carbodiimide **1.38** was reacted with benzyl alcohol under microwave irradiation the reaction was less successful compared with the preparation of the methyl derivative. Although the isourea band at 1655 cm^{-1} was present in the IR spectrum of the product, two strong bands were also present at 1640 and 1555 cm^{-1}, indicating the presence of a urea group. When the resin was resubmitted to further heating in the absence of benzyl alcohol using THF as solvent an increase of the urea bands at the expense of the isourea band was observed. This result was attributed to the rearrangement of the desired isourea **3.58** to the urea **3.59** (whose structure was assumed based on IR analysis) as depicted in Scheme 3.20. Some precedents for similar rearrangements have been reported for *O*-allylisoureas,[113] although in our hands heating soluble *N,N'*-diisopropyl-*O*-benzyl isourea under microwave-irradiation (150 °C) did not cause any rearrangement.



Scheme 3.20 Attempted microwave-assisted synthesis of polymer-supported *O*-benzylisourea **3.58**.

Since it was suspected that the urea forming reaction was induced by heating, the formation of these isoureas at room temperature had to be reinvestigated. It was hence decided to return to the copper-catalysed reaction but with other copper-sources than CuCl. The first copper salt that was investigated was copper (II) triflate. Compared to copper (I) chloride, which is normally used for the preparation of soluble *O*-alkylisoureas, it has a better solubility in organic solvents. Reaction of polymer-supported carbodiimide **1.38** with a 1/1 mixture of methanol in anhydrous THF using ca. 0.5 molar equivalents of copper triflate overnight afforded a product whose IR did not show any carbodiimide band. However, the IR spectrum did not match that of the authentic resin obtained with the microwave-assisted reaction. At this point it was strongly believed that the presence of the copper species bound to the resin was responsible for this observation, and a suitable washing procedure was sought.

Repeated washings with various solvents (DMF, THF, methanol, DCM and mixtures of these) did not have any effect. Considering the strong affinity of copper for nitrogen ligands, washing with solutions of various amines dissolved in DCM or DMF was attempted. Both propylamine and triethylamine did not have any effect, but when a solution of tetramethylethylenediamine (TMEDA) in DCM was used the solution immediately became dark blue, evidencing the formation of a diamine-copper complex in solution (Figure 3.3). After 3 washings the diamine solution remained colourless, indicating that all the copper had been removed. After the subsequent washings to remove any traces of TMEDA (DMF, MeOH, DCM) and drying overnight under vacuum, the resin showed an IR spectrum identical to the authentic samples. It is worth emphasising that while amine hydrochloride salts and amino acids are known to react with isoureas, amines themselves do not react with unactivated isoureas. No degradation of **3.57** was observed after prolonged treatment with the diamine solution, even in the presence of $Cu(OTf)_2$.

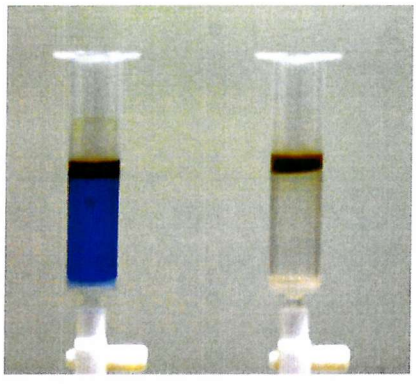
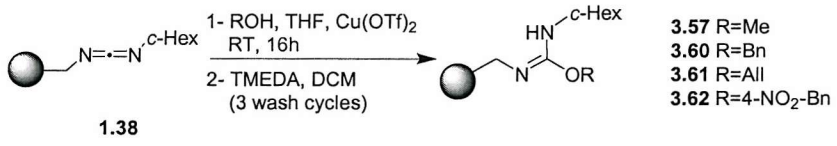


Figure 3.3 Effect of resin washing with TMEDA solutions in DCM: (left) first washing; (right) third washing. The resin is floating on top of the solvent.

A series of optimisation reactions was performed to find how much copper catalyst was necessary to complete the reaction within 16 hours and it was found that 7 mol% were sufficient. The reaction could be successfully applied for the preparation of *O*-benzyl, *O*-allyl and *O*-4-nitrobenzyl isoureas **3.60**, **3.61** and **3.62** (Scheme 3.21).



1.38

Scheme 3.21 Synthesis of polymer-supported *O*-alkylisoureas using copper catalysis.

The reaction did not proceed so smoothly for the 2-trimethylsilyl derivative **3.64** (Scheme 3.22). In this case the presence of significant urea bands was detected in the IR spectrum. Analysis by gel-phase ^{13}C-NMR and MAS ^{1}H-NMR proved that only a minor amount of trimethylsilyl groups were present on the resin. Presumably, the Cu^{2+} cation is a strong enough Lewis acid to induce an E1 type elimination on the isourea, since the TMS group would stabilise a carbocation on its β-position.

As *N,N'*-diisopropyl-*O*-(2-trimethylsilylethyl)isourea is known in the literature and could be prepared using copper (I) chloride, the reaction was tested using CuCl as catalyst.[114] In this case the reaction proceeded well, without significant urea formation. However, the copper catalyst proved to be impossible to remove with the TMEDA protocol. Eventually, it was found that copper (I) triflate (commercially available as a 2:1 complex with toluene) gave satisfactory reactions and could be removed with the usual protocol. The reaction carried out with THF as solvent still showed presence of the urea, but if anhydrous DMF was used only the isourea bands could be seen in the IR spectrum of the resulting resin.

Scheme 3.22 Synthesis of polymer-supported *O*-trimethylsilylisourea using copper (I) catalysis.

Unfortunately, the only isourea which proved not to be possible to synthesise was the *tert*-butyl derivative **3.65**. A number of conditions were tested (Table 3.2) but in all cases only residual carbodiimide and urea bands could be observed in the IR spectrum. No significant isourea band was ever observed. As it was thought that the easy formation of the *tert*-butyl cation must be the reason of the failure of the reaction on solid-support, any further work on the *tert*-butyl system was abandoned.

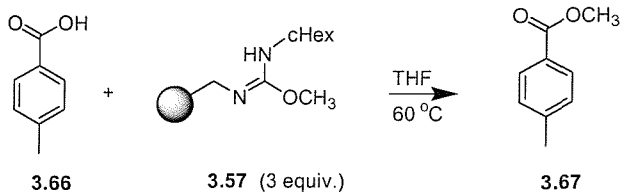
Table 3.2. Attempted synthesis of polymer-supported *O-tert*butylisourea.

Entry	tert-Butanol (equiv)	Catalyst	Solvent	Time (h)
1	10	$Cu(OTf)_2$	THF	16
2	10	$Cu(OTf)_2$	THF	3
3	10	CuOTf.toluene	THF	16
4	1.3	$Cu(OTf)_2$	THF	16
5	1.3	CuOTf.toluene	THF	16
6	10	CuOTf.toluene	DMF	16
7	10	CuOTf.toluene	DMF	3
8	1.3	CuOTf.toluene	DMF	16
9	1.3	CuCl	DMF	16
10	1.3	CuCl	THF	16

3.4 Esterification of carboxylic acids using immobilised *O*-alkylisoureas

For reasons which will become clear later, it is relevant to point out that this project was started using the immobilised *O*-methyl isourea prepared with the microwave-assisted method from commercial carbodiimide **1.38a**

With the polymer-supported isoureas in hand, their reactivity towards carboxylic acids was tested. As a test-substrate, 4-methylbenzoic acid **3.66** was chosen, which was reacted with 3 equivalents (based on the theoretical loading) of resin **3.57** in refluxing THF (Scheme 3.23). After overnight reaction the expected methyl ester **3.67** was obtained after simple filtration of the resin, followed by two resin washes with methanol and DCM and finally evaporation of the solvents. TLC of the reaction mixture and NMR analysis of the crude reaction mixture showed that all the carboxylic acid had been consumed.



3.66 **3.57** (3 equiv.) **3.67**

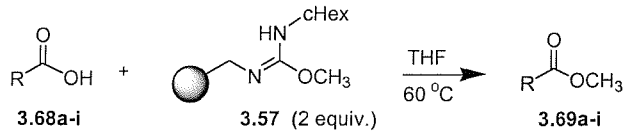
Scheme 3.23 Methylation of 4-methylbenzoic acid using resin **3.57.**

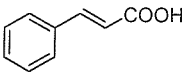
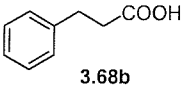
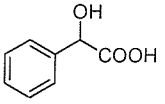
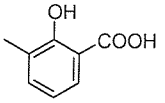
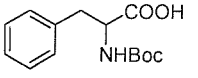
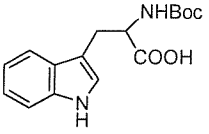
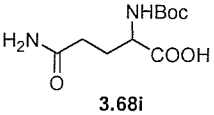
Next, a series of experiments were conducted to assess the best conditions for the reaction, always using THF as solvent as it represents a good compromise between ability to swell

the resin, ability to solubilise the acid substrates and ease of removal after the reaction. First, the reaction was attempted at room temperature. The reaction proved to be too sluggish under these conditions, and was still incomplete after 3 days. Hence, the reaction requires heating. Next, 3 experiments were set up using different amounts of resin **3.57**: 1.2, 1.5 and 1.8 equivalents. After reaction overnight at 60 °C, it was found that only the reaction employing 1.8 equivalents of reagent showed complete consumption of starting material (TLC analysis). Similarly, a reaction employing 2 equivalents of resin was followed by TLC over time, and it was found that at least 10 hours were necessary for the reaction to go to completion.

Having thus optimised the conditions, a set of carboxylic acids bearing different functional groups was tested. To allow for slight differences of reactivity for different acids, 2 equivalents of resin were used and the reactions were left to run overnight. The results are summarised in Table 3.3.

Table 3.3 Synthesis of carboxylic esters using **3.57.**



entry	Acid	time (h)	yield[a]	purity[b]
1	 **3.68a**	16	81%	>98%
2	 **3.68b**	16	94%	>98%
3	$CH_3(CH_2)_{16}COOH$ **3.68c**	40	91%	>98%
4	C_7H_{15} $(CH_2)_6COOH$ **3.68d**	40	88%	>98%
5	 **3.68e**	16	90%	>98%
6	 **3.68f**	16	78%	93%[c]
7	 **3.68g**	16	74%	>98%
8	 **3.68h**	16	81%	>98%
9	 **3.68i**	16	82%	>98%

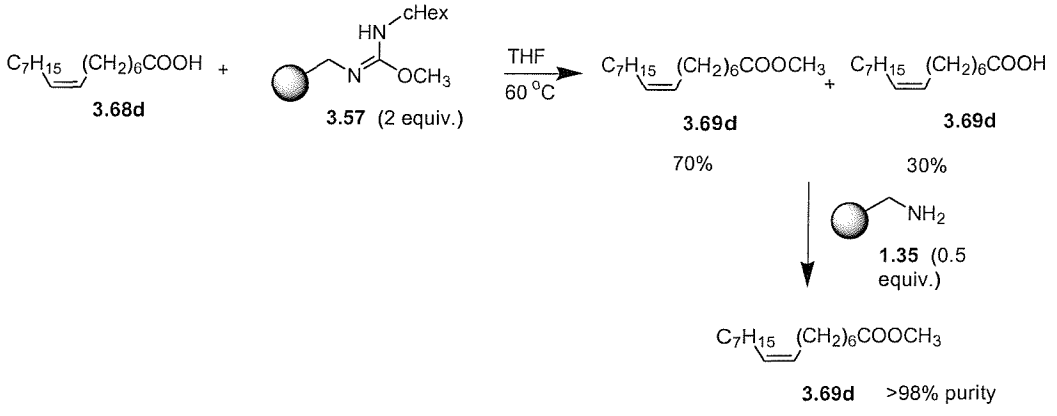
[a] Isolated yield; [b] Determined by ^{1}H-NMR; [c] 3.5% of **3f** and 3.5% of dimethylated product could be detected.

Simple carboxylic acids (entries 1-4) were alkylated in good yields and excellent purities. The reaction required longer times with long-chain aliphatic acids (compare entries 3-4 with entry 2). Hydroxy-acids (entry 5) were also cleanly alkylated to give the corresponding hydroxy-ester. No alkylation of the alcohol moiety was detected. When phenolic groups were present (entry 6), a small amount of dialkylation was observed. However the selectivity remained very good, and only about 3.5% of dialkylated product was formed (as judged by ^{1}H-NMR integration). Boc protected amino acids (entries 7 to

9) could also be cleanly transformed in the corresponding amino esters. In contrast, Fmoc groups were cleaved under the reaction conditions: when Fmoc-glycine was employed as a substrate no expected ester could be observed. Some of the product was soluble in $CDCl_3$ and turned out to be dibenzofulvene, while the rest dissolved in CD_3OD and proved to be a mixture of several products, probably arising from different stages of *N*-alkylation. It is believed that the Fmoc deprotection was caused by the basicity of the isourea moiety. Amides were untouched as exemplified by the clean conversion of Boc-protected glutamine into the corresponding methyl ester (entry 9). The effect of the reaction on the optical purity of products derived from enantiopure α-chiral acids was not investigated.

Very importantly, all products except for **3.69f** were obtained in very good purity without need for any purification except for the filtration of the resin. A typical NMR spectrum of one of the crude products obtained is reproduced in Figure **3.4**.

For applications in parallel synthesis, it is of utmost importance that all members of a library are obtained in high purity, regardless of their reactivity. While the conditions that were selected initially were sufficient to give complete conversions for most substrates, a few required longer reaction times. However, for large libraries individual optimisation of reaction conditions for each substrate is impractical, so a strategy leading to pure products regardless of the reactivity of each reactant was sought. For our system, an obvious choice is to employ a carboxylic acid scavenging strategy. Reaction of oleic acid with isourea **3.57** gave a product of only 70% purity after 16h, with 30% unreacted oleic acid (NMR determination). When, after the reaction, 100 mg (0.08 mmol) of aminomethylpolystyrene resin was added followed by a filtration, a product >98% purity was obtained (Scheme 3.24).[115]



Scheme 3.24 Use of a basic scavenger to remove unreacted acid for library generation.

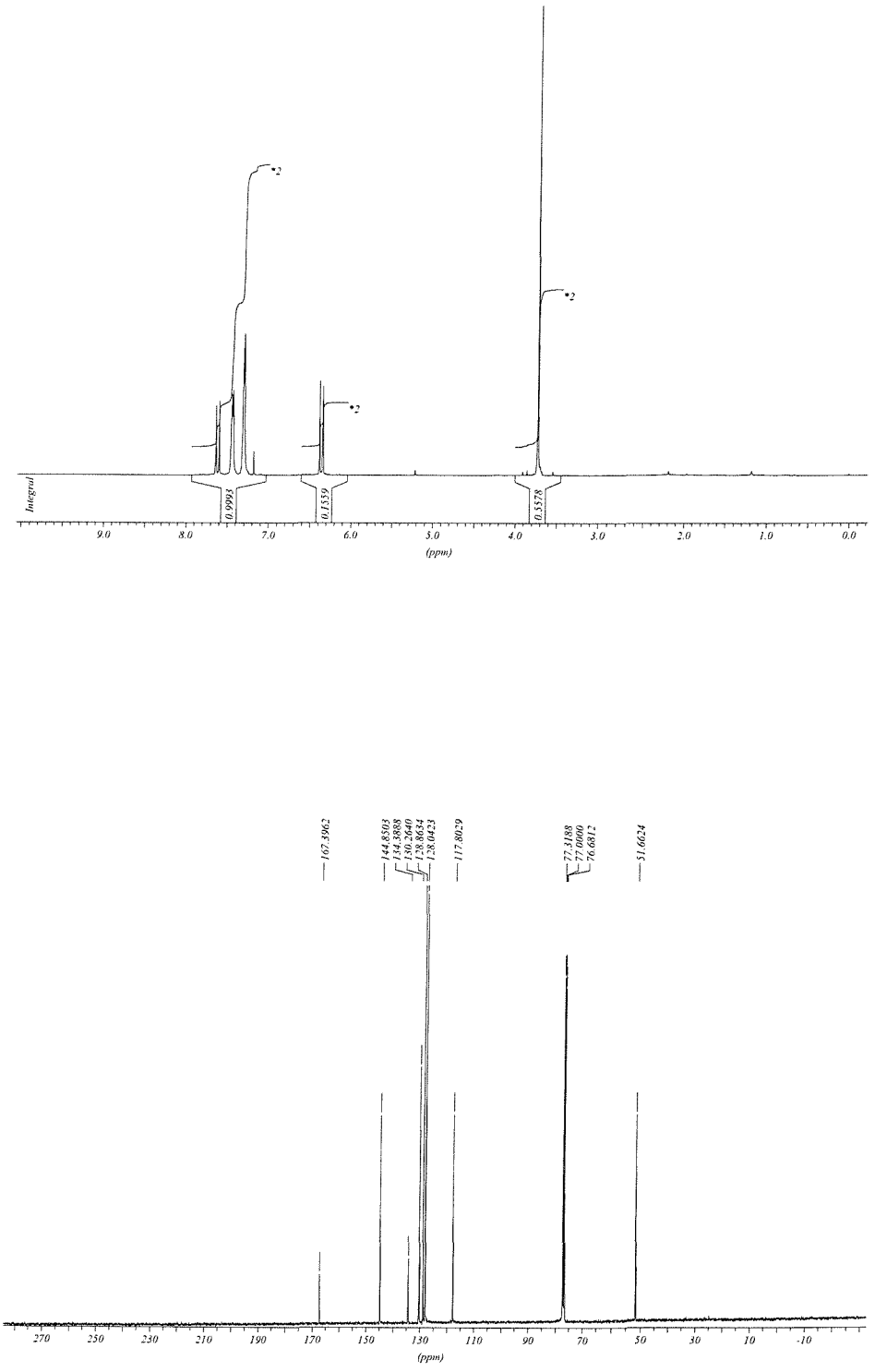


Figure 3.4 NMR analysis of the crude methyl cinnamate **3.69a**.

With polymer-supported *O*-methyl, *O*-benzyl and *O*-allyl isoureas prepared *via* the copper catalysed procedure, carboxylic acids could be quantitatively converted into the corresponding esters under analogous reaction conditions. However, the NMR spectra of the products were considerably less clean than expected. In particular, a series of unidentified broad peaks were always present in the 1-2 ppm region of the ^{1}H spectrum. Esterifications performed using *O*-methylisourea **3.57** obtained with the copper catalysed procedure gave contaminated products, despite the fact that use of **3.57** prepared with the microwave-assisted procedure under the same conditions afforded clean products. Several experiments were carried out to try to identify the source of the problem. Up to this point, the commercial version of carbodiimide **1.38a** had always been used. In the event, that resin proved to be the source of the problem. In fact, if the precursor carbodiimide resin **1.38a** was subjected to heating for some hours in THF a very similar NMR could be obtained after evaporation of the solvent. Identification of the species present proved to be impossible, and HPLC-MS analysis showed that several apolar molecules were present with molecular weight varying from 160 to 655 Da.

It was inferred that the impurities are only released at high temperature. The microwave-assisted protocol used to form the methyl isourea caused the release of these impurities during the isourea-formation step, so that products obtained from the esterification reaction were clean. Instead, if the isourea–forming step was carried out at room-temperature (as was the case when copper catalysis was used) all the impurities were released during the second step which necessitated heating. In fact, if methylisourea **3.57** prepared with the copper catalysed reaction was heated in THF for 1 hour, washed and dried and then used for the esterification reaction, the product obtained was much cleaner than if the resin was used straight after the copper catalysed reaction. However, the purity was still not ideal. Moreover, heating the *O*-benzylisourea **3.60** caused some rearrangement to the urea as previously described.

Resin **1.38a** is prepared industrially in two steps from aminomethylpolystyrene, by reaction first with cyclohexylisocyanate to afford urea **1.37** followed by dehydration using tosyl chloride and TEA.[35] Following discussions with the suppliers of resin **1.38a**, it was suspected that these impurities could be generated in the second step of this synthesis, probably because the reaction is carried out at high temperature for prolonged times. For this reason, it was decided to use the polymer-supported carbodiimide **1.38b** prepared with our modified procedure (see 3.2). Reaction of the methyl derivative **3.57** prepared with the

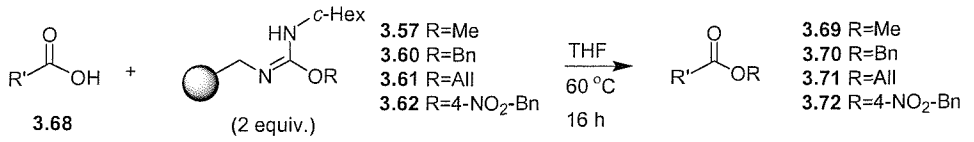
carbodiimide thus prepared (**1.38b**) with two different carboxylic acids gave good results, with no traces of the impurities visible.

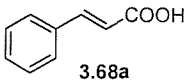
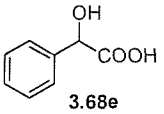
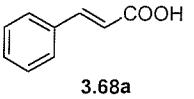
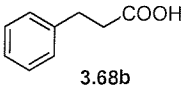
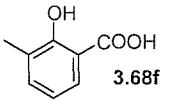
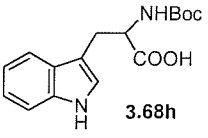
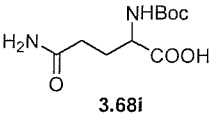
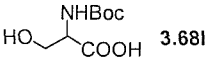
The other polymer-supported *O*-alkylisoureas were then used on a number of substrates (Table 3.4). In all the cases, very good yields could be obtained after reaction overnight and the products were obtained in good purities. Again, the chemoselectivity of the reaction was excellent and all the functional groups present survived.

Some of the products were contaminated with traces of triphenylphosphine oxide (<3 mol% by ^{1}H-NMR), which must be due to insufficient washing after the dehydration step. This problem was not observed if the resins were washed repeatedly with a 1-1 mixture of methanol and DCM before use.

Unfortunately, reactions with 2-(trimethylsilyl)ethyl derivative **3.64** did not prove to be as successful. Even when several equivalents of reagent were employed (4 equivalents) for prolonged times (4 days) at 60 °C, the reaction of cinnamic acid could not be driven to completion. After scavenging the residual acid with aminomethyl resin, a yield of just 60% was obtained. Most unsatisfactorily, the purity of the product was very low with unidentified impurities present. Quite interestingly, if the reaction was carried out at room temperature for the same time a higher conversion could be observed by TLC, but the purity of the product was even lower. As the IR spectrum of the recovered resin clearly showed presence of a urea group and disappearance of the isourea bands, it was assumed that decomposition of this resin (probably via an elimination reaction) is competitive with the reaction with the carboxylic acid. This would explain the difficulty in achieving complete conversions. However, the source of the impurities remains unclear, especially if it is considered that the reaction at room temperature was performed under milder conditions than normal.

Table 3.4 Synthesis of carboxylic esters using polymer-supported isoureas **3.57**, **3.60**, **3.61** and **3.62**.



Entry	Acid	R	yield[a]	purity[b]
1	 **3.68a**	Me	83%	>95%
2	 **3.68e**	Me	85%	>95%
3	 **3.68a**	Bn	96%	>95%
4	 **3.68b**	Bn	99%	>95%
5	 **3.68f**	Bn	96%	>95%
6	 **3.68h**	Bn	97%	>95%
7	 **3.68i**	Bn	98%	>95%
8	 **3.68l**	Bn	99%	>95%
9	**3.68a**	All	82%	>95%
10	**3.68b**	All	85%	>95%
11	**3.68f**	All	90%	>95%
12	**3.68h**	All	93%	>95%
13	**3.68i**	All	94%	>95%
14	**3.68l**	All	98%	>95%
15	**3.68a**	*p*-nitrobenzyl	94%	>95%
16	**3.68f**	*p*-nitrobenzyl	99%	>95%
17	**3.68h**	*p*-nitrobenzyl	98%	>95%
18	**3.68l**	*p*-nitrobenzyl	99%	>95%

[a] Isolated yield; [b] Determined by ^{1}H and ^{13}C-NMR.

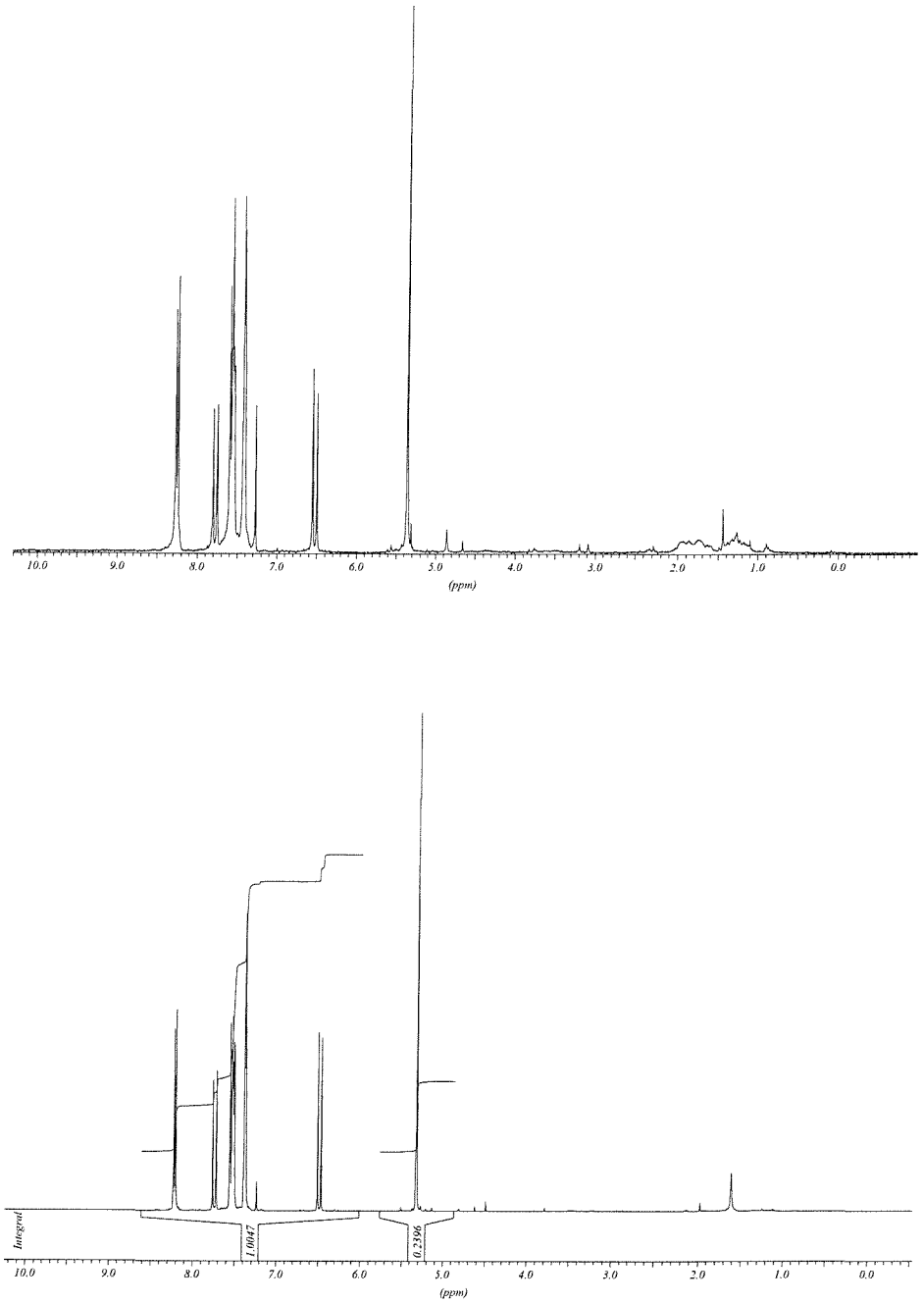


Figure 3.5 Comparison of the crude *p*-nitrobenzyl cinnamate **3.72a** obtained using the polymer-supported isoureas derived from respectively the commercial carbodiimide **1.38a** (top) and carbodiimide **1.38b** prepared in-house.

3.5 Microwave-assisted esterifications

3.5.1 Using soluble *O*-alkylisoureas

Our next goal was to reduce the time needed to complete the reactions. In order to achieve this, it was decided to exploit microwave irradiation once again.

As microwave irradiation had not yet been used to accelerate reactions of isoureas, the idea was first tested on a number of soluble isoureas. Several isoureas (*O*-methyl, *O*-benzyl, *O*-*tert*-butyl and *O*-trifluoroethyl) were reacted with a variety of acids.

Apart for **3.22**, which is commercially available, all other isoureas were prepared by reaction of DIC with the appropriate alcohol under CuCl catalysis. Isoureas **3.19** and **3.73** were then purified by filtration on a plug of neutral alumina using hexane as eluant to remove the copper catalyst. However, this filtration could not be applied to the *tert*-butyl derivative **3.15**, as decomposition was observed in this case. Hence, the *tert*-butyl isourea was used without removal of CuCl.

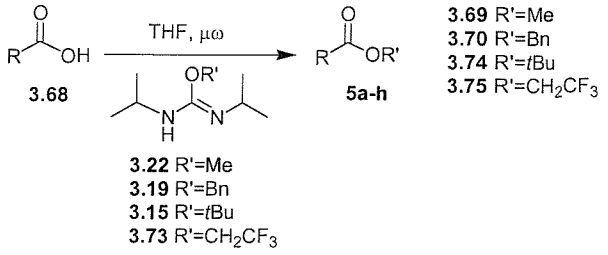
Microwave-assisted esterification of carboxylic acids using isoureas **3.22** and **3.19** proceeded smoothly. At 130 °C all the reactions were complete within 5 minutes using a slight excess of isourea (Table 3.5). Quite interestingly, no loss of chemoselectivity was observed even under these more forcing conditions.

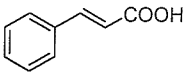
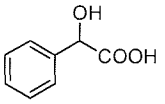
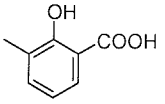
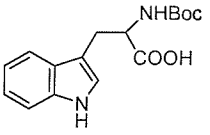
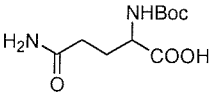
Unfortunately, the trifluoroethyl derivative **3.73** proved to be completely unreactive.[116]

In the case of *tert*-butyl derivative **3.15**, some reaction was observed. However, a large excess of isourea (4.5 equivalents) had to be employed to drive the reaction to completion. This is consistent with literature precedents and is due to the tendency of this isourea to form isobutene *via* an E1-type side reaction.[89,117] The formation of gaseous isobutene was confirmed by the fact that a higher pressure was found inside the reaction vessel compared to other reactions at the same temperature: when performing the reaction on a 1.0 mmol scale the overpressure was 1.8 bar.

In all cases, filtration of the precipitated DIU followed by column chromatography was necessary to obtain the pure products.

Table 3.5 Synthesis of carboxylic esters using soluble *O*-alkylisoureas.

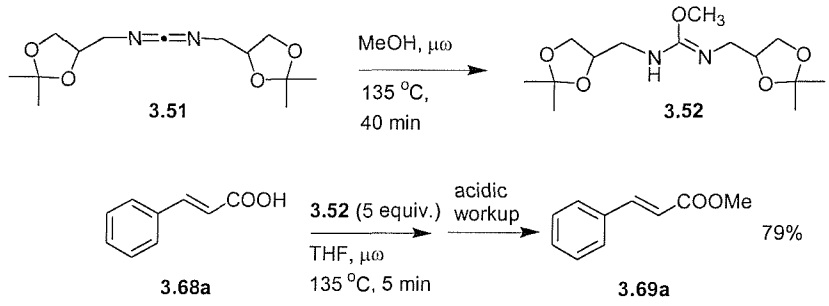


entry	Isourea/ equiv.	Acid	T (°C)	Time (min)	yield[a]
1	**3.22**/1.1	 **3.68a**	130	5	94%
2	**3.22**/1.1	 **3.68e**	130	5	81%
3	**3.22**/1.1	 **3.68f**	130	5	89%
4	**3.22**/1.1	 **3.68h**	130	5	92%
5	**3.22**/1.1	 **3.68i**	130	5	87%
6	**3.19**/1.3	**3.68a**	130	5	90%
7	**3.19**/1.3	**3.68f**	130	5	83%
8	**3.19**/1.3	**3.68h**	130	5	94%
9	**3.15**/4.5	**3.68a**	120	5	85%
10	**3.15**/4.5	**3.68e**	120	5	75%
11	**3.15**/4.5	**3.68h**	120	5	87%
12	**3.73**/1.3	**3.68a**	130	15	0%

[a] Isolated yield after column chromatography.

3.5.2 Using phase-tagged isoureas

The possibility to use microwave irradiation in conjunction with the phase-tagged isourea proposed by Rapoport was also investigated (Scheme 3.25).[109] The corresponding carbodiimide is commercially available. However, severe problems were encountered in the preparation of the isourea reagent. The traditional copper (I) chloride procedure did not work particularly well in this case, yielding a product of poor purity which failed to alkylate the carboxylic acid substrate quantitatively. Consequently, the synthesis of the reagent was modified: the corresponding methyl isourea was formed by microwave-assisted reaction of the carbodiimide in excess methanol, without the use of any copper catalyst. After evaporation of the methanol, the isourea was used directly in the next step. After the microwave-assisted reaction with the carboxylic acid, 1N HCl was used to unmask the alcoholic groups and the by-products could be removed by aqueous extraction as described by Rapoport. Using this technique, cinnamic acid could be cleanly converted into the corresponding methyl ester. However, the high cost and difficulty of manipulation of carbodiimide **3.51** rendered the method not particularly attractive from a practical point of view. Also, the need for an acid workup could restrict the scope of the reaction with respect to the presence of acid-labile groups in the substrates.



Scheme 3.25 Microwave-assisted preparation and use of Rapoport's isourea.

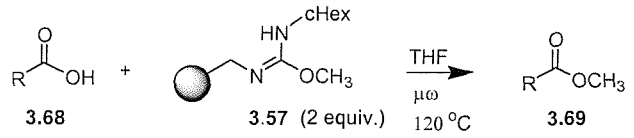
3.5.3 Using polymer-supported *O*-alkylisoureas

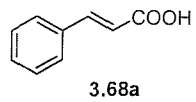
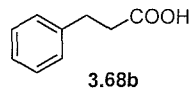
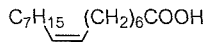
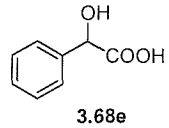
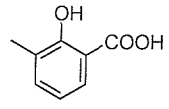
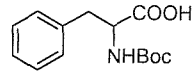
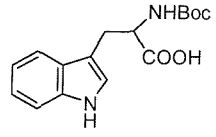
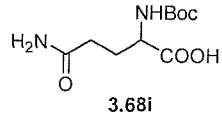
Having verified that the esterification of carboxylic acids with isoureas could be successfully carried out under microwave irradiation without loss of chemoselectivity, the possibility of combining microwave-irradiation with the use of our polymer-supported reagent was investigated. Again, the use of the methyl derivative **3.57** was investigated at first.

A series of reactions employing cinnamic acid as the substrate were set up to determine the optimal temperature and reaction time. THF was used as solvent in order to be able to compare the results with the normal heating experiments. At 120 °C 15 minutes were found to be necessary to complete the reaction. Employing higher reaction temperatures was not feasible: THF is a poor solvent for the absorption of microwaves and reaching a higher temperature proved to require a long time so that the overall time could not be reduced. More than 5 minutes were necessary to reach the reaction temperature (120 °C, the time necessary to complete the reach the desired temperature is part of the reaction time given).

A series of carboxylic acids was then subjected to the same conditions (15 min, 120 °C), and the results are described in Table 3.6.

Table 3.6 Synthesis of carboxylic esters using resin **3.57**.



entry	acid	time (min)	yield[a]	purity[b]
1	 **3.68a**	15	86%	>98%
2	 **3.68b**	20	79%	98%
3[c]	 **3.68d**	20	85%	>98%
4	 **3.68e**	15	84%	>98%
5	 **3.68f**	15	75%	98%
6	 **3.68g**	15	82%	>98%
7	 **3.68h**	15	92%	>98%
8	 **3.68i**	15	75%	>98%

[a] Isolated yield; [b] Determined by ^{1}H-NMR; [c] 2.5 equiv of **2** were used.

All the substrates gave complete reactions in those conditions, with the exception of 3-phenylpropionic acid **3.68b** (entry 2), that required a slightly longer reaction time and oleic acid **3.68h** (entry 3) that required the use of 2.5 equivalents of resin for 20 minutes. Under the high-temperature conditions used, no significant degradation of the resin was observed. None the functional groups that were unreactive towards the reagent using

conventional heating were affected in the microwave-accelerated reactions. All the products still exhibited very high purities as evidenced from the NMR spectra.

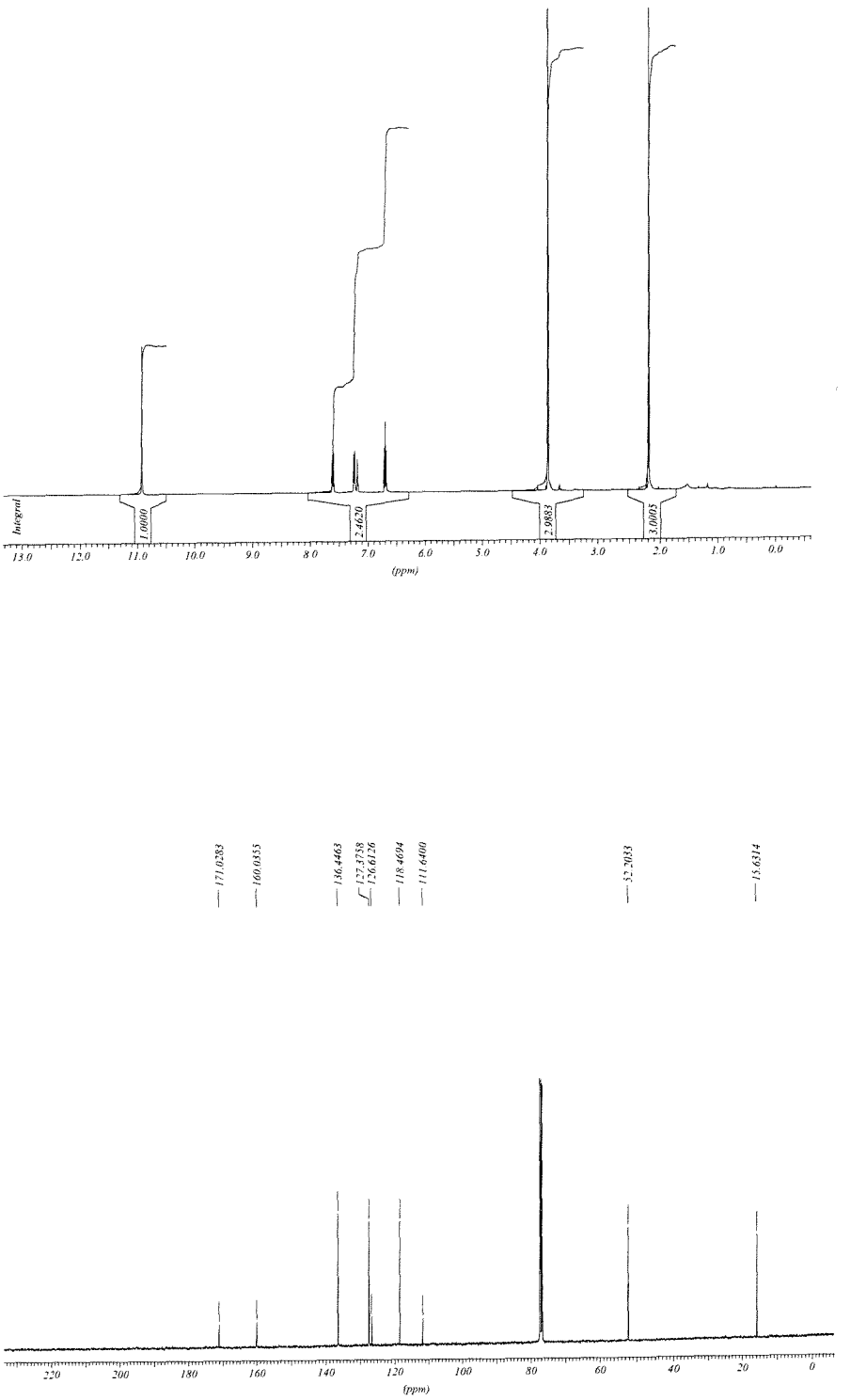
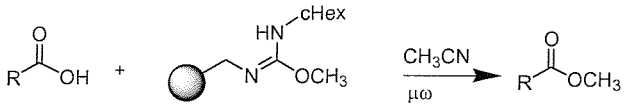


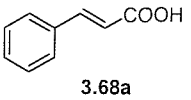
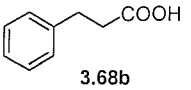
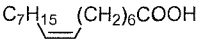
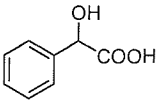
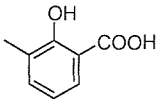
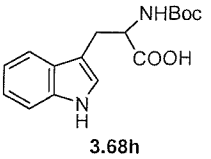
Figure 3.6 NMR analysis of the crude methyl (3-methyl)salicylate **3.69f** prepared under microwave irradiation.

In order to further decrease the time needed to achieve complete reactions, changing the reaction solvent proved advantageous. As reported before, the use of a relatively apolar solvent like THF both limits the temperature that can be achieved and increases the time needed to reach the desired temperature. It was decided to switch to acetonitrile, which is much more efficient in converting microwave radiation to heat (larger tan δ) and is able to dissolve the carboxylic acids. In these conditions, a range of substrates could be reacted quantitatively within 5 minutes (Table 3.7).

Table 3.7 Synthesis of carboxylic esters using resin **3.57** in acetonitrile.



3.68 **3.57** (2 equiv.) **3.69**

entry	acid	time (min)	yield[a]	purity[b]
1	 **3.68a**	5	90%	>98%
2	 **3.68b**	5	83%	>98%
3	 **3.68d**	8	96%	>98%
4	 **3.68e**	5	76%	>98%
5	 **3.68f**	5	78%	89%
6	 **3.68h**	5	94%	>98%

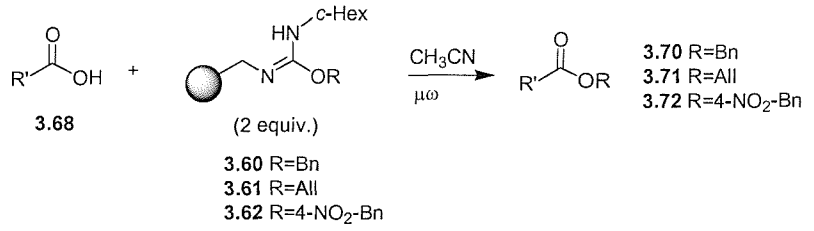
[a] Isolated yield; [b] Determined by ^{1}H-NMR.

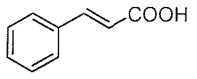
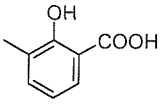
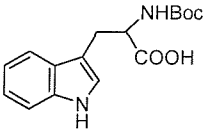
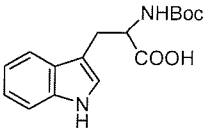
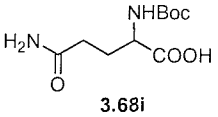
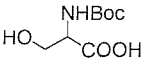
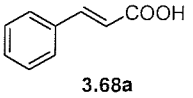
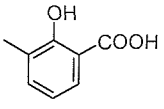
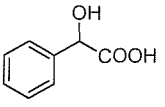
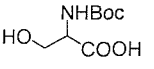
Using the more reactive immobilised *O*-benzyl and *O*-allyl isoureas, all reactions were complete in 3 minutes (Table 3.8), while with the *p*-nitrobenzyl derivative 5 minutes at 130 °C were required. In all cases, excellent isolated yields and purities were obtained.

While it is not possible to exclude that rearrangement to the corresponding *N*-benzyl or *N*-allyl urea products as shown in Scheme 20 did not occur at the high reaction temperature, the excellent isolated yields suggest that the ester formation is a faster process.

Reaction of cinnamic acid with trimethylsilylethyl derivative **3.64** proceeded only to a minimal extent under microwave irradiation under these conditions. This seemed to confirm the trend observed in the thermal reaction, in that reactions seemed to give lower yields on increasing the reaction temperature.

Table 3.8 Microwave-assisted synthesis of carboxylic esters using **3.60**, **3.61** and **3.62** in acetonitrile.



Entry	acid	R	Temp (°C)	time (min)	yield[a]	purity[b]
1	 **3.68a**	Bn	125	3	96%	>95%
2	 **3.68f**	Bn	125	3	93%	>95%
3	 **3.68h**	Bn	125	3	89%	>95%
4	 **3.68h**	All	125	3	93%	>95%
5	 **3.68i**	All	125	3	91%	>95%
6	 **3.68l**	All	125	3	94%	>95%
7	 **3.68a**	*p*-nitrobenzyl	130	5	89%	>95%
8	 **3.68f**	*p*-nitrobenzyl	130	5	97%	>95%
9	 **3.68e**	*p*-nitrobenzyl	130	5	98%	>95%
10	 **3.68l**	*p*-nitrobenzyl	130	5	88%	>95%

[a] Isolated yield; [b] Determined by ^{1}H-NMR.

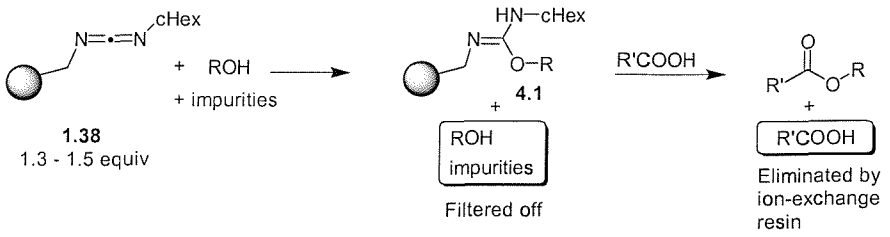
3.6 Conclusions

We have demonstrated that it is possible to prepare a range of polymer-supported *O*-alkylisoureas in an easy, scalable manner from commercially available resins. The only exception was the *tert*-butyl derivative, which proved to be too unstable and was never isolated. These reagents efficiently convert carboxylic acids into esters in high yields and with excellent purities and chemoselectivities. A scavenger protocol has also been developed to ensure that only products with high purities are obtained even if less reactive substrates are employed. The potential of microwave-assisted chemistry for the use of the polymer-supported isoureas has also been demonstrated. The combination of the short reaction times achievable under microwave irradiation with the extremely simple work-up procedure granted by our polymer-supported reagents is particularly advantageous, with the total time required to obtain the final product being less than an hour.

4. Catch-and-release synthesis of esters

4.1 Introduction

The previous chapter described the use of polymer-supported *O*-alkylisoureas for the conversion of carboxylic acids into simple esters. It was decided to investigate the use of polymer-supported *O*-alkylisoureas as intermediates in a catch-and-release esterification procedure. The strategy is illustrated in Scheme 4.1.



Scheme 4.1 Concept of the catch-and-release synthesis of esters.

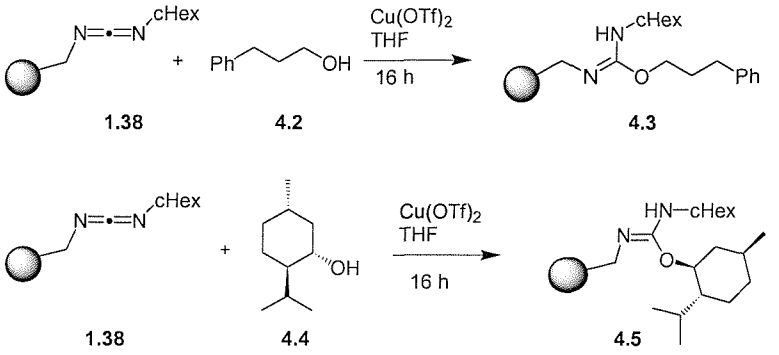
An alcohol would be immobilised onto a resin as the corresponding isourea. The subsequent purification would remove the catalyst, any impurities present in the starting material, as well as any unreacted alcohol. The second step would effect the "release" of the alcohol moiety back into solution through reaction with a carboxylic acid. Both reactions were employed in the previous chapter and, as was demonstrated, excess carboxylic acid could easily be removed using a basic resin resulting in the formation of pure esters. However, there is a crucial difference compared to the application described in the previous chapter: the alcohol moiety is not merely a single protecting group, but is considered as the substrate (point of diversity in library synthesis). As a result, the use of an excess of alcohol in the synthesis of the polymer-supported isoureas had to be avoided.

The "loading" step will be discussed first.

4.2 The "loading" step

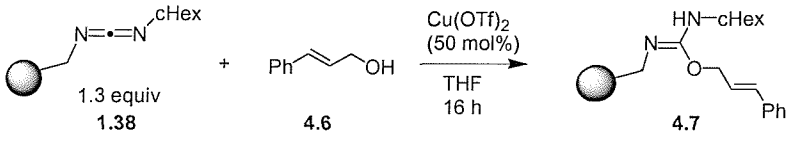
The first condition that needed to be verified in order to be able to implement this strategy was whether it was possible to load the alcohols in high yields by using only one equivalent. In all the previous examples, for the synthesis of immobilised isoureas the alcohols had been used in large excess.

To compensate for the reduced number of equivalents of alcohol, larger amounts of catalyst were used. Using ca. 50 mol% of $Cu(OTf)_2$ and only 1.1 equivalents of 3-phenyl-1-propanol, the reaction was complete (disappearance of the carbodiimide IR band) within 16 hours. The same result was obtained using the more hindered menthol (Scheme 4.2).



Scheme 4.2 Synthesis of polymer-supported isoureas using 1.1 equivalents of alcohols.

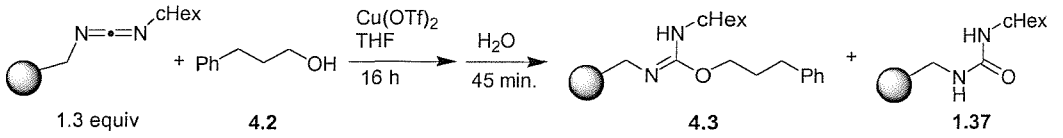
As it was deemed more important to maximise the yields with respect to the substrate and not to the resin, the use of an excess of resin was subsequently investigated. Under these conditions (Scheme 4.3), and using an alcohol bearing a chromophore (cinnamyl alcohol) to facilitate detection, complete disappearance of the alcohol after overnight reaction (TLC analysis) was observed.



Scheme 4.3 Synthesis of polymer-supported isoureas using an excess of polymer-supported carbodiimide.

When an excess of resin was used, some carbodiimide groups were still available on the resin after the reaction, as evidenced by IR analysis. Their presence would constitute a problem for the next step of the reaction, as reaction with excess of acid would give rise to the corresponding anhydride. In order to cap these remaining carbodiimide groups, an excess of water was added to the reaction mixture after the standard 16 hours of reaction time. The water did not interfere with the isourea, but under copper catalysis it reacted with the carbodiimide to form inert urea (Scheme 4.4).

It was found that 45 minutes were sufficient to cap all positions (IR analysis). When the capping was prolonged for over an hour, removal of the copper species from the resin via the usual TMEDA washings proved unexpectedly more complicated. The reasons for this behaviour have never been elucidated.



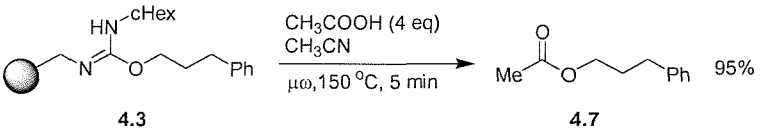
Scheme 4.4 Synthesis of polymer-supported isoureas using an excess of polymer-supported carbodiimide with water capping for remaining carbodiimide functions.

4.3 The "release" step

Having achieved a satisfactory first step of the procedure, the release reaction was investigated. In order to decrease the time needed for the optimisation studies, microwave irradiation was employed.

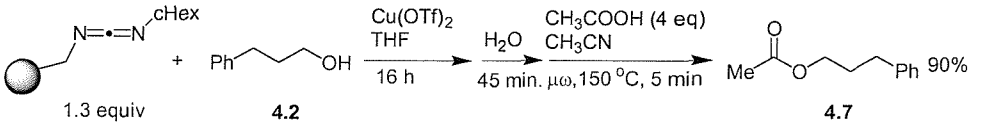
At first, polymer-supported isoureas prepared using an excess of alcohol were employed.

The first results were encouraging (Scheme 4.5): when isourea **4.3** was reacted with two equivalents of acetic acid the corresponding acetate was obtained in 65% yield (calculated from the theoretical loading of the carbodiimide over the two steps), and a 95% isolated yield was obtained when four equivalents of acetic acid were used. In both cases, removal of the excess acid was accomplished using DOWEX® 550A OH resin. The crude esters thus obtained were satisfactorily pure by ^{1}H and ^{13}C-NMR.



Scheme 4.5 Synthesis of 3-phenylpropyl acetate from immobilised *O*-(3-phenylpropyl)isourea.

The complete catch-and-release strategy was then applied: 3-phenyl-propanol was reacted with an excess of carbodiimide resin (Scheme 4.6). Subsequently, 12 equivalents of water were added to cap the remaining carbodiimide groups. The resin was filtered and the copper catalyst removed with TMEDA. The resulting resin was treated with 4 equivalents of acetic acid under microwave irradiation. Addition of the ion-exchange resin followed by filtration and evaporation of the solvent afforded pure acetate **4.7** in 90% isolated yield.



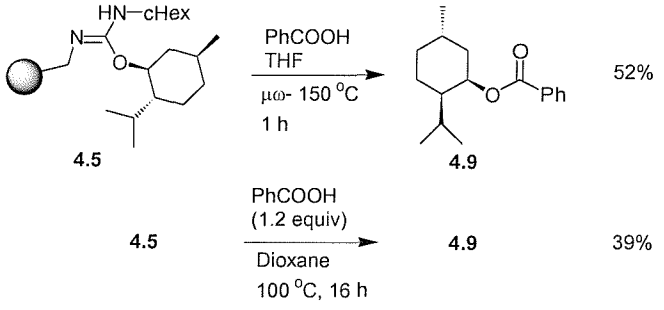
Scheme 4.6 Catch-and-release synthesis of 3-phenylpropyl acetate.

A reaction was also performed on a 1:1 mixture of substrate **4.3** and "impurity" **4.8**. After the same reaction sequence previously described, only the desired ester **4.7** could be found, with no traces of the contaminant (Scheme 4.7). This proves that that it is possible to obtain products with high purity from impure starting materials.

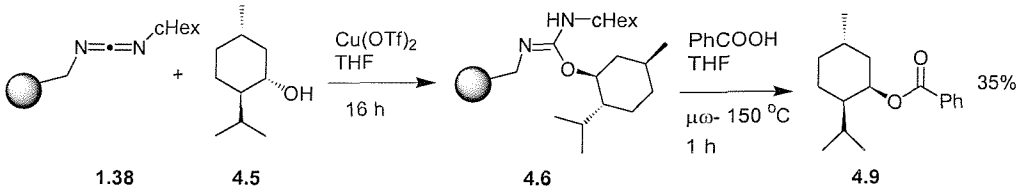
Scheme 4.7 Purification of mixture of products through the catch-and-release esterification.

As mentioned in the introduction, Kaulen had demonstrated that chiral secondary isoureas undergo reactions with carboxylic acids to form esters with inversion of configuration.[94] As a result, if the catch-and-release protocol could be successfully applied to chiral secondary alcohols it would be a viable alternative to Mitsunobu esterifications.

Menthol was the first chiral secondary substrate that was tested (Scheme 4.8). Reaction of the polymer-supported isourea of menthol with excess benzoic acid (5 equivalents) gave 52% isolated yield under microwave irradiation and 39% yield using thermal heating (100 °C in dioxane). The entire catch-and-release procedure starting for menthol afforded the benzoate in 35% overall yield over the two steps (Scheme 4.9). In all three cases only the ester with inverted configuration were present, which confirmed Kaulen's observations.

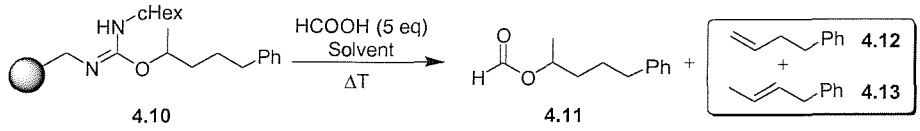


Scheme 4.8 Reaction of polymer-supported *O*-menthyl isourea **4.5** with benzoic acid under thermal and microwave-assisted conditions.



Scheme 4.9 Catch-and-release esterification of menthol.

However, when a simpler secondary alcohol, 4-phenyl-2-butanol, was used unexpected contaminants were found in the reaction: the corresponding alkenes arising from elimination of the isourea (Scheme 4.10).



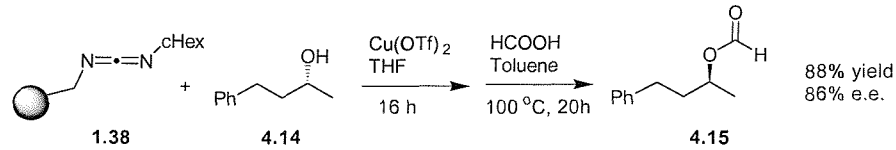
4.10 4.11

Scheme 4.10 Reaction of polymer-supported isourea of 4-phenyl-2-butanol with carboxylic acids.

The reason why elimination products had not been identified in the reactions involving menthol probably lies in the volatility of these products, which caused them to be evaporated under vacuum during the removal of the solvents. As Kaulen had only reported traces of elimination products, this problem was unexpected.[94]

Studying the reaction of 4-phenyl-2-butanol isourea **4.10**, it was found that using an apolar solvent like toluene instead of acetonitrile improved the substitution vs. elimination ratio. Also, formic and benzoic acid gave better results than acetic acid. Eventually, the lowest level of elimination (<5 mol% by ^{1}H-NMR) was obtained for the reaction performed using 5 equivalents of formic acid in toluene with thermal heating (100 °C, 16 hours).

It was thus possible to perform the catch-and-release esterification of enantiopure (*R*)-4-phenyl-2-butanol **4.14** (Scheme 4.11) which resulted in an excellent isolated yield (88%, <5 mol% elimination products by ^{1}H-NMR). The enantiomeric excess of the product was determined as 86% (HPLC with chiral column), revealing that a small amount of racemisation was occurring during the process.

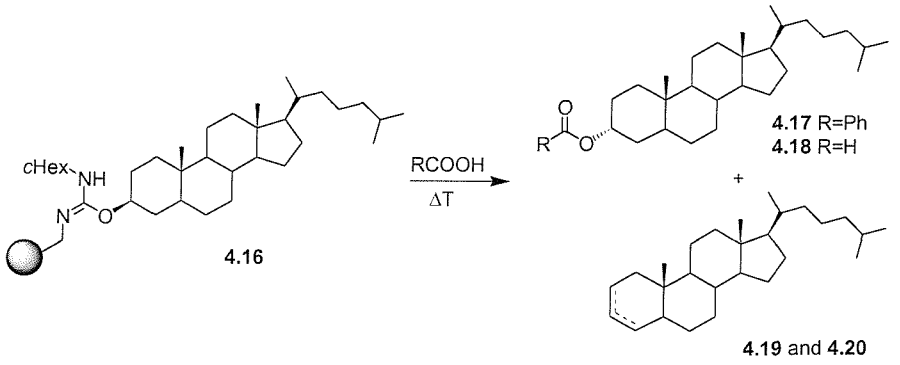


1.38 4.14 4.15

Scheme 4.11 Catch-and-release esterification of enantiomerically pure (*R*)-4-phenyl-2-butanol.

The competitive elimination reaction proved to be a more serious problem when a more hindered alcohol was employed. When 3-β-cholestanol was used as substrate, a 1 : 1 mixture of ester and alkenes was found, as judged by the ^{1}H-NMR. Both possible alkenes are formed, with the Δ-2 isomer formed in major amount. A number of different conditions were tested in order to minimise the amount of alkene being formed (Table 4.1).

Table 4.1 Esterifications on 3-β-cholestanol.



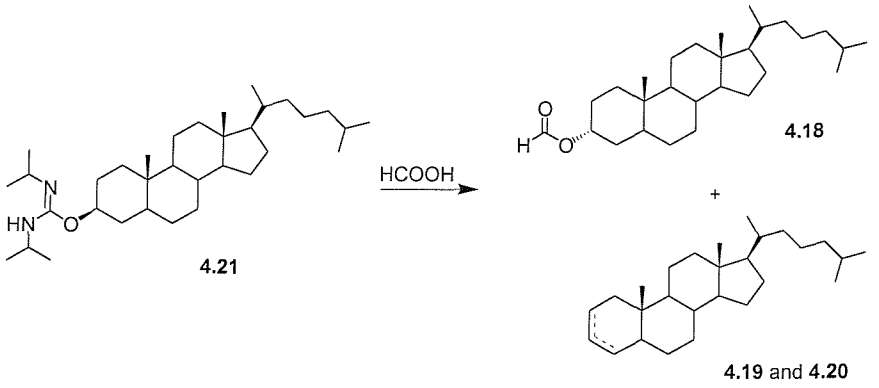
Entry	Acid (equiv)	solvent	T (°C)	time	Total yield	Subst. Vs. elim.
1	PhCOOH (5)	CH_3CN	150[1]	5 min	47%	4 : 6
2	HCOOH (5)	toluene	150[1]	5 min	32%	3 : 7
3	HCOOH (5)	toluene	100	20 h	35%	5 : 5
4	HCOOH (1)	toluene	100	40 h	60%[2]	<1 : >9
5	--	toluene	100	40 h	52%	0 : 1

[1] Microwave heating. [2] Column chromatography of this crude reaction mixture afforded a mixture of regioisomeric alkenes in 50% isolated yield.

Switching from microwave irradiation to thermal heating and from benzoic acid to formic acid had little effect (entries 1-4). The number of equivalents of carboxylic acid employed seemed to have a far greater impact: when only 1 equivalent of formic acid was used, almost exclusive elimination was observed, while using 5 equivalents of formic acid a 1 : 1 ratio of products was obtained. If no acid was present in the reaction mixture, a comparable yield of elimination products could be obtained (entry 5).

At this point, a series of experiments were conducted using the soluble isourea (Table 4.2).

Table 4.2. Reaction with *O*-(3-β-cholestanyl)isourea.

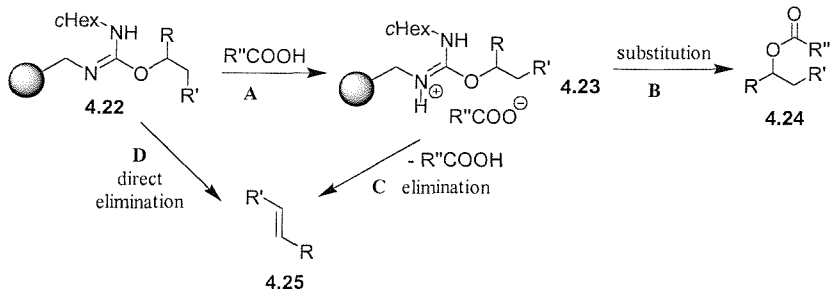


Entry	Acid (equiv)	solvent	T (°C)	time	Ester[1]	Alkenes[1,2]	Total yield	Subst. vs. elim.
1	HCOOH (1)	toluene	150[3]	10 min	68%	17%	85%	80 : 20
2	HCOOH (5)	toluene	100[4]	20 h	49%	12%	61%	80 : 20
3	HCOOH (1)	toluene	100[4]	20 h	62%	4%	66%	94 : 6
4	--	toluene	100[4]	40 h	--	7%	--	--

[1] Isolated yields after column chromatography. [2] Mixture of regioisomeric alkenes. [3] Microwave heating. [4] Conventional heating.

In all cases, the level of elimination observed in solution-phase was much lower than that observed in the experiments performed with the polymer-supported isourea.

Very interestingly, the use of either microwave irradiation or of an excess of carboxylic acid increased the level of elimination (entries 1 and 2 vs. entry 3). Spontaneous elimination without the presence of acid can be achieved, but with much lower yields compared to the polymer-supported version (compare entry 4, Table 4.2 with entry 5 Table 4.1).



Scheme 4.12. Possible routes in the reaction of secondary *O*-alkylisoureas with carboxylic acids.

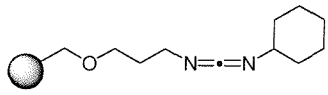
It seems evident from these results that the formation of the elimination product could arise from two different pathways (Scheme 4.12). One is the direct elimination of the O-alkylisourea without intervention of the carboxylic acid (pathway **D**). This mechanism accounts for the formation of the alkenes in the absence of acids (entry 4, Table 4.2 and entry 5 Table 4.1). Another possible mechanism for the formation of the alkenes is pathway **C**, in which the protonated isourea **4.23** undergoes elimination (with the carboxylate anion acting as base) instead of the expected substitution (path **B**). The experiments run in solution indicate that microwave irradiation and/or using more than one equivalent of carboxylic acid renders path **C** more competitive with path **B** (elimination levels increase increasing the amount of acid used).

However, in contrast with this observation, when only one equivalent of acid was used in the experiments involving the polymer-supported isourea, elimination predominated. Confronting this result with the experiment run in the absence of acid (which affords almost the same amount of alkene as the reaction with one equivalent of formic acid), it seems a safe assumption that in this instance most of the elimination product is formed through path **D**. Unfortunately, increasing the proportion of molecules following path **A-B** by increasing the number of equivalents of acid used did not improve the substitution vs. elimination ratio to a satisfactory level, as path **C** becomes competitive.

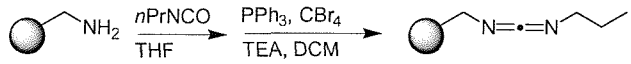
What remained unexplained was the remarkable difference in the level of elimination found between the solution-phase and solid-phase experiments. For some reasons, it seems that both paths C and D are favoured by performing the reaction on the solid-support (compare for example entry 4, Table 4.2 with entry 5 Table 4.1).

As the presence of the solid-support seemed to have such a crucial influence, it was decided to investigate the effect of the nature of the polymer-supported carbodiimide. As substitution reactions are known to be more sensitive to steric hindrance than elimination reactions, two polymer-supported carbodiimides with assumed reduced steric hindrance

were studied (Scheme 4.13 and Table 4.3, entries 1 and 2). Resin **3.55** (commercially available) possessed a longer spacer between the resin backbone and the carbodiimide functionality, while the **4.26** (prepared as outlined in Scheme 4.13) was less sterically hindered near the second (outward) nitrogen atom.



3.55 Commercially available



1.35 **4.26**

Scheme 4.13 Alternative carbodiimides.

However, neither of those gave better results than the standard resin in terms of elimination vs. substitution ratio. In addition, lower yields were observed as well (Table 4.3, entries 1 and 2).

Table 4.3. Further esterification reactions of polymer-supported *O*-(3-β-cholestanyl)isoureas.

Entry	Acid (equiv)	Carbodiimide	Total yield	Subst. Vs. elim.[1]
1[2]	HCOOH (5)	**3.55**	14%	5 : 5
2[2]	HCOOH (5)	**4.26**	33%	3 : 7
3[3]	$ClCH_2COOH$ (1)	**1.38**	50%	4 : 6
4[3]	$Cl_2CHCOOH$ (1)	**1.38**	45%	5 : 5

[1] Determined by ^{1}H-NMR. [2] Catch-and-release procedure starting from the alcohol and the appropriate carbodiimide. [3] Release step starting from isolated isourea **4.16**.

Finally, it was decided to study the behaviour of carboxylic acids with a lower pKa. Carboxylic acids with suitably low pKa values should protonate quantitatively the polymer-supported isoureas even in the absence of an excess of carboxylic acid. Thus, path **D** should not be available, while the competition between paths **B** and **C** could be in favour of path **B** since no excess of carboxylic acid is employed. To this end, chloroacetic acid and dichloroacetic acid (1 equiv) were used in conjunction with polymer-supported isourea **4.16** (Table 4.3, entries 3-4). However, while the isolated yields obtained were

slightly higher compared with previous experiments, this was at the expense of the purity of the products, while the substitution vs. elimination ratio did not improve detectably.

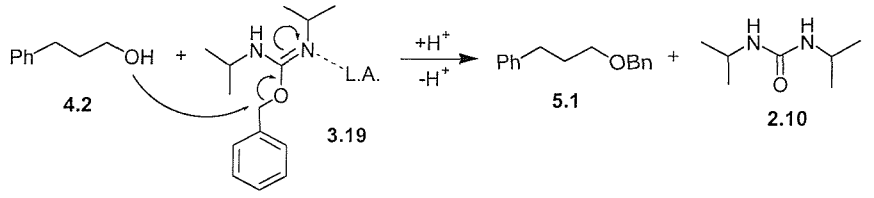
4.4 Conclusions

The concept of the catch-and-release esterification of alcohols using intermediate polymer-supported *O*-alkylisoureas has been explored. The methodology proved to be successful when primary alcohols were employed as substrates, and the possibility of obtaining pure products from impure starting materials was demonstrated. When secondary alcohols were employed, unexpected levels of competitive elimination were encountered. The level of elimination was found to be heavily dependent on the nature of the substrate. Variations in the nature and quantity of the carboxylic acid and/or of the polymer-supported carbodiimide failed to improve the substitution vs. elimination ratio.

5. Novel reactions of *O*-alkylisoureas

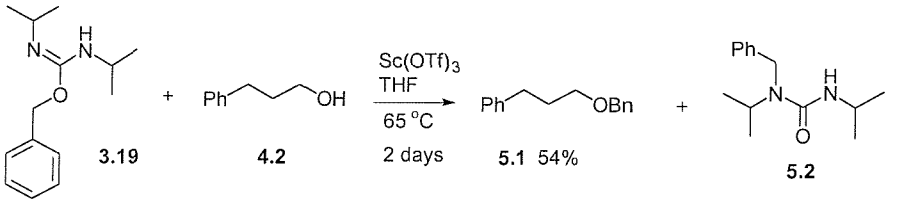
5.1 Reactions of isoureas with alcohols catalysed by Lewis acid

The typical way to activate *O*-alkylisoureas towards substitution is by protonation, either by the reagent itself (e.g. RCOOH) or by an external acid (e.g. CF_3SO_3H). It was decided to investigate whether Lewis acids could be used to activate the isourea towards substitution. This would provide an alternative to react isoureas with non-acidic molecules such as alcohols. The mechanism that was hypothesised is depicted in Scheme 5.1.



Scheme 5.1 Proposed mechanism for the reaction of alcohols and O-alkylisoureas catalysed with Lewis acids.

The idea was first tested using 3-phenyl-1-propanol as the substrate and a reactive isourea such as *N,N'*-diisopropyl-*O*-benzylisourea (1 equiv), using scandium (III) triflate as catalyst (Scheme 5.2). While no reaction could be observed at room temperature, refluxing in THF for two days gave 54% yield of the desired benzyl ether after column chromatography. Unfortunately, reactions with the less reactive non-benzylic isoureas failed, not giving any trace of product.

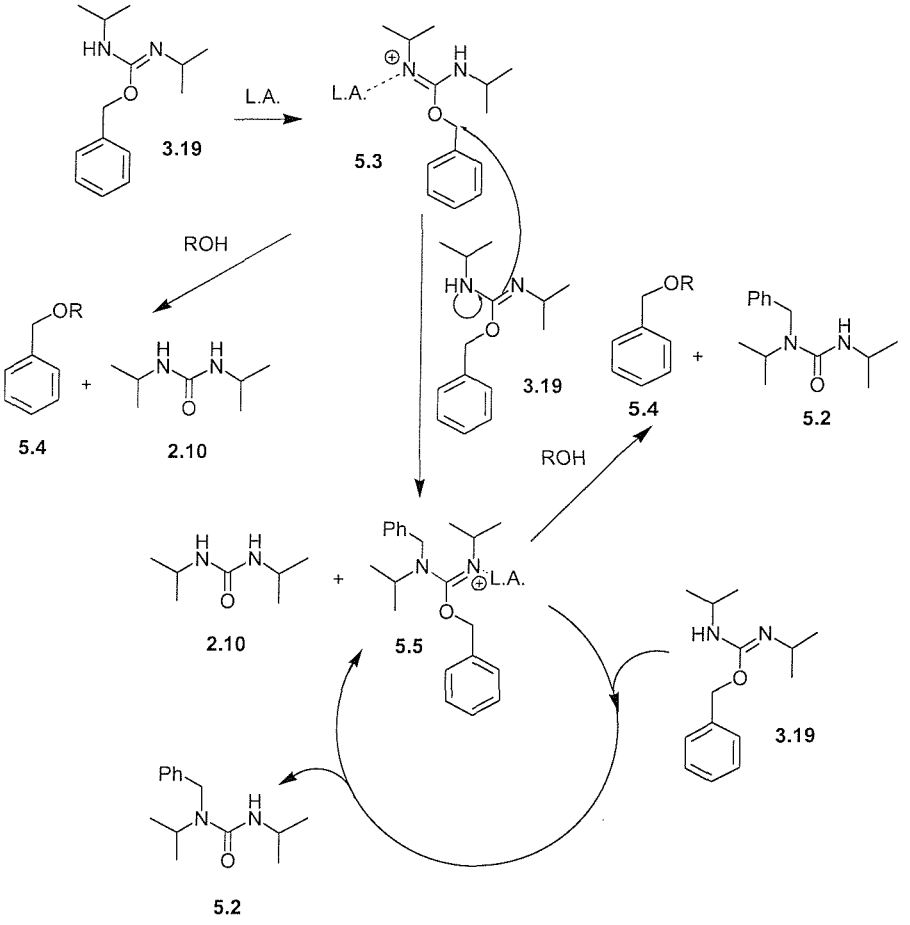


Scheme 5.2 Synthesis of benzyl ethers catalysed by scandium triflate.

Apart from the desired ether, another product was isolated from the reactions with *O*-benzylisourea and identified as the *N*-benzylated urea **5.2**.

Increasing the equivalents of isourea employed for the reaction increases the yield of benzyl ether (Table 5.1). However, it proved impossible to achieve complete conversion of the alcohol. Presumably a competing side-reaction to form **5.2** prevents complete

consumption of the alcohol. Our hypothesis is that **5.2** is formed by nucleophilic attack of **3.19** onto **5.3** (Scheme 5.3).



Scheme 5.3 Proposed mechanism for the formation of urea **5.2**.

The isourea **3.19** is activated by the Lewis acid, leading to **5.3**. Subsequent reaction with the alcohol leads to the benzyl ether **5.4**, with the urea **2.10** as by-product. However, **5.3** can also be intercepted by nucleophilic attack of **3.19**, leading to the benzylated isourea **5.5** species, which can, in turn, react with the alcohol to give **5.4** and the benzylated urea byproduct **5.2**. However, **5.5** can again react with **3.19** to form **5.2** with **5.5**, being regenerated in the process, thus acting as a propagating species.

As a control experiment, the reaction was carried out in the absence of alcohol substrate and the *N*-benzylated urea **5.2** was obtained in 79% yield.

Hence, as the *O*-benzyl isourea is consumed in the side-reactions, increasing the number of equivalents of **3.19** does increase the yields (Table 5.1, entry 2 vs. 1). When the reaction was carried out in a microwave oven at 150 °C with a reaction time of 5 minutes instead of 40 hours, the yield did not change significantly (entry 4 vs. 2). Changing the

solvent to DMF gave a much reduced yield (entry 5) while in acetonitrile the reaction failed completely (entry 6).

A further increase in yield was achieved when the concentration of the isourea was kept low, by adding **3.19** in portions. In the mechanism postulated in Scheme 5.3, the side reaction leading to **5.2** is of higher order in *O*-benzylisourea than the desired process, hence lower concentration should favour the benzyl ether formation. However, only a modest improvement was achieved (entry 3 vs. 2)

The relative rate of the two reactions seemed to depend on the electronic properties of the isourea: reaction of 3-phenylpropanol with *O*-(4-methoxybenzyl)isourea gave a lower yield (35 %), which could be explained assuming that the rearrangement reaction became competitive at an earlier stage (no residual isourea was found after the reaction).

Table 5.1 Synthesis of 3-phenylpropyl-benzyl ethers.

Entry	solvent	Isourea (equiv)	T (°C)	time	Yield
1	THF	1	65	48 h	54%
2	THF	2.5	65	48 h	75%
3	THF	2.5[a]	65	48 h	79%
4	THF	2.5	150	5 min	70%
5	DMF	2	150	5 min	17%
6	CH_3CN	2	150	5 min	--

[a] Isourea added in 4 portions over 8 hours.

Subsequently, it was attempted to influence the process by modifying the isourea structure. As the competing process proceeds by nucleophilic attack of the isourea nitrogen atoms, isourea **5.6** was expected to be less nucleophilic for steric reasons and isourea **5.7** for electronic reasons. These isoureas were prepared and used in the reaction (under microwave irradiation), but without success. The former gave a yield of benzyl ether of 64%, while the latter gave just a 40% yield of **5.1**.

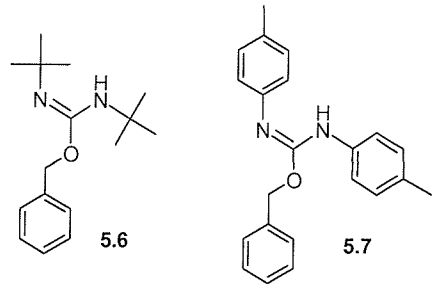
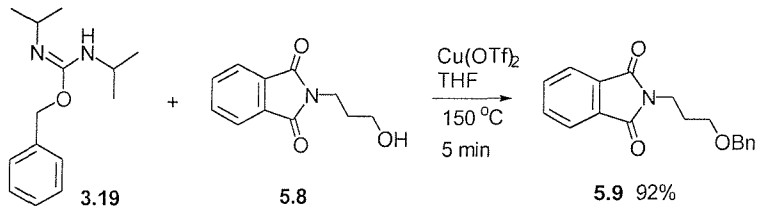


Figure 5.1 Alternative *O*-benzyl isoureas.

Finally a solution was found to the rearrangement problem. As it was thought that the rearrangement was intermolecular, it was necessary for some isoureas to act as nucleophiles. This was possible only because a sub-stoichiometric amount of Lewis acid was used. If one equivalent of Lewis acid was to be used, no isourea would remain uncoordinated, hence able to act as the nucleophile. This strategy was tested using copper (II) triflate as it was evident from our previous experiments that it binds strongly to isoureas. It is also considerably less expensive than scandium triflate. In the event, a reaction using 1.5 equivalents of both isourea and copper triflate afforded ether **5.9** in 92% yield (Scheme 5.4). The assumption that the rearrangement is intermolecular seems to be confirmed by the experimental observation that there is no rearrangement taking place under these conditions.



Scheme 5.4 Synthesis of benzyl ethers using a stoichiometric amount of copper triflate.

Interestingly, the use of one equivalent of a protic acid ($HBF_4.Et_2O$) gave a markedly lower yield (35%, with 40% recovered starting material).

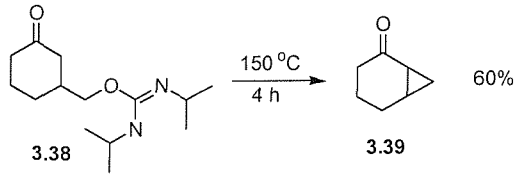
However, this research was not pursued further: even if these results proved that the reaction between alcohols and *O*-alkylisoureas could be performed to yield ethers, the amount of Lewis acid necessary to achieve high yields made us judge that the method would not be competitive with existing methods (e.g. trichloroacetimidates[118]), especially considered that the reaction is limited to benzylic isoureas.

5.2 Synthesis of nitrogen-containing heterocycles

5.2.1 Introduction

Amides are another class of molecules which, like alcohols, do not react with isoureas under normal conditions. Again, this is due to the pKa of these substrates, which is too high to enable the activation of the isourea.

However, in the literature there are a limited number of examples of *intramolecular* reactions of isoureas with compounds with a pKa comparable to amides (e.g. ketones). An example is the synthesis of bicyclo[4.1.0]heptan-2-one from a γ-hydroxyketone, through the formation of the corresponding isourea and subsequent cyclisation (Scheme 5.5).[103]

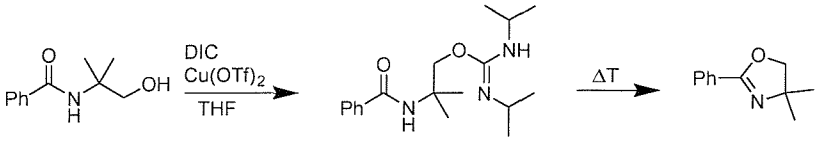


Scheme 5.5 Cyclisation of isoureas to form cyclopropanes.

5.2.2 Oxazoline synthesis

We were intrigued by the possibility of using a similar strategy for the synthesis of nitrogen containing heterocycles, such as 2-oxazolines. Over the years, these molecules have emerged as a very interesting class of heterocycles.[119] Applications in organic synthesis include protection of carboxylic acids, ortho-lithiation of benzoic acids, synthesis of enantiomerically enriched carboxylic acids and they are also widely used as chiral ligands. In addition, several molecules of biological and pharmaceutical interest possess this core structure. Among the many synthetic strategies employed for the preparation of 2-oxazolines, cyclisation of the corresponding β-hydroxyamides has proved to be one of the most popular. To accomplish this cyclisation, a number of methods are currently available: conversion of the hydroxy group to halogens[120] or sulfonic esters[121] followed by base-induced cyclisation, or cyclisations induced by treatment with DAST,[122] Burgess reagent,[123] triphenylphosphine/DEAD[124] or catalytic dichlorodimethylstannane.[125]

It was also decided to investigate whether cyclisation of an intermediate isourea as shown in Scheme 5.6 could provide an alternative, especially with regard to subsequent development of a solid-phase protocol.



5.10 5.11 5.12

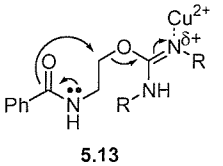
Scheme 5.6 Proposed isourea-mediated synthesis of 2-oxazolines.

It was decided to investigate the process starting from the alcohol, without isolation of the intermediate isourea.

In the event, when hydroxyamide **5.10** was treated with 1 equivalent of DIC and 5 mol% $Cu(OTf)_2$ under microwave irradiation (10 minutes at 120 °C), oxazoline **5.12** could be isolated from the reaction mixture in 61% yield. As TLC of the reaction mixture still showed presence of the intermediate isourea, the reaction temperature was increased to 150 °C in order to obtain complete cyclisation. Reaction at 150 °C for 5 minutes afforded the desired product in 93% isolated yield.

The reaction can be carried out without the use of a microwave reactor: formation of some 2-oxazoline can be detected after a few hours even at room temperature, but 2 days in refluxing THF are needed to achieve a 74% yield. The possibility to carry out the reaction thermally is particularly important if the reaction needs to be scaled-up. However, all subsequent reactions were carried out under microwave irradiation as it is more advantageous in terms of yields and reaction times on a laboratory scale.

In order to get more insight into the mechanism of the reaction, it was decided to investigate whether the cyclisation was catalysed by the copper salt, as a mechanism like the one depicted in Scheme 5.7 could be envisaged.



5.13

Scheme 5.7 Possible copper-catalysed cyclisation mechanism.

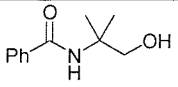
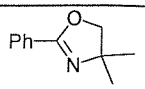
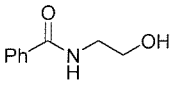
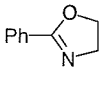
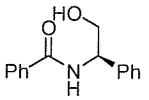
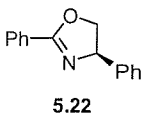
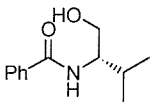
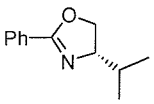
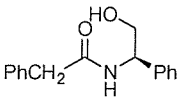
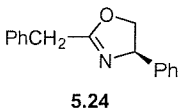
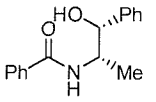
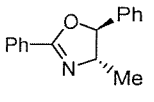
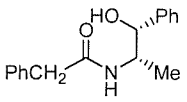
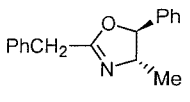
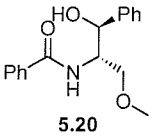
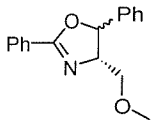
Amide **5.10** was reacted with DIC at room temperature in the presence of the usual quantity of copper (II) triflate. After 4 hours, IR and TLC analysis showed that both

carbodiimide and **5.10** had been consumed, and that the corresponding isourea **5.11** plus a minor amount of cyclised product were present. The copper catalyst was removed by filtration on an alumina plug, using DCM as eluant. The solution was concentrated under vacuum, placed in a microwave vial and subjected to the usual conditions. TLC showed complete conversion of the isourea to the oxazoline and column chromatography afforded pure **5.12** in 84% yield (based on the starting alcohol). This indicates that the copper species does not play a significant role in the second step of the reaction.

With these preliminary experiments in hand, the scope of the reaction was tested on a number of differently substituted β-hydroxyamides, which were easily prepared by reaction of the corresponding amino alcohols and acyl chlorides.

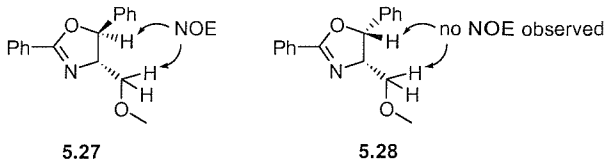
As can be seen from Table 5.2, it was found that the cyclisation of all the investigated substrates(entries 1-9) proceeded in excellent yield. Cyclisation of compounds bearing an alkyl group in the 2- position proved to be more difficult and required higher temperatures and slightly longer reaction times (entries 6 and 8). In the case of substrate **5.17** in particular, pre-forming the isourea at a lower temperature (100 °C) before raising the temperature to 175 °C to complete the cyclisation was found to be advantageous. If the temperature was set immediately to 175 °C, formation of the isourea was not complete and small amounts of unreacted amide could be found after the reaction. A similar phenomenon of apparent inactivation of the isourea formation at high temperature with a different copper catalyst will be described in more detail in section 5.3.

Table 5.2 Microwave-assisted synthesis of 2-oxazolines.

Entry	substrate	T (°C)	Time (min.)	Product	Yield	Trans:cis ratio
1	 **5.10**	150	5	 **5.12**	93%	-
2	 **5.14**	150	5	 **5.21**	87%	-
3	 **5.15**	150	5	 **5.22**	87%	-
4	 **5.16**	150	5	 **5.23**	92%	-
5	 **5.17**	a- 100 b- 175	a- 5 b- 10	 **5.24**	79%	-
6	 **5.18**	150	5	 **5.25**	88%	>95 : <5
7	 **5.19**	150	15	 **5.26**	83%	>95 : <5
8	 **5.20**	150	5	 **5.27 - 5.28**	86%	1 : 4

Of particular interest to us were the reactions of amides which possessed a chiral centre in the β position. The first such substrate investigated was **5.18**, derived from (1*R*,2*S*)-norephedrine (entry 7). Only one diastereoisomer was obtained from the reaction. Comparison with literature data confirmed that only the *trans*-substituted oxazoline had been produced. This implies that the reaction occurred with inversion of configuration, as expected on the basis of the other known reactions of isoureas. A similar result was obtained with substrate **5.19**. However, a lower level of diastereoselectivity was observed

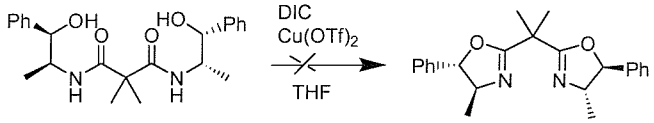
with the amide derived from (1*S*,2*S*)-2-amino-3-methoxy-1-phenyl-1-propanol (**5.20**): only a 4:1 ratio in favour of the expected cis oxazoline **5.28** over the trans isomer **5.27** (entry 9). In this case, given that the reaction occurs at a benzylic position, it is possible to envisage a competing S_N1 pathway that proceeds with retention of configuration to minimise steric hindrance occurring in the product caused by the cis-substitution.



5.27 **5.28**

Figure 5.2 Verification of the stereochemistry of **5.28** by NOE experiments.

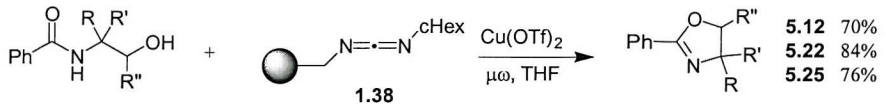
A reaction to form a bis(oxazoline) starting from a bis(amide) was attempted but failed (Scheme 5.8). Based on IR analysis, the persistent presence of both the carbodiimide band and alcohol bands suggest that the isourea formation itself is cumbersome. A possible explanation is inactivation of the copper catalyst via bidentate complexation by either the bis(isourea) itself or by the bis(oxazoline) formed.



5.29 **5.30**

Scheme 5.8 Attempted synthesis of a bis(oxazoline).

With a very efficient reaction in hand, the use of polymer-supported carbodiimide was investigated. As the cyclisation occurs partially even at room temperature, the intermediate polymer-bound isourea was not isolated for a true catch-and-release approach. Instead, three substrates were treated with 1.5 equivalents of PS-carbodiimide **1.38** and 25 mol% of $Cu(OTf)_2$ under microwave irradiation (15 minutes at 100 °C followed by 5 minutes at 150 °C). TLC and HPLC analysis showed complete disappearance of the starting material and formation of only one product (Scheme 5.9). Filtration of the resin followed by filtration of the solution on a small plug (ca. 2 cm) of alumina in order to remove the copper catalyst afforded the products in good isolated yields and excellent purities (>95% HPLC and one peak by HPLC-MS, Figure 5.3).



Scheme 5.9 Synthesis of oxazolines using polymer-supported carbodiimide.

These examples illustrate the potential of this methodology for parallel library generation, as the products are obtained in good yields and work-up required is minimal and easy to automate.[126,127]

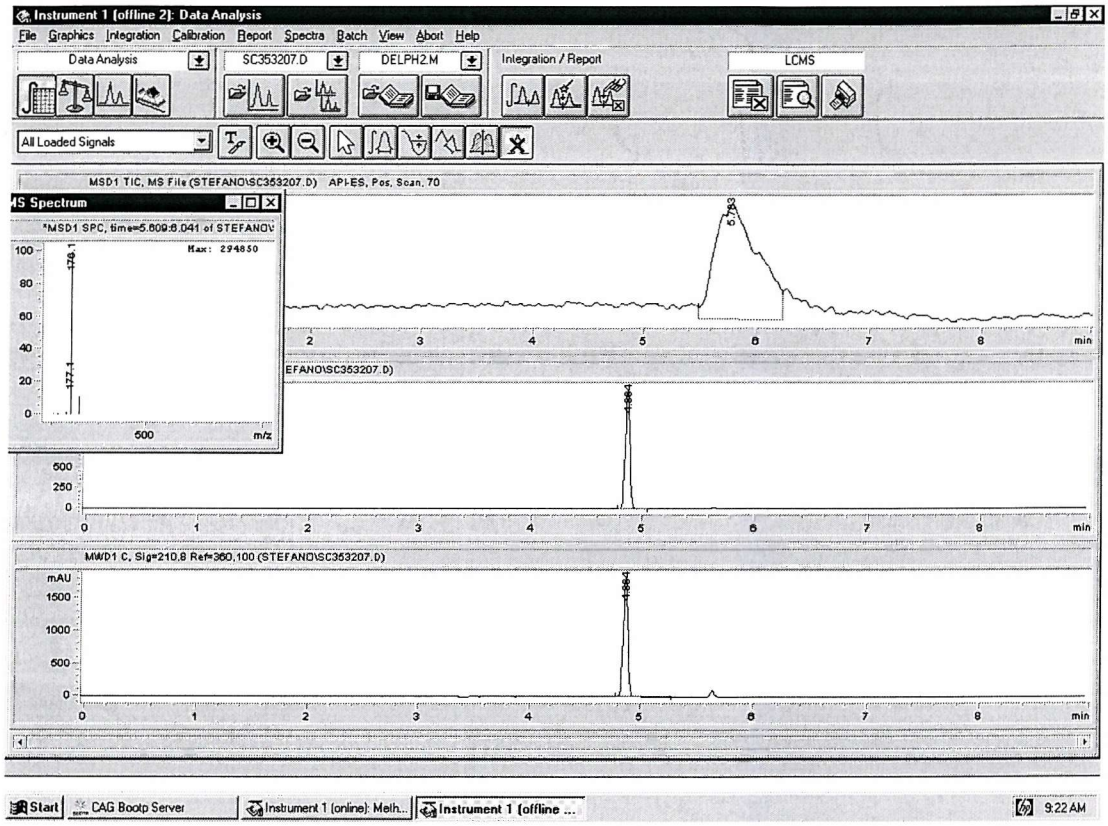
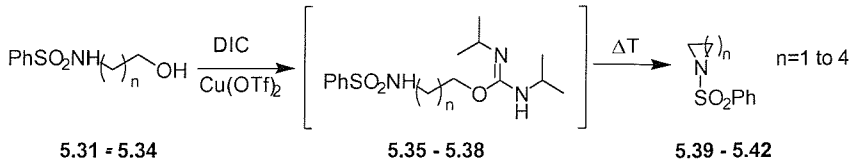


Figure 5.3 HPLC and HPLC-MS of oxazoline **5.12** prepared using polymer-supported carbodiimide.

5.2.3 Saturated *N*-heterocycles.

Another interesting class of compounds that we believed could be easily accessed through isourea chemistry is that of sulfonylpyrrolidines and sulfonylpiperidines (Scheme 5.10).

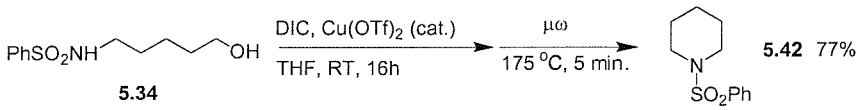


Scheme 5.10 Proposed synthesis of *N*-sulphonyl heterocycles.

In this case it was anticipated that the sulfonamide proton would be acidic enough to allow for an intramolecular reaction.

A series of hydroxysulfonamides were easily prepared by reaction of the corresponding aminoalcohols with benzenesulphonyl chloride.

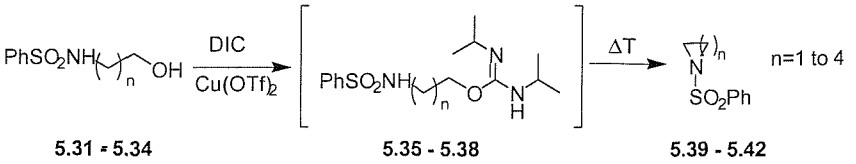
The first substrate tested was *N*-(5-hydroxypentyl)-benzenesulfonamide **5.34**. The isourea could be easily formed at room temperature. As opposed to the oxazoline case, no cyclised product could be detected after the reaction at room temperature. However, upon heating the reaction at 175 °C for 5 minutes under microwave irradiation the expected product **5.42** is formed in 77% isolated yield (Scheme 5.11)



Scheme 5.11 Synthesis of phenylsulfonyl-piperidine through an isourea intermediate.

Next, a series of experiments was conducted in order to study the effect of ring size on the reaction (Table 4.3). The necessary *N*-(hydroxyalkyl)sulfonamides were easily prepared by reacting the appropriate amino alcohols with benzenesulfonyl chloride.

Table 5.3 Microwave-assisted synthesis of sulfonamides.



5.31 - 5.34 5.35 - 5.38 5.39 - 5.42

Entry	n	T (°C)	Time (min.)	Product	Yield
1	1	130[a]	5		complex mixture
2	1	60[b]	960 (16 h)		48%
3	1	60[b]	4200 (70 h)		68%
4	2	175[a]	5		13%
5	3	175[a]	5		93%
6	4	175[a]	5		77%

[a] Reaction run under microwave irradiation. [b] Reaction run with thermal heating.

For n=1, reactions under microwave irradiation were not successful, NMR and TLC analysis indicating that a complex mixture was formed. The fact that the isourea was consumed (as showed by IR and TLC analysis) and the formation of a diisopropylurea precipitate could indicate that the reaction was probably taking place, but that the desired product decomposed during the reaction.

The reaction was more successful under thermal heating, and gave 48% yield after 16 hours and 68% after 70 hours at 60 °C. No product decomposition was observed under these conditions. This behaviour could be explained by the instability of the strained sulfonyl aziridine at high temperature. On the other hand, these products can be formed under much milder conditions than other sulfonamides. This is in line with the cyclisation of hydroxyketones mentioned previously (Scheme 5.6): in that case, only the formation of 3-membered cycles was possible.

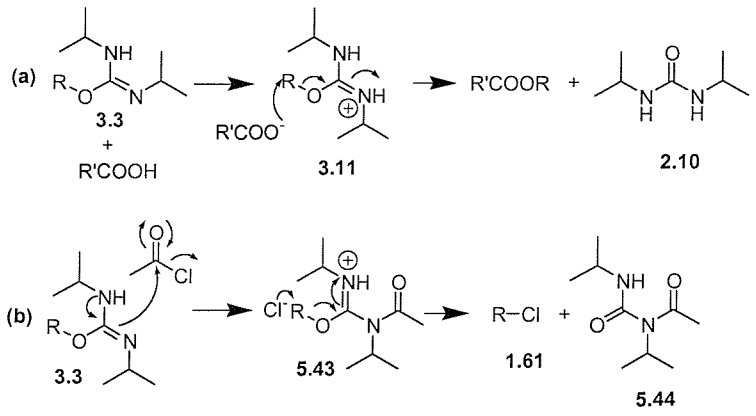
The reaction of substrate **5.32** (n=2) gave low yields even under forcing conditions (remaining material appeared to be unreacted isourea by IR), while **5.33** (n=3) gave an

excellent yield (93%). The formation of 4-membered rings is normally entropically disfavoured compared to 5 and 6 membered rings, so this result can be easily rationalised.

5.3 A novel activation for *O*-alkylisoureas: synthesis of haloalkanes[128]

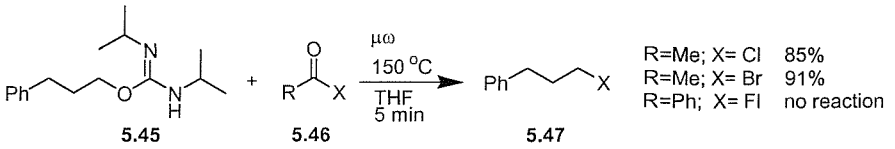
5.3.1 Reaction of *O*-alkylisoureas with acetyl halides.

The overwhelming majority of the reactions of isoureas require the presence of a Brønsted or Lewis acid in order to activate the isourea. In order to broaden the scope of isourea reactivity, it was decided to explore the possibility of using different methods to activate isoureas. As well as being a base, an isourea is also a nucleophile. Hence, it was envisaged that isoureas could react with electrophiles. This would result in a positively charged species which should be activated towards nucleophilic substitution. For example, reaction of an isourea with acetyl chloride was expected to lead to intermediate **5.43** (Scheme 5.12b), which subsequently would react with the chloride anion which was formed in the last step.



Scheme 5.12 Mechanisms of isourea activation with (a)- protic acids and (b)- proposed for acetyl chloride.

In order to test this strategy, *O*-(3-phenylpropyl)isourea **5.45** was prepared, isolated and reacted with 1 equivalent of acetyl chloride under microwave irradiation (150 °C for 5 minutes). At the end of the reaction (3-chloropropyl)benzene could be isolated in 78% yield (Scheme 5.13). This yield could be improved to 85% using 1.5 equivalents of acetyl chloride. When 1.5 equivalents of acetyl bromide were used, (3-bromopropyl)benzene was obtained in 91% yield. Unfortunately, no reaction was observed when the same substrate was treated with benzoyl fluoride.



5.45 5.46 5.47

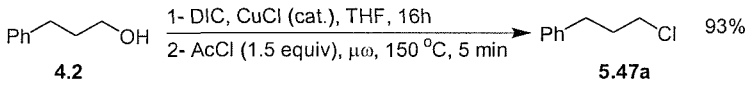
Scheme 5.13 Reaction of *O*-alkylisoureas with acetyl halides.

5.3.2 One-pot conversion of alcohols into alkyl halides.

These results demonstrated that alternative activation for isoureas was possible through reaction with electrophiles, opening a new area of research.

The process described above gave access to a viable alternative to the existing methods to convert alcohols into alkyl halides, as isoureas are readily available from the corresponding alcohols. In order to make this reaction of practical interest, however, the purification of the intermediate isourea should be avoided, so it was decided to investigate the possibility of performing the whole transformation as a one-pot process.

To this end, 3-phenyl-propanol was reacted with DIC under CuCl catalysis overnight in THF. The resulting isourea was not isolated, and acetyl chloride (1.5 equivalents) was directly added to the reaction mixture, which was then subjected to microwave irradiation for 5 minutes (Scheme 5.14). Gratifyingly, a yield of 93% of the expected product was obtained.



4.2 5.47a

Scheme 5.14 One-pot protocol for the synthesis of 3-phenylpropyl chloride.

In order to achieve the overall transformation of the alcohol into the corresponding alkyl halide in the shortest possible time, the use of microwave irradiation was investigated for the isourea formation step as well: a number of reaction conditions were tested for the microwave-assisted synthesis of isoureas starting form a primary and a secondary alcohol. All reactions were carried out using 1 equivalent of DIC and analysed by IR to verify the disappearance of the carbodiimide band at 2110 cm^{-1}(Table 5.4).

Table 5.4 Microwave-assisted synthesis of isoureas.

Alcohol	Catalyst (mol%)	T (°C)	time	Yield[a]
3-Ph-propanol	CuCl (2)	100	5	100%
4-Ph-2-butanol	CuCl (2.5)	100	5	50%
4-Ph-2-butanol	CuCl (2.5)	150	5	50%
4-Ph-2-butanol	CuCl (2.5)	100	15	90%
4-Ph-2-butanol	CuCl (20)	100	5	90%
4-Ph-2-butanol	CuCl (20)	100	10	100%
4-Ph-2-butanol	$Cu(OTf)_2$ (0.5)	100	5	20%
4-Ph-2-butanol	$Cu(OTf)_2$ (5)	100	5	100%
4-Ph-2-butanol	$Cu(OTf)_2$ (2)	100	5	100%

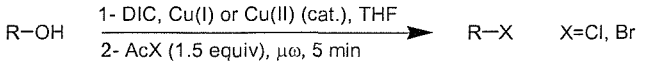
[a] Estimated by IR analysis (disappearance of carbodiimide band at 2110 cm^{-1} and appearance of the isourea band at 1655 cm^{-1}.

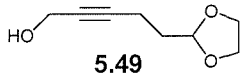
Reactions of the primary alcohol substrate proceeded smoothly using CuCl as catalyst at 100 °C.With the secondary substrate, reactions catalysed with CuCl were not complete in 5 minutes and increasing the temperature did not improve the yield at all. Increasing the reaction time improved the situation but did not allow complete conversions and only a significant increase in the amount of catalyst gave satisfactory results. The reaction did not improve significantly by increasing the reaction temperature over 100 °C. It was thought that inactivation of the catalyst at high temperatures occurs, although no clear reason for this has been discovered. Better results were obtained using $Cu(OTf)_2$ instead of CuCl as the catalyst, for which only 2 mol% were sufficient to achieve complete conversions.

In order to test the one-pot alcohol to halide transformation, a series of alcohols were reacted with DIC and the catalyst under microwave irradiation for 5 minutes. Acetyl chloride or bromide (1.5 equivalents) were then added and the resulting mixtures were resubjected to microwave irradiation. As catalyst, CuCl was only used for reaction involving primary alcohols in reactions with acetyl chloride. With secondary substrates $Cu(OTf)_2$ was used due to its higher activity. This last catalyst was also used for all the bromination reactions, as the presence of the chloride anion could lead to a Finkelstein-type reaction with the alkyl bromide produced, which would have resulted in product mixtures (see below).

The results are summarised in Table 5.5.

Table 5.5 One-pot synthesis of haloalkanes.



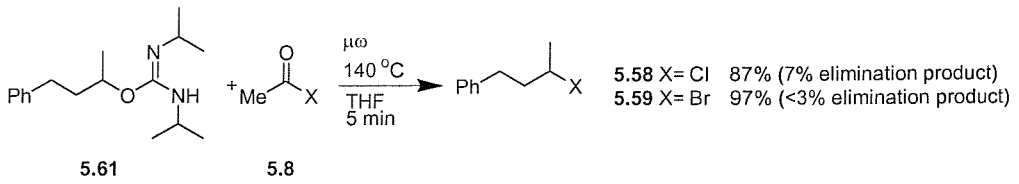
Entry	Alcohol	Catalyst (mol%)	Activator (1.5 equiv)	1 step	2 step	Product (yield)
1	3-phenyl-propanol **4.2**	CuCl (2%)	AcCl	100 °C, 5 min	150 °C 5 min	**5.47a** 100%
2	*N*-(3-hydroxypropyl) phthalimide **5.8**	CuCl (2%)	AcCl	100 °C, 5 min	150 °C 5 min	**5.52** 92%
3	*p*-nitrobenzyl alcohol **5.48**	CuCl (2%)	AcCl	100 °C, 5 min	150 °C 5 min	**5.53** 95%
4	 **5.49**	CuCl (1%)	AcCl	RT, 16 h	150 °C 5 min	**5.54** 82%
5	3-phenyl-propanol **4.2**	$Cu(OTf)_2$ (2%)	AcBr	100 °C 5 min	150 °C 5 min	**5.47b** 98%
6	6-chloro-1-hexanol **5.50**	$Cu(OTf)_2$ (2%)	AcBr	100 °C 5 min	150 °C 5 min	**5.55** 96%
7	*N*-(3-hydroxypropyl) phthalimide **5.8**	$Cu(OTf)_2$ (2%)	AcBr	100 °C 5 min	150 °C 5 min	**5.56** 89%
8	*p*-nitrobenzyl alcohol **5.48**	$Cu(OTf)_2$ (2%)	AcBr	100 °C 5 min	150 °C 5 min	**5.57** 98%
9	4-phenyl-2-butanol **4.14**	$Cu(OTf)_2$ (5%)	AcCl	100 °C 5 min	140 °C 5 min	**5.58** 80% (14%)[a]
10	4-phenyl-2-butanol **4.14**	$Cu(OTf)_2$ (5%)	AcBr	100 °C 5 min	120 °C 5 min	**5.59** 95% (<3%)[a]
11	3-β-cholestanol **5.51**	$Cu(OTf)_2$ (5%)	AcBr	RT, 16 h	150 °C 5 min	**5.60** 80% (8%)[a, b]
12	3-β-cholestanol **5.51**	CuCl (5%)	AcBr	RT, 16 h	150 °C 5 min	Complex mixture
13	(*R*)-4-phenyl-2-butanol **4.14**	$Cu(OTf)_2$ (5%)	AcBr	100 °C 5 min	120 °C 5 min	**5.59** 88% (<3%)[a, c]

[a] Elimination product (ratio determined by ^{1}H-NMR). [b] Only the 3-α isomer was observed. [c] $[\alpha]_D$= +66.2 ($CHCl_3$, c=0.85). A sample prepared using Ph_3P/CBr_4 had $[\alpha]_D$= +64.7 ($CHCl_3$, c=0.80).

The reactions of all primary substrates gave excellent yields. Only in the case of propargylic alcohol **5.49** it was found that performing the first step at under microwave irradiation led to extensive decomposition. However, if the first step was performed at room temperature the corresponding isourea could be formed in quantitative yield. Subsequent treatment with acetyl chloride gave the propargylic chloride in good yield. Unfortunately, the reaction failed with allylic substrates, but benzylic alcohols gave the corresponding chlorides and bromides in excellent yield. It is worth noting that the absence of protic acids means that acid-labile groups such as the acetal in substrate **5.49** were not touched.

When performing the reaction on secondary substrates, the situation was complicated by the competitive elimination reaction of secondary isoureas, already described in the previous chapter.

Test reactions carried out on isolated secondary isourea **5.61** had already demonstrated that small amounts of elimination products contaminated the desired haloalkane (Scheme 5.15). Interestingly, the amount of elimination product was substantially lower in the reactions involving acetyl bromide than when acetyl chloride was used.

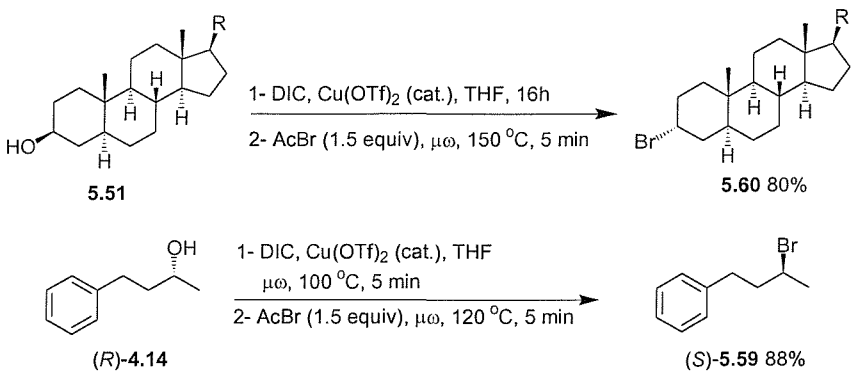


5.61 **5.8**

Scheme 5.15 Reaction of secondary isoureas with acetyl halides.

Similar results were obtained in the one-pot reactions (Table 5.5, entries 9-13). The level of elimination was also dependent on the steric bulk around the secondary alcohol: the relatively unhindered 4-phenyl-2-propanol gave much less elimination than 3-β-cholestanol.

Very interestingly, reaction with chiral alcohols proved to be completely stereoselective (Scheme 5.16). When 3-β-cholestanol was reacted with acetyl bromide, only the 3α-bromo diastereoisomer was formed, proving that an S_N2 inversion process is taking place (entry 11). A clean inversion of configuration was also observed with enantiopure (*R*)-4-phenyl-2-butanol (entry 13). No racemisation was observed, as evidenced by comparison of the optical rotation with a sample of (*S*)-4-phenyl-2-bromobutane, prepared from (*R*)-4-phenyl-2-butanol using Ph_3P/CBr_4.

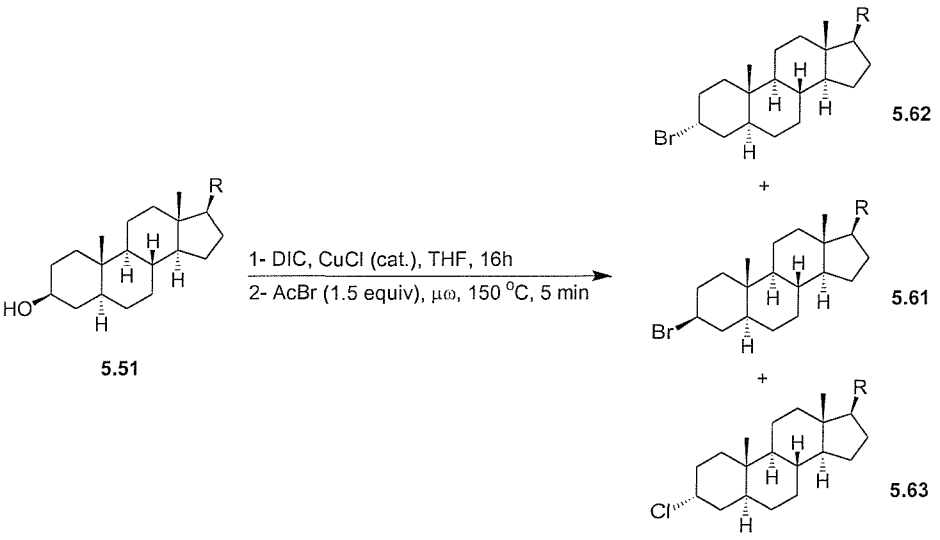


Scheme 5.16 Reactions of chiral alcohols occur with inversion of configuration.

It is worth repeating that the procedure described by Golding[124] for the conversion of isoureas to haloalkanes, using 1 equivalent of triflic acid to activate the isourea, is not stereoselective, with extensive racemisation observed even at only 30% conversion. The racemisation was most probably cause by the presence of an access of free halide anions giving rise to a series of Finkelstein exchanges on the product.

It was predicted that a similar scenario would take place when CuCl would be used as Lewis acid, as in that case extra halide anions are added to the reaction mixture. This was proven by a control experiment where 3-β-cholestanol was reacted with DIC under CuCl catalysis, followed by treatment with acetyl bromide (entry 12).

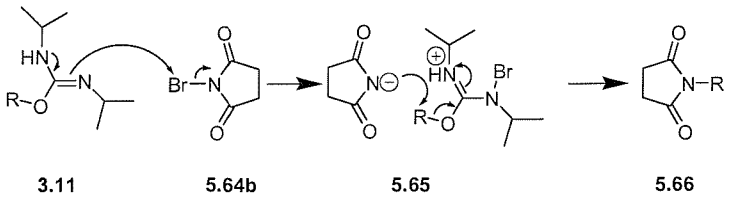
In this case, a complex reaction mixture was obtained consisting of the desired 3α-bromo derivative, as well as the 3α-chloro, the 3β-bromo and the elimination products (Scheme 5.17). This clearly demonstrates that Finkelstein reaction does take place with chloride anions originating from the copper catalyst. Alternatively, the chloride ions could react with the activated isoureas, which would give rise to 3α-chloro isomer **5.63**. Both processes lead to residual bromide ions which cause the formation of the 3-β-bromocholestanol derivative through Finkelstein reaction with the corresponding 3-α-bromo derivative. With $Cu(OTf)_2$ as catalyst instead of CuCl, no such epimerisation was observed.



Scheme 5.17 Using CuCl as catalyst leads to mixtures of products.

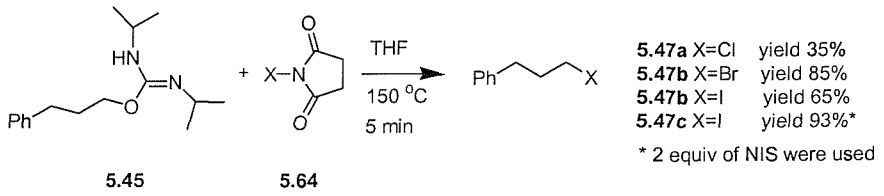
5.3.3 Reactions with *N*-halo-succinimides

Another group of electrophiles which were used in conjunction with isoureas is that of *N*-halosuccinimides (NCS, NBS and NIS). The first experiments were done using *N*-bromosuccinimide (NBS). As this molecule is normally considered a source of Br^+ equivalents, a possible mechanism such as the one depicted in Scheme 5.18 was envisaged, leading to the formation of *N*-alkylsuccinimides.



Scheme 5.18 Hypothetic reaction of *O*-alkylisoureas with NBS.

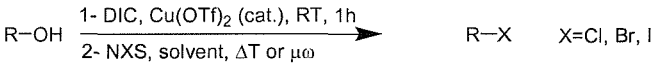
However, when *O*-(3-phenylpropyl)isourea was reacted with NBS under microwave irradiation the expected product **5.66** was not observed. Instead, 3-phenylpropyl bromide **5.47b** was isolated in 85% yield (Scheme 5.19).



Scheme 5.19 Reaction of *O*-alkylisoureas with *N*-halosuccinimides yields the corresponding haloalkanes.

The same reaction was carried out with NCS and NIS. Good yields of 3-phenylpropyl chloride and iodide respectively were obtained, although 2 equivalents of NIS had to be used to achieve a satisfactory yield.

This reaction was further investigated within the group by Dr. Zhengning Li, who developed it into an efficient one-pot reaction for the conversion of alcohols into haloalkanes (Scheme 5.20).[129]



Scheme 5.20 One-pot conversion of alcohols into haloalkanes using *N*-halosuccinimides.

5.4 Conclusions

Four novel reactions of *O*-alkylisoureas have been discovered. Although the reaction of isoureas with alcohols catalysed by Lewis acids was not considered to be of particular synthetic interest, the cyclisation of aminoalcohols and hydroxysulfonamides through intermediate *O*-alkylisoureas have demonstrated a good synthetic potential. In particular, the cyclisation of β-hydroxyamides using polymer-supported carbodiimide appears of particular interest for the preparation of libraries and deserves further studies. Finally, the reaction of isoureas with acetyl halides not only provides an alternative way of converting alcohols into the corresponding haloalkanes, but potentially opens the field for a number of other reactions as it successfully demonstrated a completely novel activation procedure for isoureas.

6. Experimental

6.1 General

^{1}H- and ^{13}C-NMR spectra were recorded using a BRUKER AC300 spectrometer or a BRUKER DPX400 spectrometer. IR spectra were recorded using a BioRad 135 spectrophotometer or a Thermo Mattson Satellite FTIR. HPLC were performed using a Phenomenex Luna C_{18} RP column, eluting with a gradient from 95% acetonitrile / water to 5% acetonitrile / water in 6 minutes and examining $\lambda = 252$ nm.

Anhydrous DMSO was distilled prior to use and stored under nitrogen using Schlenk bottles. Anhydrous THF was distilled from sodium-benzophenone and DCM was distilled from calcium hydride immediately prior to use.

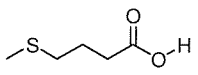
Reagents were purchased from Aldrich and Fluka and used without further purification. Merrifield resin (chloromethyl PS-DVB) was purchased from Polymer Laboratories, loading 1.91 mmol/g, 150-300 μm. *N*-Cyclohexyl-*N'*-methylpolystyrenecarbodiimide **1.38a** (loading 1.7 to 1.9 mmol/g depending on batch) and aminomethyl polystyrene **1.35** (loading 3.2 mmol/g) were donated by Novabiochem.

Microwave-assisted reactions were carried out in a Smith Synthesizer™.

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

6.2 Experimental for Chapter 2

Synthesis of 4-(methylsulfanyl)-butyric acid 2.17



2.17

A potassium hydroxide solution in water (3 N, 33.7 mL, 0.101 mol) was added to methanol (100 mL) under stirring, then methyl-4-(methylsulfanyl)-butyrate (4.83 mL, 33.7 mmol) was added via a micropipette. Vigorous stirring was continued at room temperature for 16 h, and then the methanol was evaporated under vacuum. The solution was then extracted with 100 mL of diethyl ether, the organic phase was discarded and the aqueous

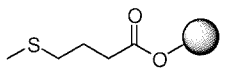
solution was cooled to 5 °C with an ice bath. HCl (conc.) was added slowly under vigorous stirring until the pH of the solution was *ca.* 3. The solution was then extracted 3 times with Et_2O, the ethereal portions were combined, dried over $MgSO_4$, filtered and evaporated under vacuum to afford 4.26 g (94.0%) of a pale yellow oil.

IR (neat): ν_{max} / (cm^{-1}) 3100br, 1702s, 933br.

^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 9.4 (1H, bs, COO<u>H</u>); 2.53 (2H, t, J=7.5 Hz, C<u>H</u>$_2$S); 2.48 (2H, t, J=7.5 Hz, C<u>H</u>$_2$COOH); 2.08 (3H, s, SC<u>H</u>$_3$); 1.91 (2H, quintet, J=7.5 Hz, $CH_2C\underline{H}_2CH_2$).[130]

^{13}C-NMR (75.47 MHz; $CDCl_3$) δ_C: 179.2; 33.4; 32.7; 23.9; 15.4.

Synthesis of the resin bound sulfide 2.18

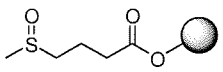


2.18

In a flask, a solution of KOH in water (30.0 mL of a 0.80 M solution, 24.0 mmol) was added to 4-(methylsulfanyl)butyric acid (3.221 g, 24.0 mmol). The solution was stirred for 10 minutes, then the water was evaporated under vacuum at 50 °C for 1h and the residual solid dried under high vacuum for 48 h. The solid was dissolved in dry DMF (25 mL), then Merrifield resin (2.510 g, 4.80 mmol) was added and the suspension heated at 100 °C for 20 h. The resin was filtered, washed with MeOH (3×10 mL), THF (3×10 mL) and DCM (3×10 mL) and dried under vacuum for 16 h. 2.848 g of resin were obtained.

IR (neat): ν_{max} / (cm^{-1}) 2914w, 1731s, 1130s.

Synthesis of the resin-bound sulfoxide 2.19 by oxidation



2.19

The resin bound sulfide **2.18** (1.000 g, 1.61 mmol) was swollen in DCM (2 mL), then HFIP (18 mL) was added, followed by H_2O_2 (685 μL of a 27.5% solution, 5.73 mmol). The suspension was stirred for 4 h, then the resin was filtered and washed with DCM

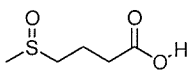
(2×10 mL), MeOH (3×10 mL), DCM (3×10 mL). The resin was dried under vacuum for 16 h at 40 °C to give 0.999 g of product.

IR (neat): ν_{max} / (cm^{-1}) 2919w, 1730s, 1165s, 1040s.

^{13}C-NMR (75.47 MHz; $CDCl_3$) δ_C: 172.0 (COOH); 66.3 ($PhCH_2O$); 53.1 (CH_2SO); 38.3 (CH_3); 32.5 (CH_2COOH); 17.9 ($CH_2CH_2CH_2$).

Elem. Anal. Cl 0.00 S 4.63. Loading 1.45 mmol/g.

Synthesis of 4-(methylsulfinyl)-butyric acid 2.20



2.20

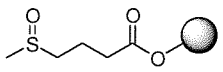
4-(Methylsulfanyl)-butyric acid **2.17** (0.521 g, 3.88 mmol) was dissolved in methanol (7.5 mL) and was cooled to 0 °C with a salt/ice bath. A sodium metaperiodate solution in water (7.75 mL of a 0.5M solution, 3.875 mmol) was then added under vigorous stirring. Stirring at 0 °C was continued for 3 h, then the reaction was refrigerated overnight (14 h). The solvents were removed under vacuum at room temperature, then the white solid obtained was washed 4 times with 10 mL of DCM. The DCM filtrates were combined and evaporated under vacuum to obtain 0.546 g of a yellow oil (94%).

IR (neat): ν_{max} / (cm^{-1}) 2800br, 1710s, 987s, 940s.

^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 9.2 (1H, bs, COOH); 2.92 (1H, dtd, J=13.0 Hz, 7.0 Hz, 2.0 Hz, SO-CHH'-); 2.83 (1H, dt, J=13.0 Hz, 7.0 Hz, SO-CHH'-); 2.64 (3H, s, $SO-CH_3$); 2.50 (2H, td, J=7.0 Hz, 2.0 Hz, $-CH_2-COOH$); 2.08 (2H, quintet, J=7.0 Hz, , $-CH_2-CH_2-CH_2-$).

^{13}C-NMR (75.5 MHz; $CDCl_3$) δ_C: 175.8 (COOH); 52.8 (CH_2SO); 38.0 (CH_3); 32.6 (CH_2COOH); 18.3 ($CH_2CH_2CH_2$).

Synthesis of the resin bound sulfoxide 2.19 by direct coupling

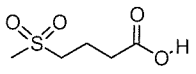


2.19

In a round-bottom flask, a solution of KOH in water (2.62 mL of a 0.844 M solution, 2.21 mmol) was added to 4-(methylsulfinyl)-butyric acid **2.20** (0.332 g, 2.21 mmol). The solution was stirred for 10 minutes, then water was evaporated under vacuum at 50 °C for 1h and the residual solid dried under high vacuum for 48 h (obtained 0.385 g). The solid was dissolved in dry DMF, then Merrifield resin (0.116 g, 0.221 mmol) was added and the suspension heated at 100 °C for 20 h. The resin was filtered, washed with MeOH (3×5 mL), THF (3×5 mL) and DCM (3×5 mL) and dried under vacuum for 16 h. 120 mg of resin were obtained.

The IR and ^{13}C-NMR correspond to the data obtained for **2.19** prepared via the oxidation of resin-bound sulfide **2.19**.

Synthesis of 4-(methylsulfonyl)-butyric acid 2.21



2.21

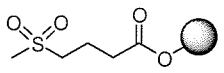
4-(Methylsulfinyl)-butyric acid **2.17** (1.140 g, 7.59 mmol) was dissolved in MeOH (40 mL), then a solution of sodium metaperiodate (44.87 g, 22.80 mmol, dissolved in 60 mL of water) was added. The solution was stirred at 50 °C for 40 h. The solvent was then removed under vacuum and the white solid obtained was washed with DCM (4×25 mL). The organic solvent was then removed under vacuum to afford the title product (1.152 g, 91% yield).

IR (neat): ν_{max} / (cm^{-1}) 2920 (br), 1686 (s), 1407 (m), 1243 (s), 1122 (s), 1056 (w), 963 (m), 911 (m), 774 (s)

^{1}H-NMR (300 MHz; D_2O) δ_H: 3.18 (2H, t, J=7.0 Hz, SO_2-C<u>H</u>$_2$); 2.97 (3H, s, SO_2-C<u>H</u>$_3$); 2.45 (2H, t, J=7.0 Hz, -C<u>H</u>$_2$-COOH); 1.96 (2H, quintet, J=7.0 Hz, -CH_2-C<u>H</u>$_2$-CH_2-).

^{13}C-NMR (75.47 MHz; D_2O) δ_C: 179.4 (<u>C</u>OOH); 55.2 (<u>C</u>H$_2$SO$_2$); 42.1 (<u>C</u>H$_3$); 34.3 (<u>C</u>H$_2$COOH); 19.7 (CH_2<u>C</u>H$_2$$CH_2$).

Synthesis of the resin bound sulfone 2.22

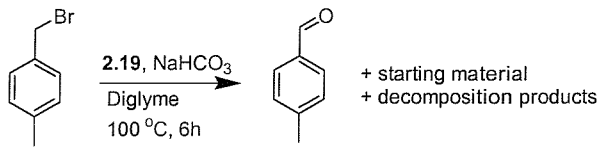


2.22

In a flask, a solution of KOH in water (1.50 mL of a 0.803 M solution, 1.20 mmol) was added to 4-(methylsulfonyl)-butyric acid **2.21** (0.200 g, 1.20 mmol). The solution was stirred for 10 minutes, then the water was evaporated under vacuum at 50 °C for 1 h and the residual solid was dried under high vacuum for 48 h. The solid was dissolved in dry DMF (2 mL), then Merrifield resin (0.126 g, 0.24 mmol) was added and the suspension was heated at 100 °C for 20 h. The resin was filtered, washed with MeOH (3×4 mL), THF (3×4 mL) and DCM (3×4 mL) and dried under vacuum for 16 h. 161 mg of resin were obtained.

IR (neat): ν_{max} / (cm^{-1}) 2928w, 1727s, 1295s, 1175s, 1115s, 954m.

Oxidation of *p*-methylbenzyl bromide with 2.19 and $NaHCO_3$



2.23 2.24

Resin **2.19** (100 mg, 0.157 mmol) was swollen in anhydrous diglyme and *p*-methylbenzyl bromide (26 mg, 0.141 mmol) and anhydrous $NaHCO_3$ (27 mg, 0.785 mmol) were added. The mixture was heated at 100 °C for 24 h. The mixture was then allowed to cool to room temperature and the resin was filtered and washed with DCM (3×5 mL). The filtrate was evaporated under vacuum, dissolved in hexane (30 mL) and washed three times with water (30 mL), dried on $MgSO_4$ and evaporated under vacuum to gave 24 mg of crude product. NMR analysis showed presence of the desired aldehyde, some alcohol and many different other products, probably derived by the decomposition of **2.19**.

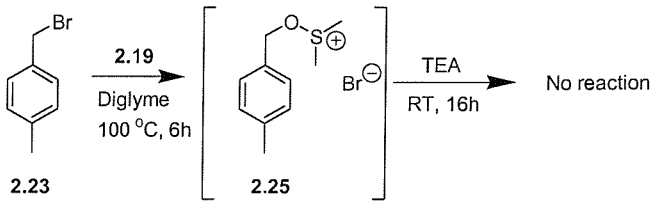
p-methylbenzyl bromide **2.23**

^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 7.28 (2H, d, J=8.0 Hz, Ar$\underline{H}^2$); 7.14 (2H, d, J=8.0 Hz, Ar$\underline{H}^3$); 4.47 (2H, s, PhC$\underline{H}_2$Br); 2.33 (3H, s, C$\underline{H}_3$).

p-methylbenzaldehyde **2.24**

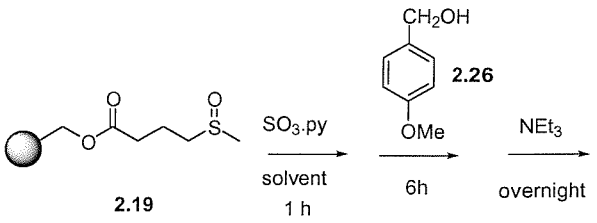
^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 9.94 (1H, s, C$\underline{H}$O); 7.76 (2H, d, J= 8.0 Hz, Ar$\underline{H}^2$); 7.31 (2H, d, J= 8.0 Hz, Ar$\underline{H}^3$); 2.42 (3H, s, PhC$\underline{H}_3$).

Oxidation of *p*-methylbenzyl bromide with 2.19 and TEA



Resin **19** (100 mg, 0.157 mmol) was swollen in anhydrous diglyme and *p*-methylbenzyl bromide (26 mg, 0.141 mmol) was added. The mixture was heated at 100 °C for 6 h. The mixture was then allowed to cool at room temperature, then TEA (200 μL, 1.32 mmol) was added and the mixture stirred overnight. The resin was filtered and washed with DCM (3×5 mL). The organic phase was washed with water (3×15 mL), dried on $MgSO_4$ and evaporated under vacuum to give 0.5 mg of crude product (not further characterised). The IR spectrum of resin **2.19** appears unchanged (band at 1040 cm^{-1}).

Oxidations of *p*-methoxy-benzyl-alcohol using 2.19 and SO_3.py



General method: Resin **2.19** (100 mg, 0.157 mmol) was swollen in the solvent (1 mL) in a dry, stoppered flask. SO_3.py (22.5 mg, 0.141 mmol) was then added and the mixture

stirred for 1 h. Then *p*-methoxybenzyl alcohol (19.5 mg, 0.141 mmol) was added and stirring was continued for 5h. TEA (200 μL, 1.32 mmol) was then added via syringe. Stirring was continued overnight, the resin was filtered, washed with DCM (3×5 mL) and dried under vacuum at 40 °C for 16 h. The filtrate was evaporated under vacuum, diluted with water (20 mL) and extracted with Et_2O (20 mL). The ethereal layer was washed twice with water (20 mL), dried over $MgSO_4$ and evaporated under vacuum to give the crude product. The weight of the crude material obtained and the composition determined by ^{1}H-NMR are listed below.

In experiment 4 the work-up procedure was slightly different: following the resin washing, all the solvent was removed by evaporation without extraction and the crude analysed by ^{1}H-NMR. In all cases the IR spectrum of the resin showed no change of the peak at ca. 1040 cm^{-1} (S-O stretch).

EXP.	SOLVENT	RECOVERED	**2.26**	**2.28**	**2.27**
1	DMF	15 mg	100%	0%	--
2	Nitromethane	10 mg	100%	0%	--
3	NMP	0 mg	--	--	--
4	Nitromethane	51 mg	40%	0%	60%

p-methoxybenzaldehyde **2.28**

^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 9.87 (1H, s, C<u>H</u>O); 7.81 (2H, d, J= 9.0 Hz, Ar<u>H</u>^{2}); 6.99 (2H, d, J= 9.0 Hz, Ar<u>H</u>^{3}); 3.88 (3H, s, OC<u>H</u>$_3$).

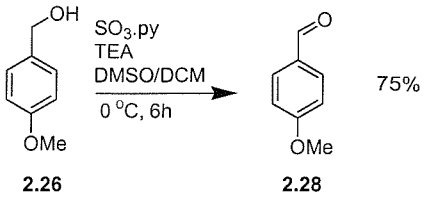
p-methoxybenzyl alcohol **2.26**

^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 7.30 (2H, d, J= 7.0 Hz, Ar<u>H</u>^{2}); 6.87 (2H, d, J= 7.0 Hz, Ar<u>H</u>^{3}); 4.56 (2H, s, C<u>H</u>$_2$OH); 3.80 (3H, s, OC<u>H</u>$_3$).

Triethylammonium *p*-methoxybenzyl sulphate **2.27**

^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 10.6 (2H, bs, N<u>H</u>$^+$); 7.20 (2H, d, J=8.0 Hz, Ar<u>H</u>^{2}); 6.70 (2H, d, J=8.0 Hz, Ar<u>H</u>^{3}); 4.96 (2H, s, C<u>H</u>$_2$OSO$_3^-$); 3.64 (3H, s, OC<u>H</u>$_3$); 3.1 (12H, q, J=7.5 Hz, C<u>H</u>$_2$CH$_3$); 1.4 (18H, t, J=7.5 Hz, CH$_2$C<u>H</u>$_3$).

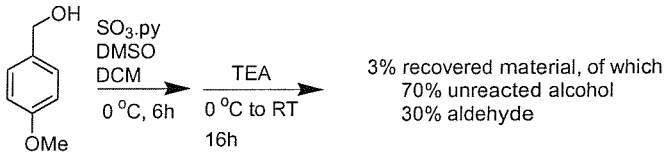
Oxidation of *p*-methoxybenzyl alcohol using SO_3.py in solution (method 1)



2.26 **2.28**

p-Methoxybenzyl alcohol (100 mg, 0.723 mmol) was dissolved in DCM (3.5 mL), then DMSO was added (7 mL) and the solution was cooled at 0 °C. In a second flask SO_3.py (288 mg, 1.81 mmol) and TEA (300 μL, 1.98 mmol) were dissolved in DCM (1.5 mL) and DMSO (3 mL). The solution in flask 2 was then added dropwise to flask 1 under nitrogen, and stirring was continued at 0 °C for 6 h. The reaction mixture was then poured into a 1:1 solution of half-saturated NH_4Cl and hexane and the phases were separated. The organic layer was washed thrice with water, dried over $MgSO_4$ and evaporated under vacuum. *p*-Methoxybenzaldehyde (75 mg, 74% yield) was obtained, which was pure by NMR analysis.

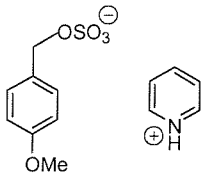
Oxidation of *p*-methoxybenzyl alcohol using SO_3.py in solution (method 2)



2.26

p-Methoxybenzyl alcohol (100 mg, 0.723 mmol) was dissolved in DCM (3.5 mL), then DMSO was added (7 mL) and the solution was cooled at 0 °C. In a second flask SO_3.Py (288 mg, 1.81 mmol) was dissolved in DCM (1.5 mL) and DMSO (3 mL). The solution in flask 2 was then added dropwise to flask 1 under nitrogen, and stirring was continued at 0 °C for 6 h. Then TEA (300 μL, 1.98 mmol) was added and stirring was continued at room temperature overnight. The reaction was then poured into a 1:1 solution of half-saturated NH_4Cl and hexane and the phases were separated. The organic layer was washed thrice with water, dried over $MgSO_4$ and evaporated under vacuum to give 3 mg (yield 3.0 %) of a white solid. ^{1}H-NMR analysis shows 70:30 ratio alcohol **2.26** : aldehyde **2.28**.

Synthesis of 4-methoxybenzyl sulphate 2.27 as the pyridinium salt

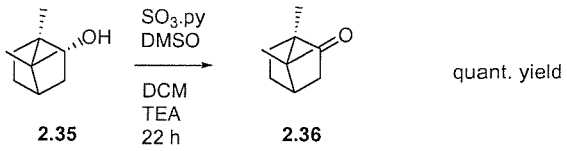


2.27

4-Methoxybenzyl alcohol (100 mg, 0.72 mmol) and SO_3.py (172 mg, 1.08 mmol) were dissolved in dry pyridine (3 mL). Stirring was continued overnight, then the solvent was evaporated under vacuum to give 288 mg of an oily product. ^{1}H-NMR analysis showed that the title compound was formed quantitatively.

^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 15.55 (bs, N$\underline{H}^+$); 8.9 (bs, Py$\underline{H}_2$); 9.2 (bs, Py$\underline{H}_4$); 7.8(bs, Py$\underline{H}_3$); 7.20 (2H, d, J=8.0 Hz, Ph$\underline{H}^2$); 6.70 (2H, d, J=8.0 Hz, Ph$\underline{H}^3$); 4.96 (2H, s, $C\underline{H}_2OSO_3^-$); 3.64 (3H, s, $OC\underline{H}_3$)
ESMS m/z 216.9 (M^-)

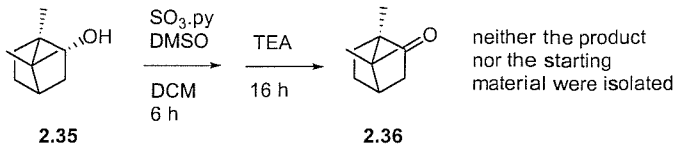
Oxidation of *endo*-borneol using SO_3.py in solution (method 1)



2.35 **2.36**

The procedure was the same as for the preceding experiment, except that the TEA (same quantity) was added directly in flask 2, and the reaction was quenched in the same way after 6 h at 0 °C. Camphor (110 mg, quant. yield) was obtained. The ^{1}H-NMR and ^{13}C-NMR corresponded to the reported data.[131]

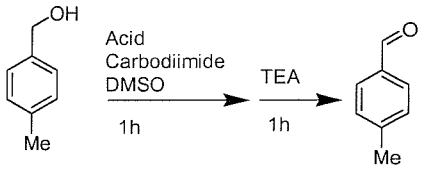
Oxidation of *endo*-borneol using SO_3.py in solution (method 2)



2.35 **2.36**

Endo-borneol (112 mg, 0.72 mmol) was dissolved in DCM (3.5 mL), then DMSO was added (7 mL) and the solution was cooled at 0 °C. In a second flask SO_3.py (288 mg, 1.81 mmol) was dissolved in DCM (1.5 mL) and DMSO (3 mL). The solution in flask 2 was then added dropwise to flask 1 under nitrogen, and stirring was continued at 0 °C for 6 h. Then TEA (300 μL, 1.98 mmol) was added and stirring was continued at room temperature overnight. The reaction was then poured into a 1 : 1 solution of half-saturated NH_4Cl and Et_2O and the phases were separated. The organic layer was washed thrice with water, dried over $MgSO_4$ and evaporated under vacuum to give 20 mg of product. NMR analysis showed that only pyridine and triethylammonium chloride were present, while both *endo*-borneol and camphor were absent.

Oxidation of *p*-methylbenzyl alcohol using DMSO, an acid and carbodiimides



2.39 **2.40**

General procedure: *p*-Methylbenzyl alcohol (34mg, 0.282 mmol) and the carbodiimide were dissolved in anhydrous DMSO (1 mL) under nitrogen, then the acid was added. After 1 hour, TEA was added and stirring was continued for an additional hour. Then ethyl ether (30 mL) was added and the organic phase was washed twice with water (if a solid was present prior to the washing, it was filtered away). The organic phase was dried over $MgSO_4$ and evaporated under vacuum to give a crude mixture which was analysed by ^{1}H-NMR and ^{13}C-NMR.

p-methylbenzaldehyde **2.40**

^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 9.94 (1H, s, C<u>H</u>O); 7.76 (2H, d, J= 8.0 Hz, Ar<u>H</u>); 7.31 (2H, d, J= 8.0 Hz, Ar<u>H</u>); 2.42 (3H, s, PhC<u>H</u>$_3$).

p-methylbenzyl alcohol **2.39**

^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 7.26 (2H, d, J= 7.5 Hz, Ar<u>H</u>); 7.16 (2H, d, J= 7.5 Hz, Ar<u>H</u>); 4.63 (2H, s, C<u>H</u>$_2$OH); 2.32 (3H, s, PhC<u>H</u>$_3$).

Entry	Acid (equiv)	Carbodiimide (equiv)	TEA (equiv)	Yield[a]
1	Cl_3COOH (0.5)	DIC (3)	0	10%
2	Cl_3COOH (0.5)	DIC (3)	10	20%
3	Cl_3COOH (0.5)	DCC (3)	10	20%
4	$(PhO)_2P(=O)OH$ (0.5)	DCC (3)	10	25%
5	$(PhO)_2P(=O)OH$ (2)	DCC (5)	10	Complex mixture
6	$(PhO)_2P(=O)OH$ (4*0.5)	DIC (3)	20	60%
7	**$HBF_4.Et_2O$ (2)**	**DIC (3)**	**20**	**70%**
8	$HBF_4.Et_2O$ (2)	DIC (3)	0	0%

Oxidation of *p*-methylbenzyl alcohol using DMSO, DIC and HBF_4: method A

p-Methylbenzyl alcohol **2.39**, DIC and anhydrous DMSO were dissolved in the appropriate anhydrous solvent (1 mL) under nitrogen, then tetrafluoroboric acid (54% w/w solution in diethyl ether) was added. After 1 hour, TEA was added and stirring was continued for an additional hour. Then ethyl ether (30 mL) was added and the organic phase was washed twice with water (if a solid was present prior to the washing, it was filtered away). The organic phase was dried over $MgSO_4$ and evaporated under vacuum to give a crude mixture, which was analysed by ^{1}H-NMR.

p-methylbenzaldehyde **2.40**

^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 9.90 (1H, s, C<u>H</u>O); 7.72 (2H, d, J= 7.5 Hz, Ar<u>H</u>); 7.30 (2H, d, J= 7.5 Hz, Ar<u>H</u>); 2.4 (3H, s, PhC<u>H</u>$_3$).

p-methylbenzyl alcohol **2.39**

^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 7.26 (2H, d, J= 7.5 Hz, ArH); 7.16 (2H, d, J= 7.5 Hz, ArH); 4.65 (2H, s, CH_2OH); 2.35 (3H, s, $PhCH_3$).

Alcohol	DIC	HBF_4	DMSO	Solvent	Yield
34 mg	74 μL	42 μL	40 μL		
(0.28 mmol)	(0.85 mmol)	(0.56 mmol)	(0.28 mmol)	DCM	15%
34 mg	74 μL	42 μL	40 μL		
(0.28 mmol)	(0.85 mmol)	(0.56 mmol)	(0.28 mmol)	THF	5%
34 mg	74 μL	42 μL	40 μL		
(0.28 mmol)	(0.85 mmol)	(0.56 mmol)	(0.28 mmol)	$MeNO_2$	0%
68 mg	150 μL	130 μL	80 μL		
(0.56 mmol)	(1.7 mmol)	(1.7 mmol)	(1.1 mmol)	DCM	25%
68 mg	150 μL	130 μL	160 μL		
(0.56 mmol)	(1.7 mmol)	(1.7 mmol)	(2.3 mmol)	DCM	60%
68 mg	150 μL	130 μL	160 μL		Complex
(0.56 mmol)	(1.7 mmol)	(1.7 mmol)	(2.3 mmol)	DMF	mixture
34 mg	74 μL	42 μL	1 mL		
(0.28 mmol)	(0.85 mmol)	(0.56 mmol)	(0.6 mmol)	DMSO	70%

Oxidation of *p*-methylbenzyl alcohol using DMSO, DIC and HBF_4: method B

Anhydrous DMSO and DIC were dissolved in the appropriate anhydrous solvent (1 mL) under nitrogen, then tetrafluoroboric acid (54% w/w solution in diethyl ether) was added. After 15 minutes *p*-methylbenzyl-alcohol was added. After 1 hour, TEA was added and stirring was continued for an additional hour. Then ethyl ether (30 mL) was added and the organic phase was washed twice with water. The organic phase was dried over $MgSO_4$ and evaporated under vacuum to give a crude mixture, which was analysed by ^{1}H-NMR.

Alcohol	DIC	HBF4	DMSO	Solvent	Yield
136 mg (1.12 mmol)	300 μL (3.4 mmol)	260 μL (3.4 mmol)	160 μL (2.3 mmol)	DCM*	15%
68 mg (0.56 mmol)	150 μL (1.7 mmol)	130 μL (1.70 mmol)	160 μL (2.3 mmol)	DCM	<10%
272 mg (2.24 mmol)	300 μL (3.4 mmol)	260 μL (3.4 mmol)	320 μL (4.5 mmol)	DCM*	<10%
68 mg (0.56 mmol)	75 μL (0.85 mmol)	65 μL (0.85 mmol)	80 μL (1.1 mmol)	DCM	<10%
68 mg (0.56 mmol)	150 μL (1.7 mmol)	130 μL (1.7 mmol)	160 μL (2.3 mmol)	DCM	<10%
68 mg (0.56 mmol)	150 μL (1.7 mmol)	130 μL (1.7 mmol)	160 μL (2.3 mmol)	DMF	<10%
68 mg (0.56 mmol)	150 μL (1.7 mmol)	130 μL (1.7 mmol)	1 mL (0.6 mmol)	DMSO	20%

* 2 mL of DCM used instead of 1 mL.

Oxidation of *p*-methylbenzyl alcohol using DMSO, DIC and HBF_4: method C

p-Methylbenzyl alcohol **46** (68 mg, 0.56 mmol), tetrafluoroboric acid (54% w/w solution in diethyl ether, 130 μL, 1.7 mmol) and anhydrous DMSO (160 μL, 2.3 mmol) were dissolved in dry DCM (1 mL) under nitrogen, then DIC (150 μL, 1.7 mmol) was added. After 1 hour, TEA (800 μL) was added and stirring was continued for an additional hour. Then ethyl ether (30 mL) was added and the organic phase was washed twice with water. The organic phase was dried over $MgSO_4$ and evaporated under vacuum to give a crude mixture, which was analysed by ^{1}H-NMR, giving a yield of 55%.

Oxidation of *p*-methylbenzyl alcohol using DMSO, DIC and HBF_4: method D

Anhydrous DMSO and tetrafluoroboric acid (54% w/w solution in diethyl ether) were dissolved in the appropriate anhydrous solvent (1 mL) under nitrogen, then DIC was

added. After 15 minutes *p*-methylbenzyl-alcohol was added. After 1 hour, TEA (800 μL) was added and stirring was continued for an additional hour. Then ethyl ether (30 mL) was added and the organic phase was washed twice with water. The organic phase was dried over $MgSO_4$ and evaporated under vacuum to give a crude mixture, which was analysed by ^{1}H-NMR.

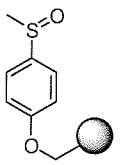
Alcohol	DIC	HBF4	DMSO	Solvent	Yield
68 mg (0.56 mmol)	75 μL (0.85 mmol)	65 μL (0.85 mmol)	80 μL (1.1 mmol)	DCM	<10%
68 mg (0.56 mmol)	75 μL (0.85 mmol)	65 μL (0.85 mmol)	80 μL (1.1 mmol)	DMF	<10%

Oxidation of *p*-methyl-benzyl alcohol using DMSO, DIC and a HBF_4/TEA mixture

4-Methylbenzyl alcohol (68 mg, 0.564 mmol), dry DMSO (80 μL, 1.69 mmol), TEA (500 μL, 3.3 mmol) were dissolved in dry DCM (2 mL). HBF_4 (115 μL, 0.84 mmol) was then added under stirring, followed after 5 minutes by DIC (135 μL, 0.84 mmol). The solution was stirred for an additional hour, then it was poured in Et_2O (30 mL) and the solution obtained was extracted first with a half-saturated NH_4Cl solution, then with water. The organic layer was then dried over $MgSO_4$ and then evaporated under vacuum to give 60 mg of an oily product.

^{1}H-NMR analysis of this product showed only starting material.

Synthesis of 4-(methylsulfinyl)-phenomethyl-polystyrene 26



2.42

Merrifield resin (1.000 g, 1.91 mmol) was swollen in dry DMF (5 mL), then 4-(methylsulfinyl)-phenol **2.45** (894 mg, 5.73 mmol), caesium carbonate (1.850 g, 5.73

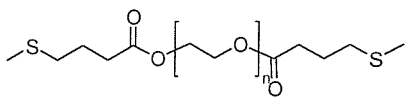
mmol) and sodium iodide (286 mg, 1.91 mmol) were added. The mixture was stirred for 24 hours at room temperature, then for 40 h at 100 °C. After cooling at R.T., the resin was filtered in a peptide vessel. The resin was washed first with water (2×10 mL), then with MeOH (5×20 mL) and DCM (3×20 mL). After 24 in a vacuum oven at 40 °C, the title resin was obtained (1.150 g, 94%).

IR (neat): ν_{max} / (cm^{-1}) 1592 (m), 1245 (s), 1089 (m), 1047 (s).

^{13}C-NMR (75.47 MHz; $CDCl_3$) δ_C: 161.6 (Ar$\underline{C}^1$); 137.4 (Ar$\underline{C}^4$); 126.0 (Ar$\underline{C}^3$); 116.1 (Ar$\underline{C}^2$); 70.8 ($\underline{C}H_2$); 44.5 (SO$\underline{C}H_3$).

Elem Anal. S 5.13 (1.60 mmol/g); Cl 0.22 (0.062 mmol/g)

Synthesis of polyethylene glycol-4-(methylsulfanyl)butyrate 2.47



2.47

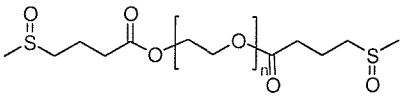
Polyethylene glycol 4600 (9.200 g, 2.00 mmol) and 4-(methylsulfanyl)butyric acid (0.938 g, 7.40 mmol) were dissolved in dry DCM (30 mL). Dimethylamino pyridine (86 mg, 0.7 mmol) and DIC (1.100 mL, 7.00 mmol) were then added under stirring. Stirring was continued overnight, then the white precipitate (diisopropylurea) was filtered off and the solution concentrated to about 15 mL. Et_2O (150 mL) was then added under vigorous stirring. After ca. 30 min, the white solid that was formed was filtered, washed with ether and dried under vacuum to give 8.181 g (84.6%) of the title compound.

IR (neat): ν_{max} / (cm^{-1}) 2881br, 1732w, 1098s, 957s.

^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 4.1 (2H, t, J= 7.5 Hz, OCH$_2$C$\underline{H}_2$OCO); 3.55 (s, >80H, PEG), 2.45 (2H, t, 7.5 Hz, S-C$\underline{H}_2$-); 2.35 (2H, d, J=7.5 Hz, -C$\underline{H}_2$-COOR); 2.08 (3H, s, S-C$\underline{H}_3$); 1.87 (2H, q, J=7.5 Hz, -CH$_2$-C$\underline{H}_2$-CH$_2$-).

^{13}C-NMR (75.47 MHz; $CDCl_3$) δ_C: 188.8 ($\underline{C}$OOR); 69.2 (PEGOCH$_2$$\underline{C}H_2$OCOR), 63.6 (PEGO$\underline{C}H_2CH_2$OCOR), 33.4 ($\underline{C}H_2$S); 32.9 ($\underline{C}H_2$COOH); 24.1 (CH$_2$$\underline{C}H_2CH_2$); 15.3 (S$\underline{C}H_3$).

Synthesis of polyethylene glycol-4-(methylsulfinyl)butyrate 2.48



2.48

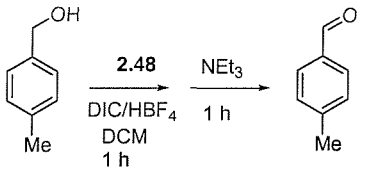
Polyethylene glycol-4-(methylsulfanyl)butyrate **2.47** (15.500 g, 3.00 mmol) was dissolved in MeOH (60 mL) and water (15 mL). The solution was cooled to 0 °C with an ice bath, then $NaIO_4$ (15.8 mL of a 0.4 M solution in water, 6.3 mmol) was slowly added. Stirring was continued at the same temperature for 3 hours, then the mixture was kept in a fridge overnight. The solvent was then evaporated under vacuum and the solid residue was extracted with four portions of DCM (50 mL each). Drying with $MgSO_4$ and evaporating the solvent under vacuum gives the title compound (13.354 g, 86.0%) as a white solid.

IR (neat): ν_{max} / (cm^{-1}) 2881br, 1732w, 1098s, 957s. Also a very weak band at 3336 cm^{-1}

^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 4.1 (2H, t, J= 7 Hz, $OCH_2\underline{CH_2}OCO$); 3.55 (s, >80H, PEG); 2.72 (2H, m, SO-$\underline{CH_2}$-); 2.64 (3H, s, SO-$\underline{CH_3}$); 2.50 (2H, t, J=7.3 Hz, -$\underline{CH_2}$-COOR); 2.08 (2H, m, $-CH_2-\underline{CH_2}-CH_2-$).

^{13}C-NMR (75.47 MHz; $CDCl_3$) δ_C: 172.2 ($\underline{C}$OOR); 70.5 (PEG), 68.9 ($PEGOCH_2\underline{C}H_2OCOR$), 63.6 ($PEGO\underline{C}H_2CH_2OCOR$), 53.3 ($\underline{C}H_2SO$); 38.5 ($\underline{C}H_3$); 32.6 ($\underline{C}H_2COOH$); 18.1 ($CH_2\underline{C}H_2CH_2$).

Oxidation of *p*-methylbenzyl alcohol using polyethylene glycol-4-(methylsulfinyl)butyrate 2.48



2.39 **2.40**

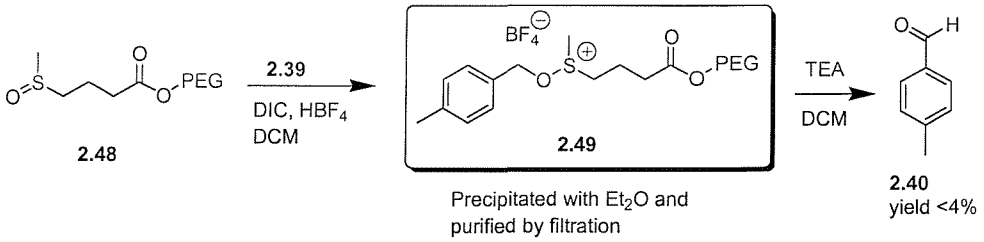
Polyethylene glycol-4-(methylsulfanyl)butyrate **2.48** (1.00 g, 0.205 mmol) and *p*-methylbenzyl alcohol were dissolved in dry DCM. When appropriate, molecular sieves were added, and the mixture was stirred for 15 min. DIC and HBF_4 were added in this

order under vigorous stirring. After 1 hour, TEA (300 μL, 2 mmol) was added and stirring was continued for an additional hour. Addition of ether (20 mL) caused the formation of a white precipitate that was filtered off. The obtained solution was then extracted first with a half-saturated NH_4Cl solution, then with water. The organic layer was then dried over $MgSO_4$ and then evaporated under vacuum. The crude products obtained were then analysed by ^{1}H-NMR.

2.39 (mmol)	DIC (equiv)	HBF_4 (equiv)	**2.48** (equiv)	**2.40** (%)
0.2	1.5	1.5	2	25
0.2	1.5	0.75	2	15
0.1	3	3	4	5
0.1	1.5	1.5	4	55*
0.2	1.5	1.5	2	50*

* reaction run in presence of 4Å mol. Sieves

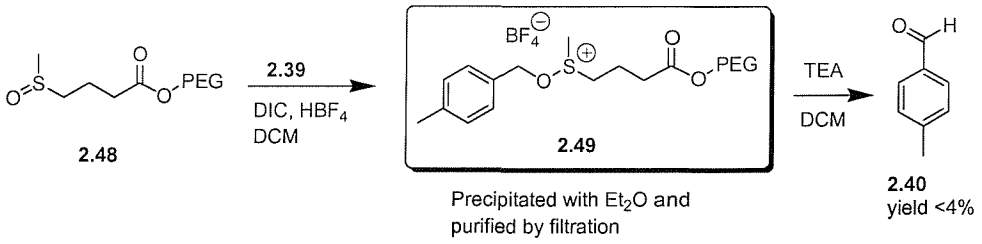
Catch-and-release oxidation of *p*-methyl-benzyl alcohol using 54. Method I



A special apparatus was used to perform this reaction: it comprises of two 50 mL three-neck dropping funnels equipped with a sinter, one on top of the other. On the top funnel, molecular sieves (4 Å, beads) and dry ether freshly distilled from CaH_2 were added. On the bottom flask, **2.49** (1.000 g, 0.205 mmol) and 4-methylbenzyl alcohol (24 mg, 0.20 mmol) were dissolved in dry DCM (1.5 mL), then molecular sieves (4 Å, powdered, ca. 50 mg) were added. After 15 min under stirring, DIC (46 μL, 0.30 mmol) and HBF_4 (38 μL, 0.28 mmol) were added. Stirring was continued for 1 hour, then ca. 10 mL of the ether contained in the upper funnel were dropped on the reaction under vigorous stirring. After 10 minutes, the ether was pushed out of the vessel using N_2. The white solid that remained

added. After 1 hour under stirring, Et_2O (30 mL) was added, the white precipitate was filtered off and the organic solution was extracted first with a half-saturated NH_4Cl solution, then with water. The organic layer was then dried over $MgSO_4$ and then evaporated under vacuum to give 5 mg of an oil. ^{1}H-NMR analysis of the crude product showed no aldehyde, just a little quantity of starting material plus DIC and diisopropylurea.

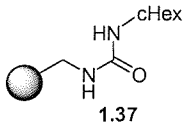
Catch-and-release oxidation of *p*-methyl-benzyl alcohol using 54. Method II



The same apparatus used for the previous experiment was used. On the top funnel, molecular sieves (4 Å, beads) and dry ether freshly distilled from CaH_2 were added. On the bottom flask, **2.49** (1.000 g, 0.205 mmol) and 4-methylbenzyl alcohol (24 mg, 0.20 mmol) were dissolved in dry DCM (1.5 mL), then molecular sieves (4 Å, powdered, ca. 50 mg) were added. After 15 min under stirring, DIC (46 μL, 0.30 mmol) and HBF_4 (38 μL, 0.28 mmol) were added. Stirring was continued for 1 hour, then the DCM was evaporated using a vacuum pump. A white solid was formed. *Ca.* 2 mL of the ether contained in the upper funnel were dropped on the reaction. The solvent was then filtered away using vacuum (nitrogen pressure was not strong enough to push the solvent down). The white solid that remains in the vessel was re-dissolved in dry DCM (1.5 mL) then TEA (300 μL, 2.0 mmol) was added. After 1 hour under stirring, Et_2O (30 mL) was added, the white precipitate was filtered off and the organic solution was extracted first with a half-saturated NH_4CI solution, then with water. The organic layer was then dried over $MgSO_4$ and then evaporated under vacuum to give 9 mg of an oil. ^{1}H-NMR analysis of the crude product showed ca. 4% aldehyde plus starting material. Only a small amount of DIC and diisopropylurea was present.

6.3 Experimental for Chapter 3

Synthesis of *N*-cyclohexyl-*N'*-methylpolystyrene-urea 1.37[35]

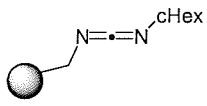


1.37

Aminomethyl polystyrene (5.00 g, 16 mmol) was swollen in anhydrous THF (40 mL) in a round-bottom flask. Cyclohexyl isocyanate (10 mL, 80 mmol) was added in one portion under stirring. Gentle stirring was continued overnight, then the reaction was heated at reflux for 6 hours. The resin was filtered, washed with DCM (3×40 mL), DMF (3×40 mL), MeOH (3×30 mL), DCM (5×40 mL), dried overnight in a vacuum-oven at 40 °C to give the title compound (6.85 g).

IR (neat): ν_{max} / (cm^{-1}) 2925s, 1627s, 1552s, 1449m, 1251m, 758m, 699s.
NMR: The resin proved impossible to analyse by ^{1}H-MAS-NMR or ^{13}C-NMR. The reason for this behaviour is not known.

Synthesis of *N*-cyclohexyl-*N'*-methylpolystyrene-carbodiimide 1.38

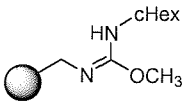


1.38

N-Cyclohexyl-*N'*-methylpolystyrene-urea **1.37** (2.00 g, 4.6 mmol) was swollen in dry DCM (30 mL) and triphenilphosphine (3.46 g, 13.2 mmol) was added. The mixture was stirred for 10 minutes to allow complete dissolution of the triphenilphosphine, then CBr_4 (4.40 g, 13.2 mmol) was added, immediately followed by dropwise addition of anhydrous TEA (6.0 mL, 43 mmol). The dark reaction mixture was gently stirred overnight, then the resin was filtered, washed with DCM (3×20 mL), DMF (3×20 mL) and DCM (5×20 mL), dried overnight in a vacuum-oven at 40 °C to give the title compound (1.82 g).

IR (neat): ν_{max} / (cm^{-1}) 2930m; 2117s; 1450m; 1338m; 1020m; 813m; 759s.
^{13}C-NMR (75.47 MHz; $CDCl_3$) δ_C: 145.1; 55.6; 50.5; 34.8; 25.5; 24.5.

Synthesis of *O*-methyl-*N*-cyclohexyl-*N'*-methylpolystyrene-isourea 3.57



3.57

Method 1: using microwave-irradiation

N-Cyclohexyl-*N'*-methylpolystyrenecarbodiimide **1.38** (0.500 g, 0.900 mmol) was placed in a microwave vial. The vial was capped and anhydrous methanol (3 mL) was added under nitrogen via a syringe. The vial was then heated in a Smith Synthesizer^{TM} at 135 °C for 70 minutes (internal pressure 9 bar). The resin was then filtered, washed with DCM (3×10 mL) and dried overnight in a vacuum-oven at 40 °C to give the title compound (0.490 g).

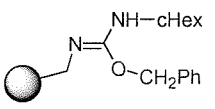
Method 2: using copper (II) catalysis

Polymer-supported carbodiimide **1.38** (2.00 g, 3.60 mmol) and $Cu(OTf)_2$ (50 mg, 0.14 mmol) were suspended in a mixture of anhydrous THF (6 mL) and dry methanol (4 mL, 99 mmol). The mixture was gently stirred at room temperature for 16 hours, then the resin was filtered, washed with a 10% solution of TMEDA in DCM until the washing solution remained uncoloured, then with DMF (3×5 mL), MeOH (3×5 mL) and DCM (5×5 mL). The resin was dried at 40 °C under vacuum for 24 hours to afford the title compound (2.04 g).

IR(neat): ν_{max} / (cm^{-1}) .2921 (s); 1655 (s); 1448 (s); 1329 (s).

NMR: The resin proved impossible to analyse by ^{1}H-MAS-NMR or ^{13}C-NMR. The reason for this behaviour is not known.

Synthesis of *O*-benzyl-*N*-cyclohexyl-*N'*-methylpolystyrene isourea 3.60



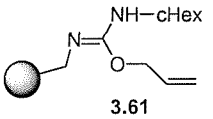
3.60

Polymer-supported carbodiimide **1.38** (2.00 g, 3.60 mmol) and $Cu(OTf)_2$ (50 mg, 0.14 mmol) were suspended in a mixture of anhydrous THF (10 mL) and benzyl alcohol (5 mL, 48 mmol). The mixture was gently stirred at room temperature for 16 hours, then the resin was filtered, washed with a 10% solution of TMEDA in DCM until the washing solution remained uncoloured, then with DMF (3×5 mL), MeOH (3×5 mL) and DCM (5×5 mL). The resin was dried at 40 °C under vacuum for 24 hours to afford the title compound (2.390 g).

IR(neat): ν_{max} / (cm^{-1}) 2924 (s), 1656 (s), 1321 (s), 1028 (s).

^{13}C-NMR (75.47 MHz; $CDCl_3$) δ_C: 67.0 ($Ph\underline{C}H_2O$); 55.6; 50.3; 34.8; 25.5; 24.5.

Synthesis of *O*-allyl-*N*-cyclohexyl-*N'*-methylpolystyrene isourea 3.61



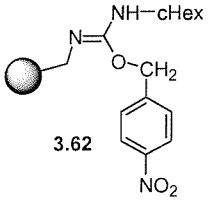
3.61

Polymer supported carbodiimide **1.38** (2.00 g, 3.80 mmol) and copper (II) triflate (50 mg) were suspended in anhydrous THF (10 mL) in a 50 mL round-bottom flask, then allyl alcohol (5 mL, 74 mmol) was added. Gentle stirring was continued overnight, then the resin was filtered, washed with a solution of TMEDA (10% in DCM, 3×20 mL), DMF (3×20 mL), MeOH (3×20 mL) and DCM (5×20 mL) and dried for 40 h in a vacuum oven, giving the title compound (2.183 g).

IR (neat): ν_{max} / (cm^{-1}) 2922 (m), 1656 (s), 1316 (s), 1029 (s).

^{13}C-NMR (75.47 MHz; $CDCl_3$) δ_C: 133.7 ($\underline{C}H=CH_2$); 115.9 ($CH=\underline{C}H_2$); 65.7 ($\underline{C}H_2CH=CH_2$); 55.4; 49.9; 34.5; 34.0; 25.2; 24.3.

Synthesis of *O*-*p*-nitrobenzyl-*N*-cyclohexyl-*N'*-methylpolystyrene isourea 3.62



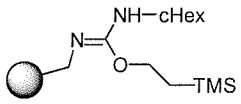
3.62

Polymer supported carbodiimide **1.38** (1.00 g, 2.0 mmol) and copper (II) triflate (50 mg) were suspended in anhydrous THF (20 mL) in a 50 mL round-bottom flask, then *p*-nitrobenzyl alcohol (2.2 g, 15 mmol) was added. Gentle stirring was continued overnight, then the resin was filtered, washed with a solution of TMEDA (10% in DCM, 3×20 mL), DMF (3×20 mL), MeOH (3×20 mL) and DCM (5×20 mL) and dried for 40 h in a vacuum oven, giving the title compound.

IR (neat): ν_{max} / (cm^{-1}) 2926 (m), 1664 (s), 1521 (s), 1340 (s), 1319 (s), 1059 (m).

^{13}C-NMR (75.47 MHz; $CDCl_3$) δ_C: 145.6 (Ar<u>C</u>^{3}); 123.2 (Ar<u>C</u>^{2}); 65.2 (Ar<u>C</u>H_2O); 50.1; 34.0; 24.5.

Synthesis of *O*-(2-trimethylsilylethyl)-*N*-cyclohexyl-*N'*-methylpolystyrene isourea 3.64



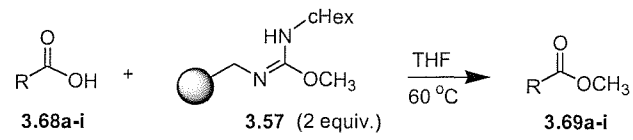
3.64

Polymer-supported carbodiimide **1.38** (1.00 g, 1.80 mmol), 2-trimethylsilylethanol (2.00 mL, 14 mmol) and copper (I) triflate- toluene complex (2:1) (20 mg, 0.077 mmol of Cu) were suspended in anhydrous DMF (10 mL). Stirring was continued overnight, then the resin was washed with a solution of TMEDA (10% in DCM, 3×20 mL), DMF (3×20 mL), MeOH (3×20 mL) and DCM (5×20 mL) and dried for 40 h in a vacuum oven, giving the title compound (1.12 g).

IR (neat): ν_{max} / (cm^{-1}) 2924 (m), 1654 (s), 1319 (s), 1245 (s), 1029 (s), 832 (s).

^{13}C-NMR (75.47 MHz; $CDCl_3$) δ_C: 63.2 (<u>C</u>H_2O); 49.6; 33.8; 24.5; 17.2 (<u>C</u>H_2Si); -1.6 (Si<u>C</u>H_3).

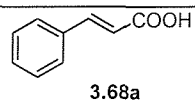
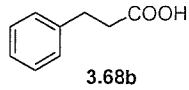
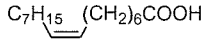
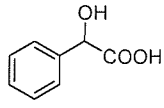
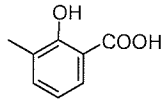
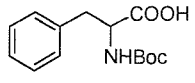
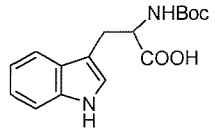
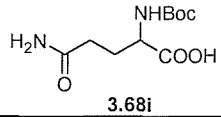
General procedure for esterifications using *O*-methylisourea 3.57 with conventional heating



3.68a-i **3.57** (2 equiv.) **3.69a-i**

A carboxylic acid **3.68** (0.175 mmol) was dissolved in THF (2 mL) and the resulting solution was added to the resin **3.57** (200 mg, 0.35 mmol) in a round-bottom flask. The mixture was heated at 60 °C under gentle stirring for the time indicated, then the resin was filtered and washed with MeOH (3×5 mL) and DCM (3×5 mL). The combined filtrates were evaporated together to afford the desired carboxylic ester.

No purification was performed before NMR analysis.

entry	Acid		time (h)	Product
1	 **3.68a**	26.0 mg	16	23.0 mg (81%)
2	 **3.68b**	26.2 mg	16	26.9 mg (94%)
3	$CH_3(CH_2)_{16}COOH$ **3.68c**	49.7 mg	40	47.5 mg (91%)
4	 **3.68d**	44.5 mg	40	41.3 mg (88%)
5	 **3.68e**	26.6 mg	16	26.1 mg (90%)
6	 **3.68f**	26.6 mg	16	22.7 mg (78%)
7	 **3.68g**	44.3 mg	16	34.6 mg (74%)
8	 **3.68h**	51.1 mg	16	43.4 mg (81%)
9	 **3.68i**	41.0 mg	16	35.6 mg (82%)

3.69a[132]

^{1}H-NMR (400 MHz; $CDCl_3$) δ_H: 7.68 (1H, d, J= 6.0 Hz, C<u>H</u>=CHCOO); 7.51 (2H, m, Ar<u>H</u>); 7.37 (3H, m, Ar<u>H</u>); 6.42 (1H, d, J=6.0 Hz, CH=C<u>H</u>COO); 3.79 (3H, s, COOC<u>H</u>$_3$).

^{13}C-NMR (100.6 MHz; $CDCl_3$) δ_C: 167.4; 144.9; 134.4; 130.3; 128.9; 128.0; 117.8; 51.7.

3.69b[133]

^{1}H-NMR (400 MHz; $CDCl_3$) δ_H: 7.61-7.35 (5H, m, Ar<u>H</u>); 3.70 (3H, s, C<u>H</u>$_3$); 2.99 (2H, t, J= 7.5 Hz, PhC<u>H</u>$_2$); 2.67 (2H, t, J=7.5 Hz, C<u>H</u>$_2$COO).

^{13}C-NMR (100.6 MHz; $CDCl_3$) δ_C: 173.3; 140.5; 128.5; 128.3; 126.3; 51.6; 35.7; 31.0.

3.69c[134]

^{1}H-NMR (400 MHz; $CDCl_3$) δ_H: 3.64 (3H, s, COOC<u>H</u>$_3$); 2.28 (2H, t, J=7.5 Hz, -C<u>H</u>$_2$COOMe); 1.59 (2H, q, J= 7.5 Hz, C<u>H</u>$_2$-CH$_2$-COOCH$_3$); 1.31-1.19 (28 H, m, CH$_2$-C<u>H</u>$_2$-CH$_2$-); 0.85 (3H, t, J= 6.5 Hz, CH$_2$-C<u>H</u>$_3$).

^{13}C-NMR (100.6 MHz; $CDCl_3$) δ_C: 174.3; 51.4; 34.1; 31.9; 29.7 (multiple C); 29.6; 29.5; 29.4; 29.3; 29.2; 25.0; 22.7; 14.1.

3.69d[134]

^{1}H-NMR (400 MHz; $CDCl_3$) δ_H: 5.38-5.32 (2H, m, C<u>H</u>=C<u>H</u>); 3.67 (3H, s, COOC<u>H</u>$_3$); 2.31 (2H, t, J= 7.5 Hz, C<u>H</u>$_2$COOMe); 2.05-1.97 (4H, m, 2×C<u>H</u>$_2$); 1.62 (2H, m, C<u>H</u>$_2$-CH$_2$COOMe); 1.36-1.24 (16 H, m, CH$_2$-C<u>H</u>$_2$-CH$_2$-); 0.89 (3H, t, J= 6.5 Hz, CH$_2$-C<u>H</u>$_3$).

^{13}C-NMR (100.6 MHz; $CDCl_3$) δ_C: 174.3; 130.0; 129.7; 51.4; 34.1; 31.9; 29.8; 29.7; 29.5; 29.1; 29.1; 29.1; 27.2; 27.1; 24.9; 22.7; 14.1.

3.69e[135]

^{1}H-NMR (400 MHz; $CDCl_3$) δ_H: 7.29-7.42 (5H, m, Ar<u>H</u>); 5.16 (1H, s, C<u>H</u>OH); 3.75 (3H, s, C<u>H</u>$_3$); 3.39 (1H, bs, O<u>H</u>).

^{13}C-NMR (100.6 MHz; $CDCl_3$) δ_C: 174.1; 138.2; 128.6; 128.5; 126.6; 72.9; 53.0.

3.69f[136]

^{1}H-NMR (400 MHz; $CDCl_3$) δ_H: 10.98 (1H, s, ArO<u>H</u>); 7.66 (1H, d, J= 8 Hz, Ar<u>H</u>^{6}); 7.29 (1H, d, J= 8 Hz, Ar<u>H</u>^{4}); 6.76 (1H, t, J=8.0 Hz, Ar<u>H</u>^{5}); 3.92 (3H, s, COOC<u>H</u>$_3$); 2.25 (3H, s, ArC<u>H</u>$_3$).

^{13}C-NMR (100.6 MHz; $CDCl_3$) δ_C: 171.0; 160.0; 136.4; 127.4; 126.6; 118.5; 111.6; 52.2; 15.6.

3.69g[137]

^{1}H-NMR (400 MHz; d_6-DMSO, 373 K) δ_H: 7.29-7.18 (5H, m, ArH); 6.55 (1H, bs, NH), 4.26 (1H, td, J= 9 Hz, J= 5.5 Hz, CHCOO), 3.62 (3H, s, $COOCH_3$); 3.03 (1H, dd, J= 14.0 Hz, J= 5.5 Hz, CHH'Ar), 2.92 (1H, dd, J= 14.0 Hz, J= 9.0 Hz, CHH'Ar), 1.35 (9H, s, CCH_3).

^{13}C-NMR (100.6 MHz; d_6-DMSO) δ_C: 172.7; 155.5; 137.7; 129.2; 128.3; 126.6; 78.4; 55.3; 51.9; 36.6; 28.3.

3.69h[138]

^{1}H-NMR (400 MHz; d_6-DMSO, 373 K) δ_H: 11.0 (1H, bs, NH); 7.49 (1H, d, J= 7.5 Hz, ArH); 7.34 (1H, d, J= 7.5 Hz, ArH); 7.11 (1H, s, ArH); 7.08 (1H, t, J=7.5 Hz, ArH), 6.97 (1H, t, J=7.5 Hz, ArH), 6.44 (1H, d, J=8.0 Hz, NH), 4.30 (1H, td, J=8.0 Hz, J=6.0 Hz, CHCOO), 3.61 (3H, s, $COOCH_3$); 3.16 (1H, dd, J= 15.0 Hz, J= 6.0 Hz, CHH'Ar), 3.06 (1H, dd, J= 15.0 Hz, J= 8.0 Hz, CHH'Ar), 1.35 (9H, s, CCH_3).

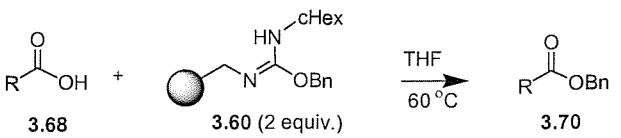
^{13}C-NMR (100.6 MHz; $CDCl_3$) δ_C: 172.7; 155.2; 136.1; 127.7; 122.7; 122.1; 119.6; 118.7; 111.2; 110.2; 79.8; 54.2; 52.2; 28.3, 28.0.

3.69i[139]

^{1}H-NMR (400 MHz; d_6-DMSO) δ_H: 3.88 (1H, m, CHCOOMe); 3.62 (3H, s, $COOCH_3$); 2.13 (2H, t, J= 7.5 Hz, CH_2CONH_2); 1.94 (1H, m, CH'H''CHCOO); 1.82 (1H, m, CH'H''CHCOOMe); 1.38 (9H, s, $C(CH_3)_3$).

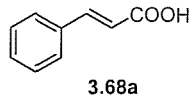
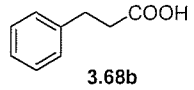
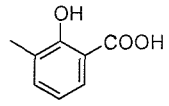
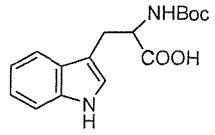
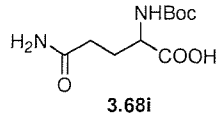
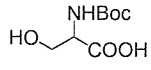
^{13}C-NMR (100.6 MHz; CD_3OD) δ_C: 177.6; 174.4; 158.0; 80.7; 54.6; 52.7; 32.5; 28.7; 28.4.

General procedure for esterifications using *O*-benzylisourea 3.60 with conventional heating



A carboxylic acid **3.68** (0.175 mmol) was dissolved in THF (2 mL) and the resulting solution was added to the resin **3.60** (250 mg, 0.35 mmol) in a round-bottom flask. The mixture was heated at 60 °C under gentle stirring overnight, then the resin was filtered and washed with MeOH (3×5 mL) and DCM (3×5 mL). The combined filtrates were evaporated together to afford the desired carboxylic ester.

No purification was performed before NMR analysis.

entry	Acid		yield
1	 **3.68a**	26.0 mg	40.1 mg (96%)
2	 **3.68b**	26.2 mg	41.5 mg (99%)
3	 **3.68f**	26.6 mg	40.7 mg (96%)
4	 **3.68h**	51.1 mg	64.8 mg (97%)
5	 **3.68i**	41.0 mg	55.6 mg (98%)
6	 **3.68l**	35.8 mg	51.0 mg (99%)

3.70a[133]

^{1}H-NMR (400 MHz; $CDCl_3$) δ_H: 7.62 (1H, d, J= 16.0 Hz, C<u>H</u>=CHCOOBn); 7.42-7.36 (3H, m, Ar<u>H</u>); 7.33-7.20 (7H, m, Ar<u>H</u>); 6.38 (1H, d, J= 16.0 Hz, CH=C<u>H</u>COOMe); 5.15 (3H, s, COOC<u>H</u>$_2$).

^{13}C-NMR (100.6 MHz; $CDCl_3$) δ_C: 166.7; 145.1; 136.0; 134.3; 130.3; 128.8; 128.5; 128.2; 128.2; 128.0; 117.8; 66.2.

3.70b[140]

^{1}H-NMR (400 MHz; $CDCl_3$) δ_H: 7.45-7.20 (10H, m, Ar<u>H</u>); 5.16 (2H, s, COOC<u>H</u>$_2$); 3.02 (2H, t, J= 7.5 Hz, PhC<u>H</u>$_2$); 2.73 (2H, t, J=7.5 Hz, C<u>H</u>$_2$COO-).

^{13}C-NMR (100.6 MHz; $CDCl_3$) δ_C: 172.7; 140.4; 135.9; 128.5; 128.5; 128.3; 128.3; 128.2; 126.3; 66.3; 35.9; 30.9.

3.70f

^{1}H-NMR (400 MHz; $CDCl_3$) δ_H: 10.90 (1H, s, ArO<u>H</u>); 7.62 (1H, d, J= 8 Hz, Ar<u>H</u>^{6}); 7.34-7.17 (6H, m, Ar<u>H</u>); 6.49 (1H, t, J=8.0 Hz, Ar<u>H</u>^{5}); 5.26 (2H, s, COOC<u>H</u>$_2$); 2.16 (3H, s, ArC<u>H</u>$_3$).

^{13}C-NMR (100.6 MHz; $CDCl_3$) δ_C: 170.4 (<u>C</u>=O); 160.2 (Ar<u>C</u>^{2}); 136.5 (Ar<u>C</u>^{4}); 135.4 (Ar<u>C</u>$^{1'}$); 128.7 (Ar<u>C</u>$^{3'}$); 128.5 (Ar<u>C</u>$^{4'}$); 128.2 (Ar<u>C</u>$^{2'}$); 127.5 (Ar<u>C</u>^{6}); 126.6 (Ar<u>C</u>^{3}); 118.5 (Ar<u>C</u>^{5}); 111.6 (Ar<u>C</u>^{1}); 66.8 (<u>C</u>H$_2$Ph); 15.6 (<u>C</u>H$_3$).

EIMS m/z 77.1 (16%); 91 (100%); 242.2 (9%, $M^{+\cdot}$)

high res. mass 242.0947 (calc. 242.09429)

3.70h[141]

^{1}H-NMR (400 MHz; d_6-DMSO) δ_H: 10.85 (1H, bs, N<u>H</u>); 7.48 (1H, d, J= 7.5 Hz, Ar<u>H</u>); 7.39-7.18 (6H, m, Ar<u>H</u>); 7.13 (1H, s, Ar<u>H</u>); 7.06 (1H, t, J=7.5 Hz, Ar<u>H</u>), 6.97 (1H, t, J=7.5 Hz, Ar<u>H</u>), 5.05 (2H, s, COOC<u>H</u>$_2$Ph), 4.24 (1H, m, C<u>H</u>COO), 3.13 (1H, dd, J= 14.0 Hz, J= 6.0 Hz, C<u>H</u>H'Ar), 3.02 (1H, dd, J= 14.0 Hz, J= 9.0 Hz, CH<u>H'</u>Ar), 1.32 (9H, s, CC<u>H</u>$_3$).

^{13}C-NMR (100.6 MHz; d_6-DMSO) δ_C: 172.6; 155.6; 136.3; 136.1; 128.5; 128.1; 127.8; 127.2; 124.0; 121.1; 118.6; 118.2; 111.6; 109.8; 78.5; 66.0; 55.1; 28.3; 27.0.

3.70i[142]

^{1}H-NMR (400 MHz; d_6-DMSO) δ_H: 7.40-7.25 (5H, m, Ar<u>H</u>); 6.8 (1H, bs, N<u>H</u>); 5.15 (1H, d, J= 13.0 Hz, COOCH<u>H</u>'Ph); 5.08 (1H, d, J= 13.0 Hz, COOCH<u>H'</u>Ph); 3.99 (1H, m, C<u>H</u>COOMe); 2.14 (2H, t, J= 7.5 Hz, C<u>H</u>$_2$CONH$_2$); 1.94 (1H, m, C<u>H</u>H'CHCOOMe); 1.74 (1H, m, CH<u>H'</u>CHCOOMe); 1.37 (9H, s, C(C<u>H</u>$_3$)$_3$).

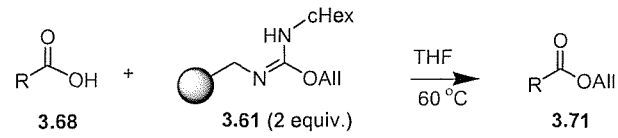
^{13}C-NMR (100.6 MHz; d_6-DMSO) δ_C: 173.5; 172.6; 155.8; 136.2; 128.6; 128.2; 127.9; 78.4; 66.0; 53.6; 31.4; 28.3; 26.4.

3.701

^{1}H-NMR (400 MHz; d_6-DMSO) δ_H: 7.41-7.30 (5H, m, ArH); 7.02 (1H, d, J= 8.0 Hz, NH); 5.15 (1H, d, J= 12.5 Hz, COOCHH'Ph); 5.09 (1H, d, J= 12.5 Hz, COOCHH'Ph); 4.93 (1H, t, J= 6.5 Hz, OH); 4.12 (1H, dt, J= 8.0 Hz, 5.5 Hz, CHCOOMe); 3.67 (2H, t, J= 5.5 Hz, CH_2OH); 1.38 (9H, s, $C(CH_3)_3$).

^{13}C-NMR (100.6 MHz; d_6-DMSO) δ_C: 171.1 (C=O); 155.5 (OC=ON); 136.2 (ArC); 128.5 (ArC); 128.1 (ArC); 127.8 (ArC); 78.5 (CCH_3); 66.0 (CH_2Ph); 61.5 (CH_2OH); 56.7 (CHCOO); 28.3 (CH_3).

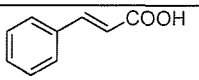
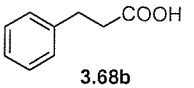
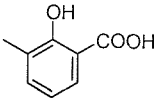
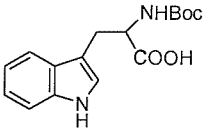
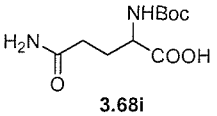
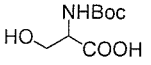
General procedure for esterifications using *O*-allylisourea 3.61 with conventional heating



3.68 3.61 (2 equiv.) 3.71

A carboxylic acid **3.68** (0.175 mmol) was dissolved in THF (2 mL) and the resulting solution was added to the resin **3.61** (225 mg, 0.35 mmol) in a round-bottom flask. The mixture was heated at 60 °C under gentle stirring overnight, then the resin was filtered and washed with MeOH (3×5 mL) and DCM (3×5 mL). The combined filtrates were evaporated together to afford the desired carboxylic ester.

No purification was performed before NMR analysis.

entry	Acid		yield
1	 **3.68a**	26.0 mg	27.0 mg (82%)
2	 **3.68b**	26.2 mg	28.2 mg (85%)
3	 **3.68f**	26.6 mg	30.2 mg (90%)
4	 **3.68h**	51.1 mg	54.0 mg (93%)
5	 **3.68i**	41.0 mg	45.1 mg (94%)
6	 **3.68l**	35.8 mg	41.9 mg (98%)

3.71a[143]

^{1}H-NMR (400 MHz; $CDCl_3$) δ_H: 7.69 (1H, d, J= 16.0 Hz, C<u>H</u>=CHCOOMe); 7.51 (2H, m, Ar<u>H</u>); 7.37 (3H, m, Ar<u>H</u>); 6.45 (1H, d, J= 16.0 Hz, CH=C<u>H</u>COOMe); 5.98 (1H, ddt, J= 17.5 Hz, 10.0 Hz, 6.0 Hz, C<u>H</u>=CH_2); 5.36 (1H, dd, J= 17.5 Hz, 1.5 Hz, CH=C<u>H</u>H *trans*); 5.26 (1H, dd, J= 10.0 Hz, 1.5 Hz, CH=C<u>H</u>H *cis*); 4.70 (2H, d, J= 6.0 Hz, COOC<u>H_2</u>-).

^{13}C-NMR (100.6 MHz; $CDCl_3$) δ_C: 166.6; 145.1; 134.4; 132.3; 130.3; 128.9; 128.1; 118.3; 117.9; 65.2.

3.71b[144]

^{1}H-NMR (400 MHz; $CDCl_3$) δ_H: 7.34-7.21 (5H, m, Ar<u>H</u>); 5.91 (1H, ddt, J= 16.5 Hz, 10.0 Hz, 5.0 Hz, C<u>H</u>=CH_2); 5.30 (1H, dd, J= 16.5 Hz, 2.0 Hz, CH=C<u>H</u>H *trans*); 5.25 (1H, dd, J= 10.0 Hz, 2.0 Hz, CH=C<u>H</u>H *cis*); 4.60 (2H, d, J= 5.0 Hz, COOC<u>H_2</u>-); 2.99 (2H, t, J= 7.5 Hz, PhC<u>H_2</u>); 2.68 (2H, t, J=7.5 Hz, C<u>H_2</u>COO).

^{13}C-NMR (100.6 MHz; $CDCl_3$) δ_C: 172.6; 140.4; 132.1; 128.5; 128.3; 126.3; 118.3; 65.2; 35.9; 30.9.

3.71f

^{1}H-NMR (400 MHz; $CDCl_3$) δ_H: 10.98 (1H, s, ArOH); 7.71 (1H, dd, J= 7.5 Hz, 1.5 Hz, ArH^6); 7.30 (1H, d, J= 7.5 Hz, ArH^4); 6.76 (1H, t, J=7.5 Hz, ArH^5); 6.02 (1H, ddt, J= 17.0 Hz, 9.5 Hz, 6.0 Hz, CH=CH_2); 5.41 (1H, dd, J= 17.0 Hz, 1.5 Hz, CH=CHH *trans*); 5.30 (1H, d, J= 9.5 Hz, CH=CHH *cis*); 4.82 (2H, d, J= 6.0 Hz, $COOCH_2$-); 2.25 (3H, s, $ArCH_3$).

^{13}C-NMR (100.6 MHz; $CDCl_3$) δ_C: 170.3 (C=O); 160.2 (ArC^2); 136.5 (ArC^4); 131.7 (CH=CH_2); 127.4 (ArC^6); 126.6 (ArC^3); 118.7 (CH=CH_2); 118.5 (ArC^5); 111.6 (ArC^1); 65.7 ($COOCH_2$); 15.7 (CH_3).

EIMS m/z 77.1 (41%); 106.1 (45%); 134.0 (100%); 192.1 (34%, $M^{+\cdot}$)

high res. mass 192.0785 (calc. 192.07864)

3.71h

^{1}H-NMR (400 MHz; d_6-DMSO) δ_H: 10.85 (1H, bs, NH); 7.49 (1H, d, J= 7.5 Hz, ArH); 7.34 (1H, d, J= 7.5 Hz, ArH); 7.25 (1H, d, J= 8.0 Hz, NH); 7.16 (1H, s, ArH); 7.06 (1H, t, J=7.5 Hz, ArH), 6.98 (1H, t, J=7.5 Hz, ArH), 5.81 (1H, ddt, J= 17.0 Hz, 10.5 Hz, 5.0 Hz, CH=CH_2); 5.26 (1H, dd, J= 17.0 Hz, 1.5 Hz, CH=CHH *trans*); 5.15 (1H, d, J= 10.5 Hz, CH=CHH *cis*); 4.53 (2H, d, J= 5.0 Hz, $COOCH_2$); 4.23 (1H, m, CHCOO); 3.13 (1H, dd, J= 15.0 Hz, J= 5.0 Hz, CHH'Ar), 3.03 (1H, dd, J= 15.0 Hz, J= 9.0 Hz, CHH'Ar), 1.33 (9H, s, CCH_3).

^{13}C-NMR (100.6 MHz; d_6-DMSO) δ_C: 172.3 (C=O); 155.6 (OC=ON); 136.3 (ArC); 132.6 (CH=CH_2); 127.2 (ArC); 124.0 (ArC); 121.1 (ArC); 118.6 (ArC); 118.2 (ArC); 117.7 and 111.6 (CH=CH_2 and ArC); 109.9 (ArC); 78.5 (CCH_3); 64.9 ($COOCH_2$); 55.0 (CHCOO); 28.3 (CH_3); 26.9 ($ArCH_2$).

3.71i

^{1}H-NMR (400 MHz; d_6-DMSO) δ_H: 7.27 (2H, d, J= 8.0 Hz, $CONH_2$); 6.76 (1H, bs, CONH); 5.88 (1H, ddt, J= 17.0 Hz, 10.0 Hz, 5.0 Hz, CH=CH_2); 5.30 (1H, dd, J= 17.0 Hz, 1.5 Hz, CH=CHH *trans*); 5.19 (1H, d, J= 10.0 Hz, CH=CHH *cis*); 4.82 (2H, m, $COOCH_2$); 3.95 (1H, m, CHCOO); 2.13 (2H, t, J= 8.0 Hz, CH_2CONH_2); 1.91 (1H, m, CH'H''CHCOO); 1.71 (1H, m, CH'H''CHCOO); 1.37 (9H, s, $C(CH_3)_3$).

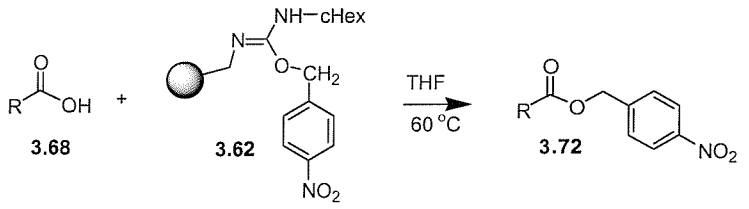
^{13}C-NMR (100.6 MHz; d_6-DMSO) δ_C: 173.6 (CONH); 172.4 (C=O); 155.8 (OC=ON); 132.7 ($CH=CH_2$); 117.8 ($CH=CH_2$); 78.4 (CCH_3); 64.8 ($COOCH_2$); 53.5 (CHCOO); 31.4 (CH_2CONH_2); 28.4 (CH_3); 26.5 ($CH_2CH_2CONH_2$).

3.71l[145]

^{1}H-NMR (400 MHz; d_6-DMSO) δ_H: 7.02 (1H, d, J= 8.0 Hz, NH); 5.88 (1H, ddt, J= 17.0 Hz, 9.5 Hz, 6.0 Hz, $CH=CH_2$); 5.32 (1H, dd, J= 17.5 Hz, 1.5 Hz, $CH=CHH$ *trans*); 5.18 (1H, dd, J= 10.0 Hz, 1.5 Hz, $CH=CHH$ *cis*); 4.90 (1H, bs, OH); 4.57 (2H, m, $COOCH_2$-); 4.07 (1H, dt, J= 8.0 Hz, 5.0 Hz, CHCOO); 3.64 (2H, m, CH_2OH); 1.37 (9H, s, $C(CH_3)_3$).

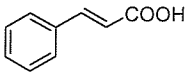
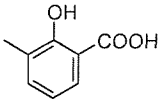
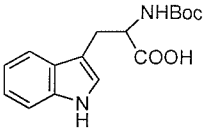
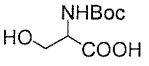
^{13}C-NMR (100.6 MHz; d_6-DMSO) δ_C: 170.9; 155.5; 132.6; 117.5; 78.5; 64.8; 61.5; 56.6; 28.3.

General procedure for esterifications using *O-p*-nitrobenzylisourea 3.62 with conventional heating



A carboxylic acid **3.68** (0.175 mmol) was dissolved in THF (2 mL) and the resulting solution was added to the resin **3.62** (250 mg, 0.35 mmol) in a round-bottom flask. The mixture was heated at 60 °C under gentle stirring overnight, then the resin was filtered and washed with MeOH (3×5 mL) and DCM (3×5 mL). The combined filtrates were evaporated together to afford the desired carboxylic ester.

No purification was performed before NMR analysis.

entry	Acid		yield
1	 3.68a	26.0 mg	46.6 mg (94%)
3	 3.68f	26.6 mg	49.5 mg (99%)
4	 3.68h	51.1 mg	73.7 mg (98%)
6	 3.68l	35.8 mg	65.7 mg (99%)

3.70a

^{1}H-NMR (400 MHz; $CDCl_3$) δ_H: 8.22 (2H, d, J= 9.0 Hz, ArH'^{3}); 7.74 (1H, d, J= 16.0 Hz, CH=CHCOOCH$_2$Ar'); 7.55 (2H, d, J= 9.0 Hz, Ar'H^2); 7.54-7.50 (2H, m, ArH); 7.39-7.37 (3H, m, ArH); 6.49 (1H, d, J= 16.0 Hz, CH=CHCOOCH$_2$Ar'); 5.32 (3H, s, COOCH$_2$).

^{13}C-NMR (100.6 MHz; $CDCl_3$) δ_C: 166.4 (COO); 147.7 (Ar'C^4); 146.0 (CH=CHCOOCH$_2$Ar'); 143.4 (Ar'C^1); 134.1 (ArC^1); 130.6 (ArC); 128.9 (ArC); 128.3 (Ar'C^2); 128.2 (ArC); 123.8 (Ar'C^3); 117.1 (CH=CHCOOCH$_2$Ar'); 64.8 (CH$_2$).

3.70f

^{1}H-NMR (400 MHz; $CDCl_3$) δ_H: 10.80 (1H, s, ArOH); 8.26 (2H, d, J= 8.5 Hz, Ar'H^3); 7.76 (1H, d, J= 8 Hz, ArH^6); 7.61 (2H, d, J= 8.5 Hz, Ar'H^2); 7.36 (1H, d, J= 8.5 Hz, ArH^4); 6.82 (1H, t, J=8.0 Hz, ArH^5); 5.48 (3H, s, COOCH$_2$); 2.28 (3H, s, ArCH$_3$).

^{13}C-NMR (100.6 MHz; $CDCl_3$) δ_C: 170.0 (C=O); 160.3 (ArC^2); 147.9 (Ar'C^4); 142.6 (Ar'C^1); 137.0 (ArC^4); 128.4 (Ar'C^2); 127.3 (ArC^6); 126.9 (ArC^3); 123.9 (Ar'C^3); 118.7 (ArC^5); 111.1 (ArC^1); 65.3 (COOCH$_2$Ar); 15.6 (CH$_3$).

3.70h[146]

^{1}H-NMR (400 MHz; d_6-DMSO) δ_H: 10.85 (1H, bs, NH); 8.12 (2H, d, J= 8.5 Hz, Ar'H^3); 7.50 (1H, d, J= 7.5 Hz, ArH); 7.41-7.33 (3H, m, ArH and Ar'H); 7.16 (1H, s, ArH); 7.07 (1H, t, J=7.5 Hz, ArH), 6.98 (1H, t, J=7.5 Hz, ArH), 5.18 (2H, s, COOCH$_2$Ar'), 4.33 (1H, m, CHCOO), 3.16 (1H, dd, J= 14.5 Hz, J= 6.5 Hz, CHH'Ar), 3.08 (1H, dd, J= 14.5 Hz, J= 9.0 Hz, CHH'Ar), 1.34 (9H, s, CCH$_3$).

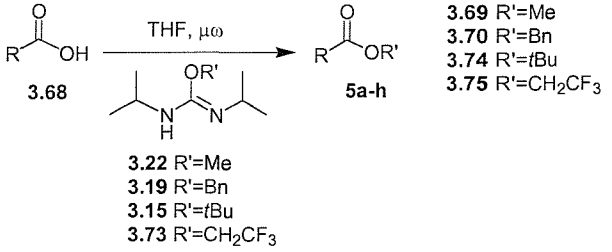
^{13}C-NMR (100.6 MHz; d_6-DMSO) δ_C: 172.5; 155.6; 147.1; 143.9; 136.3; 128.3; 127.2; 124.0; 123.5; 121.2; 118.6; 118.2; 111.6; 109.7; 78.6; 64.7; 55.1; 28.3; 27.0.

3.70l[147]

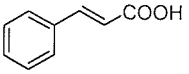
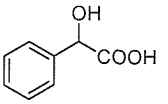
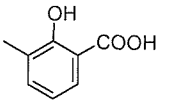
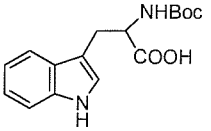
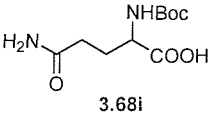
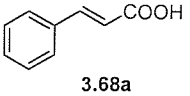
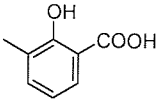
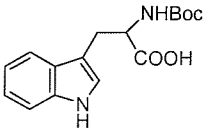
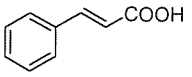
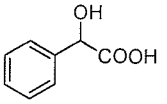
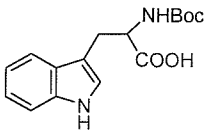
^{1}H-NMR (400 MHz; d_6-DMSO) δ_H: 8.20 (2H, d, J= 8.5 Hz, Ar'H^3); 7.63 (2H, d, J= 8.5 Hz, Ar'H^2); 7.04 (1H, d, J= 8 Hz, NH); 5.31 (1H, d, J= 14.0 Hz, COOCHH'); 5.26 (1H, d, J= 14.0 Hz, COOCHH'); 4.95 (1H, t, J= 6.0 Hz, OH); 4.16 (1H, dt, J= 8.0 Hz, 5.0 Hz, CHCOO); 3.69 (2H, m, CH_2OH); 1.37 (9H, s, $C(CH_3)_3$).

^{13}C-NMR (100.6 MHz; d_6-DMSO) δ_C: 171.0; 155.6; 147.2; 144.1; 128.4; 123.6; 78.6; 64.8; 61.5; 56.6; 28.3.

General method for the microwave-assisted synthesis of carboxylic esters using soluble isoureas



The carboxylic acid **3.68** (1.00 mmol) and the *O*-alkylisourea were dissolved in THF (2 mL) in a microwave vial, then the vial was capped and heated using a Smith Synthesizer™ at the appropriate temperature for 5 minutes. If residual pressure was present when the cooling was complete, it was released from the vial using a needle before opening the vial. The white solid was filtered off, the solvent evaporated and the residue purified by column chromatography.

entry	Isourea/equiv.	Acid		T (°C)	yield[a]
1	**3.22** 174 mg (1.1 mmol)	 **3.68a**	148 mg	130	152 mg (94%)
2	**3.22** 174 mg (1.1 mmol)	 **3.68e**	152 mg	130	135 mg (81%)
3	**3.22** 174 mg (1.1 mmol)	 **3.68f**	152 mg	130	148 mg (89%)
4	**3.22** 174 mg (1.1 mmol)	 **3.68h**	304 mg	130	293 mg (92%)
5	**3.22** 174 mg (1.1 mmol)	 **3.68i**	246 mg	130	226 mg (87%)
6	**3.19** 305 mg (1.3 mmol)	 **3.68a**	148 mg	130	214 mg (90%)
7	**3.19** 305 mg (1.3 mmol)	 **3.68f**	152 mg	130	201 mg (83%)
8	**3.19** 305 mg (1.3 mmol)	 **3.68h**	304 mg	130	370 mg (94%)
9	**3.15** 900 mg (4.5 mmol)	 **3.68a**	148 mg	120	173 mg (85%)
10	**3.15** 900 mg (4.5 mmol)	 **3.68e**	152 mg	120	156 mg (75%)
11	**3.15** 900 mg (4.5 mmol)	 **3.68h**	304 mg	120	314 mg (87%)

Compounds **3.69a**, **3.69e**, **3.69f**, **3.69h**, **3.69i**, **3.70a**, **3.70f** and **3.70h** exhibited ^{1}H and ^{13}C-NMR spectra identical to those described previously.

3.74a

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H: 7.59 (1H, d, J=16.0 Hz , PhC<u>H</u>=CHCOO); 7.52-7.49 (2H, m, Ar<u>H</u>); 6.37 (1H, d, J= 16.0 Hz, PhCH=C<u>H</u>COO); 1.54 (9H, s, C(C<u>H</u>$_3$)$_3$).

^{13}C RMN (75 MHz, $CDCl_3$) δ_C: 166.5 (C=O); 143.7 (CH=CHCOO); 134.8 (ArC^1); 130.1 (ArC^4); 129.0 (ArC^3); 128.1 (ArC^2); 120.3 (CH=CHCOO); 80.71 (CCH_3); 28.3 (CCH_3).

3.74e[135]

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H: 7.44-7.31 (5H, m, ArH); 5.05 (1H, d, J= 6.0 Hz, OH); 3.62 (1H, d, J= 6.0 Hz, CHOH); 1.42 (9H, s, $C(CH_3)_3$).

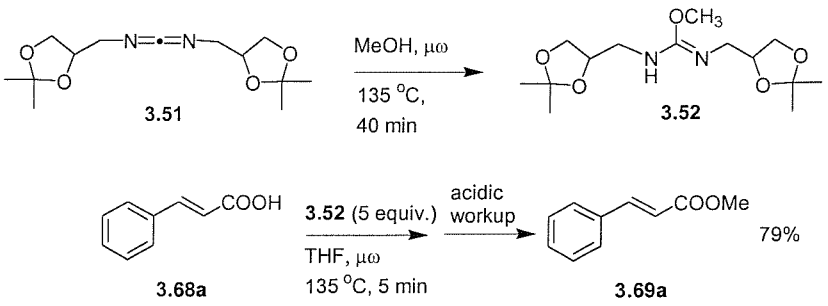
^{13}C RMN (75 MHz, $CDCl_3$) δ_C: 172.8; 138.9; 128.3; 128.0; 126.3; 82.9; 72.9; 27.7.

3.74h[148]

^{1}H-NMR (400 MHz; $CDCl_3$) δ_H: 8.35 (1H, bs, NH); 7.60 (1H, d, J= 7.5 Hz, ArH); 7.32 (1H, d, J= 7.5 Hz, ArH); 7.12 (1H, t, J=7.5 Hz, ArH); 7.09 (1H, t, J=7.5 Hz, ArH), 6.97 (1H, s, ArH), 5.08 (1H, d, J=8.0 Hz, NH), 4.54 (1H, td, J=8.0 Hz, J= 6.0 Hz, CHCOO); 3.26 (1H, dd, J= 15.0 Hz, J= 6.0 Hz, CHH'Ar), 3.22 (1H, dd, J= 15.0 Hz, J= 8.0 Hz, CHH'Ar); 1.42 (9H, s, CCH_3); 1.37 (9H, s, CCH_3).

^{13}C-NMR (100.6 MHz; $CDCl_3$) δ_C: 171.4; 155.3; 136.0; 127.8; 122.7; 121.9; 119.3; 119.0; 111.1; 110.4; 81.7; 79.6; 54.7; 28.1; 27.9.

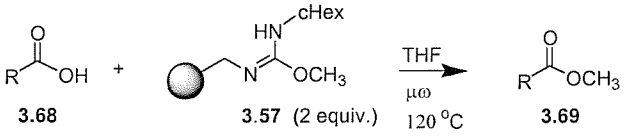
Synthesis of methyl cinnamate using isourea 3.52



Carbodiimide **3.51** (340 mg, 1.25 mmol, 5 equiv) was dissolved in anhydrous methanol (2 mL) in a microwave vial. The solution was heated in a Smith Synthesizer™ at 135 °C for 40 minutes, then the solution was transferred to a round-bottom flask and the solvent evaporated under vacuum. The oily product thus obtained was redissolved in THF and transferred to a microwave vial. Cinnamic acid (37.5 mg, 0.25 mmol, 1 equiv) was added, and the mixture was heated in a Smith Synthesizer™ at 130 °C for 5 minutes. The solution was then diluted with Et_2O (20 mL) and washed twice with an equal volume of HCl (1N

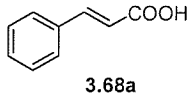
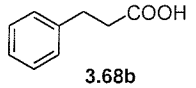
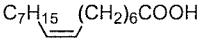
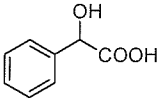
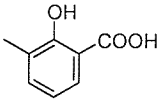
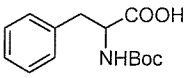
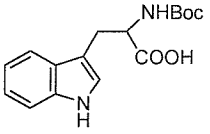
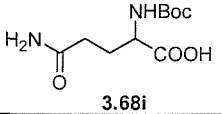
in water), then with $NaHCO_3$ (5% in water) and finally with water. The organic layer was dried over $MgSO_4$ and evaporated to give the title compound (32 mg, 79%).
The compound exhibited ^1H and ^{13}C-NMR spectra identical to those described previously.

General method for the microwave-assisted synthesis of methyl esters using resin 3.57 in THF



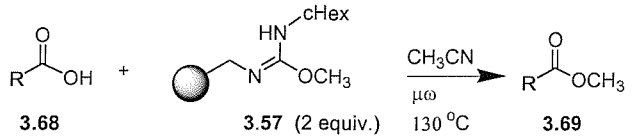
3.68 3.57 (2 equiv.) 3.69

The carboxylic acid **3.68** (0.175 mmol) was dissolved in THF (2 mL) and the resulting solution was added to the resin **3.57** (200 mg, 0.35 mmol) in a microwave vial. The vial was capped and heated at 120 °C using a Smith Synthesizer™ for the time indicated, then the resin was filtered and washed with MeOH (3×5 mL) and DCM (3×5 mL). The combined filtrates were evaporated together to afford the desired carboxylic ester. No purification was performed before NMR analysis.

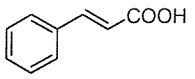
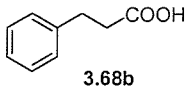
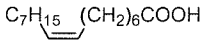
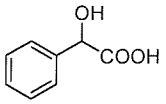
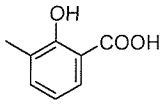
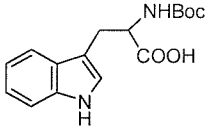
entry	Acid		time (min)	Product
1	 **3.68a**	26.0 mg	15	24.4 mg (86%)
2	 **3.68b**	26.2 mg	20	22.6 mg (79%)
3	 **3.68d**	44.5 mg	20	39.9 mg (85%)
4	 **3.68e**	26.6 mg	15	24.3 mg (84%)
5	 **3.68f**	26.6 mg	15	21.8 mg (75%)
6	 **3.68g**	44.3 mg	15	38.3 mg (82%)
7	 **3.68h**	51.1 mg	15	49.2 mg (92%)
8	 **3.68i**	41.0 mg	15	32.6 mg (75%)

All compounds exhibited ^{1}H and ^{13}C-NMR spectra identical to those described previously.

General method for the microwave-assisted synthesis of methyl esters using resin 3.57 in acetonitrile

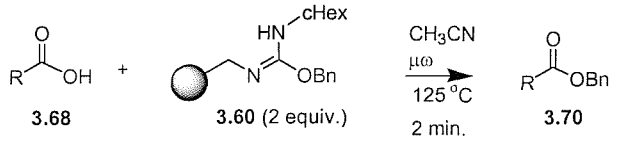


The carboxylic acid **3.68** (0.175 mmol) was dissolved in CH_3CN (2 mL) and the resulting solution was added to the resin **3.57** (200 mg, 0.35 mmol) in a microwave vial. The vial was capped and heated at 130 °C using a Smith Synthesizer™ for the time indicated, then the resin was filtered and washed with DCM (3×5 mL). The combined filtrates were evaporated together to afford the desired carboxylic ester. No purification was performed before NMR analysis.

entry	Acid		time (min)	Product
1	 **3.68a**	26.0 mg	5	25.5 mg (90%)
2	 **3.68b**	26.2 mg	5	23.7 mg (83%)
3	 **3.68d**	44.5 mg	8	45.1 mg (96%)
4	 **3.68e**	26.6 mg	5	22.0 mg (76%)
5	 **3.68f**	26.6 mg	5	22.7 mg (78%)
6	 **3.68h**	51.1 mg	5	50.3 mg (94%)

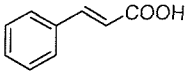
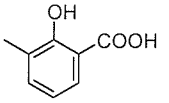
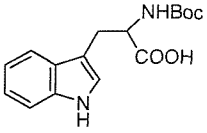
All compounds exhibited ^{1}H and ^{13}C-NMR spectra identical to those described previously.

General procedure for esterifications using *O*-benzylisourea 3.60 with microwave irradiation



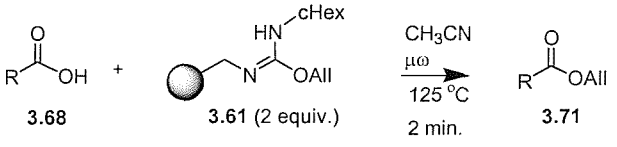
3.68 3.60 (2 equiv.) 3.70

The carboxylic acid **3.68** (0.175 mmol) was dissolved in CH_3CN (2 mL) and the resulting solution was added to the resin **3.60** (250 mg, 0.35 mmol) in a microwave vial. The vial was capped and heated at 125 °C using a Smith Synthesizer^{TM} for 120 seconds, then the resin was filtered and washed with MeOH (3×5 mL) and DCM (3×5 mL). The combined filtrates were evaporated together to afford the desired carboxylic ester. No purification was performed before NMR analysis.

entry	Acid		yield
1	 **3.68a**	26.0 mg	40.1 mg (96%)
2	 **3.68f**	26.6 mg	39.4 mg (93%)
3	 **3.68h**	51.1 mg	59.5 mg (89%)

All compounds exhibited ^{1}H and ^{13}C-NMR spectra identical to those described previously.

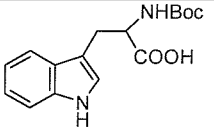
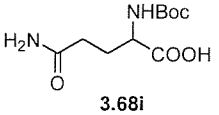
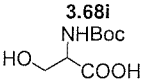
General procedure for esterifications using *O*-allylisourea 3.61 with microwave irradiation



3.68 3.61 (2 equiv.) 3.71

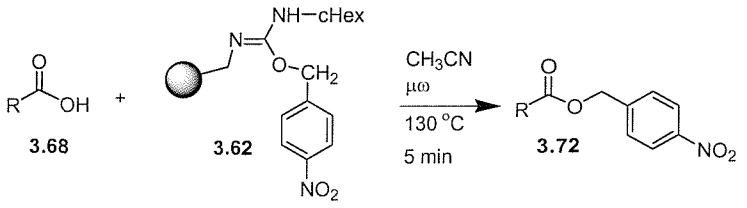
The carboxylic acid **3.68** (0.175 mmol) was dissolved in CH_3CN (2 mL) and the resulting solution was added to the resin **3.61** (225 mg, 0.35 mmol) in a microwave vial. The vial

was capped and heated at 125 °C using a Smith Synthesizer™ for 120 seconds, then the resin was filtered and washed with MeOH (3×5 mL) and DCM (3×5 mL). The combined filtrates were evaporated together to afford the desired carboxylic ester. No purification was performed before NMR analysis.

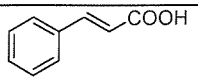
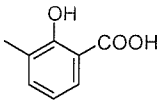
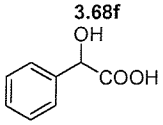
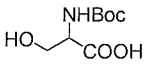
entry	Acid		yield
1	 **3.68h**	51.1 mg	54.0 mg (93%)
2	 **3.68i**	41.0 mg	43.7 mg (91%)
3	 **3.68l**	35.8 mg	40.1 mg (94%)

All compounds exhibited ^{1}H and ^{13}C-NMR spectra identical to those described previously.

General procedure for esterifications using *O-p*-nitrobenzylisourea 3.62 with microwave irradiation



The carboxylic acid **3.68** (0.175 mmol) was dissolved in CH_3CN (2 mL) and the resulting solution was added to the resin **3.62** (225 mg, 0.35 mmol) in a microwave vial. The vial was capped and heated at 130 °C using a Smith Synthesizer™ for 5 minutes, then the resin was filtered and washed with MeOH (3×5 mL) and DCM (3×5 mL). The combined filtrates were evaporated together to afford the desired carboxylic ester. No purification was performed before NMR analysis.

entry	Acid		yield
1	 **3.68a**	26.0 mg	44.1 mg (89%)
2	 **3.68f**	26.6 mg	48.3 mg (97%)
3	 **3.68e**	26.6 mg	49.2 mg (98%)
4	 **3.68l**	35.8 mg	59.4 mg (88%)

Compounds **3.70a**, **3.70f** and **3.70l** exhibited ^{1}H and ^{13}C-NMR spectra identical to those described previously.

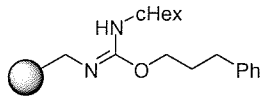
3.70e[147]

^{1}H-NMR (400 MHz; $CDCl_3$) δ_H: 8.05 (2H, d, J= 8.5 Hz, Ar'H^3); 7.36-7.28 (5H, m, Ar<u>H</u>); 7.18 (2H, d, J= 8.5 Hz, Ar'H^2); 5.23 (1H, d, J= 13.5 Hz, COOC<u>H</u>H); 5.19 (1H, d, J= 5.0 Hz, C<u>H</u>OH); 5.16 (1H, d, J= 13.5 Hz, COOCH<u>H</u>); 3.33 (1H, d, J= 5.0 Hz, O<u>H</u>).

^{13}C-NMR (100.6 MHz; $CDCl_3$) δ_C: 173.2; 147.7; 142.2; 137.8; 128.8; 128.7; 127.9; 126.6; 123.7; 73.0; 65.9.

Experimental for Chapter 4

Synthesis of *O*-(3-phenylpropan-1-yl)-*N*-cyclohexyl-*N'*-methylpolystyrene isourea 4.3

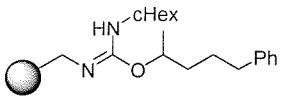


4.3

N-Cyclohexyl-*N'*-methylpolystyrene-carbodiimide **1.38** (1.00 g, 1.9 mmol), 3-phenylpropanol (1.36 g, 10 mmol) and $Cu(OTf)_2$ (200 mg, 0.52 mmol) were placed in a dry round-bottom flask. Anhydrous THF (20 mL) was added and the mixture was stirred overnight. The resin was filtered, washed with a 10% solution of TMEDA in DCM until the washing solution remained uncoloured, then with DMF (3×20 mL), MeOH (3×20 mL) and DCM (5×20 mL). The resin was dried at 40 °C under vacuum for 24 hours to afford the title compound (1.23 g).

IR(neat): ν_{max} / (cm^{-1}) 2926 (s), 1657 (s), 1450 (m), 1318 (m), 1293 (m), 1240 (s), 1154 (m), 1029 (s), 755 (s).

Synthesis of *O*-(4-phenylpropan-2-yl)-*N*-cyclohexyl-*N'*-methylpolystyrene isourea

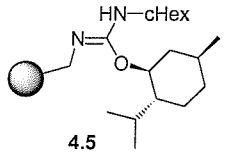


4.10

N-Cyclohexyl-*N'*-methylpolystyrene-carbodiimide **1.38** (0.500 g, 0.95 mmol), 4-phenyl-2-butanol (750 mg, 5 mmol), $Cu(Otf)_2$ (150 mg, 0.40 mmol) and anhydrous THF (10 mL) were placed in a round bottom flask and stirred overnight. The resin was filtered, washed with a 10% solution of TMEDA in DCM until the washing solution remained uncoloured, then with DMF (3×10 mL), MeOH (3×10 mL) and DCM (5×10 mL). The resin was dried at 40 °C under vacuum for 24 hours to afford the title compound (0.618 g).

IR(neat): ν_{max} / (cm^{-1}) 2926 (s), 1651 (s), 1450 (s), 1365 (m), 1290 (m), 1235 (s), 1155 (m), 1030 (s), 755 (s).

Synthesis of *O*-(menthyl)-*N*-cyclohexyl-*N'*-methylpolystyrene isourea 4.5

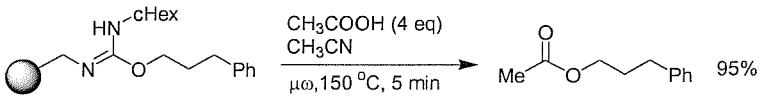


4.5

Resin **1.38** (200 mg, 0.34 mmol), menthol (265 mg, 1.70 mmol) and $Cu(OTf)_2$ (80 mg, 0.2 mmol) were placed in a dry round-bottom flask, and anhydrous THF (3 mL) was added under nitrogen with a syringe. The mixture was stirred overnight, then the resin was filtered. A 10% solution of TMEDA in DMF was used to wash the resin until the washing solution remained colourless, then the resin was washed with DMF (3×5 mL), MeOH (3×5 mL) and DCM (5×5 mL). The resin was then dried in a vacuum oven overnight.

IR(neat): ν_{max} / (cm^{-1}) 2922 (s), 1654 (s), 1330 (m), 1306 (m), 1238 (m), 1028 (s).

Reaction of *O*-(3-phenylpropan-1-yl)-*N*-cyclohexyl-*N'*-methylpolystyrene isourea 4.3 with acetic acid



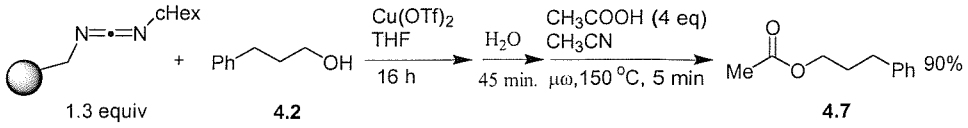
4.3 4.7

Resin **4.3** (200 mg, 0.3 mmol) was suspended in acetonitrile (2 mL) and acetic acid was added (75 μL, 1.2 mmol). The suspension was heated in a microwave oven at 150 °C for 5 minutes, then DOWEX® 550A OH resin (750 mg) was added. After 10 minutes under stirring, the resin was filtered and washed with DCM (3×5 mL). The solvent was evaporated under vacuum to give 51 mg (95%) of the title compound.

^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 7.34-7.16 (5H, m, ArH); 4.10 (2H, t, J= 6.5 Hz, -CH_2-OCO); 2.70 (2H, t, J=7.0 Hz, Ph-CH_2); 2.07 (3H, s, OCOCH_3); 1.95 (2H, m, CH_2-CH_2-CH_2).[149]

^{13}C-NMR (75.47 MHz; $CDCl_3$) δ_C: 171.2; 141.1; 128.4; 128.3; 126.0; 63.8; 32.1; 30.1; 20.9.

Catch-and-release synthesis of 3-phenylpropyl acetate



Polymer-supported carbodiimide **1.38** (200 mg, 0.38 mmol), 3-phenyl-1-propanol (34 mg, 0.25 mmol), copper (II) triflate (40 mg, 0.1 mmol) and anhydrous THF (2 mL) were placed in a dry round-bottom flask. After stirring overnight, water (110 μL, 6 mmol) was added and stirring was continued for 45 minutes. The resin was filtered and washed with a 10% solution of TMEDA in DCM until the washing solution remained uncoloured, then with DMF (3×5 mL), MeOH (3×5 mL) and DCM (5×5 mL). The resin was placed in a round-bottom flask, swollen in acetonitrile (2 mL) and acetic acid (60 μL, 1 mmol) was added. The suspension was heated at 150 °C for 5 minutes under microwave irradiation, then the resin was filtered and washed with DCM (3×5 mL). The solvent was evaporated under vacuum, giving the title compound (40 mg, 90%).

The compound exhibited ^{1}H and ^{13}C-NMR spectra identical to those described previously.

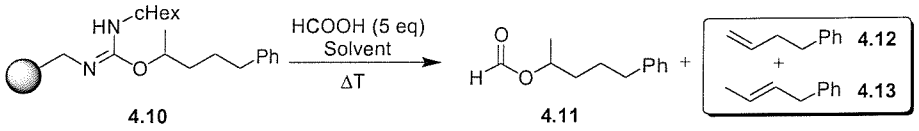
Catch-and-release synthesis of 3-phenylpropyl acetate starting from "contaminated" alcohol

Polymer-supported carbodiimide **1.38** (200 mg, 0.38 mmol), 3-phenyl-1-propanol (34 mg, 0.25 mmol), phenylacetic methyl ester **4.8** (37 mg, 0.25 mmol), copper (II) triflate (70 mg, 0.18 mmol) and anhydrous THF (2 mL) were placed in a dry round-bottom flask. After stirring overnight, water (110 μL, 6 mmol) was added and stirring was continued for 45 minutes. The resin was filtered and washed with a 10% solution of TMEDA in DCM until the washing solution remained uncoloured, then with DMF (3×5 mL), MeOH (3×5 mL) and DCM (5×5 mL). The resin was placed in a round-bottom flask, swollen in acetonitrile (2 mL) and acetic acid (60 μL, 1 mmol) was added. The suspension was heated at 150 °C for 5 minutes under microwave irradiation, then the resin was filtered and washed with

DCM (3×5 mL). The solvent was evaporated under vacuum, giving the title compound (38 mg, 86%). NMR analysis does not show any trace of the contaminant **4.8**.

The compound exhibited ^{1}H and ^{13}C-NMR spectra identical to those described previously.

Reaction of *O*-(4-phenylpropan-2-yl)-*N*-cyclohexyl-*N'*-methylpolystyrene isourea 4.10 with formic acid



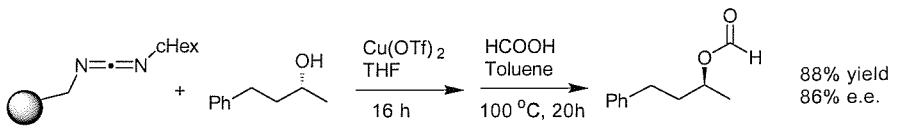
4.10 4.11

Resin **4.10** (200 mg, 0.3 mmol) was suspended in toluene (1 mL) and formic acid was added (190 μL, 5 mmol). The suspension was heated at 100 °C in an oil bath overnight. The resin was then filtered, washed with DCM (3×5 mL) and the organic phase washed with a 1 N solution of NaOH. The organic phase was dried over $MgSO_4$ and the solvent was evaporated under vacuum giving the title compound (48 mg, 90%).

^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 8.09 (1H, s, HCOO); 7.33-7.16 (5H, m, ArH); 5.08 (1H, m, COOCH); 2.78-2.58 (2H, m, Ph-CH_2-); 2.05-1.79 (2H, m, CH_2-CH_2-CH); 1.31 (3H, d, J= 6.5 Hz, $CHCH_3$).[150]

^{13}C-NMR (100 MHz; $CDCl_3$) δ_C: 160.2; 142.0; 128.4 (4C); 125.8; 67.5; 32.1; 23.6.

Catch-and-release synthesis of (*S*)-4-phenyl-2-formyl-butane



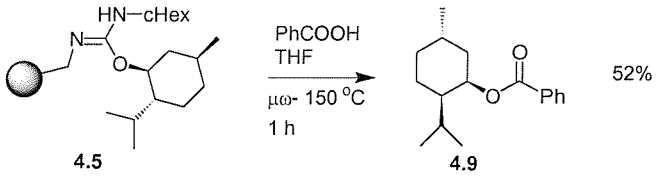
1.38 4.14 4.15

Polymer-supported carbodiimide **1.38** (225 mg, 0. 43 mmol), (*R*)-4-phenyl-2-propanol (44 mg, 0.29 mmol), copper (II) triflate (70 mg, 0.18 mmol) and anhydrous THF (2 mL) were placed in a dry round-bottom flask. After stirring overnight, water (125 μL, 7 mmol) was added and stirring was continued for 45 minutes. The resin was filtered and washed with a 10% solution of TMEDA in DCM until the washing solution remained uncoloured, then

with DMF (3×5 mL), MeOH (3×5 mL) and DCM (5×5 mL). The resin was placed in a round-bottom flask, swollen in toluene (1 mL) and formic acid (75 μL, 2 mmol) was added. The suspension was heated at 100 °C for 20 hours, then the resin was filtered and washed with DCM (3×5 mL). The organic phase was washed with a 1 N solution of NaOH and dried over $MgSO_4$. The solvent was evaporated under vacuum, giving the title compound (46 mg, 88%). The enantiomeric excess was determined using a Chiralpack AD-RH chiral HPLC column.

The compound exhibited ^{1}H and ^{13}C-NMR spectra identical to those described previously. HPLC (flow rate 0.5 mL/min., eluant CH_3CN / H_2O 50 : 50). Retention times: 14.6 min. (minor, 6.35%) and 16.1 min. (major, 84.7%). e.e. = 86%

Microwave-assisted synthesis of neomenthyl benzoate 4.9

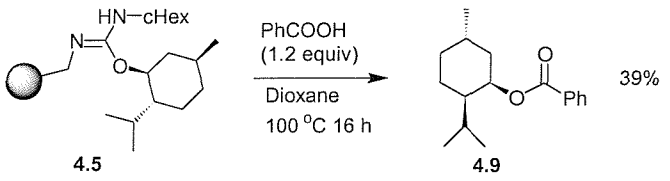


Resin **4.5** (100 mg, 0.134 mmol) and benzoic acid (82 mg, 0.67 mmol) in THF (2 mL) were placed in a microwave vial. The vial was then heated at 150 °C for 1 hour, then the resin was filtered and washed with MeOH (3×5 mL) and DCM (3×5 mL). The solvents were evaporated under vacuum and the residue was purified by column chromatography (eluant hexane : ethyl acetate 9:1) to give the title compound (19 mg, 52%).

^{1}H-NMR (400 MHz; $CDCl_3$) δ_H: 8.03 (2H, d, J=7.5 Hz, Ar$\underline{H}_2$); 7.53 (1H, t, J=7.5 Hz, Ar$\underline{H}_4$); 7.42 (2H, t, J=7.5 Hz, Ar$\underline{H}_3$); 5.44 (1H, s, C$\underline{H}$OCOPh); 2.07 (1H, ddd, J= 6.0 Hz, J=3.5 Hz, J=2.5 Hz, C$\underline{H}_2$CHOCOPh); 1.81 (2H, m); 1.69 (1H, m); 1.58-1.46 (2H, m); 1.17-0.95 (4H, m); 0.95-0.80 (10H, m) ppm.[151]

^{13}C-NMR (100 MHz; $CDCl_3$) δ_C: 165.9; 132.7; 131.1; 129.5; 128.3; 71.7; 47.1; 39.3; 34.9; 29.4; 26.8; 25.4; 22.2; 21.0; 20.8 ppm.

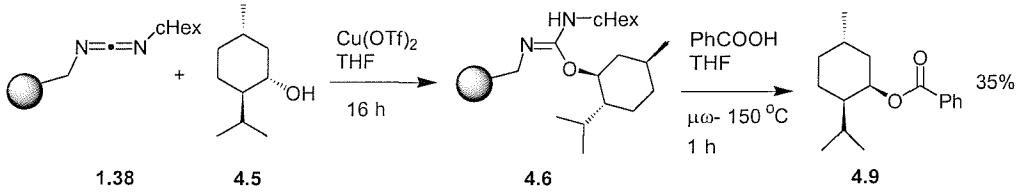
Thermal synthesis of neomenthyl benzoate 4.9



Resin **10** (100 mg, 0.134 mmol) and benzoic acid (19.5 mg, 0.16 mmol, 1.2 equiv) in dioxane (2 mL) were heated at reflux for 2 days. The solvent was then evaporated under vacuum and the residue was purified by column chromatography (eluant hexane : ethyl acetate 9:1) to give the title compound (14 mg, 39%).

The compound exhibited ^{1}H and ^{13}C-NMR spectra identical to those described previously.

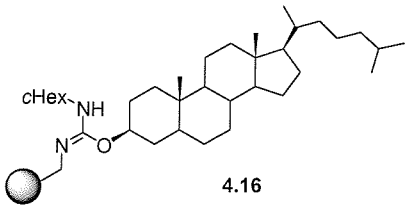
Catch-and-release synthesis of neomenthyl benzoate 4.9



Resin **1.38** (200 mg, 0.34 mmol), menthol (44 mg, 0.28 mmol) and $Cu(OTf)_2$ (40 mg, 0.10 mmol) were placed in a dry round-bottom flask, and anhydrous THF (2 mL) was added under nitrogen with a syringe. After stirring overnight, the resin was filtered, a 10% solution of TMEDA in DMF was used to wash the resin until the washing solution remained colourless, then the resin was washed with DMF (3×5 mL), MeOH (3×5 mL) and DCM (5×5 mL). The resin was then dried in a vacuum oven overnight. The resin was transferred to a microwave vial, and benzoic acid (170 mg, 1.40 mmol, 5 equiv) dissolved in THF (2 mL) was added. The vial was heated at 150 °C for 1 hour, then the resin was filtered and washed with MeOH (3×5 mL) and DCM (3×5 mL). The solvents were evaporated under vacuum and the residue was purified by column chromatography (eluant hexane : ethyl acetate 9:1) to give 26 mg (35.4% yield)

The compound exhibited ^{1}H and ^{13}C-NMR spectra identical to those described previously.

Synthesis of *O*-(3-β-cholestanyl)-*N*-cyclohexyl-*N'*-methylpolystyrene isourea 4.16

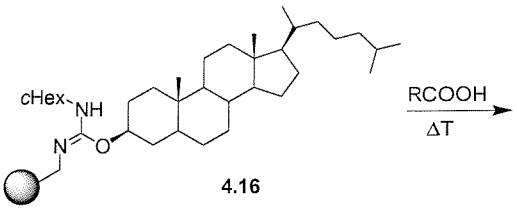


4.16

N-Cyclohexyl-*N'*-methylpolystyrene-carbodiimide (1.00 g, 1.9 mmol), 3-β-cholestanol (3.88 g, 10 mmol) and $Cu(OTf)_2$ (200 mg, 0.52 mmol) were placed in a dry round-bottom flask. Anhydrous THF (20 mL) was added and the mixture was stirred overnight. The resin was filtered, washed with a 10% solution of TMEDA in DCM until the washing solution remained uncoloured, then with DMF (3×20 mL), MeOH (3×20 mL) and DCM (5×20 mL). The resin was dried at 40 °C under vacuum for 24 hours to afford the title compound (1.65 g).

IR(neat): ν_{max} / (cm^{-1}) 2926 (s), 1686 (s), 1645 (s), 1574 (w), 1451 (s), 1345 (m), 1290 (s), 1236 (s), 1156 (s), 1029 (s), 759 (s).

Reactions of *O*-(3-β-cholestanyl)-*N*-cyclohexyl-*N'*-methylpolystyrene isourea 4.16 with carboxylic acids



4.16

O-(3-β-Cholestanyl)-*N*-cyclohexyl-*N'*-methylpolystyrene isourea **4.16** (200 mg, 0.2 mmol) was swollen in the appropriate solvent (CH_3CN or toluene). The carboxylic acid was the added and the mixture heated either in an oil-bath or in a microwave reactor. The resin was then filtered, washed with DCM (3×5 mL) and the organic phase washed with a 1 N solution of NaOH. The organic phase was dried over $MgSO_4$ and the solvent was evaporated under vacuum. The product was obtained as a white solid which whose composition was determined by NMR.

Acid (equiv)		solvent	T (°C)	time	Product	Subst. Vs. elim.
PhCOOH (5)	122 mg	CH_3CN	150[1]	5 min	47 mg	4 : 6
HCOOH (5)	38 μL	toluene	150[1]	5 min	27 mg	3 : 7
HCOOH (5)	38 μL	toluene	100	20 h	29 mg	5 : 5
HCOOH (1)	8 μL	toluene	100	40 h	44 mg	<1 : >9
--	--	toluene	100	40 h	38 mg	0 : 1
$ClCH_2COOH$ (1)	20 mg	toluene	100	20 h	47 mg	4 : 6
$Cl_2CHCOOH$ (1)	16 μL	toluene	100	20 h	45 mg	5 : 5

[1] Microwave heating.

3-α-Cholestanyl benzoate 4.17[152]

^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 8.05 (2H, d, J= 6.0 Hz, ArH); 7.48-7.44 (3H, m, ArH); 5.26 (1H, bs, CH-OCO); 2.01-0.64 (44H, m).

3-α-Cholestanyl formate 4.18

^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 8.04 (1H, s, HCOO); 5.14 (1H, m, CH-OCO); 1.97-0.62 (44H, m).

^{13}C-NMR (75.5 MHz; $CDCl_3$) δ_C: 160.8; 70.4; 56.5; 56.2; 54.2; 42.5; 40.0; 39.9; 39.5; 36.1; 35.8; 35.7; 35.4; 32.8; 32.7; 31.9; 28.3; 28.2; 28.0; 26.1; 24.1; 23.8; 22.8; 22.5; 20.7; 18.6; 12.0; 11.3.

Δ^2 and Δ^3 Cholestene[153,154]

^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 5.57 (2H, bs, CH=CH); 1.98-0.64 (44H, m).

^{13}C-NMR (75.5 MHz; $CDCl_3$) δ_C: 131.5 (Δ^3-cholestene); 126.0 (Δ^2-cholestene); 125.8 (Δ^2-cholestene); 125.4 (Δ^3-cholestene).

3-α-Cholestanyl chloroacetate

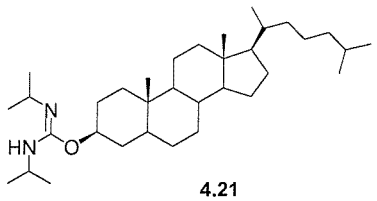
^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 5.01 (1H, m, COOCH); 4.14-4.03 (2H, m, $ClCH_2COO$); 2.03-0.65 (44H, m).

3-α-Cholestanyl dichloroacetate

^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 5.92 (1H, s, $Cl_2C\underline{H}COO$); 5.11 (1H, s, $COOC\underline{H}$); 2.00-0.61 (44H, m).

^{13}C-NMR (75.5 MHz; $CDCl_3$) δ_C: 164.0; 74.6; 64.8; 56.4; 56.2; 54.1; 42.5; 39.9; 39.5; 36.1; 35.8; 35.7; 35.4; 32.7; 32.4; 31.8; 31.6; 28.3; 28.0; 25.7; 24.1; 23.8; 22.8; 22.6; 22.5; 20.8; 18.6; 14.1; 12.0; 11.3.

Synthesis of *O*-(3-β-cholestanyl)-*N,N'*-diisopropylisourea 4.21



4.21

3-β-Cholestanol (1.940 g, 5 mmol), DIC (0.800 mL, 5 mmol) and $Cu(OTf)_2$ (50 mg, 0.14 mmol) were dissolved in anhydrous THF (10 mL) and the solution was stirred overnight. DCM (50 mL) was added and the solution was extracted with aqueous ammonia (1N, 20 mL). The organic phase was dried over $MgSO_4$ and the solvent evaporated to give 2.550 g (100%) of the title compound.

IR(neat): ν_{max} / (cm^{-1}) 2931 (s), 1659 (s), 1466 (m), 1382 (m), 1334 (s), 1315 (m), 1301 (m), 1171 (m), 1075 (s), 1020 (m), 739 (s).

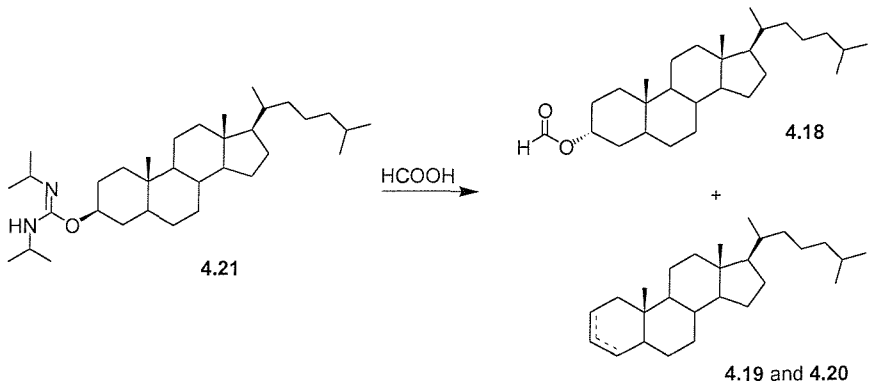
^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 4.66 (1H, bs, $C\underline{H}$-O); 3.70 (1H, bs, $C\underline{H}$-CH_3); 3.31 (1H, bs, $N\underline{H}$); 3.11 (1H, bs, $C\underline{H}$-CH_3); 1.96-0.62 (44H, m).

^{13}C-NMR (75.5 MHz; $CDCl_3$) δ_C: 150.7; 77.2; 72.6; 56.5; 56.3; 54.4; 46.2; 44.5; 43.3; 42.6; 40.1; 39.5; 36.8; 36.2; 35.8; 35.6; 35.5; 34.3; 32.1; 28.8; 28.2; 28.0; 27.7; 24.3; 24.2; 23.9; 23.8; 22.8; 22.6; 21.2; 18.7; 12.3; 12.1.

ESMS m/z 515.6 $(M+H)^+$

HRMS (ES^+) 515.4940 (calc. 515.4935) $(M+H)^+$

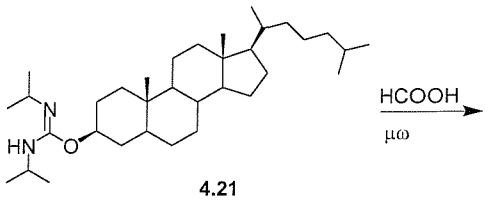
Reactions of *O*-(3-β-cholestanyl)-*N,N'*-diisopropylisourea with formic acid with thermal heating



O-(3-β-cholestanyl)-*N,N'*-diisopropylisourea (514 mg, 1 mmol) was dissolved in toluene (2 mL) and formic acid (40 μL or 200 μL, 1 or 5 mmol) was added under stirring. The solution was heated at 60 °C for 16 hours. The white precipitate obtained was filtered off, the solvent evaporated under vacuum and the residue purified by column chromatography. Eluting with hexane afforded alkenes **4.19** and **4.20**, subsequent elution with hexane : ethyl acetate 90 : 10 afforded ester **4.18**.

HCOOH	**4.19** and **4.20**	**4.18**
40 μL	15 mg (4%)	256 mg (62%)
200 μL	42 mg (12%)	202 mg (49%)

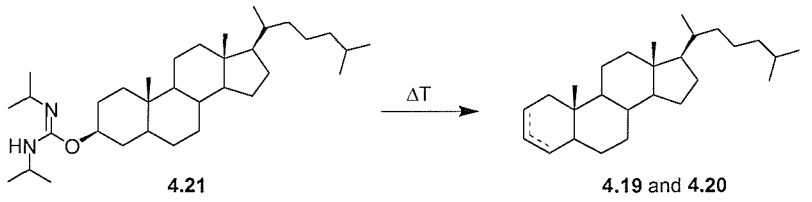
Reactions of *O*-(3-β-cholestanyl)-*N,N'*-diisopropylisourea with formic acid under microwave irradiation



O-(3-β-cholestanyl)-*N,N'*-diisopropylisourea (514 mg, 1 mmol) was dissolved in toluene (2 mL) and formic acid (40 μL, 1 mmol) was added under stirring. The solution was heated at 150 °C for 5 minutes in a Smith Synthesizer™. The white precipitate obtained

was filtered off, the solvent evaporated under vacuum and the residue purified by column chromatography. Eluting with hexane afforded alkenes **4.19** and **4.20** (68 mg, 17%), subsequent elution with hexane : ethyl acetate 90 : 10 afforded ester **4.18** (283 mg, 68%).

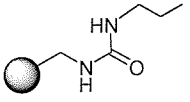
Thermal elimination of *O*-(3-β-cholestanyl)-*N,N'*-diisopropylisourea



4.21 **4.19** and **4.20**

O-(3-β-cholestanyl)-*N,N'*-diisopropylisourea (514 mg, 1 mmol) was dissolved in toluene (2 mL). The solution was heated at 60 °C for 40 hours. The solvent was evaporated under vacuum and the residue purified by column chromatography (eluant hexane), affording alkenes **4.19** and **4.20** (28 mg, 7%).

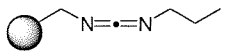
Synthesis of *N*-propyl-*N'*-methylpolystyrene-urea



Aminomethyl polystyrene (1.00 g, 3.20 mmol) was swollen in anhydrous THF (5 mL) in a round-bottom flask. Propyl isocyanate (0.935 mL, 10 mmol) was added in one portion under stirring. Gentle stirring was continued overnight, then the reaction was heated at reflux for 6 hours. The resin was filtered, washed with DCM (3×20 mL)DMF (3×20 mL), MeOH (3×20 mL), DCM (5×20 mL), dried overnight in a vacuum-oven at 40 °C to give the title compound (1.15 g).

IR (neat): ν_{max} / (cm^{-1}) 3300 (s), 2925 (s), 1633 (s), 1562 (s), 1452 (m), 1258 (s), 759 (s).

Synthesis of *N*-propyl-*N'*-methylpolystyrene-carbodiimide 4.26



4.26

N-Propyl-*N'*-methylpolystyrene-urea (1.00 g, 2.4 mmol) was swollen in dry DCM (20 mL) and triphenylphosphine (1.75 g, 6.6 mmol) was added. The mixture was stirred for 10 minutes to allow complete dissolution of the triphenylphosphine, then CBr_4 (2.20 g, 6.6 mmol) was added, immediately followed by dropwise addition of anhydrous TEA (3.0 mL, 21.5 mmol). The dark reaction mixture was gently stirred overnight, then the resin was filtered, washed with DCM (3×10 mL), DMF (3×10 mL) and DCM (5×10 mL), dried overnight in a vacuum-oven at 40 °C to give the title compound (0.87 g).

IR (neat): ν_{max} / (cm^{-1}) 2927 (m), 2121 (s), 1451 (m), 1334 (m), 758 (m).

Catch-and-release reaction of 3-β-cholestanol using carbodiimide 3.55

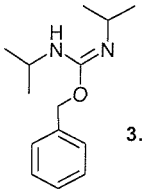
Polymer-supported carbodiimide **3.55** (250 mg, 0.55 mmol), 3-β-cholestanol (171 mg, 0.44 mmol), copper (II) triflate (70 mg, 0.18 mmol) and anhydrous THF (2 mL) were placed in a dry round-bottom flask. After stirring overnight, water (125 μL, 7 mmol) was added and stirring was continued for 45 minutes. The resin was filtered and washed with a 10% solution of TMEDA in DCM until the washing solution remained uncoloured, then with DMF (3×5 mL), MeOH (3×5 mL) and DCM (5×5 mL). The resin was placed in a round-bottom flask, swollen in toluene (1 mL) and formic acid (75 μL, 2 mmol) was added. The suspension was heated at 100 °C for 20 hours, then the resin was filtered and washed with DCM (3×5 mL). The organic phase was washed with a 1 N solution of NaOH and dried over $MgSO_4$. The solvent was evaporated under vacuum, giving a white solid (25 mg), whose composition was determined by NMR (Table 4.3).

Catch-and-release reaction of 3-β-cholestanol using carbodiimide 4.26

Polymer-supported carbodiimide **4.26** (200 mg, 0.52 mmol), 3-β-cholestanol (171 mg, 0.44 mmol), copper (II) triflate (70 mg, 0.18 mmol) and anhydrous THF (2 mL) were placed in a dry round-bottom flask. After stirring overnight, water (125 μL, 7 mmol) was added and stirring was continued for 45 minutes. The resin was filtered and washed with a 10% solution of TMEDA in DCM until the washing solution remained uncoloured, then with DMF (3×5 mL), MeOH (3×5 mL) and DCM (5×5 mL). The resin was placed in a round-bottom flask, swollen in toluene (1 mL) and formic acid (75 μL, 2 mmol) was added. The suspension was heated at 100 °C for 20 hours, then the resin was filtered and washed with DCM (3×5 mL). The organic phase was washed with a 1 N solution of NaOH and dried over $MgSO_4$. The solvent was evaporated under vacuum, giving a white solid (25 mg), whose composition was determined by NMR (Table 4.3).

Experimental for Chapter 5

Synthesis of *O*-benzyl-*N,N'*-diisopropylisourea 3.19



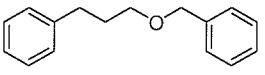
3.19

Benzyl alcohol (4.773 g, 45.1 mmol), DIC (5.764 g, 45.1 mmol) and CuCl (6 mg, 0.06 mmol) were placed in a dry round-bottom flask and the green mixture was stirred overnight. Hexane (100 mL) was added to the mixture and the resulting slurry was filtered through a pad of neutral alumina (ca. 5 cm, diameter 10 cm), washing the alumina with hexane (100 mL). The solvent was evaporated under vacuum to give the desired product as a colourless oil (9.698 g, 91%).

IR (neat): ν_{max} / (cm^{-1}) 3437 (w); 2962 (m); 1656 (s); 1386 (m); 1302 (s); 1169 (m); 1068 (s); 732 (m); 695 (s).

^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 7.38-7.26 (5H, m, ArH); 5.08 (2H, s, Ph-CH_2-O); 3.80 (1H, m, CH); 3.44 (1H, d, J= 7.0 Hz, NH); 3.20 (1H, septet, J=7.7 Hz, J=6.5 Hz, CH); 1.11 (12H, d, J= 6.5 Hz, CH_3).[155]

Synthesis of (3-phenyl-1-propyl)-benzyl ether 5.1



5.1

3-Phenyl-1-propanol (55 μL, 0.40 mmol), *O*-benzyl-*N,N'*-diisopropyl-isourea (250 μL, 1.0 mmol) and scandium triflate (20 mg, 0.04 mmol) were dissolved in 2.5 mL of dry THF under nitrogen. The solution was heated at reflux for 72 hours, then the white precipitate was filtered off. The solution was diluted with DCM (20 mL) and extracted with water (20 mL). The aqueous phase was back-extracted with DCM (2×20 mL) and the combined organic phases dried over $MgSO_4$ and evaporated to dryness. The resulting oil was

purified by column chromatography (eluant Hexane : AcOEt 95 : 5), affording the title compound (68 mg, 75%) as a colourless oil.

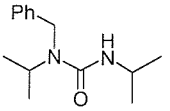
IR (neat): ν_{max} / (cm^{-1}) 2920 (br), 1686 (s), 1407 (m), 1243 (s), 1122 (s), 1056 (w), 963 (m), 911 (m), 774 (s)

^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 7.44-7.16 (10H, m, ArH); 4.44 (2H, s, Ph-CH_2-O); 3.43 (2H, t, J=6.5 Hz, O-CH_2-CH_2); 2.65 (2H, t, J= 7.5 Hz, CH_2-CH_2-Ph); 1.88 (2H, tt, J=7.5 Hz, J=6.5 Hz, CH_2-CH_2-CH_2).[156]

^{13}C-NMR (75.47 MHz; $CDCl_3$) δ_C: 128.6; 128.5; 128.4; 128.2; 127.8; 127.7; 126.7; 125.9; 73.1 (PhCH_2O); 69.7 (OCH_2CH_2); 32.5 (CH_2CH_2Ph); 31.5 ($CH_2CH_2CH_2$).

EIMS m/z 91 (100%); 105 (38.5%)

Synthesis of *N*-benzyl-*N,N'*-diisopropylurea 5.2



5.2

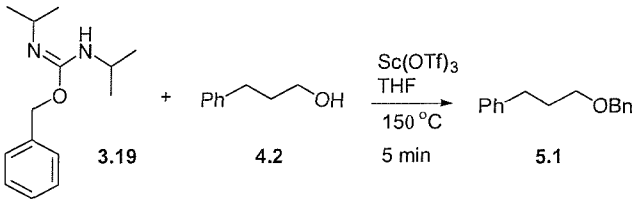
O-Benzyl-*N,N'*-diisopropylisourea (234 mg, 1.0 mmol) and scandium triflate (20 mg, 0.04 mmol) were dissolved in anhydrous THF (2 mL) under nitrogen. The solution was heated at reflux for 72 hours, then the white precipitate was filtered off. The solution was diluted with DCM (20 mL) and extracted with water (20 mL). The aqueous phase was back-extracted with DCM (2×20 mL) and the combined organic phases dried over $MgSO_4$ and evaporated to dryness. The resulting oil was purified by column chromatography (eluant Hexane : AcOEt 60 : 40), affording the title compound (185 mg, 79%) as white solid.

^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 7.35-7.21 (5H, m, ArH); 4.69 (1H, septet, J= 7.0 Hz, CH); 4.28 (2H, s, N-CH_2-Ph); 3.94 (1H, bs, NH); 3.90 (1H, septet, J= 6.5 Hz, CH); 1.11 (6H, d, J= 7.0 Hz, CH_3); 0.94 (6H, d, J=6.5Hz, CH_3).

^{13}C-NMR (75.5 MHz; $CDCl_3$) δ_C: 157.6 (C=O); 138.7 (ArC^1); 128.7 (ArC^3); 127.1 (ArC^4); 126.0 (ArC^2); 45.6 (NCH_2Ph); 44.8 (CH); 42.2 (CH); 23.1 (CH_3); 20.6 (CH_3).

ESMS m/z 235 ($(M+H)^+$, 15%); 257 ($(M+Na)^+$, 20%); 298.2 ($(M+Na+CH_3CN)^+$, 100%); 491.4 ($(2M+Na)^+$, 95%).

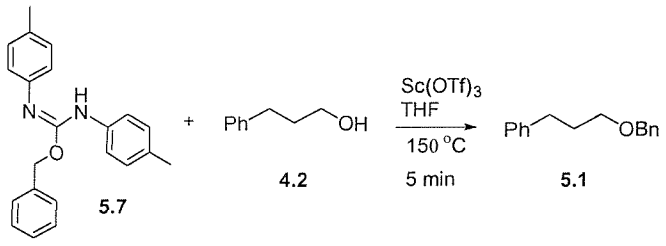
Synthesis of (3-phenyl-1-propyl)-benzyl ether 5.1 with microwave irradiation



3-Phenyl-1-propanol (110 μL, 0.81 mmol), *O*-benzyl-*N,N'*-diisopropyl-isourea (500 μL, 2.5 mmol) and scandium triflate (10 mg, 0.02 mmol) were dissolved in 2 mL of dry THF under nitrogen in a microwave vial. The solution was heated under microwave irradiation at 150 °C for 5 minutes, then the white precipitate was filtered off. The solution was diluted with DCM (20 mL) and extracted with water (20 mL). The aqueous phase was back-extracted with DCM (2×20 mL) and the combined organic phases dried over $MgSO_4$ and evaporated to dryness. The resulting oil was purified by column chromatography (eluant Hexane : AcOEt 95 : 5), affording the title compound (128 mg, 70%) as a colourless oil.

The compound exhibited ^{1}H and ^{13}C-NMR spectra identical to those described previously.

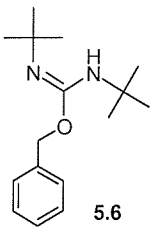
Synthesis of (3-phenyl-1-propyl)-benzyl ether 5.1 using *O*-benzyl-*N,N'*-ditolyl-isourea 5.6 prepared *in situ*



A solution of ditolyl carbodiimide (222 mg, 1 mmol), benzyl alcohol (103 μL, 1 mmol) and $Cu(OTf)_2$ (20 mg, 0.05 mmol) in anhydrous THF (2 mL) was stirred at room temperature overnight in a microwave vial. 3-Phenyl-propanol (122 mg, 0.9 mmol) was added and the reaction mixture heated in a microwave oven at 150 °C for 5 minutes. Filtration of the white precipitate and purification by column chromatography as described in the previous experiment afforded the title compound (91 mg, 40%)

The compound exhibited ^{1}H and ^{13}C-NMR spectra identical to those described previously.

Synthesis of *O*-benzyl-*N,N'*-di*tert*butyl-isourea 5.6 using the Radau procedure[157]

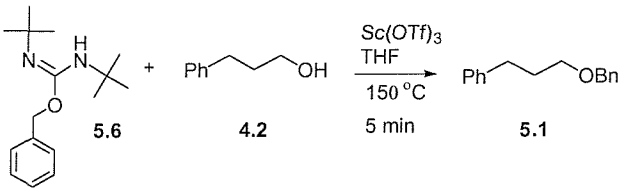


5.6

To a solution of *N,N'*-di*tert*butyl-carbodiimide (1.000 g, 6.5 mmol) in anhydrous DCM (2.5 mL) was added benzyl alcohol (2.00 mL, 19.5 mmol). The solution was cooled at 0 °C and $HBF_4.Et_2O$ (54% w/w, 755 µL, 6.5 mmol) was added. Stirring was continued for 1 hour, then Et_2O (20 mL) was added and the organic phase was washed with an aqueous solution of KOH (400 mg, 7 mmol, in 5 mL). The organic phase was dried over $MgSO_4$ and the solvent evaporated under vacuum to afford the title compound (790 mg, 47%). The product was used without purification for the next step.

^{1}H-NMR (400 MHz; $CDCl_3$) δ_H: 7.34-7.16 (5H, m, ArH); 4.98 (2H, s, Ph-CH_2-O); 3.59 (1H, bs, NH); 1.92 (9H, s, CH_3); 1.16 (9H, s, CH_3).

Synthesis of (3-phenyl-1-propyl)-benzyl ether 5.1 using *O*-benzyl-*N,N'*-di*tert*butyl-isourea 5.6

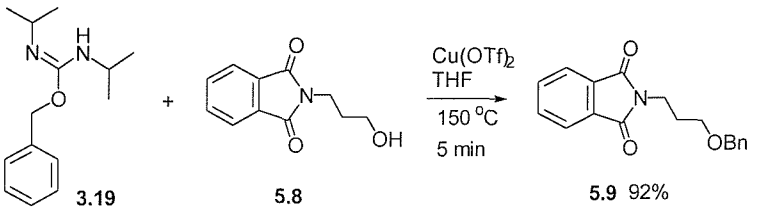


5.6 4.2 5.1

A solution of 3-phenyl-propanol (68 mg, 0.50 mmol), *O*-benzyl-*N,N'*-di*tert*butyl-isourea **5.6** (200 mg, 0.76 mmol) and scandium triflate (25 mg, 0.05 mmol) in anhydrous THF (2 mL) was subjected to microwave irradiation (150 °C, 5 minutes). Filtration of the precipitate and purification by column chromatography afforded the desired product (72 mg, 64%)

The compound exhibited ^{1}H and ^{13}C-NMR spectra identical to those described previously.

Synthesis of 3-phthalimido-propyl benzyl ether



3.19 5.8 5.9 92%

To a solution of 3-phthalimido-1-propanol (205 mg, 1 mmol) and *O*-benzyl-*N,N'*-diisopropyl-isourea (351 mg, 1.5 mmol) in anhydrous THF prepared in a microwave vial was added copper (II) triflate (542 mg, 1.5 mmol). The resulting suspension was heated under microwave irradiation at 150 °C for 5 minutes. The precipitate formed was filtered off and the solvent removed under vacuum. The residue was purified by column chromatography (hexane : ethyl acetate 80 : 20) to give the desired product (274 mg, 93%) as a low-melting solid.

IR (neat): ν_{max} / (cm^{-1}) 2800br, 1704s, 1392m, 1368m, 1100m, 1043m, 896w, 717s, 696s.

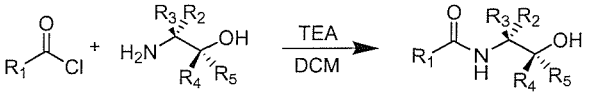
^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 7.83 (2H, dd, J=5.5Hz, 3.0 Hz, Ar$\underline{H}^2$); 7.70 (2H, dd, J=5.5Hz, 3.0 Hz, Ar$\underline{H}^3$); 7.32-7.27 (5H, m, Ar'$\underline{H}$); 4.48 (2H, s, O-C$\underline{H}_2$-Ph); 3.85 (2H, t, J=6.5 Hz, N-C$\underline{H}_2$-); 3.57 (2H, t, J= 6.5 Hz, -C$\underline{H}_2$-O); 2.02 (2H, quintet, J=6.5Hz, -CH_2-C$\underline{H}_2$-CH_2-).

^{13}C-NMR (75.5 MHz; $CDCl_3$) δ_C: 168.4 (C=O); 138.2 (Ar$\underline{C}'^1$); 133.8 (Ar$\underline{C}^3$); 132.1 (Ar$\underline{C}^1$); 128.2 and 127.6 (ArC'^{2} and Ar$\underline{C}'^3$); 127.4 (Ar$\underline{C}'^4$); 123.1 (Ar$\underline{C}^2$); 73.0 (Ph-$\underline{C}H_2$-O); 67.9 (CH_2-$\underline{C}H_2$-O); 35.6 (N-$\underline{C}H_2$-); 28.6 (CH_2-$\underline{C}H_2$-CH_2).

ESMS m/z 318.1 $(M+Na)^+$

HRMS (ES) m/z 318.1105 (calc. 318.1100) $(M+Na)^+$

General procedure for the preparation of amides

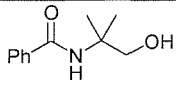
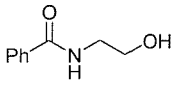
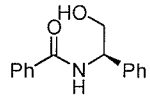
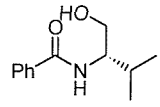
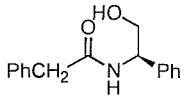
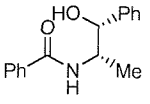
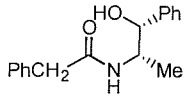
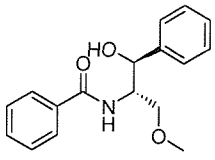


A solution of the appropriate aminoalcohol (1.0 equiv) and TEA (1.1 equiv) in anhydrous DCM was cooled with an ice-bath. The appropriate acyl chloride (1.0 equiv) was added dropwise. The ice-bath was removed and the solution stirred overnight at room

temperature. The solution was transferred in a separatory funnel and washed with aqueous HCl (1 N), $NaHCO_3$ (5% w/w) and water, dried with MgSO4 and the solvent was removed under vacuum to afford the amides as white solids.

In the cases of amides **5.15** and **5.17** a different work-up procedure was employed, as the product precipitated from the reaction mixture. The white solid was simply collected by filtration and washed with DCM.

All products were found to be sufficiently pure by ^{1}H-NMR to be used without further purification, except 5.14 which was purified by column chromatography (eluant hexane : AcOEt 50:50).

product	Aminoalcohol	Acyl chloride	TEA	DCM	Product
 **5.10**	10 mmol 0.891 g	10 mmol 1.320 mL	11 mmol 1.530 mL	20 mL	1.562 g (81%)
 **5.14**	10 mmol 0.611 g	10 mmol 1.320 mL	11 mmol 1.530 mL	20 mL	0.263 g (16%)
 **5.15**	5 mmol 0.691 g	5 mmol 0.580 mL	5.5 mmol 0.765 mL	15 mL	0.904 g (75%)
 **5.16**	5 mmol 0.516 g	5 mmol 0.580 mL	5.5 mmol 0.765 mL	15 mL	0.976 g (94%)
 **5.17**	10 mmol 1.310 g	10 mmol 1.320 mL	11 mmol 1.530 mL	20 mL	1.811 g (71%)
 **5.18**	5 mmol 0.756 g	5 mmol 0.580 mL	5.5 mmol 0.765 mL	15 mL	1.036 g (81%)
 **5.19**	10 mmol 1.510 g	10 mmol 1.320 mL	11 mmol 1.530 mL	20 mL	2.221 g (83%)
 **5.20**	4 mmol 0.725 g	4 mmol 0.465 mL	4.4 mmol 0.612 mL	10 mL	0.730 g (64%)

5.10[158]

^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 7.70 (2H, m, ArH); 7.48-7.37 (3H, m, ArH); 6.24 (1H, bs, NH); 3.66 (2H, s, CH_2-O); 1.39 (6H, s, -CH_3).

5.14[158]

^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 7.76 (2H, d, J= 6.5 Hz, ArH); 7.52-7.38 (3H, m, ArH); 6.63 (1H, bs, NH); 3.83 (1H, q, J= 4.5 Hz, CH_2-NH); 3.62 (2H, q, J= 4.5 Hz, CH_2-OH); 2.63 (1H, t, J= 4.5 Hz, -OH).

5.15[159]

^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 7.79 (2H, m, ArH); 7.51-7.33 (8H, m, ArH); 6.81 (1H, bs, NH); 5.27 (1H, dt, J= 6.5 Hz, J= 4.5 Hz, CH-Ph); 4.01 (2H, m, CH_2-OH); 2.53 (1H, t, J= 6.5 Hz, OH).

5.16[160]

^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 7.74 (2H, m, ArH); 7.50-7.37 (8H, m, ArH); 6.42 (1H, d, J= 8.0 Hz, NH); 3.91 (1H, m, CONH-CH); 3.75 (2H, m, CH_2-OH); 2.94 (1H, bs, OH); 1.97 (1H, octet, J= 6.5 Hz, CH-CH_3); 1.00 (3H, d, J= 6.5 Hz, CH-CH_3); 0.98 (3H, d, J= 6.5 Hz, CH-CH_3).

5.17[161]

^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 7.40-7.25 (8H, m, ArH); 7.14 (2H, m, ArH); 6.26 (1H, bs, NH); 5.04 (1H, dt, J= 6.0 Hz, J= 5.0 Hz, CH-Ph); 3.78 (1H, d, J= 5.0 Hz, CH_2-OH); 3.61 (2H, s, PhCH_2CONH); 2.9 (1H, bs, OH)

5.18[162]

^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 7.7.8 (2H, m, ArH); 7.50-7.29 (8H, m, ArH); 6.27 (1H, bs, NH); 5.01 (1H, m, CH-O); 4.59 (1H, m, CH-N); 3.46 (1H, d, J= 4.0 Hz, OH); 1.15 (3H, d, J= 6.5 Hz, CH_3)

5.19

^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 7.35-7.16 (5H, m, ArH); 5.43 (1H, bs, NH); 4.75 (1H, d, J= 3.0 Hz, CH-O); 4.31 (1H, quintet d, J= 7.5 Hz, 3.0 Hz, CH-CH_3); 3.57 (1H, d, J=15.0 Hz, PhCHHCON); 3.54 (1H, d, J=15.0 Hz, PhCHHCON); 0.91 (3H, d, J=7.5Hz, CH_3).

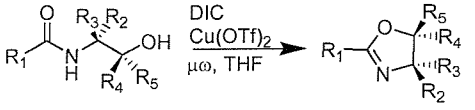
^{13}C-NMR (75.5 MHz; $CDCl_3$) δ_C: 171.9; 140.2; 134.6; 129.4; 129.0; 128.1; 127.6; 127.4; 126.3; 51.1; 43.8; 15.0.

5.20

^{1}H-NMR (400 MHz; $CDCl_3$) δ_H: 7.62 (2H, d, J= 8.0 Hz, Ar$\underline{H}^3$); 7.38 (1H, t, J= 7.0 Hz, Ar$\underline{H}$); 7.33-7.27 (4H, m, Ar$\underline{H}$); 7.22 (2H, t, J= 7.5 Hz, Ar$\underline{H}$), 7.15 (1H, t, J= 7.0 Hz, Ar$\underline{H}$); 6.81 (1H, d, J= 7.5 Hz, N$\underline{H}$); 5.00 (1H, d, J= 4.0 Hz, C$\underline{H}$OH); 4.32 (1H, dq, J= 8 Hz, J= 4.0 Hz, CONH-C$\underline{H}$); 3.99 (1H, bs, O$\underline{H}$); 3.56 (1H, dd, J= 9.5 Hz, 4.0 Hz, C$\underline{H}$H'-OCH_3); 3.48 (1H, dd, J= 9.5 Hz, 4.0 Hz, CH$\underline{H}$'-OCH_3); 3.28 (3H, s, $OC\underline{H}_3$).

^{13}C-NMR (100 MHz; $CDCl_3$) δ_C: 167.9 (C$\underline{O}$NH); 141.1 (Ar$\underline{C}$); 134.1 (Ar$\underline{C}$); 131.5 (Ar$\underline{C}$); 128.4 (Ar$\underline{C}$); 128.3 (Ar$\underline{C}$); 127.6 (Ar$\underline{C}$); 126.9 (Ar$\underline{C}$); 125.9 (Ar$\underline{C}$); 74.3 ($\underline{C}$HOH); 73.3 ($\underline{C}H_2OCH_3$); 59.2 ($CH_2O\underline{C}H_3$); 55.0 (CONH-$\underline{C}$H).

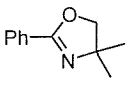
General procedure for the synthesis of 2-oxazolines



A solution of the appropriate β-hydroxyamide (1.0 mmol), DIC (126 mg, 1.0 mmol) and $Cu(OTf)_2$ (20 mg, 0.05 mmol) in anhydrous THF (2 mL) was prepared in a dry microwave vial. The vial was heated as described in Table **5.2**. The white precipitate (diisopropylurea) was removed by filtration and washed with ethyl acetate (3-4 mL). The solvent was removed under vacuum and the products purified by column chromatography.

In all cases the spectral data were consistent with literature precedents. The stereochemistry of oxazoline **5.28** (which has not been previously described) has been confirmed using NOE experiments (see chapter 5.3).

3,3-Dimethyl-2-phenyl-2-oxazoline **5.12**[163] 162 mg (93%) (colourless oil)



Eluant- hexane : AcOEt 60:40

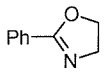
^{1}H-NMR (400 MHz; $CDCl_3$) δ_H: 7.91 (2H, m, ArH); 7.46-7.34 (3H, m, ArH); 4.08 (2H, s, -O-CH_2-); 1.36 (6H, s, -C-CH_3).

^{13}C-NMR (100.6 MHz; $CDCl_3$) δ_C: 162.0; 131.1; 128.2; 128.2; 126.7; 79.0; 67.5; 28.3.

ESMS m/z 176.1 $(M+H)^+$

IR (neat): ν_{max} / (cm^{-1}) 2967 (m); 1649 (s); 1450 (m); 1351 (m); 1319 (m); 1059 (s); 1025 (m); 965 (m); 779 (m).

2-Phenyl-2-oxazoline **5.21**[164] 127 mg (87%) (colourless oil)



Eluant- hexane : AcOEt 60:40

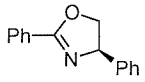
^{1}H-NMR (400 MHz; $CDCl_3$) δ_H: 7.92 (2H, m, ArH); 7.47-7.36 (3H, m, ArH); 4.41 (2H, t, J= 9.5 Hz, -CH_2-O); 4.04 (2H, t, J=9.5 Hz, -CH_2-N).

^{13}C-NMR (100.6 MHz; $CDCl_3$) δ_C: 164.6; 131.2; 128.3; 128.2; 127.8; 67.5; 54.9.

ESMS m/z 147.9 $(M+H)^+$.

IR (neat): ν_{max} / (cm^{-1}) 2967 (m); 1647 (s); 1358 (s); 1258 (s); 1078 (m); 1062 (s); 1024 (m); 942 (s); 778 (m).

(*R*)-2,4-Diphenyl-2-oxazoline **5.22**[165] 200 mg (87%) (white solid)



Eluant- hexane : AcOEt 80:20

^{1}H-NMR (400 MHz; $CDCl_3$) δ_H: 7.94 (2H, m, ArH); 7.41-7.18 (8H, m, ArH); 5.29 (1H, dd, J=10.0 Hz, 8 Hz, N-CH-CH_2-); 4.70 (1H, dd, J=10 Hz, 7.0 Hz, O-CHH'-CH); 4.17 (1H, t, J= 8.0 Hz, -O-CHH'-CH).

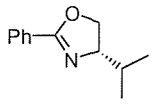
^{13}C-NMR (100.6 MHz; $CDCl_3$) δ_C: 164.8; 142.4; 131.5; 128.8; 128.5; 128.4; 127.6; 127.5; 126.8; 74.9; 70.2.

ESMS m/z 223.1 $(M+H)^+$

m.p. 32-33 °C (lit. 32-32.5 °C).

$[\alpha]_D$= +38.2° (c=1.08, $CHCl_3$), lit. 38.6° (c= 1.09, $CHCl_3$).

(*S*)-4-Isopropyl-2-phenyl-2-oxazoline **5.23**[166] 174 mg (92%) (colourless oil)



Eluant- hexane : AcOEt 85:15

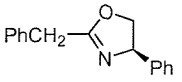
^{1}H-NMR (400 MHz; $CDCl_3$) δ_H: 7.92 (2H, m, ArH); 7.45-7.36 (3H, m, ArH); 4.38 (1H, m, N-CH-CH_2-); 4.14-4.05 (2H, m, O-CH_2-CH); 1.84 (1H, octuplet, J= 7.0 Hz, -CH-CH_3); 1.01 (3H, d, J= 7.0 Hz, CH_3); 0.91 (3H, d, J= 7.0 Hz, CH_3).

^{13}C-NMR (100.6 MHz; $CDCl_3$) δ_C: 163.3; 131.1; 128.2; 128.2; 128.0; 72.6; 70.1; 32.8; 19.0; 18.1.

ESMS m/z 190.1 $(M+H)^+$

$[\alpha]_D$= -66.4° (c=1.44, $CHCl_3$), lit. –72° (c= 6.5, $CHCl_3$).

(*R*)-2-Phenylmethyl-4-phenyl-2-oxazoline **5.24**[167] 187 mg (79%) (colourless oil)



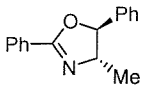
Eluant- hexane : AcOEt 85:15

^{1}H-NMR (400 MHz; $CDCl_3$) δ_H: 7.22-7.05 (8H, m, ArH); 5.03 (1H, dd, J=9.5 Hz, 9 Hz, N-CH-CH_2-); 4.70 (1H, dd, J=9.5 Hz, 9.0 Hz, -O-CHH-CH); 4.17 (1H, t, J= 9.0 Hz, -O-CHH'-CH); 3.58 (2H, s, Ph-CH_2).

^{13}C-NMR (100.6 MHz; $CDCl_3$) δ_C: 167.2; 142.3; 135.2; 129.0; 128.7; 128.6; 127.5; 127.1; 126.5; 74.9; 69.6; 34.9.

IR (neat): ν_{max} / (cm^{-1}) 1662 (s); 1494 (m); 1454 (m); 1358 (m); 1238 (m); 1160 (m); 982 (s).

(4*S*,5*S*)-2,5-Diphenyl-4-methyl-2-oxazoline **5.25**[162] 210 mg (88%) (colourless oil)



Eluant- hexane : AcOEt 85:15

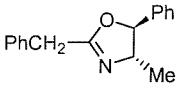
^{1}H-NMR (400 MHz; $CDCl_3$) δ_H: 7.95 (2H, m, ArH); 7.44-7.22 (8H, m, ArH); 5.02 (1H, d, J= 7.0 Hz, O-CH-CH-); 4.12 (1H, quintet, J=7.0 Hz, N-CH-CH); 1.41 (3H, d, J= 7.0 Hz, CH_3).

^{13}C-NMR (100.6 MHz; $CDCl_3$) δ_C: 163.7; 140.5; 131.4; 129.8; 128.3 (4C); 128.2; 127.8; 125.6; 88.2; 71.0; 21.4.

ESMS m/z 237.1 $(M+H)^+$

$[\alpha]_D$= 68.1° (c=1.85, $CHCl_3$), lit. 71° (c= 1.15, $CHCl_3$).

(4*S*,5*S*)-4-Methyl-2-phenylmethyl-5-phenyl-2-oxazoline **5.26**[168] 209 mg (83%) (colourless oil)



Eluant- hexane : AcOEt 85:15

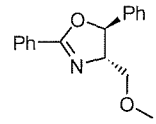
^{1}H-NMR (400 MHz; $CDCl_3$) δ_H: 7.31-7.08 (10H, m, ArH); 4.83 (1H, d, J= 7.0 Hz, O-CH-CH-); 3.92 (1H, quintet, J=7.5 Hz, -N-CH-CH); 3.63 (2H, s, Ph-CH_2); 1.31 (3H, d, J= 7.0 Hz, CH_3).

^{13}C-NMR (100.6 MHz; $CDCl_3$) δ_C: 165.1; 140.5; 135.2; 129.0; 128.7; 128.6; 128.1; 127.0; 125.4; 88.2; 70.5; 35.0; 21.4.

ESMS m/z 252 $(M+H)^+$

$[\alpha]_D$=-3.0° (c=0.506, $CHCl_3$)

(4*S*,5*S*)-4-Methoxymethyl-2,5-diphenyl-2-oxazoline **5.27**[165] 45 mg (17%) (colourless oil)

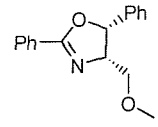


Eluant- hexane : AcOEt 90:10 (1st fraction)

^{1}H-NMR (400 MHz; $CDCl_3$) δ_H: 7.97 (2H, m, ArH); 7.45-7.22 (8H, m, ArH); 5.42 (1H, d, J=6.5 Hz, O-CH-CH-); 4.26 (1H, td, J=6.5 Hz, 4.5 Hz, N-CH-CH); 3.66 (1H, dd, J= 10 Hz, 4.5 Hz, CHH-OCH_3); 3.54 (1H, dd, J= 10 Hz, 6.5 Hz, CHH-OCH_3); 3.37 (3H, s, O-CH_3).

^{13}C-NMR (100.6 MHz; $CDCl_3$) δ_C: 164.1; 140.9; 131.5; 129.8; 128.5; 128.4; 128.1; 127.6; 125.5; 83.6; 75.0; 74.4; 59.3.

(4*S*,5*R*)-4-Methoxymethyl-2,5-diphenyl-2-oxazoline **5.28** 185 mg (69%) (white solid)



Eluant- hexane: AcOEt 90:10 (2nd fraction)

^{1}H-NMR (400 MHz; $CDCl_3$) δ_H: 8.00 (2H, d, J= 8 Hz, ArH); 7.46-7.18 (8H, m, ArH); 5.75 (1H, d, J=10 Hz, O-CH-CH-); 4.62 (1H, dt, J=10 Hz, 6.0 Hz, N-CH-CH); 3.23 (1H, dd, J= 9.5 Hz, 6 Hz, CHH-O); 2.93 (1H, covered under singlet at 2.92, CHH-O); 2.92 (3H, s, O-CH_3).

^{13}C-NMR (100.6 MHz; $CDCl_3$) δ_C: 166.4 (C=N); 136.6 (ArC); 131.6 (ArC); 128.5 (ArC); 128.4 (ArC); 128.1 (ArC); 128.0 (ArC); 127.5 (ArC); 126.5 (ArC); 83.0 (O-CH-CH-); 72.3 (CH_2-OCH_3); 69.9 (N-CH-CH); 58.7 (CH_2O-CH_3).

ESMS m/z 268.2 $(M+H)^+$

HRMS (ES) m/z 268.1331, calc. m/z 268.1332 $(M+H)^+$

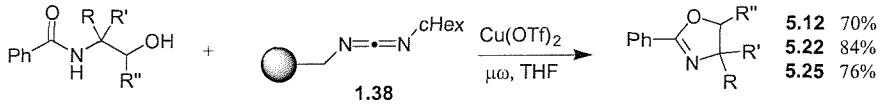
m.p. 110-112 °C.

IR (neat): ν_{max} / (cm^{-1}) 2930 (w); 2885 (w); 1642 (s); 1336 (s); 1126 (s); 1106 (s); 1088 (s); 1065 (s); 1026 (m); 968 (s); 783 (m); 757 (s).

$[\alpha]_D$= -294.6° (c=0.562, $CHCl_3$)

Elem. Anal.: found C 76.36, H 6.44, N 5.24 ($C_{17}H_{17}NO_2$ requires C 76.38, H 6.41, N 5.24)

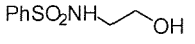
General procedure of synthesis of 2-oxazolines using polymer-supported carbodiimide



N-Cyclohexyl-*N'*-methylpolystyrenecarbodiimide (200 mg, 0.36 mmol), the appropriate β-hydroxyamide (0.24 mmol) and $Cu(OTf)_2$ (35 mg, 0.09 mmol) were placed in a microwave vial and anhydrous THF (2 mL) was added. The vial was heated under microwave irradiation for 15 minutes at 100 °C. The resin was filtered off and washed with 5 mL of DCM. The filtrate was passed on a 2 cm plug of alumina and eluted with 10 mL of DCM. The solvent was removed under vacuum to give the desired products, which were analysed by HPLC-MS.

5.12: retention time 4.86 min (96.1%, 254 nm), m/z 176.1 $(M+H)^+$.
5.22: retention time 5.45 min (98.6%, 254 nm), m/z 223.1 $(M+H)^+$
5.25: retention time 5.63 min (93.2%, 254 nm), m/z 237.1 $(M+H)^+$

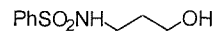
Synthesis of *N*-(2-hydroxyethyl)-benzenesulfonamide 5.31



To a solution of the 2-aminoethanol (3.00 mL, 50 mmol) and $NaHCO_3$ (7.787 g, 57 mmol) in water (40 mL) was added benzenesulfonyl chloride (7.25 mL, 57 mmol) under stirring. Vigorous stirring was maintained for 3 hours, then HCl (conc.) was added until pH=2. The organic phase was extracted with ethyl acetate (100 mL), the organic phase was dried over $MgSO_4$ and the solvent evaporated under vacuum to afford the title compound (8.140 g, 82%).

^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 7.81 (2H, m, ArH); 7.51-7.43 (3H, m, ArH); 5.99 (1H, t, J= 5.0 Hz, NH); 3.59 (2H, t, J= 5.0 Hz, CH_2-OH); 2.99 (2H, q, J= 5.0 Hz, CH_2-$NHSO_2$).
^{13}C-NMR (75 MHz; $CDCl_3$) δ_C: 139.3; 132.6; 129.1; 126.9; 61.0; 45.1.

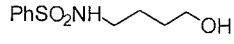
Synthesis of *N*-(3-hydroxypropyl)-benzenesulfonamide 5.32



To a solution of 3-amino-1-propanol (3.80 mL, 50 mmol) and $NaHCO_3$ (7.787 g, 57 mmol) in water (40 mL) was added benzenesulfonyl chloride (7.25 mL, 57 mmol) under stirring. Vigorous stirring was maintained for 3 hours, then HCl (conc.) was added until pH=2. The organic phase was extracted with ethyl acetate (100 mL), the organic phase was dried over $MgSO_4$ and the solvent evaporated under vacuum. The oily residue was purified by column chromatography (hexane : ethyl acetate 40 : 60) to afford the title compound (4.102 g, 38%) after 8 hours under high-vacuum.

^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 7.85 (2H, m, ArH); 7.59-7.48 (3H, m, ArH); 3.73 (2H, t, J= 6.0 Hz, CH_2-OH); 3.12 (2H, t, J= 6.0 Hz, CH_2-$NHSO_2$); 1.70 (2H, quintet, J= 6.0 Hz, CH_2-CH_2-CH_2).
^{13}C-NMR (75 MHz; $CDCl_3$) δ_C: 139.6; 132.6; 129.1; 126.9; 60.3; 40.9; 31.4.

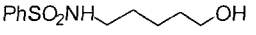
Synthesis of *N*-(4-hydroxybutyl)-benzenesulfonamide 5.33



To a solution of 4-amino-1-butanol (4.60 mL, 50 mmol) and $NaHCO_3$ (7.787 g, 57 mmol) in water (40 mL) was added benzenesulfonyl chloride (7.25 mL, 57 mmol) under stirring. Vigorous stirring was maintained for 3 hours, then HCl (conc.) was added until pH=2. The organic phase was extracted with ethyl acetate (100 mL), the organic phase was dried over $MgSO_4$ and the solvent evaporated under vacuum. The oily residue was purified by column chromatography (hexane : ethyl acetate 40 : 60) to afford the title compound (3.807 g, 33%) after 24 hours under high-vacuum.

^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 7.84 (2H, m, ArH); 7.59-7.47 (3H, m, ArH); 3.61 (2H, t, J= 6.0 Hz, CH_2-OH); 2.98 (2H, t, J= 6.5 Hz, CH_2-$NHSO_2$); 1.60-1.52 (4H, m, CH_2-CH_2-CH_2).

Synthesis of *N*-(5-hydroxypentyl)-benzenesulfonamide 5.34



To a solution of 5-amino-1-pentanol (5.43 mL, 50 mmol) and $NaHCO_3$ (7.787 g, 57 mmol) in water (40 mL) was added benzenesulfonyl chloride (7.25 mL, 57 mmol) under stirring. Vigorous stirring was maintained for 3 hours, then HCl (conc.) was added until pH=2. The organic phase was extracted with ethyl acetate (100 mL), the organic phase was dried over $MgSO_4$ and the solvent evaporated under vacuum. The oily residue was purified by column chromatography (hexane : ethyl acetate 40 : 60) to afford the title compound (7.112 g, 59%).

^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 7.84 (2H, m, ArH); 7.59-7.47 (3H, m, ArH); 4.50 (1H, t, J= 6.0 Hz, NH); 3.58 (2H, t, J= 6.0 Hz, CH_2-OH); 2.95 (2H, q, J= 6.0 Hz, CH_2-$NHSO_2$); 1.54-1.29 (6H, m, CH_2-$(CH_2)_3$-CH_2).

Synthesis of N-(phenylsulfonyl)-aziridine 5.39

N-(2-Hydroxyethyl)-benzenesulfonamide (201 mg, 1 mmol), DIC (126 mg, 1 mmol) and copper (II) triflate (20 mg, 0.05 mmol) were dissolved in anhydrous THF and stirred at room temperature for 16 hours. The resulting solution was then heated at 60 °C for 72 hours, then the white precipitate was filtered off. The solvent was removed under vacuum and the green residue was purified by column chromatography (hexane : ethyl acetate 80 : 20) to give the title compound (124.5 mg, 68%). An identical reaction with a heating time of 16 hours gave 84 mg (46%).

^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 7.90 (2H, m, Ar$\underline{H}^2$); 7.61 (1H, m, Ar$\underline{H}^4$); 7.59 (2H, m, Ar$\underline{H}^3$); 2.35 (4H, s, N-C$\underline{H}_2$-C$\underline{H}_2$-).[169]

^{13}C-NMR (75 MHz; $CDCl_3$) δ_C: 133.7 (Ar$\underline{C}^1$); 132.9 (Ar$\underline{C}^4$); 129.3 and 128.1 (Ar$\underline{C}^2$ and Ar$\underline{C}^3$); 27.7 (N-$\underline{C}H_2$-$\underline{C}H_2$-).

Synthesis of 1-(benzenesulfonyl)-azetidine 5.40

N-(3-Hydroxypropyl)-benzenesulfonamide (215 mg, 1 mmol), DIC (126 mg, 1 mmol) and copper (II) triflate (20 mg, 0.05 mmol) were dissolved in anhydrous THF in a microwave vial. The solution was heated in a microwave reactor at 175 °C for 5 minutes. The white precipitate was filtered off. The solvent was removed under vacuum and the green residue was purified by column chromatography (hexane : ethyl acetate 80 : 20) to give the title compound (26 mg, 13%).

^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 7.82 (2H, m, Ar$\underline{H}^2$); 7.65-7.53 (3H, m, Ar$\underline{H}^{3,4}$); 3.75 (4H, t, J=8.0 Hz, N-C$\underline{H}_2$-CH_2-); 2.03 (2H, quint, J=8.0 Hz, N-CH_2-C$\underline{H}_2$-).

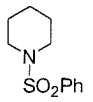
Synthesis of 1-(benzenesulfonyl)-pyrrolidine 5.41

N-(4-Hydroxybutyl)-benzenesulfonamide (229 mg, 1 mmol), DIC (126 mg, 1 mmol) and copper (II) triflate (20 mg, 0.05 mmol) were dissolved in anhydrous THF in a microwave vial. The solution was heated in a microwave reactor at 175 °C for 5 minutes. The white precipitate was filtered off. The solvent was removed under vacuum and the green residue was purified by column chromatography (hexane : ethyl acetate 80 : 20) to give the title compound (196 mg, 93%).

^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 7.82 (2H, m, Ar$\underline{H}^2$); 7.58-7.48 (3H, m, Ar$\underline{H}^{3,4}$); 3.23 (4H, m, N-C$\underline{H}_2$-CH_2-); 1.73 (2H, m, N-CH_2-C$\underline{H}_2$-).

^{13}C-NMR (75 MHz; $CDCl_3$) δ_C: 136.8 (Ar$\underline{C}^1$); 132.5 (Ar$\underline{C}^4$); 129.0 and 127.4 (Ar$\underline{C}^2$ and Ar$\underline{C}^3$); 47.9 (N-$\underline{C}H_2$-CH_2-); 25.2 (N-CH_2-$\underline{C}H_2$-).

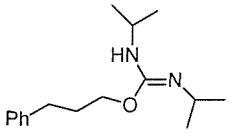
Synthesis of 1-(benzenesulfonyl)-piperidine 5.42



N-(5-Hydroxypentyl)-benzenesulfonamide (243 mg, 1 mmol), DIC (126 mg, 1 mmol) and copper (II) triflate (20 mg, 0.05 mmol) were dissolved in anhydrous THF in a microwave vial. The solution was heated in a microwave reactor at 175 °C for 5 minutes. The white precipitate was filtered off. The solvent was removed under vacuum and the green residue was purified by column chromatography (hexane : ethyl acetate 80 : 20) to give the title compound (174 mg, 77%).

^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 7.72 (2H, m, Ar$\underline{H}^2$); 7.60-7.46 (3H, m, Ar$\underline{H}^{3,4}$); 2.95 (4H, t, J= 5.5 Hz, N-$\underline{C}H_2$-CH_2-); 1.61 (4H, quint, J= 5.5 Hz, N-CH_2-$\underline{C}H_2$-); 1.38 (2H, m, CH_2-$\underline{C}H_2$-CH_2-).
^{13}C-NMR (75 MHz; $CDCl_3$) δ_C: 136.3 (Ar$\underline{C}^1$); 132.5 (Ar$\underline{C}^4$); 129.0 and 127.4 (Ar$\underline{C}^2$ and Ar$\underline{C}^3$); 46.9 (N-$\underline{C}H_2$-CH_2-); 25.1 (N-CH_2-$\underline{C}H_2$-), 23.4 (CH_2-$\underline{C}H_2$-CH_2-).

Synthesis of *N,N'*-diisopropyl-*O*-(3-phenylpropyl)isourea



19

3-Phenylpropanol (1.360 g, 10 mmol), DIC (1.260 g, 10 mmol) and CuCl () were placed in a dry round-bottom flask and the green mixture was stirred overnight. Hexane (40 mL) was added to the mixture and the resulting slurry was filtered through a pad of neutral alumina (ca. 5 cm, diameter 10 cm), washing the alumina with hexane (60 mL). The

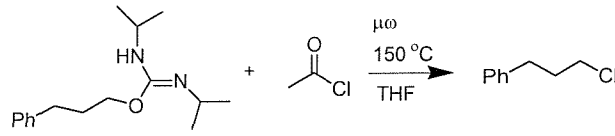
solvent was evaporated under vacuum to give the desired product as a colourless oil (1.088 g, 69%).

IR (neat): ν_{max} / (cm^{-1}) 2962 (m); 1656 (s); 1389 (m); 1311 (s); 1170 (m); 1082 (s); 744 (m); 697 (s).

^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 7.28-7.17 (5H, m, ArH); 4.06 (2H, t, J= 6.5 Hz, -CH_2-O); 3.77 (1H, m, CH); 3.41 (1H, bs, NH); 3.12 (1H, m, CH); 2.71 (2H, t, J= 8.0 Hz; Ph-CH_2); 1.95 (2H, m, -CH_2-CH_2-CH_2); 1.13 (6H, d, J= 6.5 Hz, CH_3); 1.08 (6H, d, J= 6.5 Hz, CH_3).

^{13}C-NMR (75 MHz; $CDCl_3$) δ_C: 151.9 (C=N); 142.2 (ArC); 128.5 (ArC); 128.5 (ArC); 125.9 (ArC); 64.4 (PhCH_2); 46.3 (CH); 43.6 (CH); 32.7 (CH_2-CH_2-CH_2); 31.0 (Ph-CH_2); 24.4 (CH_3); 24.2 (CH_3).

Reaction of *N,N'*-diisopropyl-*O*-(3-phenylpropyl)isourea with acetyl chloride



19 **20a-b** **21a-b**

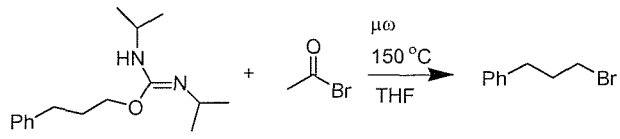
To a solution of *N,N'*-diisopropyl *O*-(3-phenylpropyl)isourea (0.262 g, 1.00 mmol) in anhydrous THF (2 mL) in a microwave vial acetyl chloride (107 μL, 1.5 mmol) was added. The vial was heated under microwave irradiation at 150 °C for 5 minutes. The solvent was removed under reduced pressure and the crude product purified by column chromatography (eluant hexane:AcOEt 98:2). The title compound was obtained as an oil (153 mg, 85%)

^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 7.25-7.10 (5H, m, ArH), 3.45 (2H, t, J=6.5 Hz, CH_2Cl), 2.71 (2H, t, J=6.5 Hz, CH_2Ph), 2.02 (2H, q, J=6.5 Hz, $CH_2CH_2CH_2$).[170]

^{13}C-NMR (75.47 MHz; $CDCl_3$) δ_C: 140.7, 128.6, 128.5, 126.1, 44.2, 34.0, 32.8.

CIMS m/z 91 ($Bn^{+\cdot}$,100%); 154 and 156 (($M^{+\cdot}$), 35% and 11.5%)

Reaction of *N,N'*-diisopropyl-*O*-(3-phenylpropyl)isourea with acetyl bromide



19 20a-b 21a-b

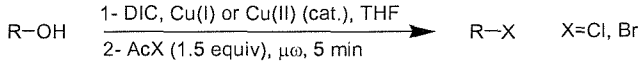
To a solution of *N,N'*-diisopropyl *O*-(3-phenylpropyl)isourea (0.262 g, 1.00 mmol) in anhydrous THF (2 mL) in a microwave vial acetyl bromide (111 μL, 1.5 mmol) was added. The vial was then heated under microwave irradiation at 150 °C for 5 minutes. The solvent was removed under reduced pressure and the crude product purified by column chromatography (eluant hexane:AcOEt 98:2). The title compound was obtained as an oil (204 mg, 91%).

^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 7.26-7.10 (5H, m, ArH), 3.32 (2H, t, J=6.5 Hz, CH_2Cl), 2.70 (2H, t, J=6.5 Hz, CH_2Ph), 2.10 (2H, q, J=6.5 Hz, $CH_2CH_2CH_2$).[171]

^{13}C-NMR (75.47 MHz; $CDCl_3$) δ_C: 140.5, 128.6, 128.5, 126.2, 34.2, 34.0, 33.1.

CIMS m/z 91 ($Bn^{+\cdot}$,100%); 198 and 200 ($M^{+\cdot}$, 20% and 20%).

One-pot transformations of alcohols into the corresponding halides



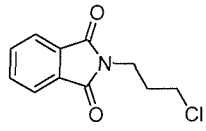
3-phenyl-1-chloropropane 5.47a

A solution of 3-phenylpropanol (272 mg, 2.0 mmol), DIC (252 mg, 2.00 mmol) and copper chloride (4 mg, 0.04 mmol) in anhydrous THF (2 mL) was prepared in a microwave vial. The vial was then heated under microwave irradiation at 100 °C for 5 minutes. The completion of the reaction could be monitored by IR, verifying the disappearance of the carbodiimide band at 2115 cm^{-1} and the appearance of the band at 1656 cm^{-1}. Acetyl chloride (214 μL, 3.00 mmol) was added via a syringe, and the vial was again heated under microwave irradiation at 150 °C for 5 minutes. The solvent was removed under reduced pressure and the crude product purified by column

chromatography (eluant hexane : AcOEt 98:2). The title compound was obtained as a colourless oil (308 mg, 100%)

The compound exhibited ^{1}H and ^{13}C-NMR spectra identical to those described previously.

N-(3-Chloropropyl)phthalimide 5.52

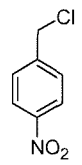


A solution of *N*-(3-hydroxypropyl)-phthalimide (325 mg, 1.58 mmol), DIC (200 mg, 1.58 mmol) and copper chloride (6 mg, 0.03 mmol) in anhydrous THF (2 mL) was prepared in a microwave vial. The vial was then heated under microwave irradiation at 100 °C for 5 minutes. Acetyl chloride (0.169 mL, 2.38 mmol) was added via a syringe, and the vial was again heated under microwave irradiation at 150 °C for 5 minutes. The solvent was removed under reduced pressure and the crude product purified by column chromatography (eluant hexane : AcOEt 85:15). The title compound was obtained as a colourless oil (326g, 92%)

^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 7.71 (2H, dd, J= 5.5Hz, 3.0 Hz, Ar$\underline{H}^2$); 7.63 (2H, dd, J= 5.5Hz, 3.0 Hz, Ar$\underline{H}^3$); 3.73 (2H, t, J= 6.5 Hz, NC$\underline{H}_2$); 3.48 (2H, t, J= 6.5 Hz, C$\underline{H}_2$-Cl); 2.07 (2H, quintet, J= 6.5Hz, -CH_2-C$\underline{H}_2$-CH_2-).

^{13}C-NMR (75.5 MHz; $CDCl_3$) δ_C: 167.8 ($\underline{C}$=O); 133.7 (Ar$\underline{C}^3$); 131.7 (Ar$\underline{C}^1$); 122.9 (Ar$\underline{C}^2$); 41.8 ($\underline{C}H_2$-Cl); 35.3 (N$\underline{C}H_2$); 31.1 ($CH_2\underline{C}H_2CH_2$).

p-Nitrobenzyl chloride 5.53



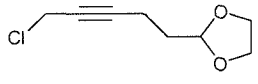
A solution of *p*-nitrobenzyl alcohol (242 mg, 1.58 mmol), DIC (199 mg, 1.58 mmol) and copper chloride (6 mg, 0.03 mmol) in anhydrous THF (2 mL) was prepared in a

microwave vial. The vial was then heated under microwave irradiation at 100 °C for 5 minutes. Acetyl chloride (0.169 mL, 2.38 mmol) was added via a syringe, and the vial was again heated under microwave irradiation at 150 °C for 5 minutes. The solvent was removed under reduced pressure and the crude product purified by column chromatography (eluant hexane : AcOEt 85:15). The title compound was obtained as a white solid (258 mg, 95%).

^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 8.24 (2H, d, J=9.0 Hz, Ar$\underline{H}^3$); 7.58 (2H, d, J=9.0 Hz, Ar$\underline{H}^2$); 4.66 (2H, s, Ph-C$\underline{H}_2$-Cl).[172]

^{13}C-NMR (75.5 MHz; $CDCl_3$) δ_C: 147.2; 144.3; 129.3; 123.9; 44.5.

2-(5-Chloro-pent-3-ynyl)-[1,3]dioxolane 5.54



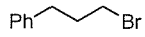
A solution of 5-[1,3]-dioxolane-2-yl-pent-2-yn-1-ol (156 mg, 1.0 mmol), DIC (126 mg, 1.00 mmol) and copper chloride (2 mg, 0.02 mmol) in anhydrous THF (2 mL) was prepared in a microwave vial. The solution was stirred overnight at room temperature. The completion of the reaction could be monitored by IR, verifying the disappearance of the carbodiimide band at 2115 cm^{-1} and the appearance of the band at 1656 cm^{-1}. Acetyl chloride (0.107 mL, 1.5 mmol) was added, and the vial was heated under microwave irradiation at 150 °C for 5 minutes. The solvent was removed under reduced pressure and the crude product purified by column chromatography (eluant hexane:AcOEt 95:5). The title compound was obtained (143 mg, 82%) as a colourless oil.

^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 4.93 (1H, d, J=4.5 Hz, O-C$\underline{H}$-O); 4.10 (2H, t, J=2.0 Hz, C$\underline{H}_2$Cl); 3.96-3.81 (4H, m, O-C$\underline{H}_2$-C$\underline{H}_2$-O); 2.35 (2H, tt, J= 7.5 Hz, 2.0 Hz, -C$\underline{H}_2$-CH_2-CH); 1.84 (2H, td, J= 7.5 Hz, 4.5 Hz, CH_2-C$\underline{H}_2$-CH).[173]

^{13}C-NMR (75.5 MHz; $CDCl_3$) δ_C: 103.0; 86.4; 75.1; 65.0; 32.5; 31.1; 13.6.

CIMS m/z 46.2 (100%); 73.1 (65%); 80.1 (37%); 141.1 (35%).

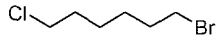
3-Phenylbromopropane 5.47b



A solution of 3-phenylpropanol (272 mg, 2.0 mmol), DIC (252 mg, 2.00 mmol) and copper triflate (15 mg, 0.04 mmol) in anhydrous THF (2 mL) was prepared in a microwave vial. The vial was then heated under microwave irradiation at 100 °C for 5 minutes. Acetyl bromide (222 μL, 3.00 mmol) was added via a syringe, and the vial was again heated under microwave irradiation at 150 °C for 5 minutes. The solvent was removed under reduced pressure and the crude product purified by column chromatography (eluant hexane : AcOEt 98:2). The title compound was obtained as a colourless oil (390 mg, 98%)

The compound exhibited ^{1}H and ^{13}C-NMR spectra identical to those described previously.

6-Chloro-1-bromohexane 5.55

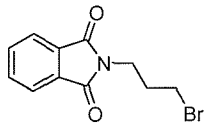


A solution of 6-chlorohexanol (273 mg, 2.0 mmol), DIC (255 mg, 2.00 mmol) and copper triflate (15 mg, 0.04 mmol) in anhydrous THF (2 mL) was prepared in a microwave vial. The vial was then heated under microwave irradiation at 100 °C for 5 minutes. Acetyl bromide (225 μL, 3.00 mmol) was added via a syringe, and the vial was again heated under microwave irradiation at 150 °C for 5 minutes. The solvent was removed under reduced pressure and the crude product purified by column chromatography (eluant hexane : AcOEt 98:2). The title compound was obtained as a colourless oil (383 mg, 96%).

^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 3.55 (2H, t, J=6.0 Hz, $C\underline{H}_2$-Cl); 3.44 (2H, t, J=6.0 Hz, $C\underline{H}_2$-Br); 2.13-1.71 (4H, m, $C\underline{H}_2$-X); 1.58-1.21 (4H, m, CH_2-$C\underline{H}_2$-CH_2).[174]

^{13}C-NMR (75.5 MHz; $CDCl_3$) δ_C: 44.9; 33.6; 32.7; 32.5; 27.4; 26.2.

N-(3-Bromopropyl)phthalimide 5.56

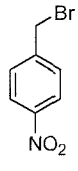


A solution of *N*-(3-hydroxypropyl)-phthalimide (339 mg, 1.65 mmol), DIC (209 mg, 1.65 mmol) and copper triflate (12 mg, 0.03 mmol) in anhydrous THF (2 mL) was prepared in a microwave vial. The vial was then heated under microwave irradiation at 100 °C for 5 minutes. Acetyl bromide (0.184 mL, 2.49 mmol) was added via a syringe, and the vial was again heated under microwave irradiation at 150 °C for 5 minutes. The solvent was removed under reduced pressure and the crude product purified by column chromatography (eluant hexane : AcOEt 85:15). The title compound was obtained as a colourless oil (394 mg, 89%)

^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 7.72 (2H, dd, J= 5.5Hz, 3.0 Hz, Ar$\underline{H}^2$); 7.63 (2H, dd, J= 5.5Hz, 3.0 Hz, Ar$\underline{H}^3$); 3.72 (2H, t, J= 6.5 Hz, NC$\underline{H}_2$); 3.33 (2H, t, J= 6.5 Hz, C$\underline{H}_2$-Br); 2.15 (2H, quintet, J= 6.5Hz, -CH_2-C$\underline{H}_2$-CH_2-).[175]

^{13}C-NMR (75.5 MHz; $CDCl_3$) δ_C: 167.8; 133.7; 131.6; 122.9; 36.3; 31.3; 29.8.

p-Nitrobenzyl bromide 5.57

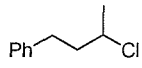


A solution of *p*-nitrobenzyl alcohol (272 mg, 1.77 mmol), DIC (224 mg, 1.77 mmol) and copper triflate (10 mg, 0.02 mmol) in anhydrous THF (2 mL) was prepared in a microwave vial. The vial was then heated under microwave irradiation at 100 °C for 5 minutes. Acetyl bromide (0.197 mL, 2.66 mmol) was added via a syringe, and the vial was again heated under microwave irradiation at 150 °C for 5 minutes. The solvent was removed under reduced pressure and the crude product purified by column chromatography (eluant hexane : AcOEt 85:15). The title compound was obtained as a white solid (376 mg, 98%)

^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 8.20 (2H, d, J=9.0 Hz, Ar$\underline{H}^3$); 7.56 (2H, d, J=9.0 Hz, Ar$\underline{H}^2$); 4.53 (2H, s, Ph-C$\underline{H}_2$-Br).[172]

^{13}C-NMR (75.5 MHz; $CDCl_3$) δ_C: 147.6; 144.7; 129.9; 124.0; 30.9.

4-Phenyl-2-chlorobutane 5.58

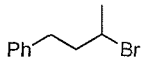


A solution of 4-phenyl-2-butanol (300 mg, 2.0 mmol), DIC (255 mg, 2.00 mmol) and $Cu(OTf)_2$ (40 mg, 0.1 mmol) in anhydrous THF (2 mL) was prepared in a microwave vial. The vial was then heated under microwave irradiation at 100 °C for 5 minutes. Acetyl chloride (0.214 mL, 3.0 mmol) was added, and the vial was again heated under microwave irradiation at 140 °C for 5 minutes. The solvent was removed under reduced pressure and the crude product purified by column chromatography (eluant hexane:AcOEt 98:2). The title compound was obtained (375 mg, 88%) together with a mixture of the corresponding alkenes (14 mol % as judged by ^{1}H-NMR).

^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 7.40-7.28 (5H, m, Ar$\underline{H}$); 4.06 (1H, sextet, J= 6.5 Hz, C$\underline{H}$Cl); 2.99-2.77 (2H, m, PhC$\underline{H}_2$); 2.09 (2H, m, C$\underline{H}_2$-CH_2Cl); 1.60 (3H, d, J= 6.5 Hz, C$\underline{H}_3$).[152]

^{13}C-NMR (75.47 MHz; $CDCl_3$) δ_C: 141.0; 128.5; 128.4; 126.0; 57.9; 41.9; 32.8; 25.4.

4-Phenyl-2-bromobutane 5.59

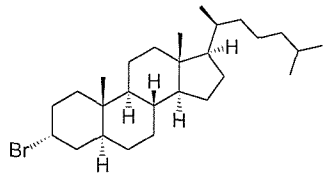


A solution of 4-phenyl-2-butanol (300 mg, 2.0 mmol), DIC (255 mg, 2.00 mmol) and $Cu(OTf)_2$ (39 mg, 0.1 mmol) in anhydrous THF (2 mL) was prepared in a microwave vial. The vial was then heated under microwave irradiation at 100 °C for 5 minutes. Acetyl bromide (0.225 mL, 3.0 mmol) was added, and the vial was again heated under microwave irradiation at 120 °C for 5 minutes. The solvent was removed under reduced pressure and the crude product purified by column chromatography (eluant hexane:AcOEt 98:2). The

title compound was obtained (405 mg, 95%) together with a small amount of alkene (<3 mol % as judged by ^{1}H-NMR).

^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 7.37-7.25 (5H, m, ArH); 4.12 (1H, m, CHBr); 2.96-2.74 (2H, m, $PhCH_2$); 2.14 (2H, m, CH_2-CH_2Br); 1.77 (3H, d, J= 6.5 Hz, CH_3).[176]
^{13}C-NMR (75.47 MHz; $CDCl_3$) δ_C: 140.8; 128.5; 128.4; 126.0; 50.9; 42.6; 33.9; 26.5.

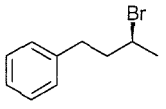
3-α-bromocholestane 5.60



A solution of 3-β-cholestanol (389 mg, 1.0 mmol), DIC (126 mg, 1.0 mmol) and $Cu(OTf)_2$ (20 mg, 0.05 mmol) in anhydrous THF (2 mL) was prepared in a microwave vial. The solution was stirred overnight at room temperature. Acetyl bromide (0.113 mL, 1.5 mmol) was added, and the vial was again heated under microwave irradiation at 150 °C for 5 minutes. The solvent was removed under reduced pressure and the crude product purified by column chromatography (eluant hexane:AcOEt 98:2). The product obtained (414 mg) was analysed by ^{1}H-NMR and found to be composed of 3-α-bromocholestane (80% yield) and a mixture of regioiomeric alkenes (14% yield).

^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 4.70 (1H, m, CHBr), 2.07-0.67 (44H, m).[177]
^{13}C-NMR (100 MHz; $CDCl_3$) δ_C: 56.5; 56.3; 56.1; 53.9; 42.6; 40.2; 40.1; 39.6; 37.4; 36.3; 36.2; 35.9; 35.6; 33.0; 31.9; 31.1; 28.3; 28.1; 28.0; 24.2; 23.9; 22.9; 22.6; 20.9; 18.7; 12.4; 12.1.

(*S*)-4-phenyl-2-bromobutane 5.59

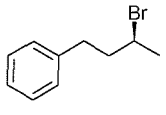


A solution of (*R*)-4-phenyl-2-butanol (300 mg, 2.0 mmol), DIC (255 mg, 2.00 mmol) and $Cu(OTf)_2$ (36 mg, 0.1 mmol) in anhydrous THF (2 mL) was prepared in a microwave vial. The vial was then heated under microwave irradiation at 100 °C for 5 minutes. Acetyl bromide (0.225 mL, 3.0 mmol) was added, and the vial was again heated under microwave irradiation at 120 °C for 5 minutes. The solvent was removed under reduced pressure and the crude product purified by column chromatography (eluant hexane:AcOEt 98:2). The title compound was obtained (375 mg, 88%) together with a small amount of alkene (<3 mol % as judged by ^{1}H-NMR).

The compound exhibited ^{1}H and ^{13}C-NMR spectra identical to those described previously.

$[\alpha]_D$= +66.2° ($CHCl_3$, c=0.85)

Synthesis of (*S*)-4-phenyl-2-bromobutane using Ph_3P-CBr_4

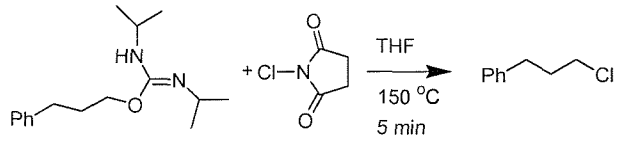


To an ice-cold solution of (*R*)-4-phenyl-2-butanol (150 mg, 1.0 mmol) and triphenylphosphine (236 mg, 0.9 mmol) in anhydrous DCM (10 mL) was added CBr_4 (300 mg, 0.9 mmol). Stirring was continued for 3 hours at room temperature. The reaction mixture was concentrated under vacuum and the desired product isolated by column chromatography (eluand hexane : ethyl acetate 98:2). Obtained 162 mg (76%).

The compound exhibited ^{1}H and ^{13}C-NMR spectra identical to those described previously.

$[\alpha]_D$= +64.7° ($CHCl_3$, c=0.80)

Reaction of *N,N'*-diisopropyl-*O*-(3-phenylpropyl)isourea with *N*-chlorosuccinimide

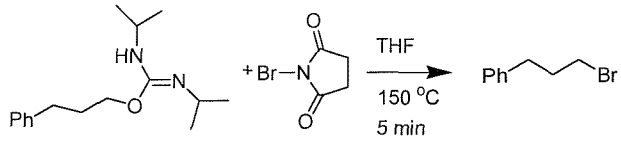


19 28a-c 21a-c

A solution of *N,N'*-diisopropyl-*O*-(3-phenylpropyl)isourea (0.262 g, 1.00 mmol) and *N*-chlorosuccinimide (0.133 g, 1.00 mmol) in anhydrous THF (2 mL) were prepared in a microwave vial. The vial was heated under microwave irradiation at 150 °C for 5 minutes. The solvent was removed under reduced pressure and the crude product purified by column chromatography (eluant hexane:AcOEt 98:2), giving 3-phenyl-1-chloropropane as a colourless oil (54 mg, 35%).

The compound exhibited ^{1}H and ^{13}C-NMR spectra identical to those described previously.

Reaction of *N,N'*-diisopropyl-*O*-(3-phenylpropyl)isourea with *N*-bromosuccinimide

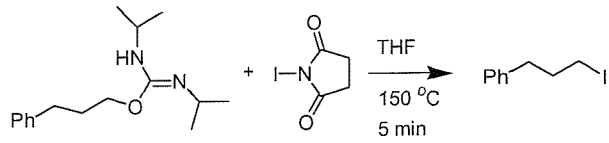


19 28a-c 21a-c

A solution of *N,N'*-diisopropyl-*O*-(3-phenylpropyl)isourea (0.262 g, 1.00 mmol) and *N*-bromosuccinimide (0.178 g, 1.0 mmol) in anhydrous THF (2 mL) were prepared in a microwave vial. The vial was heated under microwave irradiation at 150 °C for 5 minutes. The solvent was removed under reduced pressure and the crude product purified by column chromatography (eluant hexane:AcOEt 98:2), giving 3-phenyl-1-bromopropane as a colourless oil (169 mg, 85%).

The compound exhibited ^{1}H and ^{13}C-NMR spectra identical to those described previously.

Reaction of *N,N'*-diisopropyl-*O*-(3-phenylpropyl)isourea with *N*-iodosuccinimide



19 **28a-c** **21a-c**

A solution of *N,N'*-diisopropyl-*O*-(3-phenylpropyl)isourea (0.262 g, 1.00 mmol) and *N*-iodosuccinimide (0.450 g, 2.00 mmol) in anhydrous THF (2 mL) were prepared in a microwave vial. The vial was heated under microwave irradiation at 150 °C for 5 minutes. The solvent was removed under reduced pressure and the crude product purified by column chromatography (eluant hexane:AcOEt 98:2), giving 3-phenyl-1-iodopropane as a colourless oil (229.3 mg, 93%).

^{1}H-NMR (300 MHz; $CDCl_3$) δ_H: 7.26-7.10 (5H, m, Ar<u>H</u>), 3.09 (2H, t, J=6.5 Hz, C<u>H</u>$_2$I), 2.66 (2H, t, J=6.5 Hz, C<u>H</u>$_2$Ph), 2.01 (2H, q, J=6.5 Hz, $CH_2C\underline{H}_2CH_2$) ppm.[178]

^{13}C-NMR (75.47 MHz; $CDCl_3$) δ_C: 140.4, 128.6, 128.5, 126.2, 36.2, 34.9, 6.5 ppm.

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