Microwave-Assisted Alkylation Reactions
Employing $O$-alkylisoureas

by

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February 2009
A mia nonna Gisella
ABSTRACT

Doctor of Philosophy

Microwave-Assisted Alkylation Reactions employing O-alkylisoureas

by Alessandra Chighine

In recent years, the use of microwave irradiation to accelerate chemical reactions has become increasingly popular. A protocol for the synthesis of esters via reaction of carboxylic acids with O-alkylisoureas under microwave heating was studied. Efficient processes were developed using pre-formed O-alkylisoureas or via an in-situ isourea formation sequence starting from primary and secondary alcohols. It was demonstrated that under these microwave conditions ester formation with primary and secondary alcohols proceeded in good yields and, in the latter case, with clean inversion of configuration of the esters. O-alkylisoureas were used as reactive intermediate also in the alkylation of substituted phenols. A polymer-assisted solution phase procedure was also developed by employing pre-formed polymer-supported isoureas, and by an efficient "catch-and-release" esters formation procedure in which alcohols are caught on resin as isoureas by reaction with immobilised carbodiimide, and released as ester by subsequent treatment with a carboxylic acid. Polymer-supported isoureas were also employed in the synthesis of 2-oxazolines.
DECLARATION

I declare that:

- This thesis has been composed by myself

- The work presented in this thesis is my own

- No part of this thesis has been previously submitted at this or any other University for any other degree or professional qualification.

Signed:

Date:
PREFACE

The research described in this thesis was carried out under the supervisions of Prof. Mark Bradley and Dr. Bruno Linclau at the University of Southampton (Jan. 2004 – Jan. 2005) and at the University of Edinburgh (Feb. 2005 – Feb. 2007).

Part of the work is in the process of being published:

- "Microwave-assisted ester formation using O-alkylisoureas: a convenient method for the synthesis of esters with inversion of configuration"
  Chighine, A.; Crosignani, S.; Arnal, M-C.; Bradley, M.; Linclau, B. manuscript in preparation.
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ABBREVIATIONS

A  Arrhenius pre-exponential factor
Ac  acetyl
BEMP  2-tert-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorin
Bn  benzyl
Boc  tert-butyloxycarbonyl
BOP-CI  \(N, N'\)-bis(2-oxo-3-oxazolidinyl)-phosphonic chloride
br  broad
bz  benzoyl
Cbz  carboxybenzyl
cHex  cyclohexyl
d  doublet
Da  dalton
DAST  (diethylamino)sulfur trifluoride
DCC  \(N,N'\)-dicyclohexylcarbodiimide
DIC  \(N,N'\)-diisopropylcarbodiimide
DCE  dichloroethene
DCM  dichloromethane
DCU  dicyclohexylurea
de  diastereomeric excess
DIU  diisopropylurea
DEAD  diethylazodicarboxylate
DEPT  distortionless enhanced polarization transfer
DIAD  diisopropylazodicarboxylate
DIEA  \(N,N'\)-diisopropylethylmine
DMAP  4-dimethylaminopyridine
DMBQ  2,6-dimethyl-1,4-benzoquinone
DMF  \(N,N'\)-dimethylformamide
DMSO  dimethylsulfoxide
DNA  deoxyribonucleic acid
DPAT  diphenylammonium triflate
\(\varepsilon'\)  dielectric constant
\(\varepsilon''\)  loss factor
\(E_0\)  activation energy
ee    enantiomeric excess
EI    electron impact
ELSD  evaporative light scattering detector
equiv equivalents
ES    electrospray
FRET  fluorescence resonance energy transfer
FT-IR fourier transform infrared
GC-MS gas chromatography-mass spectrometry
GHz   gigahertz
Gly   glycine
h     hour
HATU  O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HBTU  O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HOBt  1-hydroxy-1H-benzotriazole
HPLC  high performance liquid chromatography
HR    high resolution
IIDQ  2-isobutoxy-1-isobutoxycarbonyl-1,2-dihydroquinoline
IR    infrared spectroscopy
J     coupling constant
k     rate constant
λ     wavelength (nm)
LCMS  liquid chromatography – mass spectrometry
m     multiplet (NMR) or medium (IR)
MAOS  microwave-assisted organic synthesis
m-CPBA 3-chloroperoxybenzoic acid
MHz   megahertz
min   minute
Mp    melting point
MS    mass spectrometry
MTPA  a-methoxy- a -trifluoromethylphenylacetic acid
μW    microwave irradiation
m/z   mass/charge ratio
ν     frequency (cm⁻¹)
NMR   nuclear magnetic resonance spectroscopy
nr    no reaction
p     para
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>PASP</td>
<td>polymer-assisted solution phase synthesis</td>
</tr>
<tr>
<td>PEG</td>
<td>polyethylene glycol</td>
</tr>
<tr>
<td>PFPAT</td>
<td>pentafluorophenylammonium triflate</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>Phe</td>
<td>phenylalanine</td>
</tr>
<tr>
<td>PivCl</td>
<td>trimethylacetyl chloride</td>
</tr>
<tr>
<td>PS</td>
<td>polystyrene</td>
</tr>
<tr>
<td>PyBOP</td>
<td>benzotriazol-1-yl oxytri(pyrrolidino) phosphonium hexafluorophosphate</td>
</tr>
<tr>
<td>q</td>
<td>quartet</td>
</tr>
<tr>
<td>R</td>
<td>gas constant</td>
</tr>
<tr>
<td>ROMP</td>
<td>ring opening polymerization</td>
</tr>
<tr>
<td>RT</td>
<td>room temperature</td>
</tr>
<tr>
<td>s</td>
<td>singlet (NMR) or strong (IR)</td>
</tr>
<tr>
<td>SPOS</td>
<td>solid phase organic synthesis</td>
</tr>
<tr>
<td>SPE</td>
<td>solid phase extractor</td>
</tr>
<tr>
<td>t</td>
<td>triplet</td>
</tr>
<tr>
<td>T</td>
<td>temperature</td>
</tr>
<tr>
<td>TAI</td>
<td>trichloroacetylisocyanate</td>
</tr>
<tr>
<td>tanδ</td>
<td>loss tangent</td>
</tr>
<tr>
<td>tert</td>
<td>tertiary</td>
</tr>
<tr>
<td>TEA</td>
<td>triethylamine</td>
</tr>
<tr>
<td>TEMPO</td>
<td>2,2,6,6-tetramethylpiperidine-1-oxyl</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMAD</td>
<td>N,N,N',N'-tetramethylazodicarboxamide</td>
</tr>
<tr>
<td>TMEDA</td>
<td>N,N,N',N'-tetramethylethylenediamine</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>TPP</td>
<td>triphenylphosphine</td>
</tr>
<tr>
<td>TPPO</td>
<td>triphenylphosphinoxide</td>
</tr>
<tr>
<td>tR</td>
<td>retention time</td>
</tr>
<tr>
<td>TS</td>
<td>transition state</td>
</tr>
<tr>
<td>Ts</td>
<td>triazene</td>
</tr>
<tr>
<td>UV/VIS</td>
<td>ultraviolet/visible spectroscopy</td>
</tr>
<tr>
<td>Val</td>
<td>valine</td>
</tr>
<tr>
<td>w</td>
<td>weak</td>
</tr>
</tbody>
</table>
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1. Introduction

1.1 Polymer-assisted solution-phase synthesis

1.1.1 General overview

Since the first report by Merrifield\(^1\) in 1963, solid-phase organic synthesis (SPOS), has shown its tremendous power in enabling the rapid synthesis of a variety of oligomers (i.e. peptides, DNA and carbohydrates\(^2\)). In contrast with the time-consuming methods of traditional synthetic chemistry, Merrifield's revolutionary method offered the first insights into high-throughput synthesis by the transformation of a laborious solution approach to a solid-phase variant that took hours rather than weeks. With the advent of combinatorial chemistry\(^3\)\(^-\)\(^10\) in the late 1980's, solid phase organic synthesis has subsequently been employed for parallel synthesis of drug-like compound libraries with high diversity. The key to this approach is the attachment of a substrate onto an insoluble support, with reaction workup drastically simplified to a simple filtration. At the end of the process the product can be cleaved from the solid support and subsequently isolated in high purity (Scheme 1.1).

![Scheme 1.1 General scheme for solid phase methodology](image)

Since the first small-molecule combinatorial library based on a known drug scaffold was synthesised in the early 1990's,\(^11\) thousands of unique libraries have been produced by SPOS. However, this approach also has significant disadvantages, such as difficult reaction monitoring and the fact that unreacted substrates or side-products will all be linked onto the insoluble support. Polymer-assisted solution phase chemistry (PASP)\(^12\)\(^-\)\(^15\) has been developed to overcome and help to solve these issues.
In polymer assisted solution phase synthesis, reagents are attached to an insoluble polymer support, while substrates and products remain in solution (Scheme 1.2). Typically attachment has been achieved by either covalent or ionic interactions.

As in SPOS, reaction workup consists of a simple filtration, but the desired product is now sited in the filtrate. This methodology thus combines the main advantages of traditional solution phase chemistry (e.g. reaction monitoring using conventional analytical methods) with those of solid-supported chemistry (e.g. ease of workup, the use of reagent excesses to drive the reactions to completion and time efficiency because the process can be easily automated). Several polymer supported reagents and catalysts have been developed over the years and used in parallel synthesis. Thus for example, Bradley\textsuperscript{16} reported the synthesis and application of polymer-supported 2-isobutoxy-1-isobutoxycarbonyl-1,2-dihydroquinoline (PS-IIDQ) as a coupling reagent that did not require pre-activation. PS-IIDQ was more efficient for general amide bond-formation than many classic agents (HATU; BOP-Cl; PyBOP), while the supported reagent could be readily regenerated, yielding recycled polymer-supported IIDQ with a coupling efficiency similar to the original material (Scheme 1.3).
Recently other materials than functionalised cross-linked polystyrenes have also been proposed. For example Poly-N-Trz-MM, a polymeric dehydrocondensing reagent comprising of an activated triazine possessing a high dehydrocondensing activity loading capacity (ca. 3 mequiv/g), allowed the condensation by a simple mixing a carboxylic acid and an amine with the polymer in solvent such as water or alcohol (Scheme 1.4).

![Scheme 1.4 Condensation of carboxylic acids with amines by Poly-N-Trz-MM](image)

1.1. 2 Polymer-assisted purification

The removal of excess reagents or side products is a critical step in every chemical transformation. For compounds synthesised conventionally, reagent removal generally consists of an organic/aqueous extraction procedure and chromatographic purification. An alternative possibility is to use polymer-assisted purification protocols, three related variants have been reported:

- Solid-supported scavengers
• Sequestration enabling reagents

• "Catch and release" procedures

Scavengers were introduced in the modern era in 1997, and are called as such because they are functionalised resins able to remove excess starting materials, or side-products by ionic (basic or acidic) or by covalent (nucleophilic or electrophilic) interaction (Scheme 1.5).

![Scheme 1.5 General scheme for scavenging](image)

A wide range of scavenger reagents has become available and successfully employed in multistep and automated synthesis (Table 1.1).

<table>
<thead>
<tr>
<th>Acidic</th>
<th>Basic</th>
<th>Electrophilic</th>
<th>Nucleophilic</th>
</tr>
</thead>
<tbody>
<tr>
<td>COOH</td>
<td>N</td>
<td>S-Cl</td>
<td>SH</td>
</tr>
<tr>
<td>SO$_3$H</td>
<td>O</td>
<td>O</td>
<td>N$_2$NH$_2$</td>
</tr>
</tbody>
</table>

Cationic and anionic exchange resins are widely used in industry to achieve separations. Purification is readily automated with conventional liquid handling systems for high-throughput purification.
Chapter 1. Introduction

For example the sulfonic acid form of an ion exchange resin has been employed for the parallel purification of a library of amide analogues, with more than 225 analogues were prepared in high yields and purities (Scheme 1.6).

Scheme 1.6 Libraries of amides purified utilising product scavenging-release method

In some cases it is difficult to remove the by-product or the excess of reagent since a suitable scavenger does not exist or the by-products is not reactive enough to be scavenged. In this case sequestration enabling reagents can be used to convert the less-reactive functional group into an easily scavenged species (Scheme 1.7).

Scheme 1.7 General scheme for scavenging method using sequestration enabling reagents

Dondoni described the synthesis of oligosaccharides by using trichloroacetylisocyanate (TAI) as sequestration enabling reagents of sugar alcohols (Scheme 1.8). In the first step an excess of primary alcohol (acceptor) was used followed by derivatisation with TAI and sequestration of the trichloroacylated urethane with PS-BEMP to afford the disaccharide in quantitative yield and in 95% purity.
Finally, a technique called "catch-and-release," described by Siegel\textsuperscript{22} in 1997 has been utilised as an efficient purification tool.\textsuperscript{23} The approach is a hybrid between scavenging and solid-phase synthesis. Substrate A is captured onto a resin by reaction with an immobilised reagent with the resulting immobilised intermediate/product subsequently, after resin wash, released from the resin by a second reaction (Scheme 1.9).

\textbf{Scheme 1. 8} Application of sequestration enabling reagents in the synthesis of oligosaccharides

An example is the synthesis of 2-aminobenzoxazoles.\textsuperscript{24} The aminophenol was attached onto the Merrifield resin with CS\textsubscript{2} in the presence of DIC in CH\textsubscript{3}CN. Oxidation of the resulting resin followed by treatment with amines gave rise to the desired 2-aminobenzoxazoles in solution. These release conditions reactions generally proceeded...
to give the product in high yield and excellent purity without need for further purification steps (Scheme 1.10).

![Scheme 1.10 Application of "catch-and-release" strategies to the synthesis of 2-aminobenzoxazoles](image)

### 1.1.3 Multistep Synthesis

Polymer supported scavenger reagents and catalysts have been applied successfully for the multistep solution phase synthesis of drug-like molecules. Every synthetic step can be accomplished using different supported reagents and scavengers for the purification protocol. A simple example to illustrate the power of polymer-assisted multistep synthesis is seen in a preparation of 3,4-dihydropyrimidin-2-(1H)-ones. The synthesis was carried out using a solid supported ytterbium (III) catalyst and each member of the library was purified using a sequence of basic and acidic polymer-supported scavengers. (Scheme 1.11).

![Scheme 1.11 Parallel synthesis of dihydropyrimidinones](image)

Two or more polymeric reagents can also be used at the same time because the majority
of the reactive groups do not come into contact.\textsuperscript{26} A synthesis shown in Scheme 1.12 was performed using three different polymeric reagents simultaneously.\textsuperscript{27} The combination of a supported free radical (PS-TEMPO), resin bound chlorite and immobilised hydrogen phosphate led to the desired acids as a pure products with no need for further purification.

\begin{center}
\includegraphics[width=\textwidth]{Scheme1.12.png}
\end{center}

\textbf{Scheme 1.12} Simultaneous multistep synthesis of carboxylic acids

Polymer-supported reagents have also been used in the synthesis of more complex targets like natural products.\textsuperscript{28} Recently Ley\textsuperscript{29} described the synthesis of a new bis-nitrogen containing family of alkaloids. The application of polymer-supported reagents avoided the time consuming chromatographic purification leading to the final alkaloid (-)-oblique identical to the reported authentic material (Scheme 1.13).

\begin{center}
\includegraphics[width=\textwidth]{Scheme1.13.png}
\end{center}

\textbf{Scheme 1.13} Synthesis scheme for the preparation of (-)-oblique
1.2 Microwave-assisted organic synthesis

1.2.1 Theory of microwave heating

In the electromagnetic spectrum, the microwave region is located between infrared radiation and radio frequencies, with wavelengths ranging from 1 cm to 1 m, corresponding to 30 GHz - 300 MHz (Figure 1.1). An international convention dictates that industrial and domestic microwave ovens operate at 2.45 GHz to avoid interference with radar or other telecommunications devices. At this wavelength, oscillations occur $4.9 \times 10^9$ times per second.

The electric component of microwave electromagnetic field generates heat by two mechanisms: dipolar polarisation and ionic conduction. When a molecule possessing a dipole moment is irradiated with an electromagnetic field it will tend to rotate and align to the applied electric field. As the applied field oscillates the dipole tends to orient itself according to the direction of the electric field. The heating mechanism is illustrated for H$_2$O in Figure 1.2a. The changing electric field of the microwave radiation leads to a rotation of the water molecule. The frequency of 2.45 GHz ($\lambda = 12.24$ cm) gives the water molecule time to partially align to the field but not enough to follow the alternating field precisely. The phase difference between the field and the molecule causes energy to be lost in the form of heat through "internal molecular friction" and dielectric loss. The second mechanism, ionic conduction, is correlated to the presence
of ions in solution. The ions can couple with the oscillating field, and their movement through the solution again causes heat by frictional losses. The heat generated is related to the size charge and conductivity of the ions (Figure 1.2 b).

![Diagram of microwave heating mechanisms](image)

**Figure 1.2** Dipolar mechanism (a) and ionic mechanism (b) involved in microwave heating

The coupling of the microwave heating and the substance irradiated is correlated with two properties: (1) the dielectric properties that represent the efficiency with which the substance adsorbs and store the microwave energy $\varepsilon'$ and (2) the efficiency of with the absorbed energy is converted into heat, called dielectric loss $\varepsilon''$. For example if two solvents such as acetone and ethanol, that have comparable dielectric constants, are heated under microwave irradiation, the temperature reached for the same energy is much higher for the ethanol than acetone because of the difference in the loss factor $\varepsilon''$ (Figure 1.3).

![Temperature profile graph](image)

**Figure 1.3** Difference in temperature profiles for a sample of ethanol and acetone heated under microwave irradiation (adapted from ref. 32)
In order to compare directly two solvents with similar dielectric constants their capabilities to absorb microwave heating must be considered. Equation (1) is usually used to calculate the ability of different materials to convert microwave energy into thermal energy.\(^{33}\)

\[
(1) \quad \tan \delta = -\frac{\varepsilon''}{\varepsilon'}
\]

**Table 1.2 Loss factors for solvents commonly used in organic synthesis\(^3\)**

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Tan(\delta)</th>
<th>Solvent</th>
<th>Tan(\delta)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol</td>
<td>0.941</td>
<td>Water</td>
<td>0.123</td>
</tr>
<tr>
<td>DMF</td>
<td>0.161</td>
<td>THF</td>
<td>0.047</td>
</tr>
<tr>
<td>CH(_3)CN</td>
<td>0.062</td>
<td>Toluene</td>
<td>0.040</td>
</tr>
</tbody>
</table>

\(^a\) 2.45 GHz, 20 °C

When the dielectric properties of the solvent are too poor to absorb microwaves, the addition of small quantities of an additive (e.g. an ionic liquid) can be considered. One of the most important aspects of microwave energy is the rate at which it heats (Figure 1.4). Considering Arrhenius law (\(K = A e^{-\frac{E_a}{RT}}\)) the reaction rate constant is dependent on two factors: the pre-exponential factor \(A\) that is related to the steric factor and the collisional frequency, and a second factor correlated to the fraction of these molecules with the minimum energy required to overcome the activation energy barrier (\(e^{-\frac{E_a}{RT}}\)). Microwave energy affects mainly the temperature parameter in this equation; an increase of temperature is directly correlated to an increase in the number of collisions. Many of the rate enhancements observed using microwave heating can be explained by a simple thermal effect such as the superheating effect of solvents. This phenomenon results in the boiling points being raised up above the conventional values. However there are some debates regarding the possibility of "non thermal microwave effects" also
called non-thermal effects.\textsuperscript{36} It has been argued that microwave heating can interact with specific molecules and changes the pre-exponential factor $A$, or the activation energy $E_a$ by polar reaction mechanisms, where the polarity is increased going from the ground state to the transition state. In contrast to traditional heating where the energy is transferred by conduction/convection, microwaves generate heat from within the sample (in-core volumetric heating) by direct coupling with the molecules present in the vessel. In this way the heat exchange is rapid and uniform. Figure 1.4 shows the difference between the two methods: (a) after 1 min of microwave irradiation and (b) treatment in an oil bath. In the case of microwave heating it’s clear from the temperature profile that the internal heat is efficiently transferred with minimised wall effects (no hot vessel surface).

![Figure 1.4 Comparison between microwave and conventional heating (adapted from Biotage AB (formally Personal Chemistry AB), www.biotage.com)](image)

The use of microwave radiation as an alternative method of heating is over five decades old. In 1946, the engineer Dr. Spencer, who worked for the Raytheon Corporation, was working on magnetrons. On one occasion, Spencer noticed that a chocolate bar in his pocket began to melt when working on a magnetron, the power that
drives a radar set. He realised that the microwaves he was working with had caused it to melt. After experimenting, he realised that microwaves would cook foods quickly even faster than conventional ovens. In 1954 the Raytheon Corporation produced the first commercial microwave oven and since then the development has been gradual. In the mid-1980's it was introduced in the chemical industry for extraction and digestion of chemicals. In 1986, two groups Gedye\textsuperscript{37} and Giguere/Majetich\textsuperscript{38} reported the first use of microwave heating in organic synthesis. In the initial years, many researchers were using kitchen-type domestic ovens, but in 2000, the first custom-built commercial chemical synthesis microwave ovens were built and since then the trend is to use dedicated instruments for synthesis. The microwave instruments are now equipped with fibre-optic probes or infrared sensors for on-line temperature and pressure control. Currently there are two types of microwave reactor design: multimode and monomode (also known as single-mode). The multimode system is similar to a domestic oven: the microwaves produced by the magnetron are directed through a waveguide in a large volume (40-50 litres) and are reflected by the walls, before interacting with the sample in a chaotic manner. For this reason the heating efficiency can vary at different positions within such a cavity (Figure 1.5 a).

![Multimode microwave reactor (a), single-mode microwave reactor (b)](image_url)

**Figure 1.5** Multimode microwave reactor (a), single-mode microwave reactor (b)

In the monomode system (Figure 1.5 b) the cavity is much smaller and the microwaves are directed by an accurate wave guide into the reaction vessel, mounted a fixed distance
from the radiation source, thus creating a standing wave. This system precludes the formation of "hot and cold spots" within the sample resulting in uniform heating patterns. This is really important when microwave heating is used in organic chemistry because a controlled and uniform heating pattern allows high reproducibility, predictability of results and optimisation of yield. One of the limitations of single-mode heating is that only one vessel can be irradiated at a time. However the system can be coupled with auto-samplers and fully automated, single mode instruments are currently used for small-scale synthesis and parallel applications.

1.2. 2 Organic reactions under microwave heating

Microwave-assisted organic chemistry\textsuperscript{39-42} is in principle applicable to all chemical transformations requiring heat. Whereas in the past microwave heating was applied only for a slow or difficult reaction step in synthesis, today the number of examples in which microwave heating is used in most or in all steps of the synthesis is rapidly growing.\textsuperscript{43} Nicolaou,\textsuperscript{44} for example, reported the total synthesis of artomachin J applying microwave heating for the key reaction step. After synthesising stilbene, the artomachin skeleton was obtained via a cascade sequence that required catalytic amounts of Ph\textsubscript{3}PO under microwave heating (Scheme 1.14).

\begin{center}
\textbf{Scheme 1. 14 Total synthesis of artomachin J using microwave heating}
\end{center}
1.3 Enabling techniques

Kirshning\textsuperscript{45,46} defined enabling techniques as:

"..various traditional techniques as well as new techniques which have been developed to speed up synthetic transformations and importantly ease workup as well as isolation of products."

Enabling techniques (solid-phase assisted synthesis, new reactor design, microwave irradiation, new solvents, continuous flow technique) have been employed in organic chemistry for many years. The combination of several of them to create new synthetic technology platforms have emerged in the past decade. In particular the combination of microwave heating and polymer supported reagents have gained interest and also immobilised catalysts/biocatalysts with continuous flow processes has attracted researchers from academia and industry.

1.3.1 The use of solid-support chemistry combined with microwave-heating

The advantage of microwave technology in terms of heating can be applied to high-throughput techniques, such as solid-phase synthesis and polymer-assisted solution-phase synthesis. The combination of solid phase organic synthesis and microwave technology has emerged as a powerful tool in recent years. Peptides have been synthesised almost exclusively on solid supports at room temperature, although there are now few reports regarding the advantages of solid-phase peptide synthesis using microwave irradiation.\textsuperscript{47,48} Bradley\textsuperscript{49} recently described the synthesis of fluorescence resonance energy transfer (FRET)-peptides and FRET-peptoids using DIC/HOBt as the coupling reagents under microwave irradiation; the method labels peptides with a variety of fluorophores and quenchers in high yields and with purities >90% (Scheme 1.15).
Chapter 1. Introduction

The combination of microwave chemistry and polymer-assisted solution-phase synthesis has also attracted much interest and been used in many chemistry transformations. Wang\textsuperscript{50} described the synthesis of 1,3,4-oxadiazoles using two different solid-supported reagents, PS-BEMP and PS-PPh\textsubscript{3}, to give the desired cyclised products with >98% purity following a simple filtration to remove the solid-supported reagents (Scheme 1.16).

Scheme 1.15 SPOS of FRET-peptides using microwave heating

Scheme 1.16 Microwave assisted synthesis of 1,3,4-oxadiazoles using PS-BEMP and polymer supported triphenylphosphine
Polymer-supported scavengers were successfully used under microwave heating,\textsuperscript{51,52} most scavenging protocols in fact require long reaction times due to the nature of the heterogeneous reaction conditions. Microwave heating helped to overcome this drawback. For example a polymer-supported anthracene\textsuperscript{53} was employed to scavenge dienophiles in a Diels-Alder cycloaddition in the preparation of natural product-like compounds. In this case only ten minutes were necessary to purify the final product from the dienophile (Scheme 1.17).

\begin{center}
\textbf{Scheme 1. 17 Dienophile scavenging using polymer-bound anthracene under microwave heating}
\end{center}
Chapter 2. *O*-Alkylisourea mediated alkylation of primary alcohols

2. *O*-Alkylisourea mediated alkylation of primary alcohols

2. 1 Introduction and project aims

2.1. 1 Esterification methods

The formation of esters from carboxylic acids and alcohols is a fundamental reaction in synthetic organic chemistry and a wide variety of methods for the preparation of carboxylic esters have been developed over the years. In the presence of protic acids or Lewis acids, esterification is generally carried out (a) using one of the two components, the carboxylic acid or the alcohol, in large excess or (b) by the azeotropic removal of water in order to shift the equilibrium in favour of the ester. However, mild and high-yielding procedures for the formation of carboxylic acid esters are desirable and necessary for highly functionalised and sensitive compounds. In the field of peptide synthesis, for example, the nature of the *N*-terminus and side-chain protecting groups precludes the use of many normal esterification procedures. With other complex organic compounds, degradation and side reactions may reduce the yield and purity of the desired esters. Some procedures have inherently undesirable characteristics such as forming difficult-to-remove impurities (e.g., the *N*-acylureas formed in the carbodiimide method), the danger of explosion (diazomethane) or the high toxicity of some alkylating reagents (methyl iodide or dimethyl sulfate). The preparation of esters from equimolar amounts of carboxylic acids, alcohols and DCC has been developed, though a catalyst such as DMAP or HOBt are usually necessary. However, to promote atom efficiency and to improve environmental compatibility, the use of large amounts of condensing reagents or excesses of substrates should be avoided. Over the past few years, there has been a growing interest in developing new methods for esterification reactions using stoichiometric amounts of coupling reagents that activate carboxylic acids. This approach has been employed for the protection of hydroxyl and carboxylic group but also in the synthesis of natural products.
Nevertheless, the catalytic condensation between equimolar amounts of carboxylic acids and alcohols remains the most ideal green-method for the synthesis of esters. Many methods have been proposed over the last years, for example Yamamoto proposed the use of Hf (IV) or Zr (IV) salts. These catalysts were suitable for condensing various carboxylic acids with primary and secondary alcohols in very short times and in good yields. Other catalysts like water-tolerant Zn(ClO$_4$)$_2$·6H$_2$O or a combination of Zr (IV) and Fe (III) were also explored as an alternative to the common catalysts employed in the synthesis of esters. Recently, metal-free catalysts have been proposed for esters formation to avoid contamination of the final product with metals. Diphenylammonium triflate (DPAT) and also pentafluorophenylammonium triflate (PFPAT) have been employed as new organo-catalysts that are air-stable and easily removed from the reaction mixtures. In addition these types of catalysts did not necessitate the use of a dehydration reagent and/or a technique for azeotropic water removal (Scheme 2.1).

![Scheme 2.1 Esterification between a 1:1 mixture of carboxylic acids and alcohols using PFPAT catalyst](image)

All the above methods, including the use of mineral acid, suffer from the drawback of a long reaction time. The esterification reaction is equilibrium-limited and for this reason usually takes up to several hours for completion. Microwave heating has been used as an alternative source of heating to accelerate and improve the process. Acid, base, and enzyme catalysed esterifications have been reported during the years including various scale-up systems capable of processing hundreds of grams of material under microwave conditions. However only a few papers documented the use of equimolar
Chapter 2. O-Alkylisourea mediated alkylation of primary alcohols

coupling reagent/alcohol/acid combinations with the use of microwave irradiation. Baldwin, \( ^{89} \) for example, reported a microwave synthesis of esters using an equimolar amount of anhydrides \( 2.6 \) and alcohols in the presence of imidazole \( 2.7 \) as a promoting agent for the reaction. With this technique it was possible to prepare esters from primary, secondary and phenolic groups (Scheme 2.2).

\[
\begin{align*}
R' &= 1^\circ, 2^\circ, \text{Ph} \\
R' &= \text{alkyl, aromatic} \\
R'' &= \text{alkyl, aryl} \\
R'' &= \text{alkyl}
\end{align*}
\]

**Scheme 2.2** Synthesis of esters with imidazole catalysis under microwave heating

Esters were produced in good yield and in very short time, moreover the promotion agent used, imidazole, is also lower in toxicity than some esterification catalyst such as 4-dimethylaminopyridine (DMAP). The side-products (imidazole and a carboxylic acid) are relatively benign in contrast to esterification with carboxylic acid chlorides, which produce HCl. Of course this method is less valuable with an expensive or difficult-to-make \( R' \) group.

### 2.1.2 Synthesis and properties of O-alkylisoureas

A low-toxicity alternative to the methods described previously is the use of O-alkylisoureas, \( ^{61} \) which have already been known for 50 years as suitable alkylating agents (Figure 2.1). \( ^{62} \)

**Figure 2.1** Structure of \( N,N' \)-substituted O-alkylisoureas
Chapter 2. O-Alkylisourea mediated alkylation of primary alcohols

O-Alkylisoureas are usually prepared by reaction of a carbodiimide with an alcohol. Because of the weakly nucleophilic properties of alcohols the reaction is usually catalysed by a copper–based Lewis-acid, typically CuCl or CuCl₂ (Scheme 2.3).⁶³,⁶⁴

![Scheme 2.3 Synthesis of O-alkylisoureas from carbodiimides](image)

The catalytic action of metal ions apparently occurs by formation of a coordination complex between the carbodiimide and the metal ion. The formation of the complex leads to an increase in the electrophilicity of the central carbon atom of the carbodiimide (Scheme 2.4).

![Scheme 2.4 Mechanism of copper-catalysed synthesis of O-alkylisoureas](image)

In Scheme 2.5, the conventional application (path a) of carbodiimides in ester formation is contrasted with the isourea procedure (path b). In both procedures, the reactive carbodiimide is eventually converted to the stable and generally insoluble urea derivative 2.14. In the standard method O-acylisourea 2.12 is formed as an intermediate in the reaction. Rearrangement of this species to the N-acylisourea 2.13 usually occurs as a side-reaction, which decreases the overall yield and, more importantly, produces a side-product which can be difficult to remove from the desired material. Thus, the need for careful temperature control, somewhat limits the application of the normal
method. Furthermore, rigorous exclusion of water is necessary to prevent hydrolysis of the intermediate 2.12.

Scheme 2.5 Carboxylic esters formation using carbodiimides method (a) and by isourea method (b)

In the O-alkylisourea procedure (path b), the carbodiimide first reacts with the alcohol to form the O-alkylisourea 2.9, which subsequently reacts with the carboxylic acid (Scheme 2.5). The initial step involves simple protonation of the basic O-alkylisourea by the carboxylic acid, which is followed by nucleophilic attack of the carboxylate anion on the α carbon to the oxygen of the O-alkylisourea (Scheme 2.6).

Scheme 2.6 Mechanism of the reaction of O-alkylisoureas with carboxylic acids
Chapter 2. O-Alkylisourea mediated alkylation of primary alcohols

O-Alkylisoureas may be purified prior to use and, more importantly, can be stored for several months. Moisture causes gradual hydrolysis to the alcohol and the urea, although for ester alkylation reactions, complete drying of solvents is not necessary for high yields. Another advantage, compared to other alkylating agents, is that they have low toxicity and reduced associated hazards. For these reasons over the years, the use of O-alkylisoureas in ester formation reactions has found widely application, especially for the introduction of protecting groups for carboxylic acids, but also for O-alkylation and synthesis of alkyl halides (Table 2.1). Various isoureas have been used for this purpose such as O-methyl, benzyl, alyl, p-methoxybenzyl, tert-butyl and diphenylmethyl isoureas, which have all been prepared via copper catalysis from the corresponding alcohols and a carbodiimides.

Table 2.1 Substrates transformations using O-alkyl-isoureas

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>R&quot;-O-H</td>
<td>R&quot;-O-R&quot;</td>
<td>90</td>
</tr>
<tr>
<td>Ph-OH</td>
<td>Ph-OR</td>
<td>91</td>
</tr>
<tr>
<td>Ph-SH</td>
<td>Ph-SR</td>
<td>92</td>
</tr>
<tr>
<td>HO &gt; HO</td>
<td>C&gt;</td>
<td>93</td>
</tr>
<tr>
<td>HCl</td>
<td>R'Cl</td>
<td>94</td>
</tr>
</tbody>
</table>

The use of O-alkylisoureas has been reported in total synthesis. For example, in the synthesis of a chiral precursor for the preparation of (+)-zaragozic acid C, 95-98 N,N'-diisopropyl-O-tert-butyliourea was employed to obtain the triester after reaction of the tetraol with Swern and Pinnick reagents (Scheme 2.7). 99
Chapter 2. O-Alkylisourea mediated alkylation of primary alcohols

Scheme 2. 7 O-tert-buty1 isourea in synthesis of (+)-zaragozic acid C

Amines can be alkylated,\(^{93,100}\) for example \(O\-methylisourea\) has been used for the alkylation of an aminoacid\(^{101}\) (Scheme 2.8). Unfortunately a partial alkylation is not possible and the reaction always proceeds to the betaines. In water and methanol only \(N\)-alkylation was observed, however if the reaction is carried out in absence of solvent or in \(\text{CH}_3\text{CN/THF}\) ester formation is also observed.

Scheme 2. 8 \(N\)-alkylation of an aminoacid using \(O\-methylisourea\)

2.1. 3 Novel applications for \(O\-alkylisoureas\)

There are very few examples of \(O\-alkylisoureas\) being used in cyclisation reactions.\(^{102,103}\) Recently Linclau\(^{104}\) reported that heating isoureas derived from \(\beta\)-hydroxyamides leads to the corresponding 2-oxazolines in good yields. In this case aminoalcohols reacted with 1 equiv of diisopropylcarbodiimide (DIC) with copper catalysis. Without removing the copper salt, the isourea intermediate was heated under
microwave irradiation. Purification by filtration of DIU followed by column chromatography gave 4,4-dimethyl-2-phenyl-2-oxazoline in 74% yield (Scheme 2.9).

Scheme 2.9 Formation of 2-oxazolines by cyclisation of isourea intermediate

In 2004, Link\textsuperscript{105} used the O-alkylisoureas as alkylating reagents for the activation of the N-acyl-sulfonamide linker.\textsuperscript{106} The reaction with O-alkylisourea lead to alkyl substituted N-acyl-sulfonamides in an easier and cheaper protocol compared to the existing methods (Scheme 2.10).

Scheme 2.10 O-alkylisoureas as alkylating agents for N-acylsulfonamides synthesis
Pentafluorobenzyl alcohol and 4-nitrobenzyl alcohols were used to synthesise the isoureas,\textsuperscript{107} and subsequently these pre-formed $O$-alkylisoureas were reacted with polymer-bound 4-phenoxybutyric acid, attached via the Kenner linker.

### 2.2 Project aims

The use of soluble $O$-alkylisoureas and polymer-supported isoureas derived from methanol and benzylic alcohols has been established in the literature precedent\textsuperscript{108} as a mild protocol for the protection of acids. The first aim of the project was to prepare a library of new $O$-alkylisoureas from more complex primary and secondary alcohols. It is known that the synthesis of $O$-alkylisoureas can be accelerated using conventional heating. Badache\textsuperscript{109} described a series of $O$-alkylisoureas prepared from DCC and DIC using conventional heating and demonstrated that the reaction was complete after a few hours. The effect of microwave irradiation as an alternative heating source was investigated. Microwave heating would allow the $O$-alkylisoureas synthesis to be carried out in minutes instead several hours. Once that a microwave-assisted synthesis of $O$-alkylisoureas have been explored, these new soluble $O$-alkylisoureas will be used for the direct esterification of carboxylic acids under microwave irradiation in a one-pot method without isolation of the $O$-alkylisoureas (Scheme 2.11).

\begin{center}
\begin{tikzpicture}
\node (first) at (0,0) {$\text{N}=\text{N}$};
\node (second) at ([xshift=2cm]first.east) {$\text{N}=\text{N}$};
\node (ROH) at ([xshift=-2cm]first.west) {$\text{R'O}$};
\node (product) at ([yshift=-2cm]first.south) {$\text{R'O}$};
\node (catalyst) at ([yshift=-0.5cm]first.south) {catalyst, $\mu W$};
\draw[->] (first) -- (second) node[midway, above, sloped] {First Step};
\draw[->] (second) -- (ROH) node[midway, left, sloped] {2.26};
\draw[->] (ROH) -- (product) node[midway, below, sloped] {2.5};
\end{tikzpicture}
\end{center}

\begin{center}
\begin{tikzpicture}
\node (R'OH) at (0,0) {$\text{R'OH}$};
\node (R'COOH) at (1,0) {$\text{R'}\text{COOH}$};
\node (R'COOR') at (2,0) {$\text{R'}\text{COOR'}$};
\node (isourea) at (3,0) {$\text{N}=\text{N}$};
\node (product) at (4,0) {$\text{N}=\text{N}$};
\draw[->] (R'OH) -- (R'COOH) node[midway, above, sloped] {2.11};
\draw[->] (R'COOH) -- (R'COOR') node[midway, above, sloped] {2.8};
\draw[->] (R'COOR') -- (isourea) node[midway, above, sloped] {$\text{N}=\text{N}$};
\draw[->] (isourea) -- (product) node[midway, above, sloped] {$\text{N}=\text{N}$};
\end{tikzpicture}
\end{center}

**Scheme 2.11** One-pot synthesis of esters under microwave heating
Chapter 2. O-Alkylisourea mediated alkylation of primary alcohols

However, despite the reduction in reaction time using microwave heating, chromatography will be necessary to separate the desired ester from the urea by-product. Therefore a solid phase version of the method would also be explored. The new supported reagents would be thus synthesised using polymer-supported DCC\textsuperscript{110} and tested in esterification reactions. This will involve in particular a "catch-and-release" strategy (Scheme 2.12).

Thus an alcohol would be immobilised onto a resin as the corresponding O-alkylisourea 2.28. 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 in solution through reaction with carboxylic acid to form an ester. Any excess unreacted carboxylic acid would be easily removed using a basic resin resulting in the formation of pure esters.

\textbf{2.3 Result and discussion}

\textbf{2.3. 1 Microwave-assisted synthesis of O-alkylisoureas}

In order to achieve the one-pot esterification described in Scheme 2.17, the effect of microwave heating to accelerate the formation of O-alkylisoureas was investigated. For this purpose a series of O-alkylisoureas were synthesised at room temperature and under
microwave conditions to compare yields and purities. Taking into account the limited volume of microwave vials, and since the carboxylic acid was most conveniently added as a solution in the second step, O-alkylisourea formation was investigated neat. \(N,N'\)-diisopropylcarbodiimide (DIC) was chosen as carbodiimide because it is a liquid and it is more reactive than \(N,N'\)-dicyclohexylcarbodiimide (DCC). Soluble O-alkylisoureas were prepared from DIC and different alcohols in the presence of a catalyst using the method proposed by Mathias\(^6\) (Table 2.2 entry: 1, 4, 6, 8). The alcohols were reacted with 1 equiv of DIC in the presence of copper (I) chloride (1 mol%) as a catalyst for 18 h. The reaction was monitored for the disappearance of the IR absorption at 2100 cm\(^{-1}\) of the carbodiimide and the appearance of the \(O\)-alkylisourea band at 1660 cm\(^{-1}\). Subsequently the synthesis of O-alkylisoureas was investigated under microwave conditions without using any solvent. Two catalysts, copper (I) chloride and copper (II) triflate were tested for the variety of alcohols (Table 2.2).

### Table 2.2 Catalyst optimisation for the synthesis of O-alkylisoureas 2.16 c-f

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Amount of Catalyst</th>
<th>(T , ^\circ\C) (Time)</th>
<th>(O)-alkylisourea</th>
<th>Conversion (%)(^a)</th>
<th>Yield %(^b) (purity %(^c))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuCl</td>
<td>1 mol%</td>
<td>RT (18 h)</td>
<td><img src="2.16c" alt="Image of O-alkylisourea" /></td>
<td>100</td>
<td>74(≥98)</td>
</tr>
<tr>
<td>2</td>
<td>CuCl</td>
<td>1 mol%</td>
<td>µW 120 (^\circ\C) (10 min)</td>
<td><img src="2.16c" alt="Image of O-alkylisourea" /></td>
<td>97</td>
<td>80(≥98)</td>
</tr>
</tbody>
</table>
Chapter 2. O-Alkylisourea mediated alkylation of primary alcohols

<table>
<thead>
<tr>
<th>Step</th>
<th>Catalyst</th>
<th>Mol%</th>
<th>Temp</th>
<th>Time</th>
<th>Yield</th>
<th>Conversion</th>
<th>Spectra</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Cu(OTf)₂</td>
<td>2 mol%</td>
<td>W 100 °C</td>
<td>5 min</td>
<td>2.16c</td>
<td>100</td>
<td>85 (≥98)</td>
</tr>
<tr>
<td>4</td>
<td>CuCl</td>
<td>1 mol%</td>
<td>RT</td>
<td>18 h</td>
<td>2.16d</td>
<td>100</td>
<td>76 (≥98)</td>
</tr>
<tr>
<td>5</td>
<td>CuCl</td>
<td>1 mol%</td>
<td>W 120 °C</td>
<td>10 min</td>
<td>2.16d</td>
<td>80</td>
<td>80 (≥98)</td>
</tr>
<tr>
<td>6</td>
<td>CuCl</td>
<td>1 mol%</td>
<td>RT</td>
<td>18 h</td>
<td>2.16e</td>
<td>100</td>
<td>62 (≥98)</td>
</tr>
<tr>
<td>7</td>
<td>CuCl</td>
<td>1 mol%</td>
<td>W 120 °C</td>
<td>10 min</td>
<td>2.16e</td>
<td>97</td>
<td>80 (≥98)</td>
</tr>
<tr>
<td>8</td>
<td>CuCl</td>
<td>1 mol%</td>
<td>RT</td>
<td>18 h</td>
<td>2.16e</td>
<td>100</td>
<td>36 (≥98)</td>
</tr>
<tr>
<td>9</td>
<td>CuCl</td>
<td>1 mol%</td>
<td>W 120 °C</td>
<td>10 min</td>
<td>(±) 2.16f</td>
<td>92</td>
<td>75 (≥98)</td>
</tr>
<tr>
<td>10</td>
<td>Cu(OTf)₂</td>
<td>2 mol%</td>
<td>W 100 °C</td>
<td>5 min</td>
<td>(±) 2.16f</td>
<td>100</td>
<td>79 (≥98)</td>
</tr>
</tbody>
</table>

*aConversion by IR. bIsolated yield after filtration by passage through an activated neutral alumina column. cDetermined by ¹H-NMR spectroscopy.*

After 10 min with microwave irradiation at 120 °C, the band of the carbodiimide was considerably reduced. Figure 2.2 shows the I.R. spectra of the O-alkylisourea obtained from 3-phenyl-1-propanol at room temperature after 18 h (Table 2.2, entry 4). Figure 2.3 shows the O-alkylisourea obtained under microwave irradiation using CuCl as a catalyst (Table 2.2, entry 5). In the second case the reaction was not complete, as shown by the presence of unreacted carbodiimide (2116 cm⁻¹).
Reaction of the primary alcohol substrate proceeded smoothly using CuCl, 1 mol% at RT (Table 2.2 entries 1, 4). Under microwave conditions, reactions catalysed with CuCl 1 mol% were not complete (entry 2). However when Cu(OTf)$_2$ 2 mol% was employed
complete conversion was observed in only 5 min under microwave heating (entry 3). In the case of secondary alcohols such as 4-phenyl-2-butanol, Cu(OTf)$_2$ proved to be more efficient than CuCl; 2 mol% of Cu(OTf)$_2$ led to complete conversion in only 5 min at 100 °C (entries 9, 10). This last catalyst was chosen for the formation of O-alkylisoureas under microwave heating not only due to its higher activity with primary and secondary alcohol, but also for its better solubility in the reaction mixture.

2.3.2 Microwave-assisted synthesis of esters using pre-formed O-alkylisoureas

Having verified that the synthesis of O-alkylisoureas could be successfully carried out under microwave conditions using Cu(OTf)$_2$ as a catalyst, the second step of the one-pot method was attempted (Scheme 2.11). The esterification using soluble isoureas of carboxylic acids usually requires several hours. For example, synthesis of 2.8a with O-methylisourea 2.16b under conventional heating has been reported to require 3 hours at 60 °C.\textsuperscript{111} Employing microwave irradiation as alternative source of heat only 5 min at 120 °C was necessary to obtain the corresponding esters in high yields.\textsuperscript{108} A series of pre-formed O-alkylisoureas from primary alcohols like methanol, benzyl alcohol and phenethyl alcohol, were subjected to the same conditions.\textsuperscript{108} The results are summarised in Table 2.3.

<table>
<thead>
<tr>
<th>Entry</th>
<th>O-alkylisourea</th>
<th>Product</th>
<th>T °C/min/solvent</th>
<th>Yield %* (purity %)\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.16b'</td>
<td>2.8a</td>
<td>130/5.0/THF</td>
<td>81(≥98)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>120/5.0/CH$_3$CN</td>
<td>92(≥98)</td>
</tr>
</tbody>
</table>
THF and acetonitrile were suitable solvents, however, due to its low polarity, THF did not absorb microwave irradiation efficiently. In contrast, using acetonitrile higher reaction temperatures could be achieved in a very short time under microwave
irradiation leading to higher yields (entries 1, 6). Hydroxy acids (entry 1) were cleanly alkylated to give the corresponding hydroxy ester, with no alkylation of the alcohol moiety detected. Sterically hindered acids were converted to their esters with short reaction times (entries 2, 3, 7, 8). In one experiment, the reactive O-benzylisourea effected ester formation in excellent yield in less than a minute (entry 6).

2.3. 3 Microwave-assisted synthesis of aryl ethers using pre-formed O-alkylisoureas

Phenols are another class of substrate which, like acids, can react with O-alkylisoureas. The alkylation of phenol using O-alkylisoureas was first reported in 1966 by Vowinkel,91 aryl ethers from m- and p-substituted phenols can be obtained after 24 hours in 84-91% yields. However for o-substituted phenols the reaction requires 2-4 days heating before yields of the same order are obtained. Having verified that the esterification of carboxylic acid could be successfully carried out under microwave irradiation, it was decided to evaluate if the microwave heating could be used to accelerate the reaction time also in aryl ether formation. The method proved to be applicable for the rapid synthesis of phenyl alkyl ethers, in fact at 180 °C only 10 min were needed to obtain the aryl ethers in good to high yields (Table 2.8).

Table 2.8 Microwave-assisted synthesis of alkyl phenyl ether using O-alkylisoureas

<table>
<thead>
<tr>
<th>Entry</th>
<th>O-alkylisourea</th>
<th>Product</th>
<th>Yield %a (purity %)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.16h</td>
<td>2.30a</td>
<td>62(≥98)</td>
</tr>
</tbody>
</table>

![Reaction scheme](image-url)
Using the reactive O-allylisourea 2.16h, p-phenyl-phenol was alkylated in moderate yield (entry 1), however using the more reactive o- and p-nitrophenol, excellent yields were obtained (entries 2-3). This suggested that activation of the O-alkylisourea by protonation is the rate determining step. Equally excellent yields were obtained with unactivated O-alkylisourea 2.16d and 2.16e, when an electro withdrawing group was present on the phenol moiety (entries 4, 6).

2.3.4 Microwave-assisted synthesis of esters via in situ generated O-alkylisoureas

Having optimised the first and the second step of the synthesis presented in Scheme 2.11, the combination of the two steps was attempted in a one-pot. A series of primary alcohols 2.31 (1 equiv) were reacted with DIC 2.26 (1 equiv) and Cu(OTf)2 (2 mol%).
The mixture was heated neat under microwave irradiation at 100 °C for 5 min, followed by addition of a solution of carboxylic acid (0.9 equiv) in acetonitrile, with the resulting mixture re-subjected to microwave irradiation for 5 min at 120 °C. Due to the polar nature of the by-product (DIU), purification of the esters (0.5 mmol scale) was accomplished by chromatography using a 20 mL SPE reservoir, filled with silica gel. At the top of the silica layer, separated by a frit, a layer of a neutral alumina was used to remove the copper catalyst from the solution. The crude mixtures were purified using hexane/ethyl acetate as the eluent in different proportions depending on the ester synthesised.

Figure 2.4 Purification of esters library using SPE reservoirs

Using a manifold more than one purification could be carried out simultaneously under gravity, avoiding the use of large quantities of silica-gel and solvents.
Table 2.4 One-pot O-alkylisourea mediated microwave-assisted esters synthesis using primary alcohols

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alcohol</th>
<th>Product</th>
<th>Yield %a (purity %)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph-CH₂OH</td>
<td>2.31a</td>
<td>Ph₂CO₂(Ph)₂Ph₂₂₃</td>
</tr>
<tr>
<td>2</td>
<td>2.31a</td>
<td>2.8j</td>
<td>Ph₂CO₂(Ph)₂Ph₂₂₃</td>
</tr>
<tr>
<td>3</td>
<td>2.31a</td>
<td>2.8k</td>
<td>Ph₂CO₂(Ph)₂Ph₂₂₃</td>
</tr>
<tr>
<td>4</td>
<td>2.31a</td>
<td>2.8l</td>
<td>Ph₂CO₂(Ph)₂Ph₂₂₃</td>
</tr>
<tr>
<td>5</td>
<td>2.31a</td>
<td>2.8m</td>
<td>Ph₂CO₂(Ph)₂Ph₂₂₃</td>
</tr>
<tr>
<td>6</td>
<td>2.31b</td>
<td>2.8n</td>
<td>Ph₂CO₂(Ph)₂Ph₂₂₃</td>
</tr>
<tr>
<td>7</td>
<td>2.31b</td>
<td><img src="image" alt="Image" /></td>
<td>87(≥98)</td>
</tr>
<tr>
<td>---</td>
<td>--------</td>
<td>----------------</td>
<td>---------</td>
</tr>
<tr>
<td>8</td>
<td>2.31b</td>
<td><img src="image" alt="Image" /></td>
<td>82(≥98)</td>
</tr>
<tr>
<td>9</td>
<td>2.31b</td>
<td><img src="image" alt="Image" /></td>
<td>74(≥98)</td>
</tr>
<tr>
<td>10</td>
<td>2.31b</td>
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<td>72(≥98)</td>
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<tr>
<td>12</td>
<td>2.31c</td>
<td><img src="image" alt="Image" /></td>
<td>90(≥98)</td>
</tr>
<tr>
<td>13</td>
<td>2.31c</td>
<td><img src="image" alt="Image" /></td>
<td>80(≥98)</td>
</tr>
<tr>
<td>14</td>
<td>2.31c</td>
<td><img src="image" alt="Image" /></td>
<td>87(≥98)</td>
</tr>
<tr>
<td>15</td>
<td>2.31d</td>
<td><img src="image" alt="Image" /></td>
<td>82(≥98)</td>
</tr>
<tr>
<td>16</td>
<td>2.31d</td>
<td><img src="image" alt="Image" /></td>
<td>83(≥98)</td>
</tr>
<tr>
<td>17</td>
<td>2.31e</td>
<td><img src="image" alt="Image" /></td>
<td>nr</td>
</tr>
</tbody>
</table>
Results obtained for primary alcohols are summarised in Table 2.4. A variety of carboxylic acids were selected in order to exemplify the use of the method. It was found that the esterification proceeded smoothly with long chain acids (entries 2, 9, 11). This procedure also worked well for the alkylation of substituted benzoic carboxylic acids (entries 1, 15) and with sterically hindered carboxylic acids (entries 5, 6, 13). The reaction failed in case of 3-phenylprop-2-yn-1-ol and p-methoxy-benzyl alcohol (entries 17-20). In addition it was observed that when a phenolic group was present in the substrate no etherification took place under these conditions (entry 8). In all cases, the yields and purities obtained were excellent.
2.4 Conclusions

It has been demonstrated that it is possible to prepare a series of O-alkylisoureas using copper catalysis and microwave heating to accelerate the process. These alkylating reagents were rapidly prepared in 5 min instead of several hours, and efficiently used to convert carboxylic acids into esters and phenols in the corresponding ethers. A one-pot protocol was optimised, such that esters were synthesised in 10 min, by generation of the O-alkylisoureas in situ. The combination of the short reaction time by microwave heating with the easy purification, obtained with the manifold system, have demonstrated this to be a valuable alternative for the synthesis of esters.
3. Use of O-alkylisoureas as an alternative to the Mitsunobu protocol

3.1 The Mitsunobu reaction

3.1.1 General overview

The Mitsunobu reaction\textsuperscript{112-117} plays an important role in organic synthesis and it has been used in a wide variety of synthetic applications. The reaction involves the dehydrative coupling of an acidic pronucleophile and an alcohol promoted by a reducing phosphine agent (triphenylphosphine TPP) and an oxidising azo-reagent such as diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD). The reaction occurs under mild and neutral reaction conditions. Scheme 3.1 shows the mechanism: in the first step a betaine 3.3 is formed by nucleophilic addition of TPP to DEAD. This betaine can react with at least two different pathways, in path a it can react with two molecules of the alcohol to produce DEAD-H\textsubscript{2} 3.6 and dialkoxyphosphorane 3.5, which then decompose to alkoxyphosponium species 3.7. In path b the betaine can deprotonate the acid/pronucleophile to form eventually, again, DEAD-H\textsubscript{2}, 3.7, and a carboxylate. Regardless of the pathway followed nucleophilic displacement of triphenylphosphine oxide (TPPO) from 3.7 by the carboxylate leads to the coupled product 3.9i with the inversion of stereochemistry relative to the alcohol. In rare cases, if the alcohol is sterically hindered and the pK\textsubscript{a} of the acid/pronucleophile is very low, the carboxylate anion can compete with the alcohol to generate the final product 3.9r with retention of configuration and the anhydride. Many primary and some secondary alcohols can be displaced in a one-pot reaction to provide several new functionalities including amines, amides, esters and ethers. Unfortunately, careful chromatography is usually required to isolate the product from the unreacted reagents and phosphine oxide and hydrazinedicarboxylate as by-products. Furthermore, the pK\textsubscript{a} of the usable acid component must be below 13, preferably <11.\textsuperscript{118-120} These drawbacks have limited the direct application of the Mitsunobu reaction especially in combinatorial library
Chapter 3. Use of O-alkylisoureas as an alternative to the Mitsunobu protocol

synthesis, for these reasons much effort has been put to develop new alternative separation-friendly strategies.

One drawback associated with the Mitsunobu's reaction is the formation of elimination products. Recently Jenkins\textsuperscript{121} reported that when menthol reacted with p-nitrobenzoic acid under Mitsunobu's conditions, 12% of 2-menthene was isolated. It has also demonstrated that the presence of salt or using a polar solvent might favour the elimination over substitution. The Mitsunobu reaction is much slower in polar solvents,

Scheme 3.1 Postulate mechanism of Mitsunobu reaction
the reason could be correlated with the formation of ion pair aggregates. In the $S_{\text{N}2}$ reaction the carboxylate and the alkoxyphosphonium ion are oppositely charged and they must be separated to form the transition state TS 3.14 (Scheme 3.2). The charge separation is not necessary if one ion pair is partially neutralised by another ion pair forming the so-called clusters. If the reaction is carried out in polar solvents or in the presence of salts, this interferes with this mechanism leading to an inhibition of the substitution process in favour of the elimination mechanism, that is not correlated to the formation of these clusters.

Normally the Mitsunobu reaction is carried out at room temperature and requires long reaction times but recently it has been discovered that high reaction rates can be obtained via microwave heating.\textsuperscript{122-124}

\textbf{Scheme 3.2} Postulate mechanism of elimination versus substitution in the Mitsunobu reaction
For example complete conversion of sulcatol 3.17 to the acetate 3.18 was achieved under microwave conditions whereas under typical Mitsunobu conditions the reaction failed (Scheme 3.3).

Scheme 3.3 Microwave-assisted Mitsunobu esterification

3.1.2 Alternative reagents for Mitsunobu reaction

In order to overcome the drawbacks associated with the Mitsunobu reaction (restriction of $pK_a$ of the acid, purification of the final product, long reaction times), researchers have focused their attention on the development of alternative reagents for the reaction.\textsuperscript{121,125-130} Several methods have been reported including the use of $N,N,N',N'$-tetramethylazodicarboxamide (TMAD) and tributylphosphine\textsuperscript{127} (Table 3.1, entry 1) to replace the system DEAD-TPP, or with dimethylmalonyltrialkylphosphoranes\textsuperscript{131,132} (entry 2) that allowed the synthesis of esters with inversion or retention of configuration depending on the nature of reagents and solvent. Alkoxymethylene-dimethylammonium chloride\textsuperscript{133} (entry 3) enables the synthesis of inverted esters using only 2 equiv of nucleophiles, in addition innocuous and easy to remove by-products were formed in the process (DMF and potassium chloride).

Table 3.1 Alternative Mitsunobu reagents

<table>
<thead>
<tr>
<th>Structure/ Name</th>
<th>Structure/ Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\begin{array}{c} \text{Entry 1 Tsunoda's Method} \ N=\text{N} \text{=N} \text{=N} \text{=N} \end{array}$</td>
<td>$\begin{array}{c} \text{Entry 2 Mc Nulty's Method} \ \text{Bu}_3\text{P}=\text{O} \end{array}$</td>
</tr>
</tbody>
</table>
Recently Mukaiyama\textsuperscript{134,135} reported a new protocol for the synthesis of esters and ethers with complete inversion of stereochemistry (Table 3.1, entry 4). The reaction is an oxidation–reduction condensation using benzoquinone 3.19 as the oxidant. An alkoxydiphenylphosphine generated \textit{in situ} reacts with a carboxylic acid in the presence of the quinone affording an ester with inverted alcohol configuration (Scheme 3.4).

Scheme 3.4 Mukaiyama's oxidation-reduction condensation reaction using benzoquinone

3. 2 \textit{O}-Alkylisoureas: alternative reagents for the Mitsunobu reaction

3.2. 1 Introduction

In 1987 Kaulen\textsuperscript{65} discovered that reaction of \textit{O}-alkylisoureas derived from secondary alcohols with carboxylic acid proceeded with inversion of configuration, and could be applied to a variety of secondary alcohols, and only small amounts of the corresponding
olefins were formed as by-products. Subsequently in 1998 Jaeger,136,137 fully explained the mechanism involved in the reaction of secondary O-alkylisoureas and acids. After the formation of \( O-(S)-(+)\)-octyl-isourea (+)-3.21, coupling with the acid was carried out in cyclohexane to afford the inverted ester \( (R)-(\cdot)-1\)-methylheptylacetae \( (\cdot)-3.22 \) in 84% yield. Subsequent hydrolysis of \( (\cdot)-3.22 \) with ethanolic sodium yielded \( (R)-(\cdot)-2\)-octanol in 95% yield (Scheme 3.5).

![Scheme 3.5 Esterification reactions with O-alkylisoureas under conventional heating](image)

The alcohol can be isolated after hydrolysis completely converted into its corresponding enantiomer \( (\cdot)-3.20 \). The inversion of stereochemistry occurs in the second step; neither the formation of \( O\)-alkylisourea or the hydrolysis step involves any change in the stereochemistry of the stereogenic centre. However, a percentage of olefinic product \( (Z/E)\)-2-octenes was found in the formation of \( (\cdot)-3.22 \) ranging from 5.3% to 17.6%. The reaction of \( 2-O\)-octyl-isourea and acetic acid is one example where \( S_{N1} \) and \( S_{N2} \) cooperate together. It is well known that primary substrates react preferentially via \( S_{N2} \) (bimolecular and inversion of configuration) and tertiary substrates via \( S_{N1} \) (unimolecular and racemisation). However, in the case of 2-octanol as a secondary substrate a hybrid mechanism is involved, with characteristics intermediate between \( S_{N1} \) and \( S_{N2} \).138 In the first step of the mechanism protonation of the \( O\)-alkylisourea occurs and the isouronium acetate (+)-3.23 is produced (Scheme 3.6). In path a, after
reorientation, the ion pair 3.24 is formed, which reacts monomolecularly to produce the ion pair 3.26.

Scheme 3.6 Jaeger's postulated mechanism for esterification reactions using O-alkylisoureas from secondary alcohols

In the last step of path a, the final product (-)-3.22 and the elimination products 3.29/3.30 were obtained. (E/Z)-octenes are preferentially formed as by-products typical for a S_{N}1 mechanism. In path b it was assumed that the reaction proceeds between the acetate anion and the isouronium acetate (+)-3.23 by an S_{N}2 mechanism. In intermediate 3.25 the nucleophilic attack of the acetate anion can only occur at the side of the alkyl group leading to the product with inversion of configuration (-)-3.22 and 3.29/3.30 as
by-products. In conclusion inversion of configuration of (S)-2-octanol occurs in both primary and secondary order substitution reaction because the methylcarbenium anion is shielded by the two cyclohexyl group that direct the attack of the acetate in one specific direction.

3.3 Results and discussion

3.3.1 Microwave-assisted synthesis of esters with inversion of configuration using pre-formed O-alkylisoureas

In the previous chapter O-alkylisoureas derived from primary alcohols were examined for esterification procedure using microwave heating to accelerate the reaction. Only 10 min were necessary to obtain esters in high yields without need to isolate the O-alkylisoureas which were generated in situ (Scheme 3.7).

![Scheme 3.7 One-pot isourea-mediated microwave-assisted ester synthesis using primary alcohols](image)

Following the successful esterification of primary alcohols it was decided to investigate the reaction of carboxylic acid with pure O-alkylisoureas synthesised from secondary alcohols. The results are summarised in Table 3.2. Esters were obtained in good to excellent yields (Table 3.2, entries 1, 9, 19, 20). Typically a small percentage of
elimination was found, however in all cases only between 5-13% of elimination product was found, which is comparable to what is observed under Mitsunobu conditions.

**Table 3.2** Microwave-assisted synthesis of carboxylic esters using secondary alcohols

<table>
<thead>
<tr>
<th>Entry</th>
<th>$O$-alkylisourea</th>
<th>Product</th>
<th>Yield % (purity %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(±)-2.16f</td>
<td>(±)-3.31a</td>
<td>96 (≥98)</td>
</tr>
<tr>
<td>2</td>
<td>(±)-2.16f</td>
<td>(±)-3.31b</td>
<td>48 (≥98)</td>
</tr>
<tr>
<td>3</td>
<td>(±)-2.16f</td>
<td>(±)-3.31c</td>
<td>70 (≥98)</td>
</tr>
<tr>
<td>4</td>
<td>(±)-2.16f</td>
<td>(±)-3.31d</td>
<td>90 (≥98)</td>
</tr>
<tr>
<td>5</td>
<td>(±)-2.16f</td>
<td>(±)-3.31e</td>
<td>90 (≥98)</td>
</tr>
<tr>
<td>6</td>
<td>(±)-2.16f</td>
<td>(±)-3.31f</td>
<td>95 (≥98)</td>
</tr>
</tbody>
</table>
7 (±)-2.16f

8 (±)-2.16f

9 (±)-2.16f

10 (±)-2.16f

11 (±)-2.16f

12 (±)-2.16f

13 (±)-2.16i

14 (±)-2.16i

15 (±)-2.16i

16 (±)-2.16i
In general better yields were obtained using more acidic acids. For example in the case of substituted benzoates: p-nitrobenzoic acid was superior compared to those esters obtained using less acidic acids such as p-MeO or p-Me-benzoic acids (entry 6 versus 8; entry 15 versus 17). This is in accord to the trend observed in the Mitsunobu reaction where the replacement of benzoic acid with p-nitrobenzoic acid in general improves the yields. The reaction enables the synthesis of esters in high yield also when hindered acids were used (Table 3.2, entries 1, 3, 11). In addition the reactions of O-alkylisoureas derived from 2-octanol and 4-phenyl-2-butanol with acids not only proceeded rapidly, but were really easy to purify because of the nature of the by-product (DIU) and the starting materials. With these preliminary experiments in hand the stereochemistry of the reaction was examined using two different isoureas from chiral alcohols such as (R)-(−)-2-octanol and (S)-(−)-4-phenyl-2-butanol and different enantiopure acids. The α-methoxy-α-trifluoromethylphenylacetic Mosher's acid (MTPA)\textsuperscript{39} and mandelic acid\textsuperscript{40} have been used over the years to determine the enantiomeric composition of the alcohols. These reagents can react with the alcohol forming a mixture of diastereomeric

\textsuperscript{a}Isolated yield, the crude compound was purified using a SPE cartridge. \textsuperscript{b}Determined by ELSD.
Chapter 3. Use of $O$-alkylisoureas as an alternative to the Mitsunobu protocol

Esters whose $^1$H-NMR spectra can be used for quantitative analysis by integration. Alkylation of these two enantiopure acids using $O$-alkylisoureas from enantiopure secondary alcohols proceeded smoothly in 5 min under microwave irradiation (Table 3.3). Esters were obtained, in excellent yields and purities. In all cases, $^1$H-NMR analysis showed the presence of only one diastereomeric ester.

Table 3.3 Microwave-assisted synthesis of esters using enantiopure acids

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>$O$-alkylisourea</th>
<th>Product</th>
<th>Yield(%)$^a$ (Purity(%)$^b$)</th>
<th>Ret./Inv.$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph$_2$C=CH$_2$-Ph</td>
<td>(S,R)-3.31u</td>
<td>78(≥98) (≥99.9)</td>
<td>≤0.1≥99.9$^c$</td>
</tr>
<tr>
<td>2</td>
<td>Ph$_2$C=CH$_2$-Ph</td>
<td>(S,R)-3.31v</td>
<td>60(≥98) (≥99.9)</td>
<td>≤0.1≥99.9$^c$</td>
</tr>
</tbody>
</table>
Isolated yield, the crude compound was purified using a SPE cartridge. Determined by ELSD. Retention: Inversion ratios measured by $^1$H-NMR spectroscopy.

Figure 3.1 shows the $^1$H-NMR spectrum of the crude ester synthesised in CD$_3$CN from (R)-(−)-2-octanol and (S)-(+)−mandelic acid, with only one singlet corresponding to the proton in $\alpha$ to the carbonyl group.

![Figure 3.1 $^1$H-NMR spectrum of inverted ester (S,S) 3.31x](image-url)
In contrast when racemic 2-octanol reacted with (S)-(+) mandelic acid, the $^1$H-NMR of the crude ester in CD$_3$CN, showed a doublet corresponding to the protons of the two diastereomers (Figure 3.2).

![Figure 3.2 $^1$H-NMR spectrum of racemic ester (±)-3.31x](image)

Isoureas are mildly basic species and therefore a brief investigation towards possible ester racemisation under the above mentioned microwave heating conditions was undertaken. For this purpose, the methylation of Cbz-Gly-L-Phe-Val-OH 3.32 (Scheme 3.8) was investigated. This tripeptide is used in the Anteunis's test,\textsuperscript{141} which evaluates possible epimerisation of amide bonds via coupling of Cbz-Gly-L-Phe-OH with H-L-Val-OMe. The expected (L,L)-tripeptide could easily be distinguished ($^1$H-NMR) from the (D,L)-tripeptide. Possible epimerisation in the isourea-mediated methylation of 3.32 would lead to (D,L)-tripeptide. The synthesis of the tripeptide was achieved by coupling of Cbz-Gly-L-Phe-OH and H-L-Val-OtBu using PS-DCC/1-hydroxybenzotriazole (HOBt) in DMF followed by deprotection using standard TFA/DCM (1:1) conditions. O-Methylisourea 2.16a was used to protect the tripeptide (L,L)-Cbz-Gly-Phe-Val-OH under microwave irradiation: two cycles were necessary to accomplish the complete
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protection. $^1$H-NMR analysis indicated clearly that the tripeptide was obtained as a single $(L,L)$-3.33-epimer.

![Scheme 3.8 Protection of $(L,L)$-Cbz-Gly-Phe-Val-OH using O-methylisourea 2.16a](image)

Having verified that no epimerisation occurred in the case of alkylation of a peptide under microwave condition, a series of esters using pre-formed enantiopure O-alkylisoureas was prepared. The results are summarised in Table 3.4.

**Table 3.4 Microwave-assisted synthesis of esters using enantiopure secondary O-alkylisoureas**

<table>
<thead>
<tr>
<th>Entry</th>
<th>O-alkylisourea</th>
<th>Product</th>
<th>Yield($%$)$^b$</th>
<th>Ret./Inv.$^{cd}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(S)-2.16f</td>
<td>(R)-3.31d</td>
<td>90($\geq$98)</td>
<td>$\leq$0.12$\geq$99.9</td>
</tr>
</tbody>
</table>

[(S)-2.16f](#) [(R)-3.31d](#)
Chapter 3. Use of O-alkylisoureas as an alternative to the Mitsunobu protocol

<table>
<thead>
<tr>
<th>2</th>
<th>(S)-2.16f</th>
<th>95(≥98)</th>
<th>≤0.1≥99.9</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(R)-3.31f</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

![Chemical Structure](image1)

<table>
<thead>
<tr>
<th>3</th>
<th>(S)-2.16f</th>
<th>95(≥98)</th>
<th>≤0.1≥99.9</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(R)-3.31g</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

![Chemical Structure](image2)

<table>
<thead>
<tr>
<th>4</th>
<th>(R)-2.16i</th>
<th>80(≥98)</th>
<th>≤0.1≥99.9</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(S)-3.31n</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

![Chemical Structure](image3)

<table>
<thead>
<tr>
<th>5</th>
<th>(R)-2.16i</th>
<th>77(≥98)</th>
<th>≤0.1≥99.9</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(S)-3.31q</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

![Chemical Structure](image4)

<table>
<thead>
<tr>
<th>6</th>
<th>(R)-2.16i</th>
<th>70(≥98)</th>
<th>≤0.1≥99.9</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(S)-3.31r</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

![Chemical Structure](image5)

Isolated yield, the crude compound was purified using a SPE cartridge. Determined by ELSD. Retention: Inversion ratios measured by chiral liquid chromatography using an amyllose-derivatived Chiralpack®ADTM-RH as stationary phase.

Esters were obtained in high yields, again inversion of configuration appeared complete and not affected by the microwave heating conditions as shown by chiral HPLC analysis. A control experiment was performed using O-alkylisourea from racemic 4-phenyl-2-butanol. Figure 3.3 shows the HPLC chromatogram for the esters obtained from racemic 4-phenyl-2-butyl-isourea two peaks were identified with the two enantiomers present in the mixture. In contrast figure 3.4 shows the ester obtained from
Chapter 3. Use of $O$-alkylisoureas as an alternative to the Mitsunobu protocol

$(S)$-$(+)\text{-}phenyl-2\text{-}butyl-isourea$, in this case using the same HPLC method only one peak was present in the HPLC chromatogram.

![Figure 3.3 Chiral HPLC chromatogram of racemic ester $(\pm)$-3.31d](image)

![Figure 3.4 Chiral HPLC chromatogram of enantiomeric ester $(R)$-3.31d](image)

Another control experiment was conducted using Mitsunobu conditions under microwave irradiations. For example starting from $(S)$-$(+)\text{-}4\text{-}phenyl-2\text{-}butanol$ (Scheme 3.9), the isolated ester showed the same retention time as the ester obtained using the isourea method (Figure 3.5).
3.3.2 Microwave-assisted synthesis of neo-menthyl esters using $O$-(−)-menthylisourea

The search for a mild method to prepare esters from hindered bulky group such as (L)-(−)-menthol has been matter of continuous interest over the years. Synthesis of hindered esters usually requires a long reaction time (24 h). In addition a large excess of carboxylic acids or reagents and strong acids or bases are necessary to drive the reaction to completion. In the literature precedent presented by Kaulen, $O$-(−)-menthylisourea 3.35 was successfully used in inverting esterification of (L)-(−)-menthol with >99% de.
However, using formic acid, 20 h under reflux in toluene were necessary to obtain 80% of inverted neomenthyl ester 3.36 (Scheme 3.10).

![Scheme 3. 10 Synthesis of neomenthyl ester using O-menthylisourea](image)

It is well known that in the Mitsunobu reaction inversion of menthol is dramatically influenced by the acidic component. There is a clear relationship between the pKₐ of the acid and the yields of the inverted product.¹¹⁹ For this reason p-nitrobenzoic acid was chosen as the acid in the reaction with O-(−)-menthylisourea under microwave conditions. The crude reaction mixture was analysed by GC-MS. The reaction was examined under a range of parameters including concentration, temperature and solvents (Table 3.5) in order to find the best conditions for the synthesis. It was found that using acetonitrile as solvent (entries 1, 2, 3) the major products were elimination products (2- and 3-menthene). Switching to toluene as solvent led to a higher conversion compared to the case of acetonitrile. Toluene is a microwave-transparent solvent, however the substrate O-alkylisourea/acid are polar and therefore microwave absorbing, raising the dielectric properties of the reaction medium to a level that allows sufficient heating by microwaves. Using toluene as solvent and a slight excess of O-(−)-menthylisourea (1.06 equiv), 90% conversion was obtained at 150 °C after 10 min under microwave irradiation (entry 4). No higher yields were observed when an excess of acid was employed (entry 7).
Table 3.5 Microwave-assisted synthesis of neomenthyl-4-nitrobenzoate 3.39a

![Diagram of the synthesis reaction](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>T°C/Time (min)</th>
<th>Solvent</th>
<th>Isourea/Acid(equiv)</th>
<th>Ratio&lt;sup&gt;b&lt;/sup&gt; 3.38 : 3.35 : 3.39a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>150/10</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CN</td>
<td>1.06/1.00</td>
<td>42/-/58</td>
</tr>
<tr>
<td>2</td>
<td>150/5</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CN</td>
<td>1.06/1.00</td>
<td>37/-/63</td>
</tr>
<tr>
<td>3</td>
<td>130/5</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CN</td>
<td>1.06/1.00</td>
<td>30/25/45</td>
</tr>
<tr>
<td>4</td>
<td>150/10</td>
<td>Toluene</td>
<td>1.06/1.00</td>
<td>10/-/90&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>150/10</td>
<td>Toluene</td>
<td>2.00/1.00</td>
<td>17/43/40</td>
</tr>
<tr>
<td>6</td>
<td>150/30</td>
<td>Toluene</td>
<td>1.06/1.00</td>
<td>8/-/92&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td>150/10</td>
<td>Toluene</td>
<td>1.00/2.00</td>
<td>28/-/72</td>
</tr>
<tr>
<td>8</td>
<td>150/10</td>
<td>Toluene</td>
<td>1.00/1.00</td>
<td>28/-/72</td>
</tr>
</tbody>
</table>

<sup>a</sup>All reactions were carried out in 2 mL of solvent. <sup>b</sup>Product ratios determined by GC/MS analysis. <sup>c</sup>91% isolated yield. <sup>d</sup>90% isolated yield.

Under these esterification conditions, nearly equimolar amounts of O-alkylisoureas/acids were used and only 10 min were required for high yields. Moreover, in this case, all esters were obtained with complete inversion of stereochemistry. Following the established conditions for the synthesis of neomenthyl-4-nitrobenzoate 3.39a, a library was then synthesised using these conditions (Table 3.6).
Chapter 3. Use of O-alkylisoureas as an alternative to the Mitsunobu protocol

Table 3.6 Microwave-assisted synthesis of neomenthyl-esters

\[
\text{O} + \text{R}^*\text{COOH} \rightarrow \text{O}^*\text{R}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield(%)</th>
<th>Purity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Image" /> 3.39a</td>
<td>90(≥98)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td><img src="image2.png" alt="Image" /> 3.39b</td>
<td>68(≥98)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td><img src="image3.png" alt="Image" /> 3.39c</td>
<td>66(≥98)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td><img src="image4.png" alt="Image" /> 3.39d</td>
<td>31(≥98)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td><img src="image5.png" alt="Image" /> 3.39e</td>
<td>nr</td>
<td></td>
</tr>
</tbody>
</table>

Esters display all inversion of configuration by 'H-NMR spectroscopy. Isolated yield, the crude compound was purified using 20 mL SPE reservoir containing silica:alumina. Determined by ELSD.

The substituent effect with p-substituted benzoic acids indicates that the reaction is strongly dependent of the pKₐ of the acid. Higher yields were obtained using electron-
deficient benzoic acids (Table 3.6, entries 1, 3). When acetic acid (entry 5) was used the starting O-alkylisourea was recovered and no product was isolated from the reaction mixture. However, employing a more nucleophilic thioacetic acid led to an increase in the yield (entry 4). The O-alkylisourea-mediated esterification was found to be superior in comparison to Mitsunobu's or Tsunoda's method (Table 3.7).

Table 3.7 Comparison of esterification of (L)-(−) menthol using several methods

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid</th>
<th>pKₐ</th>
<th>Time</th>
<th>Isourea</th>
<th>Time</th>
<th>Mitsunobu</th>
<th>Time</th>
<th>Mukaiyama</th>
<th>Time</th>
<th>Tsunoda</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Yield %; (I%)</td>
<td>Yield %; (I%)</td>
<td>Yield %; (I%)</td>
<td>Yield %; (I%)</td>
<td>Yield %; (I%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>COOH</td>
<td>3.41</td>
<td>10 min</td>
<td>3.39a</td>
<td>24 h</td>
<td>3.39a</td>
<td>1 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NO₂</td>
<td>3.37a</td>
<td>90; (&gt;99.9)</td>
<td>84; (&gt;99.9)</td>
<td>87; (&gt;99.9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>COOH</td>
<td>4.19</td>
<td>10 min</td>
<td>3.39b</td>
<td>24 h</td>
<td>3.39b</td>
<td>3 h</td>
<td>24 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.37b</td>
<td>68; (&gt;99.9)</td>
<td>27; (&gt;99.9)</td>
<td>86; (&gt;99.9)</td>
<td>91; (10.6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>COOH</td>
<td>4.47</td>
<td>10 min</td>
<td>3.39c</td>
<td>24 h</td>
<td>3.39c</td>
<td>1 h</td>
<td>24 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>OMe</td>
<td>3.37c</td>
<td>66; (&gt;99.9)</td>
<td>17; (&gt;99.9)</td>
<td>88; (&gt;99.9)</td>
<td>98; (&gt;99.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a = Inversion ratio. Diastereoselectivities determined by ¹H-NMR spectroscopy. b (L)-(−)-menthol (1.0 equiv), RCOOH (4.0 equiv), PPh₃ (4.0 equiv), DEAD (4.0 equiv), THF, RT, 24 h. c Step 1) (L)-(−)-menthol (1.1 equiv), nBuLi/Hexane, Ph₂PCL, THF, 0 °C-RT, 1h. Step 2) RCOOH (1.0 equiv), DMBQ (1.0 equiv), DCM, RT. d (L)-(−)-menthol (1.0 equiv), RCOOH (1.5 equiv), 'Bu₃P (1.5 equiv), Me₂NOCN=NCOMe₂ (1.5 equiv), benzene, 60 °C, 24 h.
The esterification of \textit{in situ} formed secondary \(O\)-alkylisoureas from (\(L\)-(\(-\))-menthol was attempted, however the desired esters were obtained in modest yield also when \(p\)-nitrobenzoic acid were employed (Table 3.8).

\textbf{Table 3.8} One-pot microwave-assisted synthesis of neomenthyl-esters

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid</th>
<th>Product</th>
<th>Yield (%); (I%) (^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{COOH} \quad \text{3.37a})</td>
<td>(\text{3.39a})</td>
<td>36; (&gt;99.9)</td>
</tr>
<tr>
<td>2</td>
<td>(\text{COOH} \quad \text{3.37b})</td>
<td>(\text{3.39b})</td>
<td>26; (&gt;99.9)</td>
</tr>
<tr>
<td>3</td>
<td>(\text{COOH} \quad \text{3.37c})</td>
<td>(\text{3.39c})</td>
<td>30; (&gt;99.9)</td>
</tr>
</tbody>
</table>

\(^a\)I = Inversion ratio. Diastereoselectivities determined by \(^1\text{H}-\text{NMR} \) spectroscopy.
3. 4 Conclusions

A new and efficient method for the preparation of inverted esters from various secondary \( O \)-alkylisoureas under microwave conditions was established. The corresponding carboxylic acid esters were afforded in good to high yields using strong acids such as \( p \)-nitrobenzoic acid. Microwave heating was used successfully to accelerate the reaction time, only 10 min were necessary using pre-formed \( O \)-alkylisourea to obtain the corresponding inverted products. When bulky hindered alcohol such as \((L)-(-)-\text{menthol}\) were employed toluene was necessary as solvent to avoid the competitive elimination, leading to the esters with complete inversion of stereochemistry in good to high yield.
4. Alkylation reactions using PS-O-alkylisoureas

4.1 Introduction

4.1.1 Alkylating polymers

Different polymer supported reagents have been used to alkylate carboxylic acids and sulfonic phosphonic acids to the corresponding esters, generally they are supported coupling reagents or solid supported catalyst. An elegant solution for clean ester formation, which avoids the use of toxic or explosive reagents and/or difficult work-up procedures, was reported independently by Bräse and Rademann, in which a solid-supported triazene, prepared from Merrifield resin, was used to effect the transformation. More recently polymer supported triazenes were prepared via an optimised synthesis from commercially available polystyrene resin (Scheme 4.1).

\[
\text{NaNO}_2, \text{HCl}, 0 \, ^\circ\text{C}, 2\text{h} \quad \text{PhNHNH}_2, \text{Li} \quad 0 \, ^\circ\text{C} \text{to RT, 16 h}
\]

\[
\text{R'}\text{NH}_2, 0 \, ^\circ\text{C} \text{to RT, 16 h}
\]

\[
\text{NaNO}_2, \text{HCl}, 0 \, ^\circ\text{C}, 2\text{h} \quad \text{PhNHNH}_2, \text{Li} \quad 0 \, ^\circ\text{C} \text{to RT, 16 h}
\]

\[
\text{R'}\text{COO}^- \quad \text{R'}\text{COOH}
\]

Scheme 4.1 Preparation of polymer-supported triazenes (PSTs) from polystyrene resin and their application in the synthesis of esters
A selection of acids were treated with the alkylation-polymers PSTs 4.1a-d at RT, esters were obtained in excellent yields under mild conditions and in high purity after a simple filtration. Another example of an alkylation-polymer is the supported version of the popular Mukaiyama reagent\(^{148}\) 4.2 that proved to be a good coupling reagent for the synthesis of both amides and esters. The products were obtained in high purities and high yields with a very simple and easily automated workup (Scheme 4.2).

Scheme 4.2 Synthesis of esters using polymer-supported Mukaiyama’s reagent

The use of solid supported acids has also been explored with polymer-supported methyl sulfonate 4.4, prepared in one step from sulfonic acid resin 4.3 and trimethyl orthoacetate. Carboxylic, phosphonic, and sulfonic acids were alkylated in high yield. Moreover the polymeric reagent 4.4 can be easily regenerated and reused without loss of activity (Scheme 4.3).

Scheme 4.3 Esterification reactions using polymer-supported methyl sulfonate
The Mitsunobu reaction\textsuperscript{112} has also been carried out for the synthesis of esters using polymer supported reagents\textsuperscript{149} like phosphine-functionalised polymers\textsuperscript{150} or polymer supported DEAD.\textsuperscript{151} The simultaneous use of the supported system DEAD-TPP has been reported using ring-opening polymerisation (ROMP), with esters synthesised successfully with inverted configuration and without the need of any purification step.\textsuperscript{152} Other approaches such as the use of fluorous/ tagged reagents\textsuperscript{153,154} or ionic liquids have also been explored. For example Poupon\textsuperscript{155} reported the use of the system DEAD-TPP tagged with tetraarylphosphonium perchlorate and hexafluorophosphate salts 4.6, 4.7. These salts were completely insoluble in ether and therefore at the end of the reaction diethyl ether was added to precipitate the by-products leading to pure esters (Scheme 4.4).

Scheme 4.4 Phosphonium tagged reagents for the synthesis of inverted esters

### 4.1.2 Alkylating reactions using polymer-supported $O$-alkylisoureas

Polymer-supported $O$-alkylisoureas have been used as an alternative approach to the methods described above.\textsuperscript{110,156,157} These alkylating polymers have been successfully employed for the protection of acids (Scheme 4.5).

Scheme 4.5 Synthesis of solid supported $O$-alkylisoureas
The synthesis of polymer-supported $O$-alkylisoureas was achieved in one step using a large excess of alcohol (99 equiv) and a carbodiimide resin\textsuperscript{158} in presence of 7 mol\% of Cu(OTf)$_2$. After the first step a washing with TMEDA was required to remove the copper catalyst from the resin. The polymer-supported $O$-alkylisoureas 2.28a-d (2 equiv) were used to convert a series of carboxylic acids to the corresponding methyl, allyl or benzyl esters using thermal or microwave heating. Using the solid-supported isourea the urea byproduct and any excess of isourea remained immobilised on the resin, with a simple filtration of the resin affording the products. The esters were obtained with high purity (>95\% by NMR) and in good yields (Scheme 4.6).

![Scheme 4.6 Protection of carboxylic acid with $O$-alkylisoureas 2.28a-d](image)

4.2 Results and discussion

4.2.1 Microwave-assisted esterifications using PS-$O$-alkylisoureas

Further to the use of simple immobilised $O$-alkylisoureas as polymer-supported reagents to protect carboxylic acids, it was investigated whether substrate-alcohols could be used. In order to implement the method, it was first investigated whether it was possible to load the alcohols in high yields using as few equivalents as possible. To compensate for the reduced number of equivalents of alcohol, larger amounts of catalyst were used. Using 25 mol\% of Cu(OTf)$_2$ and only 1.2 equiv of alcohol, the reaction was complete within 16 h at RT. The IR spectrum of the resin revealed the disappearance of the band at 2110 cm$^{-1}$ and the presence of two new bands at 1655 and 1329 cm$^{-1}$ which were attributed to the PS-$O$-alkylisourea, by comparison with the IR spectrum of the
corresponding soluble isourea. Under these conditions polymer-supported \( O \)-alkylisoureas 2.28e-f were synthesised using commercially available PS-DCC 2.27 in one step (Scheme 4.7). The resin was filtered and washed with a 10\% solution of TMEDA in DCM to remove the copper and dried overnight.

\[
\text{NN-cHex} + \text{ROH} \xrightarrow{(1.2 \text{ equiv})} i) \text{THF}, \text{Cu(OTf)}_2, 16 \text{ h} \xrightarrow{\text{ii) TMEDA, DCM (3 wash cycles)}} \text{O-alkylisourea} 2.28e-f
\]

Scheme 4.7 Synthesis of PS-\( O \)-alkylisoureas 2.28e-f

To try to confirm the structure of the functionalised resin NMR spectroscopy was used, for example Figure 4.1 shows the \( ^{13} \text{C-NMR} \) of PS-\( O \)-phenethylisourea 2.28f.

Figure 4.1 \( ^{13} \text{C-NMR} \) spectrum of PS-\( O \)-phenethylisourea 2.28f

Subsequently the new supported reagents 2.28e-f were tested in alkylation reactions. An excess of acids (4 equiv) were used for the esterification reactions under microwave
irradiation (Table 4.1). Dowex® 550A OH resin was used to remove the excess of acid employed.

Table 4.1 Microwave-assisted esterification using PS-\(O\)-alkylisoureas

\[
\text{NH-cHex} \quad + \quad \text{RCOOH} \quad \xrightarrow{\text{i) CH}_3\text{CN, } \mu\text{W 5 min, 150 °C}} \quad \text{R"COOR'}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>PS-(O)-alkylisourea</th>
<th>Product</th>
<th>Yield %* (purity %)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.28e</td>
<td>(\text{NH-cHex}) (\text{O-Me}) (\text{Ph}) (\text{Bn})</td>
<td>80((\geq 98))</td>
</tr>
<tr>
<td>2</td>
<td>2.28e</td>
<td>(\text{NH-cHex}) (\text{O-Me}) (\text{Ph}) (\text{Bn})</td>
<td>90((\geq 98))</td>
</tr>
<tr>
<td>3</td>
<td>2.28e</td>
<td>(\text{NH-cHex}) (\text{O-Me}) (\text{Ph}) (\text{Bn})</td>
<td>85((\geq 98))</td>
</tr>
<tr>
<td>4</td>
<td>2.28e</td>
<td>(\text{NH-cHex}) (\text{O-Me}) (\text{Ph}) (\text{Bn})</td>
<td>66((\geq 98))</td>
</tr>
<tr>
<td>5</td>
<td>2.28e</td>
<td>(\text{NH-cHex}) (\text{O-Me}) (\text{Ph}) (\text{Bn})</td>
<td>4.8e</td>
</tr>
<tr>
<td>6</td>
<td>2.28e</td>
<td>(\text{NH-cHex}) (\text{O-Me}) (\text{Ph}) (\text{Bn})</td>
<td>4.8f</td>
</tr>
<tr>
<td>7</td>
<td>2.28e</td>
<td>(\text{NH-cHex}) (\text{O-Me}) (\text{Ph}) (\text{Bn})</td>
<td>4.8g</td>
</tr>
</tbody>
</table>
All primary substrates gave esters in good to high yield and purities. The reaction proceeded smoothly for the alkylation of aliphatic acids (Table 4.1; entries 4, 9) and also when bulky groups were present in the acid moiety (entries 3, 5, 8). The yields obtained in the case of phenethyl alcohols were comparable with those obtained using the one-pot isourea mediated microwave assisted synthesis (entries 8, 9).

4.2.2 Microwave-assisted "catch-and-release" synthesis of esters

The previous section described the use of polymer supported O-alkylisoureas for the esterification of carboxylic acids. The reaction was successful for a range of different alcohols and acids. However it is important to maximise the yields with respect to the substrate and not to the resin, for this reason an excess of resin was subsequently investigated in a "catch-and-release" esterification procedure (Table 4.2). Firstly the alcohol was immobilised onto the resin as the corresponding isourea using an excess of PS-DCC. When an excess of resin was used some carbodiimide groups were still available on the resin, as evidenced by IR spectroscopy. In order to cap the remaining
carbodiimide groups an excess of water was added to the mixture to form an inert urea. The second step effected the "release" of the alcohol moiety back into solution through reaction with carboxylic acid (4 equiv) to form an ester under microwave conditions. Any excess of unreacted carboxylic acid was finally easily removed using a basic resin DOWEX® 550A OH (Table 4.2).

Table 4.2 Microwave-assisted "catch-and-release" synthesis of esters

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alcohol</th>
<th>Product</th>
<th>Yield %&lt;sup&gt;a&lt;/sup&gt; (purity %)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.9a</td>
<td>4.8a</td>
<td>34(&gt;98)</td>
</tr>
<tr>
<td>2</td>
<td>4.9a</td>
<td>4.8b</td>
<td>40(&gt;98)</td>
</tr>
<tr>
<td>3</td>
<td>4.9a</td>
<td>4.8d</td>
<td>70(&gt;98)</td>
</tr>
<tr>
<td>Step</td>
<td>Reagent 1</td>
<td>Reagent 2</td>
<td>Product 1</td>
</tr>
<tr>
<td>------</td>
<td>-----------</td>
<td>-----------</td>
<td>-----------</td>
</tr>
<tr>
<td>4</td>
<td>Ph-CH₂OH</td>
<td>O(CH₂)₅Ph</td>
<td>4.9b</td>
</tr>
<tr>
<td>5</td>
<td>4.9b</td>
<td>O(CH₂)₅Ph</td>
<td>4.8i</td>
</tr>
<tr>
<td>6</td>
<td>Ph-CH₂OH</td>
<td>O(CH₂)₅Ph</td>
<td>2.32a</td>
</tr>
<tr>
<td>7</td>
<td>2.32a</td>
<td>O(CH₂)₅Ph</td>
<td>2.8i</td>
</tr>
<tr>
<td>8</td>
<td>2.32a</td>
<td>O(CH₂)₅Ph</td>
<td>2.8j</td>
</tr>
<tr>
<td>9</td>
<td>2.32a</td>
<td>O(CH₂)₅Ph</td>
<td>2.8d</td>
</tr>
<tr>
<td>10</td>
<td>2.32b</td>
<td>O(CH₂)₅Ph</td>
<td>2.8o</td>
</tr>
<tr>
<td>11</td>
<td>2.32b</td>
<td>O(CH₂)₅Ph</td>
<td>2.8p</td>
</tr>
<tr>
<td>12</td>
<td>Ph-CH₂OH</td>
<td>O(CH₂)₅Ph</td>
<td>(S)-3.34</td>
</tr>
</tbody>
</table>

Chapter 4. Alkylation Reactions using PS-O-alkylisoureas
Despite the excellent purities that were obtained in all case, the "catch-and-release" method proved to be less efficient in terms of yield than the corresponding synthesis using an excess of alcohol. Only in the case of n-hexanol were obtained high yields (Table 4.3 entries 10, 11). Under these conditions, reactions of secondary alcohols also did not prove to be as successful as the corresponding solution phase. The reaction of PS-(S)-(+)4-phenyl-2-butyl-isourea led to the product with inverted configuration, however the elimination products were found to be the main product in the reaction mixture. A number of different conditions were tested in order to minimise the amount of alkene being formed but without success.

4.2. 3 Microwave-assisted synthesis of 2-oxazolines

4.2.3 1 Introduction

We were intrigued by the possibility of using similar strategy for the synthesis of 2-oxazolines. Over the years these molecules have appeared in numerous medicinally active compounds and are found in natural products of biological significance.\textsuperscript{159} The most common mode of oxazoline synthesis involves the preparation of a $\beta$-hydroxyamides followed by cyclisation. Typical cyclisation reagents include include Burgess reagent,\textsuperscript{160} PPh\textsubscript{3}/DIAD,\textsuperscript{161} molybdenum oxide,\textsuperscript{162} DAST/Deoxo-Fluor\textsuperscript{163} and Mukaiyama's reagent.\textsuperscript{164} There are very few examples of isoureas being used in cyclisation reactions, however there are a limited number of examples of intramolecular
cyclisation involving compounds such as γ-hydroxyketone, which have a pKₐ comparable to amides. Previous work in our laboratory had demonstrated that the reaction between DIC and β-hydroxyamide in the presence of 5 mol% of Cu(OTf)₂ under microwave heating afforded the desired 2-oxazoline in high yield (Scheme 4.8).

![Scheme 4.8 Microwave-assisted O-alkylisourea mediated synthesis of 2-oxazolines](image)

When β-hydroxyamides bearing a chiral centre in the β position like (1R,2S)-norephedrine 4.12 were used, only the trans-substituted diastereoisomer oxazoline 4.13 was obtained, confirming that the process must have occurred with inversion of configuration (Scheme 4.9). However, a lower level of diastereoselectivity was observed with β-hydroxyamides 4.14, derived from (1S,2S)-2-amino-3-methoxy-1-phenyl-1-propanol, with only a 4:1 ratio in favour of the expected cis-substituted oxazoline 4.15 over the trans-substituted 4.16 isomer being observed (Scheme 4.9).

![Scheme 4.9 Diastereoselective formation of 2-oxazolines derived from (1R,2S)-norephedrine and (1S,2S)-2-amino-3-methoxy-1-phenyl-1-propanol](image)
Given the basicity of isoureas, an intermolecular acid–base reaction would take place leading to the protonated intermediate 4.18, upon which cyclisation can occur to give the 2-oxazoline product 4.15 with inversion of configuration at the reacting centre. However, because the urea is a good leaving group, the reaction could proceed through an \( \text{SN}_1 \) type mechanism featuring 4.19, especially when the cation is stabilised by a phenyl group. The formation of 4.16 can thus be explained by a subsequent rotation about the C–C bond to give 4.20, followed by cyclisation (Scheme 4.10).

![Scheme 4.10 Suggested mechanism for diastereoselective formation of oxazolines derived from (1S,2S)-2-amino-3-methoxy-1-phenyl-1-propanol](image)

With secondary benzylic alcohols, an \( \text{SN}_2 \) mechanism operates but if \( \alpha \)-substitution is present, unfavourable steric interactions may favour an \( \text{SN}_1 \)-type process. In this way, rotation can relieve steric strain that otherwise would build up in the formation of cis-substituted 2-oxazolines.

### 4.2.3 2 "Catch-and-release" synthesis of 2-oxazolines

The use of polymer supported carbodiimide was investigated. In order to test this strategy four simple \( \beta \)-hydroxyamides were treated with 1.5 equiv of \( N \)-cyclohexyl-\( N' \)-methylpolystyrenecarbodiimide 2.27 and 25 mol\% of Cu(OTf)\(_2\) under microwave irradiation (15 min at 150 °C). Filtration of the resin followed by filtration of the crude
solution on a small plug (ca. 2 cm) of alumina in order to remove the copper catalyst afforded the products in good yield and purities (Table 4.3).

Table 4.3 Microwave-assisted "catch-and-release" synthesis of 2-oxazolines

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield %a (purity %)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.21a</td>
<td>4.22a</td>
<td>70(&gt;95)</td>
</tr>
<tr>
<td>2</td>
<td>4.21b</td>
<td>4.22b</td>
<td>72(&gt;95)</td>
</tr>
<tr>
<td>3</td>
<td>4.21c</td>
<td>4.22c</td>
<td>47(&gt;95)</td>
</tr>
<tr>
<td>4</td>
<td>4.21d</td>
<td>4.22d</td>
<td>56(&gt;95)</td>
</tr>
</tbody>
</table>

*aYield after filtration and washing of the resin with DCM. bDetermined by 1H-NMR spectroscopy.
These examples illustrate the potential of this method in particular for parallel synthesis as the products were obtained in high yields and purity without need a work-up. Next a series of experiments were conducted using β-hydroxyamides 4.14 in order to find the best conditions to favour the synthesis of cis-substituted oxazoline 4.15 over the trans isomer 4.16.

Table 4.4 Solvent Optimisation for diastereoselective formation of 2-oxazolines

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Ratio ( \text{4.15} : \text{4.16} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toluene</td>
<td>70 : 30</td>
</tr>
<tr>
<td>2</td>
<td>CH(_3)CN</td>
<td>96 : 4</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>98 : 2</td>
</tr>
</tbody>
</table>

\( ^a \) Determined by \( ^1 \text{H-NMR} \) spectroscopy.

THF and CH\(_3\)CN proved to be suitable solvents for the cyclisation step, however it was found that in THF (Table 4.4; entry 3) the expected cis-substituted oxazoline 4.15 was obtained in 98 : 2 ratio over the trans-substituted isomer 4.16.
4. 3 Conclusions

A range of polymer supported O-alkylisoureas were prepared from carbodiimide resin. Using an excess of the primary alcohols compared to the PS-carbodiimide led to esters in high yield. Under microwave heating only 5 min were necessary to obtain the esters, after filtration and washing of the resin the compounds were found 98% pure. Unfortunately the same results were not obtained when using a "catch-and-release" approach, in fact using an excess of carbodiimide the yield of the esters were substantially lower, especially when performing the reaction of secondary substrates because of the competitive elimination reaction. Polymer supported O-alkylisoureas have demonstrated a good synthetic potential for the preparation of 2-oxazolines, the cyclisation of the β-hydroxyamides proceeded smoothly after a simple resin filtration and solvent evaporation routine.
5. Experimental section

5.1 General procedures

Reaction solvents were used as follows: THF was distilled from Na/benzophenone. Anhydrous DMF was purchased from commercial sources and stored in a Schlenk flask. Chromatography refers to flash column chromatography and was performed on 230-400 mesh silica gel. Reactions were monitored by TLC (Merck) with detection under UV light illumination or through alkaline KMnO4 oxidation. The melting points are reported uncorrected. 1H- and 13C-NMR spectra were recorded on a Brucker ARX 250 NMR and AV 300 NMR, using CDCl3 referenced to residual solvent peaks; chemical shifts are quoted in ppm and J values given in Hz. All 13C-NMR experiments were supported with a DEPT experiment. IR spectra were obtained on a Thermo Mattson Satellite FTIR spectrometer or a Bruker Tensor 27 Spectrometer, with 16 scans, at a resolution of ± 4 cm⁻¹. The FTIR spectrometer was fitted with a Specac single reflection diamond ATR Golden Gate, and neat compounds were used for analysis. Frequencies are reported in cm⁻¹ and only frequencies corresponding to significant functional groups are reported. Abbreviations used for reporting data are s = strong, m = medium, w = weak, br = broad. LC-Mass spectra were recorded either on a water ZMD single quadrupole MS, with a 2700 Autosampler and a 600 Pump, or an Agilent Technologies LC/MSD Series 1100 Quadrupole Mass Spectrometer (QMS), both with an electrospray ion source. HPLC/ELSD analyses were obtained using Agilent 1100 series system coupled to a Polymer Lab 100 ES ELS Detector. Eluants used were analytical grade. The following methods were used:

**Method A:** eluant A: water + 0.1% formic acid, eluant B: methanol + 0.1% formic acid. Gradient: 95 % to 5 % A over 15 min.

**Method B:** eluant A: water + 0.1% formic acid, eluant B: methanol + 0.1% formic acid. Gradient: 95 % to 5 % A over 6 min.

GC/MS analyses were performed on a VG Trio 1000. Maspec II was used to acquire and process the GC/MS data. The following method was used: injection port temperature
250 °C; oven temperature 60 °C, 60-250 °C (15 °C/min), 40 min. Optical purity of the chiral esters was established by chiral HPLC analysis using a Chiralpak® AD-RH (150 x4.6 mm), λ = 220 nm, λ = 254 nm. The following methods were used:

**Method C:** gradient from 40% water/ 60% acetonitrile to 20% water/ 80% acetonitrile over 16 min. Flow = 1.00 mL/min.

**Method D:** gradient from 30% Water/ 70% acetonitrile to 14% water/ 76% acetonitrile /10% water + 0.1% formic acid over 15 min. Flow = 0.40 mL/min.

**Method E:** gradient from 30% water/70% acetonitrile to 27% water/ 73% acetonitrile over 15 min. Flow = 0.40 mL/min.

HRMS analyses were performed by the Mass Spectrometry Service of the University of Southampton and the University of Edinburgh.

Reagents were purchased from Aldrich and used without further purification. N-cyclohexyl-N'-methylpolystyrenecarbodiimide 2.27 was purchased from Polymer Laboratories. Microwave-assisted experiments were performed on a Smith Synthesizer,™ which was donated by Biotage (Personal Chemistry). 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. The numbering systems adopted to assign protons and carbon signals in the NMR spectra in some structures is different from the numbering following IUPAC nomenclature. The IUPAC names of each compound are reported in brackets.
5.2 Experimental for chapter II

General method for the synthesis of O-alkylisoureas at RT

The respective alcohols 2.5 (10.0 mmol) were added under stirring to a mixture of copper (I) chloride (0.010 g, 0.100 mmol) in N,N'-diisopropylcarbodiimide 2.26 (10.0 mmol) at 0 °C over a 10 min period. After an additional 1 h at 0 °C, the reaction was typically greater than 95% complete as indicated by disappearance of the IR absorption at 2100 cm⁻¹ (carbodiimide) and the appearance of the band at 1660 cm⁻¹ (isourea). The green mixture was stirred overnight at room temperature for 18 h. Hexane (100 mL) was added and the solution was applied to a filter pad of a neutral alumina. The product was eluted with a total volume of (3×100 mL) of hexane, at which time the IR spectrum indicates that all the isourea has been removed from the alumina. The solvent was evaporated under reduced pressure.

[1,3-Diisopropyl-2-phenethylisourea] 2.16c (1.83 g, 74% yield, colourless oil)

IR (neat): νmax / (cm⁻¹) 2961 (w); 1660 (s); 1315 (s); 748 (m).

¹H-NMR (300 MHz, CDCl₃) δH: 7.32-7.16 (5H, m, H₉₋₁₁); 4.23 (2H, t, J = 6.7 Hz, H₆); 3.68 (1H, m, H₂); 3.27 (1H, br, NH); 3.11 (1H, m, H₄); 2.86 (2H, t, J = 6.7 Hz, H₇); 1.07 (6H, d, J = 6.4 Hz, H₃); 1.05 (6H, d, J = 6.4 Hz, H₅).
$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta_{C}$: 151.5 (C$_1$); 139.2 (C$_8$); 129.1 (C$_{10}$); 128.2 (C$_9$); 126.1 (C$_{11}$); 65.6 (C$_5$); 46.2 (C$_4$); 43.4 (C$_2$); 35.5 (C$_7$); 24.3 (C$_3$); 23.9 (C$_5$).

LRMS $m/z$ (%): 250 (100).

HRMS $m/z$: calculated for C$_{15}$H$_{25}$N$_2$O [M+H]$^+$ 249.1961, found 249.1958.

[1,3-Diisopropyl-2-(3-phenylpropyl)isourea] 2.16d (1.99 g, 76% yield, colourless oil)

IR (neat): $\nu_{max}$ / (cm$^{-1}$) 2962 (m); 1658 (s); 1390 (m); 1311 (s); 1083 (s) 745 (m).

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta_{H}$: 7.33-7.01 (5H, m, H$_{10-12}$); 3.97 (2H, t, $J = 6.2$ Hz, H$_6$); 3.66 (1H, m, H$_2$); 3.28 (1H, br, NH); 3.05 (1H, m, H$_4$); 2.60 (2H, t, $J = 7.7$ Hz, H$_8$); 2.0 (2H, m, H$_7$); 1.00 (12H, d, $J = 6.2$ Hz, H$_{3,5}$).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta_{C}$: 151.5 (C$_1$); 142.0 (C$_9$); 128.4 (C$_{11}$); 128.4 (C$_{10}$); 125.8 (C$_{12}$); 64.2 (C$_5$); 46.2 (C$_4$); 43.4 (C$_2$); 32.6 (C$_8$); 30.9 (C$_7$); 24.4 (C$_3$); 24.1 (C$_5$).

LRMS [ES+] $m/z$: 263 (100).

HRMS [ES+] $m/z$: calculated for C$_{16}$H$_{27}$N$_2$O [M+H]$^+$ 263.2188, found 263.2111.

The compound exhibited $^1$H and $^{13}$C-NMR spectra identical to those described previously.$^{157}$

[1,3-Diisopropyl-2-(pent-4-enyl)isourea] 2.16e (1.31 g, 62% yield, colourless oil)
Chapter 5. Experimental section

IR (neat): $v_{\text{max}}$ (cm$^{-1}$) 2963 (m); 1659 (s); 1392 (m); 1313 (s); 1088 (s) 910 (m).

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$: 5.76 (1H, m, H$_9$); 4.97 (1H, m, H$_{10}$); 4.90 (1H, m, H$_{10}$); 3.97 (2H, t, $J = 6.6$ Hz, H$_9$); 3.70 (1H, m, H$_2$); 3.31 (1H, br, NH); 3.09 (1H, m, H$_4$); 2.12-2.05 (2H, m, H$_8$); 1.65 (2H, m, H$_7$) 1.06 (6H, d, $J = 6.6$ Hz, H$_5$); 1.03 (6H, d, $J = 6.6$ Hz, H$_3$).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$: 151.6 (C$_1$); 138.2 (C$_9$); 114.6 (C$_{10}$); 64.2 (C$_6$); 46.1 (C$_4$); 43.3 (C$_2$); 30.4 (C$_8$); 28.3 (C$_7$); 24.2 (C$_3$); 23.9 (C$_5$).

LRMS [ES+] m/z: 213 (100).

HRMS [ES+] m/z: calculated for C$_{12}$H$_{25}$N$_2$O [M+H]$^+$ 213.1889, found 213.1957.

$[(\pm)-1,3$-Diisopropyl-2-(4-phenylbutan-2-yl)isourea] ($\pm$)-2.16f (0.99 g, 36% yield, colourless oil)

IR (neat): $v_{\text{max}}$ (cm$^{-1}$) 2964 (m); 1657 (s); 1363 (s); 1304 (s); 1064 (s); 746 (m).

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$: 7.21-7.06 (5H, m, H$_{11-13}$); 4.95 (1H, m, H$_2$); 3.68 (1H, m, H$_4$); 3.30 (1H, br, NH); 3.09 (1H, m, H$_2$); 2.69-2.52 (2H, m, H$_9$); 1.92-1.64 (2H, m, H$_8$); 1.16 (3H, d, $J = 6.2$ Hz, H$_6$); 1.06 (6H, d, $J = 6.5$ Hz, H$_5$); 1.03 (6H, d, $J = 6.5$ Hz, H$_3$).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$: 150.6 (C$_1$); 142.6 (C$_{10}$); 128.4 (C$_{12}$); 128.3 (C$_{11}$); 125.6 (C$_{13}$); 69.4 (C$_7$); 46.2 (C$_2$); 43.3 (C$_4$); 38.1 (C$_8$); 31.9 (C$_9$); 24.4 (C$_3$); 24.1 (C$_5$); 19.7 (C$_6$).

LRMS [ES+] m/z: 277 (100).

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

165
Microwave-assisted synthesis of $O$-alkylisourea 2.16c-f using CuCl 1 mol% 

\[
\begin{align*}
N &= N \quad + \quad R'OH \quad \xrightarrow{\text{CuCl 1 mol\%}} \quad \text{CuCl 1 mol\%} \\
&\quad \text{120 °C, } \mu W, \text{ 10 min} \\
2.26 &\quad 2.5 \\
&\quad \text{2.16c-f}
\end{align*}
\]

The respective alcohol 2.5 (5.0 mmol) was added to a mixture of copper (I) chloride (0.005 g, 0.050 mmol) in $N, N'$-diisopropylcarbodiimide 2.26 (5.0 mmol) in a microwave vial (0.5-2.0 mL). The green mixture was heated under stirring at 120 °C using a Smith Synthesizer$^{TM}$ for 10 min. Hexane (10 mL) was added and the solution was applied to a filter pad of a neutral alumina. The product was eluted with a total volume of 50 mL of hexane; the solvent was evaporated under reduced pressure. The compounds exhibited $^1$H and $^{13}$C-NMR spectra identical to those described previously.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product/Isolated Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.16c/80</td>
</tr>
<tr>
<td>2</td>
<td>2.16d/80</td>
</tr>
<tr>
<td>3</td>
<td>2.16e/80</td>
</tr>
<tr>
<td>4</td>
<td>2.16f/75</td>
</tr>
</tbody>
</table>

*Isolated yield after filtration by passage through an activated neutral alumina column.

Microwave-assisted synthesis of $O$-alkylisourea 2.16c-f using Cu(OTf)$_2$ 2 mol% 

\[
\begin{align*}
N &= N \quad + \quad R'OH \quad \xrightarrow{\text{Cu(OTf)$_2$ 2 mol\%}} \quad \text{Cu(OTf)$_2$ 2 mol\%} \\
&\quad \text{100 °C, } \mu W, \text{ 5 min} \\
2.26 &\quad 2.5 \\
&\quad \text{2.16c-f}
\end{align*}
\]
The respective alcohol 2.5 (10.0 mmol) was added to a mixture of copper (II) triflate (0.072 g, 0.200 mmol) in \(N, N'-\text{diisopropylcarbodiimide} \ 2.26\) (10.0 mmol) in a microwave vial. The green mixture was heated under stirring at 100 °C using a Smith Synthesizer\textsuperscript{TM} for 5 min. Hexane (10 mL) was added and the solution was applied to a filter pad of a neutral alumina. The product was eluted with a total volume of 50 mL of hexane; the solvent was evaporated under reduced pressure. The compounds exhibited \(^1\text{H} \text{ and } ^{13}\text{C}-\text{NMR spectra identical to those described previously.}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product(^a)/Isolated Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.16c/85</td>
</tr>
<tr>
<td>2</td>
<td>2.16f/79</td>
</tr>
</tbody>
</table>

\(^a\)Isolated yield after filtration by passage through an activated neutral alumina column.

**General method for the synthesis of esters using isolated \(O\)-alkylisoureas 2.16b, c, g**

\[
\text{RO} \begin{array}{c} \text{N} \end{array} \begin{array}{c} \text{N} \end{array} \text{H} + \text{R'}\text{COOH} \xrightarrow{\text{Solvent}} \xrightarrow{\text{\(\mu\)W, 120 °C, 5 min}} \text{R'}\text{COOR'} + \text{\(O\)-alkylisourea} 2.16b, c, g
\]

A microwave vial was charged with the carboxylic acid (2.0 mmol) and \(O\)-alkylisourea 2.16b, c, g (2.1 mmol) followed by addition of \(\text{CH}_3\text{CN or THF (4mL). The vial was capped and heated at 120 °C for 5 min in a Smith Synthesizer.\textsuperscript{TM} The 1,3-diisopropylurea was removed by filtration and the solvent evaporated under vacuum. The residue was then further purified by column chromatography.}\)
[Methyl 2-hydroxy-2-phenylacetate] 2.8a (0.30 g, 92% yield, colourless oil)

\[
\begin{align*}
\text{H-NMR} &\ (250 \text{ MHz, CDCl}_3) \ \delta_H: 7.44-7.30 (5 \text{ H, m, H5,7}); 5.18 (1 \text{ H, d, } J = 5.9 \text{ Hz, H2}); \\
&\ 3.77 (3 \text{ H, s, H3}); 3.46 (1 \text{ H, d, } J = 5.9, \text{ OH}). \\
\text{C-NMR} &\ (62 \text{ MHz, CDCl}_3) \ \delta_C: 173.3 (\text{C1}); 138.4 (\text{C4}); 128.8 (\text{C6}); 128.7 (\text{C5}); 126.8 \\
&\ (\text{C7}); 73.0 (\text{C2}); 53.2 (\text{C3}).
\end{align*}
\]

The compound exhibited 'H and 13C-NMR spectra identical to those described previously.\(^{166}\)

[Methyl 2,2-diphenylpropanoate] 2.8b (0.46 g, 96% yield, colourless oil).

\[
\begin{align*}
\text{Rf:} &\ 0.50 (\text{Eluant: hexane/ethyl acetate; 9/1}). \\
\text{H-NMR} &\ (250 \text{ MHz, CDCl}_3) \ \delta_H: 7.18-7.09 (10 \text{ H, m, H5,7}); 3.60 (3 \text{ H, s, H8}); 1.83 (3 \text{ H, s, H3}). \\
\text{HPLC (Method A):} &\ t_R = 9.90 \text{ min.}
\end{align*}
\]

The compounds exhibited 'H and 13C-NMR spectra identical to those described previously.\(^{166}\)
[Methyl 2-iodobenzoate] 2.8c (0.50 g, 96% yield, pale yellow oil)

RF: 0.50 (Eluant: hexane/ethyl acetate; 9/1).

IR (neat): $v_{\text{max}}$ (cm$^{-1}$) 2949 (w); 1730 (s); 1132 (s); 741 (s).

$^1$H-NMR (250 MHz, CDCl$_3$) $\delta_H$: 7.86 (1H, dd, $J = 7.9, 1.1$ Hz, H$_5$); 7.72 (1H, dd, $J = 7.8, 1.7$ Hz, H$_8$); 7.32 (1H, dt, $J = 7.5, 1.2$ Hz, H$_7$); 7.07 (1H, dt, $J = 7.5, 1.8$ Hz, H$_6$); 3.86 (3H, s, H$_2$).

$^{13}$C-NMR (62 MHz, CDCl$_3$) $\delta_C$: 166.7 (C$_1$); 141.2 (C$_5$); 134.9 (C$_3$); 132.6 (C$_6$); 130.8 (C$_8$); 127.8 (C$_7$); 94.0 (C$_4$); 52.4 (C$_2$).

LRMS [FAB+] $m/z$ (%): 263 (48); 105 (67); 91 (68); 77 (34); 43 (100).

HRMS [FAB+] $m/z$: calculated for C$_8$H$_8$I0$_2$ [M+H]$^+$ 262.9564, found 262.9569.

HPLC (Method A): $t_R = 8.92$ min.

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

[Phenethyl 4-phenoxybenzoate] 2.8d (0.51 g, 80% yield, white solid)

RF: 0.55 (Eluant: hexane/ethyl acetate; 8/2).

Mp: 84-86 °C.
IR (neat): \( \nu_{\text{max}} / (\text{cm}^{-1}) \) 3062 (br); 1720 (s); 1268 (s); 1176 (m); 1007 (s); 752 (s).

\(^1\)H-NMR (300 MHz, CDCl\(_3\)) \( \delta \): 8.21 (2H, d, \( J = 9.0 \) Hz, H\(_9\)); 7.65-7.18 (12H, m, H\(_{5-7, 10, 13-15}\)); 4.74 (2H, t, \( J = 7.0 \) Hz, H\(_2\)); 3.29 (2H, t, \( J = 7.0 \) Hz, H\(_3\)).

\(^{13}\)C-NMR (75 MHz, CDCl\(_3\)) \( \delta \): 166.1 (C\(_1\)); 161.9 (C\(_{11}\)); 155.7 (C\(_{12}\)); 138.1 (C\(_4\)); 131.8 (C\(_9\)); 130.1 (C\(_6\)); 129.1 (C\(_{14}\)); 128.6 (C\(_3\)); 126.7 (C\(_7\)); 124.7 (C\(_8\)); 124.6 (C\(_{13}\)); 120.2 (C\(_{15}\)); 117.4 (C\(_{10}\)); 65.5 (C\(_2\)); 35.4 (C\(_3\)).

LRMS [FAB+] \( m/z \) (%): 319 (41); 197 (82); 105 (100); 91 (32); 77 (64); 43 (14).

HRMS [EI] \( m/z \) (%): calculated for C\(_{21}\)H\(_{18}\)O\(_3\) [M]\(^+\) 318.1256, found 318.1250.

HPLC (Method A): \( t_R = 10.92 \) min.

[Phenethyl 2-hydroxy-2-phenylacetate] 2.8e (0.48 g, 94% yield, white solid)

\[
\begin{align*}
\text{IR (neat):} & \quad \nu_{\text{max}} / (\text{cm}^{-1}) \quad 3454 \text{ (br)}; 1714 \text{ (s)}; 1494 \text{ (w)}; 1176 \text{ (s)}; 1062 \text{ (m)}; 726 \text{ (s)}. \\
\text{IR (neat):} & \quad \nu_{\text{max}} / (\text{cm}^{-1}) \quad 3454 \text{ (br)}; 1714 \text{ (s)}; 1494 \text{ (w)}; 1176 \text{ (s)}; 1062 \text{ (m)}; 726 \text{ (s)}. \\
\text{IR (neat):} & \quad \nu_{\text{max}} / (\text{cm}^{-1}) \quad 3454 \text{ (br)}; 1714 \text{ (s)}; 1494 \text{ (w)}; 1176 \text{ (s)}; 1062 \text{ (m)}; 726 \text{ (s)}. \\
\end{align*}
\]

\text{Mp:} 62-64 °C.

IR (neat): \( \nu_{\text{max}} / (\text{cm}^{-1}) \) 3454 (br); 1714 (s); 1494 (w); 1176 (s); 1062 (m); 726 (s).

\(^1\)H-NMR (300 MHz, CDCl\(_3\)) \( \delta \): 7.33-6.94 (10H, m, H\(_{5-7, 11-13}\)); 5.06 (1H, d, \( J = 5.6 \) Hz, H\(_9\)); 4.36-4.23 (2H, m, H\(_2\)); 3.34 (1H, d, \( J = 5.8 \) Hz, OH); 2.8 (2H, m, H\(_3\)).

\(^{13}\)C-NMR (75 MHz, CDCl\(_3\)) \( \delta \): 173.6 (C\(_1\)); 138.2 (C\(_4\)); 137.2 (C\(_{10}\)); 128.8 (C\(_{11}\)); 128.6 (C\(_{12}\)); 128.5 (C\(_6\)); 128.4 (C\(_{14}\)); 126.6 (C\(_5\)); 126.6 (C\(_7\)); 72.9 (C\(_8\)); 66.5 (C\(_2\)); 34.9 (C\(_3\)).

LRMS [EI] \( m/z \) (%): 165 (2); 150 (27); 122 (12); 107 (100); 91 (45); 77 (86); 51 (31).

HRMS [FAB+] \( m/z \): calculated for C\(_{21}\)H\(_{18}\)O\(_3\) [M+H]\(^+\) 257.1172, found 257.1178.

HPLC (Method A): \( t_R = 9.06 \) min.
Chapter 5. Experimental section

[Benzyl 2,2-diphenylpropanoate] 2.8g (0.50 g, 80% yield, white solid)

\[
\begin{align*}
\text{Rf: } & 0.70 \text{ (Eluant: hexane/ethyl acetate; 9/1).} \\
\text{Mp: } & 53-54 ^\circ C. \\
\text{IR (neat): } & \nu_{\max }/(\text{cm}^{-1}) 3032 \text{ (w); 1730 (s); 1213 (s); 737 (s); 697 (s).} \\
^1\text{H-NMR} \text{ (250 MHz, CDCl}_3) & \delta_H: 7.54-7.42 \text{ (15H, m, H}_{4-6, 10-12}; 5.44 \text{ (2H, s, H}_2; 2.22 \text{ (3H, s, H}_8).} \\
^{13}\text{C-NMR} \text{ (62 MHz, CDCl}_3) & \delta_C: 174.8 \text{ (C}_1; 144.4 \text{ (C}_9; 135.9 \text{ (C}_3; 128.4 \text{ (C}_11; 128.2 \text{ (C}_9; 128.1 \text{ (C}_10; 128.0 \text{ (C}_6; 127.9 \text{ (C}_4 126.9 \text{ (C}_12; 66.9 \text{ (C}_2; 56.7 \text{ (C}_7; 27.1 \text{ (C}_8.} \\
\text{LRMS [FAB+] } m/z \text{ (%): } 317 (7); 181 (82); 91 (100); 77 (33); 43 (13). \\
\text{HRMS [FAB+] } m/z: \text{ calculated for } C_{22}H_{21}O_2 \text{ [M+H]}^+ 317.1536, \text{ found 317.1542.} \\
\text{HPLC (Method A): } \text{t}_R = 10.55 \text{ min.}
\end{align*}
\]

[1-Adamantane carboxylic acid benzyl ester] 2.8 h (0.49 g, 92% yield, white solid)

\[
\begin{align*}
\text{Rf: } & 0.70 \text{ (Eluant: hexane/ethyl acetate; 9/1).} \\
\text{Mp: } & 63-64 ^\circ C. \\
\text{IR (neat): } & \nu_{\max }/(\text{cm}^{-1}) 2907 \text{ (s); 1725 (s); 1608 (s); 1229 (s); 738(s).}
\end{align*}
\]
Chapter 5. Experimental section

$^1$H-NMR (250 MHz, CDCl$_3$) $\delta_H$: 7.30-7.20 (5H, m, H$_{4-6}$); 5.01 (2H, s, H$_2$); 1.92 (3H, br); 1.83 (6H, br); 1.62 (6H, br).

$^{13}$C-NMR (62 MHz, CDCl$_3$) $\delta_C$: 177.5 (C$_1$); 136.6 (C$_3$); 128.5 (C$_5$); 128.0 (C$_6$); 127.7 (C$_4$); 65.7 (C$_2$); 40.8 (C$_7$); 38.9 (C$_8$, C$_{12-13}$); 36.5 (C$_{10}$, C$_{15-16}$); 28.0 (C$_9$, C$_{11}$, C$_{14}$).

LRMS [FAB+] m/z (%): 270 (6); 135 (87); 91 (100); 77 (54).

HRMS [FAB+] m/z: calculated for C$_{18}$H$_{23}$O$_2$ [M+H]$^+$ 271.1693, found 271.1698.

HPLC (Method A): $t_R = 11.11$ min.

The compound exhibited $^1$H and $^{13}$C-NMR spectra identical to those described previously.\textsuperscript{168}

[Benzyl 1-cyclobutene-1-carboxylate] 2.8i (0.40 g, 93% yield, colourless oil)

Rf: 0.64 (Eluant: hexane/ethyl acetate; 9/1).

IR (neat): $v_{\text{max}}/\text{cm}^{-1}$: 3033 (w); 2935 (s); 1712 (s); 1232 (s); 745 (s); 697 (s).

$^1$H-NMR (250 MHz, CDCl$_3$) $\delta_H$: 7.41-7.32 (5H, m, H$_{4-6}$); 7.06 (1H, m, H$_{12}$); 5.20 (2H, s, H$_2$); 2.34-2.28 (2H, m, H$_8$); 2.24-2.15 (2H, m, H$_{11}$); 1.71-1.55 (4H, m, H$_{9,10}$).

$^{13}$C-NMR (62 MHz, CDCl$_3$) $\delta_C$: 167.3 (C$_1$); 140.2 (C$_3$); 136.5 (C$_{12}$); 130.2 (C$_2$); 128.5 (C$_5$); 128.0 (C$_6$); 128.0 (C$_4$); 65.9 (C$_2$) 25.8 (C$_{11}$); 24.2 (C$_{10}$); 22.1 (C$_8$); 21.5 (C$_9$).

LRMS [FAB+] m/z (%): 217 (42); 109 (83); 91 (100); 77 (37); 43 (32).

HRMS [FAB+] m/z: calculated for C$_{14}$H$_{17}$O$_2$ [M+H]$^+$ 217.1223, found 217.1229.

HPLC (Method A): $t_R = 10.25$ min.

The compound exhibited $^1$H and $^{13}$C-NMR spectra identical to those described previously.\textsuperscript{169}
General method for microwave-assisted synthesis of alkyl phenyl ethers using O-alkylisoureas

![Chemical structure diagram]

To a solution of O-alkylisourea 2.16d, e, h (0.500 mmol) in CH$_3$CN (1 mL) in a microwave vial, was added the substituted phenol (0.470 mmol). The vial was heated at 180 °C using a Smith Synthesizer$^\text{TM}$ for 10 min. The 1,3-diisopropylurea was filtered off, the solvent evaporated and the residue purified by chromatography using a SPE cartridges (20 mL) packed with silica and alumina.

[3-(4-Biphenyloxy)-1-prop-2-ene] 2.30a (0.06 g, 62% yield, colourless solid)

$^1$H-NMR (250 MHz, CDCl$_3$) $\delta$: 7.60-7.53 (4H, m, H$_3$, H$_6$); 7.47-7.41 (2H, m, H$_7$); 7.33 (1H, m, H$_8$); 7.02 (2H, d, $J = 8.9$ Hz, H$_2$); 6.11 (1H, m, H$_{11}$); 5.47 (1H, dd, $J_{trans} = 17.4$, 1.5 Hz, H$_{12}$); 5.34 (1H, dd, $J_{cis} = 10.4$ Hz, 1.5, H$_{14}$); 4.60 (2H, dt, $J = 5.3$, 1.5 Hz, H$_9$).

$^{13}$C-NMR (62 MHz, CDCl$_3$) $\delta$: 158.6 (C$_1$); 141.2 (C$_5$); 134.3 (C$_{10}$); 133.7 (C$_4$); 129.1 (C$_7$); 128.6 (C$_3$); 127.2 (C$_6$); 127.1 (C$_8$); 118.1 (C$_{13}$); 115.5 (C$_2$); 69.3 (C$_9$).

HPLC (Method A): $t_R = 10.15$ min.

The compound exhibited $^1$H and $^{13}$C-NMR spectra identical to those described previously.$^{170}$
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[1-(Allyloxy)-4-nitrobenzene] 2.30b (0.09 g, 97% yield, yellow pale oil)

\[
\begin{array}{c}
\text{O}_2\text{N} \\
\text{H} \\
\text{H} \\
\text{H} \\
\text{H} \\
\end{array}
\]

RF: 0.60 (Eluant: hexane/ethyl acetate; 8/2).

IR (neat): \( v_{\text{max}} \text{/(cm}^{-1}) \) 3000 (w); 1660 (s); 1500 (s); 1000 (m).

\(^1\text{H-NMR}\) (250 MHz, CDCl\(_3\)) \( \delta_H \): 8.17 (2H, d, \( J = 9.3 \text{ Hz, H}_3 \)); 6.95 (2H, d, \( J = 9.3 \text{ Hz, H}_2 \)); 6.03 (1H, m, H\(_7\)); 5.41 (1H, dd, \( J_{\text{trans}} = 17.4, 1.3 \text{ Hz, H}_9 \)); 5.35 (1H, dd, \( J_{\text{cis}} = 10.4, 1.3 \text{ Hz, H}_10 \)); 4.62 (2H, dt, \( J = 5.2, 1.6 \text{ Hz, H}_5 \)).

\(^13\text{C-NMR}\) (62 MHz, CDCl\(_3\)) \( \delta_C \): 164.0 (C\(_1\)); 141.9 (C\(_4\)); 132.3 (C\(_6\)); 126.2 (C\(_3\)); 119.0 (C\(_8\)); 115.1 (C\(_2\)); 69.8 (C\(_5\)).

LRMS \( m/z \) (%): 179 (10); 145 (100); 77 (61); 43 (35).

HRMS [FAB(+)] \( m/z \): calculated for C\(_9\)H\(_{10}\)NO\(_3\) \([\text{M+H}]^+\) 180.0655, found 180.0662.

HPLC (Method A): \( t_R = 8.76 \text{ min.} \)

[1-(Allyloxy)-2-nitrobenzene] 2.30c (0.08 g, 90% yield, yellow pale oil).

\[
\begin{array}{c}
\text{O} \\
\text{H} \\
\end{array}
\]

RF: 0.40 (Eluant: hexane/ethyl acetate; 8/2).

IR (neat): \( v_{\text{max}} \text{/(cm}^{-1}) \) 3000 (w); 1605 (s); 1519 (s); 1275 (m).

\(^1\text{H-NMR}\) (250 MHz, CDCl\(_3\)) \( \delta_H \): 7.81 (1H, d, \( J = 8.1 \text{ Hz, H}_3 \)); 7.50 (1H, m, H\(_3\)); 7.04 (2H, m, H\(_2\), H\(_4\)); 6.01 (1H, m, H\(_3\)); 5.47 (1H, dd, \( J_{\text{trans}} = 16.0, 1.5 \text{ Hz, H}_10 \)); 5.31 (1H, dd, \( J_{\text{cis}} = 11.0, 1.5 \text{ Hz, H}_{12} \)); 4.67 (2H, dt, \( J = 5.0, 1.5 \text{ Hz, H}_7 \)).
**Chapter 5. Experimental section**

$^{13}$C-NMR (62 MHz, CDCl$_3$) $\delta_C$: 152.0 (C$_1$); 134.1 (C$_3$); 131.8 (C$_6$); 125.7 (C$_4$); 120.6 (C$_5$); 118.4 (C$_{11}$); 115.0 (C$_2$); 70.1 (C$_7$).

**LRMS [FAB(+) $m/z$ (%): 180 (19); 43 (100).**

**HRMS [FAB(+) $m/z$: calculated for C$_9$H$_9$NO$_3$ [M]$^+$ 179.0582, found 180.0583.**

**HPLC (Method A): $t_R = 8.18$ min.**

[1-Nitro-4-(pent-4-enyloxy)benzene] 2.30d (0.09 g, 95% yield, yellow pale oil)

![Chemical Structure](image)

**RF**: 0.46 (Eluant: hexane/ethyl acetate; 8/2).

**IR (neat): $\nu_{\max }$ (cm$^{-1}$): 2940 (w); 1591 (s); 1469 (s); 1256 (m).**

$^1$H-NMR (250 MHz, CDCl$_3$ $\delta_H$: 8.16 (2H, d, $J = 9.4$ Hz, H$_3$); 6.92 (2H, d, $J = 9.3$ Hz, H$_2$); 5.83 (1H, m, H$_{11}$); 5.05 (1H, dd, $J_{\text{trans}} = 16.0$, 1.5 Hz, H$_{10}$); 4.98 (1H, dd, $J_{\text{cis}} = 10.0$, 1.5 Hz, H$_{12}$); 4.05 (2H, t, $J = 7.0$ Hz, H$_5$); 2.22 (2H, m, H$_7$); 1.91 (2H, m, H$_6$).

$^{13}$C-NMR (62 MHz, CDCl$_3$ $\delta_C$: 164.6 (C$_1$); 141.7 (C$_4$); 137.7 (C$_8$); 126.6 (C$_3$); 116.0 (C$_9$); 114.8 (C$_2$); 68.4 (C$_5$); 30.3 (C$_7$); 28.5 (C$_6$).

**LRMS [FAB(+) $m/z$ (%): 208 (100); 73 (78).**

**HRMS [FAB(+) $m/z$: calculated for C$_{11}$H$_{13}$NO$_3$ [M]$^+$ 207.0895, found 207.0889.**

**HPLC (Method A): $t_R = 9.60$ min.**
[4-(Pent-4-enyloxy)benzaldehyde] 2.30e (0.07 g, 82% yield, colourless oil)

\[\text{H-NMR (250 MHz, CDCl}_3\text{)} \delta \text{H: } 9.87 (1\text{H, s, H}_6); 7.81 (2\text{H, d, } J = 9.0 \text{ Hz, H}_3); 6.98 (2\text{H, d, } J = 9.0 \text{ Hz, H}_2); 5.85 (1\text{H, m, H}_{13}); 5.06 (1\text{H, dd, } J_{\text{trans}} = 17.0, 1.5 \text{ Hz, H}_{12}); 4.99 (1\text{H, dd, } J_{\text{cis}} = 10.0, 1.5 \text{ Hz, H}_{14}); 4.05 (2\text{H, t, } J = 6.0 \text{ Hz, H}_7); 2.25 (2\text{H, m, H}_9); 1.91 (2\text{H, m, H}_8).

\[\text{C-NMR (62 MHz, CDCl}_3\text{)} \delta \text{C: } 191.2 (\text{C}); 164.6 (\text{C}_1); 137.8 (\text{C}_{10}); 132.4 (\text{C}_3); 130.2 (\text{C}_4); 115.9 (\text{C}_{11}); 115.1 (\text{C}_2); 67.9 (\text{C}_7); 30.4 (\text{C}_9); 28.6 (\text{C}_8).

The compound exhibited \(^1\text{H} \text{ and } ^{13}\text{C-NMR spectra identical to those described previously.}^{171}\]

[1-Nitro-4-(3-phenylpropoxy)benzene] 2.30f (0.12 g, 98% yield, white solid)

\[\text{H-NMR (250 MHz, CDCl}_3\text{)} \delta \text{H: } 8.16 (2\text{H, d, } J = 9.4 \text{ Hz, H}_3); 7.33-7.16 (5\text{H, m, H}_{9-11}); 6.90 (2\text{H, d, } J = 9.0 \text{ Hz, H}_2); 4.02 (2\text{H, t, } J = 6.3 \text{ Hz, H}_5); 2.81 (2\text{H, t, } J = 7.3 \text{ Hz, H}_7); 2.19-2.08 (2\text{H, m, H}_6).

\[\text{C-NMR (62 MHz, CDCl}_3\text{)} \delta \text{C: } 164.5 (\text{C}_1); 141.8 (\text{C}_4); 141.4 (\text{C}_8); 128.9 (\text{C}_{10}); 128.9 (\text{C}_9); 126.6 (\text{C}_{11}); 126.3 (\text{C}_3); 114.8 (\text{C}_2); 68.1 (\text{C}_5); 32.4 (\text{C}_7); 30.9 (\text{C}_6).

\text{HPLC (Method A): } t_R = 10.04 \text{ min.}
The compound exhibited $^1$H and $^{13}$C-NMR spectra identical to those described previously.\textsuperscript{152}

**General method for one-pot $O$-alkylisourea mediated microwave-assisted esters synthesis using primary alcohols**

![Chemical Reaction Diagram]

The primary alcohol \textit{2.31a-d} (2.0 mmol) was added to a mixture of copper (II) triflate (0.014 g, 0.040 mmol) in \textit{N,N'-diisopropylcarbodiimide 2.26} (2.0 mmol) in a microwave vial. The vial was capped and the green mixture heated at 100 °C using a Smith Synthesizer\textsuperscript{TM} for 5 min. A solution of acid (1.9 mmol) in CH$_3$CN (2 mL) was added to the oil, subsequently the vial was re-capped and heated at 120 °C using a Smith Synthesizer\textsuperscript{TM} for 5 min. The 1,3-diisopropylurea was filtered off, the solvent evaporated and the residue purified by chromatography using a SPE cartridges (20 mL) packed with silica and alumina.

\textit{[Phenethyl 4-phenoxybenzoate] 2.8d} (0.51 g, 84% yield, white solid). Spectral data (IR, NMR) were identical to those previously reported (page 87).
[Phenethyl decanoate] 2.8j (0.37 g, 70% yield, colourless oil)

\[ \text{RF: 0.50 (Eluant: hexane/ethyl acetate; 98/2).} \]

\[ \text{IR (neat): } \nu_{\text{max}} / (\text{cm}^{-1}) \text{ 3028 (w); 2925 (s); 1737 (s); 699 (m).} \]

\[ \text{\textsuperscript{1}H-NMR (250 MHz, CDCl}\textsubscript{3} \text{ } \delta_{\text{H}}: 7.47-7.34 (5H, m, H_5,7); 4.40 (2H, t, } J = 7.0 \text{ Hz, H}_2); \]

\[ 3.08 (2H, t, J = 7.0 \text{ Hz, H}_3); 2.43 (2H, t, J = 7.3 \text{ Hz, H}_8); 1.77-1.71 (2H, m, H_9); 1.41 \]

\[ (12H, \text{ br, H}_{10-15}); 1.04 (3H, t, J = 7.0 \text{ Hz, H}_{16}). \]

\[ \text{\textsuperscript{13}C-NMR (62 MHz, CDCl}\textsubscript{3} \text{ } \delta_{\text{C}}: 173.9 (C_1); 138.0 (C_4); 129.0 (C_6); 128.6 (C_3); 126.6 \]

\[ (C_7); 64.8 (C_2); 35.3 (C_3); 34.4 (C_8); 32.0 (C_14); 29.5 (C_12); 29.4 (C_{11}); 29.2 \]

\[ (C_{10}); 25.0 (C_9); 22.8 (C_{15}); 14.2 (C_{16}). \]

\[ \text{LRMS [FAB(+)]} \text{ } m/z (\%): 277 (14); 105 (100); 91 (41); 77 (28); 43 (81); 27 (64). \]

\[ \text{HRMS [FAB(+)]} \text{ } m/z: \text{ calculated for C}_{18}H_{29}O_2 [M+H]^+ 277.2162, \text{ found 277.2168.} \]

\[ \text{HPLC (Method A): } t_R = 11.59 \text{ min} \]

[Phenethyl 4-iodobenzoate] 2.8k (0.58 g, 87% yield, white solid)

\[ \text{RF: 0.7 (Eluant: hexane/ethyl acetate; 9/1).} \]

\[ \text{IR (neat): } \nu_{\text{max}} / (\text{cm}^{-1}) \text{ 3053 (br); 1719 (s); 1587 (s); 1266 (s); 1117 (s); 739 (s).} \]

\[ \text{\textsuperscript{1}H-NMR (250 MHz, CDCl}\textsubscript{3} \text{ } \delta_{\text{H}}: 7.69-7.57 (4H, m, H_{9,10}); 7.24-7.11 (5H, m, H_{5,7}); 4.40 \]

\[ (2H, t, J = 7.0 \text{ Hz, H}_2); 2.95 (2H, t, J = 7.0 \text{ Hz, H}_3). \]
\(^{13}\)C-NMR (62 MHz, CDCl\(_3\)) \(\delta_C\): 166.1 (C\(_1\)); 137.8 (C\(_4\)); 131.1 (C\(_{10}\)); 129.8 (C\(_9\)); 129.0 (C\(_8\)); 129.0 (C\(_6\)); 128.7 (C\(_5\)); 126.8 (C\(_7\)); 100.8 (C\(_{11}\)); 65.8 (C\(_2\)); 35.3 (C\(_3\)).

LRMS [FAB(+) \(m/z\) (%): 353 (46); 231 (56); 105 (100); 91 (74); 77 (43).

HRMS [FAB(+) \(m/z\): calculated for C\(_{15}\)H\(_{14}\)I\(_2\) [M+H]\(^{+}\) 353.0033, found 353.0031.

HPLC (Method A): \(t_R = 10.72\) min.

[Phenethyl-2,2-dichloro-1-methylcyclopropanecarboxylate] 2.81 (0.45 g, 87\% yield, colourless oil)

\[
\begin{align*}
\text{IR (neat): } & \nu_{\text{max}}/(\text{cm}^{-1}) \text{ 3055 (br); 2982 (br); 1733 (s); 1455 (m); 1266 (s); 741 (s).} \\
\text{H-NMR (250 MHz, CDCl}_3\text{): } & \delta_H: 7.56-7.46 (5H, m, H\(_{5,7}\)); 4.63 (2H, t, \(J = 7.0\) Hz, H\(_2\)); 3.24 (2H, t, \(J = 7.0\) Hz, H\(_3\)); 2.50 (1H, d, \(J = 7.5\) Hz, H\(_{12}\)); 1.79 (3H, s, H\(_9\)); 1.64 (1H, d, \(J = 7.5\) Hz, H\(_{11}\)).
\end{align*}
\]

\(^{13}\)C-NMR (62 MHz, CDCl\(_3\)) \(\delta_C\): 169.2 (C\(_1\)); 137.6 (C\(_4\)); 129.0 (C\(_6\)); 128.6 (C\(_5\)); 126.8 (C\(_7\)); 66.4 (C\(_{13}\)); 67.7 (C\(_2\)); 35.5 (C\(_3\)); 35.1 (C\(_8\)); 30.9 (C\(_{10}\)); 18.3 (C\(_9\)).

LRMS [FAB(+) \(m/z\) (%): 151 (61); 105 (100); 91 (76); 77 (63).

HRMS [FAB(+) \(m/z\): calculated for C\(_{13}\)H\(_{15}\)Cl\(_2\)O\(_2\) [M+H]\(^{+}\) 273.0444, found 273.0443.

HPLC (Method A): \(t_R = 10.17\) min.
Chapter 5. Experimental section

[Phenethyl-1-adamantane carboxylate] 2.8m (0.38 g, 70% yield, white solid)

\[
\text{Rf: 0.50 (Eluant: hexane/ethyl acetate; 98/2).}
\]

IR (neat): \(\nu_{\text{max}}/(\text{cm}^{-1})\) 3027 (w); 2851 (s); 1725 (s); 1454 (s); 1233 (s); 741 (s).

\(^1\)H-NMR (250 MHz, CDCl\(_3\)) \(\delta_{\text{H}}\): 7.45-7.33 (5H, m, H\(_{5-7}\)); 4.38 (2H, t, \(J = 7.0\) Hz, H\(_2\)); 3.07 (2H, t, \(J = 7.0\) Hz, H\(_3\)); 2.12-1.82 (15H, br, H\(_{9-10,11,12,13-13'}\)).

\(^{13}\)C-NMR (62 MHz, CDCl\(_3\)) \(\delta_{\text{C}}\): 177.7 (C\(_1\)); 138.2 (C\(_4\)); 129.1 (C\(_6\)); 128.5 (C\(_5\)); 126.6 (C\(_7\)); 64.7 (C\(_2\)); 40.8 (C\(_3, C_9, C_{14}\)); 38.9 (C\(_8\)); 36.6 (C\(_{11, C_{16-17}}\)); 35.3 (C\(_3\)); 28.1 (C\(_{10, C_{12, C_{15}}}\)).

LRMS [FAB(\(+\))] \(m/z\) (%): 285 (16); 135 (81); 105 (100); 91 (55); 77 (52); 43 (13).

HRMS [FAB(\(+\))] \(m/z\): calculated for C\(_{19}\)H\(_{25}\)O\(_2\) [M+H]\(^+\) 285.1849, found 285.1851.

HPLC (Method A): \(t_R = 12.09\) min.

[Hexyl 2,2-diphenylpropanoate] 2.8n (0.53 g, 90% yield, yellow oil)

\[
\text{Rf: 0.65 (Eluant: hexane/ethyl acetate; 9/1).}
\]

IR (neat): \(\nu_{\text{max}}/(\text{cm}^{-1})\) 3058 (br); 2359 (s); 1725 (s); 1494 (m); 1265 (s); 739 (s).

\(^1\)H-NMR (250 MHz, CDCl\(_3\)) \(\delta_{\text{H}}\): 7.60-7.48 (10H, m, H\(_{11-13}\)); 4.41 (2H, t, \(J = 7.0\) Hz, H\(_2\)); 2.20 (3H, s, H\(_9\)); 1.86-1.81 (2H, m, H\(_3\)); 1.53-1.47 (6H, br, H\(_{4-6}\)); 1.12 (3H, t, \(J = 7.0\) Hz, H\(_7\)).
\(^{13}\)C-NMR (62 MHz, CDCl\(_3\)) \(\delta_C\): 175.2 (C\(_1\)); 144.7 (C\(_{10}\)); 128.2 (C\(_{12}\)); 128.1 (C\(_{11}\)); 126.8 (C\(_{13}\)); 65.4 (C\(_2\)); 56.7 (C\(_8\)); 31.4 (C\(_3\)); 28.5 (C\(_3\)); 27.2 (C\(_4\)); 25.6 (C\(_9\)); 22.6 (C\(_6\)); 14.1 (C\(_7\)).

LRMS [FAB(+)] m/z (%): 311 (37); 91 (24); 77 (28); 55 (25); 43 (100).

HRMS [FAB(+)] m/z: calculated for C\(_{21}\)H\(_{27}\)O\(_2\) [M+H]\(^+\) 311.2006, found 311.2012.

HPLC (Method A): \(t_R = 11.22\) min.

[Hexyl 2-(3-chlorophenyl)acetate] 2.8o (0.42 g, 87% yield, yellow oil)

\[\text{IR (neat): } \nu/\text{cm}^{-1} \quad 3053 \text{ (br)}; 2960 \text{ (br)}; 1731 \text{ (s)}; 1422 \text{ (s)}; 1265 \text{ (s)}; 895 \text{ (s)}; 740 \text{ (s)}.
\]

\(^1\)H-NMR (250 MHz, CDCl\(_3\)) \(\delta_H\): 7.29-7.15 (4H, m, H\(_{10}, H_{12}\)); 4.12 (2H, t, \(J = 6.5\) Hz, H\(_2\)); 3.58 (2H, s, H\(_8\)); 1.61-1.58 (2H, m, H\(_3\)); 1.33-1.27 (6H, br, H\(_{4,6}\)); 0.88 (2H, t, \(J = 7.0\) Hz, H\(_7\)).

\(^{13}\)C-NMR (62 MHz, CDCl\(_3\)) \(\delta_C\): 171.1 (C\(_1\)); 136.1 (C\(_9\)); 134.4 (C\(_{11}\)); 129.8 (C\(_{13}\)); 129.5 (C\(_{10}\)); 127.6 (C\(_{14}\)); 127.4 (C\(_{12}\)); 65.3 (C\(_2\)); 41.1 (C\(_8\)); 31.5 (C\(_3\)); 28.6 (C\(_3\)); 25.6 (C\(_4\)); 22.6 (C\(_6\)); 14.1 (C\(_7\)).

LRMS [FAB(+)] m/z (%): 255 (37); 125 (72); 91 (20); 43 (100); 27 (60).

HRMS [FAB(+)] m/z: calculated for C\(_{14}\)H\(_{20}\)ClO\(_2\) [M+H]\(^+\) 255.1146, found 255.1147.

HPLC (Method A): \(t_R = 10.64\) min.
Chapter 5. Experimental section

[Hexyl 2-hydroxybenzoate] 2.8p (0.35 g, 82% yield, colourless oil)

\[
\begin{align*}
6 & \quad 4 & \quad 2 \\
7 & \quad 5 & \quad 3 \\
\quad O & \quad \text{OH} & \quad 9 \\
\quad 10 & & \\
\end{align*}
\]

Rf: 0.75 (Eluant: hexane/ethyl acetate; 9/1).

IR (neat): \( \nu_{\text{max}} / (\text{cm}^{-1}) \): 3183 (br); 2958 (s); 2932 (s); 2858 (s); 1675 (s); 1614 (s).

\(^1\)H-NMR (250 MHz, CDCl\(_3\)) \( \delta_H \): 10.88 (1H, s, OH); 7.84 (1H, dd, \( J = 7.9, 1.7 \) Hz, H\(_{13}\)); 7.43 (1H, ddd, \( J = 8.6, 7.3, 1.7 \) Hz, H\(_{11}\)); 6.97 (1H, dd, \( J = 8.5, 1.1 \) Hz, H\(_{10}\)); 6.86 (1H, ddd, \( J = 8.1, 7.6, 1.2 \) Hz, H\(_{12}\)); 4.33 (2H, t, \( J = 6.6 \) Hz, H\(_2\)); 1.82-1.71 (2H, m, H\(_3\)); 1.49-1.28 (6H, br, H\(_4\)); 0.91 (3H, t, \( J = 7.0 \) Hz, H\(_7\)).

\(^13\)C-NMR (62 MHz, CDCl\(_3\)) \( \delta_C \): 170.2 (C\(_1\)); 161.7 (C\(_9\)); 135.5 (C\(_{11}\)); 129.9 (C\(_{13}\)); 119.0 (C\(_{12}\)); 117.6 (C\(_{10}\)); 112.7 (C\(_8\)); 65.5 (C\(_2\)); 31.5 (C\(_3\)); 28.6 (C\(_3\)); 25.7 (C\(_4\)); 22.6 (C\(_6\)); 14.0 (C\(_7\)).

LRMS [FAB(+)] \( m/z \) (%): 223 (51); 121 (100); 43 (86); 29 (53).

HRMS [FAB(+)] \( m/z \): calculated for \( \text{C}_{13}\text{H}_{19}\text{O}_3 \) [M+H]\(^+\) 223.1329, found 223.1334.

HPLC (Method B): \( t_R = 5.88 \) min.

[Hexyl decanoate] 2.8q (0.36 g, 74% yield, colourless oil)

\[
\begin{align*}
6 & \quad 4 & \quad 2 \\
7 & \quad 5 & \quad 3 \\
\quad O & \quad \text{CH} & \quad 9 \\
\quad 10 & & \\
\quad 11 & & \\
\quad 12 & & \\
\quad 13 & & \\
\quad 14 & & \\
\quad 15 & & \\
\quad 16 & & \\
\end{align*}
\]

Rf: 0.70 (Eluant: hexane/ethyl acetate; 98/2).

IR (neat): \( \nu_{\text{max}} / (\text{cm}^{-1}) \): 3054 (w); 2957 (br); 1731 (s); 1466 (m); 1265 (s); 740 (s).

\(^1\)H-NMR (250 MHz, CDCl\(_3\)) \( \delta_H \): 4.03 (2H, t, \( J = 6.6 \) Hz, H\(_2\)); 2.26 (2H, t, \( J = 7.6 \) Hz, H\(_8\)); 1.61-1.53 (4H, m, H\(_3\), H\(_9\)); 1.27-1.23 (18H, br, H\(_{4-6}, H_{10-13}\)); 0.86-0.82 (6H, br, H\(_7\), H\(_9\)).
Chapter 5. Experimental section

13C-NMR (62 MHz, CDCl3) δC: 174.0 (C1); 64.4 (C2); 34.5 (C8); 32.0 (C14); 31.5 (C3); 29.5 (C12); 29.4 (C13); 29.3 (C11); 28.7 (C10); 25.7 (C4); 25.1 (C9); 22.7 (C6); 22.6 (C15); 14.2 (C7); 14.1 (C16).

LRMS [FAB(+)] m/z (%): 257 (37); 173 (42); 43 (100); 29 (73).

HRMS [FAB(+)] m/z: calculated for C16H33O2 [M+H]+ 257.2475, found 257.2481.

[Hexyl-2,2-dichloro-1-methylcyclopropanecarboxylate] 2.8r (0.34 g, 72% yield, colourless oil)

[Rf: 0.65 (Eluant: hexane/ethyl acetate; 98/2).

IR (neat): νmax /cm⁻¹) 3054 (w); 2959 (br); 1730 (s); 1265 (s); 1175 (m); 739 (s).

1H-NMR (250 MHz, CDCl3) δH: 4.14 (2H, t, J = 6.6 Hz, H2); 2.24 (1H, d, J = 7.4 Hz, H12); 1.67-1.59 (2H, m, H3); 1.56 (3H, m, H9); 1.38 (1H, d, J = 7.5 Hz, H11); 1.36-1.24 (6H, br, H4,6); 0.87 (3H, t, J = 6.5 Hz, H7).

13C-NMR (62 MHz, CDCl3) δC: 169.3 (C1); 66.2 (C13); 62.8 (C2); 35.6 (C8); 31.5 (C10); 30.9 (C5); 28.6 (C3); 25.6 (C4); 22.6 (C6); 18.4 (C9); 14.1 (C7).

LRMS [FAB(+)] m/z (%): 253 (6); 217 (52); 91 (67); 45 (100); 29 (63).

HRMS [FAB(+)] m/z: calculated for C11H19Cl2O2 [M+H]+ 253.0757, found 253.0765.

[4-Chlorobenzyl decanoate] 2.8s (0.45 g, 80% yield, colourless oil)
Chapter 5. Experimental section

**RP 0.70 (Eluant: hexane/ethyl acetate; 9/1).**

IR (neat): $\nu_{\text{max}}$ (cm$^{-1}$) 3053 (br); 2928 (br); 1733 (s); 1265 (s); 1094 (m); 744 (s).

$^{1}$H-NMR (250 MHz, CDCl$_3$) $\delta_{H}$: 7.53-7.44 (4H, m, H$_{4,5}$); 5.25 (2H, s, H$_2$); 2.53 (2H, t, $J$ = 7.3 Hz, H$_7$); 1.83-1.79 (2H, m, H$_8$); 1.44-1.09 (12H, br, H$_{9-14}$); 1.06 (3H, t, $J$ = 7.0 Hz, H$_{15}$).

$^{13}$C-NMR (62 MHz, CDCl$_3$) $\delta_{C}$: 173.7 (C$_1$); 134.8 (C$_3$); 134.2 (C$_6$); 129.7 (C$_5$); 128.8 (C$_4$); 65.3 (C$_2$); 34.4 (C$_7$); 32.0 (C$_{13}$); 29.5 (C$_{11}$); 29.4 (C$_{10}$, C$_{12}$); 29.2 (C$_9$); 25.0 (C$_8$); 22.8 (C$_{14}$); 14.2 (C$_{15}$).

LRMS [FAB(+)] m/z (%): 296 (18); 155 (75); 91 (58); 77 (39); 55 (100).

HRMS [FAB(+)] m/z: calculated for C$_{17}$H$_{25}$ClO$_2$ [M]$^+$ 296.1543, found 296.1465.

HPLC (Method A): $t_R = 11.90$ min.

**[4-Chlorobenzyl benzoate] 2.8t** (0.42 g, 90% yield, colourless oil)

\begin{center}
\includegraphics[width=0.3\textwidth]{c5-lab2.png}
\end{center}

**Rf: 0.70 (Eluant: hexane/ethyl acetate; 9/1).**

IR (neat): $\nu_{\text{max}}$ (cm$^{-1}$) 3062 (br); 2957 (br); 1720 (s); 1493 (s); 1270 (s); 738 (s).

$^{1}$H-NMR (250 MHz, CDCl$_3$) $\delta_{H}$: 8.11-8.07 (2H, m, H$_8$); 7.60-7.33 (4H, m, H$_{4,5}$, H$_{9,10}$); 5.33 (2H, s, H$_2$).

$^{13}$C-NMR (62 MHz, CDCl$_3$) $\delta_{C}$: 166.2 (C$_1$); 134.6 (C$_3$); 134.1 (C$_6$); 133.1 (C$_{10}$); 130.0 (C$_7$); 129.7 (C$_8$); 129.6 (C$_5$); 128.8 (C$_9$); 128.4 (C$_4$); 65.8 (C$_2$).

LRMS [FAB(+)] m/z (%): 246 (28); 125 (94); 105 (100); 77 (85); 51 (60).

HRMS [FAB(+)] m/z: calculated for C$_{14}$H$_{12}$ClO$_2$ [M+H]$^+$ 247.0520, found 247.0526.

HPLC (Method A): $t_R = 10.28$ min.
[4-Chlorobenzyl 2,2-diphenylopropanoate] 2.8u (0.53 g, 80% yield, colourless oil)

\[
\begin{align*}
&\text{RI: } 0.50 \text{ (Eluant: hexane/ethyl acetate; 9/1).} \\
&\text{IR (neat): } v_{\text{max}}/(\text{cm}^{-1}) 3087 \text{ (br); 1729 (s); 1493 (s); 1445 (s); 1212 (s); 1076 (s); 699 (s).} \\
&^1\text{H-NMR (250 MHz, CDCl}_3\text{) } \delta_H: 7.60-7.36 (14H, m, H}_{4,5,10-12}; 5.42 (2H, s, H}_2; 2.02 (3H, s, H}_8). \\
&^13\text{C-NMR (62 MHz, CDCl}_3\text{) } \delta_C: 174.8 (C}_1); 144.2 (C}_9); 134.4 (C}_3); 134.0 (C}_6); 129.3 (C}_{11}); 128.7 (C}_5); 128.2 (C}_4); 127.0 (C}_{10}); 66.1 (C}_2); 56.7 (C}_7); 27.2 (C}_8). \\
&\text{LRMS [FAB(+)] } m/z: 351 (5); 181 (96); 125 (100); 91 (39); 77 (40). \\
&\text{HRMS [FAB(+)] } m/z: \text{ calculated for C}_{22}H_{20}ClO_2 [M+H]^+ 351.1146, found 351.1152. \\
&\text{HPLC (Method A): } t_R = 10.88 \text{ min.}
\end{align*}
\]

[4-Chlorobenzyl 2-phenoxyacetate] 2.8v (0.46 g, 87% yield, colourless oil)

\[
\begin{align*}
&\text{RI: } 0.35 \text{ (Eluant: hexane/ethyl acetate; 9/1).} \\
&\text{IR (neat): } v_{\text{max}}/(\text{cm}^{-1}) 3054 (br); 2986 (br); 1760 (s); 1265 (s); 1089 (s); 743 (s). \\
&^1\text{H-NMR (250 MHz, CDCl}_3\text{) } \delta_H: 7.47-7.36 (6H, m, H}_{4,5,10}; 7.15-7.00 (3H, m, H}_9, H_{11}); 5.32 (2H, s, H}_2); 4.79 (2H, s, H}_7). \\
&^13\text{C-NMR (62 MHz, CDCl}_3\text{) } \delta_C: 168.9 (C}_1); 157.8 (C}_8); 134.5 (C}_3); 133.8 (C}_6); 130.0
(C_{10}); 129.7 (C_5); 128.9 (C_4); 121.9 (C_{11}); 114.7 (C_9); 66.2 (C_2), 65.4 (C_7).

**LRMS** [FAB(+)] m/z (%): 276 (22); 125 (100); 91 (96); 77 (50).

**HRMS** [FAB(+)] m/z (%): calcd. for C_{15}H_{13}ClO_{3} [M]^+ 276.0553, found 276.0553.

**HPLC** (Method A): t_R = 9.88 min.

[4-Isopropylbenzyl 4-phenylbenzoate] 2.8w (0.51 g, 82% yield, colourless oil)

Rf: 0.56 (Eluant: hexane/ethyl acetate; 9/1).

**Mp**: 122-123 °C.

**IR** (neat): v_{max}/(cm^{-1}) 3054 (br); 1721 (s); 1525 (s); 1348 (s); 1265 (s); 740 (s).

**^{1}H-NMR** (250 MHz, CDCl_3) δ_H: 8.47 (2H, d, J = 9.0 Hz, H_{10}); 7.93-7.56 (1H, m, H_4, H_{11}, H_{14-16}); 5.68 (2H, s, H_2); 3.23 (1H, m, H_7); 1.58 (6H, d, J = 7.0 Hz, H_8).

**^{13}C-NMR** (62 MHz, CDCl_3) δ_C: 166.2 (C_1); 149.0 (C_6); 145.5 (C_{12}); 139.8 (C_3); 133.5 (C_{13}); 130.2 (C_{10}); 128.9 (C_9); 128.9 (C_{15}); 128.4 (C_{14}); 128.1 (C_{11}); 127.2 (C_{16}); 126.9 (C_4); 126.6 (C_3); 66.6 (C_2); 33.8 (C_7); 23.9 (C_8).

**LRMS** [FAB(+)] m/z (%): 331 (5); 307 (79); 154 (100); 91 (62); 77 (80).

**HRMS** [FAB(+)] m/z: calculated for C_{23}H_{23}O_{2} [M+H]^+ 331.1693, found 331.1698.

**HPLC** (Method A): t_R = 10.55 min.
[4-Isopropylbenzyl 4-iodobenzoate] 2.8x (0.60 g, 83% yield, colourless oil)

Rf: 0.62 (Eluant: hexane/ethyl acetate; 9/1).

IR (neat): $\nu_{\text{max}}$ (cm$^{-1}$) 3053 (br); 1720 (s); 1586 (s); 1113 (s); 739 (s).

$^1$H-NMR (250 MHz, CDCl$_3$) $\delta$: 7.73-7.65 (4H, m, $H_{10,11}$); 7.34-7.18 (4H, m, $H_{4,5}$); 5.28 (2H, s, $H_2$); 2.86 (1H, m, $H_7$); 1.20 (6H, d, $J = 7.0$ Hz, $H_8$).

$^{13}$C-NMR (62 MHz, CDCl$_3$) $\delta$: 165.7 (C$_1$); 149.0 (C$_6$); 137.6 (C$_{11}$); 133.1 (C$_3$); 131.0 (C$_{10}$); 129.6 (C$_4$); 128.4 (C$_9$); 126.6 (C$_5$); 100.8 (C$_{12}$); 66.8 (C$_2$); 33.8 (C$_7$); 23.9 (C$_8$).

LRMS [FAB(+)] $m/z$ (%): 380 (11); 105 (40); 91 (51); 77 (31).

HRMS [FAB(+)] $m/z$: calculated for C$_{17}$H$_{17}$IO$_2$ [M]$^+$ 380.0273, found 380.0275.

HPLC (Method A): $t_R = 11.47$ min.
Chapter 5. Experimental section

5.3 Experimental for chapter III

[(±)-Octan-2-yl isourea] (±)-2.16i (2.05 g, 80% yield, colourless oil). The compound was synthesised using general method described on page 81.

![Chemical Structure](image)

IR (neat): $\nu_{\text{max}}$ / (cm$^{-1}$) 2962 (m); 1658 (s); 1305 (m); 1169 (m); 1121 (m); 1065 (m).

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$: 4.85 (1H, m, H$_7$); 3.69 (1H, m, H$_2$); 3.30 (1H, br, NH); 3.11 (1H, m, H$_4$); 1.55-1.25 (10H, m, H$_8-12$); 1.14 (3H, d, $J=6.3$ Hz, H$_6$); 1.10-1.02 (12H, m, H$_3-5$); 0.84 (3H, d, $J=6.6$ Hz, H$_13$).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$: 150.9 (C$_1$); 69.9 (C$_7$); 46.2 (C$_2$); 43.3 (C$_8$); 36.2 (C$_9$); 31.8 (C$_{11}$); 29.4 (C$_{10}$); 25.3 (C$_{12}$); 24.4 (C$_3$); 24.1 (C$_4$); 22.7 (C$_5$); 19.7 (C$_6$); 14.1 (C$_{13}$).

LRMS [FAB(+)] $m/z$ (%): 257 (73); 145 (87); 103 (49); 91 (12); 43 (100).

HRMS [FAB(+)] $m/z$ calcd. for C$_{15}$H$_{33}$N$_2$O [$\text{M}+\text{H}^+$] 257.2587, found 257.2590.

General procedure for microwave-assisted synthesis of carboxylic esters using secondary alcohols

![Chemical Reaction](image)

A microwave vial was charged with the O-alkylisourea (0.500 mmol), the acid (0.470 mmol) and 1 mL of CH$_3$CN. The vial was capped and the mixture heated at 130 °C.
under stirring using a Smith Synthesizer™ for 5 min. The 1,3-diisopropylurea was filtered off, the solvent evaporated and the residue purified by chromatography using a SPE cartridges (20 mL) packed with silica and alumina.

\[(\pm)-4\text{-Phenylbutan-2-yl-2,2-diphenylpropanoate}\] \((\pm)-3.31\text{a}\) (0.16 g, 96% yield, colourless oil)

\[
\begin{align*}
\text{RI:} & \quad 0.62 \text{ (Eluant: hexane/ethyl acetate; 9/1).} \\
\text{IR (neat):} & \quad \nu_{\max} / (\text{cm}^{-1}) 2976 (\text{w}); 1720 (\text{s}); 1445 (\text{m}); 1375 (\text{m}); 1216 (\text{s}); 695 (\text{s}). \\
^1\text{H-NMR} (300 \text{ MHz, CDCl}_3) & \delta_{\text{H}}: 7.43-7.09 (15\text{H, m, H}_{7,9}, \text{H}_{13,13}, \text{H}_{14,14}, \text{H}_{15,15}); 5.09 (1\text{H, m, H}_3); 2.54-2.40 (2\text{H, m, H}_5), 2.05 (3\text{H, s, H}_{11}); 1.97-1.79 (2\text{H, m, H}_4); 1.34 (3\text{H, d, } J = 6.3 \text{ Hz, H}_2). \\
^{13}\text{C-NMR} (75 \text{ MHz, CDCl}_3) & \delta_{\text{C}}: 174.6 (\text{C}_1); 144.8 (\text{C}_{12}); 144.6 (\text{C}_{12}'); 141.7 (\text{C}_6); 128.5 (\text{C}_8); 128.4, \text{ d, (C}_{14}, \text{C}_{14}'); 128.2, \text{ d, (C}_{13}, \text{C}_{13}'); 128.1 (\text{C}_7); 126.9, \text{ d, (C}_{15}, \text{C}_{15}'); 126.0 (\text{C}_9); 71.6 (\text{C}_3); 56.8 (\text{C}_{10}); 37.8 (\text{C}_4), 31.6 (\text{C}_5), 27.3 (\text{C}_{11}) 19.8 (\text{C}_2). \\
\text{LRMS [FAB(+) m/z (%):} & \quad 359 (41); 227 (64); 181 (87); 91 (100); 77 (61); 43 (30). \\
\text{HRMS [FAB(+) m/z:} & \quad \text{calculated for C}_{25}\text{H}_{27}\text{O}_2 [M+H]^+ 359.2006, \text{found 359.2012.}\ \\
\text{HPLC (Method A):} & \quad t_R = 11.02 \text{ min.}
\end{align*}
\]

\[(\pm)-4\text{-Phenylbutan-2-yl decanoate}\] \((\pm)-3.31\text{b}\) (0.07 g, 48% yield, colourless oil)

\[
\begin{align*}
\text{HRMS [FAB(+) m/z:} & \quad \text{calculated for C}_{25}\text{H}_{27}\text{O}_2 [M+H]^+ 359.2006, \text{found 359.2012.}\ \\
\text{HPLC (Method A):} & \quad t_R = 11.02 \text{ min.}
\end{align*}
\]
Chapter 5. Experimental section

**RF:** 0.45 (Eluant: hexane/ethyl acetate; 9/1).

**IR** (neat): $v_{\text{max}}$ (cm$^{-1}$) 2923 (w); 1731 (s); 1495 (m); 1173 (m); 746 (m); 698 (s).

**$^{1}$H-NMR** (300 MHz, CDCl$_3$) $\delta$: 7.23-7.07 (5H, m, H$_{7-9}$), 4.87 (1H, m, H$_3$); 2.66-2.46 (2H, m, H$_3$); 2.20 (2H, t, $J = 7.3$ Hz, H$_{10}$); 1.94-1.64 (2H, m, H$_4$); 1.57-1.52 (2H, m, H$_{11}$); 1.21-1.15 (15H, m, H$_2$), H$_{12-17}$); 0.82-0.77 (3H, t, $J = 6.4$ Hz, H$_{18}$).

**$^{13}$C-NMR** (75 MHz, CDCl$_3$) $\delta$: 173.6 (C$_1$); 141.7 (C$_6$); 128.5 (C$_7$); 128.4 (C$_7$); 126.0 (C$_9$); 70.3 (C$_3$); 37.8 (C$_4$); 34.8 (C$_{10}$); 32.0 (C$_{16}$); 31.9 (C$_{14}$); 29.6 (C$_5$); 29.4 (C$_{13}$); 29.4 (C$_{15}$); 29.3 (C$_{12}$); 25.2 (C$_{11}$); 22.7 (C$_{17}$); 20.2 (C$_2$); 14.2 (C$_{18}$).

**LRMS [FAB(+)] m/z (%):** 305 (29); 133 (69); 91 (87); 77 (49); 43 (100).

**HRMS [FAB(+)] m/z:** calculated for C$_{20}$H$_{33}$O$_2$ [M+H]$^+$ 305.2475 found 305.2481.

**HPLC (Method A):** $t_R = 12.16$ min.

[(±)-4-Phenylbutan-2-yl-2,2-dichloro-1-methylcyclopropanecarboxylate] (±)-3.31c (0.10 g, 70% yield, colourless oil)

**RF:** 0.37 (Eluant: hexane/ethyl acetate; 9/1).

**IR** (neat): $v_{\text{max}}$ (cm$^{-1}$) 2977 (w); 1729 (s); 1454 (s); 1278 (s); 1175 (s); 744 (s); 697 (s).

**$^{1}$H-NMR** (300 MHz, CDCl$_3$) $\delta$: 7.27-7.06 (5H, m, H$_{7-9}$), 4.91 (1H, m, H$_3$); 2.60-2.55 (2H, m, H$_3$); 2.17 (1H, dd, $J = 7.5$, 3.5 Hz, H$_{14}$); 1.89-1.74 (2H, m, H$_4$); 1.49 (3H, d, $J = 4.8$ Hz, H$_{11}$); 1.3 (1H, dd, $J = 7.5$, 2.2 Hz, H$_{13}$); 1.2 (3H, dd, $J = 6.3$, 3.3 Hz, H$_2$).

**$^{13}$C-NMR** (75 MHz, CDCl$_3$) $\delta$: 168.7 (C$_1$); 141.5 (C$_6$); 128.5 (C$_7$); 128.4 (C$_7$); 126.1 (C$_9$); 72.6 (C$_3$); 62.7 (C$_{15}$); 37.5 (C$_4$); 35.6 (C$_{10}$); 31.8 (C$_{14}$); 30.8 (C$_5$); 20.0 (C$_2$); 18.4 (C$_{11}$).

**LRMS [FAB(+)] m/z (%):** 301 (29); 215 (27); 133 (63); 91 (88); 29 (100).

**HRMS [FAB(+)] m/z:** calculated for C$_{15}$H$_{19}$Cl$_2$O$_2$ [M+H]$^+$ 301.0757, found 301.0762.
HPLC (Method A): $t_R = 10.53$ min.

[(±)-4-Phenylbutan-2-yl 2-phenoxyacetate] (±)-3.31d (0.12 g, 90% yield, colourless oil).

\[ \text{RF: 0.35 (Eluant: hexane/ethyl acetate; 9/1).} \]

IR (neat): $\nu_{\text{max}}$ (cm$^{-1}$) 2932 (w); 1754 (s); 1728 (s); 1599 (s); 1085 (m); 750 (s).

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$: 7.46-7.03 (10H, m, H$_{7.9, 12.14}$); 5.20 (1H, m, H$_3$); 4.71 (2H, s, H$_{10}$); 2.79-2.66 (2H, m, H$_5$); 2.16-1.90 (2H, m, H$_4$); 1.41 (3H, d, $J = 6.3$ Hz, H$_2$).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$: 168.8 (C$_1$); 158.0 (C$_{11}$); 141.4 (C$_6$); 129.7 (C$_{13}$); 128.5 (C$_8$); 128.4 (C$_7$); 126.1 (C$_9$); 121.8 (C$_{14}$); 114.7 (C$_{12}$); 72.0 (C$_3$); 65.5 (C$_{10}$); 37.5 (C$_4$); 31.8 (C$_5$) 20.1 (C$_2$).

LRMS [FAB(+)] $m/z$ (%): 285 (25); 133 (75); 91 (100); 77 (80); 43 (63).

HRMS [FAB(+)] $m/z$: calculated for C$_{18}$H$_{20}$O$_3$ [M]$^+$ 284.1412, found: 284.1412.

HPLC (Method A): $t_R = 10.08$ min.

The enantiomeric excess was determined by chiral HPLC (Method C), $t_R = 6.52$ min ((R)-3.31d) and 6.93 min ((S)-3.31d), ee = 0%.

[(±)-1-Methyl-3-phenylpropyl benzoate] (±)-3.31e (0.11 g, 90% yield, colourless oil)
**Chapter 5. Experimental section**

RF: 0.53 (Eluant: hexane/ethyl acetate; 9/1).

**IR** (neat): $\nu_{\text{max}}$ / (cm$^{-1}$) 2975 (w); 1712 (s); 1450 (s); 1313 (s); 709 (s); 697 (s).

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$H: 7.95 (2H, dd, $J = 8.2$ Hz, H$_{11}$); 7.48-7.07 (8H, m, H$_{7-9}$, H$_{12-13}$); 5.10 (1H, m, H$_3$); 2.73-2.53 (2H, m, H$_5$); 2.07-1.77 (2H, m, H$_4$); 1.28 (3H, d, $J = 6.2$ Hz, H$_2$).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$C: 166.2 (C$_1$); 141.6 (C$_6$); 132.9 (C$_{13}$); 131.0 (C$_{10}$); 129.6 (C$_{11}$); 128.5 (C$_{12}$); 128.4 (C$_8$); 128.4 (C$_7$); 126.0 (C$_9$); 71.2 (C$_3$); 37.8 (C$_4$); 31.9 (C$_5$); 20.2 (C$_2$).

**LRMS** [FAB(+)] $m/z$ (%): 255 (42); 105 (100); 91 (98); 77 (90).

**HRMS** [FAB(+)] $m/z$: calculated for C$_{17}$H$_{19}$O$_2$ [M+H]$^+$ 255.1380, found 255.1385.

**HPLC** (Method A): $t_R = 10.65$ min.

The compound exhibited $^1$H and $^{13}$C-NMR spectra identical to those described previously.$^{172}$

[(±)-4-Phenylbutan-2-yl 4-nitrobenzoate] (±)-3.31f (0.13 g, 95% yield, pale yellow oil)

![Chemical structure](image)

RF: 0.35 (Eluant: hexane/ethyl acetate; 9/1).

**IR** (neat): $\nu_{\text{max}}$ / (cm$^{-1}$) 2977 (w); 1717 (s); 1524 (s); 1217 (s); 1117 (m); 717 (s).

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$H: 8.15 (2H, d, $J = 8.9$ Hz, H$_{12}$); 8.04 (2H, $J = 8.9$ Hz, H$_{11}$); 7.19-7.03 (5H, m, H$_{7-9}$); 5.12 (1H, m, H$_3$); 2.63 (2H, t, $J = 8.0$ Hz, H$_5$); 2.10-1.80 (2H, m, H$_4$); 1.31 (3H, d, $J = 6.3$ Hz, H$_2$).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$C: 164.2 (C$_1$); 150.4 (C$_{13}$); 141.2 (C$_6$); 136.1 (C$_{10}$); 130.6 (C$_{11}$); 128.5 (C$_8$); 128.3 (C$_7$); 126.1 (C$_9$); 123.5 (C$_{12}$); 72.6 (C$_3$); 37.4 (C$_4$); 31.9 (C$_5$);
Chapter 5. Experimental section

20.0 (C₂).

**LRMS [FAB(+)] m/z (%)**: 300 (10); 150 (79); 91 (100); 77 (16); 43 (96).

**HRMS [FAB(+)] m/z**: calculated for C₁₇H₁₈NO₄ [M+H]^⁺ 300.1230, found 300.1236.

**HPLC (Method A)**: tᵣ = 10.50 min.

The enantiomeric excess was determined by chiral HPLC (Method C), tᵣ = 9.60 min ((S)-3.31f) and 10.23 min ((R)-3.31f), ee = 0%.

\[(\pm)-4\text{-Phenylbutan-2-yl 2,6-dichlorobenzoate}] \quad (\pm)-3.31g \quad (0.14 \text{ g}, 96\% \text{ yield}, \text{colourless oil})

Rᶠ: 0.50 (Eluant: hexane/ethyl acetate; 9/1).

**IR (neat)**: νₑᵣ / (cm⁻¹) 2978 (w); 1733 (s); 1563 (m); 1432 (s); 1274 (s); 1149 (s); 1015 (s); 779 (m).

**¹H-NMR (300 MHz, CDCl₃)** δ: 7.25-7.07 (8H, m, H₇-₉, H₁₂-₁₃); 5.21 (1H, m, H₃); 2.83-2.56 (2H, m, H₅), 2.06-1.75 (2H, m, H₄); 1.33 (3H, d, J = 6.3 Hz, H₂).

**¹³C-NMR (75 MHz, CDCl₃)** δ: 164.5 (C₁); 141.6 (C₆); 134.1 (C₁₁); 131.8 (C₁₀); 130.8 (C₁₃); 128.6 (C₈); 128.5 (C₇); 128.0 (C₁₂); 126.1 (C₉) 73.3 (C₃); 37.8 (C₄); 31.8 (C₅) 20.0 (C₂).

**LRMS [FAB(+)] m/z (%)**: 323 (14); 173 (24); 133 (62); 91 (100); 77 (48); 43 (45).

**HRMS [FAB(+)] m/z**: calculated for C₁₇H₁₇Cl₂O₂ [M+H]^⁺ 323.0600, found 323.0606.

**HPLC (Method A)**: tᵣ = 10.72 min.

The enantiomeric excess was determined by chiral HPLC (Method C), tᵣ = 7.36 min ((R)-3.31g) and 7.84 min ((S)-3.31g), ee = 0%.
[(±)-4-Phenylbutan-2-yl 4-methylbenzoate] \((±)-3.31h\) (0.10 g, 80% yield, colourless oil).

\[
\text{Rf: } 0.37 \text{ (Eluant: hexane/ethyl acetate; 9/1}.)
\]

\textbf{IR} (neat): \(v_{\text{max}} / \text{(cm}^{-1})\) 2933 (w); 1704 (s); 1276 (s); 1110 (m); 904 (s); 725 (s).

\textbf{\(^{1}\)H-NMR} (300 MHz, CDCl\textsubscript{3}) \(\delta\): 7.84 (2H, d, \(J = 7.9\) Hz, H\textsubscript{11}); 7.21-7.08 (7H, m, H\textsubscript{7-9}, H\textsubscript{12}); 5.08 (1H, m, H\textsubscript{3}); 2.73-2.54 (2H, m, H\textsubscript{5}); 2.32 (3H, s, H\textsubscript{14}); 2.04-1.77 (2H, m, H\textsubscript{4}); 1.28 (3H, d, \(J = 6.3\) Hz, H\textsubscript{2}).

\textbf{\(^{13}\)C-NMR} (75 MHz, CDCl\textsubscript{3}) \(\delta\): 166.3 (C\textsubscript{1}); 143.5 (C\textsubscript{13}); 141.7 (C\textsubscript{6}); 129.7 (C\textsubscript{11}); 129.1 (C\textsubscript{12}); 128.5 (C\textsubscript{8}); 128.4 (C\textsubscript{7}); 128.1 (C\textsubscript{10}); 126.0 (C\textsubscript{9}); 71.0 (C\textsubscript{3}); 37.9 (C\textsubscript{4}); 31.9 (C\textsubscript{5}) 21.7 (C\textsubscript{14}); 20.3 (C\textsubscript{2}).

\textbf{LRMS [FAB(+)] m/z} (%): 269 (55); 133 (69); 91 (97); 77 (66); 43 (100).

\textbf{HRMS [FAB(+)] m/z}: calculated for C\textsubscript{18}H\textsubscript{21}O\textsubscript{2} [M+H]\textsuperscript{+} 269.1536, found 269.1542.

\textbf{HPLC (Method A)}: \(t_R = 10.70\) min.

The compound exhibited \(^1\)H and \(^{13}\)C-NMR spectra identical to those described previously.\textsuperscript{173}

[(±)-4-Phenylbutan-2-yl 4-methylbenzoate] \((±)-3.31i\) (0.13 g, 87% yield, colourless oil)

\[
\text{Rf: } 0.37 \text{ (Eluant: hexane/ethyl acetate; 9/1).}
\]
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IR (neat): $\nu_{\text{max}}$ (cm$^{-1}$) 2976 (w); 1713 (s); 1589 (m); 1356 (s); 1115 (s); 735 (s).

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta_H$: 7.78 (2H, d, $J = 8.5$ Hz, H$_{11}$); 7.47 (2H, d, $J = 8.5$ Hz, H$_{12}$); 7.21-7.07 (5H, m, H$_{7-9}$); 5.08 (1H, m, H$_3$); 2.72-2.53 (2H, m, H$_5$); 2.11-1.77 (2H, m, H$_4$); 1.29 (3H, d, $J = 6.3$ Hz, H$_2$).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta_C$: 165.0 (C$_1$); 141.0 (C$_6$); 131.2 (C$_{12}$); 130.7 (C$_{11}$); 129.2 (C$_{10}$); 128.0 (C$_8$); 128.0 (C$_7$); 127.4 (C$_{13}$); 125.6 (C$_9$) 71.2 (C$_3$); 37.2 (C$_4$); 31.4 (C$_5$) 19.7 (C$_2$).

LRMS [FAB(+) $m/z$ (%): 333 (8); 183 (69); 133 (69); 91 (100); 77 (62); 43 (76).

HRMS [FAB(+) $m/z$: calculated for C$_{17}$H$_{18}$BrO$_2$ [M+H]$^+$ 333.0485 found 333.0490.

HPLC (Method A): $t_R = 10.97$ min.

[(±)-4-Pheny1butan-2-yl 2-methoxyacetate] (±)-3.31$^j$ (0.09 g, 82% yield, colourless oil)

Rf: 0.48 (Eluant: hexane/ethyl acetate; 9/1).

IR (neat): $\nu_{\text{max}}$ (cm$^{-1}$) 2931 (w); 1747 (s); 1191 (s); 1124 (s); 947 (w); 698 (s).

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta_H$: 7.21-7.05 (5H, m, H$_{7-9}$), 5.00 (1H, m, H$_3$); 3.88 (2H, s, H$_{10}$); 3.35 (3H, s, H$_{11}$); 2.65-2.49 (2H, m, H$_5$); 2.03-1.66 (2H, m, H$_4$); 1.20 (3H, m, H$_2$).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta_C$: 169.9 (C$_1$); 141.3 (C$_6$); 128.4 (C$_8$); 128.3 (C$_7$); 125.9 (C$_9$); 71.2 (C$_3$); 69.9 (C$_{10}$); 59.3 (C$_{11}$); 37.4 (C$_4$); 31.8 (C$_5$); 20.0 (C$_2$).

LRMS [FAB(+) $m/z$ (%): 445 (23); 133 (62); 91 (80); 45 (100).

HRMS [FAB(+) $m/z$: calculated for C$_{13}$H$_{19}$O$_3$ [M+H]$^+$ 223.1329, found 223.1334.

HPLC (Method A): $t_R = 9.08$ min.
[(±)-4-Phenylbutan-2-yl 3-benzylbenzoate] (±)-3.31k (0.14 g, 85% yield, colourless oil).

\[\text{Rf: 0.60 (Eluant: hexane/ethyl acetate; 9/1).}\]

\[\text{IR (neat): } v_{\max} / (\text{cm}^{-1}) 2974 (\text{w}); 1711 (\text{s}); 1251 (\text{s}); 1125 (\text{s}); 1071 (\text{s}); 737 (\text{s}); 695(\text{s}).}\]

\[\text{\textsuperscript{1}H-NMR (300 MHz, CDCl}_3\text{) } \delta_{\text{H}}: 7.76 (1\text{H, d, } J = 7.7 \text{ Hz, H}_{11}); 7.35-7.02 (13\text{H, m, H}_{13}, \text{H}_{7}, \text{H}_{9}, \text{H}_{12-14}, \text{H}_{18-20}), 5.02 (1\text{H, m, H}_{3}); 4.31 (2\text{H, s, H}_{16}); 2.60-2.43 (2\text{H, m, H}_{3}); 1.94-1.66 (2\text{H, m, H}_{4}); 1.16 (3\text{H, d, } J = 6.3 \text{ Hz, H}_{2}).\]

\[\text{\textsuperscript{13}C-NMR (75 MHz, CDCl}_3\text{) } \delta_{\text{C}}: 167.4 (\text{C}_1); 141.9 (\text{C}_{17}); 141.6 (\text{C}_{15}); 141.1 (\text{C}_8); 131.9 (\text{C}_{13}); 131.7 (\text{C}_{11}); 131.0 (\text{C}_{19}); 130.5 (\text{C}_8); 129.0 (\text{C}_{18}); 128.5 (\text{C}_{14}); 128.4 (\text{C}_7); 128.4 (\text{C}_{20}); 126.4 (\text{C}_{12}); 126.0 (\text{C}_9); 71.2 (\text{C}_3); 39.6 (\text{C}_{16}); 37.8 (\text{C}_4); 32.0 (\text{C}_5); 20.1 (\text{C}_2).\]

\[\text{LRMS [FAB(+)] } m/z (\%): 345 (5); 91 (100); 77 (46); 39 (62).\]

\[\text{HRMS [FAB(+)] } m/z: \text{ calculated for C}_{24}\text{H}_{25}\text{O}_2 [M+H]^+ 345.1849, \text{ found 345.1855.}\]

\[\text{HPLC (Method A): } t_R = 11.16 \text{ min.}\]

[(±)-(E)-4-phenylbutan-2-yl-3-(3,4,5-trimethoxyphenyl)acrylate] (±)-3.31l (0.08 g, 47% yield, colourless oil)

\[\text{Rf: 0.60 (Eluant: hexane/ethyl acetate; 8/2).}\]

\[\text{IR (neat): } v_{\max} / (\text{cm}^{-1}) 2937 (\text{w}); 1704 (\text{m}); 1582 (\text{m}); 1273 (\text{s}); 1126 (\text{s}); 1005 (\text{w}).}\]
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\(^{1}\text{H-NMR}\) (300 MHz, CDCl\(_3\)) \(\delta_{\text{H}}:\) 7.51 (1H, d, \(J = 15.9\) Hz, H\(_{11}\)); 7.24-7.10 (5H, m, H\(_{7-9}\)); 6.70 (2H, s, H\(_{13,13}'\)); 6.27 (1H, d, \(J = 15.9\) Hz, H\(_{10}\)); 5.01 (1H, m, H\(_3\)); 3.82 (9H, s, H\(_{16,16}'\), H\(_{17}\)); 2.73-2.53 (2H, m, H\(_4\)); 2.03-1.74 (2H, m, H\(_3\)); 1.26 (3H, d, \(J = 6.3\) Hz, H\(_2\)).

\(^{13}\text{C-NMR}\) (75 MHz, CDCl\(_3\)) \(\delta_{\text{C}}:\) 166.7 (C\(_1\)); 153.6 (C\(_{14}, C_{14}'\)); 144.6 (C\(_{11}\)); 141.7 (C\(_{15}\)); 140.0 (C\(_8\)); 130.1 (C\(_{12}\)); 128.6 (C\(_8\)); 128.5 (C\(_7\)); 126.0 (C\(_9\)); 118.0 (C\(_{10}\)); 105.3 (C\(_{13}, C_{13}'\)); 70.8 (C\(_3\)); 61.1 (C\(_{16}, C_{16}'\)); 56.3 (C\(_{17}\)); 37.9 (C\(_4\)); 32.0 (C\(_3\)); 20.3 (C\(_2\)).

LRMS [FAB(\(+\)) \(m/z\) (%): 371 (48); 221 (63); 91 (84); 77 (60); 43 (89).

HRMS [FAB(\(+\)) \(m/z\): calculated for C\(_{22}H_{26}O_5\) [M\(^+\)] 370.1780, found 370.1780.

HPLC (Method A): \(t_R = 10.28\) min.

\([\pm]-\text{Octan-2-yl decanoate}\) (\(\pm\)-3.31m) (0.08 g, 60\% yield, colourless oil)

Rf: 0.53 (Eluant: hexane/ethyl acetate; 9/1).

IR (neat): \(\nu_{\text{max}} / (\text{cm}^{-1})\) 2924 (s); 1732 (s); 1464 (m); 1274 (m); 733 (s).

\(^{1}\text{H-NMR}\) (300 MHz, CDCl\(_3\)) \(\delta_{\text{H}}:\) 4.88 (1H, m, H\(_3\)); 2.25 (2H, t, \(J = 7.2\) Hz, H\(_{10}\)); 1.56 (4H, m, H\(_4, H_{11}\)); 1.48-1.16 (20H, br, H\(_5, H_{12-17}\)); 1.18 (3H, d, \(J = 6.3\) Hz, H\(_2\)); 0.86 (6H, t, \(J = 6.8\) Hz, H\(_9, H_{18}\)).

\(^{13}\text{C-NMR}\) (75 MHz, CDCl\(_3\)) \(\delta_{\text{C}}:\) 173.7 (C\(_1\)); 70.8 (C\(_3\)); 36.1 (C\(_4\)); 34.9 (C\(_{10}\)); 32.0 (C\(_{16}\)); 31.9 (C\(_7\)); 29.6 (C\(_{12}\)); 29.4 (C\(_{14}\)); 29.4 (C\(_{16}\)); 29.3 (C\(_{15}\)); 29.2 (C\(_{13}\)); 25.5 (C\(_3\)); 25.2 (C\(_{11}\)); 22.8 (C\(_{17}\)); 22.7 (C\(_8\)); 20.1 (C\(_2\)); 14.2 (C\(_{18}\)); 14.2 (C\(_9\)).

LRMS [FAB(\(+\)) \(m/z\) (%): 285 (6); 277 (20); 91 (63); 77 (14); 43 (94); 29 (100).

HRMS [FAB(\(+\)) \(m/z\): calculated for C\(_{18}H_{37}O_2\) [M+H]\(^+\) 285.2788, found 285.2799.
The compound exhibited \(^{1}\text{H}\) and \(^{13}\text{C-NMR}\) spectra identical to those described previously.\(^{133}\)
[(±)-Octan-2-yl benzoate] (±)-3.31n (0.09 g, 80% yield, colourless oil)

![Chemical structure of (±)-Octan-2-yl benzoate](image)

**Rf:** 0.43 (Eluant: hexane/ethyl acetate; 95/5).

**IR** (neat): $v_{max}$ / (cm$^{-1}$) 2928 (w); 1714 (s); 1271 (s); 1107 (s); 708 (m).

**$^1$H-NMR** (250 MHz, CDCl$_3$) $\delta$H: 8.05 (2H, d, $J = 7.2$ Hz, H$_{11}$); 7.46-7.40 (3H, m, H$_{12,13}$); 5.15 (1H, m, H$_3$); 1.76-1.53 (2H, m, H$_{1,14}$); 1.35-1.27 (11H, br, H$_2$, H$_{5,8}$); 0.86 (3H, t, $J = 6.8$ Hz, H$_9$).

**$^{13}$C-NMR** (62 MHz, CDCl$_3$) $\delta$C: 166.3 (C$_1$); 132.8 (C$_3$); 131.1 (C$_{10}$); 129.6 (C$_{11}$); 128.4 (C$_{12}$); 71.9 (C$_3$); 36.2 (C$_4$); 31.9 (C$_7$); 29.3 (C$_6$); 25.5 (C$_5$); 22.7 (C$_8$); 20.2 (C$_2$); 14.2 (C$_9$).

**LRMS [FAB+]** m/z (%): 235 (38); 123 (70); 91 (63); 77 (60); 43 (93).

**HRMS [FAB+]** m/z: calculated for C$_{15}$H$_{23}$O$_2$ [M+H]$^+$ 235.1693, found 235.1698.

**HPLC (Method A):** $t_R = 11.15$ min.

The enantiomeric excess was determined by chiral HPLC (Method C), $t_R = 8.37$ min ((R)-3.31n) and 8.66 min ((S)-3.31n), $ee = 0\%$.

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

[(±)-Octan-2-yl 4-nitrobenzoate] (±)-3.31o (0.12 g, 95% yield, colourless oil)

![Chemical structure of (±)-Octan-2-yl 4-nitrobenzoate](image)

[(±)-Octan-2-yl 4-nitrobenzoate] (±)-3.31o (0.12 g, 95% yield, colourless oil)
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**Rf:** 0.53 (Eluant: hexane/ethyl acetate; 9/1).

**IR** (neat): $\nu_{\text{max}}$ (cm$^{-1}$) 2929 (w); 1719 (s); 1526 (s); 1272 (s); 1167 (s); 718 (m).

**$^1$H-NMR** (250 MHz, CDCl$_3$) $\delta$: 8.29-8.17 (4H, m, H$_{11,12}$); 5.17 (1H, m, H$_3$); 1.80-1.55 (2H, m, H$_4$); 1.36-1.26 (11H, m, H$_2$, H$_{5,8}$); 0.86 (3H, t, $J = 6.8$ Hz, H$_9$).

**$^{13}$C-NMR** (62 MHz, CDCl$_3$) $\delta$: 164.4 (C$_1$); 150.5 (C$_{13}$); 136.4 (C$_{10}$); 130.7 (C$_{11}$); 123.6 (C$_{12}$); 73.2 (C$_3$); 36.0 (C$_4$); 31.8 (C$_7$); 29.2 (C$_6$); 25.5 (C$_8$); 22.7 (C$_9$); 20.1 (C$_2$); 14.1 (C$_9$).

**HRMS [FAB(+)] m/z:** calculated for C$_{15}$H$_{22}$NO$_4$ [M+H]$^+$ 280.1543, found 280.1582.

**HPLC** (Method A): $t_R = 11.10$ min.

The compound exhibited $^1$H and $^{13}$C-NMR spectra identical to those described previously.$^{175}$

**[(±)-Octan-2-yl 2,6-dichlorobenzoate] (±)-3.31p** (0.13 g, 90% yield, colourless oil)

![Chemical structure of the compound](image)

**Rf:** 0.53 (Eluant: hexane/ethyl acetate; 9/1).

**IR** (neat): $\nu_{\text{max}}$ (cm$^{-1}$) 2928 (w); 1732 (s); 1431 (s); 1271 (s); 727 (m).

**$^1$H-NMR** (300 MHz, CDCl$_3$) $\delta$: 7.54-7.14 (3H, m, H$_{12,13}$); 5.16 (1H, m, H$_2$); 1.71-1.50 (2H, m, H$_4$); 1.31-1.20 (11H, m, H$_2$, H$_{5,8}$); 0.80 (3H, t, $J = 6.8$ Hz, H$_9$).

**$^{13}$C-NMR** (62 MHz, CDCl$_3$) $\delta$: 164.5 (C$_1$); 134.3 (C$_{11}$); 131.8 (C$_{10}$); 130.7 (C$_{13}$); 128.0 (C$_{12}$); 127.9 (C$_{12}$); 73.9 (C$_2$); 35.9 (C$_4$); 31.9 (C$_7$); 29.1 (C$_6$); 25.4 (C$_5$); 22.7 (C$_8$); 20.0 (C$_3$); 14.2 (C$_9$).

**LRMS [FAB(+)] m/z (%)**: 303 (19); 173 (62); 91 (24); 77 (32); 43 (97).

**HRMS [FAB(+)] m/z:** calculated for C$_{15}$H$_{21}$Cl$_2$O$_2$ [M+H]$^+$ 303.0913 found 303.0919.

**HPLC** (Method A): $t_R = 11.41$ min.
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[(±)-Octan-2-yl 4-methylbenzoate] (±)-3.31q (0.09 g, 78% yield, colourless oil)

\[
\begin{array}{c}
\text{CH}_3 \quad \text{O} \\
\text{CH}_2 \quad \text{C} \\
\text{CH}_2 \quad \text{C} \\
\text{CH}_2 \quad \text{C} \\
\text{CH}_2 \quad \text{C} \\
\text{CH}_2 \quad \text{C} \\
\text{CH}_2 \quad \text{C} \\
\text{CH}_2 \quad \text{C} \\
\text{CH}_2 \quad \text{C} \\
\text{CH}_2 \quad \text{C} \\
\end{array}
\]

**Rf:** 0.38 (Eluant: hexane/ethyl acetate; 95/5).

**IR** (neat): \(\nu_{\text{max}} / (\text{cm}^{-1})\) 2928 (w); 1713 (s); 1612 (w); 1272 (s); 753 (m).

**\(^1\text{H}-\text{NMR}\)** (300 MHz, CDCl\(_3\)) \(\delta_H:\) 7.94 (2H, d, \(J = 8.0 \text{ Hz}, \text{ H}_{11}\)); 7.23 (2H, d, \(J = 8.0 \text{ Hz}, \text{ H}_{12}\)); 5.14 (1H, m, \text{ H}_3); 2.40 (3H, s, \text{ H}_{14}); 1.78-1.53 (2H, m, \text{ H}_{14}); 1.33-1.28 (11H, m, \text{ H}_2, \text{ H}_{5.8}); 0.88 (3H, t, \(J = 6.5 \text{ Hz}, \text{ H}_9\)).

**\(^{13}\text{C}-\text{NMR}\)** (75 MHz, CDCl\(_3\)) \(\delta_C:\) 166.4 (C\(_1\)); 143.3 (C\(_{13}\)); 129.6 (C\(_{11}\)); 129.1 (C\(_{12}\)); 128.3 (C\(_{10}\)); 71.6 (C\(_3\)); 36.2 (C\(_4\)); 31.9 (C\(_7\)); 29.3 (C\(_6\)); 25.5 (C\(_{14}\)); 22.7 (C\(_3\)); 21.7 (C\(_8\)); 20.2 (C\(_2\)); 14.2 (C\(_9\)).

**LRMS [FAB(\(+)\)] m/z (%):** 249 (45); 119 (85); 91 (76); 77 (55); 43 (100).

**HRMS [FAB(\(+)\)] m/z:** calculated for C\(_{16}\)H\(_{25}\)O\(_2\) [M+H]\(^+\) 249.1849, found 249.1855.

**HPLC** (Method A): \(t_R = 12.48 \text{ min}\).

The enantiomeric excess was determined by chiral HPLC (Method E), \(t_R = 15.05 \text{ min}\) ((S)-3.31q) and 17.66 min ((R)-3.31q), ee = 0%.

The compound exhibited \(^1\text{H}\) and \(^{13}\text{C}-\text{NMR}\) spectra identical to those described previously.\(^{133}\)

[(±)-Octan-2-yl 4-bromobenzoate] (±)-3.31r (0.10 g, 72% yield, colourless oil)

\[
\begin{array}{c}
\text{Br} \\
\text{CH}_2 \quad \text{C} \\
\text{CH}_2 \quad \text{C} \\
\text{CH}_2 \quad \text{C} \\
\text{CH}_2 \quad \text{C} \\
\text{CH}_2 \quad \text{C} \\
\text{CH}_2 \quad \text{C} \\
\text{CH}_2 \quad \text{C} \\
\text{CH}_2 \quad \text{C} \\
\end{array}
\]

**Rf:** 0.40 (Eluant: hexane/ethyl acetate; 95/5).
IR (neat): $\nu_{\max}$ / (cm$^{-1}$) 2928 (w); 1714 (s); 1268 (s); 1101 (s); 1011(s); 755 (s).

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$: 7.89 (2H, d, $J = 8.7$ Hz, H$_{11}$); 7.55 (2H, d, $J = 8.7$ Hz, H$_{12}$); 5.13 (1H, m, H$_{3}$); 1.76-1.52 (2H, m, H$_{4}$); 1.33-1.27 (11H, m, H$_{2}$, H$_{5-8}$); 0.87 (3H, t, $J = 6.9$ Hz, H$_9$).

$^{13}$C-NMR (62 MHz, CDCl$_3$) $\delta$: 165.6 (C$_1$); 131.7 (C$_{11}$); 131.2 (C$_{12}$); 129.9 (C$_{10}$); 127.8 (C$_{13}$); 72.3 (C$_3$); 36.1 (C$_4$); 31.8 (C$_7$); 29.2 (C$_6$); 25.5 (C$_5$); 22.7 (C$_8$); 20.1 (C$_2$); 14.2 (C$_9$).

LRMS [FAB(+)] m/z (%): 313 (20); 183 (46); 91 (15); 77 (32); 43 (100).

HPLC (Method A): $t_R = 13.01$ min.

The enantiomeric excess was determined by chiral HPLC (Method F), $t_R = 16.34$ min ((S)-3.31r) and 18.05 min ((R)-3.31r), $ee = 0\%$.

[±)-Octan-2-yl 4-methoxybenzoate] (±)-3.31s (0.09 g, 74% yield, colourless oil)

Rf: 0.36 (Eluant: hexane/ethyl acetate; 95/5).

IR (neat): $\nu_{\max}$ / (cm$^{-1}$) 2930 (w); 1708 (s); 1606 (s); 1255 (s); 771 (m).

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$: 7.99 (2H, d, $J = 9.0$ Hz, H$_1$); 6.90 (2H, d, $J = 9.0$ Hz, H$_{12}$); 5.12 (1H, m, H$_3$); 3.84 (3H, s, H$_{14}$); 1.78-1.54 (2H, m, H$_4$); 1.39-1.30 (11H, m, H$_2$, H$_{5-8}$); 0.87 (3H, t, $J = 6.8$ Hz, H$_9$).

$^{13}$C-NMR (62 MHz, CDCl$_3$) $\delta$: 166.1 (C$_1$); 163.3 (C$_{13}$); 131.6 (C$_{11}$); 123.5 (C$_{10}$); 113.6 (C$_{12}$); 71.4 (C$_3$); 55.5 (C$_{14}$); 36.2 (C$_4$); 31.8 (C$_7$); 29.3 (C$_6$); 25.5 (C$_5$); 22.7 (C$_8$); 20.2 (C$_2$); 14.2 (C$_9$).

LRMS [FAB(+)] m/z (%): 265 (58); 135 (92); 91 (38); 77 (66); 43 (100).

HRMS [FAB(+)] m/z: calculated for C$_{16}$H$_{25}$O$_3$ [M+H]$^+$ 265.1798, found 265.1804.

HPLC (Method A): $t_R = 12.03$ min.
The compound exhibited $^1$H and $^{13}$C-NMR spectra identical to those described previously. \(^{133}\)

$[(±)-(E)-Octan-2-yl 3-(3,4,5-trimethoxyphenyl)acrylate] (±)-3.31t (0.12 g, 74% yield, colourless oil)

$\text{Rf: } 0.31$ (Eluant: hexane/ethyl acetate; 8/2).

$\text{IR (neat): } \nu_{\text{max}} / (\text{cm}^{-1}) 2929 (\text{w}); 1703 (\text{s}); 1635 (\text{s}); 1272 (\text{s}); 1123 (\text{s}); 826 (\text{s}).$

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$: 7.60 (1H, d, $J = 15.8$ Hz, H$_{11}$); 6.74 (2H, s, H$_{12,13}$); 6.33 (1H, d, $J = 15.8$ Hz, H$_{10}$); 5.03 (1H, m, H$_3$); 3.88 (6H, s, H$_{16,16'}$); 3.87 (3H, s, H$_{17}$); 1.68-1.47 (2H, m, H$_4$); 1.33-1.27 (11H, m, H$_2$, H$_{5-8}$) 0.87 (3H, t, $J = 7.0$ Hz, H$_9$).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$: 166.7 (C$_1$); 153.5 (C$_{14}$); 144.4 (C$_{11}$); 130.2 (C$_{15}$); 118.2 (C$_{12}$); 105.3 (C$_{10}$); 71.3 (C$_{13}$, C$_{13'}$); 61.1 (C$_3$); 56.2 (C$_{16}$, C$_{16'}$); 36.2 (C$_4$); 31.9 (C$_7$); 29.3 (C$_6$); 25.5 (C$_5$); 22.7 (C$_8$); 20.2 (C$_2$); 14.2 (C$_9$).

LRMS [FAB(+)]: $m/z$ (%): 351 (39); 221 (50); 91 (35); 77 (33); 43 (87); 29 (100).

HRMS [FAB(+)]: $m/z$: calculated for C$_{20}$H$_{30}$O$_5$ [M]$^+$ 350.2093, found 350.2093.

HPLC (Method A): $t_R = 10.78$ min

General procedure for the synthesis of O-alkylisoureas from secondary alcohols\(^{62}\)
The respective alcohols (5.0 mmol) was added with stirring to a mixture of copper (II) triflate (0.050 g, 0.140 mmol) in \( N, N'-\)diisopropylcarbodiimide 2.26 (0.959 g, 5.0 mmol). The green mixture was stirred overnight at room temperature to ensure complete reaction. Hexane (5 mL) was added and the solution was applied to a filter pad of a neutral alumina. The product was eluted with a total volume of 100 ml of hexane, at which time the IR spectrum indicates that all the isourea has been removed from the alumina. The solvent was evaporated under reduced pressure overnight.

\[
[(S-1,3-Diisopropyi-2-(4-phenylbutan-2-yi)isourea)] \quad (S)-2.16f \quad (1.150 \text{ g, 83\% yield, pale yellow oil})
\]

Spectral data (IR, NMR) obtained were in agreement with that obtained for (\(\pm\))-2.16f prepared using racemic 4-phenyl-2-butanol (page 83).

\[
[(R)-Octan-2-yl isourea] \quad (R)-2.16i \quad (1.060 \text{ g, 83\% yield, colourless oil}).
\]

Spectral data (IR, NMR) obtained were in agreement with that obtained for (\(\pm\))-2.16i prepared using racemic 2-octanol (page 106).
[(2S)-(R)-4-phenylbutan-2-yl-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate] (S,R)-3.31u (0.13 g, 78% yield, white solid). The compound was synthesised using general method described on page 106.

Rf: 0.36 (Eluant: hexane/ethyl acetate; 95/5).

IR (neat): ν max (cm⁻¹) 2947 (w); 1738 (s); 1504 (m); 1271 (s); 1162 (s); 987 (s).

¹H-NMR (300 MHz, CDCl₃) δH: 7.85-7.81 (2H, m, H₁₅); 7.68-7.62 (3H, m, H₁₄,1₆); 7.54-7.33 (3H, m, H₈,₉); 7.33-7.29 (2H, m, H₇); 5.39 (1H, m, H₃); 3.83 (3H, q, J = 1.3 Hz, H₁₁); 2.87-2.70 (2H, m, H₅); 2.31-2.00 (2H, m, H₄); 1.62 (3H, d, J = 6.3 Hz, H₂).

¹³C-NMR (75 MHz, CDCl₃) δC: 166.2 (C₁); 141.2 (C₆); 132.7 (C₁₃); 129.7 (C₁₄); 128.6 (C₁₅); 128.5 (C₈); 128.4 (C₇); 127.4 (C₁₆); 126.1 (C₉); 125.9 (C₁₂); 84.7 (C₁₀); 73.5 (C₃); 55.5 (C₁₁); 37.5 (C₄); 31.4 (C₅); 19.9 (C₂).

LRMS [FAB(+)] m/z (%): 367 (63); 105 (100); 91 (100); 77 (97); 43 (24); 29 (19).

HRMS [FAB(+)] m/z: calculated for C₂₀H₂₂F₃O₃ [M+H]⁺ 367.1516, found 367.1521.

[(2S)-(R)-4-phenylbutan-2-yl-2-hydroxy-2-phenylacetate] (S,R)-3.31v (0.08 g, 60% yield, white solid). The compound was synthesised using general method described on page 106.

Mp: 34-36 °C.
Chapter 5. Experimental section

Rf: 0.30 (Eluant: hexane/ethyl acetate; 8/2).

IR (neat): $\nu_{\text{max}}$ (cm$^{-1}$): 3500 (s); 2929 (s); 1729 (s); 1184 (m); 1066 (s); 698 (s).

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$: 7.23-7.06 (10H, m, H$_{7-9}$, H$_{13-15}$); 5.01 (1H, s, H$_{11}$); 4.91 (1H, m, H$_3$); 3.38 (1H, m, OH); 2.60-2.53 (2H, m, H$_5$); 1.97-1.59 (2H, m, H$_4$); 1.02 (3H, d, $J = 6.3$ Hz, H$_2$).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$: 173.4 (C$_1$); 141.3 (C$_6$); 138.6 (C$_{12}$); 128.6 (C$_{13}$); 128.6 (C$_{14}$); 128.5 (C$_8$); 128.4 (C$_7$); 126.5 (C$_{15}$); 126.2 (C$_9$); 73.1 (C$_{10}$); 73.0 (C$_3$); 37.3 (C$_4$); 31.8 (C$_5$); 19.7 (C$_2$).

LRMS [FAB(+)] $m/z$ (%): 285 (81); 239 (81); 91 (100); 77 (96); 43 (52); 29 (32).

HRMS [FAB(+)] $m/z$: calculated for C$_{18}$H$_{21}$O$_3$ [M+H]$^+$ 285.1485, found 285.1491.

[(2S)-(S)-octan-2-yl-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate] $(S,S)$-3.31w (0.13 g, 80% yield, colourless oil). The compound was synthesised using general method described on page 106.

Rf: 0.40 (Eluant: hexane/ethyl acetate; 95/5).

Mp: 43-45 °C.

IR (neat): $\nu_{\text{max}}$ (cm$^{-1}$): 2947 (w); 1738 (s); 1504 (m); 1271 (s); 1162 (s); 987 (s).

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$: 7.55-7.50 (2H, m, H$_{14}$); 7.42-7.36 (3H, m, H$_{13,15}$); 5.14 (1H, m, H$_3$); 3.56 (3H, q, $J = 1.3$ Hz, H$_{11}$); 1.94-1.80 (2H, m, H$_4$); 1.34-1.24 (11H, m, H$_2$, H$_5$-8); 0.86 (3H, d, $J = 7.0$ Hz, H$_9$).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$: 166.3 (C$_1$); 132.6 (C$_{12}$); 129.6 (C$_{13}$); 128.4 (C$_{14}$); 127.5 (C$_{15}$); 125.8 (C$_{16}$); 121.2 (C$_{10}$); 74.3 (C$_3$); 55.5 (C$_{11}$); 35.7 (C$_4$); 31.8 (C$_7$); 29.1 (C$_6$); 25.4 (C$_5$); 22.6 (C$_8$); 19.6 (C$_2$); 14.1 (C$_9$).
Chapter 5. Experimental section

**LRMS [FAB(+)] m/z (%):** 347 (100); 189 (100); 105 (100); 91 (85); 77 (94); 43 (100); 29 (100).

**HRMS [FAB(+)] m/z:** calculated for C_{18}H_{26}F_{3}O_{3} [M+H]^{+} 347.1829, found 347.1834.

The compound exhibited $^1$H and $^{13}$C-NMR spectra identical to those described previously.\(^{176}\)

[(2S)-(S)-octan-2-yl 2-hydroxy-2-phenylacetate] (S,S)-3.31x (0.11 g, 90% yield, white solid). The compound was synthesised using general method described on page 106.

\[
\begin{align*}
\text{Rf:} & \quad 0.47 \text{ (Eluant: hexane/ethyl acetate; 8/2).} \\
\text{IR (neat):} & \quad \nu_{\max} / (cm^{-1}) 3500 (s); 2923 (s); 1724 (s); 1211 (s); 1184 (s); 1065 (s); 692 (s). \\
\text{$^1$H-NMR} & \quad (300 MHz, CDCl}_3) \delta_H: 7.23-7.15 (5H, m, H_{13-15}); 5.01 (1H, s, H_{11}); 4.88 (1H, m, H_3); 3.59 (1H, s, OH); 1.37-0.69 (16H, m, H_2, H_4,9). \\
\text{$^{13}$C-NMR} & \quad (75 MHz, CDCl}_3) \delta_C: 173.6 (C_1); 138.8 (C_{12}); 128.5 (C_{14}); 128.4 (C_{13}); 126.6 (C_{15}); 73.5 (C_{10}); 73.1 (C_3); 35.8 (C_4); 31.6 (C_7); 28.8 (C_6); 24.8 (C_5); 22.5 (C_8); 20.1 (C_2); 14.1 (C_9).
\end{align*}
\]

**LRMS [FAB(+)] m/z (%):** 265 (98); 188 (57); 91 (91); 77 (63); 43 (63); 29 (81).

**HRMS [FAB(+)] m/z:** calculated for C_{16}H_{24}O_{3} [M]^{+} 264.1725, found 264.1720.

The compound exhibited $^1$H and $^{13}$C-NMR spectra identical to those described previously.\(^{140}\)
Synthesis of \((L,L)\)-Cbz-Gly-Phe-Val-OMe, \((L,L)\)-3.33 (0.09 g, 75% yield).

A microwave vial was charged with Cbz-Gly-Phe-Val-OH \((L,L)\)-3.32 (0.116 g, 0.256 mmol) and CH\(_3\)CN (2 mL), \(O\)-methylisourea \(2.16a\) (0.047 g, 0.300 mmol) was added. The vial was capped and the mixture heated at 80 °C for 20 min. and at 100 °C for 20 min. using a Smith Synthesizer.\(^\text{TM}\) The 1,3-diisopropylurea was filtered off, the solvent evaporated and the residue purified by chromatography. Spectral data of the product \((L,L)\)-3.33 \((^1\text{H-NMR})\) were identical to those previously reported.\(^{141}\)

\(^1\text{H-NMR}\) (300 MHz, CDCl\(_3\)) \(\delta_{\text{H}}\): 7.23-7.10 (11 H, m, Ar-H, NH), 6.85 (1H, br, NH), 5.77 (1H, br, NH), 5.11 (2H, s, Ph-CH\(_2\)-O), 4.84 (1H, m, CH\(^*\)phe), 4.44 (1H, dd, \(J = 8.0, 5.1\) Hz, CH\(^*\)Val), 3.87 (2H, m, NH-CH\(_2\)), 3.67 (3H, s, OCH\(_3\)), 3.03 (2H, d, \(J = 4.0\) Hz, CHCH\(_2\)Ph), 2.07 (1H, m, CH(CH\(_3\))\(_2\)), 0.85 (3H, d, \(J = 6.5\) Hz, CH\(_3\)), 0.81 (3H, d, \(J = 6.5\) Hz, CH\(_3\)).

LRMS [ES\(^+\)] \(m/z\) (%): 470 (100).

HPLC (Method A): \(t_R = 10.30\) min.

\([\text{R-4-Phenylbutan-2-yl 2-phenoxyacetate}]\) \((R)-3.31d\) (0.12 g, 90% yield). The compound was synthesised using general method described on page 106. Spectral data (IR, NMR) obtained were in agreement with that obtained for (±)-3.31d prepared using racemic 4-phenyl-2-butanol. The enantiomeric excess was determined by chiral HPLC (Method C), \(t_R = 6.54\) min, \(ee \geq 99\%\).
[(R)-4-Phenylbutan-2-yl 4-nitrobenzoate] (R)-3.31f (0.13 g, 95% yield). The compound was synthesised using general method described on page 106. Spectral data (IR, NMR) obtained were in agreement with that obtained for (±)-3.31f prepared using racemic 4-phenyl-2-butanol. The enantiomeric excess was determined by chiral HPLC (Method C), $t_R = 10.40$ min, ee $\geq 99\%$.

[(R)-4-Phenylbutan-2-yl 2,6-dichlorobenzoate] (R)-3.31g (0.14 g, 95% yield). The compound was synthesised using general method described on page 106. Spectral data (IR, NMR) obtained were in agreement with that obtained for (±)-3.31g prepared using racemic 4-phenyl-2-butanol. The enantiomeric excess was determined by chiral HPLC (Method C), $t_R = 7.39$ min, ee $\geq 99\%$.

[(S)-Octan-2-yl benzoate] (S)-3.31n (0.09 g, 80% yield). The compound was synthesised using general method described on page 106. Spectral data (IR, NMR) obtained were in agreement with that obtained for (±)-3.31n prepared using racemic 2-octanol. The enantiomeric excess was determined by chiral HPLC (Method C), $t_R = 8.64$ min, ee $\geq 99\%$.

[(S)-Octan-2-yl 4-methylbenzoate] (S)-3.31q (0.09 g, 77% yield). The compound was synthesised using general method described on page 106. Spectral data (IR, NMR) obtained were in agreement with that obtained for (±)-3.31q prepared using racemic 2-octanol. The enantiomeric excess was determined by chiral HPLC (Method D), $t_R = 14.58$ min, ee $\geq 99\%$.

[(S)-Octan-2-yl 4-bromobenzoate] (S)-3.31r (0.10 g, 70% yield). The compound was synthesised using general method described on page 106. Spectral data (IR, NMR) obtained were in agreement with that obtained for (±)-3.31r prepared using racemic 2-phenyl-2-butanol. The enantiomeric excess was determined by chiral HPLC (Method E), $t_R = 16.94$ min, ee $\geq 99\%$. 
Microwave-assisted synthesis of (R)-4-phenylbutan-2-yl 2-phenoxyacetate (R)-3.31d under classical Mitsunobu conditions

A microwave vial was charged with a stir bar, the alcohol (S)-3.34 (0.195 g, 1.30 mmol) was added followed by PPh₃ (0.760 g, 2.88 mmol), 2-phenoxyacetic acid (0.438 g, 2.88 mmol) and DIAD (0.257 g, 1.27 mmol) in 4 mL of anhydrous THF. The vial was capped and the mixture heated at 180 °C using a Smith Synthesizer™ for 7 min. The residue was purified by chromatography (0.31 g 83% yield colourless oil). Spectral data (IR, NMR) obtained were in agreement with that obtained for (±)-3.31d prepared using racemic 4-phenyl-2-butanol. The enantiomeric excess was determined by chiral HPLC (Method C), tᵣ = 6.45 min, ee ≥ 99%.

Optimisation for the synthesis of neomenthyl-ester: a microwave vial was charged with the O-alkylisourea (0.320 mmol) and the acid (0.300 mmol) in the appropriate solvent. The vial was capped and the mixture heated at the indicate temperature using a Smith Synthesizer™. An aliquot (10 µL in 1 mL of MeOH) of the crude reaction was analysed by GC/MS to established the conversion of the p-nitrobenzoic acid into the corresponding neomenthyl ester 3.39.

[1,3-Diisopropyl-2-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)isourea] 3.35 (1.16 g, 82% yield). The compound was synthesised using general method described on page 120.
$^1$H-NMR (250 MHz, CDCl$_3$) $\delta$: 4.81-4.70 (1H, dt, $J = 11.0$, 4.0 Hz, H$_6$); 3.72 (1H, m, H$_2$); 3.30 (1H, br, NH); 3.13 (1H, m, H$_4$); 2.09-1.02 (18H, m, H$_7$-$11$, H$_{13}$-$14$); 0.90-0.78 (12H, m, H$_3$-$5$).

The compound exhibited $^1$H and $^{13}$C-NMR spectra identical to those described previously.$^{177}$

**General procedure for microwave-assisted synthesis of neomenthyl-esters**

A microwave vial was charged with isourea 3.35 (0.09 g, 0.32 mmol) and the acid (0.30 mmol) in 1 mL of toluene. The vial was capped and the mixture heated at 150 °C using a Smith Synthesizer$^{TM}$ for 10 min. The 1,3-diisopropylurea was filtered off, the solvent evaporated and the residue purified by chromatography.

[(1S,2S,5R)-2-Isopropyl-5-methylcyclohexyl 4-nitrobenzoate] 3.39a (0.08 g, 90% yield)
Rf: 0.69 (Eluant: hexane/ethyl acetate; 9/1).

IR (neat): $\nu_{\max} / (\text{cm}^{-1})$: 2951 (s); 1717 (s); 1527 (s); 1269 (s); 1100 (s).

$^1$H-NMR (250 MHz, CDCl$_3$) $\delta_H$: 8.22 (2H, d, $J = 8.9$ Hz, H$_{13}$); 8.13 (2H, d, $J = 8.9$ Hz, H$_{12}$). 5.42 (1H, br, H$_2$); 2.00-0.80 (18H, m, H$_{3-10}$)

$^{13}$C-NMR (62 MHz, CDCl$_3$) $\delta_C$: 164.1 (C$_1$); 150.5 (C$_{14}$); 136.5 (C$_{11}$); 130.7 (C$_{12}$); 123.7 (C$_{13}$); 73.3 (C$_2$); 47.0 (C$_8$); 39.2 (C$_3$); 34.8 (C$_6$); 29.5 (C$_4$); 26.9 (C$_9$); 25.5 (C$_7$); 22.2 (C$_5$); 21.0 (C$_{10}$); 20.9 (C$_{10}$).

The compound exhibited $^1$H and $^{13}$C-NMR spectra identical to those described previously.$^{119}$

[[(1S,2S,5R)-Isopropyl-5-methylcyclohexyl benzoate] 3.39b (0.05 g, 68% yield)]

Rf: 0.60 (Eluant: hexane/ethyl acetate; 9/1).

IR (neat): $\nu_{\max} / (\text{cm}^{-1})$: 2951 (s); 1714 (s); 1269 (s); 1112 (s).

$^1$H-NMR (250 MHz, CDCl$_3$) $\delta_H$: 8.07-8.04 (2H, m, H$_{12}$); 7.51-7.41 (3H, m, H$_{13,14}$); 5.40 (1H, br, H$_2$); 1.88-0.85 (18H, m, H$_{3-10}$).

$^{13}$C-NMR (62 MHz, CDCl$_3$) $\delta_C$: 166.0 (C$_1$); 132.8 (C$_{14}$); 131.2 (C$_{11}$); 129.6 (C$_{12}$); 128.4 (C$_{13}$); 71.8 (C$_2$); 47.2 (C$_8$); 39.4 (C$_3$); 35.0 (C$_6$); 29.5 (C$_4$); 26.9 (C$_9$); 25.5 (C$_7$); 22.3 (C$_5$); 21.1 (C$_{10}$); 20.9 (C$_{10}$).

HPLC (Method A): $t_R = 11.02$ min.

The compound exhibited $^1$H and $^{13}$C-NMR spectra identical to those described previously.$^{119}$
Chapter 5. Experimental section

[(1S,2S,5R)-Isopropyl-5-methylcyclohexyl 4-methoxybenzoate] 3.39c (0.06 g, 66% yield)

\[
\begin{array}{c}
\text{6} & \text{5} \\
\text{4} & \text{3} \\
\text{2} & \text{1} \\
\text{8} & \text{7} \\
\text{9} & \text{10} \\
\end{array}
\]

Rf: 0.56 (Eluant: hexane/ethyl acetate; 8/2).

IR (neat): \( \nu_{\max} / \text{(cm}^{-1}) \): 2917 (s); 1703 (s); 1605 (s); 1510 (s); 1251 (s); 1165 (s); 769 (s).

\(^1\)H-NMR (250 MHz, CDCl\(_3\)) \( \delta_{\text{H}}: 8.00 \ (2\text{H, td, } J = 9.0, \text{ H}_12); 6.92 \ (2\text{H, td, } J = 9.0, \text{ H}_13); 5.42 \ (1\text{H, m, H}_2); 3.85 \ (3\text{H, s, H}_15); 1.20-0.85 \ (18\text{H, m, H}_3-10). \)

\(^{13}\)C-NMR (62 MHz, CDCl\(_3\)) \( \delta_{\text{C}}: 165.8 \ (\text{C}_1); 163.3 \ (\text{C}_{14}); 131.6 \ (\text{C}_{12}); 123.6 \ (\text{C}_{11}); 113.7 \ (\text{C}_{13}); 71.4 \ (\text{C}_2); 55.5 \ (\text{C}_{15}); 47.2 \ (\text{C}_8); 39.4 \ (\text{C}_3); 35.0 \ (\text{C}_6); 29.5 \ (\text{C}_4); 26.9 \ (\text{C}_9); 25.6 \ (\text{C}_7); 22.3 \ (\text{C}_3); 21.1 \ (\text{C}_{10}); 20.9 \ (\text{C}_{10}). \)

HPLC (Method A): \( t_R = 10.93 \text{ min.} \)

The compound exhibited \(^1\)H and \(^{13}\)C-NMR spectra identical to those described previously.\(^{119}\)

[(1S,2S,5R)-2-Isopropyl-5-methylcyclohexyl ethanethioate] 3.39d (0.02 g, 31% yield)

\[
\begin{array}{c}
\text{6} & \text{5} \\
\text{4} & \text{3} \\
\text{2} & \text{1} \\
\text{8} & \text{7} \\
\text{9} & \text{10} \\
\end{array}
\]

Rf: 0.60 (Eluant: hexane/ethyl acetate; 25/1).

\(^1\)H-NMR (250 MHz, CDCl\(_3\)) \( \delta_{\text{H}}: 4.40 \ (1\text{H, m, H}_2); 2.82 \ (3\text{H, s, H}_{11}); 1.20-0.85 \ (18\text{H, m, H}_{3-10}). \)

The compound exhibited \(^1\)H and \(^{13}\)C-NMR spectra identical to those described previously.\(^{178}\)
General procedure for one-pot synthesis of neomenthyl-ester

L-(−)-menthol 3.40 (2.0 mmol) was added to a mixture of copper (II) triflate (14 mg, 0.04 mmol) in N,N'-diisopropylcarbodiimide 2.26 (2.0 mmol) in a microwave vial. The vial was capped and the green mixture heated at 100 °C using a Smith Synthesizer™ for 5 min. A solution of carboxylic acid (1.9 mmol) in toluene (2 mL) was added to the oil, subsequently the vial was capped and heated at 150 °C using a Smith Synthesizer™ for 10 min. The 1,3-diisopropylurea was filtered off, the solvent evaporated and the residue purified by chromatography using a SPE cartridges (20 mL) packed with silica and alumina.
5.4 Experimental for chapter IV

General procedure for synthesis of O-alkyl-polystyrene-isoureas

\[ \text{NN—cHex} + \text{ROH} \]
\[ \text{(1.2 equiv)} \]
\[ \text{i) THF, Cu(OTf)_2, 16 h} \]
\[ \text{ii) TMEDA, DCM (3 wash cycles)} \]

\[ \text{OR‘} \]

\[ \text{N-cyclohexyl-N’-methylpolystyrenecarbodiimide 2.27 (0.33 g, 0.7 mmol), alcohol (0.84 mmol) and Cu(OTf)_2 (0.066 g, 0.182 mmol) were placed in a dry round-bottom flask. Anhydrous THF (5 ml) was added and the mixture was stirred overnight. The resin was filtered, washed with a 10% solution of TMEDA in DCM until the washing solution remained uncoloured, then with DMF (3×20 mL), MeOH (3×20 mL), DCM (5×20 mL). Resins 2.28e-f were dried overnight under vacuum at 40 °C for 24 hours.} \]

PS-O-pentenylisourea (2.28e): IR (neat): \( \nu_{\text{max}}/\text{(cm}^{-1}) \) 2924 (s); 1652 (s); 1238 (s); 1029 (s); 890 (m). \(^{13}\text{C-NMR (75 MHz, CDCl}_3)\) \( \delta_{\text{C}} \): 139.1; 115.9; 35.2; 31.4; 29.3.

PS-O-phenethylisourea (2.28f): IR (neat): \( \nu_{\text{max}}/\text{(cm}^{-1}) \) 2923 (s); 1653 (s); 1448 (m); 1239 (m); 1029 (m). \(^{13}\text{C-NMR (75 MHz, CDCl}_3)\) \( \delta_{\text{C}} \): 68.4; 26.1.

General procedure for microwave-assisted esterification using PS-O-alkylisoureas

\[ \text{N—cHex} + \text{R‘COOH} \]
\[ \text{i) CH}_3\text{CN, µW 5 min, 150 °C} \]
\[ \text{ii) Dowex® 550A OH resin} \]

\[ \text{R‘COOR‘} \]

\[ 4.8/2.8 \]
The acid (0.45 mmol) was dissolved in CH$_3$CN (2 mL) and the resulting solution is added to the resins 2.28e-f (0.18 g, 0.30 mmol) in a microwave vial. The vial was capped and heated at 150 °C using a Smith Synthesizer$^\text{TM}$ for 5 min, after cooling DOWEX® 550A OH (0.750 g) was added. After shaking for 1 h, the resin was filtered and washed with DCM (3×5 mL). The combined filtrates were evaporated to afford the desired carboxylic esters. No purification was performed before NMR analysis.

**[Pent-4-enyl 4-methoxybenzoate] 4.8 a** (0.05 g, 80% yield, pale yellow oil)

\[
\begin{align*}
\text{Rf:} & \quad 0.60 \text{ (Eluant: hexane/ethyl acetate; 9/1).} \\
\text{IR} \text{ (neat):} & \quad v_{\max} / \text{(cm}^{-1}) \quad 2954 \text{ (br); 1710 (s); 1606 (s); 1510 (s); 1255 (s); 770 (s).} \\
\text{H$^1$-NMR} \text{ (300 MHz, CDCl$_3$)} & \quad \delta_{H}: 7.99 (2H, d, J = 9.2 \text{ Hz, H}_11); \quad 6.91 (2H, d, J = 8.8, H$_{12}$); \quad 5.85 (1H, m, H$_6$); \quad 5.00 (1H, dd, J$_{\text{trans}} = 17.0, 1.8 \text{ Hz, H}_8); \quad 4.93 (1H, dd, J$_{\text{cis}} = 10.0, 1.8 \text{ Hz, H}_9); \quad 4.30 (2H, t, J = 6.6 \text{ Hz, H}_2); \quad 3.86 (3H, s, H_{14}); \quad 2.25-2.18 (2H, m, H_4); \quad 1.91-1.82 (2H, m, H_3). \\
\text{C$^{13}$-NMR} \text{ (75 MHz, CDCl$_3$)} & \quad \delta_{C}: 163.4 (C_1); \quad 163.3 (C_{13}); \quad 137.6 (C_3); \quad 131.5 (C_{11}); \quad 122.9 (C_{10}); \quad 115.3 (C_7); \quad 113.6 (C_{12}); \quad 64.1 (C_2); \quad 55.4 (C_{14}); \quad 30.2 (C_4); \quad 28.0 (C_3). \\
\text{LRMS} \text{ [EI] m/z (}): & \quad 135 (100); \quad 77 (22). \\
\text{HRMS} \text{ [EI] m/z:} & \quad \text{calculated for C}_{16}H_{16}O_3 [M]^+ 220.1099, \text{ found 220.1098.} \\
\text{HPLC (Method A):} & \quad t_R = 11.54 \text{ min.} \\
\end{align*}
\]

The compound exhibited $^1$H and $^{13}$C-NMR spectra identical to those described previously.$^{179}$
[Pent-4-enyl 4-chlorobenzoate] 4.8 b (0.06 g, 90% yield, pale yellow oil)

Rf: 0.60 (Eluant: hexane/ethyl acetate; 8/2).

IR (neat): $\nu_{\text{max}}$ (cm$^{-1}$) 2931 (br); 1720 (s); 1595 (w); 1488 (w); 1401 (w); 849 (w).

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$: 7.96 (2H, d, $J = 9.2$ Hz, H$_{11}$); 7.40 (2H, d, $J = 8.8$, H$_{12}$); 5.83 (1H, m, H$_6$); 5.05 (1H, dd, $J_{\text{trans}} = 17.3, 1.9$ Hz, H$_8$); 5.03 (1H, dd, $J_{\text{cis}} = 10.9, 1.2$ Hz, H$_9$); 4.33 (2H, t, $J = 6.6$ Hz, H$_2$); 2.25-2.17 (2H, m, H$_4$); 1.91-1.78 (2H, m, H$_3$).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$: 163.9 (C$_1$); 137.4 (C$_{13}$); 135.5 (C$_5$); 129.1 (C$_{11}$); 126.8 (C$_{10}$); 126.4 (C$_{12}$); 113.6 (C$_7$); 62.7 (C$_2$); 28.2 (C$_4$); 25.9 (C$_3$).

LRMS [EI] $m/z$ (%): 139 (74); 111 (48); 77 (4); 68 (100); 51 (6).

HRMS [EI] $m/z$: calculated for C$_{12}$H$_{13}$ClO$_2$ [M]$^+$ 224.0604, found 224.0610.

[Pent-4-enyl 3,3,3-triphenylpropanoate 4.8 c (0.10 g, 90% yield, yellow oil)

Rf: 0.60 (Eluant: hexane/ethyl acetate; 9/1).

IR (neat): $\nu_{\text{max}}$ (cm$^{-1}$) 2935 (br); 1732 (m); 1145 (m); 750 (m); 698 (s).

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$: 7.24-7.09 (15H, m, H$_{13-15}$); 5.6 (1H, m, H$_6$); 4.90-4.84 (2H, m, H$_{8,9}$); 3.72 (2H, t, $J = 6.4$ Hz, H$_2$); 3.65 (2H, s, H$_{10}$); 1.95-1.77 (2H, m, H$_4$); 1.40-1.31 (2H, m, H$_3$).
Chapter 5. Experimental section

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta_C$: 169.2 (C$_1$); 144.8 (C$_{12}$); 135.7 (C$_5$); 127.4 (C$_{14}$); 126.0 (C$_{13}$); 124.4 (C$_{15}$); 113.3 (C$_7$); 62.0 (C$_2$); 54.0 (C$_{10}$); 44.7 (C$_{11}$); 28.1 (C$_4$); 25.7 (C$_3$).

LRMS [EI] m/z (%): 243 (100); 165 (56); 77 (4); 51 (2).

HRMS [EI] m/z: calculated for C$_{26}$H$_{26}$O$_2$ [M]$^+$ 370.1933, found 370.1936.

[Pent-4-enyl dodecanoate] 4.8 d (0.05 g, 66% yield, colourless oil).

![Pent-4-enyl dodecanoate structure]

Rf: 0.63 (Eluant: hexane/ethyl acetate; 9/1).

IR (neat): $\nu_{\max}$ (cm$^{-1}$) 2923 (s); 1737 (s); 1465 (br); 1170 (br); 912 (m).

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta_H$: 5.78 (1H, m, H$_6$); 4.97 (1H, dd, $J_{\text{trans}}$ = 16.8, 1.8 Hz, H$_8$); 4.91 (1H, dd, $J_{\text{cis}}$ = 10.0, 1.5 Hz, H$_9$); 4.06 (2H, t, $J$ = 6.6 Hz, H$_2$); 2.28 (2H, t, $J$ = 7.7 Hz, H$_{10}$); 2.15-2.07 (2H, m, H$_4$); 1.76-1.66 (2H, m, H$_3$); 1.65-1.58 (2H, m, H$_{11}$); 1.24 (16H, br, H$_{12-19}$); 0.86 (3H, t, $J$ = 6.6 Hz, H$_{20}$).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta_C$: 173.9 (C$_1$); 137.5 (C$_5$); 115.2 (C$_7$); 63.6 (C$_2$); 34.4 (C$_{10}$); 31.9 (C$_{18}$); 29.6 (C$_4$); 29.5 (C$_{14-16}$); 29.3 (C$_{13, 17}$); 29.3 (C$_{12}$); 27.8 (C$_3$); 25.0 (C$_{11}$); 22.7 (C$_{19}$); 14.1 (C$_{20}$).

LRMS [EI] m/z (%): 183 (10); 113 (5); 100 (28); 68 (100); 55 (24).

HRMS [EI] m/z: calculated for C$_{17}$H$_{32}$O$_2$ [M]$^+$ 268.2402, found 268.2405.

[Pent-4-enyl 2-benzylbenzoate] 4.8 e (0.07 g, 85% yield, colourless oil)
Experimental section

Rf: 0.63 (Eluant: hexane/ethyl acetate; 9/1).

IR (neat): $v_{\text{max}}$ ($\text{cm}^{-1}$) 2927 (w); 2359 (w); 1718 (s), 1494 (w).

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta_H$: 7.81 (1H, d, $J = 9.4$ Hz, H$_{11}$); 7.33 (1H, td, $J = 7.5$, 1.5 Hz, H$_{13}$); 7.26-7.04 (7H, m, H$_{12,14}$, H$_{18-20}$); 5.71 (1H, m, H$_6$); 4.97 (1H, dd, $J_{\text{trans}} = 17.7$, 1.9 Hz, H$_8$); 4.92 (1H, dd, $J_{\text{cis}} = 9.5$, 1.4 Hz, H$_9$); 4.39 (2H, s, H$_{16}$); 4.24 (2H, t, $J = 6.4$ Hz, H$_2$); 2.17-2.10 (2H, m, H$_4$); 1.80-1.73 (2H, m, H$_3$).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta_C$: 167.7 (C$_1$); 142.0 (C$_{17}$); 140.9 (C$_{13}$); 137.5 (C$_3$); 131.9 (C$_{12}$); 131.6 (C$_{11}$); 130.4 (C$_{19}$); 128.9 (C$_{18}$); 128.3 (C$_{14}$); 126.3 (C$_{20}$); 125.9 (C$_{12}$); 115.3 (C$_7$); 64.3 (C$_2$); 39.5 (C$_{16}$); 30.1 (C$_4$); 27.8 (C$_3$).

LRMS [El] $m/z$ (%): 211 (12); 194 (100); 165 (49); 133 (4).

HRMS [El] $m/z$: calculated for C$_{19}$H$_{20}$O$_2$ [M]$^+$ 280.1463, found 268.1462.

**[Pent-4-enyl 2-methyl-2-phenylpropanoate] 4.8 f** (0.06 g, 90% yield, yellow oil)

\[ \text{H}_8 \quad \text{H}_{10} \quad \text{H}_{11} \quad \text{H}_{12} \quad \text{H}_{13} \quad \text{H}_{14} \]

Rf: 0.50 (Eluant: hexane/ethyl acetate; 9/1).

IR (neat): $v_{\text{max}}$ ($\text{cm}^{-1}$) 2931 (br); 1726 (s); 1253 (s); 1144 (s); 1100 (s).

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta_H$: 7.29-7.13 (5H, m, H$_{13-15}$); 5.72 (1H, m, H$_6$); 4.90-4.83 (2H, m, H$_{8,9}$); 4.07 (2H, t, $J = 6.8$ Hz, H$_2$) 2.02-1.95 (2H, m, H$_4$); 1.72-1.60 (2H, m, H$_3$); 1.58 (6H, s, H$_{11}$).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta_C$: 174.9 (C$_1$); 142.8 (C$_{17}$); 135.6 (C$_3$); 126.5 (C$_{14}$); 124.8 (C$_{13}$); 123.8 (C$_{15}$); 113.4 (C$_7$); 62.3 (C$_2$); 44.7 (C$_{10}$); 28.0 (C$_4$); 25.8 (C$_3$); 24.6 (C$_{11}$).

LRMS [El] $m/z$ (%): 119 (100); 91 (35); 77 (6); 68 (10); 51 (4).

HRMS [El] $m/z$: calculated for C$_{15}$H$_{20}$O$_2$ [M]$^+$ 232.1463, found 232.1464.
[Pent-4-enyl benzo[b]thiophene-3-carboxylate] 4.8 g (0.07 g, 90% yield, yellow oil)

Rf: 0.70 (Eluant: hexane/ethyl acetate; 9/1).

IR (neat): ν_{max} / cm^{-1}: 2928 (br); 1718 (s); 1494 (w); 1256 (s); 741 (s).

$^1$H-NMR (300 MHz, CDCl$_3$) δ$_H$: 8.59 (1H, d, J = 8.0 Hz, H$_{17}$); 8.38 (1H, s, H$_{11}$); 7.86 (1H, d, J = 8.0 Hz, H$_{14}$); 7.51-7.38 (2H, m, H$_{15,16}$); 5.86 (1H, m, H$_6$); 5.01 (1H, dd, J\textsubscript{trans} = 17.3, 1.7 Hz, H$_8$); 4.95 (1H, dd, J\textsubscript{cis} = 10.2, 1.5 Hz, H$_9$); 4.39 (2H, t, J = 6.4 Hz, H$_2$); 2.29-2.02 (2H, m, H$_4$); 1.97-1.87 (2H, m, H$_3$).

$^{13}$C-NMR (75 MHz, CDCl$_3$) δ$_C$: 161.0 (C$_1$); 138.2 (C$_{12}$); 135.6 (C$_5$); 134.9 (C$_{10}$); 134.7 (C$_{11}$); 123.6 (C$_{16}$); 123.2 (C$_{15}$); 122.9 (C$_{14}$); 120.7 (C$_{17}$); 113.6 (C$_7$); 62.3 (C$_2$); 28.4 (C$_4$); 26.2 (C$_3$).

LRMS [EI] m/z (%): 246 (6); 178 (100); 161 (60); 133 (14); 89 (34); 68 (4).

[Phenethyl 2,2-dichloro-1-methylcyclopropanecarboxylate] 2.8l (0.06 g, 68% yield). Spectral data (IR, NMR) were identical to those previously reported (page 97).

[Phenethyl decanoate] 2.8j (0.07 g, 90% yield). Spectral data (IR, NMR) were identical to those previously reported (page 96).

[Phenethyl-adamantate] 2.8 m (0.05 g, 56% yield). Spectral data (IR, NMR) were identical to those previously reported (page 98).

[Phenethyl 4-phenoxybenzoate] 2.8d (0.05 g, 53% yield). Spectral data (IR, NMR) were identical to those previously reported (page 87).
General procedure for microwave-assisted "catch-and-release" synthesis of esters

\[ \text{N-cyclohexyl-}N'\text{-methylpolystyrenecarbodiimide 2.27 (0.200 g, 0.38 mmol), alcohol (0.25 mmol) copper (II) triflate (0.010 g, 0.10 mmol) and anhydrous THF (2 mL) were placed in a dry round-bottom flask. After shaking overnight, water (110 µL, 6.0 mmol) was added and shaking was continued for 45 min. 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), DCM (3×5 mL). The resin was placed in a vial swollen in CH\textsubscript{3}CN (2 mL), and acid (1.00 mmol) was added. The resulting suspension was heated at 150 °C using a Smith Synthesizer\textsuperscript{TM} for 5 min, after cooling DOWEX\textsuperscript{®} 550A OH (0.750 g) was added. After shaking for 1 h, the resin was filtered and washed with DCM (3×5 mL). The combined filtrates were evaporated to afford the desired carboxylic esters. No purification was performed before NMR analysis.}

[Pent-4-enyl 4-methoxybenzoate] 4.8a (0.02 g, 34% yield). Spectral data (IR, NMR) were identical to those previously reported (page 133).

[Pent-4-enyl 4-chlorobenzoate] 4.8b (0.02 g, 40% yield). Spectral data (IR, NMR) were identical to those previously reported (page 134).
[Pent-4-enyl dodecanoate] 4.8d (0.04 g, 70% yield). Spectral data (IR, NMR) were identical to those previously reported (page 135).

[3-phenylpropyl dodecanoate] 4.8h (0.03 g, 40% yield, colourless oil)

\[
\text{Rf: 0.60 (Eluant: hexane/ethyl acetate; 8/2).}
\]

\[
\text{IR (neat): } v_{\text{max}} \, \text{(cm}^{-1}) \quad 2923 \, \text{(br)}; \quad 1736 \, \text{(s)}; \quad 1679 \, \text{(m)}; \quad 1496 \, \text{(w)}; \quad 1454 \, \text{(m)}.
\]

\[
^1\text{H-NMR (300 MHz, CDCl}_3\text{)} \delta_H: \quad 7.18-7.08 (5\text{H, m, H}_6-\text{H}_8); \quad 4.02 (2\text{H, t, } J = 6.6 \, \text{Hz, H}_2); \quad 2.62 (2\text{H, t, } J = 7.3 \, \text{Hz, H}_4); \quad 2.22 (2\text{H, t, } J = 7.7 \, \text{Hz, H}_{10}); \quad 1.94-1.84 (2\text{H, m, H}_3); \quad 1.58-1.52 (2\text{H, m H}_{11}); \quad 1.18 (16\text{H, br, H}_{12-19}); \quad 0.80 (3\text{H, t, } J = 7.0 \, \text{Hz, H}_{20}).
\]

\[
^13\text{C-NMR (75 MHz, CDCl}_3\text{)} \delta_C: \quad 173.9 \, \text{(C}_1\text{)}; \quad 141.3 \, \text{(C}_3\text{)}; \quad 128.4 \, \text{(C}_7\text{)}; \quad 128.4 \, \text{(C}_6\text{)}; \quad 126.0 \, \text{(C}_8\text{)}; \quad 63.5 \, \text{(C}_2\text{)}; \quad 34.4 \, \text{(C}_{10}\text{)}; \quad 32.2 \, \text{(C}_4\text{)}; \quad 31.9 \, \text{(C}_{10}\text{)}; \quad 30.3 \, \text{(C}_3\text{)}; \quad 29.6 \, \text{(C}_{16}\text{)}; \quad 29.5 \, \text{(C}_{14}\text{)}; \quad 29.3 \, \text{(C}_{17}\text{)}; \quad 29.3 \, \text{(C}_{13}\text{)}; \quad 29.2 \, \text{(C}_{12}\text{)}; \quad 25.0 \, \text{(C}_{11}\text{)}; \quad 22.7 \, \text{(C}_{19}\text{)}; \quad 14.1 \, \text{(C}_{20}\text{)}.
\]

\[
\text{LRMS [EI] m/z (%): 118 (100); 91 (34.8); 77 (2); 51(2).}
\]

\[
\text{HRMS [EI] m/z: calculated for C}_{21}\text{H}_{34}\text{O}_2 [M]^+ \quad 318.2559, \text{ found 318.2559.}
\]

[3-Phenylpropyl 4-phenoxybenzoate] 4.8i (0.07 g, 90% yield, colourless oil)

\[
\text{Rf: 0.50 (Eluant: hexane/ethyl acetate; 8/2).}
\]

\[
\text{IR (neat): } v_{\text{max}} \, \text{(cm}^{-1}) \quad 2955 \, \text{(w)}; \quad 1712 \, \text{(s)}; \quad 1586 \, \text{(s)}; \quad 1488 \, \text{(s)}; \quad 1270 \, \text{(s)}; \quad 1235 \, \text{(s)}.
\]
$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$H: 8.06 (2H, d, $J = 9.0$ Hz, H$_{11}$); 7.46-7.02 (12H, m, H$_{6-8}$, H$_{12}$, H$_{15-17}$); 4.37 (2H, t, $J = 6.2$ Hz, H$_2$); 2.82 (2H, t, $J = 7.0$ Hz, H$_4$); 2.19-2.08 (2H, m, H$_3$).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$C: 166.1 (C$_1$); 161.8 (C$_{13}$); 155.7 (C$_{14}$); 141.2 (C$_3$); 131.7 (C$_{11}$); 130.0 (C$_7$); 128.5 (C$_{16}$); 126.0 (C$_6$); 124.8 (C$_{10}$); 124.5 (C$_8$); 120.1 (C$_{17}$); 117.4 (C$_{15}$); 64.2 (C$_2$); 32.4 (C$_4$); 30.4 (C$_3$).

LRMS [El] m/z (%): 214 (48); 168 (5); 118 (100); 91 (29); 77 (15); 51(6).

HRMS [El] m/z: calculated for C$_{22}$H$_{20}$O$_3$ [M]+ 332.1412, found 332.1413.

[Phenethyl-adamantate] 2.8 m (0.03 g, 40% yield). Spectral data (IR, NMR) were identical to those previously reported (page 98).

Phenethyl 2,2-dichloro-1-methylcyclopropanecarboxylate] 2.8l (0.02 g, 30% yield). Spectral data (IR, NMR) were identical to those previously reported (page 97).

[Phenethyl decanoate] 2.8j (0.02 g, 30% yield). Spectral data (IR, NMR) were identical to those previously reported (page 96).

[Phenethyl 4-phenoxybenzoate] 2.8d (0.02 g, 23% yield). Spectral data (IR, NMR) were identical to those previously reported (page 87).

[Hexyl 2-(3-chlorophenyl)acetate] 2.8o (0.05 g, 80% yield). Spectral data (IR, NMR) were identical to those previously reported (page 99).

[Hexyl 2-hydroxybenzoate] 2.8p (0.04 g, 72% yield). Spectral data (IR, NMR) were identical to those previously reported (page 100).

[(R)-4-Phenylbutan-2-yl 4-nitrobenzoate] (R)-3.31f (0.02 g, 30% yield). Spectral data (IR, NMR) were identical to those previously reported (page 110).
[(R)-4-Phenylbutan-2-yl-2,6-dichlorobenzoate]  (R)-3.31g: (0.02 g, 26% yield).
Spectral data (IR, NMR) were identical to those previously reported (page 111).

General procedure for the preparation of β-hydroxyamides

\[
\begin{align*}
\text{R}_1\text{Cl} + \text{H}_2\text{N}\text{R}_4\text{R}_5\text{OH} & \xrightarrow{\text{TEA, DCM}} \text{R}_1\text{N}\text{R}_4\text{R}_5\text{OH} \\
\end{align*}
\]

A solution of the appropriate aminoalcohol (10.0 mmol) and TEA (1.1 equiv) in anhydrous DCM (20 mL) was cooled in 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 (1N, 40 mL), NaHCO₃ (5% w/w, 40 mL) and water (40 mL), dried with MgSO₄ and the solvent was removed under vacuum to afford the products as white solids. In the case of 4.9c a different work up was employed, as the product precipitate from the reaction mixture, the white solid was simply collected by filtration and washed with DCM. All products were found to be sufficient pure by $^1\text{H}$-NMR to be used without further purification.

[N-(1-hydroxy-2-methylpropan-2-yl)benzamide] 4.9b (1.70 g, 88% yield)

$^1\text{H}$-NMR (250 MHz, CDCl₃) $\delta$: 7.88-7.84 (2H, m, H₃); 7.59-7.46 (3H, m, H₄,5); 6.71 (1H, br, NH); 3.74 (2H, m, H₇); 1.52 (6H, s, H₈).

The compound exhibited $^1\text{H}$ and $^{13}\text{C}$-NMR spectra identical to those described previously.¹⁸⁰
[N-((S)-1-hydroxy-3-methylbutan-2-yl)benzamide] 4.9c (1.86 g, 90% yield)

![Chemical structure of 4.9c](image)

\[^1\text{H-NMR}\ (250 \text{ MHz, CDCl}_3) \delta: 7.79-7.76 (2\text{H, m, H}_3); 7.51-7.26 (3\text{H, m, H}_{4,5}); 6.41 (1\text{H, d, } J = 8.0 \text{ Hz, NH}); 3.94 (1\text{H, m, H}_6); 3.79 (2\text{H, m, H}_7); 2.85 (1\text{H, br, OH}); 2.04 (1\text{H, m, H}_8); 1.03 (3\text{H, d, } J = 6.5 \text{ Hz, H}_9); 0.78 (3\text{H, d, } J = 6.5 \text{ Hz, H}_9).\]

The compound exhibited \(^1\text{H}\) and \(^{13}\text{C-NMR}\) spectra identical to those described previously.\(^{181}\)

[N-((1S,2S)-1-hydroxy-3-methoxy-1-phenylpropan-2-yl)benzamide] 4.9e (2.13 g, 75% yield)

![Chemical structure of 4.9e](image)

\[^1\text{H-NMR}\ (250 \text{ MHz, CDCl}_3) \delta: 7.60 (2\text{H, d, } J = 8.0 \text{ Hz, H}_3); 7.38-7.14 (8\text{H, m, H}_{4,5, \text{H}_9,11}); 6.87 (1\text{H, d, } J = 7.5 \text{ Hz, NH}); 4.95 (1\text{H, d, } J = 4.5 \text{ Hz, H}_7); 4.29 (1\text{H, m, H}_6); 3.51 (1\text{H, dd, } J = 9.5, 4.5 \text{ Hz, H}_{12}); 3.49 (1\text{H, dd, } J = 9.5, 4.5 \text{ Hz, H}_{12}); 3.20 (3\text{H, s, H}_{13}).\]

The compound exhibited \(^1\text{H}\) and \(^{13}\text{C-NMR}\) spectra identical to those described previously.\(^{104}\)
General procedure for microwave-assisted "catch-and-release" synthesis of 2-oxazolines

\[ \text{N-cyclohexyl-N'-methylpolystyrenecarbodiimide 2.27 (0.200 g, 0.37 mmol), the appropriate 0-hydroxyamide 4.22a-d (0.25 mmol) and copper (II) triflate (0.035 g, 0.09 mmol) were placed in a microwave vial and anhydrous THF (2 mL) was added. The vial was heated at 130 °C using a Smith Synthesizer™ for 15 min. The resin was filtered off and washed with 5 mL 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 \(^1\text{H-NMR}.} \]

\[ \text{[4,5-dihydro-2-phenyloxazole] 4.22a (0.03 g, 70% yield)} \]

\[^1\text{H-NMR (250 MHz, CDCl}_3\text{)} \delta: \text{7.95 (2H, m, H}_2\text{); 7.58-7.42 (3H, m, H}_3\text{,}\text{H}_4\text{); 4.13 (2H, t, J = 6.0 Hz, H}_6\text{); 3.89 (2H, t, J = 6.0 Hz, H}_7\text{).} \]

The compound exhibited \(^1\text{H and }^{13}\text{C-NMR spectra identical to those described previously.}^{182}\]
[3,3-Dimethyl-2-phenyl-2-oxazoline] 4.22b (0.03 g, 72% yield)

\[
\begin{array}{c}
\text{\includegraphics[width=0.2\textwidth]{diagram.png}}
\end{array}
\]

\[ ^1\text{H-NMR} \ (250 \text{ MHz, CDCl}_3) \delta: \ 7.88-7.84 \ (2\text{H, m, H}_2); \ 7.39-7.19 \ (3\text{H, m, H}_{3,4}); \ 4.13 \ (2\text{H, s, H}_6); \ 1.32 \ (6\text{H, s, H}_8). \]

The compound exhibited \(^1\text{H} and \(^{13}\text{C-NMR spectra identical to those described previously.}^{183}\)

[(S)-4-Isopropyl-2-phenyl-2-oxazoline] 4.22c (0.02 g, 47% yield)

\[
\begin{array}{c}
\text{\includegraphics[width=0.2\textwidth]{diagram.png}}
\end{array}
\]

\[ ^1\text{H-NMR} \ (250 \text{ MHz, CDCl}_3) \delta: \ 7.88 \ (2\text{H, m, H}_2); \ 7.36-7.31 \ (3\text{H, m, H}_{3,4}); \ 4.33 \ (1\text{H, m, H}_7); \ 4.09-3.97 \ (2\text{H, m, H}_6); \ 1.77 \ (1\text{H, m, H}_8); \ 0.96 \ (3\text{H, d, J = 7.0 Hz, H}_9); \ 0.91 \ (3\text{H, d, J = 7.0 Hz, H}_9). \]

The compound exhibited \(^1\text{H} and \(^{13}\text{C-NMR spectra identical to those described previously.}^{184}\)

[(R)-2,4-Diphenyl-2-oxazoline] 4.22d (0.03 g, 56% yield)

\[
\begin{array}{c}
\text{\includegraphics[width=0.2\textwidth]{diagram.png}}
\end{array}
\]
Chapter 5. Experimental section

**[4S, 5R)-4-Methoxymethyl-2,5-diphenyl-2-oxazoline]** 4.15

\[\text{^1H-NMR} \text{ (250 MHz, CDCl}_3\text{) } \delta_H: 7.97 \text{ (2H, m, H}_2\text{); 7.48-7.18 \text{ (8H, m, H}_3,\text{H}_4,\text{H}_9,\text{H}_{11}\text{); 5.30 \text{ (1H, dd, } J = 10.0, 8.0 \text{ Hz, H}_7\text{); 4.74 \text{ (1H, dd, } J = 10.0, 7.0 \text{ Hz, H}_6\text{); 4.21 \text{ (1H, t, } J = 8.0 \text{ Hz, H}_8\text{).}}\]

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

**[4S, 5S)-4-Methoxymethyl-2,5-diphenyl-2-oxazoline]** 4.16

\[\text{^1H-NMR} \text{ (250 MHz, CDCl}_3\text{) } \delta_H: 8.06 \text{ (2H, m, H}_2\text{); 7.50-7.23 \text{ (8H, m, H}_3,\text{H}_4,\text{H}_{11},\text{H}_{13}\text{); 5.80 \text{ (1H, d, } J = 10.0 \text{ Hz, H}_6\text{); 4.68 \text{ (1H, dt, } J = 10.0, 6.0 \text{ Hz, H}_7\text{); 3.40 \text{ (1H, m, H}_8\text{); 3.01-2.92 \text{ (4H, m, H}_8,\text{H}_9\text{).}}\]

The compound exhibited \(^1\text{H} \text{ and } \text{^{13}C-NMR spectra identical to those described previously.}\)
References:

References


(31) Nuechter, M.; Ondruschka, B.; Bonrath, W.; Gum, A. Green Chem. 2004, 6, 128-141.


(33) Hayes, B. L. Microwave Synthesis: Chemistry at the speed of Light; CEM Publishing, Matthews, NC, 2002.


(64) Daebritz, E. Angew. Chem. 1966, 78, 483-490.


