Novel Applications of α-Diazocarbonyl Compounds and Enabling Technologies in Stereoselective Synthesis

A Thesis Submitted to Cardiff University in Fulfilment of the Requirements for the Degree of Doctor of Philosophy by

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Acknowledgments

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Micol
A mia madre, mio padre ed Elen
Abstract

α-Diazocarbonyl compounds are widely used in organic chemistry as versatile carbenec precursors which enable concise synthesis towards complex asymmetric molecules. Due to their intrinsic highly energetic nature, flow technology can be applied to ensure safer, scalable and efficient protocols. Other modern enabling tools such as Design of Experiment (DoE) and online analysis, provide great advantages to achieve faster analysis and optimisations of chemical transformations.

In the first part of this work, α-diazocarbonyl compounds have been used in the enantioselective synthesis of novel trans-indolines.1

\[
\text{CO}_2\text{Me} \quad \text{p-NBSA, DBU} \quad \begin{array}{c} \text{Ph} \\ \text{Ts} \end{array} \quad \text{N} \quad \xrightarrow{\begin{array}{c} \text{flow system} \\ \text{batch} \end{array}} \quad \begin{array}{c} \text{Ph} \\ \text{Ts} \end{array} \
\]

The synthesis of the diazo precursors, previously investigated in batch, was translated into a flow system and optimised following a DoE-approach. Moreover, highly Lewis acidic boranes were found to enable related α-diazocarbonyl compounds to undergo a metal-free transfer/rearrangement cascade reaction towards asymmetric benzofuran-3H-ones.2

\[
\text{CO}_2\text{R}^1 \quad \xrightarrow{\text{BAR}_3} \quad \begin{array}{c} \text{Ar} \\ \text{X} \\ \text{R}^2 \end{array} \quad \xrightarrow{-\text{BAR}_2\text{OR}^1} \quad \begin{array}{c} \text{X} \end{array} \
\]

The focus in the final part of this work was on the development of a faster analytical method for an accelerated optimisation of stereoselective reactions. The reactions were performed in a continuous flow electrochemical reactor directly coupled to a 2D-HPLC for immediate online analysis, which allowed a fast screening of reaction conditions using DoE.3
Publications


List of Abbreviations

°C   Degree Celsius
λ    Wavelength
δ    Chemical Shift
¹D   First dimension (2D-HPLC)
²D   Second dimension (2D-HPLC)
1D-LC One-dimensional Liquid Chromatography
2D-LC Two-dimensional Liquid Chromatography
2D-HPLC Two-dimensional High Performance Liquid Chromatography
2FI  Two-factor Interaction
Ac   Acetyl
A    Ampere
AN   Acceptor Number
APCI Atmospheric Pressure Chemical Ionisation
API   Active Pharmaceutical Ingredient
Ar   Aryl
ASAP Atmospheric Solid Analysis Probe
BDD   Boron Doped Diamond
BPR   Back-pressure Regulator
calc. calculated
cat.   catalytic
CCD   Circumscribed Composite Design
CCF   Central Composite Faced design
conv. conversion
CV    Cyclic Voltammetry
DBU   1,8-Diazabicyclicloundec-7-ene
dec.  decomposition
DFT   Density Functional Theory
DIAD  Diisopropyl azodicarboxylate
DMAP  4-Dimethylaminopyridine
DIPEA  N,N-diisopropylethylamine
DOSP  Dodecylphenylsulfonylprolinate
DMF   N,N-Dimethylformamide
DMSO Dimethyl sulfoxide
DoE   Design of Experiments
<table>
<thead>
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<tbody>
<tr>
<td>d.r.</td>
<td>diastereomeric ratio</td>
</tr>
<tr>
<td>EDA</td>
<td>Ethyl diazoacetate</td>
</tr>
<tr>
<td>EDG</td>
<td>Electron Donating Group</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>e.r.</td>
<td>enantiomeric ratio</td>
</tr>
<tr>
<td>EI</td>
<td>Electron Ionisation</td>
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<tr>
<td>equiv.</td>
<td>equivalent</td>
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<tr>
<td>ES</td>
<td>Electrospray Ionisation</td>
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<tr>
<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>EWG</td>
<td>Electron Withdrawing Group</td>
</tr>
<tr>
<td>F</td>
<td>Faraday</td>
</tr>
<tr>
<td>FD</td>
<td>Full Design</td>
</tr>
<tr>
<td>FFD</td>
<td>Full Factorial Design</td>
</tr>
<tr>
<td>FLPs</td>
<td>Frustrated Lewis Pairs</td>
</tr>
<tr>
<td>g</td>
<td>gram</td>
</tr>
<tr>
<td>GC</td>
<td>Gas Chromatography</td>
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<tr>
<td>h</td>
<td>hour</td>
</tr>
<tr>
<td>HPLC</td>
<td>High Performance Liquid Chromatography</td>
</tr>
<tr>
<td>HRMS</td>
<td>High Resolution Mass Spectrometry</td>
</tr>
<tr>
<td>HTC</td>
<td>Hard-To-Change</td>
</tr>
<tr>
<td>HTS</td>
<td>High-Throughput-Screening</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>Ile</td>
<td>Isoleucine</td>
</tr>
<tr>
<td>i-Pr</td>
<td>iso-Propyl</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant</td>
</tr>
<tr>
<td>L</td>
<td>litre</td>
</tr>
<tr>
<td>LC</td>
<td>Liquid Chromatography</td>
</tr>
<tr>
<td>LCxLC</td>
<td>Comprehensive two-dimensional Liquid Chromatography</td>
</tr>
<tr>
<td>LC-LC</td>
<td>Heart-cutting two-dimensional Liquid Chromatography</td>
</tr>
<tr>
<td>LDA</td>
<td>Lithium diisopropylamide</td>
</tr>
<tr>
<td>LiHMDS</td>
<td>Lithium bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>M</td>
<td>molarity</td>
</tr>
<tr>
<td>m</td>
<td>meter</td>
</tr>
<tr>
<td>m.p.</td>
<td>melting point</td>
</tr>
<tr>
<td>m/z</td>
<td>mass over charge ratio</td>
</tr>
<tr>
<td>Me</td>
<td>Methyl</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
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<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>MS</td>
<td>Mass Spectrometry</td>
</tr>
<tr>
<td>Ms</td>
<td>Mesyl</td>
</tr>
<tr>
<td>min</td>
<td>minute</td>
</tr>
<tr>
<td>mol</td>
<td>mole</td>
</tr>
<tr>
<td>MRC</td>
<td>Metallo-radical Catalysis</td>
</tr>
<tr>
<td>n-BuLi</td>
<td>normal butyllithium</td>
</tr>
<tr>
<td>NBR</td>
<td>N-bromosuccinimide</td>
</tr>
<tr>
<td>NHS</td>
<td>N-hydroxysuccinimide</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>NP-LC</td>
<td>Normal-phase Liquid Chromatography</td>
</tr>
<tr>
<td>NSI</td>
<td>Nanospray Ionisation</td>
</tr>
<tr>
<td>p-ABSA</td>
<td>p-Acetamidobenzenesulfonyl azide</td>
</tr>
<tr>
<td>PET</td>
<td>Positron Emission Tomography</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>PMP</td>
<td>p-Methoxyphenyl</td>
</tr>
<tr>
<td>p-NBSA</td>
<td>p-Nitrobenzenesulfonyl azide</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>PTAD</td>
<td>N-Phthalimido-1-adamantyl acetate</td>
</tr>
<tr>
<td>PTFE</td>
<td>Polytetrafluoroethylene</td>
</tr>
<tr>
<td>PTTL</td>
<td>N-phthamido-1-tert-leucinate</td>
</tr>
<tr>
<td>Pyr</td>
<td>Pyridine</td>
</tr>
<tr>
<td>Rf</td>
<td>Retention factor</td>
</tr>
<tr>
<td>RP-LC</td>
<td>Reverse-phase Liquid Chromatography</td>
</tr>
<tr>
<td>RSM</td>
<td>Response Surface Model</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>t-Bu</td>
<td>tert-Butyl</td>
</tr>
<tr>
<td>TEA</td>
<td>Triethylamine</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>Ts</td>
<td>Tosyl</td>
</tr>
<tr>
<td>vs</td>
<td>versus</td>
</tr>
<tr>
<td>V</td>
<td>Volt</td>
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CHAPTER 1: Introduction

1.1 α-Diazocarbonyl Compounds in Organic Synthesis

Diazo compounds are a class of neutral organic reagents presenting a terminal dinitrogen moiety (Scheme 1.1).

\[
\begin{array}{c}
\text{Scheme 1.1: Diazo compound 1 as precursor for carbene species 2.}
\end{array}
\]

The highly energetic carbon-nitrogen bond can be cleaved, releasing molecular nitrogen \(\text{N}_2\) and generating the reactive carbene species 2. For this reason, since their discovery in 1858 by Peter Griess,\(^1\) diazo compounds are widely used in organic chemistry as versatile building blocks. However, due to their intrinsic reactivity, diazo intermediates are also highly toxic and explosive.\(^2\) Several explosions due to diazomethane have been reported as result of its fast decomposition at higher temperatures or in contact with scratched glassware.\(^3\) This high reactivity has limited their applications especially in industrial setting.

Diazo compounds can be classified into three groups according to the electronic properties of their substituents (Figure 1.1).\(^4\)

**Class I**

\[
\begin{array}{c}
\text{EWG}_2 \underset{\text{N}_2}{\text{R}} \\
\text{used for: cyclopropanation, intramolecular X–H insertion (X=C,N,O), carbonyl ylides generation}
\end{array}
\]

- \(^*\text{acceptor/acceptor}\), \(R = \text{EWG}\)
- \(^*\text{acceptor}\), \(R = \text{H, alkyl}\)

**Class II**

\[
\begin{array}{c}
\text{EWG}_2 \underset{\text{EDG}}{\text{R}} \\
\text{used for: cyclopropanation, intra- and intermolecular X–H insertion (X = C,N,O)}
\end{array}
\]

- \(^*\text{donor/acceptor}\)

**Class III**

\[
\begin{array}{c}
\text{EDG}_2 \underset{\text{N}_2}{\text{R}} \\
\text{used for: intramolecular C–H insertion}
\end{array}
\]

- \(^*\text{donor/donor}\), \(R = \text{EDG}\)
- \(^*\text{donor}\), \(R = \text{H, alkyl}\)

**Figure 1.1:** Diazo compounds classified according to the electronic properties of the substituents: \(\text{EWG} = \text{carbonyl, sulfonyl, cyano, nitro, phosphonate group}; \text{EDG} = \text{aryl, heteroaryl, vinyl group.}**
Early works in the area of diazo chemistry focused on the first class of diazo compounds bearing one (“acceptor”) or two (“acceptor/acceptor”) electron-withdrawing groups (EWG) such as dicarbonyl diazo or α-diazo ester. These electrophilic molecules generate highly reactive carbene intermediates that found applications in a wide range of transformations from cyclopropanation\(^5\) to X–H insertion (X = C, O, N)\(^6\) and generation of ylides.\(^7\) However, due to the high electrophilic nature of the carbon atom and the inability of the EWG to stabilise the carbene centre, this class of compounds is characterised by low selectivity especially in intermolecular insertions, therefore they are mainly used for intramolecular processes. Subsequently, Davies and co-workers explored how proximal electron-donating groups (EDG), such as aryl or vinyl moieties, provide more stable carbene precursors (Class II). For this reason, and due to their slightly attenuated reactivity, “donor/acceptor” diazo compounds can be engaged in more selective intermolecular reactions.\(^8\) While these first two classes have received more attention, just a few examples have been reported using the third class of diazo compounds. The “donor/donor” carbene precursors have been known for many years but their electron-rich character makes their isolation problematic and an \textit{in situ} generation is often required.\(^{4a,9}\) Furthermore, these types of diazo compounds are reported to be highly explosive and they are subjected to a fast dimerisation which limits their applicability (Scheme 1.2).

Scheme 1.2: Dimerisation of “donor/acceptor” and “donor/donor” diazo compounds.

This work of thesis mainly focuses on the synthesis and reactivity of donor/acceptor diazo compounds such as 6, that are generally preferred over diazoalkane intermediates because of their higher stability (Scheme 1.3). The additional resonance structure 6\(^{III}\) presents a negative charge located on the more electronegative oxygen atom which stabilises the dipole of the diazo functional group. On the contrary, when the negative and the positive charge are located next to each other as in diazomethane (7), the loss of N\(_2\) is thermodynamically favoured and therefore the compound is less stable.
The thermal properties of diazo compounds are the reason why large-scale syntheses are still scarce, despite the advantages on selectivity of “donor/donor” carbene and the increased stability of “donor/acceptor” carbenes. Nevertheless, in the last two decades, continuous flow chemistry has proven to be a safer alternative for the synthesis of diazo compounds. As discussed later in this chapter, due to the better control of the temperature and the possibility to generate in situ highly energetic diazo precursors, flow chemistry enables “safer” protocols for the synthesis of diazo compounds, even in large-scale reactions.\textsuperscript{10,11}

1.1.1 Synthesis of $\alpha$-Diazocarbonyl Compounds

Diazocarbonyl compounds are widely used as valuable intermediate in organic chemistry and some diazo-containing compounds such as the kinamycins and Lomaiviticin A were also isolated from natural products (Figure 1.2).\textsuperscript{12}
(d), acylation of diazoalkanes (e), substitution/cross-coupling (f) and substituent modification (g).^{13}

Scheme 1.4: Classic routes to \( \alpha \)-diazocarbonyl compounds (6): a) diazotisation of amino acids; b) diazo-transfer reactions; c) dehydrogenation of hydrazones; d) modification of azides; e) acylation of diazoalkanes; f) substitution/cross-coupling; g) substituent modification.

The first reported approach toward diazo compounds dates back to 1883, with the pioneering work of Curtius on the diazotisation of amino acids as a way of preparing ethyl diazoacetate (EDA, 11) from ethyl glycine ester (10) hydrochloride (Scheme 1.5).^{14} Nowadays, this reaction is mainly used for the synthesis of diazonium salts^{15} and azides,^{16} while the introduction of a diazo moiety via diazotisation is less common.

Scheme 1.5: First reported synthesis of ethyl \( \alpha \)-diazoacetate 11 via diazotisation of amino acid 10.^{14}

In 1910, Dimroth reported the reaction between the malonic ester amide (12) and phenyl azide (13) to give diazomalonic ester (16) via triazole intermediate 15 (Scheme 1.6).^{17} A few years later Curtius and Klavehn prepared methyl diazo-\( N \)-tosylamide 20 from dimethyl malonate 17 using \( p \)-toluenesulfonyl azide 18a and suggesting 19 as intermediate.^{18} However, these reactions remained unacknowledged until 1964 when Regitz, inspired by the above-mentioned works, investigated the reaction between the sulfonyl azide 18a and the ketone anthrone (22) in pyridine/ethanol and isolated the corresponding diazocarbonyl 23 and tosylsulfonamide 21 as the side product.^{19} This base-promoted transfer of a diazo group from a sulfonyl azide reagent onto an activated...
methyl or methylene group carries the name of Regitz diazo-transfer, in honour of the German chemist who first explained the mechanism in 1964.\(^{20}\)

\textit{Dimroth (1910)}:

\[
\begin{align*}
\text{MeO} & \quad \text{O} & \quad \text{NH}_{2} \\
\text{12} & \quad \text{13} & \quad \text{N} \equiv \text{N} \\
\text{14} & \quad \text{O} & \quad \text{MeO} & \quad \text{OH} \\
\text{15} & \quad \text{MeO} & \quad \text{N}_{2} & \quad \text{16}
\end{align*}
\]

\textit{Curtius and Klavehn (1926)}:

\[
\begin{align*}
\text{MeO} & \quad \text{O} & \quad \text{O} & \quad \text{MeO} & \quad \text{18a} \\
\text{17} & \quad \text{N} \equiv \text{N} & \quad \text{N} \equiv \text{N} & \quad \text{SO}_{2} \text{N}_{3} \quad \text{NaOCH}_{3} \\
\text{18a} & \quad \text{19} & \quad \text{MeO} & \quad \text{N}_{2} & \quad \text{20} & \quad \text{SO}_{2} \text{NH}_{2} \quad \text{21}
\end{align*}
\]

\textit{Regitz (1964)}:

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{22} & \quad \text{18a} \quad \text{pyperidine} \quad \text{EtOH} \\
\text{23} & \quad \text{21}
\end{align*}
\]

\textbf{Scheme 1.6}: First examples of diazo-transfer reactions.

According to the general mechanism, the diazo group is transferred from a diazo-transfer reagent 18, which is generally a sulfonyl azide, to the desired substrate bearing an activated methylene moiety such as the 1,3-dicarbonyl 24 under basic conditions (Scheme 1.7).

\[
\begin{align*}
\text{R}^{1} & \quad \text{O} & \quad \text{H} & \quad \text{Base} \\
\text{24} & \quad \text{25} & \quad \text{18}^{I} & \quad \text{18}^{II} \\
\text{26} & \quad \text{21} & \quad \text{27}
\end{align*}
\]

\textbf{Scheme 1.7}: General mechanism of the α-diazo-transfer between the 1,3-dicarbonyl 24 and a sulfonyl azide 18.
The activated substrates 24 bearing one or more EWG can be deprotonated in the α-position by a relatively weak base such as triethylamine (TEA), diethylamine or pyridine forming the enolate 25. This reacts with the sulfonyl azide 18 generating the triazene 26 that decomposes into the α-diazo-β-dicarbonyl compound 27 and releases sulfonamide 21 as the side product. When less acidic methylene moieties are present, as in “donor/acceptor” precursors, it is necessary to use a slightly stronger base. For instance, α-aryl carbonyl substrates react better with 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU)21 than with TEA, and for α-aryl amides stronger bases, such as LiHMDS22 and LDA,23 are typically used. However, even with strong bases, the diazo-transfer does not occur at the α-position of simple cyclic and acyclic ketones bearing no additional EWG in β-position. To overcome this problem, Regitz and co-workers developed a deformylative diazo-transfer reaction using pre-functionalised substrates (Scheme 1.8).24 The ketone 28 is activated via a Claisen-type condensation with ethyl formate (29) generating 30a. The activated methylene group is able to undergo a 1,3-dicarbonyl cycloaddition in the presence of tosyl azide 18a and TEA to form the triazole 31. Next, the intermediate 31 decomposes to the α-diazoketone 6 releasing N-formylamide 32 as the side product.

Regitz and co-workers (1968):

Several modifications have been made to improve the efficiency of this reaction. For example, Danheiser and co-workers reported a two-step process using 2,2,2-trifluoroethyl trifluoroacetate (33) for the formation of the activated 30b from an in situ generated lithium enolate for high-yielding synthesis of diazoketones 6 (Scheme 1.9).25 Alternatively, Taber et al. reported an efficient benzoylation for the preparation of α-diazo esters 36, which avoids the use of strong bases and cryogenic conditions.26 In this case, the α-benzoyl intermediate 30c is achieved via a titanium chloride-mediated benzoylation followed by a milder diazo-transfer reaction which affords the diazo compound 36 from a base-sensitive precursor 34.
Danheiser and co-workers (1990): 

\[ R^1\text{O} + R^2\text{O} \rightarrow \text{N}_2 \]

Taber and co-workers (2005): 

Scheme 1.9: Modification of the Regitz deformylative diazo-transfer approach.

The main drawback of the diazo-transfer approach is the potential hazards associated with the azides used as diazo-transfer reagents (Figure 1.3). The first sulfonyl azides to be used for this purpose were \( p \)-toluenesulfonyl azide (18a, TsN\(_3\))\(^{20a} \) and mesyl azide (18b).\(^{27} \) After stability studies, \( p \)-dodecylbenzenesulfonyl azide (18c, \( p \)-DBSA)\(^{28} \) and 2,4,6-triisopropylbenzenesulfonyl azide (18d, trisyl azide)\(^{29} \) were proposed later as safer alternatives.\(^{30} \) Nowadays, the most commonly used diazo-transfer reagents are \( p \)-acetamidobenzenesulfonyl azide (18e, \( p \)-ABSA)\(^{31} \) and 4-nitrobenzenesulfonyl azide (18f, \( p \)-NBSA).\(^{32} \) Additional sulfonyl reagents are imidazole-1-sulfonyl azide salt 18h,\(^{33} \) ionic liquid sulfonyl azides,\(^{34} \) as well as polystyrene-supported benzensulfonyl azide.\(^{35} \)

Figure 1.3: Sulfonyl azides commonly used as diazo-transfer reagents 18.

Moreover, a sulfonyl-azide-free procedure has been recently reported where the diazo-transfer reagent is generated \textit{in situ} using a mixture of sodium azide and \( m \)-carboxybenzenesulfonyl chloride 37 (Scheme 1.10).\(^{36} \) Nevertheless, considering also the hazards linked to sodium azide, particular attention has to be taken when handling these reagents. Furthermore, some azides may be labelled as “safer” due to their less explosive nature but they can still be equally as toxic and shock-sensitive.
Scheme 1.10: ‘Sulfonyl-Azide-Free’ aqueous-phase diazo-transfer reaction.\textsuperscript{36}

A common but mechanistically different way to prepare donor/acceptor and donor/donor diazo compounds is the dehydrogenation of hydrazones 38 (Scheme 1.11).\textsuperscript{37} This procedure can be carried out on a simple hydrazone such as 38a, using stoichiometric quantities of different oxidants such as Pb(OAc)\textsubscript{4},\textsuperscript{37a} Ag\textsubscript{2}O\textsuperscript{37b} or more environmentally friendly “activated” DMSO\textsuperscript{38} and MnO\textsubscript{2}.\textsuperscript{39}

Scheme 1.11: Dehydrogenation of hydrazones 38a and tosylhydrazones 38b to generate 6.

The more air stable tosylhydrazones 38b can be also used to obtain diazo compounds \textit{in situ} in the presence of a base via Bamford-Stevens type reaction.\textsuperscript{9c,40} Generally, the performances are drastically improved when the oxidation occurs under continuous flow conditions,\textsuperscript{10} as the reactive diazo intermediate is generated \textit{in situ} and immediately used in a further transformation.

Over the last decade the direct conversion of azides 39 into the corresponding diazo moiety via triazene fragmentation has emerged as a new and efficient procedure to generate \(\alpha\)-diazocarbonyl compounds (Scheme 1.12).\textsuperscript{41} This convenient approach, which has recently found its application in the synthesis of natural product such as aperidine,\textsuperscript{22} was reported for the first time by Myers and Raines in 2009.\textsuperscript{41} Myers \textit{et al.} designed the phosphine 40 in order to trap 41 into an acyl triazenenophosphonium salt such as 42, which would then lead to acyl triazene 43 upon aqueous work-up. The following fragmentation of 43 under basic conditions (NaHCO\textsubscript{3} or DBU) affords the desired diazo compound 6 and the amide 44 as side product.
Scheme 1.12: Phosphine-mediated azide conversion into diazo compounds.\textsuperscript{41}

A convenient way towards terminal $\alpha$-diazo compounds 46 is the acylation of diazomethane (7) with acyl halides 45 (Scheme 1.13). It is worth mentioning that some terminal $\alpha$-diazocarbonyl compounds\textsuperscript{13b} are stable enough to be subjected to further transformations such as substituent modifications\textsuperscript{42} or cross-coupling reactions.\textsuperscript{43} This method provides access to various diazo compounds that are difficult to synthesise otherwise.

**Scheme 1.13:** Generation of terminal $\alpha$-diazo compounds 46a and 46b.

In conclusion, the research of novel synthetic pathways towards $\alpha$-diazocarbonyl compounds remains a hot topic in organic chemistry. During the last two decades several new reagents and procedures have been developed and enabling technologies, such as flow chemistry, provide valuable tools to successfully improve both efficiency and safety on the preparation of these versatile intermediates.\textsuperscript{10,13a}

### 1.1.2 Reactivity of $\alpha$-Diazocarbonyl Compounds

The intrinsic reactivity of $\alpha$-diazocarbonyl compounds driven by the release of N\textsubscript{2}, makes them valuable precursors in organic synthesis. When exposed to heat, Brønsted acids, Lewis acids or catalytic amounts of transition metals, $\alpha$-diazocarbonyl compounds react by generating useful intermediates such as free carbenes, carbenoids, enolates, ylides.
or diazonium salts, which find application in various transformations: Wolff-rearrangement (a), cyclopropanations (b), C–X insertions (c), Buchner reaction (d) and ylide formation (e) (Scheme 1.14).

Among all, the most exploited reactivity of α-diazo compounds involves carbone and carbenoid-mediated reactions. Carbone species are neutral compounds characterised by a bivalent carbon having only six valence electrons (R¹R²C:) and presenting three sp² hybridized orbitals and one p orbital. They are typically classified into singlet carbenes and triplet carbenes, depending on the localisation of the electrons (Figure 1.4). Singlet carbenes have spin-paired electrons in the nonbonding sp² hybridized orbital while the p orbital is empty, and they show a bond angle of 100–110°. Differently, the triplet carbenes present a wider bond angle (130–150°) as result of the minor repulsion due to unpaired electrons. One of the electrons is located in the sp² hybridized orbital and the other in the higher energy p orbital. All carbenes can theoretically exist in both forms, however, most of them are more stable as triplets, unless they bear highly electron-donating substituents capable of interacting with the empty p orbital stabilising the singlet state.

Due to their highly reactive nature, carbenes are mainly generated in situ through photolysis, thermal or transition metal-catalysed elimination processes, starting from precursors such as diazo compounds. When a carbone species is stabilised by a
transition metal it is referred to as a “carbenoid”. The carbenoids present a complex between the carbon bearing the lone pair and the metal, therefore the carbon structure is more like a tetravalent carbon rather than the typical bivalent carbon of a free carbene. Nevertheless, carbenes and carbenoids share similar reactivity to the point that in literature there are little distinctions and both terms are typically used as synonyms.

A famous reaction involving carbene precursors is the Wolff-rearrangement, where a $\alpha$-diazocarbonyl compound undergoes 1,2-migration to form a ketene $\text{47}$ upon nitrogen loss (Scheme 1.15). When the migration happens on a ring as starting material, the process leads to a ring contracted product. The ketene intermediate $\text{47}$ can undergo nucleophilic attack or $[2+2]$ cycloaddition depending on the substrate available. When the ketene $\text{47}$ is attacked by a nucleophile (NuH), the homologue carbonyl $\text{48}$ is formed. This homologation reaction, named Arndt-Eistert homologation, is still used nowadays to synthesise carboxylic acids or derivatives such as $\beta$-amino acids. Whereas in the presence of olefins, ketones or imines $\text{49}$, the ketenes $\text{47}$ follow a cycloaddition pathway leading to four-membered rings such as $\text{50}$.

A recent example for the enantioselective generation of trans-configured $\beta$-lactams via Wolff-rearrangement enabled by flow chemistry, was reported by Ley and co-workers (Scheme 1.16). In this work a flow-microwave reactor was used to prepare primary ketenes $\text{52}$ from 2-diazoketenes $\text{46}$ under controlled reaction conditions. The ketene $\text{52}$ reacts in situ with imines $\text{51}$ in a $[2+2]$ Staudinger cycloaddition affording $\beta$-lactams $\text{53}$ and $\text{54}$ in moderate to good yield, preferentially with trans-configuration. The stereochemical outcome of the $[2+2]$ Staudinger cycloaddition is likely to be influenced by the size of the substituent at the nitrogen atom of imines $\text{51}$ ($R_2^3$) or at the carbon atom ($R_3^2$).
Another common application of α-diazo compounds is the cyclopropanation of olefins. Considering the frequency of chiral cyclopropanes as structural motifs in pharmaceutical compounds, the interest towards cyclopropanations is strong in medicinal chemistry. During this reaction, a highly strained three-membered ring is formed by photochemically or thermally induced nitrogen loss from pyrazoline or by transition-metal catalysed decomposition of diazo compounds (Scheme 1.17). The process can occur with good stereochemical control by using chiral catalysts or auxiliary directing groups, and can be adapted from batch to flow mode. Furthermore, when the involved π-electrons belong to an aromatic ring, the cyclopropane causes a ring expansion to cycloheptatrienes (Scheme 1.18). In this two-step reaction, also known as the Büchner ring expansion, an aromatic ring reacts with α-diazocarbonyl compound generating a bicyclo[4.1.0]heptadiene derivative. This undergoes a pericyclic ring expansion to generate a 7-membered ring. However, the
equilibrium is shifted towards the bicycle 59 and not the 7-membered ring 60, when the diazo compound 6 bears an EDG as substituent.61

![Scheme 1.18: General scheme for Büchner ring expansion reaction.](image)

The carbenoids are also used for their ability to form other reactive intermediates such as oxonium, sulfur, nitrogen and carbonyl ylides upon treatment with Lewis bases (Scheme 1.19).62 In the presence of ethers, sulfides, amines or carbonyl compounds, the carbenoid 61 acts as Lewis acid generating a Lewis adduct. Once generated, the latter can either remain as a metal-stabilised ylide 62 or it can dissociate from the metal forming a “free ylide” 63. These intermediates are highly unstable and quickly undergo further inter- or intramolecular reactions including sigmatropic rearrangements,63 dipolar cycloadditions64 and 1,2-rearrangements.65

![Scheme 1.19: General mechanism for ylides formation from α-diazocarbonyl compounds.](image)

1.1.2.1 Diazo Compounds and Carbene-mediated C–X Insertions

Carbene-mediated C–X insertions from diazo compounds were reported for the first time in 1956 as an “indiscriminate” insertion of a diazomethane into n-pentane to form n-hexane, 2-methylpentane and 3-methylpentane in a 3:2:1 ratio.66 Although thermally or photochemically generated carbenes showed unselective insertions, later work conducted by Taber and co-workers reported highly regio- and stereoselective intramolecular C–H insertions towards five-membered rings when the carbene was generated by transition metal catalysis.67 Among all transition metals, copper68 and
rhodium\textsuperscript{69} were reported to efficiently catalyse this class of transformations. Especially, the dirhodium catalysts bearing carboxylate and carboxamide ligands emerged as the most efficient catalysts for chemo- and regioselective intra- and intermolecular insertions.

The reaction mechanism was proposed by Doyle \textit{et al.} in 1993\textsuperscript{69} and later confirmed by Nakamura and co-workers in 2002 (Scheme 1.20).\textsuperscript{70}

\textit{Doyle et al. (1993)}:

\begin{equation}
\text{Scheme 1.20: Mechanistic proposals for C–H insertion.}
\end{equation}
According to the Doyle proposal, the C<sup>1</sup>–C and C<sup>1</sup>–H bond formation between 64 and 65 bearing the carbene carbon C<sup>1</sup> occurs as the metal dissociates passing via the transition state 66. In this transition state, the different bond formations and cleavages happen at the same time but not necessarily with the same rate. Later, Taber <i>et al.</i> proposed 69 as alternative transition state in which a hydrogen atom is transferred from the C–H bond to the metal synchronous with the C–C bond formation. Product 70 is then released and the rhodium catalyst is regenerated. Eventually, density functional theory (DFT) calculations performed by Nakamura <i>et al.</i> in 2002 indicated a concerted but non-synchronous process as previously proposed by Doyle. Once the catalyst 71 reacts with the diazo substrate 1, a molecule of N<sub>2</sub> is released and the stabilised carbenoid 73 is formed allowing C–H insertions, among other chemical transformations. The carboxylate ligand acts as anchor for the dimer conferring a better stabilisation due to the presence of the nearby second rhodium atom. Moreover, the electron donation from one rhodium atom to the other assists the C–C bond formation and the catalyst regeneration. Nakamura <i>et al.</i> confirmed the additional stabilisation given by the dirhodium catalyst 71 by calculating a much lower activation energy for the C–H insertion with dirhodium(II) carboxylates catalyst (5.7 kcal/mol) compared to copper (15.6 kcal/mol) and ruthenium-carbenoids (27.6 kcal/mol). The presence of electron-withdrawing substituents on the carbenoids, together with the presence of a positively charge rhodium atom, enhances the electrophilicity of the carbon centre C<sup>1</sup>, hence the reactivity towards C–H insertion is increased.

Intuitively, when chiral ligands are used, it is possible to control diastereo- and enantioselectivity, thus, a big effort has been invested in the design of the most efficient ligands for each transformation. Both Doyle<sup>69</sup> and Padwa<sup>72</sup> independently reported that the nature of the ligands affects the regio- and chemoselectivity of the C–H insertion reactions. Generally, the presence of an EWG increases the reactivity to the detriment of the selectivity, while sterically hindered ligands and/or carbene substituents have a stronger influence on the stereoselectivity. In the late 90s, Davies <i>et al.</i> developed the chiral dirhodium(II) tetraprolinate catalyst Rh<sub>2</sub>(DOSP)<sub>4</sub> 71a and reported the first highly regioselective intermolecular C–H insertions of tetrahydrofuran (THF) in the donor/acceptor diazo compound 76 (Scheme 1.21). Moreover, the Rh<sub>2</sub>(DOSP)<sub>4</sub> catalyst 71a was found to suppress the side dimerisation reaction (see Scheme 1.2), affording exclusively the desired insertion product 77 in good to excellent yields (48–80%), with moderate stereoselectivity (up to 69% ee), preferentially as syn-isomer.
Since then, the Davies group reported several successful X–H insertions catalysed by 72a with excellent regiospecificity of the insertions occurring in the α-position to nitrogen or oxygen atoms as well as in the benzylic position. These afforded highly asymmetric products typically obtained via Mannich reaction, aldol condensation, Michael addition or Claisen rearrangement. Moreover, the Davies group expanded the library of carboxylated dirhodium catalysts to achieve site-selective and stereoselective inter-functionalisation of non-activated C–H bond into primary, secondary and tertiary carbon atoms, later applied to total syntheses of biologically active compounds. Simultaneously with Davies et al., Hashimoto et al. and McKervey et al. independently reported the first example of asymmetric intramolecular C–H insertion catalysed by chiral dirhodium(II) carboxylate catalysts such as 71b (Scheme 1.22).

Doyle then designed a series of chiral dirhodium(II) carboximidate catalysts such as Rh₂(5S-MEPY)₄ 71c that catalysed highly stereoselective cyclisations providing valuable lactones such as γ-lactone 82 in 62% yield and 91% ee (Scheme 1.23).
Besides C–H insertion, also N–H\(^8^4\) and O–H\(^8^5\) insertions have been widely investigated by using amines, carboxylic acids, alcohols and water. Moreover, when hydrogen halides, sulfur or silicon-based acids are involved, it is possible to insert a bond between an hydrogen atom and an halogen,\(^8^6\) a sulfur\(^8^7\) or a silicon atom.\(^8^8\) Additionally, a small selection of X–Y insertion reactions have been reported, in which neither X nor Y is a hydrogen atom, which takes the name of \(\alpha,\alpha\)-substitutions. For instance, when diazocarbonyls are treated with molecular halogens\(^8^9\) or with (dichloroiodo)benzene,\(^9^0\) \(\alpha,\alpha\)-dihalogenated products are formed. More recently, the range of metal catalysed insertions into C–C single bonds have also been included within the scope of X–Y insertions.\(^9^1\)

On the other hand, the carbene-functionalisation of an aromatic system has sometimes been misleadingly included within the “C–H insertion” classification, although it would be more appropriate to define them as “aromatic substitution”. In this case, the electrophilic addition of a carbene/carbenoid into an electron-rich aromatic ring generates a zwitterionic intermediate followed by proton transfer to restore the aromaticity.\(^9^2\)

Nevertheless, metal-promoted X–H and X–Y insertions of diazocarbonyl compounds represent a vast part of the applications involving diazo compounds and are still one of the main areas of modern organic research.

### 1.1.2.2 \(\alpha\)-Diazocarbonyl Compounds and Organoboron Compounds

In all the above mentioned reactions, the diazo compounds are exploited for their electrophilic properties in order to achieve a chemical transformation. However, they possess an ambiphilic nature and can also act as nucleophiles. Moreover, some diazo compounds are usually stable enough to undergo further modifications without losing the diazo moiety, such as generating anionic nucleophiles such as \(83\) when treated with a base (Scheme 1.24).\(^4^3c\) The anion \(83\) can then react further with carbonyl or imines such as \(84\) forming \(\beta\)-hydroxy or \(\beta\)-amino \(\alpha\)-diazocarbonyl compounds \(85\).
One of the resonance structures of the diazo compound $46^\text{II}$ presents a negative partial charge on the carbene atom, therefore $46$ can be seen as neutral nucleophile and it can react with electron-deficient atoms such as boron atoms. The first example of a reaction between $\alpha$-diazocarbonyl compounds such as diazopropanone $86$ and trialkylboranes $87$ was reported by Hooz and Linke in 1968 (Scheme 1.25). In this 1,2-group transfer, one of the alkyl groups migrates from the borane to the diazo compound forming products such as $88$.

Later, Hooz and co-workers expanded the range of this metal-free 1,2-alkyl transfer to diazoketone$^94$ to diazoaddehydes,$^95$ diazonitrile,$^96$ and EDA,$^96$ however with a narrow scope limited by steric hindrance of the boranes. According to the proposed mechanism depicted in Scheme 1.26, the diazo compound $86$ reacts with the borane $87$ to form a tetracoordinated boron intermediate $89$. Subsequently, one of the boron-substituents (-R) migrates to the carbon atom with nitrogen gas expulsion to generate the intermediate $90$, which is in tautomeric equilibrium with its enolate form $91$. Finally, the reaction with an electrophile or hydrolysis of the boron enolate $91$ affords the $\alpha$-functionalised product $88$. 

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**Scheme 1.24:** General mechanism for diazo nucleophile addition.

**Scheme 1.25:** First example of reactivity between diazocarbonyl compound $86$ and borane $87$. 

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**Scheme 1.26:** Proposed mechanism for diazo nucleophile addition.
Scheme 1.26: Proposed reaction mechanism of the 1,2-alkyl transfer from trialkylboranes 87 to α-diazocarbonyl compounds 86.

Intuitively, different electrophiles could be trapped by the boron enolate 91. From their pioneering work (see Scheme 1.25), Hooz and co-workers, followed by other research groups, started investigating the reactivity of enolate intermediates 91 with various reagents from inorganic bases to other electrophilic species (Scheme 1.27). Firstly, the simple hydrolysis of the boron-adducts 91 affords the α-functionalised esters or ketones such as 88 without the need for metal-catalysis. When D₂O is used to hydrolyse 91, the α-deuterated carbonyl 92 is afforded in quantitative yields. Compared to the classic acid- or base-promoted protocols, this is a unique way to form exclusively the α-monodeuterated carbonyl compound 92. Similarly, α-monohalogenated carbonyl compounds 93 are generated in good yield as sole products when the boron enolate 91 is treated with N-halosuccinimide (NXS). The enolate 91 can be transformed in situ into a lithium enolate upon treatment with n-BuLi, which can further react with alkyl halides or other alkylating agents such as benzyl bromide, allyl bromide and dimethyl sulfate generating α,α-disubstituted carbonyls such 94. Moreover, Hooz et al. were able to trap the boron enolate as the corresponding trimethylsilyl ether 96 by using N-(trimethylsilyl)-imidazole (95). Furthermore, imines and Eschenmoser’s salt 97 can be used as electrophiles to quench the boron enolate 91 affording amine products 98 typical of a Mannich reaction, in both high regio- and stereoselectivity. In an analogous manner, Mukaiyama et al. and later Hooz and co-workers developed a three-component reaction with aldehydes and ketones, respectively, providing condensation products 100 in good yields and stereoselectivity. This multicomponent strategy was then adopted by Miranda et al. for the synthesis of 1,3-diketones and β-ketoesters, which are valuable intermediates for the generation of pyrazole moieties. The enol borane
was also reported to react with nitriles in a cycloaddition into boroxazines, which are easily hydrolysed to α-functionalised 1,3-diketones 101.

Scheme 1.27: General scheme of the reactivity of boron enolate 91 with various reagents.

Although the versatile reactivity of boron enolates shows great utility in organic synthesis, it is generally limited due to the steric hindrance of the trialkylborane 87 (Figure 1.5). Further improvements were achieved by Levy et al. by using more reactive dialkylchloroboranes 102 or vinyl- and aryl dichloroboranes 103 while alkyldichloroboranes afforded only moderate yields.

Figure 1.5: Different boranes commonly used for the α-functionalisation of carbonyls.

Nevertheless, these reagents are typically sensitive to moisture and less available, thus further studies have been made to investigate the reactivity of different organoboranes such as boronic acids 104 or boroxines 105 towards the 1,2-aryl transfer reaction. For instance, Barluenga and co-workers used more stable and less toxic boronic acids 104 and tosylhydrazones to afford coupling products similar to 88. Alternatively, Wang
et al. used boroxines 105, prepared from corresponding boronic acids, to functionalise α-diazocarbonyl compounds.\(^{111}\)

Other organoboranes that are receiving particular attention in organic synthesis as Lewis acids are represented by triarylboranes 106a–h (Figure 1.6). In particular, tris(pentafluorophenyl)borane B(C\(_6\)F\(_5\))\(_3\) 106d has been applied to catalyse several metal-free transformations such as cyclisation,\(^{112}\) hydrogenation\(^{113}\) or hydrosilylation reactions\(^{114}\) and group migrations.\(^{115}\) Moreover, the recent works by Stephan et al.\(^{116}\) Oestreich et al.\(^{117}\) and Melen et al.\(^{118}\) showed how tris[3,5-bis(trifluoromethyl)-phenyl]borane (BAR\(_3\), 106h), tris(3,4,5-trifluorophenyl)borane 106e and tris(2,4,6-trifluorophenyl)borane 106g can be efficiently employed in metal-free hydroborations, with higher reactivity compared to 106d. A recent example was published by the Melen group, in which a catalytic hydroboration protocol was developed using 106e and microwave irradiation in order to expand the substrate scope of hydroboration to alkynes.\(^{118b}\)

![Figure 1.6: Example of aryl boranes applied in organic synthesis.](image)

Regarding the reaction between 106 and α-diazocarbonyl compounds, Stephan et al. observed that, when ethyl 2-diazopropionate 107 was treated with triphenylborane 106a, the boron enolates 108a–b were formed as a mixture of E/Z isomers (Scheme 1.28).\(^{119}\) The fluorinated 108b was found to react further with a second equivalent of 107 and, after a second aryl migration, 109 was formed.

![Scheme 1.28: Example of double 1,2-aryl migration from 106b to 2-diazopropanoate 107.](image)
Moreover, 106d was also recently reported to promote several C–X functionalisations into diazocarbonyl compounds, by activating molecules such as water alcohols or azides.\textsuperscript{120} To conclude, the reaction between $\alpha$-diazocarbonyl compounds and organoboranes offers an efficient and metal-free method towards novel C–C bond formation. Nevertheless, the reaction between triarylboranes and $\alpha$-diazocarbonyl compounds remains still under-represented.\textsuperscript{102a,106} Since more Lewis acidic compounds, such as polyfluorinated triarylboranes, showed an increased reactivity, they were investigated in metal-free aryl migration towards $\alpha$-functionalisation of esters, as discussed in more detail in chapter 3.
1.2 General Introduction on Enabling Technologies

The term “enabling technology” defines an invention or innovation that is applied to improve performances and capabilities of a process. Therefore, the concept of “enabling technologies” has a broad meaning which includes all kinds of fields, from the invention of farming tools of the classical era to the introduction of smartphones and computers in the modern era. In chemistry, it indicates those branches such as flow chemistry, mechanochemistry, electrochemistry, photochemistry and microwave-assisted reactions that are slowly changing the way chemical transformations are performed. More recently, within the wider concept of “enabling technology” have been included the 3D-printing, automated systems, machine-learning algorithms for self-optimising systems as well as statistical software for Design-of-Experiment (DoE). These technologies, not only have allowed modern chemists to achieve different reactivities from “classic” methods and discover unknown reactions, but also helped making synthetic-protocols and industrial plants safer and more sustainable, cutting down costs and waste.

In the second part of this chapter the basics of flow chemistry and DoE are introduced, as flow chemistry was used to improve synthetic protocols and process optimisations were performed following a DoE-approach. A glossary of terminology regarding the most relevant terms about DoE can be found in Appendix A.

1.2.1 Flow Chemistry

In the last two decades continuous flow chemistry has rapidly thriven in both the academic and industrial sector due to its numerous advantages such as better mixing, heat and mass transfer and easier automation. When a flow system is used to perform a chemical transformation, the reaction is conducted in a continuous stream. The reagents are pumped throughout chemically resistant channels of different shapes and dimension in which they meet, mix and react. The product is then collected from the outlet and its yield is strictly influenced by the residence time ($t$), that is the time the reagents spent in the reactor. The latter depends on the reactor volume ($V$) and the flow rate ($Q$), two parameters controlled by the operator (Equation 1).

\[
Residence\ Time\ (t) = \frac{Reactor\ Volume}{Flow\ Rate} = \frac{V}{Q}
\]

Equation 1
In order to have a higher residence time and to achieve better conversions, the reagents need to be pumped more slowly and/or a different reactor should be used. Nevertheless, it must be kept in mind that each design, as well as tubing size, has a different influence on the flow regime of the system and so on its mixing properties. For instance, a monophasic system in which two miscible liquids A and B are flowing in parallel without interruption follows a “laminar flow” regime and the mixing is achieved by diffusion and is defined as “passive mixing” (Figure 1.7a).  

\[ \text{Reynolds number (Re)} = \frac{u \times L}{v} \]

Equation 2

\[ Re = \frac{Q \times D}{v \times A} \]

Equation 3

When the mixing happens randomly in both time and space due to inner mixers, tube lengths or rough surfaces, we talk about “turbulent flow” (Figure 1.7b). The Reynolds number (Re) is a dimensionless coefficient that can predict whether specific conditions will lead to a laminar or a turbulent flow (Equation 2).

\[ \text{Re} = \frac{Q}{v} \]

Equation 3

where \( Q \) is the flow rate (m\(^3\)s\(^{-1}\)), \( D \) the internal diameter of the pipe (m), \( v \) the kinematic viscosity (m\(^2\)s\(^{-1}\)) and \( A \) the cross-sectional area (m\(^2\)). Typically, for laboratory flow equipment, the tubes have an internal diameter (ID) equal to or below 1 mm, therefore the flow regime falls in the region of microfluidics. In other words, the fluids operate at
Re below 250 with laminar flow. The number of flow regimes increases when multiphasic systems are involved. For example, for gas-liquid transformations bubble, slug or annular flow can be observed depending on flow rate, whilst for solid-liquid mixtures the packed bed, fluidised bed or mixed bed are mainly used (Figure 1.8).\textsuperscript{123a}

![Flow regimes](image)

**Figure 1.8:** Examples of flow regimes for a) gas-liquid mixtures and b) solid-liquid mixtures.

The flow technology has allowed chemists to reach a remarkable control over reaction parameters, such as temperature and mixing, that influence a reaction outcome, enhancing efficiency, reliability of the chemical processes as well as enabling new reactions.\textsuperscript{132} Due to the high surface to volume ratio of micro-devices and flow reactors, the mass and heat exchange is more efficient, increasing performances and allowing exothermic reactions to be performed in a safer manner.\textsuperscript{123g} The highly controlled generation of reactive species, together with their fast consumption in a continuous stream, avoids dangerous accumulations improving the safety profile of some reactions processes and allowing safer scale-ups.\textsuperscript{134}

Another huge advantage of continuous flow systems is their practicability in monitoring \textit{in situ} the ongoing reactions, and their easy automation. Generally, when optimising a chemical reaction it is common practise to collect a sample and perform an “offline” analysis \textit{via} GC-MS, LC-MS or NMR spectroscopy after work-up but with the advent of flow technologies there has been a remarkable improvement in developing “inline” and “online” monitoring techniques for a much faster optimisation. The difference between “online” and “inline” analysis, as introduced by Browne \textit{et al.} and Cronin \textit{et al.},\textsuperscript{135} lies in the different way the flow stream is sampled. The term “inline analysis” describes a system in which the whole flow stream is continuously monitored. For instance, IR and UV as well as flow-NMR kit are composed by an inline flow cell, thus are considered...
"inline" devices. Whereas monitoring systems such as MS or HPLC, that use injection devices such as switching valves to isolate fractions of the flow stream, are considered “online” analysis.\textsuperscript{135}

A big drawback of flow chemistry systems is the presence of solids, such as precipitate formed during the reaction or during the inline work-up. This can cause a blockage that could lead to too high pressures, leakages and may damage the system. Another drawback of using flow chemistry is the need for the appropriate equipment that must be purchased or designed and 3D-printed \textit{ad hoc} for the purpose and can be costly.\textsuperscript{123a}

However, the benefits of flow chemistry often outweigh the disadvantages. The increased safety profile offered by flow systems is one of the most important characteristics, as sensitive and/or toxic intermediates can be generated \textit{in situ} in smaller amounts avoiding dangerous accumulation of highly reactive compounds, and they can further react in the system without coming into contact with the operator.

For this reason, there has been significant interest in the application of flow technology to the generation and use of diazo compounds at both laboratory and industrial scales.\textsuperscript{136}

One of the first large-scale flow system for the synthesis of diazomethane (7) \textit{in situ} was reported by Proctor and Warr in 2002 (Scheme 1.29).\textsuperscript{137} This continuous preparation/consumption of diazomethane (7) from Diazald\textsuperscript{®} (110) in a mixture of DMSO and water allowed to safely produce the \(\alpha\)-diazoketone 112, which is an intermediate of the HIV protease inhibitor nelfinavir mesylate, in a gram-scale multi-step synthesis.

\begin{scheme}{1.29}{In situ generation of diazomethane (7) for a large-scale multi-step process.}{137}{Scheme 1.29: In situ generation of diazomethane (7) for a large-scale multi-step process.}{137}

For a similar transformation, the group of Kim \textit{et al.} designed a dual-channel micro-reactor system in which two parallel channels are separated by a thin hydrophobic membrane of poly(dimethylsiloxane) (PDMS) that prevents the passage of KOH, aqueous medium and \(p\)-toluensulfonate (Scheme 1.30).\textsuperscript{138} In the first channel an
aqueous solution of Diazald® (110) is used to generate diazomethane 7 that then diffuses through the membrane into the second channel where it can react with the substrate.

Scheme 1.30: Dual-channel micro reactor system for in situ generation, separation, and reactions of diazomethane.\textsuperscript{138}

Moreover, a few years later Kappe and co-workers and more recently Koolman and co-workers further improved this protocol by applying the tube-in-tube technology to continuous multi-step synthesis of valuable $\alpha$-halo ketones\textsuperscript{139} and cyclopropylboronic esters,\textsuperscript{140} respectively. The tube-in-tube technology consists of two concentric tubes separated from each other by a gas-permeable AF-2400 membrane. In this case, the diazomethane (7) is generated in the inner tube and diffuses through the gas-permeable membrane into the outer chamber where it reacts following a similar principle to the one showed in Scheme 1.30. More sophisticated systems such as the Vapourtec R-Series settings have also been applied to similar transformation increasing the productivity.\textsuperscript{141}

Besides increasing the safety of diazomethane-generation, flow chemistry guarantees access to highly valuable transient reactive intermediate such as donor/donor carbene precursors. In 2014, Ley and co-workers published the in situ generation of diazoalkanes 114 using a pre-packed flow cartridge of MnO$_2$ (Scheme 1.31).\textsuperscript{142}

Scheme 1.31: Flow generation and reaction of donor/donor carbene precursors 114. BPR = back pressure regulator.\textsuperscript{142}

Since then, similar systems with pre-packed cartridges have been successfully applied to different transformations such as the functionalisation of boronic acids,\textsuperscript{142} Cu-catalysed allene synthesis,\textsuperscript{143} Rh-catalysed transformations,\textsuperscript{144} cyclopropanations\textsuperscript{59} and C-C couplings.\textsuperscript{145} The Ley research group has also recently reported the in situ
synthesis of unstable diazoalkanes using a continuous-flow photoreactor and inline IR analysis (Scheme 1.32).\textsuperscript{10a} The photolysis of 1,3,4-oxadiazoline 115 is a well-established method to access the “non-stabilised” diazooalkane 116.\textsuperscript{146} The novelty introduced by Ley and co-workers lies in the continuous-flow photoreactor that allows better control over the provided irradiation which ensures good yields, improved scalability and reproducibility.

Scheme 1.32: Flow generation of non-stabilised diazo compound 116, from oxadiazolines 115 as precursor. BPR = back pressure regulator.\textsuperscript{10a}

The preparation of donor and donor/acceptor carbene precursors has also been conducted in a flow setup. The first continuous flow synthesis of ethyl diazoacetate (EDA, 9) was reported by Rutjes and co-workers (Scheme 1.33).\textsuperscript{147} For this purpose, three streams were used: an aqueous buffer solution of glycine ethyl ester 8 (pH 3.5), dichloromethane to extract EDA (9) and an aqueous solution of sodium nitrite. The biphasic mixture is then pumped into a thermo-controlled glass-microreactor where the diazotisation occurs, then into a sector to facilitate the phase separation before the inline Flow-Liquid-Liquid-Extraction (FLEEx) module.

Scheme 1.33: Continuous-flow generation of EDA 9.\textsuperscript{147}
Our group has also made some contributions to this topic. Indeed, not long ago, Wirth and co-workers reported the multi-step synthesis of β-hydroxy-α-diazo compounds \textbf{119} under flow conditions with the \textit{in situ} generation of EDA (Scheme 1.34). \cite{43b} In this setup, EDA is generated in the first microreactor within 6 minutes \textit{via} diazotisation, subsequently a first solution of aldehyde \textbf{118} and a second solution of DBU are added to the main stream yielding the desired β-hydroxy-α-diazo esters \textbf{119} in moderate to excellent yield with no inline extraction needed.

\textbf{Scheme 1.34:} Synthesis of β-hydroxy-α-diazo esters \textbf{119} under continuous-flow conditions. \cite{43b}

Moreover, with the aim of expanding the EDA addition to ketones and lactones, Wirth \textit{et al.} developed also a temperature controlled flow system for the \textit{in situ} generation of LDA using a Vapourtec E-series system (Scheme 1.35). \cite{43a} The system was dried and kept under argon \cite{148} and was composed by three reactors (R) and three cooling coils (C). The base LDA was generated within 0.8 minutes in a first coil (R1), at room temperature then cooled to $-78$ °C for 1.3 minutes (C1) before meeting the cold stream of EDA (\textbf{9}) previously cooled for 2.6 minutes (C2) and finally mixed in R2 for 0.2 minutes to form lithium ethylidiazoacetate (\textbf{120}). This was then trapped using a pre-cooled solution of ketone \textbf{121} and the outlet was quenched with a cold ($-78$ °C) benzoic acid solution in THF to afford the desired diazo compound \textbf{122} in good yields (up to 70%).
As previously mentioned, the Regitz diazo-transfer is one of the most common methods to prepare α-diazocarbonyl compounds. Nevertheless, although being documented in batch, flow applications remain limited. Our group in 2015 reported a flow protocol for the synthesis of donor/acceptor diazo compounds with an inline IR spectroscopy analysis for a faster optimisation and inline work-up. This protocol was then successfully coupled to a batch intramolecular cyclopropanation to form **125**, a key intermediate for the synthesis of Milnacipran (Scheme 1.36). A solution of allylic ester **123** and DBU in acetonitrile was mixed together with a solution of tosyl azide (**18a**) in acetonitrile to generate the allyl α-diazoester **124**. An aqueous solution of NaNO₂ was pumped after the reactor coil to quench the reaction then the product **124** was extracted in n-heptane and the phases were separated using an inline membrane separator. The organic stream was then dropped into a round-bottomed flask containing of 1 mol% Rh₂(oct)₄ affording **125** in 33% overall yield (8.2 g/day).
Scheme 1.36: Continuous-flow system for the generation of 125, key intermediate of Milnacipran analogues via Regitz diazo-transfer reaction; oct = octanoate.\textsuperscript{150}

The Collins and Maguire research groups further improved this protocol including the sulfonyl azide synthesis into a continuous flow multi-step synthesis (Scheme 1.37).\textsuperscript{151}

The hazardous tosyl and mesyl azide (18a–b) were safely generated \textit{in situ} from an aqueous solution of sodium azide and a solution of either tosyl or mesyl chloride in acetonitrile. Once generated, the sulfonyl azide 18 was mixed with a stream containing the carbonyl substrate 126 and the base to afford the desired diazo compound 128 upon inline quenching with sodium acetoacetate (127).

Scheme 1.37: Safe continuous-flow generation of tosyl azide 18a and mesyl azide 18b for Regitz diazo-transfer reaction.\textsuperscript{151}

More recently, Monbaliu \textit{et al.} coupled the synthesis of tosyl azide 18a reported by Maguire \textit{et al.} to the flow diazo-transfer step reported by Wirth \textit{et al.} and added the
intermolecular C–H insertion to the multi-step continuous-flow synthesis of N-Boc-protected Ritalin 131 (Scheme 1.38).\textsuperscript{152}

\begin{center}
\textbf{Scheme 1.38:} Continuous-flow synthesis of Ritalin 131; NMP = N-methyl-2-pyrrolidone.\textsuperscript{152}
\end{center}

At first, the tosyl azide (18a) was synthesised \textit{in situ} from stable tetrabutylammonium azide and tosyl chloride, then mixed with methyl phenylacetoacetate (129) that underwent Regitz diazo-transfer under basic conditions. Subsequently, the diazo compound was extracted from the organic phase by using an inline phase separator and further combined with a stream containing the N-Boc piperidine 130 and dirhodium catalyst. The full telescopic strategy afforded the N-Boc protected Ritalin 131 in 19\text% overall yield with a 20 minutes of residence time including the inline separation.

In summary, since the early 2000s flow technologies provided chemists with a set of tools to overcome challenges faced during synthetic processes from the handling of hazardous compounds to scale-ups, thus the interest for developing automated systems for organic synthesis is still strongly increasing in both academia and industry.

\subsection*{1.2.2 Design of Experiment}

Although flow chemistry has proven to be ideal to enable reactivities and cut reaction times, it certainly does not come without disadvantages. Flow systems are typically
composed by many modules which increases the complexity of the system, by adding
variables that can influence the reaction outcome. Moreover, despite being a precious
tool for faster high-throughput-screenings (HTS), it creates a large amount of data in a
short period of time that might be hard and time-consuming to analyse. Hence, to tackle
the problem self-optimising reactors\textsuperscript{153} that combine the use of intelligent algorithms,\textsuperscript{154} in/online devices and statistical software for Design-of-Experiment (DoE) have been
developed. The concept of DoE was introduced for the first time by Ronald Fisher in
1926 in “The Arrangement of Field Experiments” and few years later in “The Design of
Experiments”\textsuperscript{155} and it has since been applied mainly in agriculture, physics and
engineering process optimisation.\textsuperscript{156}

DoE uses a statistical approach that allows to screen many variables and to estimate the
main effects with a minimum amount of experiments. Furthermore, it can identify
interactions between two or more factors leading to an optimum that a traditional one-
factor-at-a-time (OFAT) approach could have missed.\textsuperscript{157} At first, chemists appeared to
be reluctant on embracing this new approach over the classic OFAT, perhaps intimidated
by the statistics and formulae, which makes the task look more complex than necessary.
Although an understanding of the basics of statistical tests is encouraged to meaningfully
apply a DoE, an in-depth knowledge of statistic and mathematical algorithms it is not
required, given the several simplified software commercially available nowadays (Design
procedure which aimed to guide chemists through the best decision while optimising a
reaction process using DoE.\textsuperscript{158} Later, T. Laird with his editorial on Org. Process Res.
Dev. spurred academia to introduce DoE trainings in undergraduate courses and to
embrace the DoE system more often to identify empirical relationships within a complex
system of parameters.\textsuperscript{159} This resulted in a blossom of industrial applications and
publications per year using DoE in the past two decades.\textsuperscript{160} Nowadays, DoE found
several applications in chemistry from reaction optimisation\textsuperscript{161} to crystallisations,\textsuperscript{162} and
HPLC method development.\textsuperscript{163} Furthermore, it finds large utility in industry, mainly drug
discovery, by increasing the efficiency and minimising costs and materials, saving time
and energy consumption in agreement with the twelve principle of green chemistry,\textsuperscript{164} as
well as validating robustness testing to ensure quality before releasing an active
pharmaceutical ingredient (API).\textsuperscript{165}

The classic OFAT-approach consists of varying one factor within a range of values whilst
the rest of n-parameters are fixed. Once the best condition for this factor is found it is
kept fixed and the same process is repeated for all n-parameters in order to find the
“optimum” for each factor (Figure 1.9a). This traditional approach suffers from several
drawbacks. Firstly, it investigates a relatively small fraction of chemical space and finds
only one of the possible “optimum” within the given chemical space, and it is not necessary the best one. Secondly, by keeping in consideration only the “best” run per each variable, this classic method does not gain information from the discarded experiments. Finally, it is unable to uncover interactions among factors and might confuse “noises” with an actual effect, unless a significant number of repeats are made.

On the other hand, DoE is composed by a set of statistically organised experiments, all equally distributed within the desired chemical space, and all of the run are necessary in order to find the local “optimum” (Figure 1.9b). Due to this organisation, DoE can distinguish signals that an OFAT-approach might miss in the noise, but mostly it can identify two-factor interactions (2FI) that are not detected with the OFAT method. Moreover, it allows to investigate even bigger and more complex chemical spaces that are too time consuming to be investigated using a traditional approach.

One of the drawbacks of DoE is that a complex design requires a large set of experiments which need to be perform by the same operator under similar experimental conditions, therefore in a relatively short period of time to avoid errors (e.g. nuisance). However, highly automated systems and in/online analysis methods can be adopted to speed up the analysis.

The first things to do when dealing with DoE is to learn using the right terminology (Appendix A). Once familiar with the basic terms, in order to conduct a successful DoE, it is important to follow a precise work-flow:

1) **Define the objective:** it is vital to have a clear goal (e.g. screening or optimisation) in order to select the appropriate ranges and design.

2) **Define the factors, their levels and their ranges:** to define the chemical space that is going to be studied. The factors can be numeric or categoric, continuous or discrete.
3) **Define the responses:** it is necessary to have a reliable, accurate and precise method to measure the reaction outcome (e.g. yield or conversion).

4) **Select the most appropriate experimental design:** the choice depends on the prefixed objective.

5) **Generating the experimental matrix:** a matrix of experiments is generated by the software once all the above information are included. The experiments are *randomised* in order to reduce nuisance errors. Moreover, it is important to include *central point* experiments to ensure reproducibility and to detect nonlinearity.

6) **Perform the experiments:** ideally, the experiments should be performed under same experimental and analytical conditions in a randomised order and within a restricted time to reduce nuisance error. When randomisation is not possible due to hard-to-change (HTC) factors, the run can be “blocked”.

7) **Software analysis:** the most appropriate mathematical transformation (or none) is selected by the operator upon values such as adjusted and predictive R-squared terms and by evaluating the diagnostic plots. Next, the analysis of variance (ANOVA) is providing which terms are the most significant terms by looking at *p-values* < 0.05. Finally, the software creates a table of “optimal conditions” that satisfy the objectives together with a series of contour plots and 3D-surface plots. When there is more than one response to optimise, it is possible to overlap all contour plots and highlight the “sweet spot” in which all requirements are satisfied.

8) **Confirming reactions:** it is important to verify experimentally what is predicted by the model.

There are many types of experimental models and the choice depends on the dimension of the chemical space that we are interested in, thus, it is usually a compromise between the number of variables to study and the number of experiments to perform in order to have meaningful results (Figure 1.10). Among all, the simplest two-level factorial designs are the most commonly used for screening (Figures 1.10a and 1.10b). As depicted in Figure 1.10b, the Fractional Factorial Design (FFD) uses fewer experiments to explore the same chemical space of the full factorial design (FD, Figure 1.10a), hence it has a lower resolution compared to a FD. The factorial designs are reported as $\ell^k$, where $\ell$ indicates the number of levels of each factor and $k$ the number of factors. Similarly, a fractional factorial design can be reported as $\ell^{k-p}$, where $\ell$ indicates the number of levels, $k$ the number of factors, and $p$ the size of the fraction of the FD used. In a more technical term, $p$ represents the number of generators of the FFD. For example, in case of studying
four factors, a range of values defined by two levels, a maximum and a minimum must be selected. In coded values, these levels are indicated as “+1” or simply “+” and “−1” or “−” for the highest and the lowest level, respectively. In this case, the full factorial design is expressed as $2^4$, which represents the total number of 16 experiments required by the FD. Similarly, the factorial designs can be noted as $2^{4-1}$, $2^{4-2}$, $2^{4-3}$ and the numbers of the required experiments are 8, 4 and 2, respectively. Thus, a higher number of generators ($p$) leads to a lower resolved FFD. The FD and FDD, as screening designs, are using linear models to identify main effects. For this reason, to identify the presence of any curvature, it is recommended to add central points, which are reported with the coding factor level of “0”.

When a non-linear response is detected, more resolved designs are typically used for Response-Surface-Modelling (RSM) such as the Central Composite Face (CCF, Figure 1.10c) or the Circumscribed Composite Design (CCD, Figure 1.10d). However, these designs are not recommended for a high number of factors as they require a very large number of experiments. Generally, a lower resolution design is conducted first to narrow down the number of factors. Once the number of significant parameters is reduced, a higher resolution design can be performed if needed.

![Figure 1.10: Example of models: a) Factorial Design (FD); b) Fractional Factorial Design (FFD); c) Centred Composite Face (CCF); d) Circumscribe Composite Design (CCD); The required experiments per each models are shown as dots: red = factorial points, yellow = central points; blue = axial points.](image)

To conclude, the DoE uses a statistical approach to conduct and analyse a set of experiments offering an efficient approach towards complex systems and chemical reactions optimisation. Nevertheless, it is worth mentioning that the statistical analysis is just a tool that aims to facilitate the analysis of the data and the process optimisation. It should not replace the common sense nor the scientific knowledge of the operator, who is responsible to decide whether what it is suggested by the model is chemically sensible or dangerous to perform.
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CHAPTER 2: Synthesis of Novel trans-Dihydroindoles

2.1 Introduction

The 2,3-dihydroindole scaffold, also known as indoline, can be found as the main core in several biologically active compounds and natural products. For instance, naturally occurring alkaloids such as strychnine (132), physostigmine (133), oleracein (134), aspidospermidine (135) and vinblastine (136) as well as drug molecule such as the Angiotensin-Converting-Enzyme (ACE) inhibitor pentopril (137) (Figure 2.1), present the indoline framework and therefore represents a synthetically interesting target for organic and medicinal chemists.¹

![Figure 2.1: Natural products and drug molecules containing the indoline framework.](image)

For this reason, there is an increasing interest in developing new pathways for the synthesis of optically active 2,3-dihydroindoles in both synthetic and pharmaceutical chemistry.² There are currently two main approaches towards such scaffolds. The first, is based on the dearomatisation or functionalisation of indoles (Scheme 2.1),³ which can occur through hydrogenation of the double bond,⁴ base-promoted intramolecular oxidative coupling,⁵ or by exploiting the intrinsic reactivity of the indole ring towards electrophiles.⁶ However, it is necessary to introduce/prepare the indole core in advance.⁷
Hydrogenation of Indoles:

\[
\text{R}_1^1 \quad \text{R}_2^2 \quad \text{H-source} \quad \text{catalyst} \quad \text{R}_1^1 \quad \text{R}_2^2
\]

Intramolecular Oxidative Coupling:

\[
\text{R}_2^2 \quad \text{CH}_2R_1^1 \quad \text{1) base} \quad \text{2) oxidant} \quad \text{3) } \text{Nu}^-
\]

Indole Electrophilic Activation:

Reactivity at C-3

Reactivity at C-2

\[
\text{Nu}^- \quad \text{Nu}^- \quad \text{Nu}^- \quad \text{Nu}^-
\]

Scheme 2.1: Dearomatisation/functionnalisation of indoles.

The second major approach relies on the construction of the nitrogen-containing five-membered ring via C–C and/or C–N bond formation. For this purpose, there are several available strategies depending on which of the bonds \text{a-d} needs to be constructed (Figure 2.2).

Figure 2.2: Overview of the most common retrosynthetic pathways for the \textit{de novo} synthesis of the pyrrolidine ring.

A well-established method to build the C–N bond \text{a} is the Pd-catalysed aryl amination.\(^8\) As this approach does not directly introduce new stereogenic centres the chiral backbone must be introduced in advance. On the other hand, enantioselective transition metal-catalysed C–H activation/aryl alkylations have been reported for the synthesis of bond \text{b} and offer the stereoselective generation of C3 and C2.\(^9\) Moreover, Cu-catalysed aryl and alkyl aminations\(^10\) as well as iodine(III)-mediated reactions,\(^11\) present cheaper and more sustainable alternatives for the formation of bonds \text{a or d}. Additionally, intramolecular
radical aryl aminations\textsuperscript{12} and aryl alkylation\textsuperscript{13} offer an efficient metal-free approach towards bonds \textit{a} or \textit{b}, although it is usually difficult to control the enantioselectivity. To overcome this disadvantage, metallo-radical catalysis (MRC) has been successfully applied especially for the formation of bond \textit{c} (Scheme 2.2).\textsuperscript{14}

**Intramolecular Michael Addition**

\begin{align*}
\text{Aryl Amination} & \quad \text{Radical-mediated Aryl Amination} \\
R^2 \text{H} & \quad R^2 \text{H} \\
\text{C-H Activation/Aryl Alkylation} & \quad \text{ Radical-mediated Aryl Alkylation} \\
R^3 \text{Br} & \quad R^3 \text{Br} \\
\text{Phenyldiene(III)-mediated Amination} & \quad \text{Intramolecular Carbolithiation} \\
R^4 \text{NHR}^1 & \quad R^4 \text{NHR}^1
\end{align*}

Scheme 2.2: Overview of most common strategies towards dihydroindoles.

Other methods that have been successfully adopted to synthesise the indoline \textit{de novo} include the 1,2-carboamination of dienes,\textsuperscript{15} intramolecular carbolithiation\textsuperscript{16} and intramolecular Michael addition.\textsuperscript{17} However, only a few of these reported procedures allow the direct enantio- and diastereoselective formation of C2 and C3 of the nitrogen-containing five-membered ring. In 2008, García Ruano \textit{et al.} developed an asymmetric tandem reaction to synthesise disubstituted indolines starting from optically pure sulfoxides 138 (Scheme 2.3).\textsuperscript{18}

\begin{center}
\begin{align*}
\text{(S)-138, } R^1 & = H, \text{Me, Et, Allyl, Bn} \\
139 & \quad 140 \text{ d.r. } > 98:2 \\
\text{PMP} & = p\text{-methoxyphenyl} \\
\text{CF}_3 & \quad \text{CF}_3
\end{align*}
\end{center}

Scheme 2.3: Anionic-anionic asymmetric tandem reaction towards optically active indolines.
In the presence of lithium diisopropylamide (LDA), (S)-sulfinyl derivative 138 is deprotonated in the benzylic position and undergoes stereoselective nucleophilic addition to the activated imine 139 followed by an intramolecular nucleophilic aromatic substitution leading to chiral dihydroindoles 141 in good yields and excellent stereoselectivity (>98:2).

Another efficient protocol for the construction of enantiopure indoline nuclei is the [3+2] cycloaddition between benzyne precursors 142 and α,β-unsaturated γ-aminobutyronitriles 144 (Scheme 2.4). In this case the TMS-aryl triflate 142 undergoes a fluoride-induced 1,2-elimination forming the aryne intermediate 143 in situ, which then reacts with α,β-unsaturated γ-aminobutyronitriles 144 to afford 2,3-dihydroindoles 145 in good yields and enantioselectivity.

**Scheme 2.4:** Indoline 145 construction via [3+2] cycloaddition reactions between benzynes 143 and α,β-unsaturated γ-aminobutyronitriles 144.

Recently, Zhang et al. reported the Cu-catalysed enantioselective intramolecular borylative cyclisation of 2-vinylaryl imines derivatives 146 with B₂(pin) which affords cis-2,3-dihydroindoles 148 bearing a Bpin moiety in excellent yields and selectivity without the need of a chiral starting material (Scheme 2.5).

**Scheme 2.5:** Cu-catalysed asymmetric synthesis of cis-2,3-dihydro-1H-indoles 148.
The \textit{in situ} generated chiral copper catalyst promotes the Markovnikov addition to the vinyl moiety forming an organocuprate intermediate that is then trapped by the imine as described also by the Buchwald group in 2015.\textsuperscript{21}

Intuitively, the formation of this C–C bond (disconnection \textbf{c}, Scheme 2.2) can be accomplished by using carbene chemistry.\textsuperscript{22} However, there are only a very few procedures using carbene-precursors for the synthesis of nitrogen-containing five-membered rings.\textsuperscript{23} In the early 2000s Davies \textit{et al.}\textsuperscript{24} and Saito and co-workers\textsuperscript{25} independently optimised the enantioselective synthesis of dihydrobenzofurans 150 \textit{via} intramolecular rhodium-catalysed C–H insertion using 1 mol\% Rh$_2$(S-DOSP)$_4$ (71a) and Rh$_2$(S-PTTL)$_4$ (71d), respectively (Scheme 2.6). In both cases the \textit{cis}-dihydrobenzofuran was the major isomer. When Rh$_2$(S-DOSP)$_4$ was used as catalyst, the desired products 150a–b were obtained in good yield (up to 85\%) and selectivity up to 95\% \textit{de} and 63\% \textit{ee} after 72 hours at −50 °C in \textit{n}-hexane. When Rh$_2$(S-PTTL)$_4$ was used instead, the dihydrobenzofurans 150a–b were isolated in good yields and excellent stereocontrol (up to 98\% \textit{de} and 94\% \textit{ee}) within one hour at −78 °C in toluene.

\textbf{Scheme 2.6:} Synthesis of \textit{cis}-dihydrobenzofurans 150a–b \textit{via} Rh\textsuperscript{II}-catalysed C–H insertion.

Despite these encouraging results and the advantage of installing two stereocentres in one step, the use of \textit{α}-diazocarbonyl compounds as precursors for the preparation of 2,3-dihydroindoles has received limited attention. In this chapter, the development of a general synthesis for chiral 2,3-dihydro-1\textit{H}-indoles \textit{via} the metal-catalysed C–H insertion using diazo compounds as carbene precursors is presented (Scheme 2.7).

\textbf{Scheme 2.7:} Retrosynthetic approach toward chiral 2,3-dihydro-1\textit{H}-indoles.

Some preliminary studies on the diazo-transfer optimisation, side product investigation and solvent screening for the C–H asymmetric insertion have already been reported by Dr. S. T. R. Müller in his PhD thesis work titled: “Diazo Compounds in Continuous Flow
During the work of this thesis, further optimisation studies have been carried out and the scope of diazo precursors and of trans-indolines have been expanded. Moreover, due to the well-known toxicity of diazo compounds, the diazo-transfer reaction was translated into a flow system using a DoE-approach for preliminary screening and optimisation. Parts of the following results are published in *Eur. J. Org. Chem.* 2017, 1889–1893.
2.2 Results and Discussion

In Scheme 2.8 an overview of the synthetic pathways discussed in this chapter is given.

Scheme 2.8: Overview of the synthetic pathway developed to achieve indolines 154.

Firstly, an efficient synthesis for the precursors 152 was developed. Secondly, attention was moved to the optimisation of the diazo-transfer and the optimal conditions were used to build a library of α-diazocarbonyl intermediates 153 in good yields. Moreover, the translation of the diazo-transfer reaction into a flow setup was realised using a fractional factorial design (FFD) to screen the several parameters such as temperature, equivalents of base and sulfonyl azide, time and concentration. Finally, the effects of solvent, dirhodium catalysts and temperature on the stereoselective cyclisation were studied to afford the desired trans-indoles 154 as major products in good yields and enantioselectivities.

2.2.1 Synthesis of the Starting Materials

The synthesis started with the esterification of the commercially available 2-nitrophenyl acetic acid (151) in the presence of acetyl chloride in methanol or propan-2-ol at room temperature to afford 155a and 155b in excellent yields within 16 hours (Scheme 2.9).
Although reducing a nitroaromatic group is a common procedure in organic chemistry, achieving a chemoselective reduction of the nitro group in presence of an ester moiety seemed to be more challenging. Hence, the reduction of the nitro group to the aryl amine was attempted following various literature protocols (Table 2.1).  

**Table 2.1:** Reaction conditions for the reduction of the nitro group in 155a–b.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Major Product</th>
<th>R</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaBH₄, AlCl₃, dry THF rt, 2 h</td>
<td>Me (157)</td>
<td>Me</td>
<td>17⁰</td>
</tr>
<tr>
<td>2</td>
<td>HCO₂H, Pd/C, dry MeOH rt, 12 h</td>
<td>Me (158)</td>
<td>Me</td>
<td>69</td>
</tr>
<tr>
<td>3</td>
<td>H₂ (1 atm), Pd/C, dry ROH rt, 12 h</td>
<td>Me (156a)</td>
<td>Me</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>i-Pr (156b)</td>
<td>i-Pr</td>
<td>70</td>
</tr>
</tbody>
</table>

⁰Starting material 155a recovered.

The use of a NaBH₄/AlCl₃ mixture resulted in the reduction of the ester moiety of 155a leading to alcohol 157 in 17% with mainly starting material recovered (entry 1), despite being successfully employed for the large scale reduction of 2,4-dinitrophenyl compounds. The catalytic hydrogenation of 155a using Pd/C and formic acid led to the isolation of lactam 158 in 69% yield (entry 2). The formation of 158 indicated the successful reduction of the nitro to the amino group, but the acidic conditions may have activated the ester group toward intramolecular nucleophilic attack leading to the cyclised product. Finally, the desired arylamines 156a–b were obtained in good to excellent yields using H₂ gas (1 atm) and 10% Pd/C as catalyst (entries 3,4) that are immediately tosylated in pyridine affording 159a and 159b to prevent their decomposition (Scheme 2.10).

**Scheme 2.10:** Tosylation of aryl amines 156a–b.
Next, the further N-functionalisation of 159 was investigated. Treatment of 159a with a mixture of benzyl bromide and triethylamine in acetonitrile afforded the desired product 152a in reasonable yields (Table 2.2).

### Table 2.2: Reaction conditions for the benzylation of 159a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>160 (equiv.)</th>
<th>NEt₃ (equiv.)</th>
<th>Conditions</th>
<th>152a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>2</td>
<td>48 h, rt</td>
<td>63</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>2</td>
<td>48 h, 45 °C</td>
<td>57</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>3</td>
<td>72 h, rt</td>
<td>73</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>3</td>
<td>48 h, rt</td>
<td>77–82°</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>3</td>
<td>24 h, rt</td>
<td>42</td>
</tr>
</tbody>
</table>

*General Procedure:* Reactions performed on a 4–6 mmol scale in CH₃CN; °Range of four repeats.

A large excess of the reagents and long reaction times were necessary to obtain 152a in more than 60% yields (entry 1). Furthermore, increasing the temperature did not improve the reaction outcome (entry 2). Using more equivalents of triethylamine (3 equivalents) afforded 152a in 73% yield after three days. The reaction was pushed further by increasing the amount of benzyl bromide 160 to 3 equivalents, leading to the formation of 152a in 77–82% yield after 48 hours (entry 4). Reducing the reaction time to 24 hours led to lower yield of 152a (42%; entry 5).

Different benzyl and alkyl halides 161 were used together with 159a–b under the above optimised conditions (Table 2.2, entry 4) to build a library of substrates. All investigated substituents were very well tolerated, and the desired precursors 152a–l were obtained in 62–82% yields (Scheme 2.11). When the methyl ester was replaced with an isopropyl ester, the corresponding benzylated product 152b was isolated in 62%. Highly electron-donating groups as well as highly electron-withdrawing substituents in para-position showed good reactivity affording 152c, 152d and 152e in 75%, 55% and 71% yield, respectively.
Also, substrate 152f and 152g moderate bearing electron-donating electrophiles in para- and meta-position were prepared in good yields (61% and 69%). A small electronic effect was noticed for the ortho-substituted derivatives 152h–j. The products carrying the 2-phenyl (152h) and the 2-methyl (152i) group were afforded in higher yields (79–82%) than the 2-nitro derivative 152j (62%). Bulkier derivatives such as 2-phenyl (152h) or 2-bromonaphthyl (152k) substituted precursor were also prepared in 79% and 77% yield, respectively. Non-benzylic electrophiles were investigated next. While (E)-(3-bromoprop-1-en-1-yl)benzene gave 152l in 68% yield, and allyl bromide afforded 152o in 25% yield, no reaction was observed between 2-bromobutane nor 1-bromohexane and the starting...
material 159a, therefore 152m and 152n were not formed. This is not surprising because both 2-bromobutane and 1-bromohexane are poorly reactive toward SN2 reactions. Alternatively, treatment of 159a with triphenylphosphine, diisopropyl azodicarboxylate (DIAD) and the corresponding alcohols 162 in a Mitsunobu reaction29 afforded 152m–o, in 68%, 64% and 85% yield, respectively (Scheme 2.12).

\[
\begin{align*}
\text{CO}_2\text{Me} & \quad \text{CO}_2\text{Me} \\
\text{Ts} & \quad \text{Ts} \\
\text{H} & \quad 
\end{align*}
\]

\[
\begin{align*}
\text{R}^2\text{OH} & \quad \text{R}^2\text{OH} \\
\text{THF} & \quad \text{THF} \\
\text{0 °C to rt} & \quad \text{RT} \\
\text{overnight} & \quad \text{overnight} \\
\end{align*}
\]

\[
\begin{align*}
\text{159a} & \quad \text{152m, R = n-hexyl, 68%} \\
& \quad \text{152n, R = sec-butyl, 64%} \\
& \quad \text{152o, R = allyl, 85%} \\
\end{align*}
\]

Scheme 2.12: Synthesis of alkyl derivatives 145m–o via Mitsunobu reaction.

While expanding the substrate scope to other protecting groups, the N-Boc substituted amine 159c was prepared using di-tert-butyl dicarbonate (Boc2O) and triethylamine in acetonitrile (Scheme 2.13).a

\[
\begin{align*}
\text{CO}_2\text{Me} & \quad \text{CO}_2\text{Me} \\
\text{NH} & \quad \text{NH} \\
\text{Boc}_2\text{O}, \text{NET}_3 & \quad \text{Boc}_2\text{O}, \text{NET}_3 \\
\text{CH}_3\text{CN} \quad \text{rt, 24 h} & \quad \text{rt, 24 h} \\
\end{align*}
\]

\[
\begin{align*}
\text{156a} & \quad \text{159c, 24%} \\
& \quad \text{152p} \\
& \quad \text{163, R: Bn, 84%} \\
& \quad \text{158, R: H, 10%} \\
\end{align*}
\]


The following treatment of 159c with benzyl bromide and triethylamine at room temperature did not lead to the desired benzylated product 152p leaving 159c unchanged. Performing the reaction at a higher temperature (50 °C) led to the formation of a mixture of lactams 163 and 158 in 84% and 10% yield, respectively, hence was not further investigated.

Once the diazo precursors were prepared in good yields, attention was focussed on the synthesis of the carbene-precursors, the key-intermediates of this synthetic pathway.

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a. The synthesis of 159c was carried out by Dr. S.T.R Müller
2.2.2 Synthesis of α-Diazocarbonyl Precursors

The Regitz diazo-transfer reaction\textsuperscript{30} was used to synthesize the α-diazocarbonyl substrates 153 (Scheme 2.14). As mentioned in chapter 1, this base-promoted transfer into activated methylene moieties is a convenient approach for the synthesis of donor-acceptor and acceptor-acceptor carbene. The standard protocol for 1,3-dicarbonyl compounds relies on triethylamine as base and sulfonyl azides such as tosyl azide (18a) or the safer analogues p-acetamidobenzenesulfonyl azide (p-ABSA, 18e) and p-dodecylbenzenesulfonyl (18c) as diazo-transfer reagents. The sulfonyl azide reagent are easily synthesized by adding sodium azide to a solution of substituted-sulfonylchloride in acetone and water,\textsuperscript{31} a protocol that can be easily scaled up in a flow system.\textsuperscript{32}

\begin{equation}
\text{Scheme 2.14: General scheme for a classic Regitz diazo-transfer reaction.}
\end{equation}

However, for compounds containing mono-activated methylene groups, triethylamine (pK\textsubscript{a} (CH\textsubscript{3}CN): 18.8)\textsuperscript{33} is not strong enough to deprotonate in α-position. Therefore, the slightly stronger 1,5-diazabicyclo[5.4.0]undec-7-ene (DBU, pK\textsubscript{a}(CH\textsubscript{3}CN): 24.3)\textsuperscript{33} can be used for the synthesis of α-aryl-α-diazocarbonyl compounds\textsuperscript{34} such as phenyl diazoacetate 165 (Scheme 2.15). In this case the desired α-diazo compound 165 was successfully isolated in 83% yield as orange oil after column chromatography.

\begin{equation}
\text{Scheme 2.15: Diazo-transfer reaction of phenylacetate 164.}
\end{equation}

Unfortunately, when the same conditions were used for the model substrate 152a, the desired product 153a was isolated only as minor product in 36% yield along with the corresponding azide 166 in 45% yield (Scheme 2.16).
Scheme 2.16: Diazo-transfer reaction of the model substrate 152a.

A similar azido-transfer reaction was reported for the reaction of trifluoromethanesulfonyl azide (18g) and β-keto carbonyl compounds, and for the reaction of 18g or tosyl azide (18a) and cyclic imides, but received a limited attention due to its unpredictability. Optimisation screening and mechanistic investigations were carried out next, to explain the azide formation and, ideally, avoid or at least minimise its generation.

2.2.2.1 Optimisation of the Diazo-transfer Reaction in Batch

Preliminary results showed that when the reaction was performed with p-ABSA (18e) as a diazo-transfer reagent and DBU as a base in acetonitrile, the side product 166 was obtained as the major product (up to 46% yield) irrespective of the amount of base or 18e (Table 2.3, entries 1–3). Less product (8%) was observed upon increasing either p-ABSA or DBU (entries 2 and 3) and no starting material was recovered, suggesting a decomposition of the desired diazo compound 153a or the formation of other products under those conditions. Performing the reaction in THF led to a higher conversion of the starting material 152a, however, a lower 153a/166 ratio was observed with the undesired product isolated in 62% yield (entry 4). The trend was reversed when the reaction time was significantly increased, and desired compound 153a was obtained in a moderate yield (46%) along with 29% of the azide 166 after 7 days (entry 5). A turning point was reached once p-ABSA (18e) was replaced by p-NBSA (18f) (entry 6). In accordance with the observation of Evans and co-workers for a similar reaction, when p-NBSA is used in combination with phosphate buffer as the quenching medium, an inverted chemoselectivity was observed and the desired diazo compound 153a was formed as the major product (53%) with only 14% of side product 166.
Table 2.3: Preliminary screening for the diazo-transfer reaction conditions on 152a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Sulfonyl Azide</th>
<th>Base</th>
<th>Conditions</th>
<th>153a (%)</th>
<th>166 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>p-ABSA (1.2)</td>
<td>DBU (1.7)</td>
<td>CH$_3$CN, 24 h, rt</td>
<td>36</td>
<td>45</td>
</tr>
<tr>
<td>2</td>
<td>p-ABSA (3)</td>
<td>DBU (1.7)</td>
<td>CH$_3$CN, 24 h, rt</td>
<td>8</td>
<td>42</td>
</tr>
<tr>
<td>3</td>
<td>p-ABSA (1.2)</td>
<td>DBU (4)</td>
<td>CH$_3$CN, 24 h, rt</td>
<td>8</td>
<td>46</td>
</tr>
<tr>
<td>4</td>
<td>p-ABSA (1.2)</td>
<td>DBU (1.7)</td>
<td>THF, 24 h, rt</td>
<td>20</td>
<td>62</td>
</tr>
<tr>
<td>5</td>
<td>p-ABSA (1.2)</td>
<td>DBU (1.7)</td>
<td>CH$_3$CN, 7 days, rt</td>
<td>46</td>
<td>29</td>
</tr>
<tr>
<td>6*</td>
<td>p-NBSA (2)</td>
<td>DBU (2.5)</td>
<td>CH$_3$CN, 24 h, rt</td>
<td>53</td>
<td>14</td>
</tr>
</tbody>
</table>

General Procedure: Reactions performed on a 0.25–1 mmol scale of 152a (0.5 M) and quenched with NH$_4$Cl saturated aqueous solution (pH = 5). *Quenched with 0.1 M phosphate buffer (pH = 7).

This sulfonyl azide dependent chemoselectivity can be explain by the different stabilities of the triazene intermediates 167a and 167b formed in situ during the reaction (Figure 2.3). This hypothesis was proved by performing two parallel NMR experiments, where the course of the reaction of 152a with p-ABSA (a) and p-NBSA (b) were monitored by $^1$H NMR spectroscopy over 5 days. The starting material 152a was fully converted into the intermediate 167b within 10 minutes in the case of p-NBSA, while it was still detected after 60 minutes when p-ABSA was used. Moreover, triazene 167b showed a faster decomposition compared to 167a with traces of the desired diazo compound 153a detected after 22 hours and formed slowly over time, while 167a proved to be more stable with no product formation after 3 days. The decomposition of 167 lead to the diazo compound 153a in accordance with the mechanism reported in literature.\textsuperscript{37}

To investigate the mechanism further, several attempts were made to isolate and characterise triazene 167b. The diazo intermediate 153a (0.24 mmol) was treated with 1.1 equivalents of p-NBSA and 1.1 equivalents of DBU in acetonitrile for 10 minutes before the addition of ice-cold water and extraction in dichloromethane. The protonated form of 167b was obtained as a 1:2 mixture of rotamers (in agreement with the ratio observed in situ 1:1.7) together with a $\sim$10% of unreacted starting material 152a and DBU. Unfortunately, the pH-sensitivity and thermolability of intermediate 167b made its isolation extremely difficult. Noteworthy, from the $^1$H NMR experiment, the side product 166 was detected only in traces after one hour with no further formation during the reaction. It is intuitive that the competition between diazo compound 153a and azide 166
formation must come from a different behaviour of the triazenes 167a and 167b during their fragmentation.

![Diagram of chemical reactions and structures](image)

**Figure 2.3:** $^1$H NMR spectra (300 MHz, CD$_3$CN) of **in situ** reaction monitoring of 152a (0.02 mmol scale) with DBU (2.5 equiv.) and a) p-ABSA (18e, 2 equiv.) or b) p-NBSA (18f, 2 equiv.). From the bottom: reaction mixture before DBU addition (t = 0), reaction mixture after 10 min, 1 h, 3 h and 72 h.

Consequently, the attention moved to study the parameters that could impact the triazene cleavage: reaction time, temperature and quenching (Table 2.4). Longer reaction time (48 h) increased the yield of the desired product 153a up to 63% with only 13% of azide 166 (entry 2). Additionally, a neutral phosphate buffer solution was preferred over acidic (NH$_4$Cl) or basic solution (NaHCO$_3$) as quenching medium, affording higher yields for 153a (63%) and better diazo/azide ratios (entries 2–4). Increasing the temperature to 45 °C over 12 or 24 hours did not show a significant influence on the reaction outcome (entries 5–7). When the reaction was performed at 45 °C for 48 hours, the desired product was still obtained in a good yield (65%) but the formation of the side product was reduced to 5%, with 9% of recovered starting material.
Similarly, at 65 °C only the desired diazo compound 153a was isolated (65%). In this case, the azide 166 was not observed, but 15% of starting material 152a was recovered (entry 9). Reactions performed at even higher temperatures (80 °C) were less selective with the formation of numerous decomposition products that lead to poor yields of 153a (up to 46%; entries 10–13).

<table>
<thead>
<tr>
<th>Entry</th>
<th>18f (equiv.)</th>
<th>Conditions</th>
<th>Quenching</th>
<th>153a (%)</th>
<th>166 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>24 h, rt</td>
<td>pH 7</td>
<td>53</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>48 h, rt</td>
<td>pH 7</td>
<td>63</td>
<td>13</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>48 h, rt</td>
<td>pH 5</td>
<td>50</td>
<td>18</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>48 h, rt</td>
<td>pH 10</td>
<td>53</td>
<td>29</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>24 h, 45 °C</td>
<td>pH 7</td>
<td>51</td>
<td>11</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>12 h, 45 °C</td>
<td>pH 7</td>
<td>50</td>
<td>13</td>
</tr>
<tr>
<td>7</td>
<td>4</td>
<td>24 h, 45 °C</td>
<td>pH 7</td>
<td>43</td>
<td>10</td>
</tr>
<tr>
<td>8a</td>
<td>2</td>
<td>48 h, 45 °C</td>
<td>pH 7</td>
<td>65</td>
<td>5</td>
</tr>
<tr>
<td>9a</td>
<td>2</td>
<td>24 h, 65 °C</td>
<td>pH 7</td>
<td>63</td>
<td>0</td>
</tr>
<tr>
<td>10a</td>
<td>2</td>
<td>12 h, 80 °C</td>
<td>pH 7</td>
<td>27</td>
<td>0</td>
</tr>
<tr>
<td>11a</td>
<td>4</td>
<td>12 h, 80 °C</td>
<td>pH 7</td>
<td>46</td>
<td>0</td>
</tr>
<tr>
<td>12a</td>
<td>2</td>
<td>24 h, 80 °C</td>
<td>pH 7</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>4</td>
<td>24 h, 80 °C</td>
<td>pH 7</td>
<td>decomposition</td>
<td></td>
</tr>
</tbody>
</table>

General Procedure: Reactions performed on a 0.17–0.25 mmol scale of 152a (0.5 M) in acetonitrile. a Starting material 152a was recovered.

Generally, the reactions carried out at 45–65 °C were more selective with little/no azide 166 formation. However, in contrast to previous reports in literature,38 lower conversions were observed and the unreacted starting material 152a was often recovered. Although the side reaction was prevented and the desired product was obtained in 63% after 24 hours compared to 53% at room temperature, a partial decomposition of triazene intermediate 167b back to the starting material 152a seemed to be responsible for the lower conversions. Indeed, when the reaction mixture containing 167b in CD₃CN was
heated to 45 °C for 24 hours, the characteristic peaks of 152a where observed by \textit{in situ} \textsuperscript{1}H NMR spectroscopy. Furthermore, the thermostability of the diazo compound 153a was investigated and a full decomposition was observed when exposed to 65 °C for more than 24 hours, which explains the lower yield obtained for the reaction at 80 °C. Therefore, 45 °C was chosen as the optimal temperature and a series of the diazo precursors 153a–n were prepared using the optimal conditions of Table 2.4, entry 8 (Scheme 2.17). The reactions were followed by thin-layer chromatography (TLC) but the very similar \textit{R}_{f} values for 152, 153 and 166 made it difficult to determine the progress of the reaction by TLC, therefore the reactions in most cases were carried out twice and stopped after 24 or 48 hours. The diazo precursors 153a–k were synthesised in good yields (51–79%) especially after 48 hours, showing that both EWG and EDG were well tolerated under the optimised conditions. The only exceptions were the nitro derivatives 152e and 152j which gave complex mixtures of products even under milder conditions at room temperature, and the attempts to isolate traces of product 153e or 153j were not successful. The cinnamic derivative 152l and the allylic 152o required milder conditions, as the products were highly unstable. Using 1.2 equivalents of DBU and p-NBSA at room temperature for 24 hours resulted in only 42% of 153l, while 152o led to a complex mixture but no desired product was detected. The \textit{N}-alkyl substituted diazo compounds 153m and 153n were obtained in poor to moderate yields (28–41%) and were harder to purify from unreacted starting material and side products. Therefore, due to purification and or instability issues, 153l–m were formed and used for the following step without further purifications.
Scheme 2.17: Substrate scope of the diazo compounds 153a–n. aReactions performed at room temperature using 1.2 equiv. of DBU and 1.2 equiv. of p-NBSA (18f) for 24 h; bYield by 1H NMR.

2.2.2.2 Optimisation of the Diazo-transfer Reaction in a Flow Setup

Flow technologies have shown several advantages over batch techniques when it comes to handling reactive/unstable intermediates in situ. Thanks to the higher surface area to volume ratio in flow devices, both mass and heat are quickly and efficiently transferred avoiding prolonged exposure to higher temperature or harsh reagents.
From the $^1$H NMR experiments (pg. 61) it was apparent that the starting material 152a was fully converted into the triazene intermediate 167b within a few minutes when p-NBSA (18f) was used. This encouraged further study of the diazo-transfer reaction in a flow system to accelerate the fragmentation of the triazene intermediate. Moreover, examples of diazo-transfer reactions have already been successfully reported in continuous flow setups.  

The first flow system was designed to mimic the addition of reagents performed in batch for a reliable comparison (Scheme 2.18). For this experiment a 0.1 M solution of 152a and 2 equivalents of p-NBSA (18f) in acetonitrile (2 mL) was prepared and loaded in a 2 mL syringe (Feed A). A second solution with DBU in acetonitrile (2 mL, 0.25 M) was prepared and loaded into a second 2 mL syringe (Feed B). A syringe pump was equipped with the two syringes, which were connected to the reactor with a T-piece mixer. The reactor consisted of a 3 mL FEP coil (i.d. = 0.5 mm) and was divided in two sections. The first part ($V_1 = 1$ mL) was left at room temperature to mimic the reaction mixture in batch during the DBU addition at room temperature and to ensure the conversion of 152a into 167b during $t'$. The second section ($V_2 = 2$ mL) was kept at 65 °C using a water bath to favour the fragmentation of 167b into 153a avoiding the side reaction during $t''$. The two solutions were pumped at 0.2 mL•min$^{-1}$ through the coil where they were mixed and reacted. The solution was equilibrated for 30 minutes before being collected over 15 minutes and quenched with a 0.1 M phosphate buffer solution (pH = 7). The desired diazo compound 153a was formed in 42% NMR yield along with 16% of side azide 166.

Scheme 2.18: First flow setup for the generation of 153a; $V_1 = 1$ mL; $V_2 = 2$ mL; $t' = 5$ min; $t'' = 10$ min; the reaction was quenched with phosphate buffer (pH = 7) and the shown NMR yields were based on $^1$H NMR spectroscopic analysis using 1,3,5-trimethoxybenzene as the internal standard. *Isolated yield after column chromatography.

When similar conditions were performed in batch, the DBU solution was added at room temperature over 5 minutes; then the solution was warmed up to 65 °C and stirred for
further 10 minutes before being quenched with a phosphate buffer solution (pH = 7). Also in this case, the desired compound 153a was formed in 47% NMR yield along with 18% NMR yield of 166. In both cases no complete consumption of the starting material was observed, with 152a still present after 15 minutes in 26% and 23% NMR yield under flow and batch conditions, respectively. Despite the fact that no complete consumption was observed, this experiment showed a promising starting point for further optimisation studies.

Some modifications of the reaction setup were made to adjust the reaction conditions to flow synthesis requirements. Firstly, the sulfonyl azide 18f was not well soluble in a 0.15 M solution of acetonitrile at room temperature together with 152a and tended to precipitate in the syringe over time. To overcome this problem, a solution of only p-NBSA (18f) was pumped separately and combined with a pre-mixed solution of 152a and DBU, similar to what was reported in the literature (Scheme 2.19).39

![Scheme 2.19: Modified flow system for the generation of diazo compounds 153a; BPR = back-pressure regulator.](image)

Moreover, as gas formation was observed during the reaction, a back-pressure regulator BPR (40 psi) was added at the end of the coil to pressurise the system. With the aim of finding the optimal conditions, a DoE-approach (see Chapter 1 and Appendix A for glossary) was used to identify the most significant parameters and 2-factor interactions (2FI; see Appendix A). Since a designed set of experiments is more likely to work efficiently when applied to a known system, some pilot studies were performed first to gain some experience with the reaction system and to choose the right ranges for each parameter (Table 2.5). For the experimental planning the reactor was simplified to a single sector as a 1 mL coil (i.d. = 0.5 mm). Lower concentrations (0.05 M) of 152a compromised the yield with no reaction after 10 minutes and only 14% of 153a after 50 minutes (entries 1–2). On the other hand, when the solution had a concentration of 0.5 M of 152a, an inconsistent flow rate was observed due to crystallisation of p-NBSA
in the syringe and in the coil (entry 12). Moreover, no reaction was observed when THF was used as solvent regardless of the concentration, reaction time and temperature (entries 3, 6, 7) and when p-tosyl azide (18a) was used instead of p-NBSA (18f), 166 was formed as major product (entry 11).

Table 2.5: Pilot studies for the diazo-transfer reaction in flow.

<table>
<thead>
<tr>
<th>Entry</th>
<th>152a (M)</th>
<th>18 (equiv.)</th>
<th>DBU (equiv.)</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>t (min)</th>
<th>152a (%)a</th>
<th>153a (%)a</th>
<th>166 (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.05</td>
<td>18f (1)</td>
<td>2</td>
<td>CH₃CN</td>
<td>65</td>
<td>10</td>
<td>100</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>0.05</td>
<td>18f (1)</td>
<td>2</td>
<td>CH₃CN</td>
<td>22</td>
<td>50</td>
<td>73</td>
<td>15</td>
<td>7</td>
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<td>2</td>
<td>THF</td>
<td>22</td>
<td>50</td>
<td>100</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
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<td>18f (1)</td>
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<td>CH₃CN</td>
<td>65</td>
<td>10</td>
<td>73</td>
<td>14 (12)b</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>0.1</td>
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<td>19</td>
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<td>18f (1)</td>
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<td>50</td>
<td>100</td>
<td>-</td>
<td>-</td>
</tr>
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<td>0.2</td>
<td>18f (1)</td>
<td>2</td>
<td>THF</td>
<td>65</td>
<td>10</td>
<td>100</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>0.2</td>
<td>18f (1)</td>
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<td>10</td>
<td>56</td>
<td>25</td>
<td>15</td>
</tr>
<tr>
<td>9c</td>
<td>0.2</td>
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<td>1.5</td>
<td>CH₃CN</td>
<td>65</td>
<td>10</td>
<td>53</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>10</td>
<td>0.2</td>
<td>18f (3)</td>
<td>2.5</td>
<td>CH₃CN</td>
<td>22</td>
<td>50</td>
<td>15</td>
<td>45 (40)b</td>
<td>20</td>
</tr>
<tr>
<td>11</td>
<td>0.2</td>
<td>18a (2.5)</td>
<td>2</td>
<td>CH₃CN</td>
<td>22</td>
<td>50</td>
<td>20</td>
<td>17</td>
<td>61</td>
</tr>
<tr>
<td>12d</td>
<td>0.5</td>
<td>18f (2.5)</td>
<td>2.5</td>
<td>CH₃CN</td>
<td>65</td>
<td>50</td>
<td>(8)b (51)b</td>
<td>(12)b</td>
<td></td>
</tr>
</tbody>
</table>

General Procedure: The reactions were performed using the flow system depicted in Scheme 2.19 with an overall flow rates of 0.1–0.02 mL min⁻¹ and quenched with a phosphate buffer solution (pH = 7). aYield measured by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard; bIsolated yield; cReaction quenched with saturated aqueous NH₄Cl solution (pH = 5); dInconsistent flow rate due to p-NBSA precipitate.

With this information in hand the following two-levels fractional factorial design (FFD 2⁵₋¹; see Appendix A) was designed with five numerical variables and three responses were registered (Table 2.6). The chosen parameters were: concentration of 152a (+1 = 0.1 M; −1 = 0.05 M), p-NBSA (+1 = 3 equivalents; −1 = 1 equivalent), DBU (+1 = 2.5 equivalents; −1 = 1.5 equivalents), temperature (+1 = 65 °C; −1 = 22 °C) and residence time (+1 = 50 minutes; −1 = 10 minutes); the responses (starting material residue (%), diazo compound formation (%) and azide formation (%)) were measured by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. The 16 experiments were performed in a random order over three days to minimise nuisance, and three central points were measured to identify any curvature. The acquired data
were fitted into the model and the three responses were analysed separately using pareto charts and half-normal plots to select the most significant factors.

Table 2.6: Matrix for the FFD 2^5-1 with results. Factor generator for E = A*B*C*D.

<table>
<thead>
<tr>
<th>Std</th>
<th>Run order</th>
<th>A: 152a (M)</th>
<th>B: T (°C)</th>
<th>C: DBU (equiv.)</th>
<th>D: p-NBSA (equiv.)</th>
<th>E: t (min)</th>
<th>152a (%)^a</th>
<th>153a (%)^a</th>
<th>166 (%)^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11</td>
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<td>22</td>
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<td>50</td>
<td>36</td>
<td>30</td>
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<td>7</td>
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<td>0.15</td>
<td>43.5</td>
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<td>15</td>
</tr>
<tr>
<td>18</td>
<td>18</td>
<td>0.15</td>
<td>43.5</td>
<td>2</td>
<td>2</td>
<td>30</td>
<td>42</td>
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</tr>
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<td>19</td>
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<td>0.15</td>
<td>43.5</td>
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<td>2</td>
<td>30</td>
<td>40</td>
<td>29</td>
<td>15</td>
</tr>
</tbody>
</table>

General Procedure: All reactions were performed according to Scheme 2.19. ^aYields determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard.

According to the chosen models, the concentration of 152a (A), the amount of base (C) and the residence time (E) were not significant, which means that their influence on the outcomes was not statistically relevant within the investigated chemical space. In contrast, the impact of the temperature (B) was significant for all three responses, especially for the consumption of the starting material 152a. In fact, a higher residue of 152a was observed after performing the reactions at higher temperature, which resulted in lower yields for 153a and azide 166 (Figure 2.4). As previously discussed for the batch process (pg. 61–63), despite the better yield for 153a (65%) and a better diazo/azide ratio observed for a reaction performed at 45 °C, a small amount of starting material 152a was recovered, and the decomposition of the triazene intermediate 167a was suspected. Under flow conditions, due to the bigger surface area to volume ratio, the effect due to
the temperature was enhanced leading to a faster decomposition of the triazene 167a that would explain the high amount of the starting material recovered. However, the pareto chart for the second response showed that the formation of the desired product 153a was promoted when a higher amount of ρ-NBSA was used.

![Figure 2.4: Pareto charts showing main effect for (from left to right) response R1 (starting material residue), R2 (diazo compound formation) and R3 (azide formation). A = 152a, B = Temperature, C = Base, D = ρ-NBSA, E = time; Orange = positive effect; Blue = negative effect.](image)

The three models were confirmed to be significant by the analysis of variance (ANOVA) with no significant curvature (see Appendix A for glossary). The models were then used to navigate the aforesaid chemical space to find optimal combinations of factors that, simultaneously, minimised the starting material residue and azide formation while maximising the formation of the desired diazo compound. The contour plots in Figure 2.5 provide a visual representation of the responses when the concentration of 152a (A), the DBU equivalents (C) and the time (E) are kept fixed. By overlapping these contour plots, it is possible to better visualised the “sweet spot” (highlighted in yellow) in which all the
criteria are satisfied. In particular, when a solution of 0.2 M of 152a and 2 equivalents of DBU are used with a 10 minutes residence time, the desired product 153a is formed in more than 40% NMR yield, the residue of 152a and azide formation are less than 25% and 20%, respectively.

**Figure 2.5:** Contour plots for a) starting material residue, b) diazo and c) azide formation with 152a = 0.2 M and DBU = 2 equiv. after 10 min; d) Overlay plot with highlighted “sweet spot” in yellow for the following criteria SM residue < 25%, diazo compound > 40% and azide < 19 or 17%.

Following that, the reaction mixture of a batch experiment was compared to the mixture obtained under flow conditions by crude ¹H NMR before and after work-up. As previously discussed (see Table 2.4), the batch reaction took 24 hours before traces of diazo 153a were detected by ¹H NMR spectroscopy, hence the greatest part of the triazene intermediate was cleaved during the work-up and the diazo/azide ratio depended on the quenching agent. On the contrary, the products 153a and 166 were partially formed already after 10 minutes in the flow system with no work-up. With this information in
hand, different internal diameters were modified next to investigate their influence on the mixing, and the equivalents of DBU were increased to improve the conversion of the starting material (Table 2.7).

Table 2.7: Screening of reactor internal diameters, temperatures and equivalents of DBU.

<table>
<thead>
<tr>
<th>Entry</th>
<th>ID (mm)</th>
<th>DBU (equiv.)</th>
<th>T (°C)</th>
<th>time (min)</th>
<th>152a&lt;sup&gt;a&lt;/sup&gt;</th>
<th>153a&lt;sup&gt;a&lt;/sup&gt;</th>
<th>166&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.5</td>
<td>2</td>
<td>22</td>
<td>10</td>
<td>22</td>
<td>45</td>
<td>19</td>
</tr>
<tr>
<td>2</td>
<td>0.5</td>
<td>4</td>
<td>22</td>
<td>10</td>
<td>12</td>
<td>53 (49)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>27</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>2</td>
<td>22</td>
<td>10</td>
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</tr>
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<td>0.5</td>
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<td>22</td>
<td>5</td>
<td>10</td>
<td>52</td>
<td>26</td>
</tr>
</tbody>
</table>

*General Procedure:* The reactions were performed on 0.2 M of 152a in acetonitrile using 2.5 equiv. of p-NBSA (18f);<sup>a</sup> Determined by <sup>1</sup>H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard;<sup>b</sup> Isolated yield.

No effect was found when the internal diameter was changed from 0.5 to 1.0 mm (entries 1 and 3), however, when more equivalents of DBU were used, better conversions were achieved (80% combined yield) and the desired diazo compound 153a was obtained in 53% and 50% NMR yield for 0.5 and 1.0 mm, respectively (entries 2 and 4). A smaller internal diameter (0.2 mm) and further addition of base did not lead to any improvement (entries 5, 6). In addition, 153a was formed in 52%, 53% and 54% within 5, 10 and 50 minutes, respectively (entries 2, 9, 10), showing the insignificance of the residence time \( t \). Hence, the optimal condition to achieve the \( \alpha \)-diazocarbonyl intermediate 153a in good yield were found using 4 equivalents of DBU, 0.5 mm of
internal diameter coil at room temperature (Table 2.7, entry 2). Subsequently, the Rh(II)-catalysed enantioselective cyclisation was investigated.

### 2.2.3 Optimisation of the C–H Insertion Reaction

The metal-catalysed C–H insertions of aryl diazo acetates have been widely investigated, especially for the synthesis of optically active heterocycles. Among all, chiral Rh(II)-catalysts such as Rh₂(DOSP)₄ 71a, Rh₂(PTTL)₄ 71d and Rh₂(PTAD)₄ 71e have stood out as the most efficient and selective catalysts (Figure 2.6).

#### Figure 2.6: Chiral Rh(II)-catalysts most reported in the literature for asymmetric C–H insertions.

Firstly, racemic mixtures were synthesised using Rh₂(OAc)₄ as catalyst to investigate the reactivity of substrate 153a–n. In presence of dirhodium tetraacetate catalyst in dry dichloromethane and under nitrogen atmosphere, the model diazo substrate 153a fully converted into the desired 2,3-dihydroindoles 154 in 92% yield as a 3:1 mixture of trans- and cis-isomers within 12 hours (Scheme 2.20).

#### Scheme 2.20: Achiral intramolecular dirhodium-catalysed cyclisation of 153a.

Generally, all α-diazo substrates 153a–n formed the desired indolines in quantitative yield with high d.r. toward the trans-isomer, except N-sec-butyl 153n and the N-allylic derivative 153o that did not show the desired reactivity.

With the aim of optimising the stereoselectivity several solvents were screened. Among all, n-hexane at room temperature provided the best d.r. and ee for the trans-isomer 154 when Rh₂(R-DOSP)₄ was used as chiral catalyst (Table 2.8). Indeed, when the
dodecylphenylsulfonylprolinate (DOSP) ligand was used at room temperature in \( n \)-hexane, the trans-154 was obtained as the major product in good yields (up to 82%) and enantiomeric excess (up to 86% ee), while no stereoselectivity was detected for the cis-154 (entries 2–5). Lower temperatures\(^{26} \) showed to drastically improve the d.r. (>20:1) albeit lower enantiomeric excesses were observed (entry 6).

**Table 2.8:** Screening of conditions for the synthesis of trans- and cis-indoline 154.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>R</th>
<th>Yield (%)</th>
<th>d.r.</th>
<th>(S,S)-154 ee</th>
<th>(S,R)-154 ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \text{Rh}_2(\text{OAc})_4 ) 1 mol%, CH(_2\text{Cl}_2), rt</td>
<td>C(_6\text{H}_5)</td>
<td>92</td>
<td>3:1</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>2(^{26} )</td>
<td>( \text{Rh}_2(\text{R-DOSP})_4 ) 1 mol% ( n )-hexane, rt</td>
<td>C(_6\text{H}_5)</td>
<td>72</td>
<td>10:1</td>
<td>80</td>
<td>6</td>
</tr>
<tr>
<td>3(^{26} )</td>
<td>( \text{Rh}_2(\text{S-DOSP})_4 ) 1 mol% ( n )-hexane, rt</td>
<td>C(_6\text{H}_5)</td>
<td>64</td>
<td>9:1</td>
<td>76</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>( \text{Rh}_2(\text{R-DOSP})_4 ) 1 mol% THF, rt</td>
<td>C(_6\text{H}_5)</td>
<td>35</td>
<td>5.9:1</td>
<td>38</td>
<td>n.d.</td>
</tr>
<tr>
<td>5</td>
<td>( \text{Rh}_2(\text{R-DOSP})_4 ) 0.5 mol% ( n )-hexane, rt</td>
<td>C(_6\text{H}_5)</td>
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<td>11:1</td>
<td>86</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>( \text{Rh}_2(\text{R-DOSP})_4 ) 0.5 mol% ( n )-hexane, 0 °C</td>
<td>C(_6\text{H}_5)</td>
<td>80</td>
<td>&gt;20:1</td>
<td>73</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>( \text{Rh}_2(\text{R-PTAD})_4 ) 1 mol% ( n )-hexane, rt</td>
<td>C(_6\text{H}_5)</td>
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<td>1:1:1</td>
<td>59</td>
<td>40</td>
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<tr>
<td>8</td>
<td>( \text{Rh}_2(\text{S-PTTL})_4 ) 1 mol% ( n )-hexane, rt</td>
<td>C(_6\text{H}_5)</td>
<td>63</td>
<td>1:4:5</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>9</td>
<td>( \text{Rh}_2(\text{S-PTTL})_4 ) 1 mol% ( n )-hexane, rt</td>
<td>4-Me-C(_6\text{H}_5)</td>
<td>70</td>
<td>1:1.9</td>
<td>62</td>
<td>10</td>
</tr>
</tbody>
</table>

**General Procedure:** Reactions performed on a 1 mmol scale of 153. \(^{a}\)Combined yield of trans- and cis-isomers; \(^{b}\)Determined by \(^{1}\)H NMR spectroscopy; \(^{c}\)Determined by chiral HPLC; n.a. = not applicable; n.d. = not determined.

Subsequently, the attention moved to other popular rhodium catalysts bearing the \( N \)-phthalamido-1-adamantylacetate (PTAD, 171e) and the \( N \)-phthamido-1-\( \text{tert} \)-leucinate (PTTL, 171d) ligands. Differently from 171a, when 171e or 171d were used the cis-154 was the major product formed in agreement with previous reports on dihydrobenzofurans.\(^{25} \) In particular, the \( \text{Rh}_2(\text{PTAD})_4 \) catalyst 171e showed very poor diasteroselectivity and a medium enantioselectivity for both trans- and cis-154 with 59% ee and 40% ee, respectively (entry 7). Moreover, the PTAD-ligand seems to encourage the formation of unidentified side products and only 20% of dihydroindoles 154 were isolated. On the other hand, the \( \text{Rh}_2(\text{S-PTTL})_4 \) catalyst 171d afforded the cis-154 in better yield (63%) and
better diastereoselectivity (1:4.5 trans/cis ratio). However, the interaction between the carbene precursor 153a and the PTTL ligand lead to a very poor selectivity for both trans- and cis-isomers (up to 11% ee; entry 8), while a moderate selectivity (62% ee) was detected when a different substrate (153f) was used (entry 9).

In the light of these observations, the DOSP-ligand was preferred over PTAD and PTTL for the successful synthesis of trans-indolines in both good yields and enantioselectivity. The absolute configuration of the major enantiomer (2R,3R)-2-phenyl-1-tosylindoline-3-carboxylate (154a) was confirmed by single crystal X-ray analysis of the product obtained after recrystallisation from n-hexane/2-propanol 1:1 v/v, using Rh₂(S-DOSP)₄ 71a catalyst (Figure 2.7).²⁶

![Figure 2.7: Crystal structure for (2R,3R)-2-phenyl-1-tosylindoline-3-carboxylate 154a.](image)

Subsequently, the optimal reaction conditions (Table 2.8, entry 5) were applied on various diazo precursors (153a–n) leading to the trans-products 154a–k in good yields and in good to excellent enantiomeric excesses (Scheme 2.21). The substitution of the methyl ester with a bulkier iso-propyl ester decreased the selectivity with 154b formed as a 2.2:1 diastereomeric ratio and 35% ee. Products 154c–f bearing electron-donating and electron-withdrawing groups in para-, meta- and ortho- were obtained in good yields (up to 92%) and good to excellent selectivity (up to 80% ee). The bulkier 2-phenyl substituted aryl diazo derivative 153g was slower to react, affording 154g in 73% yield after 24 hours in 80% ee, while the slightly less sterically hindered 153h–i formed 154h–i in 86% and 48% yield and 61% and 75% ee, respectively, after 12 hours. Besides the benzylic-derivatives in 153a–i, also the cinnamyl and the n-hexyl groups were well-tolerated under these conditions. The cinnamic-derivative showed the desired reactivity affording 154j in 53% yield after 24 hours despite of the presence of the double bond, although with poor enantioselectivity (33% ee). On the other hand, the n-hexyl substrate 154k was formed in good yield (64%) and excellent diastereoselectivity (>20:1) with a moderate enantiomeric excess (48% ee) within 12 hours.
Scheme 2.21: Substrate scope of trans-dihydroindoles 154a-k. Combined yields of trans and cis-154 are shown; diasteromeric ratio (d.r.) was determined by $^1$H NMR spectroscopy and the enantiomeric excess (ee) was determined by HPLC. The absolute stereochemistries were assigned in analogy to 154a.

Eventually, the C–H insertion was examined in flow with the aim to combine the generation and reaction of the carbene precursor into a single continuous-flow setup. Unfortunately, there was no reaction occurring under the investigated conditions (Table 2.9) which seem to be not appropriate for flow conditions.
Table 2.9: Flow setup for intramolecular C–H insertion.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Rh(II) catalyst</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rh₂(OAc)₄ 1 mol%</td>
<td>20</td>
<td>no reaction</td>
</tr>
<tr>
<td>2</td>
<td>Rh₂(oct)₄ 1 mol%</td>
<td>40</td>
<td>traces</td>
</tr>
<tr>
<td>3</td>
<td>Rh₂(R-DOSP)₄ 1 mol%</td>
<td>40</td>
<td>no reaction</td>
</tr>
<tr>
<td>4</td>
<td>Rh₂(R-PTAD)₄ 1 mol%</td>
<td>40</td>
<td>traces</td>
</tr>
</tbody>
</table>

The reaction in batch required 12–24 hours to occur completely, probably as result of the bulky tosyl group close to the C–H insertion site, making the translation into a flow system harder. Therefore, a synthesis for different N-substituted diazo compounds was initiated (Scheme 2.22). 2-Aminophenylacetate 156a was quantitatively converted to the imine 169 within 10–20 minutes in the presence of benzaldehyde (168) and MgSO₄ under neat reaction conditions. The Pt-catalysed reduction/methylation of 169 in the presence of formic acid and phenylsilane described by Zhu et al.,⁴¹ provided only the undesired lactone 163 as the major product. The desired product 171 was obtained by imine reduction to 170 followed by methylation. For a successful reduction, a 1:1 mixture of boric acid and NaBH₄⁴² was used to avoid ester hydrolysis observed when only NaBH₄ was used. The secondary amine 170 was then treated with methyl iodide and triethylamine in DMF to generate the N-methyl derivative 171, which was formed only in poor yield (only 16–21%) due to the competitive cyclisation to 163 (36–40% yield). Subsequently, 171 was treated with p-NBSA (2 equivalents) and DBU (2 equivalents) in acetonitrile at room temperature for 24 hours, but a complex mixture of unreacted 171, desired product 172 and the side product 173 was obtained. When the crude mixture was treated with Rh₂(OAc)₄ in dichloromethane the bright yellow solution turned pale green within 5 minutes and a gas evolution was observed. The ¹H NMR spectroscopic analysis of the crude reaction mixture showed the disappearance of the diazo
precursor 172, but the afforded reaction mixture was complex, and no product could be isolated or identified.

**Scheme 2.22**: Synthetic pathway to afford alternative N-methyl substituted indolines.
2.3 Conclusion and Outlook

In conclusion, a novel and efficient stereoselective synthesis for trans-indolines from α-diazocarbonyl compounds using Rh(II)-catalysed intramolecular C–H insertions was developed.

The library of carbene-precursors 153a–n was successfully synthesised in batch in moderate to very good yields via Regitz diazo-transfer. Furthermore, the reaction was translated in a flow system using a DOE-approach to optimise the synthesis of the model diazo intermediate 153a (up to 51% NMR yield). Moreover, a library of 11 new trans-indolines 154a–k was built in good yields and with good to excellent selectivity.

Further work can be done to expand the substrate scope in order to include substituents on the indoline aryl ring as well as investigating different N-protecting groups. Moreover, future work is focused on developing a continuous flow set-up for the diazo-transfer reaction and the asymmetric cyclisation combined with an online 2D-HPLC analytic system for a faster analysis of complex mixture of isomers. Indeed, the 2D-HPLC technique proved to speed up the analysis providing information about conversion, d.r. and ee within 40 min and it presents a convenient tool to quickly analyse asymmetric transformation in a short period of time (Figure 2.8).

\[
\begin{align*}
\text{CO}_2\text{Me} & \quad \text{Rh}_2(\text{OAc})_4 \\
\text{N}_2 & \quad \text{CH}_2\text{Cl}_2 \\
153a & \quad 12 \text{ h, rt} \\
\rightarrow & \\
\text{CO}_2\text{Me} & \\
\text{trans-154a} & \\
\text{cis-154a} & \\
\end{align*}
\]

**Figure 2.8:** 2D-HPLC double chromatogram for the resolution of the indoline mixture (λ = 254 nm): first dimension silica column separates trans- from cis-isomer (blue line); second dimension YMC chiral column separates the enantiomers (red line).
References


CHAPTER 3: Synthesis of Fluorinated Benzofuranones

3.1 Introduction

Fluorine-containing organic molecules have an important role in both medicinal and agrochemical chemistry due to the unique properties fluorine can provide to a molecule.\(^1\) The presence of fluorine atoms has a biological importance: it can improve the metabolic stability of the molecule as well as its binding affinity to protein targets. Moreover, it can increase the lipophilicity, which results in a better permeability of the molecule through the biological membrane.\(^2\) Moreover, late stage \(^{18}\text{F}\) functionalisation provides access to useful radiolabel tracers that are widely used in Positron Emission Tomography (PET) imaging.\(^3\) Additionally, polyfluoroarenes play an important role in the electronics industries, as they find applications in electronic devices such as organic light-emitting diodes (OLEDs), organic thin film transistors (OFETs), photovoltaics and sensors.\(^4\) Therefore, the research of new methods to install halogenated aryl groups represent a hot topic in organic chemistry.\(^5\)

Publications by Erker et al.\(^6\) as well as by Stephan et al.\(^7\) and the Melen group\(^8\) have shown that tris(pentafluorophenyl)borane \(\text{B(C}_6\text{F}_5)_3\) \(^{106d}\), mainly used as catalyst in metal-free cyclisations,\(^9\) hydrogenations,\(^10\) and hydrosilylation\(^11\) reactions, has the ability to undergo \(\text{C}_6\text{F}_5\) group migration (Scheme 3.1).

![Scheme 3.1: Examples of metal-free fluoroaryl-migration using \(\text{B(C}_6\text{F}_5)_3\) \(^{106d}\).](image)

However, most approaches have been limited to the use of \(\text{B(C}_6\text{F}_5)_3\) as part of a frustrated Lewis pair (FLP)\(^{10a}\) and the migratory attitude of other aryl groups from boranes is much less studied.
As mentioned earlier (Chapter 1.1.2.2), α-diazocarbonyl compounds react with trialkyl- and triarylboranes to form boron enolate intermediates which then react with various electrophiles affording α-functionalised carbonyl compounds. In this chapter the metal-free α-aryl functionalisation of esters from α-diazocarbonyl precursors 179 in the presence of halogenated and non-halogenated triarylboranes 106 is presented (Scheme 3.2). The resulting α,α-diaryl esters 182, represent a valuable class of compounds due to their role as pharmacophores, and they can be typically achieved by rhodium-mediated functionalisation of diazo compounds in the presence of arylboronic acids 180 or arylsiloxanes 181.

Scheme 3.2: Previous protocols for the synthesis of α-aryl esters 182 from α-diazo esters 179 catalysed by rhodium(I) or rhodium(II) (top); metal-free α-aryl functionalisation of esters from α-diazocarbonyl precursors 107 or 179 presented in this chapter (bottom).

Nevertheless, the main focus of the chapter is the development of a metal-free synthesis towards fluorinated asymmetric benzofuran-2(3H)-ones 159 from 2-oxygen or 2-sulfur substituted aryl-α-diazo acetates 158 in the presence of fluorinated triarylboranes 108d and 108e (Scheme 3.3).
Scheme 3.3: Novel metal-free synthesis of benzofuran-2(3H)-ones 185 using triarylboranes 106d and 106e presented in this chapter.

Benzofuran-2-(3H)-ones are oxygen-containing heterocycles which are present in many biologically active compounds such as (-)-fumimycin 186,15 rosmadial 187,16 yuccaol A 18817 and abiesinol A 189 (Figure 3.1).18 Moreover, they are used as synthons for the synthesis of flavonoid-related aurones 19019 and sesquiterpenes such as aplysin 191.20

Figure 3.1: Examples of natural products containing or synthesised from benzofuranones.

The presence of a fully substituted quaternary carbon at the C-3 position is a key structural characteristic for such compounds and, to date, there are several protocols towards the asymmetric synthesis of 3,3-disubstituted benzofuranones 185 that follow two common retrosynthetic approaches (Scheme 3.4).21 One approach is based on the double functionalisation of benzofuranone scaffolds 192, promoted by organo- or metal-based catalysts,22 whereas the other approach relies on the de novo synthesis of the lactone framework from building blocks which bear a pre-functionalised C-3 position.
For the *de novo* synthesis of the lactone core, metal-catalysed C–H activation/C–O bond formation, tandem Friedel-Crafts/lactonisation, Reppe-type cyclocarbonylation, and condensation of phenol derivatives have all been reported as successful strategies (Scheme 3.5). However, the protocols for the stereoselective synthesis of chiral lactones from achiral and acyclic starting materials are limited.

A recent example of the enantioselective synthesis of chiral benzofuranones relies on the palladium-catalysed C–H activation of 2,2-disubstituted phenylacetic acids. The activation is followed by C–O bond formation in the presence of a chiral ligand, which subsequently generates chiral benzofuranones in good yields (up to 86%) and high enantioselectivities (up to 96% ee; Scheme 3.6).
In 2018, Bella and co-workers\textsuperscript{26b} developed a stereoselective synthesis for chiral 3,3-disubstituted benzofuranones \textit{200}, via desymmetrisation of prochiral malonates \textit{197} (Scheme 3.7). In the presence of \textit{Chinchona} alkaloid derivatives, malonate \textit{197} reacts with quinone \textit{198} and the resulting arylated achiral malonate cyclises to give benzofuranones \textit{200} in good yields, preferentially as the (\textit{R})-isomer. The intermolecular desymmetrisation is suggested to occur via a transition state such \textit{199}, where the thiourea moiety of the chiral organocatalyst coordinates to both the phenolic and the carboxylic groups, favouring the formation of (\textit{R})-\textit{199}.\textsuperscript{26b}

\begin{center}
\textbf{Scheme 3.7}: Synthesis of chiral benzofuranones \textit{200} via intramolecular desymmetrisation on malonate \textit{197}.
\end{center}

In this chapter, a novel approach towards asymmetric 3,3-disubstituted benzofuranone \textit{185} is presented. The new methodology involves \textit{a}-diazo esters and highly Lewis acidic boranes, in which the lactone framework is formed and fully functionalised in the C-3 position in one single step (Scheme 3.3). Parts of the following results are published in \textit{Angew. Chem. Int. Ed.} \textbf{2019}, \textit{58}, 7861–7865.
3.2 Results and Discussion

In this work, the ability of the different Lewis acids 106a–e\(^a\) to undergo \(\alpha\)-ester functionalisation was investigated (Scheme 3.8). A library of \(\alpha\)-diazocarbonyl esters 107 and 179 was synthesised from ethyl acetoacetate 201 or from the corresponding carboxylic acids 202 over two steps. Moreover, \(\alpha\)-diazo esters 184, synthesised from 2-hydroxy phenylacetic acids 203 over three steps, were used to develop a synthesis towards asymmetric 3,3-disubstituted benzofuran-2(3\(H\))-ones 185. The relative Lewis acidity of triarylboranes 106a–e was determined by the Gutmann-Beckett method\(^b\) by Dr. Soltani and Darren M. C. Ould (Cardiff University). The Gutmann-Beckett method is an experimental method that measure the \(^{31}\)P chemical shifts of the Lewis adduct formed between a Lewis acid and triethylphosphine (Et\(_3\)PO). The difference in \(^{31}\)P chemical shifts between the adduct and the free probe is directly related to the strength of the Lewis acid and it is indicated by an Acceptor Number (AN)\(^c\).

\(\alpha\)-Aryl functionalisation of esters:

\[
\begin{align*}
\text{201} & \quad \text{or} \quad \text{202} \\
\xrightarrow{2 \text{ steps}} & \quad \xrightarrow{106} \\
107, R^1 = \text{Me}, R^2 = \text{Et} \\
179, R^1 = \text{Aryl}, R^2 = \text{Me}
\end{align*}
\]

Tandem Rearrangement/Lactonisation:

\[
\begin{align*}
\text{203} & \quad \xrightarrow{3 \text{ steps}} \quad \xrightarrow{106} \\
184 & \quad 185
\end{align*}
\]

Relative Lewis acidity:

\[
\begin{align*}
106a & \quad 106b & \quad 106c & \quad 106d & \quad 106e \\
\text{67\%} & \quad 71\% & \quad 83\% & \quad 98\% & \quad \text{100\%}
\end{align*}
\]

Scheme 3.8: Relative Lewis acidity scale for 106a–e\(^a\) and an overview of the synthetic pathways developed for the metal-free \(\alpha\)-aryl functionalisation of esters and benzofuranones 185 synthesis.

---

\(\text{a. Except 106a, which is commercially available, the synthesis of 106b–e was carried out by Dr. Y. Soltani, D. M. C. Ould, Dr. J. Wenz and J. L. Carden.}\

\(\text{b. The relative Lewis acidity was measured by Dr. Y. Soltani and D. M. C. Ould.}\)
3.2.1 \( \alpha \)-Functionalisation of Esters

Initially, the model substrate ethyl 2-diazo propanoate (107) was prepared to investigate
the reactivity of boranes 106a–e towards the 1,2-aryl transfer into diazo compounds
reaction (Chapter 1.1.2.2, Scheme 1.26). The synthesis started with the \( \alpha \)-methylation of
ethyl acetoacetate (201) in the presence of methyl iodide and sodium hydride, to afford
204 in 65\% yield (Scheme 3.9). Ethyl 2-diazo propanoate (107) was then obtained in 52\%
yield via Regitz diazo-transfer,\(^{29}\) by treating 204 with \( p \)-acetamidobenzenesulfonyl
azide (\( p \)-ABSA, 18e) and DBU in acetonitrile.

\[
\text{O} \quad \quad \text{O} \quad \quad \text{Et} \quad \quad \text{NaH, Mel} \quad \quad \text{O} \quad \quad \text{O} \quad \quad \text{Et} \\
\begin{array}{c}
\text{201} \\
\text{0 °C to reflux} \\
\text{overnight}
\end{array} \quad \quad \begin{array}{c}
\text{204, 65\%} \\
\text{p-ABSA, DBU} \\
\text{CH}_3\text{CN} \\
\text{0 °C to rt} \\
\text{overnight}
\end{array} \quad \quad \begin{array}{c}
\text{N}_2 \\
\text{Et} \\
\text{107, 52\%}
\end{array}
\]

Scheme 3.9: Preparation of ethyl 2-diazo propanoate (107).

Treatment of 107 with boranes 106a–e in a 3:1 ratio, followed by aqueous basic work-up
(1 M aqueous solution of NaOH) afforded ethyl 2-aryl propanoates 182a–e in poor to very
good yields (30–89\%; Scheme 3.10).

\[
\begin{array}{c}
\text{O} \quad \quad \text{O} \quad \quad \text{Et} \\
\begin{array}{c}
\text{B} \\
\text{106a-e (0.33 equiv.)} \\
\text{CDCl}_3 \\
\text{1 h, rt} \\
\text{then NaOH 1 M}
\end{array}
\end{array} \quad \quad \begin{array}{c}
\text{O} \quad \quad \text{O} \quad \quad \text{Et} \\
\begin{array}{c}
\text{X}_n \\
\text{182a-e 30 - 89\%}
\end{array}
\end{array}
\]

Scheme 3.10: Screening of boranes 106a–e in the 1,2-aryl transfer reaction on the model
substrate 107. The reaction was performed on a 0.1 mmol scale using 0.33 mol\% of boranes
106a–e.

The yields of the 1,2-aryl migration reaction, in the presence of triarylboranes 106a–e,
increased with the Lewis acidity of 106a–e (see Scheme 3.8). When the least Lewis
acidic triphenylborane (106a) was used, 182a was obtained in 30\% yield. The more
Lewis acidic fluorinated boranes 106b and 106c were found to be slightly more reactive.
affording 182b and 182c in 37% and 45% yield, respectively. The more Lewis acidic B(C₆F₅)₃ (106d) or 3,4,5-fluorinated borane 106e, on the other hand, led to good yields in product formation with 182d and 182e isolated in 80% and 89%, respectively. The higher reactivity of 106d–e was clearly visible, as the characteristic bright yellow colour of the substrate solution turned colourless within 10 minutes from the borane addition, suggesting a full consumption of the diazo starting material. Moreover, a gas evolution was observed as soon as the borane reagent was added which lasted about 60 minutes, indicating the formation of nitrogen. To better follow the reaction progress, the reactions were conducted in sealed Young NMR tubes under nitrogen atmosphere in CDCl₃. In the case of reactions performed using 106e, the reaction mixtures were easily followed by in situ ¹H NMR, showing full consumption of the starting material 107 after 60 minutes. On the other hand, when B(C₆F₅)₃ (106d) was used, both ¹H and ¹⁹F NMR spectra were too complex to be interpreted. Nevertheless, the yields showed that highly Lewis acidic boranes such as 106e and 106d were able to transfer more than two aryl groups, in agreement with what has been reported previously.³⁰ For this reason, they were preferred for further studied over less Lewis acidic boranes such as triphenylborane (106a) which is typically used in excess.³¹

To further investigate the reactivity of boranes 106 in the α-arylation of diazocarbonyl compounds, more sterically demanding α-aryl-α-diazo acetates 179 were prepared from the corresponding carboxylic acids over two steps. Apart from the commercially available methyl esters 164 and 205f, the other methyl esters 205a–e and 155a were prepared from the corresponding carboxylic acids 202a–e and 151 in moderate to excellent yields using acetyl chloride in methanol (Scheme 3.11).

Scheme 3.11: Preparation of ester precursors; “Commercially available.
The precursors were then treated with \( p \)-ABSA and DBU in acetonitrile to afford the desired diazo substrates 165 and 179a–g in very high yields (71–99%; Scheme 3.12).

![Scheme 3.12: Preparation of the diazo precursors 165, 179a–g.](image)

Less Lewis acidic boranes 106a–c did not show reactivity with \( \alpha \)-aryl-\( \alpha \)-diazo esters 165 and 179a even at 50 °C,
\(^2\) whereas boranes 106d and 106e afforded the pharmaceutically useful\(^3\) \( \alpha,\alpha \)-diaryl esters 182f–o in moderate to excellent yields after 12 hours at room temperature (Scheme 3.13). In this case, the boron reagents 106d–e were found to transfer only one aryl group to the \( \alpha \)-aryl-\( \alpha \)-diazo esters 165 and 179a–d after 12 hours at room temperature instead of all three as observed for 107 (see Scheme 3.10).

However, when the 3,4,5-fluorinated borane 106e reacted with methyl phenyldiazo acetate (165) in a 1:3 ratio at 50 °C, more aryl groups were transferred from 106e to 165, affording 182f in 79% yield after 7 days. Some limitations were encountered with the diazo compounds 179e–g that did not show any reaction with boranes 106d–e. While the low reactivity of 179e and 179f remains unclear, the absence of reactivity of the pyridine derivative 179g, is probably due to the equilibrium between 179g and its isomer 3-triazolopyridine (179g′), which is shifted towards the latter (Scheme 3.14).

c. The reaction between 106a–c and diazo compounds 165 and 179a were performed by Dr. J. Wanz.
Scheme 3.13: Substrate scope of α-diairester 182f–o. Reactions performed on a 0.1 mmol scale using a 1:1 ratio of diazo compounds 165, 179a–d and boranes 106d–e. *Reaction performed on a 0.5 mmol scale.

Scheme 3.14: Equilibrium between the diazo compound 179g and the triazole 179g$^1$ and crystal structure for 179g$^1$.

d. Crystallisation, characterisation and analysis for triazole 179g$^1$ was performed by D. C. M. Ould.
This metal-free 1,2-aryl migration was then applied to the synthesis of **182p**, a valuable intermediate for the synthesis of diclofensine **206** (Scheme 3.15). Diclofensine (**206**) is an antidepressant drug bearing a tetrahydroisoquinoline scaffold which can be synthesised from **182p**, typically obtained by rhodium-catalysed α-functionalisation of esters.\(^{14b}\) For this reason, the 3,4-chlorinated borane **106f** was prepared\(^{e}\) and it was found to have a relatively high Lewis acidity (98%, acceptor number \(AN = 78.06\)), similar to 3,4,5-fluorinated borane (**106e**, \(AN = 79.57\)) and \(\text{B(C}_6\text{F}_5)_3\) (**106d**, \(AN = 77.49\)). As expected, the reaction of **106f** with **179c** led to the precursor **182p** isolated in 92% yield after 12 hours (Scheme 3.15).

![Scheme 3.15: Synthesis of 182p, a synthetic intermediate for diclofensine 206.](image)

The attention was then moved to the synthesis of chiral diazo precursors **179h-j**, bearing a (−)-menthyl substituent as a chiral auxiliary, with the intention to influence the stereoselectivity of the 1,2-aryl transfer reaction.\(^32\) The (−)-menthyl group in **179h** was installed by transesterification of ethyl acetoacetate (**201**) using boronic acid as a catalyst (Scheme 3.16).\(^{33}\)

![Scheme 3.16: Transesterification of acetoacetate 201 to the chiral 207.](image)

The (−)-menthyl acetoacetate (**207**) was isolated in 55% yield and treated with sodium hydride and methyl iodide in THF overnight. The obtained α-methylated precursor **208** was then used for the Regitz diazo-transfer reaction (see Chapter 1, pg. 6)\(^{29}\) to afford the chiral diazo derivative **179h** in 30% yield (Scheme 3.17).

---

\(^e\) Synthesis, characterisation and Lewis acidity measurements for **106f** were performed by Dr. Y. Soltani.
Scheme 3.17: Synthesis of chiral diazo precursor 179h.

To synthesise the chiral α-aryl-α-diazo esters 179i and 179j, the corresponding carboxylic acids 202a and 202b were used in a Steglich esterification in the presence of N,N'-dicyclohexylcarbodiimide (DCC), (-)-menthol and 4-(dimethylamino) pyridine (DMAP), to give the (-)-menthyl derivatives 209a and 209b in 89% and 78% yield, respectively (Scheme 3.18). The chiral derivatives 209a and 209b were then used in the subsequent Regitz diazo-transfer reaction which afforded the desired chiral diazo precursor 179i and 178j in 66% and 87% yield, respectively.

Scheme 3.18: Synthesis of chiral diazo precursors 179i and 179j.

Although high yields of the α-arylated products 182q–u (76–94%) were obtained, the observed diastereomeric ratios were extremely low (up to 1.3:1 d.r.; Scheme 1.19). The best result was obtained from the reaction of 2-bromo diazo derivative 179i and 106e which afforded 182s in 96% yield with a 1.3:1 diastereomeric ratio. On the contrary, the reaction of 179i and B(C₆F₅)₃ (106d) afforded a complex mixture and the desired α-diaryl ester 182t was isolated in only 12% yield as a couple of diastereoisomers in a 1:1:1 ratio. Given the unencouraging results on inducing chirality by installing a (-)-menthyl group as a chiral auxiliary, the stereoselective α-functionalisation of menthyl esters was not further investigated.
Scheme 3.19: Stereoselective α-arylation of chiral 179h–j using 106d–e on a 0.1 mmol scale.

For further mechanistic insights, the reactions of 3,4,5-fluorinated borane 106e with diazo compounds were monitored by in situ NMR spectroscopy. In these cases, the ^1^H and ^19^F NMR spectra showed that the diazo compounds 179 were fully converted into the corresponding boron enolates 183 as a mixture of E/Z-isomers. After 30 minutes at room temperature, the reaction of 165 with one equivalent of 106e in CDCl_3 showed, by ^1^H NMR analysis, two sets of peaks for the methyl group in a 3:1 ratio (Figure 3.2). Similarly, the ^19^F NMR spectrum revealed two sets of fluorine peaks, which were also found in a 3:1 ratio. In addition, a broadened ^11^B-signal was observed at 45 ppm which supported the formation of a three-coordinated borane. The data suggested the formation of boron enolate 183a as a 3:1 ratio of E/Z-isomers, according to literature. Similar results were also observed for the reactions of 179a, 179b, 179d and 179h–j with 106e, which all showed the formation of two isomers (Table 3.1). When achiral methyl esters 179a, 179b and 179d were used as starting materials, the isomeric ratio was influenced by the steric hindrance in the ortho-position (entries 1–4). In particular, the 2-bromo phenyl derivative boron enolate 183b and the naphthyl derivative 183d were formed in a 6:1 and 3.5:1 isomeric ratio, respectively (entries 2 and 4) while the
4-trifluoromethyl boron enolate 183c was formed as a 1.5:1 mixture of isomers (entry 3). Similarly, for the (−)-methyl derivatives 183e–g (entries 5–7), the highest ratio (4:1) was registered for the most sterically hindered 2-bromoaryl substituted boron enolate 183f.

Figure 3.2: In situ $^1$H (top) and $^{19}$F NMR (bottom) spectrum of boro enolates (E/Z)-183a. The spectra show the presence of E/Z isomers as 3:1 mixture. (Major isomer = orange; Minor isomer = green).
Table 3.1: Isomer ratio for boron enolates \((E/Z)-183a–g\) measured by \(^1\)H NMR spectroscopy and crystal structure of boron enolate \(183a\). f

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting Material</th>
<th>(R^1)</th>
<th>(R^2)</th>
<th>183</th>
<th>Ratio*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>165</td>
<td>(C_6H_5)</td>
<td>Me</td>
<td>a</td>
<td>3:1</td>
</tr>
<tr>
<td>2</td>
<td>179a</td>
<td>2-Br(C_6H_4)</td>
<td>Me</td>
<td>b</td>
<td>6:1</td>
</tr>
<tr>
<td>3</td>
<td>179b</td>
<td>4-(CF(_3))(C_6H_4)</td>
<td>Me</td>
<td>c</td>
<td>1.5:1</td>
</tr>
<tr>
<td>4</td>
<td>179d</td>
<td>naphthyl</td>
<td>Me</td>
<td>d</td>
<td>3.5:1</td>
</tr>
<tr>
<td>5</td>
<td>179h</td>
<td>Me</td>
<td>(-)-menthyl</td>
<td>e</td>
<td>1.2:1</td>
</tr>
<tr>
<td>6</td>
<td>179i</td>
<td>2-Br(C_6H_4)</td>
<td>(-)-menthyl</td>
<td>f</td>
<td>4:1</td>
</tr>
<tr>
<td>7</td>
<td>179j</td>
<td>4-(CF(_3))(C_6H_4)</td>
<td>(-)-menthyl</td>
<td>g</td>
<td>1.5:1</td>
</tr>
</tbody>
</table>

General Procedure: Reactions performed on 0.1 mmol scale in CDCl\(_3\) under nitrogen atmosphere and monitored by \(^1\)H and \(^{19}\)F NMR spectroscopy; \(^a\)Only the \(E/Z\) configuration of \(183a\) was assigned according to literature.

When \(B(C_6F_5)_3\) (\(106d\)) was used, the NMR spectra were not clear enough to identify the \(E/Z\) ratio, however, regardless of the isomer for the enolate intermediate, product \(182\) were still formed in good yields after one hour upon basic work-up.

The \((E)\)-boron enolate \(183a\), derived from phenyl diazo acetate (165) and \(106e\), could be crystallised and structurally characterised, f providing further insight into the mechanism. Moreover, when \(165\) reacted with \(B(C_6F_5)_3\) (\(106d\)) at \(-40^\circ\)C, the lower reactivity led to isolation of the adduct \(210\) as a colourless crystalline solid\(^f\) (Scheme 3.20). It has been recently reported by Tang et al. that \(106d\) bonds oxygen faster than the carbon attached to the diazo moiety.\(^{36}\) For this reason, the first step is assumed to be the coordination of the triarylborane to the carbonyl group as shown by the isolation of \(210\). The latter could be in equilibrium with the intermediate \(211\) in which the boron atom coordinates to the terminal nitrogen atom of the diazo moiety. Subsequently, upon nitrogen gas expulsion, the adduct intermediate undergoes a

f. Crystallisation, characterisation and analysis for compounds \(183a\) and \(210\) were performed by D. C. M. Ould.
1,2-aryl transfer reaction leading to the intermediate 212, which is in tautomeric equilibrium with its enolate form 183, as proposed in the literature.\textsuperscript{12b,37} In the final step, the boron enolate 183 is hydrolysed to the final product 182 during the basic work-up.

\begin{center}
\textbf{Scheme 3.20:} Proposed mechanism for the 1,2-aryl transfer reaction.
\end{center}

Subsequently, attention was focussed on the development of a novel metal-free cyclisation mediated by Lewis acids.

### 3.2.2 Synthesis of \(\alpha,\alpha\)-Disubstituted Benzofuranones

As mentioned in the previous chapters, diazo carbonyl and aryl diazocarbonyl compounds have been widely used in several cyclisation reactions such as cyclopropanations\textsuperscript{38} and intramolecular C–H insertions,\textsuperscript{39} especially under catalytic conditions. In 2009, Doyle and Zhou reported the Lewis acid catalysed indole synthesis from \textit{ortho}-imino phenyl diazo acetate 213 (Scheme 3.21).\textsuperscript{40}

\begin{center}
\textbf{Scheme 3.21:} Lewis acid-catalysed synthesis of indole 214.\textsuperscript{40}
\end{center}

With the aim of investigating the reactivity of the fluorinated boranes 106d and 106e in a similar intramolecular cyclisation, the \textit{ortho}-imine derivative 213 was synthesised from 2-nitrophenylacetic acid (151; Scheme 3.22). The carboxylic acid 151 was converted
quantitatively into the corresponding methyl ester using acetyl chloride in methanol. The obtained product was directly reduced in methanol using Pd/C and hydrogen gas to afford methyl 2-aminophenylacetate (156a) in 93% yield over the two steps. The imine 169 was then obtained by reacting 156a with benzaldehyde 168. The desired diazo precursor 213 was prepared in 58% yield via Regitz diazo-transfer using p-NBSA as diazo-transfer reagent.

Scheme 3.22: Synthesis of the diazo precursor 213.

In the presence of 3,4,5-fluorinated arylborane 106e and pentafluorinated arylborane 106d (B(C$_6$F$_5$)$_3$), the ortho-imino diazo compound 213 formed the indole derivative 214 in low yields (up to 23%; Scheme 3.23). Interestingly, when 106e was used, the indoline derivative 215 was isolated as the major product in 40% yield.

Scheme 3.23: Synthesis of indole 214 and indoline 215 using 213 and boranes 106d–e.
The same reaction was investigated using 153a, synthesised as described in chapter 2. At room temperature, no reaction was observed, while the α-aryl ester 216 was isolated in 53% yield after 12 hours at 50 °C (Scheme 3.24).

![Scheme 3.24: Reaction between diazo compound 153a and borane 106e.]

With the aim to understand and explain the formation of the detosylated product 216, some more experiments were performed. In particular, the N-tosyl-N-benzylphenyl amine (218) was prepared from N-benzylphenyl amine (217), but when 218 was mixed with 106e no detosylated product 219 was observed at room temperature, nor at 50 °C, and 218 was completely recovered (Scheme 3.25). Suspecting an involvement of the boron enolate 183a in the detosylation reaction, 0.5 equivalents of 165 was added to a solution of borane 106e and 218 in CDCl₃ to form 183a. After 30 minutes at room temperature, the mixture was heated up to 50 °C for 24 hours, nevertheless, only the α-aryl ester 182f was formed while 218 did not react. The mechanism for the detosylation and the formation of 216 formation remains unclear.

![Scheme 3.25: Reactions performed to explain the formation of the detosylated product 216; NMR ratio.]

In the same context, ortho-substituted diazo ether 184a and thioether 224 were prepared to investigate the borane-mediated intramolecular cyclisation further (Scheme 3.26). The oxygen-substituted diazo precursor 184a was synthesised starting from 2-hydroxyphenylacetic acid (203) in three steps with 66% overall yield (Scheme 3.26). Firstly, the carboxylic acid 203 was converted quantitatively to the corresponding methyl...
ester using acetyl chloride in methanol. The phenolic moiety of ester 220 was benzylated to afford ether 221a in 82% yield. Finally, the diazo compound 184a was obtained in 86% yield using p-ABSA as the diazo-transfer reagent and DBU as base in acetonitrile.

On the other hand, the sulfur analogue 224 was obtained starting from 2-iodophenylacetic acid (202e; Scheme 3.27). Treatment of the in situ generated thiol 222 with benzyl bromide (160) followed by esterification using acetyl chloride in methanol afforded the desired thioether methyl acetate 223 in 22% overall yield. The final diazo precursor 224 was obtained in 40% yield by classic Regitz diazo-transfer reaction.

Interestingly, the reaction of the diazo derivative 184a with tris(3,4,5-trifluorophenyl)borane 106e lead to the formation of the rearranged lactone 185a in 79% yield in
24 hours. Analogously, the rearranged thiolactone 225 was also isolated in 55% along with the α-aryl ester 182w (38%) from the reaction of 224 with 106e after 3 days at room temperature (Scheme 2.28).

![Scheme 3.28: Reaction of diazo compounds 184a and 224 with borane 106e.](image)

The formation of the above rearranged products 185a and 225, as shown later in this chapter, is the result of a cascade reaction which starts with a 1,2-aryl transfer, followed by an aryl migration and a final lactonisation.

### 3.2.2.1 Benzofuranones Substrate Scope

The oxygen-substituted diazo compound 184a and the 3,4,5-fluorinated borane 106e were chosen as model substrates for further studies (Table 3.2). Firstly, different equivalents of diazo starting material 184a were screened while always using one equivalent of borane 106e. A much slower reaction was observed by 1H NMR analysis when a 2:1 ratio of 184a and 106e was used, with lactone 185a afforded in 45% and 63% after 24 hours or 7 days, respectively (entry 2–3). Increasing the temperature to 45 °C, did not increase the rate of lactone 185a formation, which was formed in only 55% after 24 hours (entry 4).
Table 3.2: Screening conditions for benzofuranone 185a formation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>184a (equiv.)</th>
<th>Temperature</th>
<th>Time</th>
<th>185a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>rt</td>
<td>24 h</td>
<td>72–79²</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>rt</td>
<td>24 h</td>
<td>45</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>rt</td>
<td>7 d</td>
<td>63</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>45 °C</td>
<td>24 h</td>
<td>55</td>
</tr>
</tbody>
</table>

General Procedure: Reactions performed on a 0.1 mmol scale of 106e in CDCl₃ under nitrogen atmosphere and followed by ¹H, ¹¹B and ¹⁹F NMR spectroscopy; ²Range of yields over six reactions.

The influence of the Lewis acidity on the rearrangement/cyclisation cascade was investigated next. The model substrate 184a was reacted with B(C₆F₅)₃ (106d) and the least Lewis acidic triphenyl borane (106a), and the reactions were followed by ¹H and ¹⁹F NMR spectroscopy (Scheme 3.29). In the presence of B(C₆F₅)₃ (106d), the starting material 184a was fully consumed within five minutes, however, the lactone 185b was detected only after 4 days by ¹H NMR spectroscopy and isolated in 77% yield after 7 days at room temperature.

Scheme 3.29: Screening of boranes 106a, and 106d with model diazo precursor 184a. Crystal structure for lactone 185b.<sup>g</sup>

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<sup>g</sup> Crystallisation, characterisation and analysis for lactone 185b were performed by D. C. M. Ould.
On the contrary, when the model substrate \textbf{184a} was reacted with triphenyl borane \textbf{106a}, the consumption of the starting material was slower and \textbf{184a} was still detectable after 12 hours by \textsuperscript{1}H NMR spectroscopy. After 14 days at room temperature, the desired \textbf{185c} was isolated in 21\% along with 48\% yield of the corresponding \(\alpha\)-phenyl ester \textbf{182x}. Subsequently, the influence of different substituents on the migratory aptitude was investigated. For this purpose, a library of starting materials was prepared by treating 2-hydroxyarylacetic acetates \textbf{220a–b} with sodium iodide and different aryl or alkyl halides \textbf{161} under basic reaction conditions, to afford the precursors \textbf{221a–k} in 58–88\% yield within 1–3 days (Scheme 3.30). Generally, the hydroxy-functionalisation was well-tolerated by both EWG and EDG in \textit{para}-position with \textbf{221b}, \textbf{221c}, \textbf{221d} and \textbf{221e} afforded in 87\%, 74\%, 74\% and 66\% yields, respectively. The presence of a bromo-substituent on the phenolic ring did not lower the reactivity of \textbf{220b}, which afforded \textbf{221j} in 76\% yield. More sterically hindered \textit{ortho}-substituted benzyl derivatives \textbf{221f} and \textbf{221g} were yielded also in very good yields (88\% and 81\%), as well as the allyl bromide, which afforded \textbf{221h} in 80\% yield. On the contrary, the cinnamyl derivative \textbf{221i}, as well as the \(n\)-hexyl derivative \textbf{221k}, were isolated only in moderate yields (44–58\%).

![Scheme 3.30: Preparation of ether precursors \textbf{221a–k.}](image-url)
Subsequently, the precursors 221a–k were reacted with p-ABSA and DBU in acetonitrile to obtain the desired diazo compounds 184a–k in moderate to excellent yields (Scheme 3.31). Also in this case, all electron-donating substituents, as well as electron-withdrawing substituents, in para- and meta-positions showed good reactivity affording 184b–g and 184j in 71–91% yield. The allyl-substituted compound 184h and the cinnamyl-derivative 184i were formed only in moderate yields (40–44%), while the n-hexyl substrate 184k was isolated in 84% yield.

Scheme 3.31: Preparation of diazo precursors 184a–k.

The attention moved on studying the influence of different substituents in the migrating moiety in the rearrangement (Scheme 3.32). The reaction was also found to be strongly influenced by the electronic properties of the migrating group. In particular, when an electron-poor substituent was present on the migrating benzyl group, higher reaction temperatures (50 °C) were necessary in order to observe the formation of cyclised products 185d and 185e by 1H NMR, which were then isolated in 54% and 72% yield, respectively, after 24 hours. On the other hand, the more electron-rich benzylic group was found to be faster in migrating, with the desired lactones 185g and 185i detected by 1H NMR after a few hours at room temperature and isolated in 91% and 54% yield after
16 and 72 hours, respectively. However, when 106d was employed, the enhanced reactivity led to a complex mixture of intermediates and no lactone 185h could be isolated.

Scheme 3.32: Substrate scope of the reaction diazo compounds 184b–c with boranes 106a,d,e; *Complex mixture of product formed, no desired product observed by 'H NMR spectroscopy.

The substrate scope of lactones was further expanded including moderate electron-rich benzylic and allylic migrating groups, by reacting diazo precursors 184d–k and more Lewis acidic boranes 106e and 106d as starting materials (Scheme 3.33). Generally, the reactions performed using 3,4,5-fluorinated borane 106e showed good results at room temperature in 24 hours, while B(C$_6$F$_5$)$_3$ 106d was found to afford higher yields at 50 °C. Substrates 184d, 184f, 184g and 184j bearing a moderate electron-donating group in para- or ortho-position, as well as the para-brominated benzyl derivative 184e, showed good reactivity with both boranes 106d–e, generating the desired rearranged products 185j–q and 185v in moderate to excellent yields (52–91%). Moreover, the allyl-substituted diazo precursor 184h reacted with both 106e and 106d, affording 185r and 185s in 57% and 60%, respectively. Similarly, the cinnamyl diazo derivative 184i reacted
with 106e to give 185t in 53% yield, however, the migratory aptitude of the cinnamyl group was found to be lower when reacted with 106d, affording 185u in only 33% yield.

Scheme 3.33: Extended substrate scope for 185.

A limitation was encountered when n-hexyl substituted diazo compound 184k was used, as no lactone formation was observed but the reaction stopped after the 1,2-aryl transfer step, forming 182y in 59% yield.
3.2.2.2 Mechanistic Studies

The diazo compound 184a was used as a model substrate, along with borane 106e, for an in situ NMR experiment and further mechanistic studies (Figure 3.3).

![Mechanistic Studies Diagram]

As depicted in Figure 3.3 the $^1$H NMR spectra showed that the starting material 184a was fully consumed within 5 minutes and two main intermediates, 226 (blue) and 227 (pink), were formed. When the reaction was performed for 48 hours using mesitylene as an internal standard, the boron enolate intermediate 226 (Figure 3.4, blue) was found to be fully converted into 227 (orange) within one hour. As the reaction proceeded,
intermediate 227 was consumed forming lactone 185a (yellow) and another side product, which was identified by NMR spectroscopy as the diarylboronic ether 228 (grey).

![Figure 3.4: Kinetic study for the formation of lactone 185a; mesitylene was used as the internal standard; The kinetic data are reported in Appendix B.](image)

With this information in hand, a mechanism was proposed (Scheme 3.34). It is assumed that the diazo compound 184a initially undergoes a 1,2-aryl shift with the borane 106e, leading to the boron enolate 226, with liberation of nitrogen as mentioned earlier in this chapter (see Scheme 3.20). Subsequently, the boron enolate 226 undergoes an intramolecular benzyl group migration generating 227, possibly via the seven-membered ring intermediate 229. Finally, intermediate 227 undergoes intramolecular cyclisation forming lactone 185a and diarylboronic ether 228 as the side product within 24 hours. Evidence for the formation of 226 and 227 was found by quenching the reaction after 5, 10, 15 and 20 minutes which showed the formation of the α-aryl ester 182z in 33%, 19%, 17% and 15%, 1H NMR yield, along with phenol 230a in 47%, 49%, 52% and 60% 1H NMR yield, respectively, after work-up (Table 3.3, entries 1–4). Moreover, the NMR ratio between 226 and 227 after 5 minutes (~1:1.4) reflects the ratio between 182z and 230a (1:1.35) found in the crude mixture. It was also found that increasing the temperature to 50 °C accelerated the cyclisation of intermediate 227 into lactone 185 but showed no effect on the rate of rearrangement of boron enolate 226 into 227 (entries 5–6).
Synthesis of Fluorinated Benzofuranones

Scheme 3.34: Proposed mechanism for the formation of lactone 185a.

Table 3.3: Evidence for the formation of boron enolate 226 and intermediate 227.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting Material</th>
<th>Temperature</th>
<th>Time</th>
<th>182&lt;sup&gt;a&lt;/sup&gt;</th>
<th>230&lt;sup&gt;a&lt;/sup&gt;</th>
<th>185&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>184a</td>
<td>rt</td>
<td>5 min</td>
<td>33%</td>
<td>47%</td>
<td>n.o.</td>
</tr>
<tr>
<td>2</td>
<td>184a</td>
<td>rt</td>
<td>10 min</td>
<td>19%</td>
<td>49%</td>
<td>n.o.</td>
</tr>
<tr>
<td>3</td>
<td>184a</td>
<td>rt</td>
<td>15 min</td>
<td>17%</td>
<td>52%</td>
<td>n.o.</td>
</tr>
<tr>
<td>4</td>
<td>184a</td>
<td>rt</td>
<td>20 min</td>
<td>15%</td>
<td>60%</td>
<td>n.o.</td>
</tr>
<tr>
<td>5</td>
<td>184b</td>
<td>rt</td>
<td>24 h</td>
<td>20%</td>
<td>21%</td>
<td>51%</td>
</tr>
<tr>
<td>6</td>
<td>184b</td>
<td>50 °C</td>
<td>24 h</td>
<td>25%</td>
<td>n.o.</td>
<td>57%</td>
</tr>
</tbody>
</table>

General procedure: Reactions performed on 0.1 mmol of starting material 184a using 106e for 24 h at rt; <sup>a</sup>NMR yield, mesitylene, used as internal standard; n.o. = not observed.

Despite the reactivity of the phenolic hydroxy group, some of the phenolic intermediates 230 were stable enough to be isolated and fully characterised (See Chapter 5). The
seven-membered intermediate 229 was not observed by $^1$H NMR spectroscopy, nevertheless, when 184a and 184j were reacted with 106e in a 1:1:2 ratio, only 185a and 185v were formed in a 1:1 ratio, with no crossover reaction product 185d observed, providing evidence for an intramolecular rearrangement (Figure 3.5).

![Diagram of reaction](image)

**Figure 3.5:** a) $^{19}$F NMR (376 MHz, CDCl3) of the crude reaction mixture of 184a (0.1 mmol), 184j (0.1 mmol) and 106e (0.2 mmol) at room temperature after 48 h; b) $^{19}$F NMR spectra of 185a (red) overlapped with 185v (blue); c) $^{19}$F NMR spectra of 185a (red) overlapped with 185j (green); 185j was not formed during the crossover reaction.
Although it was not possible to isolate the diaryl boronic ether 228, it was possible to find some evidence from the in situ $^{19}$F NMR spectra (Figure 3.6).

For instance, the $^{19}$F NMR for the crude mixture between the model substrate 184a and 106e showed two sets of signals for both meta- and para-$^{19}$F which were found in a 2:1 ratio, and they were linked to 228 and 185a, respectively. Similarly, the $^{19}$F NMR of the reaction between 184a, 184j and 106e showed three sets of $^{19}$F signals in a 4:1:1 ratio for 228, 185a and 185v, respectively. Moreover, the $^{11}$B NMR spectra showed a signal at 43.0 ppm which was comparable to what was reported in the literature for similar compounds.  

3.2.2.3 Stereoselective Lactonisation

It was then thought to stereoselectively drive the tandem rearrangement/lactonisation by introducing a chiral auxiliary at the ester moiety (Scheme 3.35). To install the chiral auxiliary, a Steglich esterification of 203 using DCC and DMAP was investigated first but no reaction was observed. Hence, the transesterification of 220a catalysed by Ti(OEt)$_4$ was attempted next. Despite the (−)-menthol derivative 220c, which was obtained in good yield (60%), ester 220d was obtained only in 25% and 220e was not formed. In the last two cases, lactone 231 was formed as the main product instead.
Scheme 3.35: Attempts for the synthesis of chiral esters 220c–e.

The titanium-catalysed transesterification was then carried on using the benzylated derivative 221a as a starting material (Scheme 3.36). However, under the described conditions the benzylic group was removed and only 220a and 220c were formed in 66% and 23%, respectively.

Scheme 3.36: Attempt of transesterification of 221a.

To overcome the problem, the phenolic hydroxy group of 203 was protected first, using benzyl bromide to afford the benzyl derivative 232 in 49% yield over two steps (Scheme 3.37). In this way, the chiral auxiliaries were successfully installed via Steglich esterification using 232 as starting material. Both (−)-menthol substituted 221l and (−)-borneol derivative 221m were afforded in excellent yields (95–96%), whereas the (−)-8-phenlymenthol ester 221n was obtained in 64% yield.

Scheme 3.37: An alternative route to chiral esters 221l–n.

Finally, the chiral diazo precursors 184l–n were synthesised in good yields via Regitz diazo-transfer reaction (Scheme 3.38). In this case DBU did not lead to any reaction, and a stronger base such as NaHMDS was needed. While 184l and 184m were obtained
in very good yields (83%), the diazo precursor bearing the (−)-8-phenylmenthyl substituent 184n was obtained in ~60% yield and it was not possible to separate it from the unreacted starting material 221n by flash column chromatography, hence it could only be used without further purification.

Scheme 3.38: Synthesis of chiral diazo compound 184l–n; it was not possible to separate the product from the unreacted starting material 221n.

The chiral diazo esters 184l–n were reacted with 3,4,5-fluorinated borane 106e in CDCl₃ and the reaction progress was monitored by ¹H and ¹⁹F NMR spectroscopy (Table 3.4). The (−)-menthol derivative 184l was converted to the rearranged products 230I and 230II in 86% yield as a 1:1.8 mixture of diastereomers after one hour, however, lactone 185a was not observed by NMR spectroscopy nor formed after the work-up (entry 1). The diastereomeric ratio of 230 did not change when the reaction was performed for a longer time (12 hours) and at lower temperature (−78 °C, 10 days), affording 230I and 230II in very good yields (up to 88%) but, once again, without the formation of 185a (entries 2 and 3). Nevertheless, when the reactions were carried out at 50 °C for seven days, the target 185a was formed in 45% NMR yield (entries 4 and 5). The higher temperature favoured the cyclisation of both 230 isomers forming 185a. However, it was not possible to control the selective cyclisation of only one of the two 230 isomers, and the final lactone 185a was obtained in 41–45% yield and 21–44% ee after 7 days at 50 °C (entry 4). When (−)-borneol derivative 184m was used, the diastereomeric ratio for 230 was inverted, with 230I being the major isomer formed. For the reaction performed for four days at room temperature the diastereomers 230 were formed in 83% yield with a 1:0.8 of diastereomeric ratio (entry 6). A similar result was registered for the reaction at −78 °C for 10 days (entry 8), while when the reaction was heated up at 50 °C for 3 days, 61% of 230 was converted into 185a with 29% ee (entry 7). Despite more sterically hindered, the (−)-8-phenylmenthyl ester 184n was not found to be more selective than 184l–m, with the two diastereomers 230 formed in good yields but with only 1:0.5 d.r. (entries 9 and 11). Moreover, the phenols 230I and 230II from 184n were found to be more stable and only traces of 185a were obtained after a week at 50 °C (entry 10).
Table 3.4: Enantioselective reactions between 184l–n and Lewis acid 106e.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting Material</th>
<th>T (°C)</th>
<th>Time</th>
<th>$230^1:230^1^a$</th>
<th>185a (%)$^b$</th>
<th>Yield (%)$^c$</th>
<th>185a ee (%)$^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>184l</td>
<td>rt</td>
<td>1 h</td>
<td>1 : 1.8</td>
<td>n.d.</td>
<td>86</td>
<td>n.d.</td>
</tr>
<tr>
<td>2</td>
<td>184l</td>
<td>rt</td>
<td>12 h</td>
<td>1 : 1.8</td>
<td>n.d.</td>
<td>80</td>
<td>n.d.</td>
</tr>
<tr>
<td>3</td>
<td>184l</td>
<td>−78 °C</td>
<td>10 d</td>
<td>1 : 1.6</td>
<td>n.d.</td>
<td>88</td>
<td>n.d.</td>
</tr>
<tr>
<td>4$^e$</td>
<td>184l</td>
<td>50 °C</td>
<td>5 d</td>
<td>1 : 1.2</td>
<td>41–45</td>
<td>97</td>
<td>21–44</td>
</tr>
<tr>
<td>6</td>
<td>184m</td>
<td>rt</td>
<td>4 d</td>
<td>1 : 0.8</td>
<td>traces</td>
<td>83</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>184m</td>
<td>50 °C</td>
<td>3 d</td>
<td>1 : 2.2</td>
<td>61</td>
<td>90</td>
<td>29$^f$</td>
</tr>
<tr>
<td>8</td>
<td>184m</td>
<td>−78 °C</td>
<td>10 d</td>
<td>1 : 0.8</td>
<td>n.d.</td>
<td>85</td>
<td>n.d.</td>
</tr>
<tr>
<td>9</td>
<td>184n</td>
<td>rt</td>
<td>7 d</td>
<td>1 : 0.5</td>
<td>n.d.</td>
<td>74</td>
<td>n.d.</td>
</tr>
<tr>
<td>10$^g$</td>
<td>184n</td>
<td>50 °C</td>
<td>7 d</td>
<td>1 : 0.6</td>
<td>traces</td>
<td>n.d.</td>
<td>14$^f$</td>
</tr>
<tr>
<td>11</td>
<td>184n</td>
<td>−78 °C</td>
<td>10 d</td>
<td>1 : 0.5</td>
<td>n.d.</td>
<td>84</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

General Procedure: Reactions performed on a 0.1 mmol scale of 184 and 106e (1 equiv.) in CDCl$_3$; $^a$NMR ratio; $^b$H NMR yield; $^c$Combined yield of 230$^1$, 230$^1^a$ and 185a; $^d$Determined by 2D-HPLC analysis; $^e$Range of two reactions; $^f$Opposite configuration formed; $^g$Complex mixture formed; n.d. = not determined.

Despite the mediocre selectivity observed, these preliminary results proved the concept that it is possible to induce a stereoselective rearrangement reaction by installing a chiral auxiliary, which will also be cleaved off during the same lactonisation step.
3.3 Conclusion and Outlook

In conclusion, a mild, metal free synthesis of α-aryl-substituted esters was achieved in high yields using halogenated triarylboranes. Importantly, when more Lewis acidic boranes were used on a less sterically hindered diazo compound, it was possible to use sub-stoichiometric amounts of boranes as more than one aryl group was transferred from the borane to the diazo substrate. Furthermore, a novel synthesis for asymmetric 3,3-disubstituted benzofuran-2(3H)-ones from the reaction between α-aryl-α-diazo acetates and triarylboranes was presented. After mechanistic investigations it was found that in the presence of a 2-oxy substituent on the α-aryl moiety, the initial boron enolate intermediate undergoes intramolecular rearrangement to form 3,3-disubstituted benzofuranones. To the best of my knowledge, this is the first example of lactone framework synthesis in which the C-3 position is fully substituted in a single-step under metal-free conditions.

Future work is focused on optimising the stereoselective lactone formation, expanding the substrate scope to α-diazo amides 239 as starting material (Scheme 3.39).

Preliminary results showed that the direct diazo-transfer reaction on 233 using p-ABSA (18e) or p-NBSA (18f) with DBU did not afford any product and the starting material was recovered. Stronger bases such as NaHMDS, or higher temperature (50 °C) led to decomposition, therefore, the phosphine-mediated conversion of azides into diazo
compounds was investigated as a suitable approach toward 239. The azide 235 was obtained in 60% yield over two steps, after α-bromination of 233 in the presence of NBS, followed by nucleophilic substitution with sodium azide. On the other hand, the acyl phosphine 237 was synthesised in 45% yield over three steps, from methyl acrylate (236) and diphenylphosphine. The reaction between azide 235 and phosphine 237 generated the triazene 238. A proper optimisation of the fragmentation of triazene 238, as well as installing chiral amide auxiliary, will provide access to the valuable chiral α-diazo amide 239, that can be investigated as starting materials in the stereoselective rearrangement/lactonisation reaction.
References


CHAPTER 4: Synthesis of \(N,O\)-acetals in a Flow Electrochemical Microreactor

4.1 Introduction

The \(N\)-acyl-\(N,O\)-acetal moiety is an important functionality in organic chemistry due to its presence in bioactive molecules such as the cytotoxic agents psymberin (240)\(^1\) and pederin (241; Figure 4.1).\(^2\) Moreover, it was reported by Floreancig and co-workers that the \(N,O\)-acetal moiety in 240 and 241 acts as pharmacophore, hence its presence is necessary for their bioactivity.\(^3\)

\[ \text{Figure 4.1: Examples of bioactive compounds bearing } N\text{-acyl-}N,O\text{-acetals.} \]

Besides being useful building blocks in organic chemistry, \(N\)-acyl-\(N,O\)-acetals are also used as valuable surrogates of unstable \(N\)-acylimines 243 (Scheme 4.1).\(^4\) While \(N\)-acylimines 243 are susceptible to hydrolysis in the presence of water, \(N\)-acyl-\(N,O\)-acetals 242 are air and moisture-stable. They can be readily activated by Lewis or Brønsted acids to generate reactive \(N\)-acylimines 243, which then undergo nucleophilic substitution,\(^4\) or transition metal catalysed cross-coupling.\(^5\)

\[ \text{Scheme 4.1: Utility of } N,O\text{-acetals 242 in organic synthesis.} \]

For these reasons, several protocols have been reported for the preparation of such structures. Retrosynthetically, the \(N\)-acylated \(N,O\)-acetals 242 can be generated from
amides 246, condensed with aldehydes 247, from nitriles 248 or from N-acyl amino acid derivatives 249 (Scheme 4.2).


One of the classic protocols for their synthesis is the Katritzky’s benzotriazole method, where an amide 246 condenses with an aldehyde 247 to generate an imine in situ that undergoes nucleophilic attack by benzotriazole 250 forming amide 251 (Scheme 4.3a). This α-substituted amide 251 is then treated with sodium alkoxides to install the alkoxy group on the molecule, giving the N,O-acetal 242. Similarly, amide 246 and aldehyde 247 can be mixed with the benzenesulfinic acid salt 252 to afford the α-amido sulfone 253 as a N,O-acetal precursor (Scheme 4.3c). However, the substrate scope for these reactions is limited to aryl aldehydes, as the exclusive formation of enamides 254 was observed when alkyl-aldehyde substrates were employed.

More recently, Wen and co-workers reported a concise procedure mediated by titanium ethoxide, in which \(N\)-acyl-\(O\)-ethyl \(N,O\)-acetals 242 are synthesised in one single step starting from the amide 246 and the aldehyde 247, expanding the substrate scope to both aromatic and aliphatic aldehydes 247 (Scheme 4.3b).\(^9\) An additional method is the hydrozirconation of nitriles 248, which leads to 242 after acylation and nucleophilic addition of alcohols to the imine intermediate 255 in a three step one-pot process (Scheme 4.3d).\(^10\)

The \(N,O\)-acetals 242 can be also prepared by decarboxylative oxidation of amino acid derivatives 249. For instance, the hypervalent iodine(III) reagent 256 can be used to induce an oxidative fragmentation of 249 (Scheme 4.4).\(^11\) In this case, 249 reacts with the hypervalent iodine(III) reagent 256 generating the five-membered ring 257 after two consecutive ligand exchanges. The latter undergoes oxidative cleavage releasing \(\text{CO}_2\) and forming the imine 258, which leads to the \(N\)-acyl-\(O\)-methyl \(N,O\)-acetal 242 upon addition of methanol.

\[
\begin{align*}
\text{O} & \quad \text{CO}_2\text{H} \\
\text{R}^1 & \quad \text{N} & \quad 249 \\
\text{C}_6\text{F}_5\text{I}(\text{OCOCF}_3)_2 & \quad 256 \\
\text{R}^2 & \quad \text{O} & \quad \text{N} & \quad 257 \\
\text{Ar} & \quad +\text{H}^+ & \quad -\text{CO}_2 \\
\text{MeOH} & \quad \text{R}^1 & \quad \text{N} & \quad \text{Me} & \quad 242
\end{align*}
\]

**Scheme 4.4:** Oxidative fragmentation of \(\alpha\)-amino acids 249 using iodine(III) reagent 256.

In addition to hypervalent iodine(III) compounds, electricity can be used as a tool to prepare \(N,O\)-acetals from amino acid derivatives. For example, Miyoshi *et al.* reported the electrochemical alkoxylation of proline derivatives 259 via non-Kolbe electrolysis (Scheme 4.5).\(^12\) After the electrolysis of the \(N\)-acylprolines 259 in methanol with sodium methoxide acting as supporting electrolyte and base, the \(N,O\)-acetals 260 were afforded in very good to excellent yields.

\[
\begin{align*}
\text{N} & \quad \text{CO}_2\text{H} \\
\text{COR} & \quad -2\text{e}^- \\
\text{N} & \quad \text{OMe} \\
\text{COR} & \quad \text{NaOMe} \\
\text{MeOH} & \quad 259 \\
\text{N} & \quad \text{OMe} \\
\text{COR} & \quad 260 \\
8 \text{ examples} & \quad 80 - 96\%
\end{align*}
\]

**Scheme 4.5:** Electrochemical synthesis of \(N\)-acyl-\(N,O\)-acetals 260.

Mechanistically, in a non-Kolbe oxidation,\(^13\) sometimes referred to as the Hofer-Moest reaction,\(^14\) the \(N\)-acylated amino acid 261 undergoes a one-electron oxidation followed by decarboxylation, affording the radical intermediate 263 (Scheme 4.6). A second
one-electron oxidation leads to the formation of the N-acyliminium ion 265. The intermediate 265 is then trapped by a nucleophile affording the final product 266. Conversely, a classic Kolbe reaction affords the dimerised product 270 upon anodic decarboxylation of the carboxylate 268 and consequent coupling of two of the formed radicals 269. Another electrochemical reaction which affords N,O-acetal as products is the anodic oxidation of unfunctionalised amides 271, also known as the Shono oxidation. Similar to the non-Kolbe reaction, the starting material 271 undergoes a two-electron oxidation forming the N-acyliminium ion intermediate 273, which gets trapped by a nucleophile affording the final product 274.

**Non-Kolbe Oxidation:**

\[
\begin{align*}
261 & \quad \text{Y = NH, NR}^2, O \\
\text{R}^1 & \quad \text{Y} \\
\text{R}^1 & \quad \text{Y} \\
\text{R}^1 & \quad \text{Y} \\
\text{R}^1 & \quad \text{Y} \\
\end{align*}
\]

**Kolbe Oxidation:**

\[
\begin{align*}
267 & \quad \text{R}^1 \text{O} \\
\text{R}^1 & \quad \text{O} \\
\text{R}^1 & \quad \text{O} \\
\text{R}^1 & \quad \text{O} \\
\text{R}^1 & \quad \text{O} \\
\end{align*}
\]

**Shono Oxidation:**

\[
\begin{align*}
271 & \quad \text{R}^1 \text{N}^+ \text{R}^3 \\
\text{R}^1 & \quad \text{N}^+ \text{R}^3 \\
\text{R}^1 & \quad \text{N}^+ \text{R}^3 \\
\text{R}^1 & \quad \text{N}^+ \text{R}^3 \\
\text{R}^1 & \quad \text{N}^+ \text{R}^3 \\
\end{align*}
\]

**Scheme 4.6:** Example of anodic oxidations: non-Kolbe, Kolbe and Shono oxidation.

The Shono oxidation has been widely used as a test reaction, since it was found to be very successful for the synthesis of N,O-acetals 260. Recently, the Wirth group used the Ion electrochemical reactor designed by Vapourtec to perform a regioselective methoxylation of the pyrrolidine 259 to the monoalkoxylated compound 260 (up to 86% yield) or the dialkoxylated product 275 (up to 83% yield), applying charges of 2 F or 8 F, respectively (Scheme 4.7).
One of the advantages of flow electrochemical microreactor is the reduced distance between the anode and the cathode, which allows to minimise or even eliminate the addition of wasteful supporting electrolytes. Moreover, the use of flow microchannels improves the mass transfer, and the higher electrode surface-to-reactor volume allows the substrate to reach the reaction surface more easily compared to a batch reactor. Due to the bigger active surface available, a larger volume of solution containing the starting material gets in contact with the electrode, leading to shorter reaction times. Furthermore, as the solution is constantly pumped through the reactor, as soon the substrate reacts, the product is flushed out of the reactor avoiding side reactions.

Given the presence of asymmetric $N,O$-acetal motifs in natural products and their function as synthons, there is a strong interest in developing stereoselective methods towards such structures. One approach is based on the employment of chiral Lewis or Brønsted acids to mediate the asymmetric $N,O$-acetalisation. Another method is the stereoselective electrochemical oxidation of $\alpha$-amino acids derivatives via memory of chirality. It is well-known that an enantiopure starting material such as \ref{276}, which undergoes a chemical transformation passing via an achiral intermediate such as a carbocation $sp^2$ \ref{277}, generates the final product \ref{278} as a racemic mixture (Scheme 4.8).

However, in some cases, the chirality in the starting material \ref{276} bearing a chiral $sp^3$ carbon is preserved in the product \ref{278}, although the reaction proceeds through an achiral intermediate such as a carbanion, a carbenium ion, or a monoradical or a biradical species. This phenomenon carries the name “memory of chirality” and, in order to occur, some specific requirements need to be satisfied (Scheme 4.9).
Firstly, the chiral substrate undergoes a reaction at the stereogenic centre, which generates two conformationally chiral intermediates (M) and (P), and the (M) intermediate (a) is formed faster than the (P)-intermediate. Additionally, the racemisation rate between the two chiral intermediates (b) needs to be slower than the conversion of the (M) intermediate into the (R)-product (c), which must occur with high stereospecificity. The first example of memory of chirality via carbenium ion chemistry was reported by Onomura et al. in 2000 (Scheme 4.10). They observed that when L-serine derivative was electrochemically oxidised at $-20 \, ^\circ\mathrm{C}$ with 1.2 equivalents of NaOMe, using platinum as the cathode and graphite as the anode, the optically active $\alpha$-methoxylated product was afforded in good yield and with 39% of enantiomeric excess for the (S)-isomer. Interestingly, among all the investigated anode materials, only graphite produced optically active 280. In particular, the substitution of the carboxyl group occurs with an inversion mechanism, possibly due to a specific interaction between the acyliminium ion intermediate and a graphite anode. Although the exact role of the anode material on the memory of chirality it is still not clear, an interaction between the N-acyliminium ion intermediate 265 (Scheme 4.6) and the graphite surface was suspected. When N-(2-phenyl)benzyl serine derivative 281 was used for the non-Kolbe oxidation under similar conditions, the $\alpha$-methoxylation occurred with retention of configuration affording the $N,O$-acetal (R)-282 in moderate yields but with 72% and 83% ee when graphite or platinum were used as the anode, respectively (Scheme 4.11).
Scheme 4.11: Highly enantioselective N,O-acetal 282 formation via non-Kolbe electrolysis.

The same group, with the aim to explain the retained configuration, proposed a mechanism and reported 281 bearing the ortho-phenyl substituent underneath the carboxylic group as the most stable conformation (Scheme 4.12). According to their proposal, due to the restricted rotation caused by the bulky ortho-phenyl substituent, the iminium ion intermediate 283, formed upon decarboxylation, presents one face more available towards nucleophilic attack than the other. Hence the syn-addition is preferred, explaining the major formation of product (R)-282.

Scheme 4.12: Proposed mechanism for the memory of chirality with retention of configuration.

When the non-Kolbe reaction is performed in a batch electrochemical cell with L-proline derivative 259, the chirality is completely lost and the N,O-acetal 260 is obtained as a racemate (Scheme 4.13). However, Onomura and co-workers found that the N-(2-phenyl)-benzoyl derivative 284 was able to retain some chirality, affording 285 in 72% yield and 46% ee.
In the following section of this thesis, the non-Kolbe oxidation of L-proline derivatives were translated into a flow electrochemical reactor setup, with the aim of optimising the memory of chirality on L-proline derivatives as well as L-acyclic amino acids derivatives. Moreover, the flow microreactor was coupled to a 2D-HPLC system for a faster analysis. Some of the following results are published in *Chem. Eur. J.* 2019, 25,16230–16235.

### 4.1.1 Continuous Flow Setup and 2D-HPLC

As illustrated in Figure 4.2, the entire continuous flow setup used for this project consisted of a syringe pump, an electrochemical microreactor connected to a power supply, a cooling system, an injecting valve (switching valve) and a 2D-HPLC.
The microreactor used here was the integrated version of the ion electrochemical reactor by Vapourtec (Figure 4.3). The reactor is composed by two electrode-carrier plates (1) supplied with a temperature sensor (2) and incorporated heat pipes (3) for temperature control. The ion easy-clamp™ (4) holds the two electrode-carriers together allowing operations at higher pressures (up to 5 bar). Furthermore, a FEP spacer (0.5 mm thick; 5) keeps the electrodes apart and defines the reactor channel (600 µL). The two electrodes were placed on the carriers with the FEP spacer in between, and then pressed together with the clamp. When electrodes that were supplied as a thin foil (i.e. Pt, Ni, etc.) were required, a stainless steel plate (6) was used as a backing plate to ensure the right thickness that fits into the ion reactor and ensure a good sealing. Once assembled, the ion reactor was located into a special housing (7) and connected with a Vapourtec E-Series. The outlet of the reactor was then connected to a 6-port switching valve bearing a 2 µL sample loop, which was used for the online analysis.

Figure 4.3: Integrated version of ion electrochemical microreactor; a) disassembled reactor; b) operating reactor. The system is composed of: 1) two electrode-carrier plates; 2) a temperature sensor; 3) heat pipes for precise temperature control; 4) ion easy-clamp™; 5) FEP spacer; 6) stainless steel plates; 7) housing.

4.1.2 2D-HPLC

The liquid-liquid bidimensional-chromatography (2D-LC) represents a separating technique in which the injected sample is subjected to two different separation steps. This can be achieved by using two different chromatographic columns installed in sequence with each other. The eluent is transferred from the first column into the second column, which presents a different stationary phase. Hence the elutes that were poorly resolved in the first separation can be fully separated during the second one.26

The concept of liquid-liquid bidimensional separation techniques was introduced for the first time by Dent and co-workers in 1947, when they reported the separation of 19 amino acids extracted from a potato using two-dimensional paper chromatography.27 However, the very first 2D-LC instrument was only developed in 1978 by Erin and Frei28 and it was
until the late 1990s that the interest towards this new technique started increasing. Nowadays, 2D-HPLC is a powerful tool to resolve complex mixtures without greatly increasing the analysis time. This technique finds application in proteomics,\textsuperscript{29} metabolomics\textsuperscript{30} and in the pharmaceutical field.\textsuperscript{31}

The 2D-HPLC apparatus used in this work is an Agilent Infinity 1290 2D-LC Solution, which consists of two HPLC pumps and two detectors, one for each dimension (1\textsuperscript{D}), an autosampler, a column oven and a set of three valves: two 14-port valves (deck A and deck B) and one 6-port valve for sampling eluent from the first dimension into the second dimension (sampler; Figure 4.4).

\textbf{Figure 4.4}: Picture of the Agilent Infinity 1290 2D-LC solution system (top) and simplified scheme of a 2D-LC system (bottom).

To perform an “offline” analysis, the samples are loaded in the autosampler, whereas for an “online” analysis a small volume of reaction mixture is injected using a 6-port valve
supplied with a sample loop and controlled by contact closure. Next, the ¹D pump pumps the sample through the ¹D column and the ¹D detector, generating a ¹D chromatogram. The ¹D eluent then reaches the sampler that, when triggered, controls which volumes from the ¹D will be analysed in the second dimension (²D) and which will go into the waste (Figure 4.5). Before going into the waste, the solution flows through deck A, continuously loading one of six loops with ¹D solution. At the same time, the ²D pump continuously flows solvent system through the valve and deck B without mixing with the ¹D solvent system. When a specific time or threshold is reached, the valve switches from the loading to the analysis position, which enables the ²D solvent system to carry the volume, contained in the loop, from deck A to the ²D column for the analysis. The amount of ¹D solvent system (40 µL) which is injected in the second dimension, can be neglected and does not contaminate the ²D eluent.

![Figure 4.5: Comparison between the “loading” and the “analysis” position of the sampler.](image)

Due to the presence of empty loops in both deck A and B, this system provides the opportunity to "park" volumes in the empty loops and analyse them in a second moment, while the second dimension is busy with a previous sample (Figure 4.6).
There are various ways to perform a two-dimensional analysis, depending on the reason why a 2D-LC is chosen as the separating technique. The different methods can be divided into two main groups: the comprehensive 2D-LC, also known as LC×LC, and the heart-cutting 2D-LC also known as LC-LC. During comprehensive 2D-LC (LC×LC), the 1D eluent is continuously sampled and transferred to the second dimension, providing both 1D and 2D analysis for the whole eluent. This technique finds application in the analysis of natural occurring complex mixture such as natural extracts or protein mixtures. In order to do so, the 2D analysis time must be equal or faster than the sampling time to avoid washing away samples not yet analysed. On the contrary, in the heart-cutting method (LC-LC) and multiple heart-cutting method (mLC-LC), only a few selected segments are injected into the second dimension, hence there is no time-limit for the 2D analysis. This method works better for less complex samples containing compounds with similar retention behaviour such as a mixture of isomers.

Although multi-dimensional liquid chromatography has received a lot of attention in the past decade, most applications use mainly comprehensive reverse-phase liquid chromatography (RP-LC) for highly complex mixtures, while the protocols using a chiral stationary phase in the second dimension for enantiomeric resolution are still limited. In the following work an example of normal phase heart-cutting analysis using an achiral stationary phase in the 1D and a chiral stationary phase in the 2D is presented.
4.2 Results and Discussion

In this last chapter, the stereoselective synthesis of \(N,O\)-acetals 285 is presented (Scheme 4.14). The electrochemical oxidation of the \(N\)-protected amino acids 284 was carried out using a flow electrochemical microreactor coupled to a 2D-HPLC for online analysis. The performance of this reaction was optimised in terms of yield and the enantioselectivity using a DoE approach.

\[
\text{Scheme 4.14: Overview of the project for the electrochemical stereoselective synthesis of } N,O\text{-acetals 267 via memory of chirality.}
\]

4.2.1 Synthesis of the Starting Materials and Racemates

For the synthesis of the protecting group precursor 288a, 9-fluorenone 286 was hydrolysed using potassium hydroxide in refluxing xylene, affording the biphenyl carboxylic acid 287a in 86% yield (Scheme 4.15). Treatment of 287a or the commercially available 287b with thionyl chloride and a catalytic amount of DMF, afforded the acyl chlorides 288a–b, which were used directly for the \(N\)-protection step without further purification.

\[
\text{Scheme 4.15: Synthesis of } N\text{-protecting group precursors 288a–b.}
\]
The chiral $N$-protected starting materials ($S$)-$284a$–$f$ were then prepared in very good yields from the reaction of acyl chlorides $288a$–$b$ and L-amino acids under basic conditions (Scheme 4.16).

In order to find the optimal conditions for the 2D-HPLC analysis, the racemates of the final products $N,O$-acetals $285$ were prepared. For the synthesis of the racemic $N$-acyl 2-methoxypyrrolidine $285a$ several approaches were investigated (Scheme 4.17). First, the flow $\alpha$-methoxylation of the $N$-Boc protected amine $290$ was carried out, following a literature procedure. $17c$ Pyrrolidine $289$ was quantitatively protected upon treatment with di-tert-butyl dicarbonate (Boc$_2$O) in the presence of a catalytic amount of DMAP. The $N$-Boc pyrrolidine $290$ was then subjected to a Shono oxidation conditions in a flow microreactor, affording the $\alpha$-methoxyl $N$-Boc pyrrolidine $291$ also in excellent yield. However, after deprotection with trifluoroacetic acid (TFA), the $\alpha$-methoxyl pyrrolidine $292$ was not isolated nor detected by NMR spectroscopy, and the starting material $291$ was not recovered.
Scheme 4.17: First attempts for the synthesis of racemic 285a.

Alternatively, the Shono oxidation was carried out on the already acylated pyrrolidines 293a–b bearing the carboxy biphenyl protecting group (Scheme 4.18).

Scheme 4.18: Second attempt for the synthesis of racemic 285a–d.

The acyl chlorides 288a–b were prepared as shown in Scheme 4.15 then reacted with pyrrolidine 289 affording 293a–b in good yields. Subsequently, N-acyl pyrrolidines 293a–b (0.1 M) were dissolved in methanol, ethanol or propan-2-ol and oxidised in the Ion electrochemical reactor using platinum as the cathode and graphite as the anode with NEt₄BF₄ (0.02 M) as supporting electrolyte and base. The desired N,O-acetals 285a–d were found only in traces together with unreacted 293a–b, although a gas formation was observed, probably as consequence of the oxidation of the solvent as side reaction. When acyclic N-protected amines were investigated in the above-mentioned
Shono oxidations, no product formation was observed. Using an alternative method, the racemic N,O-acetals 285e–h were afforded in moderate to good yields via non-Kolbe reaction from the N-protected amino acid 284c–f, synthesised in good yields from the reaction of acyl chloride 288a and D/L-alanine, D/L-valine, and D/L-phenylalanine, respectively (Scheme 4.19).

\[
\text{Scheme 4.19: Synthesis of racemic N,O-acetals 285e–h.}
\]

4.2.2 Optimisation of Asymmetric non-Kolbe Oxidation

As previously mentioned in this chapter (Scheme 4.13), the non-Kolbe oxidations on chiral N-protected amino acids derivatives were found to occur with memory of chirality. With the aim of investigating the memory of chirality of a non-Kolbe oxidation in a flow electrochemical microreactor, some optimisation studies were carried out using the chiral proline derivative \((S)-284a\) as model substrate.

When \((S)-284a\) was reacted in a batch electrochemical cell,\(^a\) the N,O-acetal 285a was formed in poor to moderate yields (up to 47%) and moderate stereoselectivity (up to 40% ee) when platinum was used as the anode (Table 4.1). The stereoselectivity was found to be influenced by the temperature. When the reactions were performed at \(-30 \, ^\circ\text{C}\), the desired product 285a was formed in 15% yield and 40% ee (entry 2). Moreover, the use of the sodium methoxide was found to be essential for the reaction in a batch electrochemical cell, as no reaction was observed without base and \((S)-284a\) was recovered.

\(^a\) The reactions in batch were performed by Rossana Cicala.
Table 4.1: Non-Kolbe electrolysis of (S)-284a to the N,O-acetal 285a in a batch electrochemical cell.\textsuperscript{b}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (equiv.)</th>
<th>T (°C)</th>
<th>285a yield (%)\textsuperscript{a}</th>
<th>285a ee (%)\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaOMe (10)</td>
<td>rt</td>
<td>47</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>NaOMe (10)</td>
<td>−30</td>
<td>15</td>
<td>40</td>
</tr>
</tbody>
</table>

General Procedure: Reactions performed on 0.5 mmol of (S)-284a using 2 F over 1 h using 1 cm\textsuperscript{2} electrodes; \textsuperscript{a}Isolated yield; \textsuperscript{b}Determined by chiral HPLC; \textsuperscript{c}Only starting material was recovered, no current observed; \textsuperscript{d}No desired product formed, degradation of (S)-284a observed.

Some pilot experiments were performed using the continuous flow system in order to select the factors and the corresponding ranges to be used in the DoE (Table 4.2). When platinum was used as the anode with no supporting electrolyte or base, product 285a was formed in poor yields (up to 12% HPLC yield) but with 32% ee which was increased to 43% ee when the reaction was carried out at −10 °C (entries 1–4). When the platinum was replaced with a graphite electrode as the anode, the N,O-acetal 285a was formed in 51% HPLC yield and 31% ee. A lower concentration (6.2 mM) or a lower flow-rate (0.05 mL•min\textsuperscript{−1}) reduced the yield drastically (as low as 12%, entries 5–6), while at a higher flow-rate (0.2 mL•min\textsuperscript{−1}) 285a was formed in 67% HPLC yield, but no effect was observed on the memory of chirality (entries 7–8). Furthermore, the reaction was found to be quantitative when the charge was doubled from 2 F to 4 F without side product formation and without losing memory of chirality (entry 9). It is worth pointing out that most of the Kolbe or non-Kolbe reactions need a base to form the active carboxylate species in order to form the final products.\textsuperscript{34} Therefore, it is remarkable that quantitative yields were observed here without a base. It is suspected that in the microreactor, given the miniaturised flow conditions, the methoxide formed at the cathode was sufficient to deprotonate the starting carboxylic acid and initiate the reaction without additional base. Subsequently, different electrode materials were screened as the anode. Platinum coated on niobium showed the lowest yield with only 1% of 285a formed although with 37% ee (entry 10). Surprisingly, when glassy carbon was used the product was formed in only 39% HPLC yield but with 65% ee of “memorised chirality” (entry 11). Other carbon-based electrodes such as

\textsuperscript{b} The reactions in batch shown in Table 4.1 were performed by Rossana Cicala.
Panasonic® Carbon, carbon on PTFE or boron doped diamond (BDD) electrodes did not show much improvements in terms of yields and stereoselectivities (entries 12–14).

Table 4.2: Pilot experiments for the asymmetric non-Kolbe oxidation of (S)-284a to 285a in a flow microreactor using online 2D-HPLC analysis.

![Diagram of the reaction](attachment:image.png)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Anode</th>
<th>Cathode</th>
<th>Flow-rate (mL·min⁻¹)</th>
<th>Charge (F)</th>
<th>285a (%)ᵃ</th>
<th>285a ee (%)ᵇ</th>
</tr>
</thead>
<tbody>
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<td>Pt</td>
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<td>Pt</td>
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</table>

General Procedure: Reactions performed using different electrodes, FEP spacer 0.5mm thickness; reactor volume: 600 µL, working area: 12 cm², with no additional supporting electrolyte or base; ᵃHPLC yield (¹D) with α,α,α-trifluorotoluene as internal standard; ᵇDetermined by chiral HPLC (²D); ᵈReaction performed at −10 °C; ᵉReaction performed on a 6.2 mM solution of (S)-284a; ᵊNo reaction observed.
At last, different electrodes materials were screened at the cathode using platinum as the anode (entries 15–17). Although 285a was formed with more than 40% ee, the yields were very low even when the reactions were performed at 0.2 mL•min⁻¹ and with 4 F. Hence, the platinum electrode was chosen as the cathode for the rest of the studies whereas the anode material was included in the design as one of the factors.

After this preliminary screening, the following two-level fractional factorial design (FFD 2⁵⁻¹; see Appendix A for glossary) was designed with four numeric factors (temperature, charge, flow-rate and concentration of (S)-284a) and one categoric factor (anode material). Among all the screened anodes, graphite was chosen for the better yields, while the glassy carbon was selected because despite the lower yields it was found to generate 285a with the highest memory of chirality giving the highest ee. The two responses (yield and ee%) were measured using online 2D-HPLC analysis. In particular, the yield was measured in the first dimension on an achiral stationary phase, while the enantiomeric excess was measured in the second dimension on a chiral stationary phase. The whole design was composed of a total of 24 experiments, 16 factorial points and 8 central points, and they were performed in a random order to minimise nuisance (see Appendix A). Once the acquired data were fitted into the model, the analysis of variance (ANOVA) was carried out next. The models were found to be very complex, with numerous significant terms and some anomalies in the diagnostic plots. From one of the influential plots (Cook’s distance, Figure 4.7), two factorial points (Table 4.3, entries 1 and 3) with very low yields and enantioselectivities were found to be outliers (see Appendix A), increasing the degree of complexity.

**Figure 4.7:** Cook’s distance plot showing outliers. The different yields are represented by a scale of colours from blue (= low yields) to red (= high yields).
After several repeats of the two factorial points and a careful evaluation, it was decided to not include these two experiments (Table 4.3, entries 1 and 3) in the analysis, considering they were leading into a less interesting region of the chemical space (low yield and low enantioselectivity).

Table 4.3: Matrix for the FFD 2\(^5\)-1 with results. Factor generator for E = A*B*C*D.

<table>
<thead>
<tr>
<th>Std</th>
<th>Run order</th>
<th>A: (S)-284a (mM)</th>
<th>B: Anode</th>
<th>C: Flow rate (mL/min(^{-1}))</th>
<th>D: Charge (F)</th>
<th>E: T (°C)</th>
<th>Yield (%)(^a)</th>
<th>ee (%)(^b)</th>
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<td>2</td>
<td>–10</td>
<td>20</td>
<td>34</td>
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</tbody>
</table>

General Procedure: Reactions were performed according to Table 4.3; \(^a\)HPLC yield (\(^1\)D) with \(\alpha,\alpha,\alpha\)-trifluorotoluene as internal standard; \(^b\)Determined by chiral HPLC (\(^2\)D); Light blue = these experiments were not included in the ANOVA.

Although removing two factorial points may compromise the spot-prediction ability of the model, it was possible to simplify the model and have scientifically meaningful results (Figure 4.8). From the pareto charts (see Appendix A) it emerged that the most significant parameter for the yield of the electrochemical oxidation was the charge (D; Figure 4.8a). Although a charge of 2 F should be sufficient for two consecutive single
electron-transfer reactions, the desired methoxylated amide 285a was obtained in good to quantitative yields (>80%) when a charge of 4 F was applied. Better yields were observed when graphite was used instead of glassy carbon as the anode, which was also suggested by the ANOVA, identifying a minor effect of the type of anode (B) on the yield (Figure 4.8a).

![Figure 4.8: Pareto charts showing main effects for the responses a) yield % and b) ee%.

These effects can also be visualised in the 3D-surface plots for the first response (yield) with the concentration of (S)-284a and the charge as variables, and the flow rate as well as the temperature fixed (Figure 4.9). First of all, both 3D-surfaces for the yield present sharp slopes which indicates a yield improvement when the number of electrons was increased from 2 F to 4 F. Secondly, when the glassy carbon was selected as the anode, the whole surface shifted toward lower yields, highlighting the effect of the anode material on the N,O-acetal formation.

![Figure 4.9: 3D-surface plots of the yield of 285a when a) graphite or b) glassy carbon was used in the non-Kolbe oxidation at 23 °C and 0.2 mL•min⁻¹.](image)
On the other hand, the most critical factor for the second response (enantioselectivity) was the type of material used as anode. In particular, when the oxidation of \((S)-284a\) was performed using glassy carbon at 0.2 mL min\(^{-1}\), \(285a\) was afforded in moderate (48% \(ee\)) to good enantioselectivity (70% \(ee\)), whereas graphite showed only moderate selectivity (up to 31% \(ee\)). Although the relation between anode material and memory of chirality is still unclear, this result is in agreement with previous studies in which an interaction between the carbenium ion and the electrode surface was suspected.\(^{22a}\)

On the other hand, the temperature itself (E) was not found to be significant for the memory of chirality of this transformation, in contrast with what was observed for the electrolysis in batch.\(^{22}\) A moderate two-factor interaction (2FI) between type of anode and temperature (BE) was observed. Figure 4.10 shows the 3D-surface plots for the second response (\(% ee\)) with temperature and flow-rate as variable and charge and the concentration of \((S)-284a\) as fixed values. When graphite is selected, the surface slope remains relatively flat as the temperature decreases (Figure 4.10a), whereas by selecting the glassy carbon as anode, the surface shifts to generally better \(ee\)% and the memory of chirality increases as the temperature decreases (Figure 4.10b). Hence, the temperature effect changes depending on the anodic electrode.

![Figure 4.10](image)

**Figure 4.10**: 3D-surface plots of the \(ee\) in % of \(285a\) when a) graphite or b) glassy carbon was used in the non-Kolbe oxidation performed with 12.5 mM of \((S)-284a\) and 4 F.

Although the spot-prediction ability of these models had been compromised by ignoring two factorial points, the simplified model was still good enough to provide a set of optimal conditions, guiding towards the “sweet spot” (Table 4.4). Glassy carbon was chosen as optimal anode in order to have the highest memory of chirality, and the reactions were performed on a 12.5 mM solution of \((S)-284a\) in methanol pumped at 0.2 mL mol\(^{-1}\). When a charge of 2 F was used at room temperature or at \(-10^\circ C\), the \(N,O\)-acetal \(285a\) was formed in 55% and 60% yield and with 64% and 70% of enantiomeric excess, respectively (entries 1 and 2). The yields were increased up to 73% and 77% by using
3 F and 4 F, respectively, in good stereoselectivity (>60% ee; entries 3–4). Furthermore, the desired product 285a was formed in 81% HPLC yield and with 66% ee when (S)-284a was oxidised at −10 °C (entry 5).

### Table 4.4: Optimised conditions for the asymmetric non-Kolbe oxidation of (S)-284a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Charge (F)</th>
<th>Temperature (°C)</th>
<th>285a (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>285a ee%&lt;sup&gt;b&lt;/sup&gt;</th>
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<td>5</td>
<td>4</td>
<td>−10</td>
<td>81</td>
<td>66</td>
</tr>
</tbody>
</table>

*General Procedure:* Reactions were performed using a glassy carbon anode and a Pt cathode, a FEP spacer (0.5 mm thickness; reactor volume: 600 µL; working area: 12 cm²) with no additional supporting electrolyte or base; <sup>a</sup>HPLC yield (1D) with α,α,α-trifluorotoluene as internal standard; <sup>b</sup>Determined by chiral HPLC (2D).

With these results in hand other anode materials were screened under the optimised conditions at different temperatures (Table 4.5).

### Table 4.5: Further screening of the anode influence on the anodic oxidation of (S)-284a to N,O-acetal 285a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Anode</th>
<th>Temperature (°C)</th>
<th>285a (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>285a ee%&lt;sup&gt;b&lt;/sup&gt;</th>
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<tbody>
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</tbody>
</table>

*General Procedure:* Reactions were performed on a 13 mM solution of (S)-284a with 4 F of charge, different electrodes as anode and Pt cathode electrodes, a FEP spacer (0.5 mm thickness; reactor volume: 600 µL; working area: 12 cm²) with no additional supporting electrolyte or base; <sup>a</sup>HPLC yield (1D) with α,α,α-trifluorotoluene as internal standard; <sup>b</sup>Determined by chiral HPLC (2D); BDD = boron doped diamond.
The platinum and platinum coated electrodes showed very poor yields even using higher charge, however the memory of chirality was improved to 48–54% ee compared to the ~30% ee observed in the initial pilot study (see Table 4.2). Moreover, except the platinum coated niobium, which was not affected by the temperature (Table 4.5, entries 4–5), a small improvement in ee% was observed for the platinum and the platinum coated titanium electrode. However, among all anodes, BDD was found to almost as efficient as the glassy carbon (entries 9–11). In fact, BDD formed the desired N,O-acetal 285a in good yields (up to 58%) and in 57%, 58% and 60% ee for reactions performed at 20 °C, 0 °C and −10 °C, respectively.

In conclusion, the final screening performed in a flow microreactor confirmed that, the memory of chirality was mainly influenced by the anodic material. However, it seemed to be less influenced by lower temperatures than what was observed in the batch process. For optimal memory of chirality results, the glassy carbon electrode was chosen as anodic material for future studies over the BDD because the latter was found to promote side reactions.

### 4.2.3 Substrate Scope

With the aim to study the substrate scope and to calculate the isolated yields, different N-protected amino acids (S)-284a–f (see Scheme 4.16) were subjected to the electrochemical oxidation using the optimal conditions suggested by the DoE.

Firstly, the N-acyl amino acids were oxidised using graphite as optimal anodic material for the yield, with 2 F or 4 F of charge at room temperature (Scheme 4.20). The solutions of starting material were pumped at 0.2 mL min⁻¹ and the microreactor was kept at 23 °C. The stream were equilibrated for ~20 minutes before being collected for 1.5 hours, then the N,O-acetals 285a–h were isolated and the ee% was measured offline on the pure products. The model N,O-acetal 285a and the 2-methoxyphenyl derivative 285b were isolated in 56% and 62% yield, when 2 F were applied, and in 90% and 87% yield, when 4 F were used instead. When the electrolysis of (S)-284a was performed using 2 F in ethanol or propan-2-ol instead of methanol, the desired products 285c and 285d were afforded in 53% and 40% yields, respectively. When the reactions were attempted with more electricity (>2 F), remarkably high voltages were observed, probably due to the lower conductivity of the solvents, and the reactions had to be stopped. This issue may be avoided by using supporting electrolytes or a base to help the conductivity of the electrons between the electrodes. On the other hand, the acyclic amino acid derivatives (S)-284c–f were fully consumed with 2 F of charge, and the desired products 285e–h were isolated in good yields (up to 73%). As expected, the graphite anode did not provide
great memory of chirality. In particular, the pyrrolidine derivatives 285a–d were afforded in moderate enantioselectivities (up to 26% ee), whilst less constrained derivatives 285e–h were formed with poor or no selectivity. Interestingly, when the electrolysis was performed on the sterically less hindered L-alanine derivative 284c, the (S)-285e was found as the major isomer in 8% ee, in contrast with the observation for the other substrates and with what is reported in literature.22b,35 Nevertheless, the hypothesis of an inversion of configuration seemed possible as in agreement with what reported for substrates bearing less a bulky N-protecting group.22a Moreover, no enantioselectivity was observed for the isopropyl-substituted 285f, while the N,O-acetals 285g–h bearing bulkier alkyl chains were formed as (R)-isomers, which supports the hypothesis of a relation between bulkier substrates and retention of configuration.

Scheme 4.20: Reactions were performed at 23 °C on a 13 mM scale of (S)-284a–f using a graphite anode and a Pt cathode, a FEP spacer (0.5mm thickness; reactor volume: 600 µL; working area: 12 cm²) with no additional supporting electrolyte or base; Isolated yields are shown; the absolute configuration for 285a was assigned according to literature,35 and for 285b–h were assigned in analogy to 285a. aNo starting material detected by 1H NMR.
The same library of compounds (S)-284a–f was then subjected to oxidation using the optimal conditions for the memory of chirality reported in Table 4.4, entry 2 (Scheme 4.21). The solutions of starting material were pumped at 0.2 mL·min⁻¹ and the microreactor was cooled to −10 °C. Again, the solutions were equilibrated for ~20 minutes before being collected for 1.5 hours, then the O-acetals 285a–h were isolated and the ee% was measured offline on the pure products.

Scheme 4.21: Reactions were performed at −10 °C on a 0.13 mmol (13 mM solution) of (S)-284a–f using a glassy carbon anode and a Pt cathode, a FEP spacer (0.5 mm thickness; reactor volume: 600 µL; working area: 12 cm²) with no additional supporting electrolyte or base; Isolated yields are shown; the absolute configuration for 285a was assigned according to literature, and for 285b–h were assigned in analogy with 285a. aReaction performed on a 1.25 mmol scale (50 mM solution); bReaction performed at 0.1 mL·min⁻¹; cReactions performed on recrystallised starting materials at room temperature; (*) Reactions in which the side product 294 was formed.
Generally, the products 285a–h were isolated in poor to good yields and with poor to good enantioselectivity. The model substrate 285a, was isolated in 50% yield with 60% ee. When a more electron-rich biphenyl group was used, the corresponding N,O-acetal 285b was isolated only in 28% yield with 50% ee. When the electrolysis of (S)-284a was performed in ethanol or propan-2-ol instead of methanol, the desired products 285c and 285d were isolated in 57% and 42% yield with 61% ee and 67% ee, respectively. When the reaction was performed in propan-2-ol the flow rate was reduced to 0.1 mL•min⁻¹ to avoid an unsafe high voltage, since the conductivity was lower in this solvent. A moderate memory of chirality was also observed in non-constrained acyclic amino acids (S)-284c–f, which increased with the steric demand of the side chain with 285e–h formed in 7–14% ee. Furthermore, when the oxidation was performed on L-alanine and L-leucine derivatives (S)-284c and (S)-284e, the products 285e and 285g were isolated only in 22% and 13% yield, respectively, along with the side product 294 isolated in 17% and 30% yield, respectively. This was not the case for L-valine and L-phenylalanine substrates (S)-284d and (S)-284f, which formed the tricyclic compound 294 in less than 10% yield, and the corresponding N,O-acetal 285f and 285h in 43% and 52% yield, respectively. The formation of benzocoumarin derivatives such as 294 was recently reported as product of the electrochemical cyclisation of 2-arylbenzoic acids such as 287a (Scheme 4.22).³⁶

![Scheme 4.22: Electrochemical C–H lactonization of aromatic carboxylic acids 287a.](image)

Therefore, a second recrystallisation of (S)-284c and (S)-284e was performed to remove any traces of 2-arylbenzoic acid 287a. The recrystallised (S)-284c and (S)-284e were then subjected to electrolysis with glassy carbon at room temperature affording 285e and 285g in 80% and 62% yield, respectively. In this case, when the electrolysis on (S)-284c was performed with glassy carbon as the anode, the (R)-285e enantiomer was formed as the major enantiomer with 7–10% of enantiomeric excess, instead of the (S)-isomer which was formed as the major product with a graphite anode. For a further scale-up, higher concentrated solutions (0.05 M, 1.25 mmol scale) were used and it was possible to reproduce the same results without a remarkable loss in reactivity or enantioselectivity.
Finally, to prove the importance of the biphenyl substituent on the memory of chirality, the benzoyl L-proline 259, prepared from benzoyl chloride and L-proline, was subjected to the non-Kolbe oxidation in the flow microreactor. As expected, 260 was obtained as racemate regardless the type of anode used. (Scheme 4.23).

In summary, the DoE conclusions were confirmed also in the substrate scope with the graphite anodes affording the desired products in better yields and the glassy carbon anodes providing generally better ee. Moreover, some moderate memory of chirality was observed also in unstrained substrates, albeit still poor (up to 14% ee). Additionally, the presence of the biphenyl N-protecting group was confirmed to be fundamental for the memory of chirality in the flow process, as already reported for the batch electrolysis.\textsuperscript{22a}
4.3 Conclusions and Outlook

To conclude, the asymmetric electrochemical non-Kolbe oxidation of $N$-acyl $L$-proline was successfully translated into a flow electrochemical microreactor coupled to an online 2D-HPLC and the reaction was optimised using a DoE-approach. The short reaction times combined with a fast analysis time made it possible to rapidly screen charges as well as electrodes, flow rates, concentrations and temperatures. The graphite anodes were found to provide good to quantitative yields, while the best memory of chirality (70% ee) was achieved using glassy carbon anodes. The optimal conditions were then applied to the synthesis of a series of cyclic and acyclic $N,O$-acetals in moderate to good yields and enantioselectivities. These results proved the concept that the combination of a flow system coupled with an online 2D-HPLC and DoE offers an efficient method to intensively screen several parameters and quickly optimise reactions. Hence, the presented methodology might find useful applications in the optimisation of other asymmetric transformations. Future work is focused on the complete automation of such systems with all units (reactor and HPLC) controlled by a computer.

The absolute configuration of the final products has been assigned according to literature, however the crystallisation of one of the final $N,O$-acetals could be included as part of the future work as further evidence.

Moreover, all the reactions were performed without any supporting electrolytes nor base. Although most of the Kolbe or non-Kolbe reactions need a base to form the active carboxylate species, in the flow microreactor the methoxide formed at the cathode is suspected to be enough to deprotonate the starting material and initiate the reaction. Further studies should be included in the future work to fully understand the mechanism behind this unusual base-free non-Kolbe electrolysis. Furthermore, it might be interesting to study the electrolysis in the presence of supporting electrolytes, which can be used to improve yields especially in less conductive solvents.

Future work should also investigate the role of the electrode type in the memory of chirality, which remains still unclear. For example, electrode-surface modifications might give some insights on the electrode/acyliminium ion interaction or on how to further improve the memory of chirality.
References


8 A. Bayer, M. E. Maier, Tetrahedron 2004, 60, 6665–6667.


CHAPTER 5: Experimental Part

5.1 General Methods

The reactions were performed using standard laboratory equipment. In all the reactions, standard reagent grade solvents and chemicals from Sigma Aldrich, Alfa Aesar, Acros Organic, and FluoroChem were used without further purification, unless otherwise specified. All air sensitive reactions were carried out under a nitrogen atmosphere using oven dried glassware. All the batch reactions were stirred using a stirrer plate and a magnetic stirrer bar and heating if necessary, over a hotplate with a temperature probe control and adapted heating block. Lower temperatures were achieved using ice/water bath (0 °C), ice/NaCl (−20 °C) and dry ice/acetone bath (−78 °C) or using a chiller to perform overnight reactions (0 to −20 °C). All reactions and manipulations of boranes were carried out under an atmosphere of dry, O₂-free nitrogen using standard double-manifold techniques with a rotary oil pump. A N₂-filled glove box (MBraun) was used to store the borane starting materials, setup reactions and sample preparation for analysis. Dry ether, acetonitrile, n-hexane, toluene and THF were collected from a solvent purification system (SPS) from the company MBRAUN (MB SPS-800). Dry CH₂Cl₂ was distilled over calcium hydride under nitrogen atmosphere. Büchi rotavapors were used for solvent evaporations (reduced pressure up to 8 mbar) and a high vacuum apparatus was used to further dry the products.

Thin-layer chromatography (TLC) and prep-TLC were performed on pre-coated aluminium sheets of Merck silica gel 60 F254 (0.20 mm) and visualised by UV radiation (254 nm). Manual column chromatography was performed using silica gel 60 (Merck, 230-400 mesh) under increased pressure. Automated column chromatography was performed on a Biotage® Isolera Four using Biotage® cartridges SNAP Ultra 10 g, SNAP Ultra 25 g, SNAP Ultra 50 g, SNAP Ultra 100 g. The solvents used for the purification are indicated in the text and were purchased from Fischer Scientific as laboratory grade.

The HPLC measurements were carried out on a Shimadzu apparatus or on an Agilent 1290 2D-LC Solution. The different modules of the Shimadzu apparatus: SIL-10ADVP (autoinjector), LC-10ATVP (liquid chromatograph), FCV-10ALVP (pump), DGU-14A (degasser), CTO-10ASVP (column oven), SCL-10AVP (system controller) and SPD-M10A (diode array detector). The different modules of the Agilent system: G7129A (1290 vial sampler), G1312A (1D binary pump), G1322A (degasser), G7120A (1290 high speed 2D binary pump), G1316A (1260 column oven), G7115A (1260 diode array detector),
G7114A (1260 variable wavelength detector) and G1170A (1290 valve drive). For the online analysis. For the online analysis, a Cheminert® C2-1006D switching valve was used. The solvents used were n-hexane, ethanol, methanol and 2-propanol and were bought from Fischer scientific as HPLC grade. The column used for the achiral separation was a Varian Si (250 × 4.6 mm, 5 µm pore size). The columns used for the chiral separation were Chiralcel® OD-H (250 × 4.6 mm, 5 µm pore size), Chiralcel® OB-H (250 × 4.6 mm, 5 µm pore size) and YMC Chiral Amylose-C (250 × 4.6 mm, 5 µm pore size) depending on the substrate.

1H, 13C, and 19F NMR spectra were recorded at 298 K on Bruker DPX 300, 400 or 500 MHz apparatus and referenced to the residual proton solvent peak (H: CDCl₃, δ = 7.26 ppm; CD₂CN, δ = 1.94 ppm) and residual 13C signal (CDCl₃, δ = 77.2 ppm).13C and 19F NMR spectra were measured as 1H-decoupled unless otherwise stated. Chemical shifts δ were reported in ppm downfield of Si(CH₃)₄ (1H, 13C), CFCl₃ (19F), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qi = quintet, sex = sextet, hep = septet, dd = doublet of doublets, m = multiplet, br. s = broad singulet; and coupling constants (J) in Hertz. Yields are given as isolated yields unless noted otherwise.

Mass spectrometric measurements were performed by the EPSRC Mass Spectrometry Facility in Swansea University on a Waters Xevo G2-S and on a Thermo Scientific LTQ Orbitrap XL machine S3 or by R. Jenkins, R. Hick, T. Williams and S. Waller at Cardiff University on a Water LCR Premier XE-TOF for high resolution mass spectroscopy (HRMS). Ions were generated by the Atmospheric Pressure Ionisation Techniques (APCI), Atmospheric Solids Analysis Probe (ASAP), Electrospray (ES), Electron Ionisation (EI) or Nanospray Ionisation (NSI). The molecular ion peaks values quoted for either molecular ion (M⁺), molecular ion plus or minus hydrogen (M+H⁺, M−H⁻), molecular ion minus hydride (M−H⁺), molecular ion plus ammonium ion (M+NH₄⁺) or molecular ion plus sodium (M+Na⁺).

IR spectra were recorded on a Shimadzu FTIR Affinity-1S apparatus. Wavenumbers are quoted in cm⁻¹. All compounds were measured neat directly on the crystal of the IR machine. Melting points were measured using a Gallenkamp variable heater with samples in open capillary tubes.

Optical rotations were measured with a SCHMIDT and HAENSCH UniPol polarimeter at 20 °C in cuvette of 50–100 mm length with a sodium light (589.30 nm). HPLC grade chloroform, dichloromethane or methanol were used to prepare the solution and the concentration is indicated in the experimental section.
All the flow reactions were performed using a Chemyx Fusion 200 syringe pump and FEP tubing (OD: 1/16", ID: 0.2–1 mm). The electrochemical reactions were carried out in a galvanostatic mode using a Vapourtec Ion Electrochemical flow reactor\(^1\) powered up by an Aim-tti bench power supply (300 Watt). The cyclic voltammogram studies were performed using an Orygalys OGF500 Potentiostat / Galvanostat with OGFPWR power supply.

X-Ray crystallographic studies were carried out at the X-Ray Crystallography Service at Cardiff University or by Darren M. C. Ould. The structures were solved by direct methods and refined using the SHELXTL software package. In general, all non-hydrogen atoms were refined anisotropically. Hydrogen atoms were assigned at idealised locations.
5.2 Experimental Data for Chapter 2: Synthesis of novel trans-Dihydroindoles

The Rh(II) catalyst were purchased from Strem Chemicals. The diazo-transfer reagents 
$p$-ABSA (18e) was purchased by TCI and the $p$-NBSA (18f) was synthesised according 
to the literature procedure.$^2$

5.2.1 Synthesis of Starting Materials

*General Procedure 1:*

\[
\text{CO}_2\text{H} \quad \text{AcCl} \quad \text{ROH} \quad \text{o.n., rt} \quad \text{CO}_2\text{R}
\]

\[\text{151} \quad \text{155a-b} \]

2-Nitrophenylacetic acid 151 (10.0 g, 55 mmol) was dissolved in methanol (100 mL) and 
the solution was cooled down to 0 °C before addition of acetyl chloride (9.8 mL, 
138 mmol). The reaction was stirred overnight at room temperature and checked by TLC 
(\text{$n$-hexane/ethyl acetate 4:1}). The solvent was evaporated \textit{in vacuo} and the residual oil 
was washed with an aqueous saturated solution of NaHCO$_3$ (20 mL) and extracted with 
diethyl ether (3 $\times$ 25 mL). Subsequently, the combined organic fractions were washed 
with water (20 mL) and brine (20 mL), dried over MgSO$_4$ and concentrated \textit{in vacuo} to 
afford 155a-b as a solid or oil depending on the substrate.

Methyl 2-(2-nitrophenyl) acetate 155a:

\[
\text{CO}_2\text{Me} \quad \text{Perfomed according to the General Procedure 1 on a 55 mmol scale;}
\]

155a (10.7 g, 55 mmol, 99%) was obtained as a pale-yellow oil that 
solidified at room temperature, m.p.: 36–40 °C.

$^1$H NMR (300 MHz, CDCl$_3$): $\delta = 8.13$ (dd, \(J = 8.1, 0.9\) Hz, 1H, Ar$H_I$), 7.62 (td, \(J = 7.5, 1.3\) 
Hz, 1H, Ar$H_I$), 7.49 (td, \(J = 8.1, 1.4\) Hz, 1H, Ar$H_I$), 7.37 (dd, \(J = 7.6, 1.0\) Hz, 1H, Ar$H_I$), 4.04 
(s, 2H, \(CH_2\)), 3.72 (s, 3H, OCH$_3$) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 170.4$ (C=O), 148.7 
(ArC–N), 133.6 (ArC), 133.3 (ArC), 129.7 (ArC), 128.6 (ArC), 125.3 (ArC), 52.3 (OCH$_3$), 
39.6 (CH$_2$) ppm. Spectroscopic data are in agreement with literature.$^3$
Isopropyl 2-(2-nitrophenyl) acetate 155b:

Performed according to the General Procedure 1 on a 13.8 mmol scale; 155b (2.7 g, 12.3 mmol, 88%) was obtained as a pale orange oil.

1H NMR (300 MHz, CDCl3): δ = 7.99 (d, J = 8.1 Hz, 1H, ArH), 7.47 (td, J = 7.4, 1.0 Hz, 1H, ArH), 7.35 (t, J = 7.7 Hz, 1H, ArH), 7.23 (d, J = 7.4 Hz, 1H, ArH), 4.91 (hep, J = 6.2 Hz, 1H, OCH(CH3)2), 3.87 (s, 2H, CH2), 1.12 (d, J = 6.2 Hz, 6H, OCH(CH3)2) ppm; 13C NMR (75 MHz, CDCl3): δ = 169.5 (C=O), 148.8 (ArC–N), 133.5 (ArC), 133.3 (ArC), 130.0 (ArC–CH2), 128.5 (ArC), 125.2 (ArC), 68.9 (OCH), 40.2 (CH2), 21.7 (2 × CH3) ppm; IR (neat) ν = 3726w, 3628w, 2981m, 2360s, 2341s, 728s, 1614m, 1579m, 1523s, 1465m, 1454m, 1344s, 1217s, 1176m, 1105s, 956m, 840m, 789m, 759m, 736m, 715s cm⁻¹; HRMS (ASAP): exact mass calculated for C11H14NO4 [M+H]⁺:224.0923, found: 224.0921.

General Procedure 2:

A two-neck flask was twice evacuated and filled with N2; 10% Pd/C (233 mg) was added to the flask and the residue was washed with a small amount of dichloromethane. Methanol (20 mL) was added carefully before addition of 2-nitroaryl ester 155a–b (4.0 g, 21 mmol) dissolved in methanol (2 mL). Subsequently, the flask was evacuated and filled with N2 twice, evacuated again and filled with H2 (1 atm). The reaction was stirred at room temperature for 12 hours and monitored by TLC (n-hexane/ethyl acetate 4:1). The mixture was filtered through Celite and the solvent was evaporated in vacuo to afford 156a–b as oils.

Methyl 2-(2-aminophenyl) acetate 156a:

Performed according to the General Procedure 2 on a 21 mmol scale of 155a; 156a (3.3 g, 21 mmol, 99%) was obtained as a red oil.

1H NMR (300 MHz, CDCl3): δ = 7.26–7.06 (m, 2H, ArH), 6.80–6.68 (m, 2H, ArH), 4.07 (br. s, 2H, NH2), 3.71 (s, 3H, OCH3), 3.59 (s, 2H, CH2) ppm; 13C NMR (75 MHz, CDCl3): δ = 172.4 (C=O), 145.6 (ArC–N), 131.3 (ArC), 128.7 (ArC), 119.6
Experimental Part

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(ArC–CH₂), 119.1 (ArC), 116.7 (ArC), 52.3 (OCH₃), 38.4 (CH₂) ppm. Spectroscopic data are in agreement with literature.³

Isopropyl 2-(2-aminophenyl) acetate 156b:

Performed according to the General Procedure 2 on a 8.9 mmol scale of 155b; 156b (1.21 g, 6.26 mmol, 70%) was obtained as an orange oil.

¹H NMR (400 MHz, CDCl₃): δ = 7.12–7.08 (m, 2H, ArH), 6.77–6.70 (m, 2H, ArH), 5.00 (hep, J = 6.3 Hz, 1H, OC₃H), 4.10 (s, 2H, NH₂), 3.54 (s, 2H, C₃H₂), 1.24 (d, J = 6.3 Hz, 6H, 2×C₃H₃) ppm; ¹³C NMR (75 MHz, CDCl₃): δ = 171.5 (C=O), 145.6 (ArC–N), 131.1 (ArC), 128.5 (ArC), 119.8 (ArC–CH₂), 118.9 (ArC), 116.5 (ArC), 68.5 (OCH), 38.9 (CH₂), 21.7 (2×CH₃) ppm; IR (neat) ν = 3736w, 3446w, 3365w, 2980w, 2358s, 2341s, 1712s, 1627m, 1585w, 1496m, 1458m, 1373w, 1357w, 1159m, 1103s, 964m, 908m, 731s, 669m, 648m, 522m cm⁻¹; HRMS (NSI): exact mass calculated for C₁₁H₁₆NO₂ [M+H⁺]: 194.1173, found: 194.1176.

2-(2-Nitrophenyl)ethan-1-ol 157:

To a solution of 155a (200 mg, 1 mmol) in dry THF (5 mL), NaBH₄ (79 mg, 2.2 mmol) and AlCl₃ (133 mg, 1 mmol) were added at 0 °C. After 2 hours the reaction was quenched with 1mL of water then filtered over Celite. The product was extracted with Et₂O (3 × 5 mL). The combined organic layers were washed with brine and dried over MgSO₄ before being concentrated under reduced pressure. The crude was purified by column chromatography to afford 157 (28 mg, 0.17 mmol, 17%) as a colourless oil.

¹H NMR (300 MHz, CDCl₃): δ = 7.91 (d, J = 8.1 Hz, 1H, ArH), 7.63–7.48 (m, 1H, ArH), 7.48–7.30 (m, 2H, ArH), 3.92 (td, J = 6.4, 1.2 Hz, 2H, CH₂OH), 3.15 (t, J = 6.4 Hz, 2H, CH₂), 2.05 (br, 1H, OH) ppm; ¹³C NMR (75 MHz, CDCl₃): δ = 149.7 (ArC–N), 133.7 (ArC), 133.0 (ArC), 132.8 (ArC), 127.6 (ArC), 124.8 (ArC), 62.7 (CH₂OH), 36.1 (CH₂) ppm. Spectroscopic data are in agreement with literature.⁴

Indolin-2-one 158:

To a suspension of Pd/C 10% (50 mg, 5 mol%) in dry menthol (500 μL), a solution of 155a (200 mg, 1 mmol) in dry methanol (2 mL) was added dropwise. The formic acid (500 μL, 5 mmol) was added and the suspension was stirred over night at room temperature. The solvent was evaporated, and the residue was washed with an aqueous saturated solution of NaHCO₃ (5 mL),
water (5 mL) and extracted with dichloromethane (3 × 5 mL). The combined organic layers were washed with brine and dried over MgSO₄ before being concentrated under reduced pressure. The crude was purified by column chromatography to afford 158 (92 mg, 0.69 mmol, 69%) as a pale pink solid, m.p.: 128–130 °C.

¹H NMR (300 MHz, CDCl₃) δ = 9.12 (s, 1H, NH), 7.22 (dd, J = 14.4, 6.9 Hz, 2H, ArH), 7.10–6.97 (m, 1H, ArH), 6.90 (d, J = 7.7 Hz, 1H, ArH), 3.55 (s, 2H, CH₂) ppm; ¹³C NMR (75 MHz, CDCl₃) δ = 178.7 (C=O), 142.8 (ArC–N), 128.0 (ArC), 125.4 (ArC–CH₂), 124.5 (ArC), 122.3 (ArC), 110.0 (ArC), 36.4 (CH₂) ppm. Spectroscopic data are in agreement with literature.⁵

**General Procedure 3:**

A solution of 156a–b (3 g, 18 mmol) in pyridine (20 mL) was cooled down to 0 °C. p-Toluenesulfonyl chloride (4.16 g, 22 mmol) was added dropwise. The reaction was stirred at room temperature for 24 hours and monitored via TLC (n-hexane/ethyl acetate 4:1). An aqueous solution of HCl (1 M, 25 mL) was added and the reaction mixture was extracted with ethyl acetate (2 × 20 mL), the organic layer was washed with further aqueous solution of HCl (1 M, 20 mL), water (2 × 20 mL), brine and dried over MgSO₄. Subsequent evaporation of the solvent in vacuo and liquid column chromatography furnished the desired products 159a–b as solids.

Methyl 2-(2-((4-methylphenyl)sulfonamido)phenyl) acetate 159a: Performed according to the General Procedure 3 on a 18 mmol scale of 156a; 159a (5.6 g, 17 mmol, 96%) was obtained as a pale orange solid, m.p.: 82–84 °C. 

¹H NMR (300 MHz, CDCl₃): δ = 8.04 (br. s, 1H, NH), 7.60 (d, J = 8.3 Hz, 2H ArH), 7.29 (d, J = 7.9 Hz, 1H, ArH), 7.23–7.12 (m, 3H, ArH), 7.12–7.06 (m, 2H, ArH), 3.63 (s, 3H, OCH₃), 3.33 (s, 2H, CH₂), 2.34 (s, 3H, CH₃) ppm; ¹³C NMR (75 MHz, CDCl₃): δ = 172.6 (C=O), 143.7 (ArC–N), 137.2 (ArC), 135.4 (ArC), 131.1 (ArC), 129.7 (2 × ArC), 128.6 (ArC), 128.5 (ArC), 127.0 (2 × ArC), 126.5 (ArC), 125.9 (ArC), 52.5 (OCH₃), 37.7 (CH₂), 21.5 (CH₃) ppm; IR (neat) ν = 3226m, 1708s, 1597m, 1587m, 1496m, 1435m, 1417m, 1336s, 1278s, 1238w, 1157s, 1089s,
Isopropyl 2-(2-((4-methylphenyl)sulfonamido)phenyl)acetate 159b:

Performed according to General Procedure 3 on a 6.2 mmol scale of 156b; 159b (2.1 g, 6.0 mmol, 98%) was obtained as a pale-yellow solid, m.p.: 74–78 °C. 

$^1$H NMR (400 MHz, CDCl$_3$): δ = 8.25 (br. s, 1H, NH), 7.68 (d, J = 8.3 Hz, 2H, ArH), 7.42 (d, J = 8.0 Hz, 1H, ArH), 7.35–7.20 (m, 3H, ArH), 7.13 (d, J = 4.1 Hz, 2H, ArH), 5.00 (hep, J = 6.2 Hz, 1H, OCH), 3.26 (s, 2H, CH$_2$), 2.42 (s, 3H, CH$_3$), 1.25 (d, J = 6.3 Hz, 6H, 2 × CH$_3$) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$): δ = 172.0 (C=O), 143.7 (ArC–N), 137.7 (ArC), 135.8 (ArC), 131.2 (ArC), 129.8 (2 × ArC), 128.8 (ArC), 128.0 (ArC), 127.0 (2 × ArC), 126.3 (ArC), 125.5 (ArC), 69.8 (OCH), 38.9 (CH$_2$), 21.8 (2 × CH$_3$), 21.7 (CH$_3$) ppm; IR (neat): ν = 3259m, 2980w, 1728m, 1707m, 1597w, 1585, 1492m, 1332s, 1290m, 1159s, 1089s, 956m, 898m, 812m, 659s, 547s, 528s cm$^{-1}$; HRMS (NSI): Exact mass calculated for C$_{18}$H$_{25}$N$_2$O$_4$S [M+NH$_4$]+: 365.1530, found: 365.1532.

**General Procedure 4:**

A solution of starting material 159a–b (2.6 g, 8.1 mmol) was dissolved in acetonitrile (25 mL). After the addition of triethylamine (3.2 mL, 24.3 mmol), the reaction mixture was cooled down to 0 °C. Next, aryl halide 161 was added (24.3 mmol) dropwise and the reaction mixture was stirred at room temperature for around 48–72 hours and monitored via TLC (n-hexane/ethyl acetate 4:1). Subsequently, the solvent was evaporated in vacuo and the residual oil was dissolved in CH$_2$Cl$_2$ (15 mL), washed with water (20 mL) and brine (20 mL). After drying over MgSO$_4$, the mixture was concentrated in vacuo and purified via column chromatography to afford 152a–l as solids.
Methyl 2-((N-benzyl-4-methylphenyl)sulfonamido)phenyl) acetate 152a:

Performed according to General Procedure 4 on a 2.0 mmol scale of 159a with bromo benzene; 152a (655 mg, 1.6 mmol, 82%) was obtained as a pale, pink solid, m.p.: 78–81 °C.

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 7.45 (d, $J$ = 8.3 Hz, 2H, ArH), 7.21–6.91 (m, 10H, ArH), 6.48 (dd, $J$ = 8.0, 1.0 Hz, 1H, ArH), 4.92 (d, $J$ = 13.6 Hz, 1H, NCH$_2$), 4.12 (d, $J$ = 13.6 Hz, 1H, NCH$_2$), 3.50–3.38 (m, 5H, CH$_2$CO$_2$Me + OCH$_3$), 2.30 (s, 3H, CH$_3$) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 171.4 (C=O), 143.7 (ArC–N), 137.6 (ArC), 136.0 (ArC), 135.4 (ArC), 131.3 (ArC), 129.5 (2 × ArC), 129.3 (2 × ArC), 128.3 (ArC), 128.2 (2 × ArC), 128.0 (ArC), 127.9 (2 × ArC), 127.7 (ArC), 127.4 (ArC), 56.0 (NCH$_2$), 51.6 (OCH$_3$), 35.6 (CH$_3$), 21.4 (CH$_3$) ppm; IR (neat) ν = 3062w, 3032w, 2949w, 1722s, 1597m, 1492m, 1348s, 1263s, 1161s, 1091m, 885m, 812s, 705s, 657s, 549s cm$^{-1}$; HMRS (NSI): Exact mass calculated for C$_{23}$H$_{23}$NO$_4$S [M+H]$^+$: 410.1421; found: 410.1418.

Isopropyl 2-((N-benzyl-4-methylphenyl)sulfonamido)phenyl) acetate 152b:

Performed according to General Procedure 4 on a 1.47 mmol scale of 159b with bromo benzene; 152b (398 mg, 0.91 mmol, 62%) was obtained as a pale-yellow solid, m.p.: 88–90 °C.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.50 (d, $J$ = 7.9 Hz, 2H, ArH), 7.26–6.96 (m, 10H, ArH), 6.49 (d, $J$ = 8.0 Hz, 1H, ArH), 4.93–4.81 (m, 2H, 1 × NCH$_2$ + COCH$_3$), 4.27 (d, $J$ = 13.7 Hz, 1H, 1 × NCH$_2$), 3.47 (d, $J$ = 16.8 Hz, 1H, 1 × CH$_2$), 3.41 (d, $J$ = 16.8 Hz, 1H, 1 × CH$_2$), 2.38 (s, 3H, CH$_3$), 1.13 (t, $J$ = 6.2 Hz, 6H, 2 × CH$_3$) ppm; $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ = 170.9 (C=O), 143.7 (ArC–N), 137.7 (ArC), 136.5 (ArC), 135.9 (ArC), 135.4 (ArC), 131.3 (ArC), 129.6 (2 × ArC), 129.5 (2 × ArC), 128.6 (ArC), 128.5 (2 × ArC), 128.1 (2 × ArC), 128.0 (ArC), 127.3 (ArC), 68.1 (OCH(CH$_3$)$_2$), 56.1 (NCH$_2$), 36.4 (CH$_3$), 21.9 (2 × CH$_3$), 21.7 (CH$_3$) ppm; IR (neat) ν = 2984w, 1716s, 1597w, 1490m, 1456m, 1344s, 1261s, 1161s, 1105m, 1089m, 1045m, 977m, 864m, 815m, 756s, 709s, 657s, 611s, 590s, 447w, 428w cm$^{-1}$; HMRS (NSI): Exact mass calculated for C$_{25}$H$_{28}$NO$_4$S [M+H]$^+$: 438.1734; found: 438.1734.
Methyl 2-(2-((4-methoxybenzyl)-4-methylphenyl)sulfonamido)phenyl) acetate 152c:

Performed according to General Procedure 4 on a 0.63 mmol scale of 159a with 4-methoxybenzyl chloride; 152c (206 mg, 0.47 mmol, 75%) was obtained as a pale-yellow solid, m.p.: 108–110 °C.

$^1$H NMR (300 MHz, CDCl$_3$): $\delta = 7.64–7.54$ (m, 2H, Ar$H$), 7.35–7.23 (m, 4H, Ar$H$), 7.10 (td, $J = 7.5$, 1.8 Hz, 1H, Ar$H$), 7.06–7.00 (m, 2H, Ar$H$), 6.76–6.68 (m, 2H, Ar$H$), 6.59 (dd, $J = 8.0$, 1.2 Hz, 1H, Ar$H$), 4.97 (d, $J = 13.5$ Hz, 1H, $1 \times$ NCH$_2$), 4.23 (d, $J = 13.5$ Hz, 1H, $1 \times$ NCH$_2$), 3.75 (s, 3H, OCH$_3$), 3.60 (s, 3H, OCH$_3$), 3.55 (s, 2H, C$H_2$), 2.47 (s, 3H, C$H_3$) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 171.8$ (C=O), 159.4 (Ar$C$–O), 143.7 (Ar$C$–N), 137.8 (Ar$C$), 136.4 (Ar$C$), 136.0 (Ar$C$), 131.5 (Ar$C$), 130.8 (2 × Ar$C$), 129.7 (2 × Ar$C$), 128.5 (Ar$C$), 128.4 (Ar$C$), 128.2 (2 × Ar$C$), 127.5 (Ar$C$), 127.4 (Ar$C$), 113.9 (2 × Ar$C$), 55.7, 55.3, 51.9, 35.7 (CH$_2$), 21.5 ppm; IR (neat): $\nu = 2953$w, 2835w, 1737s, 1614m, 1587m, 1514s, 1436m, 1340s, 1271m, 1244s, 1157s, 1028s, 873s, 694s, 653s, 574s cm$^{-1}$; HRMS (NSI): Exact mass calculated for C$_{24}$H$_{29}$N$_2$O$_5$S [M+NH$_4^+$]: 457.1792, found: 457.1788.

Methyl 2-(2-((4-methyl-N-(4-(trifluoromethyl)benzyl)phenyl)sulfonamido)phenyl) acetate 152d:

Performed according to General Procedure 4 on a 0.63 mmol scale of 159a with 4-(trifluoromethyl)benzyl chloride; 152d (162 mg, 0.34 mmol, 55%) was obtained as a pale pink solid, m.p.: 102–106 °C.

$^1$H NMR (300 MHz, CDCl$_3$): $\delta = 7.51$ (d, $J = 8.2$ Hz, 2H, Ar$H$), 7.42 (d, $J = 8.1$ Hz, 2H, Ar$H$), 7.30–7.16 (m, 6H, Ar$H$), 7.06 (td, $J = 8.3$, 1.4 Hz, 1H, Ar$H$), 6.56 (d, $J = 7.9$ Hz, 1H, Ar$H$), 5.0 (d, $J = 13.9$ Hz, 1H, $1 \times$ NCH$_2$), 4.27 (d, $J = 13.9$ Hz, 1H, $1 \times$ NCH$_2$), 3.58 (d, $J = 16.8$ Hz, 1H, $1 \times$ CH$_3$), 3.53–3.35 (m, 4H, OCH$_3$ $1 \times$ CH$_3$), 2.40 (s, 3H, CH$_3$) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 171.5$ (C=O), 144.0 (Ar$C$–N), 139.6 (Ar$C$), 137.7 (Ar$C$), 136.0 (Ar$C$), 135.3 (Ar$C$), 131.6 (Ar$C$), 130.0 (q, $J = 32.2$ Hz, Ar$C$–CF$_3$), 129.7 (Ar$C$), 129.6 (Ar$C$), 128.5 (Ar$C$), 128.4 (Ar$C$), 128.2 (2 × Ar$C$), 127.7 (Ar$C$), 125.3 (q, $J = 3.7$ Hz, Ar$C$), 124.0 (q, $J = 272.1$ Hz, CF$_3$), 55.6 (NCH$_3$), 51.6 (OCH$_3$), 35.8 (CH$_2$), 21.5 ppm (CH$_3$); IR (neat): $\nu = 2954$w, 2922w, 1726s, 1620w, 1595w, 1492m, 1438m, 1423m, 1348m, 1323s, 1271m, 1159s, 1109s, 1089s, 1066s, 1020s, 848m, 812m, 707m, 698m, 657m, 634m, 547s, 451w cm$^{-1}$; HRMS (NSI): Exact mass calculated for C$_{24}$H$_{26}$F$_3$N$_2$O$_4$S [M+NH$_4^+$]: 495.1560, found: 495.1547.

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Methyl 2-((4-methyl-N-(4-nitrobenzyl)phenyl)sulfonamido)phenyl) acetate 152e:

Performed according to General Procedure 4 on a 0.63 mmol scale of 159a with 4-nitrobenzyl bromide; 152e (291 mg, 0.45 mmol, 71%) was obtained after recrystallisation over Et₂O in n-hexane as a yellow solid, m.p.: 106–110 °C.

1H NMR (400 MHz, CDCl₃): δ = 8.09 (d, J = 8.3 Hz, 2H, ArH), 7.58 (d, J = 8.0 Hz, 2H, ArH), 7.53–7.23 (m, 6H, ArH), 7.14 (t, J = 7.6, 1.9 Hz, 1H, ArH), 6.61 (dd, J = 8.0, 0.9 Hz, 1H, ArH), 5.09 (d, J = 14.0 Hz, 1H, NC₃H₂), 4.42 (d, J = 14.0 Hz, 1H, NC₃H₂), 3.83–3.41 (m, 5H, CH₂ + OCH₃), 2.47 (s, 3H, CH₃) ppm;

13C NMR (75 MHz, CDCl₃): δ = 171.5 (C=O), 147.6 (ArC–N), 144.3 (ArC–N), 142.9 (ArC), 137.5 (ArC), 135.9 (ArC), 134.9 (ArC), 131.7 (ArC), 130.2 (2 × ArC), 129.8 (2 × ArC), 128.9 (ArC), 128.1 (ArC), 128.0 (2 × ArC), 127.9 (ArC), 123.7 (2 × ArC), 55.4 (NCH₂), 51.9 (OCH₃), 35.9 (CH₃), 21.7 (CH₃) ppm; IR (neat): ν = 3066w, 2949w, 2854w, 1737s, 1597m, 1519s, 1435m, 1338s, 1207m, 1155s, 1105m, 1085m, 1064m, 854m, 815m, 557s cm⁻¹; HRMS (NSI): Exact mass calculated for C₂₃H₂₆N₃O₆S [M+NH₄⁺]: 472.1537, found: 472.153.

Methyl 2-((4-methyl-N-(4-methylbenzyl)phenyl)sulfonamido)phenyl) acetate 152f:

Performed according to General Procedure 4 on a 0.63 mmol scale of 159a with 4-methylbenzyl chloride; 152f (161 mg, 0.33 mmol, 61%) was obtained as a pale white solid, m.p.: 94–96 °C.

1H NMR (300 MHz, CDCl₃): δ = 7.60 (d, J = 7.4 Hz, 2H, ArH), 7.41–7.18 (m, 4H, ArH), 7.11 (t, J = 6.7 Hz, 1H, ArH), 7.00 (s, 4H, ArH), 6.59 (d, J = 7.9 Hz, 1H, ArH), 5.01 (d, J = 13.5 Hz, 1H, 1 × NCH₂), 4.20 (d, J = 13.3 Hz, 1H, 1 × NCH₂), 3.67–3.47 (m, 5H, CH₂ + OCH₃), 2.47 (s, 3H), 2.28 (s, 3H, CH₃) ppm;

13C NMR (75 MHz, CDCl₃): δ = 171.8 (C=O), 143.8 (ArC–N), 137.8 (ArC), 137.6 (ArC), 136.3 (ArC), 135.7 (ArC), 132.1 (ArC), 131.5 (ArC), 129.6 (ArC), 129.5 (ArC), 129.1 (ArC), 128.5 (ArC), 128.2 (ArC), 128.1 (ArC), 127.5 (ArC), 55.9 (NCH₂), 51.9 (OCH₃), 35.8 (CH₃), 21.7 (CH₃), 21.3 (CH₃) ppm; IR (neat): ν = 3064w, 1722s, 1346m, 1261m, 1155s, 1089m, 1043m, 1024m, 887w, 812s, 759w, 707m, 657s, 603m, 582s, 549s cm⁻¹; HRMS (NSI): Exact mass calculated for C₂₄H₂₆N₂O₄S [M+H⁺]: 424.1577, found: 424.1577.
Methyl 2-(2-((4-methyl-N-(3-methylbenzyl)phenyl)sulfonamido)phenyl) acetate 152g:

Performed according to General Procedure 4 on a 0.60 mmol scale of 159a with 3-methylbenzyl bromide; 152g (182 mg, 0.43 mmol, 69%) was obtained as a pale white solid, m.p.: 84–86 °C.

$^1$H NMR (400 MHz, CDCl$_3$): δ = 7.54 (d, $J = 8.2$ Hz, 2H, ArH), 7.32–7.23 (m, 3H, ArH), 7.19 (t, $J = 7.5$ Hz, 1H, ArH), 7.09–6.90 (m, 4H, ArH), 6.83 (d, $J = 7.3$ Hz, 1H, ArH), 6.52 (d, $J = 8.0$ Hz, 1H, ArH), 4.98 (d, $J = 13.6$ Hz, 1H, 1 × NCH$_2$), 4.16 (d, $J = 13.6$ Hz, 1H, 1 × NCH$_2$), 3.62–3.42 (m, 5H, CH$_2$ + OCH$_3$), 2.41 (s, 3H, CH$_3$), 2.20 (s, 3H, CH$_3$) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$): δ = 171.6 (C=O), 143.7 (ArC–N), 138.9 (ArC), 137.7 (ArC), 136.1 (ArC), 135.4 (ArC), 135.1 (ArC), 131.3 (ArC), 130.0 (ArC), 129.5 (2 × ArC), 128.5 (ArC), 128.3 (ArC), 128.1 (ArC), 128.0 (2 × ArC), 127.4 (ArC), 126.3 (ArC), 56.0 (NCH$_2$), 51.8 (OCH$_3$), 35.8 (CH$_2$), 21.6 (CH$_3$), 21.3 (CH$_3$) ppm; IR (neat): ν = 3028w, 1732m, 1492w, 1344m, 1222w, 1163s, 1091w, 815w, 769s, 657m, 565m, 410m cm$^{-1}$; HRMS (NSI): Exact mass calculated for C$_{24}$H$_{26}$NO$_4$S [M+H]$^+$: 424.1577, found: 424.1577.

Methyl 2-(2-((N-[[1,1'-biphenyl]-2-ylmethyl]-4-methylphenyl)sulfonamido)phenyl) acetate 152h:

Performed according to General Procedure 4 on a 0.63 mmol scale of 159a with 2-(phenyl)benzyl bromide; 152h (207 mg, 0.50 mmol, 79%) was obtained as a pale yellow solid, m.p.: 94–96 °C.

$^1$H NMR (300 MHz, CDCl$_3$): δ = 7.74 (dd, $J = 7.8$, 1.0 Hz, 1H, ArH), 7.50–7.43, (m, 2H, ArH), 7.36 (td, $J = 7.5$, 1.3 Hz, 1H, ArH), 7.07–7.00 (m, 8H, ArH), 6.82 (dd, $J = 7.6$, 1.2 Hz, 1H, ArH), 6.87 (td, $J = 7.9$, 1.7 Hz, 1H, ArH), 6.67 (dd, $J = 8.0$, 1.3 Hz, 2H, ArH), 6.12 (dd, $J = 8.0$, 1.0 Hz, 1H, ArH), 5.00 (d, $J = 13.9$ Hz, 1H, 1 × NCH$_2$), 4.24 (d, $J = 13.9$ Hz, 1H, 1 × NCH$_2$), 3.56–3.45 (m, 5H, CH$_2$ + OCH$_3$), 2.41 (s, 3H, CH$_3$) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$): δ = 171.7 (C=O), 143.7 (ArC–N), 142.4 (ArC), 140.3 (ArC), 137.8 (ArC), 136.2 (ArC), 135.6 (ArC), 133.0 (ArC), 131.4 (ArC), 130.9 (ArC), 130.0 (ArC), 129.6 (2 × ArC), 129.2 (2 × ArC), 128.3 (ArC), 128.2 (ArC), 128.1 (2 × ArC), 127.9 (ArC), 127.8 (2 × ArC), 127.6 (ArC), 127.5 (ArC), 126.7 (ArC), 52.3 (OCH$_3$), 47.0 (NCH$_2$), 35.6 (CH$_2$), 21.6 (CH$_3$) ppm; IR (neat): ν = 3062w, 3028w, 2956w, 2929w, 1743s, 1342s, 1203m, 1190m, 1153s, 1087m, 1057m, 867m, 817m, 759m, 692s, 653s, 547s cm$^{-1}$; HRMS (NSI): Exact mass calculated for C$_{29}$H$_{31}$N$_2$O$_4$S [M+NH$_4$]$^+$: 503.1999, found: 503.1985.
Methyl 2-(2-((4-methyl-N-(2-methylbenzyl)phenyl)sulfonamido)phenyl) acetate 152i:

Performed according to General Procedure 4 on a 0.63 mmol scale of 159a with 2-methylbenzyl bromide; 152i (215 mg, 0.50 mmol, 82%) was obtained as a pale white solid, m.p.: 96–98 °C.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.60 (d, $J$ = 8.1 Hz, 2H, ArH), 7.37–7.19 (m, 4H, ArH), 7.18–7.01 (m, 3H, ArH), 6.83 (t, $J$ = 7.2 Hz, 1H, ArH), 6.80 (d, $J$ = 7.6 Hz, 1H, ArH), 6.60 (d, $J$ = 8.0 Hz, 1H, ArH), 5.19 (d, $J$ = 13.1 Hz, 1H, 1 × NCH$_2$), 4.15 (d, $J$ = 13.1 Hz, 1H, 1 × NCH$_2$), 3.55 (s, 3H, OCH$_3$), 3.50 (d, $J$ = 16.8 Hz, 1H, 1 × CH$_2$), 3.39 (d, $J$ = 16.8 Hz, 1H, 1 × CH$_2$), 2.47 (s, 3H, CH$_3$), 2.30 (s, 3H, CH$_3$) ppm; $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ = 171.5 (C=O), 143.9 (Ar–N), 137.7 (ArC), 137.6 (ArC), 136.7 (ArC), 135.3 (ArC), 132.7 (ArC), 131.5 (ArC), 131.1 (ArC), 130.6 (ArC), 129.7 (2 × ArC), 128.5 (ArC), 128.3 (2 × ArC), 128.2 (ArC), 127.8 (ArC), 127.4 (ArC), 125.8 (ArC), 53.6, 51.9, 35.5 (CH$_2$), 21.7 (CH$_3$), 19.0 (CH$_3$) ppm; IR (neat) $\nu$ = 2943w, 2362w, 1741s, 1492m, 1435m, 1338s, 1193m, 1157s, 1089m, 1037m, 879m, 823m, 746m, 727m, 694s, 655m, 569s, 547m, 536m cm$^{-1}$; HRMS (NSI): Exact mass calculated for C$_{24}$H$_{26}$NO$_4$S [M+H]$^+$: 424.1577, found: 424.1577.

Methyl 2-(2-((4-methyl-N-(2-nitrobenzyl)phenyl)sulfonamido)phenyl) acetate 152j:

Performed according to General Procedure 4 on a 0.63 mmol scale of 159a with 2-nitrobenzyl bromide; 152j (174 mg, 0.38 mmol, 62%) was obtained as a yellow solid m.p.: 116–118 °C.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.80 (d, $J$ = 7.7 Hz, 1H, ArH), 7.71 (d, $J$ = 8.1 Hz, 1H, ArH), 7.50 (t, $J$ = 7.3 Hz, 1H, ArH), 7.43 (d, $J$ = 8.2 Hz, 2H, ArH), 7.29 (t, $J$ = 7.4 Hz, 1H, ArH), 7.34–7.22 (m, 4H, ArH), 7.02 (t, $J$ = 7.6 Hz, 1H, ArH), 6.59 (d, $J$ = 7.9 Hz, 1H, ArH), 5.18 (d, $J$ = 15.7 Hz, 1H, 1 × NCH$_2$), 4.82 (d, $J$ = 15.7 Hz, 1H, 1 × NCH$_2$), 3.65–3.35 (m, 5H, CH$_2$ + OCH$_3$), 2.36 (s, 3H, CH$_3$) ppm; $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ = 171.5 (C=O), 148.8 (ArC), 144.3 (ArC), 138.1 (ArC), 135.4 (ArC), 134.4 (ArC), 133.3 (ArC), 131.8 (ArC), 131.6 (ArC), 131.5 (ArC), 129.7 (2 × ArC), 128.7 (ArC), 128.6 (ArC), 128.5 (ArC), 128.2 (2 × ArC), 127.9 (ArC), 124.6 (ArC), 52.0 (NCH$_3$), 51.9 (OCH$_3$), 36.1 (CH$_2$), 21.6 (CH$_3$) ppm; IR (neat): $\nu$ = 2951w, 2358s, 2341s, 1735s, 1597w, 1525s, 1492m, 1435m, 1346s, 1267m, 1163s, 1091m, 1058w, 1039w, 856w, 815w, 736m, 694m, 655m, 572m cm$^{-1}$; HRMS (ASAP): Exact mass calculated for C$_{23}$H$_{28}$N$_2$O$_6$S [M+H]$^+$: 455.1277, found: 455.1284.
Methyl 2-((N-((1-bromophenalen-2-yl)methyl)-4-methylphenyl)sulfonamido)phenyl) acetate \textbf{152k}:

Performed according to \textit{General Procedure 4} on a 0.63 mmol scale of \textbf{159a} with 1-bromo-2-(bromomethyl)naphthalene; \textbf{152k} (262 mg, 0.49 mmol, 77\%) was obtained as a pale white solid, m.p.: 140–142 °C.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 8.11 (d, $J$ = 8.4 Hz, 1H, ArH$_1$), 7.68 (d, $J$ = 7.8 Hz, 1H, ArH$_1$), 7.62 (d, $J$ = 8.5 Hz, 1H, ArH$_1$), 7.57–7.50 (m, 3H, ArH$_1$), 7.42 (dt, $J$ = 14.7, 6.9 Hz, 2H, ArH$_1$), 7.25 (d, $J$ = 8.0 Hz, 2H, ArH$_1$), 7.19–7.09 (m, 2H, ArH$_1$), 7.05–6.99 (m, 1H, ArH$_1$), 6.66 (d, $J$ = 7.9 Hz, 1H, ArH$_1$), 5.31 (d, $J$ = 13.8 Hz, 1H, 1 x NCH$_2$), 4.72 (d, $J$ = 13.8 Hz, 1H, 1 x NCH$_2$), 3.56 (d, $J$ = 16.8 Hz, 1H, 1 x CH$_2$), 3.46 (d, $J$ = 16.8 Hz, 1H, 1 x CH$_2$), 3.11 (s, 3H, OC$_3$H$_3$), 2.40 (s, 3H, CH$_3$) ppm; $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ = 171.5 (C=O), 144.0 (ArC–N), 137.6 (ArC), 136.3 (ArC), 135.1 (ArC), 134.1 (ArC), 132.8 (ArC), 132.3 (ArC), 131.4 (ArC), 129.7 (ArC), 128.6 (ArC), 128.4 (ArC), 128.3 (ArC), 128.2 (ArC), 127.9 (ArC), 127.9 (ArC), 127.5 (ArC), 127.5 (ArC), 126.9 (ArC), 124.9 (ArC), 56.3 (NCH$_2$), 51.5 (OCH$_3$), 35.9 (CH$_2$), 21.8 (CH$_3$) ppm; IR (neat): $\nu$ = 2953w, 1741s, 1593w, 1458w, 1340s, 1157s, 1112m, 1087m, 1072m, 993w, 854m, 815s, 767m, 746m, 715m, 690m, 549s, 530m, 505m, 495m cm$^{-1}$; HRMS (NSI): Exact mass calculated for C$_{27}$H$_{25}$BrNO$_4$S [M+H]$^+$: 538.0682, found: 538.0678.

Methyl 2-((N-cinnamyl-4-methylphenyl)sulfonamido)phenyl) acetate \textbf{159l}:

Performed according to \textit{General Procedure 4} on a 0.94 mmol scale of \textbf{159a} with (E)-(3-bromoprop-1-en-1-yl)benzene; \textbf{152l} (278 mg, 0.64 mmol, 68\%) was obtained as a white solid, m.p.: 106–110 °C.

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 7.58 (d, $J$ = 8.2 Hz, 2H, ArH$_1$), 7.41 (d, $J$ = 7.0 Hz, 1H, ArH$_1$), 7.35–7.16 (m, 8H, ArH$_1$), 7.12 (td, $J$ = 7.6, 1.1 Hz, 1H, ArH$_1$), 6.61 (d, $J$ = 7.8 Hz, 1H, ArH$_1$), 6.31 (d, $J$ = 15.8 Hz, 1H, H$_a$), 6.10 (dt, $J$ = 15.7 Hz, 6.9 Hz, 1H, H$_a$), 4.50 (dd, $J$ = 14.2 Hz, 6.2 Hz, 1H, 1 x NCH$_2$), 4.12 (d, $J$ = 16.4 Hz, 1H, 1 x CH$_2$), 4.05 (dd, $J$ = 14.3, 6.7 Hz, 1H, 1 x NCH$_2$), 3.69 (d, $J$ = 16.4 Hz, 1H, 1 x CH$_2$), 3.55 (s, 3H, OCH$_3$), 2.45(s, 3H, CH$_3$) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 172.1 (C=O), 143.8 (ArC–N), 138.3 (ArC), 136.5 (ArC), 136.4 (ArC), 135.7 (ArC), 134.5 (ArC), 131.6 (ArC), 129.6 (2 x ArC), 128.7 (ArC), 128.6 (2 x ArC), 128.5 (ArC), 128.3 (2 x ArC), 128.0 (ArC), 127.8 (ArC), 126.7 (2 x ArC), 123.5 (ArC), 54.7 (NCH$_2$), 52.0 (OCH$_3$), 36.7 (CH$_2$), 21.7 (CH$_3$) ppm; IR (neat): $\nu$ = 3034w, 2947m, 2856w, 1730s, 1597m, 1490m, 1433m, 1313m,
1257s, 1184m, 1153s, 881m, 657s, 580s cm⁻¹; HRMS (NSI): Exact mass calculated for C₂₅H₂₉N₂O₄S [M+NH₄]⁺: 453.1843, found: 453.1837.

**General Procedure 5:**

To a solution of starting material **159a** (300 mg, 0.94 mmol), triphenylphosphine (271 mg, 1.03 mmol) and alkyl alcohol **162** (128 µL, 1.03 mmol) in THF, diisopropylazodicarboxylate (DIAD, 203 µL, 1.03 mmol) was added at 0 °C. The mixture was stirred overnight refluxing and cooled to room temperature. After THF was removed under reduced pressure, the residue was purified by flash column chromatography (n-hexane/ethyl acetate) to afford **152m-o** as oils.

Methyl 2-(2-((N-hexyl-4-methylphenyl)sulfonamido)phenyl) acetate **152m**:

Performed according to **General Procedure 5** on a 0.94 mmol scale of **159a** with hexan-1-ol; **152m** (260 mg, 0.64 mmol, 68%) was obtained as a colourless oil.

¹H NMR (300 MHz, CDCl₃): δ = 7.43 (d, J = 8.1 Hz, 2H, ArH), 7.36 (d, J = 7.2 Hz, 1H, ArH), 7.24–7.14 (m, 3H, ArH), 7.04 (t, J = 7.2 Hz, 1H, ArH), 6.47 (d, J = 8.1 Hz, 1H, ArH), 4.01 (d, J = 16.5 Hz, 1H, 1 × CH₂), 3.75–3.49 (m, 5H, OCH₃ + 1 × CH₂), 3.15–2.85 (m, 1H), 2.35 (s, 3H, CH₃), 1.47–1.04 (m, 8H), 0.75 (t, J = 6.6 Hz, 3H, CH₃) ppm; ¹³C NMR (75 MHz, CDCl₃): δ = 172.1 (C=O), 143.6 (ArC–N), 138.4 (ArC), 136.4 (ArC), 135.1 (ArC), 131.4 (ArC), 129.4 (2 × ArC), 128.4 (ArC), 128.1 (2 × ArC), 127.6 (ArC), 127.4 (ArC), 52.2, 51.9, 36.4, 31.4, 28.2, 26.5, 22.5, 21.6, 14.0 ppm; IR (neat): ν = 2951m, 2929m, 2856m, 1739s, 1597w, 1492m, 1435m, 1348s, 1211w, 1165s, 1089m, 1066w, 812m, 713m, 655m, 582m cm⁻¹; HRMS (NSI): Exact mass calculated for C₂₂H₅₆NO₄S [M+H]⁺: 404.1890, found: 404.1884.
Methyl 2-((N-(sec-butyl)-4-methylphenyl)sulfonamido)phenyl) acetate 152n:

Performed according to General Procedure 5 on a 0.94 mmol scale of 159a with butan-2-ol; 152n (227 mg, 0.60 mmol, 64%) was obtained as a colorless oil as a 1:1 mixture of rotamers.

$^1$H NMR (300 MHz, CDCl$_3$): $\delta = 7.48$ (dd, $J = 8.2$, 3.0 Hz, 4H, Ar$H$), 7.39 (d, $J = 7.8$ Hz, 2H, Ar$H$), 7.29–7.04 (m, 8H, Ar$H$), 6.71 (d, $J = 7.9$ Hz, 1H, Ar$H$), 6.63 (d, $J = 7.9$ Hz, 1H, Ar$H$), 4.21–4.12 (m, 2H, NCH + NCH$_2$), 3.90 (t, $J = 16.5$ Hz, 2H), 3.75–3.60 (m, 8H), 2.34 (s, 6H, CH$_3$ + CH$_3$), 1.65–1.31 (m, 3H), 1.21–0.91 (m, 7H), 0.91–0.76 (m, 7H), 0.76–0.65 (m, 3H) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 172.2$ (C=O), 172.1 (C=O), 143.2 (ArC–N), 138.1 (ArC), 137.8 (ArC), 137.6 (ArC), 137.5 (ArC), 134.9 (ArC), 134.8 (ArC), 131.6 (ArC), 131.3 (ArC), 129.5 (ArC), 129.4 (ArC), 128.7 (ArC), 127.7 (ArC), 127.6 (ArC), 127.1 (ArC), 126.9 (ArC), 58.9 (NCH), 58.4 (NCH$_2$), 52.0 (OCH$_3$), 51.9 (OCH$_3$), 36.6, 28.6, 28.6, 21.6, 18.4, 17.9, 11.8, 11.5 ppm; IR (neat): $\nu = 2978$w, 2881w 2394m, 2341m, 1708s, 1475w, 1419w, 1361m, 1336m, 1220m, 1174w, 1159m, 1114w, 1097w, 1082m, 1037m, 964w, 912w, 842w, 790w, 763w cm$^{-1}$; HRMS (NSI): Exact mass calculated for C$_{22}$H$_{26}$NO$_4$S [M+H]$^+$: 376.1577, found: 376.1580.

Methyl 2-((N-allyl-4-methylphenyl)sulfonamido)phenyl) acetate 152o:

Performed according to General Procedure 5 on a 0.93 mmol scale of 159a and prop-2-en-1-ol; 152o (286 mg, 0.80 mmol, 86%) was obtained as a colourless oil.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.50$ (d, $J = 8.1$ Hz, 2H, Ar$H$), 7.38 (d, $J = 7.7$ Hz, 1H, Ar$H$), 7.25–7.22 (m, 3H, Ar$H$), 7.07 (t, $J = 7.7$ Hz, 1H, Ar$H$), 6.51 (d, $J = 8.0$ Hz, 1H, Ar$H$), 5.77–5.62 (m, 1H, $H^\beta$), 5.07–4.80 (m, 2H, $H^\alpha + H^\beta$), 4.32 (dd, $J = 14.1$, 5.9 Hz, 1H, $1 \times NCH_2$), 4.04 (d, $J = 16.4$ Hz, 1H, $1 \times CH_2$), 3.82 (dd, $J = 14.1$, 7.6 Hz, 1H, $1 \times NCH_2$), 3.77–3.63 (m, 4H, $1 \times CH_2 + OCH_3$), 2.39 (s, 3H, $CH_3$) ppm; $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta = 170.9$ (C=O), 142.7 (ArC–N), 137.0 (ArC), 135.1 (ArC), 134.1 (ArC), 131.3, 130.4, 128.5 (2 × ArC), 127.5, 127.2, 127.1 (2 × ArC), 126.5, 118.5 (CH=CH$_2$), 53.9 (NCH$_2$), 50.9 (OCH$_3$), 35.5 (CH$_2$), 20.5 (CH$_3$) ppm.
1-Benzylindolin-2-one 163:

To a solution of 159c\(^a\) (200 mg, 0.75 mmol) and triethylamine (210 μL, 1.5 mmol) in acetonitrile (3 mL) at 0 °C benzyl bromide (134 μL, 1.1 mmol) was added and the mixture was stirred for 24 hours at 50 °C. The solution was cooled down, the solvent was concentrated, and the residual oil was dissolved in CH\(_2\)Cl\(_2\) (10 mL), washed with water (10 mL) and then brine (10 mL). After drying over MgSO\(_4\), the mixture was concentrated \textit{in vacuo} and purified via column chromatography to afford 163 (140 mg, 0.63 mmol, 84%) as a colourless solid, m.p.: 66–70 °C.

\(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 7.36–7.17\) (m, 6H, Ar\(H\)), 7.12 (td, \(J = 7.8, 1.2\) Hz, 1H, Ar\(H\)), 6.96 (td, \(J = 7.7, 1.0\) Hz, 1H, Ar\(H\)), 6.68 (d, \(J = 7.8\) Hz, 1H, Ar\(H\)), 4.87 (s, 2H, NCH\(_2\)), 3.57 (s, 2H, CH\(_2\)) ppm; \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 175.3\) (C=O), 144.5 (ArC–N), 136.0 (ArC), 128.9 (2 × ArC), 127.9 (ArC), 127.7(ArC), 127.5 (2 × ArC), 124.6 (ArC), 124.5 (ArC), 122.5 (ArC), 109.2 (ArC), 43.9 (NCH\(_2\)), 35.9 (CH\(_2\)) ppm. Spectroscopic data are in agreement with literature.\(^6\)

Methyl 2-(2-(benzylamino)phenyl)acetate 170:

To neat starting material 156a (600 mg, 3.6 mmol) benzaldehyde 168 (3.0 mmol) was added dropwise and an exothermic reaction was observed, hence some MgSO\(_4\) (~100 mg) was added to remove the water formed. The suspension was stirred for 20 minutes then the MgSO\(_4\) was filtered off and the product was washed off the salt with CH\(_2\)Cl\(_2\) (5 mL). A pre-mixed solid mixture of 1:1 NaBH\(_4/\)H\(_3\)BO\(_3\) (3 mmol) was added portion wise and the solution was stirred vigorously overnight at room temperature. Water was added and the phases were separated. The organic layer was washed with brine and dried over MgSO\(_4\) and concentrated under reduced pressure. The crude was purified by column chromatography to afford 170 (450 mg, 1.7 mmol, 49% yield) as a colourless oil.

\(^a\) Synthesised by Dr. S. T. R. Müller.
1H NMR (500 MHz, CDCl₃): δ = 7.42–7.30 (m, 4H, ArH), 7.30–7.25 (m, 1H, ArH), 7.19–7.08 (m, 2H, ArH), 6.71 (td, J = 7.4, 1.0 Hz, 1H, ArH), 6.66 (d, J = 8.1 Hz, 1H, ArH), 4.92 (br. s, 1H, NH), 4.39 (s, 2H, NCH₂), 3.67 (s, 3H, OCH₃), 3.60 (s, 2H, CH₂) ppm; ¹³C NMR (126 MHz, CDCl₃): δ = 172.4 (C=O), 146.7 (ArC–N), 139.5 (ArC), 131.2 (ArC), 128.9 (ArC), 128.8 (2 × ArC), 127.5 (2 × ArC), 127.3 (ArC), 119.3 (ArC), 117.7 (ArC), 111.8 (ArC), 52.4 (OCH₃), 48.1 (NCH₂), 38.7 (CH₂) ppm; IR (neat): ν = 3385w, 3026w, 2949w, 2845w, 1720s, 1602m, 1516m, 1452m, 1261m, 1147m, 748s cm⁻¹; HRMS (NSI): Exact mass calculated for C₁₆H₁₈NO₂ [M+H]+: 256.1332; found: 256.1333.

Methyl 2-(2-(benzyl(methyl)amino)phenyl)acetate 171:

To a solution of starting material 170 (417 mg, 1.6 mmol) and triethylamine (3.2 mmol) in DMF (16 mL), methyl iodide (6.5 mmol) was added dropwise. The solution was stirred overnight at room temperature. The solution was concentrated under reduced pressure inside a fume-cupboard to remove the unreacted methyl iodide. The residue was washed with water (50 mL) and the product was extracted with Et₂O (5 × 20 mL). The combined organic layers were washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The crude was purified by column chromatography to afford 171 (86 mg, 0.32 mmol, 20% yield) as a colourless oil.

1H NMR (300 MHz, CDCl₃): δ = 7.31–7.10 (m, 8H, ArH), 7.08–6.98 (m, 1H, ArH), 3.90 (s, 2H, CH₂), 3.76 (s, 2H, CH₂), 3.60 (s, 3H, CH₃), 2.45 (s, 3H, CH₃) ppm; ¹³C NMR (75 MHz, CDCl₃): δ = 172.9 (C=O), 152.7 (ArC), 138.7 (ArC), 131.0 (ArC), 130.8 (ArC), 128.8 (ArC), 128.3 (ArC), 128.3 (ArC), 127.2 (ArC), 124.5 (ArC), 122.1 (ArC), 61.7, 52.0, 42.0, 36.9 ppm; IR (neat): ν = 3057w, 3032w, 2922w, 1701s, 1614s, 1466s, 1344s, 1165s, 516m cm⁻¹; HRMS (NSI): Exact mass calculated for C₁₇H₂₀NO₂ [M+H]+: 270.1489; found: 270.149.
5.2.2 Diazo-transfer Reaction in Batch

Phenyldiazoacetate 165:

\[
\begin{align*}
\text{CO}_2\text{Me} & \quad \text{p-ABSA 18e} \\
\text{164} & \quad \text{DBU} \\
\text{CH}_3\text{CN} & \quad \text{165}
\end{align*}
\]

A 0.2 M solution of methyl phenylacetate 164 (600 mg, 4.0 mmol) and p-ABSA 18e (1.9 g, 8 mmol) in acetonitrile (10 mL) was cooled to 0 °C before the addition of DBU (897 µL, 6 mmol). The reaction was stirred at room temperature for 12 hours and monitored by TLC (n-hexane/ethyl acetate). The mixture was quenched with a saturated aqueous solution of NH\(_4\)Cl and the product was extracted with CH\(_2\)Cl\(_2\) (3 × 5 mL). The combined organic layers were washed with water, brine, dried over MgSO\(_4\) and concentrated under reduced pressure. The crude was purified by flash column chromatography to afford 165 was afforded as a red oil (580 mg, 3.3 mmol, 83% yield).

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 7.52–7.45\) (m, 2H, Ar\(H\)), 7.45–7.34 (m, 2H, Ar\(H\)), 7.22–7.11 (m, 1H, Ar\(H\)), 3.87 (s, 3H, OC\(H\)\(_3\)) ppm; \(^{13}\)C NMR (126 MHz, CDCl\(_3\)): \(\delta = 165.8\) (C=O), 129.1 (Ar\(C\)), 126.0 (Ar\(C\)), 125.6 (Ar\(C\–C\)), 124.1 (Ar\(C\)), 52.1 (OCH\(_3\)) ppm (C=N\(_2\) not observed); IR (neat): \(\nu = 3059\)w, 2953w, 2843w, 2362w, 2083s, 1699s, 1597w, 1575w, 1498m, 1435m, 1352m, 1247m cm\(^{-1}\). Spectroscopic data are in agreement with the literature.\(^7\)

\(p\)-Nitrobenzenesulfonyl azide 18f:

\[
\begin{align*}
\text{SO}_2\text{Cl} & \quad \text{NaN}_3 [1.5] \\
\text{18f} & \quad \text{water} / \text{acetone (1:3)}
\end{align*}
\]

A solution of sodium azide (290 mg, 4.5 mmol) in water (2 mL) was added dropwise to a solution of \(p\)-nitrobenzenesulfonyl chloride 97%\(_{\text{wt}}\) (685 mg, 3 mmol) in acetone (6 mL) cooled to 0 °C. The mixture was allowed to warm up to room temperature and stirred overnight. Acetone was then removed under reduced pressure (water bath at 25 °C). The residue was washed with water (10 mL) and Et\(_2\)O (10 mL). The organic layer was further washed with 5%\(_{\text{wt}}\) Na\(_2\)CO\(_3\) aqueous solution, water and brine then dried over MgSO\(_4\) and concentrated under reduced pressure (water bath at 25 °C) to afford 18f (622 mg, 2.73 mmol, 91%) as a pale yellow solid, m.p.: 100–102 °C.
Experimental Part

**Micol Santi**

1H NMR (500 MHz, CDCl3): δ = 8.51–8.43 (m, 1H, ArH), 8.25–8.06 (m, 1H, ArH) ppm; 13C NMR (126 MHz, CDCl3): δ = 151.2 (ArC–N), 143.7 (ArC–S), 129.0 (2 × ArC), 125.1 (2 × ArC) ppm; IR (neat): ν = 3107m, 2318w, 2140s, 1604m, 1527s, 1404m, 1348s, 1155s, 1109m, 1083s, 1012m, 854s, 761s, 742s, 731s, cm⁻¹. Spectroscopic data are in accordance with the literature.⁸

**General Procedure 6:**

![Diagram of General Procedure 6](image)

A solution containing the ester 152a–n (1 mmol) and p-NBSA 18f (456 mg, 2 mmol) in CH₃CN (4 mL) was cooled down to 0 °C. DBU (374 μL, 2.5 mmol) was added dropwise. The reaction stirred for 48 hours at room temperature or 45 °C and checked by TLC (n-hexane/ethyl acetate 4:1). Then, the reaction mixture was cooled down to 0 °C and a pH 7 phosphate buffer (10 mL) was added to quench the reaction. The reaction mixture was extracted with CH₂Cl₂ (2 × 20 mL) and the combined organic fractions were washed with pH 7 phosphate buffer (10 mL), brine (15 mL) and dried over MgSO₄. The solvent was evaporated in vacuo (water temperature: 25 °C) and the crude reaction mixture was purified via flash column chromatography to afford 153a–n.

Methyl 2-(2-((N-benzyl-4-methylphenyl)sulfonamido)phenyl)-2-diazoacetate 153a:

Performed according to General Procedure 6 on a 1.0 mmol scale of 152a; 153a (280 mg, 0.65 mmol, 65%) was obtained as a yellow solid, m.p.: 110–112 °C (N₂ loss > 80 °C).

1H NMR (400 MHz, CDCl₃): δ = 7.64 (d, J = 8.2 Hz, 2H, ArH), 7.46 (dd, J = 7.8, 1.0 Hz, 1H, ArH), 7.33 (d, J = 8.2 Hz, 2H, ArH), 7.26 (d, J = 7.6 Hz, 1H, ArH), 7.13–7.22 (m, 3H, ArH), 7.05–7.11 (m, 3H, ArH), 6.54 (dd, J = 8.1, 1.0 Hz, 1H, ArH), 5.08 (br. s, 1H, N–CH₂), 4.07 (br. s, 1H, N–CH₂), 3.61 (s, 3H, OCH₃), 2.46 (s, 3H, CH₃) ppm; 13C NMR (75 MHz, CDCl₃): δ = 166.1 (C=O), 144.1 (ArC–N), 137.0 (ArC), 135.9 (ArC), 134.5 (ArC), 131.3 (ArC), 129.8 (2 × ArC), 129.6 (2 × ArC), 128.8 (ArC), 128.5 (3 × ArC), 128.4 (2 × ArC), 128.3 (ArC), 128.1 (ArC), 127.8 (ArC), 60.6 (C=O), 57.0 (NCH₂), 51.9 (OCH₃), 21.8 (CH₃) ppm; IR (neat): ν = 3064w, 3032w, 2954w, 2924w, 2096s, 1693s, 1494m, 1429m, 1344s, 1242m, 1159s, 1151s,
1045m, 1029s, 858m, 812m, 717s cm$^{-1}$; HRMS (NSI): Exact mass calculated for C$_{23}$H$_{22}$N$_4$O$_4$SNH$_4$ [M+Na]$^+$: 458.1145; found: 458.1142. The structure was confirmed by X-Ray analysis (Figure 5.1).

**Figure 5.1:** X-ray structure of 153a.$^b$

Methyl 2-azido-2-(2-((N-benzyl-4-methylphenyl)sulfonamido)phenyl) acetate 166:

Side product 166 (1:1.1 mixture of two rotamers) was obtained as a pale-yellow solid.

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 7.51 (dd, $J$ = 8.3, 2.9 Hz, 4H, ArH), 7.17 (m, 23H, ArH), 6.57 (t, $J$ = 7 Hz, 2H, ArH), 5.48 (s, 1H, N$_3$CH$_2$), 5.26 (s, 1H, N$_3$CH$_2$), 5.02 (d, $J$ = 13.4 Hz, 1H, NC$_2$H$_2$I), 4.90 (d, $J$ = 13.9 Hz, 1H, NCH$_2$), 4.33 (d, $J$ = 13.9 Hz, 1H, NCH$_2$), 4.11 (d, $J$ = 13.4 Hz, 1H, NC$_2$H$_2$I), 3.69 (s, 3H, OCH$_3$), 3.38 (s, 3H, OCH$_3$), 2.38 (s, 6H, 2 × Ar–CH$_3$) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 169.5 (C=O), 169.4 (C=O), 144.1 (Ar–N), 144.0 (Ar–N), 137.9 (ArC), 137.7 (ArC), 135.9 (ArC), 135.6 (ArC), 135.2 (ArC), 135.1 (ArC), 135.0 (ArC), 134.7 (ArC), 129.7 (ArC), 129.6 (ArC), 129.5 (ArC), 129.4 (ArC), 129.2 (ArC), 129.1 (ArC), 129.0 (ArC), 128.8 (ArC), 128.6 (ArC), 128.4 (ArC), 128.3 (ArC), 128.2 (ArC), 128.0 (ArC), 127.9 (ArC), 60.1 (CH–N$_3$), 59.9 (CH–N$_3$), 56.3 (NCH$_2$), 56.4 (NCH$_2$), 53.0 (OCH$_3$), 52.8 (OCH$_3$), 21.6 (2 × CH$_3$) ppm; IR (neat): ν = 3062w, 3030w, 2954m, 2926m, 2875w, 2850w, 2100s, 1735s, 1595m, 1490m, 1456m, 1448m, 1436m, 1354s, 1257w, 1211s, 1161s, 1089s, 1029s, 867m, 758m, 661s, 522m, 476w cm$^{-1}$; HRMS: Exact mass calculated for C$_{23}$H$_{22}$N$_4$O$_4$SNH$_4$ [M+NH$_4$]$^+$: 468.1700; found: 468.1695. The structure was confirmed by X-Ray analysis (Figure 5.2).

**Figure 5.2:** X-ray structure of 166.$^c$

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b. Measured by Dr. Benson Kariuki at Cardiff University, School of Chemistry
c. Measured by Dr. Benson Kariuki at Cardiff University, School of Chemistry
Isopropyl 2-(2-((N-benzyl-4-methylphenyl)sulfonamido)phenyl)-2-diazoacetate 153b:

Performed according to General Procedure 6 at 45 °C on a 0.37 mmol scale of 152b; 153b (86 mg, 0.19 mmol, 51%) obtained as yellow solid, m.p.: 86–90 °C (N₂ loss > 80 °C).

¹H NMR (300 MHz, CDCl₃): δ = 7.67 (d, J = 8.1 Hz, 2H, ArH), 7.58 (d, J = 7.2 Hz, 1H, ArH), 7.40–6.71 (m, 9H, ArH), 6.56 (d, J = 7.6 Hz, 1H), 5.23–4.70 (m, 2H, 1 × NC₄H₂ + OC₃H), 4.18 (br. s, 1H, 1 × NC₄H₂), 2.49 (s, 3H, C₃H₃), 1.16 (d, J = 6.1 Hz, 6H, 2 × C₃H₃) ppm; ¹³C NMR (75 MHz, CDCl₃): δ = 165.3 (C=O), 144.2 (ArC–N), 136.7 (ArC), 135.9 (ArC), 134.6 (ArC), 131.0 (ArC), 129.8 (2 × ArC), 129.6 (2 × ArC), 128.7 (2 × ArC), 128.5 (2 × ArC), 128.4 (2 × ArC), 128.3 (ArC), 128.2 (ArC), 127.4 (ArC), 68.5 (OCH), 60.7 (C=N₂), 56.9 (NCH₂), 22.2 (CH₃), 21.8 (CH₃) ppm; IR (neat): ν = 2916m, 2848m, 2104s, 1695s, 1595w, 1490m, 1448m, 1336s, 1238s, 1151s, 1105s, 1089s, 1012s, 910w, 856m, 817m, 715s, 698m, 659s, 615m, 586m, 547s cm⁻¹; HRMS (NSI): Exact mass calculated for C₂₅H₂₉N₂O₄S [M−N₂+NH₄]⁺: 453.1843; found: 453.1838.

Methyl 2-diazo-2-(2-((N-(4-methoxybenzyl)-4-methylphenyl)sulfonamido)phenyl)acetate 153c:

Performed according to General Procedure 6 at 45 °C on a 0.41 mmol scale of 152c; 153c (105 mg, 0.23 mmol, 56%) obtained as a yellow solid, m.p.: 132–135 °C (N₂ loss > 80 °C).

¹H NMR (400 MHz, CDCl₃): δ = 7.66 (d, J = 8.2 Hz, 2H, ArH), 7.50 (d, J = 8.1 Hz, 1H, ArH), 7.34 (d, J = 8.1 Hz, 2H, ArH), 7.29 (t, J = 7.7 Hz, 1H, ArH), 7.09 (td, J = 8.0, 1.3 Hz, 1H, ArH), 7.00 (d, J = 8.6 Hz, 2H, ArH), 6.70 (d, J = 8.6 Hz, 2H, ArH), 6.55 (d, J = 7.8 Hz, 1H, ArH), 5.05 (d, J = 11.4 Hz, 1H, 1 × NCH₂), 4.04 (d, J = 11.6 Hz, 1H, 1 × NCH₂), 3.74 (s, 3H, OCH₃), 3.65 (s, 3H, OCH₃), 2.48 (s, 3H, CH₃) ppm; ¹³C NMR (75 MHz, CDCl₃): δ = 166.1 (C=O), 159.5 (ArC–O), 144.1 (ArC–N), 136.9 (ArC), 136.0 (ArC), 131.2 (ArC), 130.8 (2 × ArC), 129.8 (ArC), 128.8 (ArC), 128.5 (ArC), 128.4 (2 × ArC), 128.2 (ArC), 127.7 (ArC), 126.6 (ArC), 113.8 (ArC), 56.5, 55.2, 51.8, 31.0, 21.7 (CH₃) ppm; IR (neat): ν = 2953w, 2096s, 1703s, 1612w, 1589w, 1492m, 1435m, 1340s, 1263s, 1240s, 1149s, 1028s, 877m, 813m, 758s, 727s, 658s, 607s cm⁻¹; HRMS (NSI): Exact mass calculated for C₂₄H₂₁N₃O₄SNa [M−N₂+Na⁺]: 488.1251; found: 488.1245.
Methyl 2-diazo-2-((4-methyl-N-(4-(trifluoromethyl)benzyl)phenyl)sulfonamido)phenyl) acetate, **153d**:

![Chemical structure](image)

Performed according to **General Procedure 6** at 45 °C on a 0.21 mmol scale of **152d**: **153d** (84 mg, 0.17 mmol, 79%) obtained as a yellow solid, m.p.: 116–118 °C (N\textsubscript{2} loss > 80 °C).

\[\text{δ} = 7.63 (d, J = 8.3 \text{ Hz}, 2H, ArH), 7.55–7.40 (m, 3H, ArH), 7.32 (d, J = 8.0 \text{ Hz}, 2H, ArH), 7.28–7.21 (m, 3H, ArH), 7.10 (td, J = 7.9, 1.6 \text{ Hz}, 1H, ArH), 6.55 (dd, J = 8.0, 1.2 \text{ Hz}, 1H, ArH), 5.09 (br. s, 1H, 1 × NCH\textsubscript{2}), 4.08 (br. s, 1H, 1 × NCH\textsubscript{2}), 3.57 (s, 3H, OCH\textsubscript{3}), 2.45 (s, 3H, CH\textsubscript{3}) \text{ ppm; } ^{13}\text{C} \text{ NMR (125 MHz, CDCl\textsubscript{3})}: \text{δ} = 165.9 (C=O), 144.5 (ArC–N), 138.8 (ArC), 137.3 (ArC), 135.8 (ArC), 131.8 (ArC), 130.4 (q, J = 32.4 \text{ Hz}, ArC–CF\textsubscript{3}), 129.9 (2 × ArC), 129.8 (2 × ArC), 129.1 (ArC), 128.5 (2 × ArC), 128.4 (ArC), 128.2 (ArC), 128.1 (ArC), 125.3 (q, J = 3.7 \text{ Hz}, ArC), 124.0 (q, J = 273.5 \text{ Hz}, ArC–CF\textsubscript{3}), 60.3 (C=N\textsubscript{2}), 56.5 (NCH\textsubscript{3}), 21.8 (CH\textsubscript{3}) \text{ ppm; IR (neat): } \nu = 2954w, 2926w, 2096s, 1741w, 1695s, 1618w, 1597w, 1492m, 1448w, 1435m, 1421w, 1323s, 1240s, 1161s, 1111s, 1066s, 1020s, 817m, 713s, 661s, 547s cm\textsuperscript{-1}; HRMS (ES): Exact mass calculated for C\textsubscript{24}H\textsubscript{20}F\textsubscript{3}N\textsubscript{3}O\textsubscript{4}SNa [M+Na\textsuperscript{+}]: 526.1024; found: 526.0999.

Methyl 2-diazo-2-((4-methyl-N-(4-methylbenzyl)phenyl)sulfonamido)phenyl) acetate **153f**:

![Chemical structure](image)

Performed according to **General Procedure 6** at 45 °C on a 0.35 mmol scale of **152f**: **153f** (108 mg, 0.24 mmol, 69%) obtained as a yellow solid, m.p.: 102–104 °C (N\textsubscript{2} loss > 80 °C).

\[\text{δ} = 7.59 (d, J = 8.1 \text{ Hz}, 2H, ArH), 7.42 (d, J = 7.3 \text{ Hz}, 1H, ArH), 7.39–7.17 (m, 3H, ArH), 7.02 (t, J = 7.0 \text{ Hz}, 1H, ArH), 6.90 (s, 4H, ArH), 6.48 (d, J = 7.7 \text{ Hz}, 1H, ArH), 4.97 (br. s, 1H, 1 × CH\textsubscript{2}), 3.98 (br. s, 1H, 1 × CH\textsubscript{2}), 3.57 (s, 3H, OCH\textsubscript{3}), 2.41 (s, 3H, CH\textsubscript{3}), 2.19 (s, 3H, CH\textsubscript{3}) \text{ ppm; } ^{13}\text{C} \text{ NMR (75 MHz, CDCl\textsubscript{3})}: \text{δ} = 166.0 (C=O), 154.6 (ArC–N), 144.0 (ArC), 137.8 (ArC), 136.8 (ArC), 135.7 (ArC), 131.3 (ArC), 131.1 (ArC), 129.7 (ArC), 129.4 (ArC), 129.0 (ArC), 128.7 (ArC), 128.3 (ArC), 128.0 (ArC), 127.6 (ArC), 60.7 (C=N\textsubscript{2}), 56.7 (NCH\textsubscript{3}), 51.8 (OCH\textsubscript{3}), 21.7 (CH\textsubscript{3}), 21.2 (CH\textsubscript{3}) \text{ ppm; IR (neat): } \nu = 2951w, 2918w, 2360m, 2100s, 1699s, 1597w, 1492m, 1435m, 1348s, 1290m, 1265m, 1246m, 1192w, 1111s, 1116s, 1116w, 1089w, 1033m, 912m, 815w, 779w, 734s, 663m, 574s cm\textsuperscript{-1}; HRMS (NSI): Exact mass calculated for C\textsubscript{24}H\textsubscript{27}N\textsubscript{2}O\textsubscript{4}SNNa [M−N\textsubscript{2}+NH\textsubscript{4}\textsuperscript{+}]: 439.1686; found: 439.1682.
Methyl 2-diazo-2-((4-methyl-N-(3-methylbenzyl)phenyl)sulfonylamido)phenyl) acetate 153g:

Performed according to General Procedure 6 at 45 °C on a 0.28 mmol scale of 152g; 153g (78 mg, 0.17 mmol, 61%) obtained as a yellow solid, m.p.: 100–102 °C (N₂ loss > 80 °C).

¹H NMR (400 MHz, CDCl₃): δ = 7.59 (d, J = 8.1 Hz, 2H, ArH), 7.42 (d, J = 7.8 Hz, 1H, ArH), 7.37–7.12 (m, 3H, ArH), 7.10–6.92 (m, 4H, ArH), 6.72 (d, J = 6.1 Hz, 1H, ArH), 6.48 (d, J = 7.9 Hz, 1H, ArH), 5.00 (br. s, 1H, 1 × CH₂), 3.98 (br. s, 1H, 1 × CH₂), 3.56 (s, 3H, OCH₃), 2.41 (s, 3H, CH₃), 2.16 (s, 3H, CH₃) ppm; ¹³C NMR (101 MHz, CDCl₃): δ = 166.1 (C=O), 144.2 (ArC–N), 138.3 (ArC), 137.1 (ArC), 136.0 (ArC), 134.5 (ArC), 131.3 (ArC), 130.3 (ArC), 129.8 (2 × ArC), 128.8 (ArC), 128.7 (ArC), 128.5 (ArC), 128.4 (2 × ArC), 128.3 (ArC), 128.2 (ArC), 127.7 (ArC), 126.6 (ArC), 60.6 (C=N₂), 57.0 (NCH₂), 51.8 (OCH₃), 21.8 (CH₃), 21.3 (CH₃) ppm; IR (neat): ν = 2951w, 2918w, 2358m, 2341m, 2098s, 1697s, 1595m, 1492m, 1435m, 1344m, 1288s, 1246m, 1155s, 1118w, 1089m, 1049m, 752m, 723s, 705m, 661s, 565s cm⁻¹; HRMS (NSI): Exact mass calculated for C₂₄H₂₃N₃O₄SNa [M+Na]⁺: 472.1301; found: 472.1295.

Methyl 2-((1,1'-biphenyl)-2-ylmethyl)-4-methylphenyl)acetate 153h:

Performed according to General Procedure 6 at 45 °C on a 0.30 mmol scale of 152h; 153h (117 mg, 0.23 mmol, 76%) was obtained as a yellow solid, m.p.: 144–146 °C (N₂ loss > 80 °C).

¹H NMR (400 MHz, CDCl₃): δ = 7.82 (d, J = 7.7 Hz, 1H, ArH), 7.49 (d, J = 8.0 Hz, 2H, ArH), 7.36–7.12 (m, 6H, ArH), 7.04–6.86 (m, 4H, ArH), 6.73 (t, J = 7.5 Hz, 1H, ArH), 6.51 (d, J = 7.2 Hz, 2H, ArH), 5.96 (d, J = 7.9 Hz, 1H, ArH), 4.94 (br. s, 1H, 1 × NCH₂), 4.10 (br. s, 1H, 1 × NCH₂), 3.51 (s, 3H, OCH₃), 2.35 (s, 3H, CH₃) ppm; ¹³C NMR (101 MHz, CDCl₃): δ = 166.0 (C=O), 144.0 (ArC–N), 142.3 (ArC), 140.1 (ArC), 137.6 (ArC), 136.1 (ArC), 132.5 (ArC), 131.8 (ArC), 130.5 (ArC), 129.9 (ArC), 129.8 (2 × ArC), 129.0 (2 × ArC), 128.5 (ArC), 128.3 (2 × ArC), 128.2 (ArC), 128.1 (ArC), 128.0 (ArC), 127.8 (ArC), 127.7 (2 × ArC), 127.4 (ArC), 126.4 (ArC), 60.2 (C=N₂), 53.1 (NCH₂), 51.7 (OCH₃), 21.7 (CH₃) ppm; IR (neat): ν = 3062w, 2953w, 2102s, 1693s, 1431m, 1342s, 1255m, 1238m, 1155s, 1045m, 854m, 712s, 659s, 569s, 542s cm⁻¹; HRMS (APCI): Exact mass calculated for C₂₉H₂₅N₃O₄SNa [M+Na]⁺: 534.1463; found: 534.1453.
Methyl 2-diazo-2-((4-methyl-N-(2-methylbenzyl)phenyl)sulfonamido)phenyl) acetate 153i:

Performed according to General Procedure 6 at 45 °C on a 0.30 mmol scale of 152i; 153i (79 mg, 0.17 mmol, 59%) was obtained as a yellow solid.

1H NMR (400 MHz, CDCl3): δ = 7.71 (d, J = 8.1 Hz, 2H, ArH), 7.51–7.33 (m, 3H, ArH), 7.33–7.19 (m, 1H, ArH), 7.18–6.99 (m, 3H, ArH), 6.90 (t, J = 7.3 Hz, 1H, ArH), 6.76 (d, J = 7.6 Hz, 1H, ArH), 6.60 (d, J = 8.0 Hz, 1H, ArH), 5.24 (br. s, 1H, 1 × NH₂CH₂), 4.03 (br. s, 1H, 1 × NH₂CH₂), 3.59 (s, 3H, OCH₃), 2.50 (s, 3H, CH₃), 2.24 (s, 3H, CH₃) ppm; 13C NMR (101 MHz, CDCl₃): δ = 165.9 (C=O), 144.3 (ArC-N), 138.0 (ArC), 137.4 (ArC), 135.7 (ArC), 132.1 (ArC), 131.7 (ArC), 130.9 (ArC), 130.4 (ArC), 129.9 (2 × ArC), 128.9 (ArC), 128.8 (ArC), 128.6 (2 × ArC), 128.2 (ArC), 127.9 (ArC), 127.8 (ArC), 125.9 (ArC), 60.4 (C=N₂), 54.7 (NCH₂), 51.8 (OCH₃), 21.8 (Ar-CH₃), 18.8 (CH₃) ppm; IR (neat): ν = 2951w, 2922w, 2858w, 2362w, 2098s, 1697s, 1595w, 1514w, 1435m, 1334s, 1155s, 1089w, 1033m, 912m, 754m, 729s, 663s, 607w, 580s, 553m cm⁻¹; HRMS (NSI): Exact mass calculated for C₂₄H₂₇N₂O₄S: [M−N₂+NH₄]+= 439.1686; found: 439.1682.

Methyl 2-(2-((N-((1-bromonaphthalen-2-yl)methyl)-4-methylphenyl)sulfonamido)phenyl) 2-diazoacetate 153k:

Performed according to General Procedure 6 at 45 °C on a 0.34 mmol scale of 152k; 153k (146 mg, 0.26 mmol, 76%) was obtained as a yellow solid, m.p.: 136–138 °C (N₂ loss >80 °C).

1H NMR (400 MHz, CDCl₃): δ = 8.11 (d, J = 8.4 Hz, 1H, ArH), 7.69 (t, J = 6.9 Hz, 3H, ArH), 7.61 (d, J = 8.4 Hz, 1H, ArH), 7.53–7.36 (m, 3H, ArH), 7.33 (d, J = 8.0 Hz, 2H, ArH), 7.20 (dt, J = 7.8, 7.0 Hz, 2H, ArH), 7.06 (t, J = 7.6 Hz, 1H, ArH), 6.62 (d, J = 8.0 Hz, 1H, ArH), 5.35 (br. s, 1H, 1 × NCH₂), 4.59 (br. s, 1H, 1 × NCH₂), 2.87 (s, 3H, OCH₃), 2.44 (s, 3H, CH₃) ppm; 13C NMR (101 MHz, CDCl₃): δ = 165.6 (C=O), 144.4 (ArC-N), 137.9 (ArC), 134.7 (ArC), 135.9 (ArC), 134.2 (ArC), 132.2 (ArC), 132.1 (ArC), 132.0 (ArC), 129.9 (2 × ArC), 128.9 (ArC), 128.6 (2 × ArC), 128.5 (ArC), 128.4 (ArC), 128.2 (ArC), 128.17 (2 × ArC), 128.16 (2 × ArC), 127.9 (ArC), 127.5 (ArC), 126.9 (ArC), 125.4 (ArC), 60.4 (C=N₂), 57.4 (NCH₂), 51.3 (OCH₃), 20.6 (CH₃) ppm; IR (neat): ν = 2956w, 2924s, 1597w, 1492m, 1438m, 1344s, 1247m, 1192w, 1155s, 854m, 813s, 752s, 736m, 717s, 661s, 648m, 590w, 576s, 547m, 528m cm⁻¹; HRMS (NSI): Exact mass for C₂₇H₂₇N₂O₄SBr [M−N₂+NH₄]+= 553.1009; found: 553.0786.
Methyl 2-(2-((N-cinnamyl-4-methylphenyl)sulfonamido)phenyl)-2-diazoacetate 153l:

Performed according to General Procedure 6 at 22 °C on a 0.62 mmol scale of 152l with 1.2 mmol p-NBSA and 1.2 mmol of DBU. 153l (116 mg, 0.25 mmol, 42%) was obtained as a yellow solid, m.p.: 106–108 °C (N₂ loss > 60 °C). The compound was unstable and decomposed during characterisation. The mixture of unreacted starting material, diazo compound and side product was used for the following step without further purification.

¹H NMR (400 MHz, CDCl₃): δ = 7.54 (d, J = 8.2 Hz, 2H, ArH), 7.26–7.10 (m, 9H, ArH), 7.08–7.03 (m, 1H, ArH), 6.59 (d, J = 8.0 Hz, 1H, ArH), 6.26 (d, J = 15.8 Hz, 1H, CH=C–H–Ph), 6.05–5.93 (m, 1H, NCH₂=CH), 4.39 (br. s, 1H, 1×NC₂H₂), 3.95 (br. s, 1H, 1×NC₂H₂), 3.55 (s, 3H, OC₃H₃), 2.37 (s, 3H, C₃H₃) ppm; ¹³C NMR (101 MHz, CDCl₃): δ = 166.4 (C=O), 144.1 (ArC–N), 137.3 (ArC), 136.2 (ArC), 135.6 (ArC), 135.2 (ArC), 131.5 (ArC), 129.7 (2×ArC), 128.9 (ArC), 128.6 (2×ArC), 128.6 (2×ArC), 128.4 (2×ArC), 128.1 (ArC), 126.6 (2×ArC), 122.6 (ArC), 54.6 (NCH₂), 52.0 (OCH₃), 21.7 (CH₃) ppm; IR (neat): v = 3038w, 2953w, 2099s, 1697s, 1491m, 1431m, 1348s, 1149s cm⁻¹. The product decomposed during mass spectrometric analysis.

Methyl 2-diazo-2-(2-((N-(n-hexyl)-4-methylphenyl)sulfonamido)phenyl) acetate 153m:

Performed according to the General Procedure 6 at 45 °C on a 0.24 mmol scale of 152m. After column chromatography 153m (41% by ¹H NMR) was still obtained as a 1.8 : 1 : 0.4 mixture of 152m, 153m and a side azide (rotamers 1.3 : 1). The mixture of unreacted starting material, diazo compound and side product was used for the following step without further purification.

Methyl 2-diazo-2-(2-((N-(sec-butyl)-4-methylphenyl)sulfonamido)phenyl) acetate 153n:

Performed according to General Procedure 6 at 45 °C on a 0.15 mmol scale of 152n; 153n (17 mg, 0.042 mmol, 28%) was obtained as a yellow oil, 1:1.3 mixture or rotamers (air-sensitive).

¹H NMR (400 MHz, CDCl₃): δ = 7.73–7.59 (m, 3H, ArH), 7.39 (t, J = 7.7 Hz, 1H, ArH), 7.35–7.28 (m, 2H, ArH), 7.22–7.12 (m, 1H, ArH), 6.75 (d, J = 8.0 Hz, 0.4H, ArH), 6.69 (d, J = 7.9 Hz, 0.6H, ArH), 4.27–4.13 (m, 1H, NCH + NCH), 3.86–3.82 (m, 3H, OCH₃ + OCH₃), 2.49–2.42 (m, 0.7H), 1.74–1.62 (m, 0.4H), 1.30–1.08 (m, 2H), 1.07–0.91 (m, 2H), 0.90–0.71 (m, 3H) ppm; ¹³C NMR (101 MHz,
CDCl₃: δ = 167.1 (C=O), 167.0 (C=O), 143.8 (ArC–N), 143.8 (ArC–N), 138.3 (ArC), 138.1 (ArC), 134.7 (ArC), 134.5 (ArC), 133.0 (ArC), 132.3 (ArC), 131.4 (ArC), 131.3 (ArC), 129.8 (2 × ArC), 129.7 (2 × ArC), 129.09 (ArC), 129.08 (ArC), 128.3 (2 × ArC), 128.1 (2 × ArC), 128.1 (ArC), 127.8 (ArC), 127.6 (2 × ArC), 59.3 (NCH), 59.1 (NCH), 52.3 (OCH₃), 28.8, 27.8, 21.7, 18.0, 11.6, 11.5 ppm; IR (neat): ν = 2960w, 2850w, 2098s, 1697s, 1358s, 1165s cm⁻¹. The isolated product decomposed during mass spectrometric analysis.

5.2.3 Diazotransfer in Flow and DoE

The starting material 152a (81.9–164 mg, 0.2–0.4 mmol) was dissolved in 2 mL of acetonitrile together with DBU (1.5–2.5 equiv.) and the internal standard (1,3,5-trimethoxybenzene 1 equiv.) and a HSW NORM-JECT® 2 mL syringe was equipped with the mixture. At the same time p-NBSA 18f (1–3 equiv.) was dissolved in 2 mL of acetonitrile and a second HSW NORM-JECT® 2 mL syringe was equipped with this solution. Next, the two syringes were loaded on a Chemyx Fusion syringe pump and connected to a flow setup via a T-piece mixer and a 1 mL coil (FEP, i.d. = 0.5 mm). The pump was then set to 0.1 mL·min⁻¹ (for t = 10 minutes) or 0.02 mL·min⁻¹ (for t = 50 minutes) and the entire setup run for 25 or 100 minutes, respectively, to ensure the achievement of the steady state. Afterwards, the solution was collected for 20–60 minutes in a 0.1 M phosphate buffer solution (pH = 7) as quenching agent. Extraction was performed with CH₂Cl₂ (3 × 5 mL), the combined organic layers were washed with water, dried over a MgSO₄ plug and concentrated under reduced pressure. When isolated the desired diazo compound 153a was purified by column chromatography (n-hexane / ethyl acetate 80:20). The data from the FFD 2⁵⁻¹ were analysed using a FFD and Design Expert® 10.⁹
Table 5.1: Real and coded values (+1 = higher level, −1 = lower level, 0 = central point) for the independent variables (k) and responses.

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Responses: 152a (%) | 153a (%) | 166 (%)

*Yield determined by ¹H NMR with 1,3,5-trimethoxybenzene as internal standard.

Table 5.2: Experimental Matrix of the FFD 2⁵⁻¹ in coded values and factor generator.

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Starting Material Residue

Shapiro-Wilk test
W-value = 0.907
p-value = 0.260

A: starting material
B: Temperature
C: DBU
D: p-NBSA
E: time

Figure 5.3: Half-normal plots for starting material 152a left.

ANOVA for R¹: Starting Material Residue

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Fit Statistics

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<tr>
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Equations in Terms of Coded Values

Starting Material Residue = 40.375 + 10.625B − 0.75C − 10.5D − 2.125E + 3.25CE
Experimental Part

Figure 5.4: Half-normal plots for diazo compound 153a formation.

**ANOVA for R²: Formation of Diazo Compound**

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<th>p-value</th>
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**Fit Statistics**

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<th>R²</th>
<th>Adjusted R²</th>
<th>Predicted R²</th>
<th>Adeq Precision</th>
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<td>0.8144</td>
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<td>0.7097</td>
<td>12.4261</td>
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</table>

**Equation in Terms of Coded Values**

Diazo Compound Formation = 31.4375 – 5.4375B + 6.8125D
**Formation of Side Azide**

- Error estimates
- Shapiro-Wilk test
  - W-value = 0.960
  - p-value = 0.771
- A: starting material
- B: Temperature
- C: DBU
- D: p-NBSA
- E: time
  - Positive effects
  - Negative effects

![Half-normal plot for azide formation](image)

**Figure 5.5:** Half-normal plot for azide formation.

### ANOVA for $R^3$: Formation of Azide

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<td>Pure Error</td>
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<tr>
<td>Cor Total</td>
<td>313.16</td>
<td>18</td>
<td></td>
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</table>

### Fit Statistics

- Std. Dev. 2.30
- $R^2$ 0.7794
- Mean 15.79
- Adjusted $R^2$ 0.7115
- C.V. % 14.58
- Predicted $R^2$ 0.5287
- Adeq Precision 9.1821

### Equations in Terms of Coded Values

\[
\text{Azide Formation} = 15.6875 - 3.4375B + 0.4375C + 1.0625E - 1.4375CE
\]
5.2.4 Synthesis of Dihydroindoles

**General Procedure 7:**

An oven-dried 25 mL round bottom flask was equipped with a magnetic stirring bar and flushed with argon. Molecular sieves (3 Å, 1.2 g), and Rh$_2$(R-DOSP)$_4$ 71a (1–0.5 mol%) were added in dry n-hexane. Subsequently, diazo compound 153a–k (0.23 mmol) were added (final concentration of starting material 0.13 M) and the yellow suspension was vigorously stirred at room temperature under inert atmosphere and checked by TLC (100% CH$_2$Cl$_2$) until all diazo compound were consumed (12–24 h). The mixture was filtered through a silica-plug, washed with CH$_2$Cl$_2$ (3 × 5 mL) and concentrated under vacuum to afford the corresponding product 154a–k as a mixture of trans and cis isomers, separated by prep-TLC or column chromatography in CH$_2$Cl$_2$.

**Methyl (2S,3S)-2-phenyl-1-tosylindoline-3-carboxylate (S,S)-154a:**

Performed according to General Procedure 7 on a 0.23 mmol scale of 153a using 0.5 mol% of Rh$_2$(R-DOSP)$_4$ over 12 h; (S,S)-154a (79 mg, 0.19 mmol, 82%, 11:1 d.r., 85% ee) was obtained as a colourless solid, m.p.: 130–134 °C.

$^1$H NMR (300 MHz, CDCl$_3$): δ = 7.76 (d, J = 8.2 Hz, 1H, ArH), 7.65 (d, J = 8.3 Hz, 2H, ArH), 7.42–7.25 (m, 7H, ArH), 7.19 (d, J = 8.0 Hz, 2H, ArH), 7.08 (td, J = 7.5, 0.9 Hz, 1H, ArH), 5.78 (d, J = 3.7 Hz, 1H, N–CH), 3.91 (d, J = 3.7 Hz, 1H, CH=CO$_2$Me), 3.55 (s, 3H, OCH$_3$), 2.36 (s, 3H, CH$_3$) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$): δ = 170.6 (C=O), 144.1 (ArC), 142.3 (ArC), 141.9 (ArC), 134.8 (ArC), 129.6 (2 × ArC), 128.9 (2 × ArC), 128.0 (ArC), 127.7 (2 × ArC), 127.5 (ArC), 126.4 (ArC), 125.9 (2 × ArC), 124.5 (ArC), 115.8 (ArC), 67.0, 55.8, 52.8, 21.7(CH$_3$) ppm; IR (neat): ν = 3032w, 2954w, 1732s, 1597m, 1477m, 1354s, 1238m, 1166s, 1155s, 1103m, 1089m, 1014m, 952m, 810m, 678s, 570s, 543s cm$^{-1}$; HMRS: Exact mass calculated for C$_{23}$H$_{21}$NO$_4$SNH$_4$ [M+NH$_4^+$]: 425.1530; found: 425.1525; HPLC (7:93 e.r.): Chiracel® OD-H (250 × 4.6 mm, 5 μm),
n-hexane/isopropanol 99:1 (v/v), 1.0 mL min⁻¹, 10 °C, \( \lambda = 254 \) nm, retention time \((R,R)-154a = 33.1\) min, retention time \((S,S)-154a = 36.7\) min.

In a similar reaction with Rh₂(S-DOSP)₄ the product \((R,R)-154a\) was obtained as the major isomer and crystallised for the determination of the X-ray structure. \((R,R)-154a: [\alpha]_D^{20} : +40^\circ \) (c 0.10, CHCl₃).

![Figure 5.6: X-ray structure of \((R,R)-154a\).
](image)

<table>
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<th>Peak #</th>
<th>Time (min)</th>
<th>Area (%)</th>
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<td>50.406</td>
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</table>

![Figure 5.7: HPLC chromatograms of trans-154a enantiomers. From the top: racemic mixture, 85% ee of \((S,S)-154a\).](image)

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<td>2</td>
<td>36.694</td>
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</table>

d. Measured by Dr. Benson Kariuki at Cardiff University, School of Chemistry
Methyl (2R,3S)-2-phenyl-1-tosylindoline-3-carboxylate (R,S)-154a:

\[
\text{cis-154a} \text{ was obtained as the minor product as a colourless oil after prep-TLC.}
\]

\[
^1H \text{ NMR (500 MHz, CDCl}_3\text{): } \delta = 7.71 (d, J = 8.2 \text{ Hz, 1H, ArH}), 7.52 (d, J = 8.0 \text{ Hz, 2H, ArH}), 7.34 (t, J = 7.5 \text{ Hz, 1H, ArH}), 7.24-7.06 (m, 9H, ArH), 5.59 (d, J = 10.0 \text{ Hz, 1H, N–C}H), 4.37 (d, J = 9.8 \text{ Hz, 1H, } CH–CO_2\text{Me}), 3.22 (s, 3H, OC\text{H}_3), 2.36 (s, 3H, CH_3) \text{ ppm; } ^{13}\text{C NMR (126 MHz, CDCl}_3\text{): } \delta = 169.7 (C=O), 144.2 (ArC), 142.8 (ArC), 137.5 (ArC), 135.4 (ArC), 129.8 (2 \times ArC), 129.1 (ArC), 128.7 (ArC), 128.5 (ArC), 128.3 (2 \times ArC), 127.3 (2 \times ArC), 127.2 (2 \times ArC), 124.7 (ArC), 116.2 (ArC), 67.4, 52.8, 51.8, 21.7 (CH_3) \text{ ppm; IR (neat): } \nu = 3032w, 2954w, 1732s, 1597m, 1477m, 1354s, 1238m, 1155s, 1103m, 1089m, 810m, 678s, 570s, 543s \text{ cm}^{-1}; \text{ HMRS: Exact mass calculated for C_{23}H_{21}NO_6SNH_4 [M+NH}_4^{+}: 425.1530; found: 425.1525; HPLC: YMC Chiral Amylose-C S (250 } \times 4.6 \text{ mm, 5 } \mu \text{m), n-hexane/isopropanol 90:10 (v/v), 1.0 mL min}^{-1}, 25 ^\circ \text C, \lambda = 254 \text{ nm, retention time first isomer = 17.5 min, retention time second isomer = 37.9 min.}
\]

Isopropyl (2S,3S)-2-phenyl-1-tosylindoline-3-carboxylate (S,S)-154b:

\[
\text{Performed according to General Procedure 7 on a 0.10 mmol scale of 153b using 1 mol\% of Rh}_2(R-DOSP)_4 \text{ over 12 h; 154b (27 mg, 0.062 mmol, 62%, 2.2:1 d.r., 35% ee) was obtained as a colourless solid m.p.: 120–124 } ^\circ \text C; [\alpha]_D^{20} = +5.6^\circ (c 0.36, CHCl}_3). \]

\[
^1H \text{ NMR (400 MHz, CDCl}_3\text{): } \delta = 7.64 (d, J = 8.1 \text{ Hz, 1H, ArH}), 7.55 (d, J = 7.8 \text{ Hz, 2H, ArH}), 7.37–7.12 (m, 7H, ArH), 7.07 (d, J = 8.1 \text{ Hz, 2H, ArH}), 6.96 (t, J = 7.5 \text{ Hz, 1H, ArH}), 5.69 (d, J = 4.0 \text{ Hz, 1H, N–C}H), 4.78 (septet, J = 6.2 \text{ Hz, 1H, OCH}_3), 3.77 (d, J = 3.8 \text{ Hz, 1H, } CH–CO_2\text{i-Pr}), 2.24 (s, 3H, CH_3), 1.10 (d, J = 6.2 \text{ Hz, 3H, CH}_3), 1.01 (d, J = 6.2 \text{ Hz, 3H, CH}_3) \text{ ppm; } ^{13}\text{C NMR (101 MHz, CDCl}_3\text{): } \delta = 169.7 (C=O), 144.0 (ArC), 142.6 (ArC), 142.0 (ArC), 134.8 (ArC), 129.6 (2 \times ArC), 129.4 (ArC), 128.9 (2 \times ArC), 128.0 (ArC), 127.7 (2 \times ArC), 127.6 (ArC), 126.3 (ArC), 126.0 (ArC), 124.3 (ArC), 115.6 (ArC), 69.4, 66.9, 56.0, 21.8 (CH_3), 21.6 (2 \times CH_3) \text{ ppm; IR (neat): } \nu = 2962w, 2341s, 2262w, 1735m, 1724w, 1597w, 1477m, 1458m, 1357m, 1323w, 1259m, 1238w, 1166s, 1101s, 1010m, 908s, 864w, 798m \text{ cm}^{-1}; \text{ HRMS (NSI): Exact mass calculated for C_{26}H_{21}NO_6S [M+H]^+: 426.1577; found: 426.1571; HPLC (32:68) YMC Chiral Amylose-C S (250 } \times 4.6 \text{ mm, 5 } \mu \text{m), n-hexane / isopropanol 90:10 (v/v), 1.0 mL min}^{-1}, 25 ^\circ \text C, \lambda = 254 \text{ nm, retention time minor isomer = 9.9 min, retention time second isomer = 14.9 min. The HPLC chromatograms are reported in literature.}^{10}
\]
Methyl (2S,3S)-2-(4-methoxyphenyl)-1-tosylindoline-3-carboxylate \( (S,S)-154c \): 

Performed according to General Procedure 7 on a 0.14 mmol scale of \( 153c \) using 1 mol% of \( \text{Rh}_2(\text{R}-\text{DOSP})_4 \) over 24 h; \( 154c \) (32 mg, 0.080 mmol, 57%, 4:1 d.r, 55% ee) was obtained as a pale yellow solid m.p.: 60–64 °C; \( [\alpha]_D^{20} \): +23.2° (c 0.11, CHCl\(_3\)).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 7.73 \) (d, \( J = 8.2 \) Hz, 1H, ArH), 7.63 (d, \( J = 8.3 \) Hz, 2H, ArH), 7.35–7.24 (m, 4H, ArH), 7.18 (d, \( J = 8.1 \) Hz, 2H, ArH), 7.06 (td, \( J = 7.5, 1.0 \) Hz, 1H, ArH), 6.84 (dt, \( J = 8.9, 2.2 \) Hz, 2H, ArH), 5.71 (d, \( J = 3.7 \) Hz, 1H, N–CH), 3.90 (d, \( J = 3.7 \) Hz, 1H, CH–CO\(_2\)Me), 3.78 (s, 3H, OCH\(_3\)), 3.54 (s, 3H, OCH\(_3\)), 2.35 (s, 3H, CH\(_3\)) ppm; \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \( \delta = 170.8 \) (C=O), 159.4 (ArC), 144.0 (ArC), 141.9 (ArC), 134.9 (ArC), 134.6 (ArC), 129.5 (2 × ArC), 127.7 (2 × ArC), 127.5 (ArC), 127.2 (2 × ArC), 126.4 (ArC), 124.4 (ArC), 115.7 (ArC), 114.3 (2 × ArC), 66.7, 55.8, 55.4, 52.7, 21.6 (CH\(_3\)) ppm; IR (neat): \( \nu = 2937\text{w}, 1740\text{s}, 1512\text{m}, 1477\text{m}, 1460\text{m}, 1362\text{m}, 1217\text{m}, 1163\text{s}, 1105\text{m}, 1090\text{m}, 1026\text{m}, 812\text{m}, 706\text{m}, 658\text{m cm}^{-1} \); HRMS (APCI): Exact mass calculated for C\(_{24}\)H\(_{23}\)NO\(_5\)S [M+H]: 438.1375; found: 438.1375; HPLC (24:76 e.r.): YMC Chiral Amylose-C S (250 × 4.6 mm, 5 \( \mu \)m), n-hexane/isopropanol 85:15 (v/v), 1.0 mL•min\(^{-1}\), 10 °C, \( \lambda = 254 \) nm, retention time minor isomer = 26.1 min, retention time major isomer = 62.5 min.

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<th>Peak #</th>
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<td>2</td>
<td>62.870</td>
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</table>

Figure 5.8: HPLC chromatograms of the racemic mixture of trans-154c.
Methyl (2S,3S)-1-tosyl-2-(4-(trifluoromethyl)phenyl)indoline-3-carboxylate (S,S)-154d:

Performed according to General Procedure 7 on a 0.12 mmol scale of 153d using 0.5 mol% of Rh$_2$(R-DOSP)$_4$ for 12 h; 154d (45 mg, 0.09 mmol, 82%, 5:1 d.r., 80% ee) was obtained as a colourless solid m.p.: 66–70 °C; $[\alpha]_{D}^{20}: +25.9^\circ$ (c 0.15, CHCl$_3$).

1H NMR (400 MHz, CDCl$_3$): $\delta = 7.78$ (d, $J = 8.2$ Hz, 1H, ArH), 7.65 (d, $J = 8.3$ Hz, 2H, ArH), 7.59 (d, $J = 8.3$ Hz, 2H, ArH), 7.50 (d, $J = 8.4$ Hz, 2H), 7.38–7.32 (m, 1H, ArH), 7.31–7.24 (m, 1H, ArH), 7.20 (d, $J = 8.0$ Hz, 2H, ArH), 7.09 (td, $J = 7.5$, 0.9 Hz, 1H, ArH), 5.81 (d, $J = 3.8$ Hz, 1H, N–C$_H$), 3.87 (d, $J = 3.8$ Hz, 1H, C$_H$–CO$_2$Me), 3.57 (s, 3H, OC$_H$$_3$), 2.35 (s, 3H, C$_H$$_3$) ppm; 13C NMR (101 MHz, CDCl$_3$): $\delta = 170.4$ (C=O), 146.1 (ArC), 144.4 (ArC), 141.7 (ArC), 134.4 (ArC), 130.0 (q, $J = 32.6$ Hz, ArC–CF$_3$), 129.8 (ArC), 129.7 (2 $\times$ ArC), 127.7 (2 $\times$ ArC), 126.9 (ArC), 126.5 (ArC), 126.4 (2 $\times$ ArC), 126.0 (q, $J = 3.7$ Hz, ArC), 124.6 (ArC), 123.7 (q, $J = 222.6$ Hz, CF$_3$), 115.8 (ArC), 66.5, 55.6, 52.9, 21.7 (CH$_3$) ppm; IR (neat): $\nu = 2955$w, 2925w, 1736s, 1597w, 1477m, 1462m, 1358s, 1323s, 1161s, 1109s, 1089s, 1066m, 812m, 752m, 656m cm$^{-1}$; HRMS (APCI): Exact mass calculated for C$_{24}$H$_{21}$NO$_4$SF$_3$ [M+H]$^+$: 476.1143, found: 476.1154; HPLC (10:90 e.r.): YMC Chiral Amylose-C S (250 × 4.6 mm, 5 $\mu$m), n-hexane/isopropanol 95:5 (v/v), 1.0 mL•min$^{-1}$, 10 °C, $\lambda = 254$ nm, retention time minor isomer = 25.3 min, retention time major isomer = 35.7 min. The HPLC chromatograms are reported in literature.$^{10}$

Methyl (2S,3S)-2-(p-tolyl)-1-tosylindoline-3-carboxylate (S,S)-154e:

Performed according to General Procedure 7 on a 0.13 mmol scale of 153f using 0.5 mol% of Rh$_2$(R-DOSP)$_4$ for 12 h; 154e (52 mg, 0.12 mmol, 92%, 14:1 d.r., 42% ee) was obtained as a colourless solid m.p.:132–134 °C; $[\alpha]_{D}^{20}: +33.7^\circ$ (c 0.29, CHCl$_3$).
$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.75$ (d, $J = 8.1$ Hz, 1H, Ar$H$), 7.65 (d, $J = 8.2$ Hz, 2H, Ar$H$), 7.37–7.22 (m, 4H, Ar$H$), 7.19 (d, $J = 8.0$ Hz, 2H, Ar$H$), 7.13 (d, $J = 7.9$ Hz, 2H, Ar$H$), 7.06 (t, $J = 7.5$ Hz, 1H, Ar$H$), 5.65 (d, $J = 3.6$ Hz, 1H, N–CH$_2$), 3.82 (d, $J = 3.4$ Hz, 1H, CO$_2$Me), 3.47 (s, 3H, OCH$_3$), 2.28 (s, 3H, CH$_3$), 2.25 (s, 3H, CH$_3$) ppm; $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta = 170.8$ (C=O), 144.0 (ArC), 142.0 (ArC), 139.4 (ArC), 137.8 (ArC), 134.9 (ArC), 129.6 (2 × ArC), 129.5 (2 × ArC), 127.7 (2 × ArC), 127.5 (ArC), 126.4 (ArC), 125.9 (2 × ArC), 124.3 (ArC), 115.7 (ArC), 66.9, 55.8, 52.7, 21.6 (CH$_3$), 21.2 (CH$_3$) ppm; IR (neat): $\nu = 3022$w, 2953w, 1735s, 1597m, 1514m, 1477m, 1460m, 1433m, 1354s, 1307w, 1238m, 1161s, 1089m, 960m, 914m, 813s, 680s, 657s, 617m, 574s cm$^{-1}$; HRMS (NSI): Exact mass calculated for C$_{24}$H$_{24}$NO$_4$S [M+H]$^+$: 422.1426; Found: 422.1428; HPLC (29:71 e.r.): YMC Chiral Amylose-C S (250 × 4.6 mm, 5 μm), n-hexane/isopropanol 90:10 (v/v), 1.0 mL•min$^{-1}$, 25 °C, λ = 254 nm, retention time minor isomer = 18.2 min, retention time major isomer = 39.2 min. The HPLC chromatograms are reported in literature.

Methyl (2S,3S)-2-(m-toly)-1-tosyldione-3-carboxylate (S,S)-154f:

![Chemical Structure](image)

Performed according to General Procedure 7 on a 0.08 mmol scale of 153g using 0.5 mol% of Rh$_2$(R-DOSP)$_4$ for 12 h; 154f (22 mg, 0.051 mmol, 73%, 8:1 d.r., 71% ee) was obtained as a colourless solid m.p.: 38–40 °C; $\lbrack\alpha\rbrack_{D}^{20} = +24.7^\circ$ (c 0.24, CHCl$_3$).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.76$ (d, $J = 8.2$ Hz, 1H, Ar$H$), 7.64 (d, $J = 7.9$ Hz, 2H, Ar$H$), 7.30–7.25 (m, 1H, Ar$H$), 7.23–7.12 (m, 5H, Ar$H$), 7.10–7.03 (m, 2H, Ar$H$), 5.74 (d, $J = 3.0$ Hz, 1H, N–CH$_2$), 3.90 (d, $J = 2.9$ Hz, 1H, CH–CO$_2$Me), 3.55 (s, 3H, OCH$_3$), 2.35 (s, 3H, CH$_3$), 2.31 (s, 3H, CH$_3$) ppm; $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta = 170.8$ (C=O), 144.0 (ArC), 142.2 (ArC), 142.0 (ArC), 138.7 (ArC), 134.9 (ArC), 129.5 (2 × ArC), 128.9 (ArC), 128.8 (ArC), 127.7 (2 × ArC), 127.5 (ArC), 126.5 (ArC), 126.4 (ArC), 124.4 (ArC), 123.0 (ArC), 115.8 (ArC), 67.0, 55.9, 52.7, 21.6 (CH$_3$), 21.6 (CH$_3$) ppm; IR (neat): $\nu = 3030$w, 2951w, 2922w, 2850w, 1735s, 1597m, 1477s, 1460s, 1433m, 1354s, 1243m, 1163s, 1089s, 1024m, 881w, 812m, 754s, 704s, 680s, 657s cm$^{-1}$; HRMS (NSI): Exact mass calculated for C$_{24}$H$_{27}$N$_2$O$_4$S [M+NH$_4$]$^+$: 439.1686; found: 439.1682; HPLC (15:85 e.r.): YMC Chiral Amylose-C S (250 × 4.6 mm, 5 μm), n-hexane/isopropanol 90:10 (v/v), 1.0 mL•min$^{-1}$, 25 °C, λ = 254 nm, retention time minor isomer = 11.6 min, retention time major isomer = 22.8 min. The HPLC chromatograms are reported in literature.
Methyl (2R,3R)-2-([1,1’-biphenyl]-2-yl)-1-tosylindoline-3-carboxylate (S,S)-154g:

Performed according to General Procedure 7 on a 0.10 mmol scale of 153h using 1 mol% of Rh₂(R-DOSP)₄ for 24 h; (S,S)-154g (35 mg, 0.072 mmol, 72%, 8:1 d.r., 80% ee) was obtained as a colourless solid m.p.: 199–201 °C; [𝛼]ᵢ_{D}^{20} : +40.0° (c 0.10, CHCl₃).

¹H NMR (400 MHz, CDCl₃): δ = 7.75 (d, J = 8.2 Hz, 1H, ArH), 7.51–7.38 (m, 8H, ArH), 7.35–7.21 (m, 4H, ArH), 7.14–7.08 (m, 3H), 7.00 (td, J = 7.5, 1.0 Hz, 1H, ArH), 5.83 (d, J = 3.6 Hz, 1H, N–C₇H₇), 3.77 (d, J = 3.6 Hz, 1H, CH–CO₂Me), 3.15 (s, 3H, OCH₃), 2.31 (s, 3H, Ar–C₇H₃) ppm; ¹³C NMR (101 MHz, CDCl₃): δ = 170.1 (C=O), 143.8 (ArC), 142.1 (ArC), 140.8 (ArC), 140.6 (ArC), 140.0 (ArC), 134.6 (ArC), 130.0 (ArC), 129.9 (2 × ArC), 129.6 (ArC), 129.4 (2 × ArC), 128.4 (ArC), 128.3 (2 × ArC), 127.8 (2 × ArC), 127.6 (ArC), 127.5 (ArC), 127.3 (ArC), 125.7 (ArC), 125.6 (ArC), 124.3 (ArC), 115.4 (ArC), 64.1, 56.0, 52.2, 21.6 (Ar–CH₃) ppm; IR (neat): ν = 2983w, 1735s, 1356m, 1228.7m, 1167m, 1091w, 959w, 752m, 692m cm⁻¹; HRMS (APCI): Exact mass calculated for C₂₉H₂₆NO₄S [M+H]⁺: 484.1583; found: 484.1573; HPLC (10:90 e.r.): YMC Chiral Amylose-C S (250 × 4.6 mm, 5 μm), n-hexane/isopropanol 95:5 (v/v), 1.0 mL·min⁻¹, 10 °C, λ = 254 nm, retention time first isomer = 21.7 min, retention time second isomer = 32.5 min.

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<th>Area (%)</th>
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Figure 5.10: HPLC chromatograms of racemic mixture of trans-154e enantiomers.
Methyl (2S,3S)-2-(o-tolyl)-1-tosylindoline-3-carboxylate (S,S)-154h:

![Image of chromatogram]

<table>
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<th>Peak #</th>
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<th>Area (%)</th>
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</table>

Figure 5.11: HPLC chromatograms of trans-154e enantiomers (80% ee).

Performed according to General Procedure 7 on a 0.08 mmol scale of 153i using 0.5 mol% of Rh$_2$(R-DOSP)$_4$ for 12 h; 154h (29 mg, 0.07 mmol, 86%, 8:1 d.r., 61% ee) was obtained as a colourless solid m.p.: 40–42 °C; [α]$_D^{20}$: +22.9° (c 0.34, CHCl$_3$).

$^1$H NMR (400 MHz, CDCl$_3$): δ = 7.68 (d, J = 8.2 Hz, 1H, ArH), 7.62 (d, J = 8.1 Hz, 2H, ArH), 7.26 (t, J = 7.8 Hz, 1H, ArH), 7.22–7.02 (m, 7H, ArH), 6.98 (t, J = 7.5 Hz, 1H, ArH), 5.94 (d, J = 3.4 Hz, 1H, N–CH$_3$), 3.72 (d, J = 3.1 Hz, 1H, CH–CO$_2$Me), 3.47 (s, 3H, OCH$_3$), 2.35 (s, 3H, CH$_3$), 2.29 (s, 3H, CH$_3$) ppm; $^{13}$C NMR (101 MHz, CDCl$_3$): δ = 170.8 (C=O), 144.0 (ArC), 142.1 (ArC), 140.5 (ArC), 135.2 (ArC), 134.1 (ArC), 130.9 (ArC), 129.6 (ArC), 129.6 (2 × ArC), 127.8 (ArC), 127.7 (2 × ArC), 127.4 (ArC), 126.7 (ArC), 126.4 (ArC), 125.9 (ArC), 124.3 (ArC), 115.4 (ArC), 64.3, 55.2, 52.7, 21.7 (CH$_3$), 19.6 (CH$_3$) ppm; IR (neat): ν = 2953w, 2922w, 1734s, 1597m, 1477s, 1460s, 1354s, 1305m, 1290s, 1089m, 1024m, 958m, 918w, 812m, 750s, 727m, 705m, 680s, 657s cm$^{-1}$; HRMS (NSI): Exact mass calculated for C$_{24}$H$_{24}$NO$_4$S [M+H]$^+$: 422.1421; found: 422.1422; HPLC (19:81 e.r.): YMC Chiral Amylose-C S (250 × 4.6 mm, 5 μm), n-hexane/isopropanol 90:10 (v/v), 1.0 mL·min$^{-1}$, 25 °C, λ = 254 nm, retention time major isomer = 11.5 min, retention time minor isomer = 30.0 min.
Figure 5.12: HPLC chromatograms of trans-154f enantiomers. From the top: racemic mixture, 61% ee.

Methyl (2S,3S)-2-(1-bromonaphthalen-2-yl)-1-tosylindoline-3-carboxylate (S,S)-154i:

Performed according to General Procedure 7 on a 0.048 mmol scale of 153k using 0.5 mol% of Rh2(R-DOSP)4 for 12 h; (S,S)-154i (13 mg, 0.023 mmol, 48%, 6:1 d.r, 75% ee) was obtained as a colourless oil; [α]D20: +14.0° (c 0.14, CHCl3).

1H NMR (300 MHz, CDCl3): δ = 8.34 (d, J = 8.1 Hz, 1H, ArH), 8.01–7.66 (m, 5H, ArH), 7.66–7.45 (m, 3H, ArH), 7.36 (t, J = 7.7 Hz, 1H, ArH), 7.31–7.09 (m, 3H, ArH), 7.06 (t, J = 7.4 Hz, 1H, ArH), 6.43 (d, J = 3.4 Hz, 1H, N–CH3), 3.90 (d, J = 2.5 Hz, 1H, CH–CO2Me), 3.56 (s, 3H, OCH3), 2.39 (s, 3H, CH3) ppm; 13C NMR (126 MHz, CDCl3): δ = 170.6 (C=O), 144.3 (ArC), 142.0 (ArC), 139.6 (ArC), 134.8 (ArC), 134.3 (ArC), 132.5 (ArC), 129.9 (ArC), 129.7 (2 × ArC), 128.7 (ArC), 128.3 (ArC), 128.0 (2 × ArC), 127.8 (ArC), 127.5 (ArC), 126.9 (ArC), 126.0 (ArC), 124.5 (ArC), 124.4 (ArC), 124.4 (ArC), 121.6 (ArC), 115.4 (ArC), 67.5, 55.3, 52.8, 21.7 (CH3) ppm; IR (neat): ν = 3752w, 3629w, 2952w, 2917w, 2849w, 2342s, 1734s, 1596m, 1478m, 1461m, 1356s, 1326m, 1255m,
1239m, 1164s, 1090s, 1024m, 962m, 906w, 812s, 729s, 575s cm\(^{-1}\); HRMS (NSI):

Exact mass calculated for C\(_{27}\)H\(_{23}\)BrNO\(_4\)S [M+H]\(^+\): 539.0526; found: 539.0522; HPLC (12.88 e.r.): YMC Chiral Amylose-C S (250 \(\times\) 4.6 mm, 5 \(\mu\)m), n-hexane/isopropanol 90:10 (v/v), 1.0 mL/min\(^{-1}\), 25 °C, \(\lambda\) = 254 nm, retention time first isomer = 24.3 min, retention time second isomer = 38.6 min. The HPLC chromatograms are reported in literature.\(^{10}\)

**Methyl (2S,3S)-2-((E)-styryl)-1-tosylindoline-3-carboxylate (S,S)-154j:**

Performed according to General Procedure 7 on a 0.11 mmol scale of 153l using 0.5 mol% of Rh\(_2\)(R-DOSP)\(_4\) for 24 h; 154j (23 mg, 0.053 mmol, 53%, 7:1 d.r., 33% ee) was obtained as a colourless solid m.p.: 52–54 °C; \([\alpha]\)\(_D\)\(^{20}\): +7.2° (c 0.28, CHCl\(_3\)).

**1H NMR (400 MHz, CDCl\(_3\))**: \(\delta = 7.70–7.59\) (m, 2H, Ar\(\text{H}\)), 7.33–7.15 (m, 8H, Ar\(\text{H}\)), 6.70 (d, \(J = 15.6\) Hz, 1H, CH=CH–Ph), 6.16 (dd, \(J = 15.8, 7.2\) Hz, 1H, CH=CH–Ph), 5.31 (dd, \(J = 6.5, 3.1\) Hz, 1H, N–C\(\text{H}\)), 3.76 (d, \(J = 2.9\) Hz, 1H, CH–CO\(_2\)Me), 3.46 (s, 3H, OCH\(_3\)), 2.28 (s, 3H, C\(_3\)H\(_3\)) ppm; **13C NMR (101 MHz, CDCl\(_3\))**: \(\delta = 170.5\) (C=O), 144.0 (Ar\(\text{C}\)), 141.4 (Ar\(\text{C}\)), 136.2 (Ar\(\text{C}\)), 135.2 (Ar\(\text{C}\)), 131.9 (Ar\(\text{C}\)), 129.6 (2 \(\times\) Ar\(\text{C}\)), 129.5, 128.5 (2 \(\times\) Ar\(\text{C}\)), 128.1, 128.0, 127.7 (2 \(\times\) Ar\(\text{C}\)), 127.6, 126.9 (2 \(\times\) Ar\(\text{C}\)), 126.4, 124.3, 116.0 (Ar\(\text{C}\)), 66.1, 53.0, 52.7, 21.6 (CH\(_3\)) ppm; IR (neat): \(\nu = 3026\)w, 2949w, 2850w, 2358w, 1735s, 1597m, 1477m, 1460m, 1435m, 1354s, 1228s, 1217s, 1163s, 1105m, 1089m, 1024m, 962m, 812m, 754m cm\(^{-1}\); HRMS (NSI): Exact mass calculated for C\(_{25}\)H\(_{24}\)NO\(_4\)S [M+H]\(^+\): 434.1400; found: 434.1410; HPLC (66:34 e.r.): Chiracel® OD-H (250 \(\times\) 4.6 mm, 5 \(\mu\)m), n-hexane/isopropanol 95:5 (v/v), 1.0 mL/min\(^{-1}\), 25 °C, \(\lambda\) = 254 nm, retention time major isomer = 22.5 min, retention time minor isomer = 29.1 min. The HPLC chromatograms are reported in literature.\(^{10}\)

**Methyl (2S,3S)-2-pentyl-1-tosylindoline-3-carboxylate (S,S)-154k:**

Performed according to General Procedure 7 on a 0.09 mmol scale of 153m using 0.5 mol% of Rh\(_2\)(R-DOSP)\(_4\) for 12 h; 154k (23 mg, 0.058 mmol, 64%, >20:1 d.r., 48% ee) was obtained as a pale yellow oil; \([\alpha]\)\(_D\)\(^{20}\): +44.1° (c 0.41, CHCl\(_3\)).

**1H NMR (300 MHz, CDCl\(_3\))**: \(\delta = 7.67\) (d, \(J = 8.1\) Hz, 1H, Ar\(\text{H}\)), 7.62–7.53 (m, 2H, Ar\(\text{H}\)), 7.33–7.22 (m, 2H, Ar\(\text{H}\)), 7.15 (d, \(J = 8.0\) Hz, 2H, Ar\(\text{H}\)), 7.04 (td, \(J = 7.6, 1.0\) Hz, 1H, Ar\(\text{H}\)), 4.62 (ddd, \(J = 8.0, 4.6, 3.1\) Hz, 1H, N–CH\(_3\)), 3.61 (d, \(J = 2.9\) Hz, 1H, CH–CO\(_2\)Me), 3.41 (s, 3H, OCH\(_3\)), 2.33 (s, 3H, CH\(_3\)), 2.03–1.86 (m, 1H), 1.86–1.64 (m, 1H), 1.44–1.20 (m, 6H), 0.88 (t, \(J = 6.9\) Hz, 3H, CH\(_3\)) ppm; **13C NMR (75 MHz, CDCl\(_3\))**: \(\delta = 13\)C NMR (101 MHz,
**5.2.5 In-Situ \(^1\)H NMR Experiment: Temperature Effect**

Figure 5.13: \(^1\)H NMR (300 MHz, CD$_3$CN). a) Comparison of crude mixtures for reaction performed at room temperature, 45 °C and 65 °C; b) Thermostability test for 153a at 65 °C for 48 h.
5.2.6 Evidence for Triazene 167

Figure 5.14: Crude NMR (300 MHz, CDCl₃) of triazene 167b as a 1:2 mixture of rotamers. The reaction was performed on a 0.24 mmol scale of 152a (100 mg), quenched with cold H₂O after 10 minutes and extracted with dichloromethane.
5.3 Experimental Data for Chapter 3: Synthesis of Fluorinated Benzofuranones

Triphenylborane **106a** was purchased from Sigma Aldrich. The synthesis of boranes **106b–f** was performed by Darren M. C. Ould, Dr. Jan Wenz, Dr. Yashar Soltani and Jamie L. Carden. The Lewis acidity was determined by Dr. Soltani according to the Gutmann-Beckett method.¹¹

5.3.1 Synthesis of Diazo Precursors

5.3.1.1 Synthesis of Diazo Compound **107**

Ethyl 2-methyl-3-oxobutanoate **204**: To a stirred suspension of NaH (60%wt in mineral oil, 2.3 g, 60 mmol), in dry THF (40 mL), acetoacetate **201** (7.6 mL, 60 mmol), was added at 0 °C. Once the grey suspension turned into a brown clear solution, methyl iodide (2.5 mL, 40 mmol) was added and the reaction was heated under reflux overnight. A saturated solution of aqueous NH₄Cl was added at room temperature, and the product was extracted with CH₂Cl₂ (3 × 20 mL). The combined organic layers were washed with brine and dried over MgSO₄ and the solvent was evaporated under reduced pressure. The crude was purified by column chromatography to afford **204** as a colourless oil (3.8 g, 26 mmol, 65% yield).

¹H NMR (500 MHz, CDCl₃): δ = 4.29–4.12 (m, 2H, OCH₂), 3.49 (q, J = 7.2 Hz, 1H, CH), 2.23 (s, 3H, CH₃), 1.34 (d, J = 7.2 Hz, 3H, CHCH₃), 1.27 (t, J = 7.0 Hz, 3H, OCH₂CH₃) ppm; ¹³C NMR (126 MHz, CDCl₃): δ = 203.8 (C=O), 170.7 (C=O), 61.5 (OCH₂), 53.8 (CHCH₃), 28.5 (CH₃), 14.2 (CH₃), 12.8 (CH₃) ppm. The spectroscopic data are in agreement with the literature.¹²

Ethyl 2-diazopropanoate **107**: To a stirred solution of **204** (1.8 g, 12 mmol) and p-acetamidobenzenesulfonyl azide, (p-ABSA, 4.3 g, 18 mmol) in acetonitrile (30 mL) at 0 °C, 8-diazabicyclo(5.4.0)undec-7-ene (DBU,
2.7 mL, 1.8 mmol) was added dropwise. The reaction was stirred for 12 hours before quenching with a saturated aqueous solution of NH₄Cl. The product was extracted with CH₂Cl₂ (3 × 20 mL). The combined organic layers were washed with water, brine and dried over MgSO₄. Compound **107** was afforded as a volatile bright yellow oil (802 mg, 6.3 mmol, 52% yield) after column chromatography.

**¹H NMR** (500 MHz, CDCl₃): δ = 4.21 (q, J = 7.1 Hz, 2H, OCH₂), 1.95 (s, 3H, CH₃), 1.27 (t, J = 7.1 Hz, 3H, OCH₂CH₃) ppm; **¹³C NMR** (126 MHz, CDCl₃): δ = 60.9 (OCH₂), 14.7 (CH₃), 8.6 (CH₃) ppm (**C=N₂** and **C=O** not observed); IR (neat): ν = 2980w, 2075s, 1682s, 1304s, 1124s, 734m cm⁻¹. The spectroscopic data are in agreement with the literature.¹³

### 5.3.1.2 Synthesis of Diazocompounds 179a–g

Except for **202f** which was commercially available, **202a–e** were obtained following **General Procedure 8**: The arylacetic acid **205a–e** (4–10 mmol) was dissolved in methanol and the 0.5 M solution was cooled down at 0 °C before addition of acetyl chloride (2.5 equiv.). The reaction was stirred at room temperature for 4–12 hours and checked by TLC (**n**-hexane/ethyl acetate). The solvent was evaporated in vacuo and the residual oil washed with a saturated solution of NaHCO₃ and extracted with diethyl ether. Subsequently, the combined organic layers were washed with water and brine, dried over MgSO₄ and concentrated in vacuo to afford the pure product **202a–e** as an oil or a solid depending on the substrate.

**Methyl 2-(2-bromophenyl)acetate 202a:**

Performed according to **General Procedure 8** on a 4.6 mmol scale of **205a; 202a** (1.1 g, 4.4 mmol, 96% yield) was obtained as a pale-yellow oil.

**¹H NMR** (400 MHz, CDCl₃): δ = 7.54 (d, J = 7.7 Hz, 1H, ArH), 7.28–7.21 (m, 2H, ArH), 7.15–7.08 (m, 1H, ArH), 3.77 (s, 2H, OCH₂), 3.68 (s, 3H, OCH₃) ppm; **¹³C NMR** (101 MHz, CDCl₃): δ = 171.0 (C=O), 134.2 (ArC), 132.9 (ArC), 131.6 (ArC), 128.9 (ArC), 127.6 (ArC), 125.1 (ArC), 52.3 (OCH₃), 41.6 (CH₃) ppm. Spectroscopic data are in accordance with the literature.¹⁴
Methyl 2-(4-(trifluoromethyl)phenyl)acetate \textbf{202b}:

Performed according to \textit{General Procedure 8} on a 4.9 mmol scale of \textbf{205b}; \textbf{202b} (900 mg, 4.1 mmol, 84% yield) was obtained as a colourless oil.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta = 7.59$ (d, $J = 8.1$ Hz, 2H, ArH), 7.40 (d, $J = 8.0$ Hz, 2H, ArH), 3.71 (s, 3H, OCH$_3$), 3.69 (s, 2H, CH$_2$) ppm; $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta = 171.3$ (C=O), 138.1 (q, $J = 1.3$ Hz, ArC), 129.8 ($2 \times$ ArC), 129.6 (q, $J = 32.5$ Hz, ArC–CF$_3$), 125.6 (q, $J = 3.8$ Hz, 2 $\times$ ArC), 124.3 (q, $J = 272.0$ Hz, CF$_3$), 52.3 (OCH$_3$), 41.0 (CH$_2$) ppm; Spectroscopic data are in accordance with the literature.$^{15}$

Methyl 2-(4-methoxyphenyl)acetate \textbf{202c}:

Performed according to \textit{General Procedure 8} on a 6.0 mmol scale of \textbf{205c}; \textbf{202c} (857 mg, 4.7 mmol, 80% yield) was obtained as a colourless oil.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.26$–$7.11$ (m, 2H, ArH), 6.95–$6.80$ (m, 2H, ArH), 3.79 (s, 3H, OCH$_3$), 3.69 (s, 3H, OCH$_3$), 3.57 (s, 2H, CH$_2$) ppm; $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta = 172.5$ (C=O), 158.8 (ArC–OMe), 130.4 ($2 \times$ ArC), 126.2 (ArC), 114.1 ($2 \times$ ArC), 55.4 (OCH$_3$), 52.1 (OCH$_3$), 40.4 (CH$_2$) ppm. Spectroscopic data are in accordance with the literature.$^{16}$

Methyl 2-(naphthalen-1-yl)acetate \textbf{202d}:

Performed according to \textit{General Procedure 8} on a 10.7 mmol scale of \textbf{205d}; \textbf{202d} (1.9 g, 9.5 mmol, 89% yield) was obtained as a colourless oil.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 8.02$–$7.97$ (m, 1H, ArH), 7.87 (dd, $J = 8.3$, 1.1 Hz, 1H, ArH), 7.81 (dd, $J = 7.5$, 1.7 Hz, 1H, ArH), 7.58–$7.39$ (m, 4H, ArH), 4.09 (s, 2H, ArCH$_2$), 3.69 (s, 3H, OCH$_3$) ppm; $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta = 172.2$ (C=O), 133.9 (ArC), 132.2 (ArC), 130.6 (ArC), 128.9 (ArC), 128.2 (ArC), 128.2 (ArC), 126.6 (ArC), 125.9 (ArC), 125.6 (ArC), 123.9 (ArC), 52.3 (OCH$_3$), 39.2 (CH$_2$) ppm. Spectroscopic data are in accordance with the literature.$^{17}$
Methyl 2-(2-iodophenyl)acetate 202e:

Performed according to General Procedure 8 on a 11.5 mmol scale of 205e; 202e (2.1 g, 7.6 mmol, 66% yield) was obtained as a colourless oil.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.85$ (dd, $J = 7.9$, 1.1 Hz, 1H, Ar$H$), 7.37–7.25 (m, 2H, Ar$H$), 7.03–6.87 (m, 1H, Ar$H$), 3.81 (s, 2H, C$H_2$), 3.73 (s, 3H, OC$_3$H$_3$) ppm; $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta = 171.1$ (C=O), 139.7 (ArC), 137.8 (ArC), 130.8 (ArC), 129.1 (ArC), 128.6 (ArC), 101.1 (ArC=I), 52.4 (OCH$_3$), 46.3 (CH$_2$) ppm. Spectroscopic data are in accordance with the literature.$^{18}$

General Procedure 9: A 0.2 M solution of methyl arylacetates 202a–f or 155a (2–4 mmol) and p-ABSA (2 equiv.) in acetonitrile was cooled down to 0 °C before the addition of DBU (2.5 equiv.). The reaction was stirred at room temperature for 4–48 hours and monitored by TLC (n-hexane/ethyl acetate). The mixture was quenched with a saturated aqueous solution of NH$_4$Cl saturated solution and the product was extracted with CH$_2$Cl$_2$. The combined organic layers were washed with water, brine, dried over MgSO$_4$ and concentrated under reduced pressure. The crudes were purified by flash column chromatography to afford the pure products 179a–g as an oil or a solid depending on the substrate.

Methyl 2-(2-bromophenyl)diazoacetate 179a:

Performed according to General Procedure 9 on a 2.0 mmol scale of 202a; 179a (500 mg, 1.9 mmol, 96% yield) was obtained as a bright yellow oil.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta = 7.63$ (dd, $J = 8.1$, 1.2 Hz, 1H, Ar$H$), 7.52 (dd, $J = 7.8$, 1.6 Hz, 1H, Ar$H$), 7.38 (td, $J = 7.6$, 1.3 Hz, 1H, Ar$H$), 7.24–7.18 (m, 1H, Ar$H$), 3.84 (s, 3H, OCH$_3$) ppm; $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta = 133.5$ (ArC), 133.1 (ArC), 130.3 (ArC), 127.9 (ArC), 125.9 (ArC–Br), 52.4 (OCH$_3$) ppm (C=N$_2$ and C=O not observed); IR (neat): $\nu = 2951\text{w}$, 2100s, 1697s, 1475m, 1433m, 1350m, 1240s, 1153s, 1066s, 1022s, 914w, 752s, 642m, 441m cm$^{-1}$. The spectroscopic data are in agreement with the literature.$^{19}$

Methyl 2-(4-(trifluoromethyl)phenyl)diazoacetate 179b:

Performed according to General Procedure 9 on a 3.8 mmol scale of 202b; 179b (941 mg, 3. mmol, 98% yield) was obtained as a bright yellow solid.
**Methyl 2-(4-(methoxy)phenyl)diazoacetate 179c:**

Performed according to **General Procedure 9** on a 2.8 mmol scale of 202c; 179c (377 mg, 1.8 mmol, 65% yield) was obtained as a red solid.

1H NMR (400 MHz, CDCl3): δ = 7.42–7.31 (m, 2H, ArH), 7.01–6.88 (m, 2H, ArH), 3.84 (s, 3H, OCH3), 3.80 (s, 3H, OCH3) ppm; 13C NMR (101 MHz, CDCl3): δ = 166.2 (C=O), 158.2 (ArC–O), 126.0 (2 × ArC), 116.9 (ArC–CN2), 114.7 (2 × ArC), 55.4 (OCH3), 52.0 (OCH3) ppm (C=N2 not observed); IR (neat): ν = 3005w, 2959w, 2839w, 2085s, 1690s, 1609m, 1510s, 1437s, 1356m, 1294m, 1244s, 1028s, 833s, 739s, 606m cm⁻¹. The spectroscopic data are in agreement with the literature.²⁰

**Methyl 2-(naphthalen-1-yl)diazoacetate 179d:**

Performed according to **General Procedure 9** on a 2.5 mmol scale of 202d; 179d (465 mg, 2.1 mmol, 84% yield) was obtained as a bright yellow oil.

1H NMR (500 MHz, CDCl3): δ = 7.94–7.88 (m, 2H, ArH), 7.87 (d, J = 8.4 Hz, 1H, ArH), 7.64 (dd, J = 7.2, 1.0 Hz, 1H, ArH), 7.58 (dd, J = 8.3, 1.4 Hz, 1H, ArH), 7.54 (dd, J = 12.4, 4.4 Hz, 2H, ArH), 3.86 (s, 3H, OCH3) ppm; 13C NMR (126 MHz, CDCl3): δ = 134.1 (ArC), 131.6 (ArC), 129.8 (ArC), 129.7 (ArC), 128.9 (ArC), 126.9 (ArC), 126.3 (ArC), 125.61 (ArC), 124.3 (ArC), 122.0 (ArC), 52.4 (OCH3) ppm (C=N2 and C=O not observed); IR (neat): ν = 2951w, 2360w, 2083s, 1701s, 1433s, 1103s, 993w, 977w, 773s, 657m cm⁻¹. The spectroscopic data are in agreement with the literature.²⁰

**Methyl 2-(2-iodophenyl)diazoacetate 179e:**

Performed according to **General Procedure 9** on a 1.8 mmol scale of 202e; 179e (480 mg, 1.6 mmol, 88% yield) was obtained as a bright yellow oil.
1H NMR (500 MHz, CDCl3): δ = 7.88 (d, J = 8.0 Hz, 1H, ArH), 7.45 (dd, J = 7.8, 1.5 Hz, 1H, ArH), 7.38 (t, J = 7.6 Hz, 1H, ArH), 7.06–6.95 (m, 1H, ArH), 3.80 (s, 3H, OCH3) ppm; 13C NMR (126 MHz, CDCl3): δ = 165.7 (C=O), 139.7 (ArC), 132.9 (ArC), 130.4 (ArC), 129.5 (ArC–CN2), 128.5 (ArC), 101.0 (ArC–I), 52.2 (OCH3) ppm (C=N2 not observed); IR (neat): ν = 2949w, 2088s, 1693s, 1579w, 1558w, 1469m, 1431m, 1348m, 1242s, 1026s, 1006s, 752s, 638m cm$^{-1}$; HRMS (NSI): Exact mass calculated for C9H8IN2O2 [M+H]+: 302.9625, found 302.9627.

Methyl 2-(2-nitrophenyl)diazoacetate 179f:

Performed according to General Procedure 9 on a 1.3 mmol scale of 155a; 179f (200 mg, 0.90 mmol, 71% yield) was obtained as a bright yellow solid.

1H NMR (500 MHz, CDCl3): δ = 8.02 (d, J = 8.2 Hz, 1H, ArH), 7.63 (t, J = 7.6 Hz, 1H, ArH), 7.53 (d, J = 7.7 Hz, 1H, ArH), 7.46 (t, J = 7.8 Hz, 1H, ArH), 3.79 (s, 3H, OCH3) ppm; 13C NMR (126 MHz, CDCl3): δ = 165.1 (C=O), 147.2 (ArC–NO2), 133.3 (ArC), 131.1 (ArC), 128.9 (ArC), 125.6 (ArC), 120.9 (ArC–CN2), 52.5 (OCH3) ppm (C=N2 not observed); IR (neat): ν = 2954w, 2362w, 2094s, 1697s, 1604m, 1523s, 1435m, 1384s, 1284s, 1246s, 1193s, 1161s, 1089m, 1029s, 956w, 916w, 852m, 783m, 543w, 516w cm$^{-1}$. The spectroscopic data are in agreement with the literature.21

Methyl 2-diazo-2-(pyridin-2-yl)acetate 179g:

Performed according to General Procedure 9 on a 2.0 mmol scale of commercially available 202f; 179g (270 mg, 1.5 mmol, 75% yield) was obtained as a white solid, m.p.: 134–138 °C.

1H NMR (400 MHz, CDCl3): δ = 8.84 (dt, J = 7.0, 1.0 Hz, 1H, ArH), 8.29 (dt, J = 8.9, 1.2 Hz, 1H, ArH), 7.56 (ddd, J = 8.9, 6.8, 1.0 Hz, 1H, ArH), 7.17 (td, J = 6.9, 1.2 Hz, 1H, ArH), 4.05 (s, 3H, OCH3) ppm; 13C NMR (126 MHz, CDCl3): δ = 161.4 (C=O), 134.8 (ArC), 129.3 (ArC), 128.9 (ArC), 125.8 (ArC), 118.9 (ArC), 116.4 (ArC), 51.8 (OCH3) ppm; IR (neat): ν = 3092m, 3044m, 2953m, 1984w, 1819w, 1693s, 1637m, 1544m, 1523s, 1215s, 1068s cm$^{-1}$. The spectroscopic data are in agreement with the literature.22
5.3.1.3 Synthesis of Diazocompound 179h

A mixture of acetoacetate 201 (1.47 mL, 12 mmol), (-)-menthol (2.8 g, 18 mmol) and catalytic amount of H_3BO_3 (74 mg, 1.2 mmol, 10 mol%) was stirred in toluene at 115 °C and refluxed overnight for 12 hours using a Dean-Stark trap to remove the ethanol. The solvent was then removed under vacuum and the crude purified by column chromatography to afford 207 (1.58 g, 6.6 mmol, 55% yield) as a pale-yellow oil (5:1 mixture of the two tautomers 207 by ¹H NMR spectroscopy).

¹H NMR (400 MHz, CDCl_3): δ = 12.18 (s, 0.19 H, O_H), 5.05–4.89 (m, 0.19 H, C=C_H), 4.72 (td, J = 10.9, 4.4 Hz, 1H, CO_2–CH), 3.42 (s, 2H, CH_2), 2.25 (s, 3H, CH_3), 2.05–1.97 (m, 1H), 1.90–1.81 (m, 1H), 1.67 (d, J = 11.6 Hz, 2H), 1.53–1.40 (m, 1H), 1.36 (t, J = 11.6 Hz, 1H), 1.11–0.80 (m, 9H), 0.75 (d, J = 7.0 Hz, 3H, CHCH_3) ppm; ¹³C NMR (101 MHz, CDCl_3): δ = 200.8 (C=O), 175.4 (CH=O), 172.5 (C=O), 166.7 (C=O), 90.2 (CH=O), 75.6 (CO_2–CH), 73.8 (CO_2–O) 50.7 (C(O)–CH_2–CO_2), 47.1 (C), 47.0 (C), 41.1 (CH_2) 40.8 (CH_2), 34.3 (CH_2), 34.2 (CH_2), 34.3, 31.5 (C), 30.2 (C), 26.4 (C), 26.2 (C), 23.6 (CH_2), 23.4 (CH_2), 22.1 (C), 21.3 (C), 20.9 (C), 20.8 (C), 16.5 (C), 16.2 (C) ppm. The spectroscopic data are in agreement with the literature.

(1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl 2-methyl-3-oxobutanoate 208:

A mixture of acetoacetate 201 (1.47 mL, 12 mmol), (-)-menthol (2.8 g, 18 mmol) and catalytic amount of H_3BO_3 (74 mg, 1.2 mmol, 10 mol%) was stirred in toluene at 115 °C and refluxed overnight for 12 hours using a Dean-Stark trap to remove the ethanol. The solvent was then removed under vacuum and the crude purified by column chromatography to afford 207 (1.58 g, 6.6 mmol, 55% yield) as a pale-yellow oil (5:1 mixture of the two tautomers 207:207 by ¹H NMR spectroscopy).

¹H NMR (400 MHz, CDCl_3): δ = 12.18 (s, 0.19 H, O_H), 5.05–4.89 (m, 0.19 H, C=C_H), 4.72 (td, J = 10.9, 4.4 Hz, 1H, CO_2–CH), 3.42 (s, 2H, CH_2), 2.25 (s, 3H, CH_3), 2.05–1.97 (m, 1H), 1.90–1.81 (m, 1H), 1.67 (d, J = 11.6 Hz, 2H), 1.53–1.40 (m, 1H), 1.36 (t, J = 11.6 Hz, 1H), 1.11–0.80 (m, 9H), 0.75 (d, J = 7.0 Hz, 3H, CHCH_3) ppm; ¹³C NMR (101 MHz, CDCl_3): δ = 200.8 (C=O), 175.4 (CH=O), 172.5 (C=O), 166.7 (C=O), 90.2 (CH=O), 75.6 (CO_2–CH), 73.8 (CO_2–O) 50.7 (C(O)–CH_2–CO_2), 47.1 (C), 47.0 (C), 41.1 (CH_2) 40.8 (CH_2), 34.3 (CH_2), 34.2 (CH_2), 34.3, 31.5 (C), 30.2 (C), 26.4 (C), 26.2 (C), 23.6 (CH_2), 23.4 (CH_2), 22.1 (C), 21.3 (C), 20.9 (C), 20.8 (C), 16.5 (C), 16.2 (C) ppm. The spectroscopic data are in agreement with the literature.

(1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl 2-methyl-3-oxobutanoate 208:

To a stirring suspension of NaH (60 wt% in mineral oil, 124 mg, 3.1 mmol), in dry THF (5 mL), 207 (750 mg, 3.1 mmol), was added at 0 °C. Once the grey suspension turned into a clear solution, methyl iodide (129 µL, 2.1 mmol) was added. The reaction was heated under reflux overnight. A saturated aqueous solution of NH_4Cl was added at room temperature, and the product was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine and dried over MgSO_4 and the solvent was evaporated under reduced pressure. The desired product 208 was obtained as a yellow
oil (365 mg, 1.36 mmol, 66% yield, as mixture of two isomers 208:208\(^1\) d.r. = 1:1 by \(^1\)H NMR spectroscopy).

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 4.79–4.42\) (m, 1H, CO\(_2\)–CH\(_j\)), 3.48–3.41 (m, 1H, C(O)–CH\(_2\)CO\(_2\)), 2.20 (s, 3H, CH\(_3\)), 1.96 (t, \(J = 5.9\) Hz, 1H, alkylH), 1.89–1.72 (m, 1H, alkylH), 1.70–1.59 (m, 2H, alkylH), 1.55–1.18 (m, 5H, alkylH), 1.14–0.75 (m, 9H), 0.75 (dd, \(J = 7.0, 2.3\) Hz, 3H, CH\(_3\)) ppm; \(^{13}\)C NMR (126 MHz, CDCl\(_3\)): \(\delta = 203.8\) (C=O), 203.7 (C=O), 170.3 (C=O), 170.2 (C=O), 75.5 (CO\(_2\)–CH), 75.4 (CO\(_2\)–CH), 54.2 (C(O)–CH\(_2\)CO\(_2\)), 54.0 (C(O)–CH\(_2\)CO\(_2\)), 47.03 (C), 47.01 (C), 40.7 (C), 40.6 (C), 34.3 (C+C), 31.52 (C), 31.51 (C), 28.49 (C), 28.47 (C), 26.4 (C), 26.2 (C), 23.5 (C), 23.3 (C), 22.1 (C+C), 20.9 (C), 20.8 (C), 16.3 (C), 16.1 (C), 12.9 (C), 12.8 (C) ppm. The crude mixture was used without further purification.

(1\(R\),2\(S\),5\(R\))-2-Isopropyl-5-methylcyclohexyl 2-diazopropanoate 179h:

208 (300 mg, 1.2 mmol) was dissolved in acetonitrile (2 mL) and \(p\)-ABSA (430 mg, 1.8 mol) was added. The solution was cooled to 0 °C before the addition of DBU (300 µL, 1.8 mmol). The solution was stirred at room temperature for 12 h. A saturated aqueous solution of NH\(_4\)Cl was added and the product was extracted with CH\(_2\)Cl\(_2\) (3 × 5 mL). The combined organic layers were washed with water, brine and dried over MgSO\(_4\). The pure compound 179h was obtained after column chromatography as a volatile yellow oil (80 mg, 0.36 mmol, 30% yield).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 4.73\) (td, \(J = 10.9, 4.4\) Hz, 1H, CO\(_2\)–CH\(_j\)), 2.06–1.99 (m, 1H), 1.95 (s, 3H, CH\(_3\)), 1.90–1.82 (m, 1H), 1.71–1.62 (m, 2H), 1.54–1.43 (m, 1H), 1.42–1.32 (m, 1H), 1.13–0.86 (m, 9H), 0.77 (d, \(J = 7.0\) Hz, 3H, CH\(_3\)) ppm; \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta = 74.8\) (CO\(_2\)–CH), 47.3, 41.5, 34.4, 31.5, 26.6, 23.8, 22.2, 20.8, 16.7, 8.6 ppm (C=N\(_2\) and C=O not observed); IR (neat): \(\nu = 2954\)w, 2926w, 2870w, 2075s, 1684s, 1456w, 1303m, 1128s, 986w, 953w, 732m cm\(^{-1}\). The spectroscopic data are in agreement with the literature.\(^{24}\)
5.3.1.4 Synthesis of Diazo Compounds 179i–j

**General Procedure 10:** The arylacetic acid 202 (5 mmol) was dissolved in CH$_2$Cl$_2$, then (-)-menthol (2.5 mmol), DCC (5 mmol) and catalytic amount of DMAP (0.75 mmol, 0.3 equiv.) were added. The reaction was stirred at room temperature for 24 hours, monitored by TLC (n-hexane/ethyl acetate) and then filtered. The filtrate was washed with a saturated aqueous solution of NaHCO$_3$ and extracted with CH$_2$Cl$_2$. The combined organic layers were dried over MgSO$_4$ and the solvent was evaporated under vacuum. The crude was purified by column to afford the pure ester 209.

(1$R$,2$R$,5$R$)-2-Isopropyl-5-methylcyclohexyl 2-(2-bromophenyl)acetate 209a:

Performed according to General Procedure 10 on a 4.7 mmol scale of 202a and 2.3 mmol of (-)-menthol; 209a (718 mg, 2.0 mmol, 89% yield) was obtained as a colourless oil.

$^1$H NMR (400 MHz, CDCl$_3$): δ = 7.54 (d, $J = 7.8$ Hz, 1H, ArH), 7.31–7.20 (m, 2H, ArH), 7.10 (ddd, $J = 8.0$, 6.8, 2.4 Hz, 1H, ArH), 4.71 (td, $J = 10.9$, 4.4 Hz, 1H, CO$_2$–C$_H$), 4.10–3.55 (m, 2H, Ar–CH$_2$–CO$_2$), 2.10–1.95 (m, 1H), 1.83 (dtd, $J = 13.9$, 7.0, 2.7 Hz, 1H), 1.72–1.58 (m, 2H), 1.53–1.41 (m, 1H), 1.39–1.27 (m, 1H), 1.13–0.79 (m, 9H), 0.73 (d, $J = 7.0$ Hz, 3H, CH$_3$) ppm; $^{13}$C NMR (101 MHz, CDCl$_3$): δ = 170.0 (C=O), 134.6 (ArC), 132.7 (ArC), 131.5 (ArC), 128.8 (ArC), 127.5 (ArC), 125.1 (ArC), 74.9 (CO$_2$–C$_H$), 47.0, 42.1, 40.8, 34.3, 31.4, 26.2, 23.4, 22.1, 20.8, 16.4 ppm; IR (neat): ν = 2948m, 2860m, 1725s, 1469m, 1234s, 1163s, 1010s cm$^{-1}$; HRMS (NSI): Exact mass calculated for C$_{18}$H$_{29}$BrO$_2$N [M+NH$_4$]$^+$: 370.1380; found: 370.1376; [$\alpha$]$^D$ +44.1° (c 0.41, CHCl$_3$).
(1R,2R,5R)-2-Isopropyl-5-methylcyclohexyl-2-(4(trifluoromethyl)phenyl)acetate 209b: Performed according to General Procedure 10 on a 5.0 mmol scale of 202b and 2.5 mmol of (−)-menthol; 209b (666 mg, 2.0 mmol, 78% yield) was obtained as a colourless oil.

**1H NMR** (500 MHz, CDCl3): δ = 7.58 (d, J = 8.1 Hz, 2H, ArH), 7.40 (d, J = 8.0 Hz, 2H, ArH), 4.68 (td, J = 10.9, 4.4 Hz, 1H, CO2–CH), 3.65 (s, 2H, ArCH2–CO2), 2.09–1.92 (m, 1H), 1.76–1.62 (m, 2H), 1.56 (d, J = 2.6 Hz, 1H), 1.52–1.42 (m, 1H), 1.35 (ddt, J = 14.3, 10.9, 3.1 Hz, 1H), 1.12–0.80 (m, 9H), 0.68 (d, J = 7.0 Hz, 3H, CH3) ppm; **13C NMR** (126 MHz, CDCl3): δ = 170.5 (C=O), 138.5 (m, ArC), 129.7 (2 × ArC), 129.5 (q, J = 32.5 Hz, ArC–CF3), 125.5 (q, J = 3.8 Hz, 2 × ArC), 124.3 (q, J = 271.9 Hz, CF3), 75.3 (CO2–CH), 47.2, 41.7, 40.9, 34.3, 31.5, 26.3, 23.5, 22.1, 20.8, 16.4 ppm; **IR** (neat): ν = 2949m, 2864m, 1730s, 1323s, 1153s, 824m, 698m, 598m cm⁻¹; **HRMS** (ASAP): Exact mass calculated for C19H24O2F [M–H]+: 341.1728; found: 341.1723; [α]D20: +44.1° (c 0.41, CHCl3).

**General Procedure 11:** A 0.2 M solution of (−)-menthyl arylacetate 209 (2 mmol) and p-ABSA (4 mmol) in THF was cooled to 0 °C before the addition of DBU (8 mmol). The reaction was stirred at room temperature for 24 hours and monitored by TLC (n-hexane/ethyl acetate). The mixture was quenched with a saturated aqueous solution of NH4Cl saturated solution and the product was extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried over MgSO4 and concentrated under reduced pressure. The crude was purified by flash column chromatography to afford the pure product 179i–j as an oil or solid depending on the substrate.

(1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl 2-diazo-2-(2-bromophenyl)acetate 179i: Performed according to General Procedure 11 on a 1.3 mmol scale of 209a; 179i (316 mg, 0.85 mmol, 66% yield) was obtained as a bright yellow oil.

**1H NMR** (400 MHz, CDCl3): δ = 7.61 (dd, J = 8.1, 1.2 Hz, 1H, ArH), 7.52 (dd, J = 7.8, 1.6 Hz, 1H, ArH), 7.36 (td, J = 7.6, 1.3 Hz, 1H, ArH), 7.19 (ddd, J = 8.0, 7.4, 1.7 Hz, 1H, ArH), 4.85 (td, J = 10.9, 4.4 Hz, 1H, CO2–CH), 2.21–2.06 (m, 1H), 1.91 (dhep, J = 6.9, 2.7 Hz, 1H), 1.69 (d, J = 11.6 Hz, 2H), 1.58–1.34 (m, 2H), 1.17–0.97 (m, 2H), 0.95–0.75 (m, 10H) ppm; **13C NMR** (101 MHz, CDCl3): δ = 165.2 (C=O), 133.4 (ArC), 133.0 (ArC), 130.0 (ArC), 127.7 (ArC), 126.1 (ArC), 124.6 (ArC), 75.5 (CO2–CH), 47.2,
41.4, 34.3, 31.5, 26.7, 23.8, 22.1, 20.8, 16.8 ppm (C=N \_2 \text{ not observed}); IR (neat): \nu = 2956 m, 2868 m, 2090 s, 1693 s, 1476 m, 1236 s, 1165 s, 1009 s, 752 s, 644 m cm\(^{-1}\); HRMS (NSI): Exact mass calculated for C\(_{18}\)H\(_{24}\)BrN\(_2\)O\(_2\) [M+H\(^+\)]: 379.1016, found 379.1016; \([\alpha]_D^{20}:-54.5^\circ \text{ (c 0.70, CH}_2\text{Cl}_2)\).

(1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl 2-diazo-2-(4-(trifluoromethyl)phenyl) acetate 179j:

Performed according to General Procedure 11 on a 1.7 mmol scale of 209b; 179j (368 mg, 1.5 mmol, 87% yield) was obtained as a bright yellow solid.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 7.61 \text{ (s, 4H, ArH)}, 4.89 \text{ (td, J = 10.9, 4.4 Hz, 1H, CO}_2\text{--CH)}, 2.19–2.00 \text{ (m, 1H), 1.99–1.81 (m, 1H), 1.75–1.68 (m, 2H), 1.61–1.41 (m, 2H), 1.17–1.03 (m, 2H), 0.98–0.85 (m, 7H), 0.81 (d, J = 7.0 Hz, 3H, \text{CH}_3) \text{ ppm};} \)\(^{13}\)C NMR (126 MHz, CDCl\(_3\)): \(\delta = 164.2 \text{ (C=O), 130.8–130.6 (m, ArC), 127.6 (q, J = 32.7 Hz, ArC--CF}_3\), 126.0 (q, J = 3.8 Hz, 2 × ArC), 124.3 (q, J = 272.2 Hz, CF\(_3\), 123.6 (2 × ArC), 75.7 (CO\(_2\)--CH), 47.3, 41.4, 34.3, 31.6, 26.7, 23.8, 22.1, 20.9, 16.7 ppm (C=N \_2 \text{ not observed}); IR (neat): \nu = 2956 m, 2930 m, 2870 w, 2087 s, 1695 s, 1616 m, 1319 s, 1238 s, 1165 s, 1115 s 1070 s, 1011 s, 841 m cm\(^{-1}\); HRMS (NSI): Exact mass calculated for C\(_{19}\)H\(_{24}\)F\(_3\)N\(_2\)O\(_2\) [M+H\(^+\)]: 369.1784, found 369.1788; \([\alpha]_D^{20}:-62.6^\circ \text{ (c 0.80, CH}_2\text{Cl}_2)\).

5.3.1.5 Synthesis of Diazo Compound 213

Methyl (E)-2-((benzylideneamino)phenyl)acetate 169:

To neat aniline derivative 156a (3 g, 18 mmol), benzaldehyde 168 (1.1 equiv.) was added dropwise. The orange solution turned into an emulsion and MgSO\(_4\) was added. The suspension was stirred for 1 hour, the salt was filtered off and washed with CH\(_2\)Cl\(_2\) and the
mixture was concentrated under vacuo to afford 169 as an orange oil (3.8 g, 15 mmol, 83% yield).

$^1$H NMR (500 MHz, CDCl$_3$): $\delta = 8.42$ (s, 1H, N=CH), 7.92–7.86 (m, 2H, ArH), 7.51–7.43 (m, 3H, ArH), 7.35–7.28 (m, 2H, ArH), 7.21 (td, $J = 7.5$, 1.2 Hz, 1H, ArH), 7.04 (dd, $J = 7.8$, 1.0 Hz, 1H, ArH), 3.84 (s, 2H, CH$_2$), 3.61 (s, 3H, OCH$_3$) ppm; $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta = 172.5$ (C=O), 160.1 (ArC–N), 150.7 (ArC), 136.5 (ArC), 131.5 (ArC), 130.6 (ArC), 129.2 (ArC), 129.1 (ArC), 129.0 (ArC), 128.9 (ArC), 128.6 (ArC), 126.3 (ArC), 117.7 (ArC), 52.0 (OCH$_3$), 37.6 (CH$_2$) ppm. The spectroscopic data are in agreement with the literature.

Methyl (E)-2-(2-(benzylideneamino)phenyl)-2-diazoacetate 213:

A solution of 169 (340 mg, 1.3 mmol) and of $p$-NBSA 18f (1.5 equiv.) in acetonitrile (5 mL) was cooled to 0 °C before the addition of DBU (4 equiv.). The dark solution was stirred for 12 hours and checked by TLC (n-hexane/ethyl acetate). A saturated aqueous solution of NH$_4$Cl (10 mL) was added and the product extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined organic layers were washed with H$_2$O, brine, dried over MgSO$_4$ and concentrated under vacuo to afford 213 (211 mg, 0.75 mmol, 58% yield) as a yellow oil.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 8.40$ (s, 1H, N=CH), 7.99–7.88 (m, 2H, ArH), 7.75–7.67 (m, 1H, ArH), 7.57–7.46 (m, 3H, ArH), 7.34–7.27 (m, 2H, ArH), 7.14–6.98 (m, 1H, ArH), 3.84 (s, 3H, CH$_3$) ppm; $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta = 166.7$ (C=O), 159.8 (ArC–N), 148.1 (ArC), 136.0 (ArC), 131.8 (ArC), 129.8 (ArC), 129.3 (ArC), 128.9 (ArC), 128.4 (ArC), 126.6 (ArC), 120.1 (ArC), 118.0 (ArC), 52.0 (OCH$_3$) ppm (C=N$_2$ not observed). The spectroscopic data are in agreement with the literature.

5.3.1.6 Synthesis of Diazo Compounds 184a–k

General Procedure 12: The corresponding aryl acetic acid 203 was dissolved in methanol and the 0.5 M solution was cooled down to 0 °C before addition of acetyl chloride (2.5 equiv.). The reaction was stirred at room temperature for 16 hours and
checked by TLC (n-hexane/ethyl acetate). The solvent was evaporated in vacuo and the residual oil washed with a saturated aqueous solution of NaHCO₃ and extracted with Et₂O. Subsequently, the combined organic layers were washed with water and brine, dried over MgSO₄ and concentrated in vacuo to afford the pure methyl 2-hydroxyaryl acetate 220 which was used without further purification.

Methyl 2-(2-hydroxyphenyl)acetate 220a:

Performed according to General Procedure 12 on a 33 mmol scale of 203a; 220a (5.1 g, 31 mmol, 93% yield) was obtained as a colourless solid, m.p.: 68–70 °C.

¹H NMR (500 MHz, CDCl₃): δ = 7.43 (s, 1H, OH), 7.17 (t, J = 7.5 Hz, 1H, ArH), 7.11 (d, J = 7.2 Hz, 1H, ArH), 6.96–6.75 (m, 2H, ArH), 3.74 (s, 3H, OCH₃), 3.69 (s, 2H, CH₂) ppm; ¹³C NMR (126 MHz, CDCl₃): δ = 174.3 (C=O), 155.0 (ArC–O), 131.1 (ArC), 129.1 (ArC), 120.8 (ArC), 120.7 (ArC), 117.1 (ArC), 52.7 (OCH₃), 37.2 (CH₂) ppm. The spectroscopic data are in agreement with the literature.

Methyl 2-(5-bromo-2-hydroxyphenyl)acetate 220b:

Performed according to General Procedure 12 on a 2.2 mmol scale of 203b; 220b (515 mg, 2.1 mmol, 96% yield) was obtained as a colourless solid, m.p.: 76–80 °C.

¹H NMR (500 MHz, CDCl₃): δ = 7.37 (s, 1H, OH), 7.32–7.05 (m, 2H, ArH), 6.66 (d, J = 8.5 Hz, 1H, ArH), 3.67 (s, 3H, OCH₃), 3.55 (s, 2H, CH₂) ppm; ¹³C NMR (126 MHz, CDCl₃): δ = 173.9 (C=O), 154.4 (ArC–O), 133.5 (ArC), 131.9 (ArC), 122.8 (ArC), 119.0 (ArC), 112.6 (ArC), 52.9 (OCH₃), 37.0 (CH₂) ppm. The spectroscopic data are in agreement with the literature.

General Procedure 13: The methyl ester 220 was dissolved in DMF (0.5 M solution), and K₂CO₃ (2.5 equiv.), NaI (1.1 equiv.) were added. The solution was cooled down to 0 °C before the addition of the corresponding halide 161 (1.2 equiv.). The reaction was performed for 12–72 hours at room temperature and checked by TLC (n-hexane/ethyl acetate).
acetate). The suspension was filtrate, washed with water (40 mL) and the product extracted with Et₂O (3 × 15 mL). The combined organic layers were washed with brine, dried over MgSO₄ and concentrate under vacuum and purified by column to afford the desired product 221 as an oil or solid depending on the substrate.

Methyl 2-(2-(benzyloxy)phenyl)acetate 221a:

- Performed according to General Procedure 13 on a 21 mmol scale of 220a; 221a (4.4 g, 17 mmol, 82% yield) was obtained as a colourless solid, m.p.: 70–72 °C.
- ¥ H NMR (400 MHz, CDCl₃): δ = 7.46–7.35 (m, 4H, ArH), 7.35–7.28 (m, 1H, ArH), 7.28–7.18 (m, 2H, ArH), 6.98–6.90 (m, 2H, ArH), 5.09 (s, 2H, OC₂H₅), 3.69 (s, 2H, CH₂), 3.64 (s, 3H, OC₃H₃) ppm; ¥ C NMR (126 MHz, CDCl₃): δ = 172.4 (C=O), 156.7 (ArC–O), 137.2 (ArC), 131.1 (ArC), 128.7 (ArC), 128.6 (2 × ArC), 127.9 (ArC), 127.2 (2 × ArC), 123.6 (ArC), 120.9 (ArC), 111.9 (ArC), 70.0 (OCH₂), 51.9 (OCH₃), 36.2 (CH₂) ppm. The spectroscopic data are in agreement with the literature.²⁸

Methyl 2-(2-((4-(trifluoromethyl)benzyl)oxy)phenyl)acetate 221b:

- Performed according to General Procedure 13 on a 1.5 mmol scale of 220a; 221b (422 mg, 1.3 mmol, 87%) was obtained as a colourless solid, m.p.: 58–60 °C.
- ¥ H NMR (400 MHz, CDCl₃): δ = 7.60 (d, J = 8.2 Hz, 2H, ArH), 7.49 (d, J = 8.0 Hz, 2H, ArH), 7.25–7.15 (m, 2H, ArH), 6.92 (td, J = 7.5, 1.0 Hz, 1H, ArH), 6.84 (d, J = 8.1 Hz, 1H, ArH), 5.10 (s, 2H, OCH₂), 3.66 (s, 2H, CH₂), 3.60 (s, 3H, OCH₃) ppm; ¥ C NMR (101 MHz, CDCl₃): δ = 172.3 (C=O), 156.4 (ArC–O), 141.3–141.2 (m, ArC), 131.4 (ArC), 130.1 (q, J = 32.4 Hz, ArC–CF₃), 128.8 (ArC), 128.3 (2 × ArC), 125.6 (q, J = 3.8 Hz, 2 × ArC), 124.3 (d, J = 276.0 Hz, CF₃), 123.6 (ArC), 121.3 (ArC), 111.8 (ArC), 69.2 (OCH₂), 51.9 (OCH₃), 36.2 (CH₂) ppm; IR (neat): ν = 2949w, 1734s, 1605m, 1499m, 1452m, 1325s, 1258s, 1175s, 1107s, 820s, 754s, 696m, 586m, 565m cm⁻¹; HRMS (ES): Exact mass calculated for C₁₇H₁₆F₃O₃ [M+H]⁺: 325.1052, found 325.1047.
Methyl 2-((4-methoxybenzyl)oxy)phenyl)acetate 221c:

Performed according to General Procedure 13 on a 3.0 mmol scale of 220a; 221c (634 mg, 2.2 mmol, 74%) was obtained as a colourless oil.

\[
\begin{align*}
\text{Ome} & \quad \text{Me} & \quad \text{Ome} \\
\text{Ome} & \quad \text{Me} & \quad \text{Ome} \\
\end{align*}
\]

\[\begin{align*}
^1\text{H NMR (500 MHz, CDCl}_3\text{): } \delta &= 7.33 (d, \ J = 8.3 \text{ Hz}, 2\text{H, ArH}, 7.28–7.17 \text{ (m, 2H, ArH)}, 6.99–6.87 \text{ (m, 4H, ArH)}, 5.01 \text{ (s, 2H, OCH}_2\text{)}, 3.82 \text{ (s, 3H, OCH}_3\text{)}, 3.66 \text{ (s, 2H, CCH}_2\text{)}, 3.63 \text{ (s, 3H, OCH}_3\text{)} \text{ ppm; } \n\end{align*}\]

\[\begin{align*}
^{13}\text{C NMR (126 MHz, CDCl}_3\text{): } \delta &= 172.4 \text{ (C=O)}, 159.4 \text{ (ArC=O), 156.8 \text{ (ArC=O), 131.1 \text{ (ArC), 129.8 \text{ (ArC), 128.9 \text{ (2 x ArC), 128.7 (ArC), 123.6 \text{ (ArC), 120.9 \text{ (ArC), 114.0 \text{ (2 x ArC), 112.0 \text{ (ArC), 69.9 \text{ (OCH}_2\text{), 55.4 \text{ (OCH}_3\text{), 51.9 \text{ (OCH}_3\text{), 36.2 \text{ (CH}_3\text{) ppm; IR (neat): } } v = 2951w, 2837w, 1735s, 1514s, 1454m, 1240s, 1174s, 1029s, 819s, 750s cm}^{-1}; HRMS (ES): Exact mass calculated for C_{17}H_{18}O_4Na [M+Na]^+: 309.1103, found 309.1116.}
\end{align*}\]

Methyl 2-((4-methylbenzyl)oxy)phenyl)acetate 221d:

Performed according to General Procedure 13 on a 1.5 mmol scale of 220a; 221d (302 mg, 1.1 mmol, 74% yield) was afforded as a colourless solid, m.p.: 42–44 °C.

\[
\begin{align*}
\text{Me} & \quad \text{Ome} \\
\text{Me} & \quad \text{Ome} \\
\end{align*}
\]

\[\begin{align*}
^1\text{H NMR (300 MHz, CDCl}_3\text{): } \delta &= 7.29 (d, \ J = 8.0 \text{ Hz}, 2\text{H, ArH}, 7.27–7.15 \text{ (m, 4H, ArH)}, 6.97–6.89 \text{ (m, 2H, ArH)}, 5.04 \text{ (s, 2H, CCH}_2\text{)}, 3.68 \text{ (s, 2H, CCH}_2\text{)}, 3.64 \text{ (s, 3H, OCH}_3\text{)}, 2.36 \text{ (s, 3H, CH}_3\text{) ppm; IR (neat): } v = 3026w, 2949w, 2866w, 1736s, 1602m, 1589m, 1492s, 1454m, 1379w, 1240s, 1174s, 1029s, 819s, 750s cm}^{-1}; HRMS (ES): Exact mass calculated for C_{17}H_{19}O_3Na [M+Na]^+: 293.1154, found 293.1157.}
\end{align*}\]

Methyl 2-((4-bromobenzyl)oxy)phenyl)acetate 221e:

Performed according to General Procedure 13 on a 3.0 mmol scale of 220a; 221e (664 mg, 2.0 mmol, 66% yield) was afforded as a colourless solid, m.p.: 48–50 °C.

\[
\begin{align*}
\text{Br} & \quad \text{Ome} \\
\text{Br} & \quad \text{Ome} \\
\end{align*}
\]

\[\begin{align*}
^1\text{H NMR (400 MHz, CDCl}_3\text{): } \delta &= 7.50 (d, \ J = 8.4 \text{ Hz}, 2\text{H, ArH}, 7.32–7.17 \text{ (m, 4H, ArH)}, 6.94 \text{ (t, } J = 7.4 \text{ Hz, 1H, ArH)}, 6.88 \text{ (d, } J = 8.2 \text{ Hz, 1H, ArH)}, 5.03 \text{ (s, 2H, OCH}_2\text{)}, 3.67 \text{ (s, 2H, CCH}_2\text{)}, 3.63 \text{ (s, 3H, OCH}_3\text{)} \text{ ppm; IR (neat): } v = \]
ppm; $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta = 172.3$ (C=O), 156.5 (ArC–O), 136.2 (ArC), 131.8 (2 × ArC), 131.3 (ArC), 128.8 (2 × ArC), 128.8 (ArC), 123.6 (ArC), 121.8 (ArC), 121.2 (ArC), 111.9 (ArC), 69.3 (OCH$_2$), 52.0 (OCH$_3$), 36.2 (CH$_2$) ppm; IR (neat): $\nu = 2951$w, 2918w, 2864, 1743s, 1602m, 1500m, 1256s, 1157s, 1117s, 1009s, 800s, 752s cm$^{-1}$; HRMS (AP): Exact mass calculated for C$_{16}$H$_{16}$O$_3$Br [M+H]$^+$: 335.0283, found 335.0287.

Methyl 2-(2-((2-methylbenzyl)oxy)phenyl)acetate 221f:

Performed according to General Procedure 13 on a 1.5 mmol scale of 220a; 221f (356 mg, 1.3 mmol, 88% yield) was afforded as a colourless solid, m.p.: 54–56 °C.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.36$ (d, $J = 7.3$ Hz, 1H, ArH), 7.32–7.05 (m, 5H, ArH), 7.03–6.78 (m, 2H, ArH), 4.99 (s, 2H, OC$_2$H$_2$), 3.62 (s, 2H, C$_2$H$_2$), 3.54 (s, 3H, OC$_3$H$_3$), 2.30 (s, 3H, C$_3$H$_3$) ppm; $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta =$ 172.4 (C=O), 156.8 (ArC–O), 136.3 (ArC), 135.0 (ArC), 131.1 (ArC), 130.3 (ArC), 128.7 (ArC), 128.1 (ArC), 128.1 (ArC), 126.1 (ArC), 123.5 (ArC), 120.9 (ArC), 111.6 (ArC), 68.5 (OCH$_2$), 51.8 (OCH$_3$), 36.1 (CH$_2$), 18.9 (CH$_3$) ppm; IR (neat): $\nu = 3076$w, 2949w, 2921w, 1736s, 1600m, 1589m, 1499m, 1456m, 1348m, 1298m, 1250s, 1201m, 1161s, 1121s, 1053s, 850m, 756s, 691s cm$^{-1}$; HRMS (ES): Exact mass calculated for C$_{17}$H$_{18}$O$_3$Na [M+Na]$^+$: 293.1154, found 293.1158.

Methyl 2-(2-[[1,1'-biphenyl]-2-ylmethoxy]phenyl)acetate 221g:

Performed according to General Procedure 13 on a 1.5 mmol scale of 220a; 221g (405 mg, 1.2 mmol, 81% yield) was afforded as a colourless oil.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.65–7.54$ (m, 1H, ArH), 7.47–7.29 (m, 8H, ArH), 7.21–7.13 (m, 2H, ArH), 6.91 (td, $J = 7.5$, 1.0 Hz, 1H, ArH), 6.72 (d, $J = 7.9$ Hz, 1H, ArH), 4.96 (s, 2H, OCH$_2$), 3.66 (s, 2H, CH$_2$), 3.62 (s, 3H, OCH$_3$) ppm; $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta =$ 172.4 (C=O), 156.6 (ArC–O), 141.6 (ArC), 140.6 (ArC), 134.2 (ArC), 131.1 (ArC), 130.1 (ArC), 129.2 (ArC), 129.0 (ArC), 128.6 (ArC), 128.5 (ArC), 128.0 (ArC), 127.7 (ArC), 127.5 (ArC), 123.4 (ArC), 120.9 (ArC), 111.8 (ArC), 68.2 (OCH$_2$), 51.9 (OCH$_3$), 36.2 (CH$_2$) ppm; IR (neat): $\nu = 3076$w, 2949w, 2921w, 1736s, 1601m, 1589m, 1499m, 1456m, 1348m, 1298m, 1250s, 1201s, 1161s, 1121s, 1053s, 815m, 756s, 691s cm$^{-1}$; HRMS (ES): Exact mass calculated for C$_{22}$H$_{20}$O$_3$Na [M+Na]$^+$: 355.1310, found 355.1317.
Methyl 2-(2-(allyloxy)phenyl)acetate 221h:

Performed according to General Procedure 13 on a 1.5 mmol scale of 220a; 221h (247 mg, 1.2 mmol, 80% yield) was afforded as a colourless oil.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.26–7.16$ (m, 2H, Ar$H$), 6.92 (td, $J = 7.4$, 1.1 Hz, 1H, Ar$H$), 6.86 (d, $J = 8.2$ Hz, 1H, Ar$H$), 6.02 (ddt, $J = 17.3$, 10.6, 4.9, 1H, CH$^a$), 5.40 (dq, $J = 17.3$, 1.7 Hz, 1H, CH$^c$), 5.26 (dq, $J = 10.6$, 1.5 Hz, 1H, CH$^b$), 4.55 (dt, $J = 4.9$, 1.6 Hz, 2H, OC$_H^2$), 3.68 (s, 3H, OC$_H^3$), 3.66 (s, 2H, CH$_2$) ppm; $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta = 172.5$ (C=O), 156.6 (Ar–O), 133.3, 131.1, 128.6, 123.6, 120.9, 117.0, 111.9, 68.8 (OCH$_2$), 52.0 (OCH$_3$), 36.2 (CH$_2$) ppm; IR (neat): $\nu = 2951$w, 1736s, 1603m, 1589w, 1493s, 1340m, 1244s, 1155s, 997s, 926m, 750s cm$^{-1}$; HRMS (ES): Exact mass calculated for C$_{12}$H$_{14}$O$_3$Na [M+Na]$^+$: 229.0841, found 229.0842.

Methyl 2-(2-(cinnamyloxy)phenyl)acetate 221i:

Performed according to General Procedure 13 on a 3.0 mmol scale of 220a; 221i (378 mg, 1.3 mmol, 44% yield) was afforded as a colourless oil.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.34–7.30$ (m, 2H, Ar$H$), 7.27–7.21 (m, 2H, Ar$H$), 7.19–7.10 (m, 3H, Ar$H$), 6.89–6.79 (m, 2H, Ar$H$), 6.64 (d, $J = 16.0$ Hz, 1H, H$^f$), 6.28 (dt, $J = 16.0$, 5.4 Hz, 1H, H$^a$), 4.61 (dd, $J = 5.4$, 1.6 Hz, 2H, OCH$_2$), 3.61 (s, 3H, OCH$_3$), 3.58 (s, 2H, CH$_2$) ppm; $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta = 172.5$ (C=O), 156.7 (Ar–O), 136.7, 132.3, 131.1, 128.7, 128.6, 127.9, 126.6, 124.6, 123.6, 120.9, 112.0, 68.7 (OCH$_2$), 52.0 (OCH$_3$), 36.2 (CH$_2$) ppm; IR (neat): $\nu = 3026$w, 2949w, 1734s, 1600m, 1589m, 1493s, 1340m, 1244s, 1155s, 997s, 926m, 750s cm$^{-1}$; HRMS (ES): Exact mass calculated for C$_{18}$H$_{18}$O$_3$Na [M+Na]$^+$: 305.1154, found 305.1157.

Methyl 2-(5-bromo-2-((4-methylbenzyl)oxy)phenyl) acetate 221j:

Performed according to General Procedure 13 on a 1.7 mmol scale of 220b; 221j (457 mg, 1.3 mmol, 76% yield) was afforded as a colourless solid, m.p.: 82–84 °C.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta = 7.35$ (d, $J = 6.4$ Hz, 2H, Ar$H$), 7.31–7.27 (m, 2H, Ar$H$), 7.21 (d, $J = 7.7$ Hz, 2H, Ar$H$), 6.81 (d, $J = 9.3$ Hz, 1H, Ar$H$), 5.04 (s, 2H, OCH$_2$), 3.67 (s, 3H, OCH$_3$), 3.65 (s, 2H, CH$_2$), 2.38 (s, 3H, CH$_3$) ppm; $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta = 171.7$ (C=O),
156.0 (ArC–O), 137.9 (ArC), 133.8 (ArC), 133.6 (ArC), 131.3 (ArC), 129.4 (ArC), 127.3 (ArC), 125.8 (ArC), 123.3 (ArC), 120.4 (ArC), 111.3 (ArC), 68.1 (OCH₃), 51.9 (OCH₃), 36.2, 31.7, 29.4, 25.8, 22.8, 14.2 ppm; IR (neat): ν = 2951w, 1738s, 1493m, 1250s, 1198s, 1157s, 1124s, 1014s, 997s cm⁻¹; HRMS (ES): Exact mass calculated for C₁₇H₁₇O₃BrNa [M+Na]⁺: 371.0259, found 371.0259.

Methyl 2-(2-(hexyloxy)phenyl) acetate 221k:

Performed according to General Procedure 13 on a 1.5 mmol scale of 220a; 221k (217 mg, 0.87 mmol, 58% yield) was afforded as a colourless oil.

¹H NMR (400 MHz, CDCl₃): δ = 7.23 (td, J = 8.0, 1.8 Hz, 1H, ArH), 7.18 (dd, J = 7.4, 1.6 Hz, 1H, ArH), 6.90 (td, J = 7.4, 1.0 Hz, 1H, ArH), 6.85 (d, J = 8.2 Hz, 1H, ArH), 3.95 (t, J = 6.4 Hz, 2H, OCH₂), 3.68 (s, 3H, OCH₃), 3.63 (s, 2H, CH₂), 1.82–1.67 (m, 2H), 1.49–1.40 (m, 2H), 1.37–1.30 (m, 4H), 0.94–0.88 (m, 3H, CH₃) ppm; ¹³C NMR (101 MHz, CDCl₃): δ = 172.5 (C=O), 157.2 (Ar–O), 131.0 (ArC), 128.6 (ArC), 123.3 (ArC), 120.4 (ArC), 111.3 (ArC), 68.1 (OCH₂), 51.9 (OCH₃), 36.2, 31.7, 29.4, 25.8, 22.8, 14.2 ppm; IR (neat) ν = 2951m, 2929m, 2858w, 1738s, 1602w, 1495m, 1456m, 1244s, 1155s, 748s cm⁻¹; HRMS (ES): Exact mass calculated for C₁₅H₂₂O₃Na [M+Na]⁺: 273.1467, found 273.1469.

General Procedure 14: A 0.2 M solution of methyl arylacetate 221a–k and p-ABSA (3 equiv.) in acetonitrile was cooled down to 0 °C before the addition of DBU (4 equiv.). The reaction was stirred at room temperature for 12–48 hours and monitored by TLC (n-hexane/ethyl acetate). The mixture was quenched with a saturated aqueous solution of NH₄Cl saturated solution and the product was extracted with CH₂Cl₂. The combined organic layers were washed with water, brine, dried over MgSO₄ and concentrated under reduced pressure (20 °C water bath). The crude was purified by flash column chromatography to afford the pure product 184a–k as a yellow oil or solid.

Methyl 2-(2-(benzyloxy)phenyl)-2-diazoacetate 184a:

Performed according to General Procedure 14 on a 1.4 mmol scale of 221a; 184a (340 mg, 1.2 mmol, 86% yield) was afforded as a bright yellow oil.

¹H NMR (400 MHz, CDCl₃): δ = 7.57 (dd, J = 7.8, 1.7 Hz, 1H, ArH), 7.44–7.32 (m, 5H, ArH), 7.27–7.21 (m, 1H, ArH), 7.04 (td, J = 7.6,
1.1 Hz, 1H, ArH), 6.97 (dd, J = 8.3, 1.1 Hz, 1H, ArH), 5.11 (s, 2H, OCH₂), 3.82 (s, 3H, OCH₃) ppm; ¹³C NMR (126 MHz, CDCl₃): δ = 166.8 (C=O), 154.8 (ArC–O), 136.4 (ArC), 130.5 (ArC), 128.7 (ArC), 128.3 (ArC), 127.7 (ArC), 121.7 (ArC), 114.1 (ArC), 112.3 (ArC), 70.8 (OCH₂), 52.1 (OCH₃) ppm (C=N₂ not observed); IR (neat): ν = 3032w, 2951w, 2093s, 1693s, 1494m, 1448m, 1246s, 1149s, 1032s, 1009s, 744s, 696s cm⁻¹.

The spectroscopic data are in agreement with the literature.²⁸

Methyl 2-(2-((4-(trifluoromethyl)benzyl)oxy)phenyl)-2-diazoacetate 184b:

Performed according to General Procedure 14 on a 0.9 mmol scale of 221b; 184b (273 mg, 0.78 mmol, 87% yield) was afforded as a bright yellow solid.

¹H NMR (400 MHz, CDCl₃): δ = 7.66 (d, J = 8.2 Hz, 2H, ArH), 7.58 (dd, J = 7.8, 1.7 Hz, 1H, ArH), 7.53 (d, J = 8.0 Hz, 2H, ArH), 7.28–7.23 (m, 1H, ArH), 7.07 (td, J = 7.5, 1.0 Hz, 1H, ArH), 6.94 (dd, J = 8.3, 1.0 Hz, 1H, ArH), 5.16 (s, 2H, OCH₂), 3.83 (s, 3H, OCH₃) ppm; ¹³C NMR (101 MHz, CDCl₃): δ = 166.6 (C=O), 154.5 (ArC–O), 140.4 (ArC), 130.7 (ArC), 130.4 (q, J = 32.5 Hz, ArC–CF₃), 128.8 (ArC), 127.6 (ArC), 125.7 (q, J = 3.8 Hz, 2 × ArC), 124.2 (q, J = 272.1 Hz, CF₃), 121.9 (ArC), 114.2 (ArC), 112.3 (ArC), 69.9 (OCH₂), 52.1 (OCH₃) ppm (C=N₂ not observed); IR (neat): ν = 2859w, 2097s, 1693s, 1497m, 1437m, 1325s, 1248s, 1155s, 824s, 750s cm⁻¹; HRMS (ES): Exact mass calculated for C₁₇H₁₄F₃O₃[M–N₂+H]⁺: 323.0895, found 323.0901.

Methyl 2-diazo-2-(2-((4-methoxybenzyl)oxy)phenyl)acetate 184c:

Performed according to General Procedure 14 on a 0.52 mmol scale of 221c; 184c (125 mg, 0.40 mmol, 77% yield) was afforded as a bright yellow solid.

¹H NMR (400 MHz, CDCl₃): δ = 7.59 (dd, J = 7.8, 1.6 Hz, 1H, ArH), 7.34 (d, J = 8.5 Hz, 2H, ArH), 7.30–7.17 (m, 1H, ArH), 7.05 (t, J = 7.6 Hz, 1H, ArH), 6.99 (d, J = 8.3 Hz, 1H, ArH), 6.94 (d, J = 8.6 Hz, 2H, ArH), 5.03 (s, 2H, OCH₂), 3.83 (s, 3H, OCH₃) ppm; ¹³C NMR (101 MHz, CDCl₃): δ = 166.6 (C=O), 159.6 (ArC–O), 154.8 (ArC–O), 130.4 (ArC), 129.4 (2 × ArC), 128.6 (ArC), 128.4 (ArC), 121.4 (ArC), 114.1 (ArC), 114.0 (2 × ArC), 112.3 (ArC), 70.5 (OCH₂) 55.3 (OCH₃), 52.01 (OCH₃) ppm (C=N₂ not observed); IR (neat): ν = 3001m, 2955m, 2839w, 2098s, 1689s, 1514s, 1435s, 1028s, 995s, 814s, 754s cm⁻¹. The spectroscopic data are in agreement with the literature.²⁹
Methyl 2-(2-((4-(methylbenzyl)oxy)phenyl)-2-diazoacetate 184d:

Performed according to General Procedure 14 on a 0.55 mmol scale of 221d; 184d (137 mg, 0.46 mmol, 84% yield) was afforded as a bright yellow solid.

\[ \delta = 7.57 (dd, J = 7.8, 1.7 Hz, 1H, ArH), 7.30 (d, J = 8.0 Hz, 2H, ArH), 7.27–7.17 (m, 3H, ArH), 7.03 (td, J = 7.6, 1.1 Hz, 1H, ArH), 6.97 (dd, J = 8.3, 0.9 Hz, 1H, ArH), 5.06 (s, 2H, CH₂), 3.82 (s, 3H, OC₃H₃), 2.37 (s, 3H, CH₃) ppm; 13C NMR (101 MHz, CDCl₃): δ = 166.8 (C=O), 154.8 (ArC–O), 138.0 (ArC), 130.5 (ArC), 129.4 (ArC), 128.7 (ArC), 127.8 (ArC), 121.5 (ArC), 114.1 (ArC), 112.3 (ArC), 70.7 (OCH₂), 52.1 (OCH₃), 21.3 (CH₃) ppm (C=N₂ not observed); IR (neat): ν = 3057w, 3030w, 2949w, 2091s, 1692s, 1429m, 1254s, 1149s, 1005s, 802s, 744s, 662m cm⁻¹. The spectroscopic data are in agreement with the literature.²⁹

Methyl 2-((4-bromobenzyl)oxy)phenyl)-2-diazoacetate 184e:

Performed according to General Procedure 14 on a 0.89 mmol scale of 221e; 184e (230 mg, 0.64 mmol, 71% yield) was afforded as a bright yellow solid.

\[ \delta = 7.48 (dd, J = 7.8, 1.4 Hz, 1H, ArH), 7.41 (d, J = 8.3 Hz, 2H, ArH), 7.20–7.08 (m, 3H, ArH), 6.95 (t, J = 7.6 Hz, 1H, ArH), 6.83 (d, J = 8.3 Hz, 1H, ArH), 4.92 (s, 2H, CH₂), 3.72 (s, 3H, OCH₃) ppm; 13C NMR (101 MHz, CDCl₃): δ = 166.6 (C=O), 154.5 (ArC–O), 135.3 (ArC), 131.8 (ArC), 130.6 (ArC), 129.2 (ArC), 128.7 (ArC), 122.2 (ArC), 121.7 (ArC), 114.1 (ArC), 112.3 (ArC), 70.0 (OCH₂), 52.1 (OCH₃) ppm (C=N₂ not observed); IR (neat): ν = 2988m, 2947m, 2947m, 2097s, 1691s, 1495s, 1431s, 1229s, 1153s, 804s, 741s cm⁻¹. HRMS (AP): Exact mass calculated for C₁₆H₁₂BrO₂: 333.0126, found 333.0117.

Methyl 2-diazo-2-(((2-methylbenzyl)oxy)phenyl)acetate 184f:

Performed according to General Procedure 14 on a 1.8 mmol scale of 221f; 184f (388 mg, 1.3 mmol, 71% yield) was afforded as a bright yellow solid.

\[ \delta = 7.53 (dd, J = 7.8, 1.6 Hz, 1H, ArH), 7.35–7.28 (m, 1H, ArH), 7.25–7.15 (m, 4H, ArH), 7.00 (td, J = 7.7, 1.1 Hz, 1H, ArH), 6.95 (dd, J = 8.3, 0.8 Hz, 1H, ArH), 5.03 (s, 2H, OCH₂), 3.76 (s, 3H,
OCH₃), 2.30 (s, 3H, CH₃) ppm; ¹³C NMR (126 MHz, CDCl₃): δ = 166.8 (C=O), 154.9 (ArC–O), 136.5 (ArC), 134.3 (ArC), 130.5 (ArC), 128.7 (ArC), 128.6 (ArC), 128.4 (ArC), 126.2 (ArC), 121.5 (ArC), 114.0 (ArC), 112.2 (ArC), 69.1 (OCH₂), 52.1 (OCH₃), 18.9 (CH₃) ppm (C=N₂ not observed); IR (neat): ν = 3055w, 2953w, 2098s, 1697s, 1497s, 1452s, 1246s, 1153s, 1003w, 733s cm⁻¹.; HRMS (AP): Exact mass calculated for C₁₀H₁₄O₃Br[M–N₂+H]⁺: 333.0126, found 333.0117.

Methyl 2-(2-((2-(phenylbenzyl)oxy)phenyl)-2-diazoacetate 184g:

Performed according to General Procedure 14 on a 1.0 mmol scale of 221g; 184g (269 mg, 0.75 mmol, 75% yield) was afforded as a bright yellow oil.

¹H NMR (300 MHz, CDCl₃): δ = 7.63–7.48 (m, 2H, ArH), 7.48–7.32 (m, 8H, ArH), 7.16 (ddd, J = 8.3, 7.5, 1.7 Hz, 1H, ArH), 7.01 (td, J = 7.6, 1.2 Hz, 1H, ArH), 6.75 (dd, J = 8.3, 0.9 Hz, 1H, ArH), 5.01 (s, 2H, OCH₂), 3.83 (s, 3H, OCH₃) ppm; ¹³C NMR (101 MHz, CDCl₃): δ = 166.8 (C=O), 154.7 (ArC–O), 141.8 (ArC), 140.5 (ArC), 133.5 (ArC), 130.4 (ArC), 130.2 (ArC), 129.3 (ArC), 129.2 (ArC), 128.7 (ArC), 128.5 (ArC), 128.3 (ArC), 127.8 (ArC), 127.5 (ArC), 121.5 (ArC), 114.0 (ArC), 112.4 (ArC), 68.8 (OCH₂), 52.1 (OCH₃) ppm (C=N₂ not observed); IR (neat): ν = 3059w, 2987m, 2951m, 2094s, 1697s, 1435s, 1246s, 1153s, 1003w, 733s cm⁻¹.; HRMS (EI): Exact mass calculated for C₂₂H₁₈N₂O₃ [M⁺]: 358.1317, found 358.1320.

Methyl 2-(2-(allyloxy)phenyl)-2-diazoacetate 184h:

Performed according to General Procedure 14 on a 0.97 mmol scale of 221h; 184h (90 mg, 0.39 mmol, 40% yield) was afforded as a bright yellow oil.

¹H NMR (500 MHz, CDCl₃): δ = 7.56 (dd, J = 7.8, 1.5 Hz, 1H, ArH), 7.26–7.22 (m, 1H, ArH), 7.03 (td, J = 7.8, 1.1 Hz, 1H, ArH), 6.90 (d, J = 8.3 Hz, 1H, ArH), 6.05 (ddt, J = 17.2, 10.5, 5.3 Hz, 1H, CHF), 5.41 (ddd, J = 17.3, 3.0, 1.6 Hz, 1H, CHF), 5.30 (dd, J = 10.6, 1.4 Hz, 1H, CHF), 4.58 (dt, J = 5.2, 1.3 Hz, 2H, OCH₂), 3.84 (s, 3H, OCH₃) ppm; ¹³C NMR (126 MHz, CDCl₃): δ = 166.8 (C=O), 154.6 (ArC–O), 132.8, 130.4, 128.6, 121.4, 118.0, 114.0, 112.1, 69.4 (OCH₂), 52.1 (OCH₃) ppm (C=N₂ not observed); IR (neat): ν = 2953w, 2099s, 1697s, 1489s, 1433s, 1246s, 742s, 702s cm⁻¹.; HRMS (EI): Exact mass calculated for C₁₂H₁₃O₃ [M–N₂+H]⁺: 205.0865, found 205.0870.
Methyl 2-(2-(cinnamyloxy)phenyl)-2-diazoacetate 184i:

Performed according to General Procedure 14 on a 0.88 mmol scale of 221i; 184i (120 mg, 0.39 mmol, 44% yield) was afforded as a bright yellow oil.

\[\text{H NMR (500 MHz, CDCl}_3\text{): } \delta = 7.51 \text{ (dd, } J = 7.8, 1.5 \text{ Hz, 1H, ArH),} \]
\[7.39-7.32 \text{ (m, 2H, ArH),} \]
\[7.30-7.24 \text{ (m, 2H, ArH),} \]
\[7.24-7.06 \text{ (m, 2H, ArH),} \]
\[6.97 \text{ (td, } J = 7.8, 1.1 \text{ Hz, 1H, ArH),} \]
\[6.88 \text{ (dd, } J = 8.3, 0.6 \text{ Hz, 1H, ArH),} \]
\[6.66 \text{ (d, } J = 16.0 \text{ Hz, 1H, CH}_3\text{),} \]
\[6.32 \text{ (dt, } J = 16.0, 5.8 \text{ Hz, 1H, CH}_3\text{),} \]
\[4.66 \text{ (d, } J = 5.8 \text{ Hz, 2H, CH}_2\text{),} \]
\[3.76 \text{ (s, 3H, OCH}_3\text{).} \]

\[\text{13C NMR (126 MHz, CDCl}_3\text{): } \delta = 166.8 \text{ (C=O),} \]
\[154.6 \text{ (ArC–O),} \]
\[136.4, 130.4, 128.7, 126.7, 128.1, 126.6, 123.9, \]
\[121.5, 114.1, 112.3, 69.3 \text{ (OCH}_2\text{),} \]
\[52.1 \text{ (OCH}_3\text{) ppm (C=N}_2\text{ not observed);} \]
\[\text{IR (neat): } v = 3025\text{w, 2951w, 2856w, 2093s, 1695s, 1493s, 1433s, 1248, 1151s, 1031s, 964s, 733s,} \]
\[690s \text{ cm}^{-1}; \]
\[\text{HRMS (AP): Exact mass calculated for } C_{18}H_{17}O_3 [M–N}_2H]^+: 281.1178, \text{ found 281.1176.} \]

Methyl 2-(5-bromo-2-(((4-methylbenzyl)oxy)phenyl)-2-diazoacetate 184j:

Performed according to General Procedure 14 on a 0.88 mmol scale of 221j; 184j (270 mg, 0.72 mmol, 91% yield) was afforded as a bright yellow solid.

\[\text{H NMR (400 MHz, CDCl}_3\text{): } \delta = 7.68 \text{ (d, } J = 2.5 \text{ Hz, 1H, ArH),} \]
\[7.27-7.16 \text{ (m, 3H, ArH),} \]
\[7.13 \text{ (d, } J = 7.9 \text{ Hz, 2H, ArH),} \]
\[6.75 \text{ (d, } J = 8.8 \text{ Hz,} \]
\[4.95 \text{ (s, 2H, OCH}_2\text{),} \]
\[3.75 \text{ (s, 3H, OCH}_3\text{),} \]
\[2.30 \text{ (s, 3H, CH}_3\text{).} \]

\[\text{13C NMR (101 MHz, CDCl}_3\text{): } \delta = 166.1 \text{ (C=O),} \]
\[154.6 \text{ (ArC–O),} \]
\[138.2 \text{ (ArC),} \]
\[132.8 \text{ (ArC),} \]
\[130.9 \text{ (ArC),} \]
\[129.4 \text{ (ArC),} \]
\[127.8 \text{ (ArC),} \]
\[116.3 \text{ (ArC),} \]
\[113.8 \text{ (ArC),} \]
\[113.7 \text{ (ArC),} \]
\[71.0 \text{ (OCH}_2\text{),} \]
\[52.2 \text{ (OCH}_3\text{),} \]
\[21.3 \text{ (CH}_3\text{) ppm (C=N}_2\text{ not observed);} \]
\[\text{IR (neat): } v = 2951w, 2856w, 2093s, 1493s, 1435s, 1404m, 1333m,} \]
\[1248s, 1153s, 1040s, 906s, 802s, 727s \text{ cm}^{-1}; \]
\[\text{HRMS (ES): Exact mass calculated for } C_{18}H_{17}O_3 [M–N}_2H]^+: 347.0283, \text{ found 347.0283.} \]

Methyl 2-(2-(hexyloxy)phenyl)-2-diazoacetate 184k:

Performed according to General Procedure 14 on a 0.40 mmol scale of 221k; 184k (93 mg, 0.34 mmol, 84%) was afforded as a bright yellow oil.

\[\text{H NMR (400 MHz, CDCl}_3\text{): } \delta = 7.56 \text{ (dd, } J = 7.8, 1.7 \text{ Hz, 1H, ArH),} \]
\[7.23 \text{ (ddd, } J = 8.3, 7.5, 1.7 \text{ Hz, 1H, ArH),} \]
\[7.00 \text{ (td, } J = 7.6, 1.1 \text{ Hz, 1H,} \]
ArH), 6.88 (dd, J = 8.3, 1.1 Hz, 1H, ArH), 3.99 (t, J = 6.5 Hz, 2H, OCH₃), 3.84 (s, 3H, OCH₃), 1.85–1.73 (m, 2H), 1.52–1.42 (m, 2H), 1.38–1.32 (m, 4H), 0.92 (t, J = 7.1 Hz, 3H, CH₃) ppm; ¹³C NMR (101 MHz, CDCl₃): δ = 166.9 (C=O), 155.1 (ArC–O), 130.2 (ArC), 128.6 (ArC), 121.0 (ArC), 113.6 (ArC), 111.6 (ArC), 68.6 (OCH₃), 52.1 (OCH₃), 31.7, 29.2, 26.0, 22.7, 14.1 ppm (C=N not observed); IR (neat): ν = 2951m, 2930m, 2858m, 2093s, 1701s, 1497m, 1450m, 1433m, 1248s, 1150s, 1032m, 746s cm⁻¹; HRMS (ES): Exact mass calculated for C₁₅H₂₁O₃[M–N₂+H]⁺: 249.1491, found 249.1495.

5.3.1.7 Synthesis of Diazo Compounds 184I–n

General Procedure 15: 2-(2-(Benzyloxy)phenyl)acetic acid 232 (4 mmol), prepared from 203 according to literature procedure,³⁰ was dissolved in CH₂Cl₂ (2 mL) and added to a solution of chiral alcohol (2 mmol) in CH₂Cl₂ (3 mL), DCC (3 mmol) and DMAP (0.6 mmol) were added. The reaction was stirred over night at room temperature. The reaction was filtered, washed with H₂O and extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were washed with brine, dried over MgSO₄ and concentrated under vacuum. The crude was purified by column chromatography to afford 221l–n as a colourless solid or an oil.

(1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl 2-(2-benzyloxy)phenyl)acetate 221l:

Performed according to General Procedure 15 on a 2.0 mmol scale of (-)-menthol; 221l (543 mg, 1.43 mmol, 95% yield) was afforded as a colourless solid, m.p.: 52–56 °C.

¹H NMR (500 MHz, CDCl₃): δ = 7.35 (d, J = 7.1 Hz, 2H, ArH), 7.32–7.26 (m, 2H, ArH), 7.23 (t, J = 7.3 Hz, 1H, ArH), 7.18–7.10 (m, 2H, ArH), 6.88–6.76 (m, 2H, ArH), 5.11–4.87 (m, 2H, ArH), 4.59 (td, J = 10.9, 4.4 Hz, 1H, OCH₃), 3.60 (s, 2H, CH₂), 1.90–1.80 (m, 1H), 1.76–1.65 (m, 1H), 1.61–1.50 (m, 2H), 1.42–1.29 (m, 1H), 1.27–1.18 (m, 1H), 0.99–0.87 (m, 1H), 0.85–0.71 (m, 8H), 0.59 (d, J = 7.0 Hz, 3H, CH₃) ppm; ¹³C NMR (126 MHz, CDCl₃): δ = 171.5 (C=O), 156.7 (ArC–O), 137.3 (ArC), 131.1 (ArC), 128.6 (ArC), 128.5 (ArC), 127.8 (ArC), 127.1 (ArC), 123.8 (ArC), 120.8 (ArC), 111.7 (ArC), 74.5 (OCH), 69.9 (OCH₂), 47.1, 40.9, 36.6,
(1R,2R)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl 2-(2-(benzyloxy)phenyl)acetate 221m:

Performed according to General Procedure 15 on a 2.0 mmol scale of (−)-borneol; 221m (545 mg, 1.44 mmol, 96% yield) was afforded as a colourless oil.

$^1$H NMR (500 MHz, CDCl$_3$): δ = 7.33 (d, $J$ = 7.7 Hz, 2H, ArH), 7.27 (t, $J$ = 7.5 Hz, 2H, ArH), 7.20 (t, $J$ = 7.1 Hz, 1H, ArH), 7.13 (dd, $J$ = 8.1, 3.7 Hz, 2H, ArH), 6.87–6.79 (m, 2H, ArH), 4.98 (s, 2H, OC$_2$H$_2$), 4.81–4.76 (m, 1H, OC$_2$H), 3.61 (s, 2H, CH$_2$), 2.27–2.14 (m, 1H), 1.73–1.63 (m, 1H), 1.62–1.48 (m, 2H), 1.13–1.04 (m, 1H), 1.04–0.96 (m, 1H), 0.81 (dd, $J$ = 13.7, 3.3 Hz, 2H), 0.77 (s, 3H, CH$_3$), 0.74 (s, 3H, CH$_3$), 0.65 (s, 3H, CH$_3$) ppm; $^{13}$C NMR (126 MHz, CDCl$_3$): δ = 172.1 (C=O), 156.7 (ArC–O), 137.2 (ArC), 131.1 (ArC), 128.6 (ArC), 128.4 (ArC), 127.8 (ArC), 127.1 (ArC), 123.9 (ArC), 120.8 (ArC), 111.7 (ArC), 80.1 (OCH$_2$), 48.8, 47.8, 44.9, 36.7, 36.5, 28.0, 27.0, 19.7, 18.9, 13.5 ppm; IR (neat): ν = 2951m, 2926m, 1730s, 1602w, 1589w, 1494s, 1452s, 1244s, 1153s, 1022s, 748s, 694s cm$^{-1}$; HRMS (ES): Exact mass calculated for C$_{25}$H$_{32}$O$_3$Na [M+Na]$^+$: 403.2249, found 403.2266; [α]$_D^{20}$: −39.5° (c 0.40, CH$_2$Cl$_2$).

(1R,2S,5R)-5-Methyl-2-(2-phenylpropan-2-yl)cyclohexyl 2-(2-(benzyloxy)phenyl)acetate 221n:

Performed according to General Procedure 15 on a 1.59 mmol scale of (−)-8-phenylmentho; 221n (468 mg, 1.02 mmol, 64% yield) was afforded as a colourless oil.

$^1$H NMR (500 MHz, CDCl$_3$): δ = 7.42–7.34 (m, 4H, ArH), 7.33–7.28 (m, 5H, ArH), 7.20 (t, $J$ = 7.8 Hz, 1H, ArH), 7.14–7.10 (m, 1H, ArH), 7.07 (d, $J$ = 7.3 Hz, 1H, ArH), 6.93–6.83 (m, 2H, ArH), 5.05 (s, 2H, OCH$_2$), 4.80 (td, $J$ = 10.6, 4.1 Hz, 1H, OCH$_2$), 3.21 (d, $J$ = 16.3 Hz, 1H, 1 × CH$_2$), 3.10 (d, $J$ = 16.4 Hz, 1H, 1 × CH$_2$), 2.94 (q, $J$ = 12.2 Hz, 1H), 1.95 (t, $J$ = 10.5 Hz, 1H), 1.80 (d, $J$ = 12.2 Hz, 1H), 1.59 (t, $J$ = 10.1 Hz, 2H), 1.46–1.34 (m, 1H), 1.28–1.13 (m, 7H), 1.08–0.94 (m, 1H), 0.92–0.76 (m, 5H) ppm; $^{13}$C NMR (126 MHz, CDCl$_3$): δ = 171.0 (C=O), 156.8 (ArC–O), 151.7 (ArC), 137.3 (ArC), 131.2 (ArC), 128.6 (ArC), 128.4 (ArC), 128.1 (ArC), 127.9 (ArC), 127.3 (ArC), 125.7 (ArC), 125.2 (ArC), 123.7 (ArC), 120.8 (ArC), 111.7 (ArC), 74.6 (OCH$_2$), 70.0 (OCH$_2$), 50.5, 41.7, 39.9, 36.2, 34.7, 31.3, 27.5, 26.8, 25.6, 21.9 ppm; IR (neat): ν =
3030w, 2951m, 2922m, 2868w, 1730s, 1601m, 1494s, 1452s, 1242s, 987s, 748s, 696s cm⁻¹; HRMS (ES): Exact mass calculated for C₃₁Hₙ₆O₃Na [M+Na]⁺: 479.2562, found 479.2564; [α]D²: +19.2° (c 0.52, CH₂Cl₂).

**General Procedure 16:**

![Chemical Structure]

To a solution of aryl acetate 221l–n in dry THF (5 mL), a 2 M THF solution of NaHMDS (1.1 equiv.) was added at −78 °C. The solution was stirred for 15 minutes before adding a solution of p-NBSA 18f (1.1 equiv.) in dry THF (1 mL) dropwise. The dark solution was stirred at −78 °C for 1 hour before being allowed to warm up to room temperature for 12–48 h. The reaction was quenched with pH 7 phosphate buffer, the product extracted with CH₂Cl₂ (3 × 10 mL), the combined organic layers washed with H₂O, brine and finally dried over MgSO₄ and concentrated under reduced pressure (20 °C water bath). The crude was purified by column chromatography to afford the products 184l–n as yellow oils.

(1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl 2-(2-(benzyloxy)phenyl)-2-diazoacetate 184l:

Performed according to General Procedure 16 on a 0.63 mmol scale of 221l; 184l (213 mg, 0.52 mmol, 83% yield) was afforded as a bright yellow oil.

¹H NMR (500 MHz, CDCl₃): δ = 7.58 (dd, J = 7.8, 1.3 Hz, 1H, ArH), 7.39–7.26 (m, 5H, ArH), 7.18 (ddd, J = 8.5, 6.8, 3.0 Hz, 1H, ArH), 6.99 (t, J = 7.6 Hz, 1H, ArH), 6.92 (d, J = 8.3 Hz, 1H, ArH), 5.07 (s, 2H, OCH₂), 4.81 (td, J = 10.9, 4.4 Hz, 1H, OCH), 2.10–2.03 (m, 1H), 1.89 (dt, J = 13.9, 6.9, 2.6 Hz, 1H), 1.68–1.61 (m, 1H), 1.52–1.42 (m, 1H), 1.41–1.34 (m, 1H), 1.11–0.96 (m, 2H), 0.87 (t, J = 6.5 Hz, 6H), 0.77 (d, J = 7.0 Hz, 3H, CH₃) ppm; ¹³C NMR (126 MHz, CDCl₃): δ = 165.9 (C=O), 154.7 (ArC=O), 136.5 (ArO), 130.3 (ArC), 128.7 (ArC), 128.4 (ArC), 128.2 (ArC), 127.6 (ArC), 121.5 (ArC), 114.5 (ArC), 112.4 (ArC), 75.0 (OCH), 70.8 (OCH₂), 47.2, 41.5, 34.4, 31.6, 26.6, 23.8, 22.2, 20.9, 16.7 ppm (C=N₂ not observed); IR (neat): ν = 2953m, 2924m, 2868m, 2093s, 1690s, 1448m, 1240m, 1011s.
746s, 694m cm$^{-1}$; HRMS (ES): Exact mass calculated for C$_{25}$H$_{31}$O$_3$ [M−N$_2$+H]$^+$: 379.2273, found 379.2272; $[\alpha]_{D}^{20}$ -49.7° (c 0.52, CH$_2$Cl$_2$).

(1$R$,2$R$)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl 2-(2-(benzyloxy)phenyl)-2-diazoacetate 184m:

Performed according to General Procedure 16 on a 1.1 mmol scale of 221m; 184m (371 mg, 0.92 mmol, 83% yield) was afforded as a bright yellow oil.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 7.62 (d, J = 7.8 Hz, 1H, ArH), 7.45–7.32 (m, 5H, ArH), 7.25–7.19 (m, 1H, ArH), 7.03 (t, J = 7.6 Hz, 1H, ArH), 6.97 (d, J = 8.3 Hz, 1H, ArH), 5.12 (s, 2H, OCH$_2$), 5.04 (d, J = 9.7 Hz, 1H, OCH$\_2$), 2.41 (td, J = 9.9, 4.9 Hz, 1H), 1.90–1.81 (m, 1H), 1.78–1.68 (m, 2H), 1.33–1.20 (m, 2H), 1.09 (dd, J = 13.7, 2.9 Hz, 1H), 0.93 (s, 3H, CH$_3$), 0.88 (s, 3H, CH$_3$), 0.87 (s, 3H, CH$_3$) ppm; $^{13}$C NMR (126 MHz, CDCl$_3$ $\delta$ = 166.6 (C=O), 154.6 (ArC–O), 136.5 (ArC), 130.2 (ArC), 128.7 (ArC), 128.4 (ArC), 128.3 (ArC), 127.7 (ArC), 121.5 (ArC), 114.4 (ArC), 112.4 (ArC), 80.8 (OCH), 70.9 (OCH$_2$), 49.1, 47.9, 45.1, 37.1, 28.2, 27.2, 19.9, 19.0, 13.7 ppm (C=N$_2$ not observed); IR (neat): $\nu$ = 2953m, 2876w, 2091s, 1693s, 1497m, 1450m, 1242s, 1151s, 1022s, 746s, 694s cm$^{-1}$; HRMS (ES): Exact mass calculated for C$_{25}$H$_{29}$O$_3$ [M−N$_2$+H]$^+$: 377.2117, found 377.2115; $[\alpha]_{D}^{20}$ -21.9° (c 0.64, CH$_2$Cl$_2$).

(1$R$,2$S$,5$R$)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl 2-(2-(benzyloxy)phenyl)-2-diazoacetate 184n:

Performed according to General Procedure 16 on a 0.63 mmol scale of 221n; It was not possible to have full conversion nor purified 184n from the starting material left and it was carried on as crude mixture material (product/starting material ratio = 1:0.6) for the following step.
5.3.1.8 Synthesis of Diazo Compound 224

Methyl 2-(2-(benzylthio)phenyl) acetate 223:

An oven-dried Schlenk tube under nitrogen was loaded with 2-iodophenylacetic acid 202e (660 mg, 2.5 mmol), CuI (10 mol%), sulfur powder (3 equiv.) and K$_2$CO$_3$ (2 equiv.). Dry DMF (5 mL) was added and the mixture was stirred at 90 °C for 16 hours under inert atmosphere. The dark brown muddy suspension was then cooled down to 0 °C before the addition of NaBH$_4$ (284 mg, 3 equiv.) and stirred for further 7 hours at 40 °C. The orange suspension was cooled down to 0 °C before the addition of benzyl bromide 160 (300 µL, 2 equiv.) then stirred at room temperature for 16 h. HCl 1 M was added to the dark solution until pH 2, and the product extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with H$_2$O (2 × 5 mL), brine then dried over MgSO$_4$ and concentrated under reduced pressure to afford a yellow oil. The oil was dissolved in MeOH (8 mL), cooled to 0 °C and treated with acetyl chloride (540 µL) dropwise. The reaction was stirred at room temperature for 6 h. The solvent was removed under reduced pressure, the residue diluted with Et$_2$O and washed with a saturated aqueous solution of NaHCO$_3$ (10 mL), H$_2$O (10 mL) and brine. The organic layer was then dried over MgSO$_4$, concentrated under reduced pressure and purified by column chromatography (10% EtOAc in petroleum ether). Compound 223 was afforded as a yellow oil (152 mg, 0.55 mmol, 22% overall yield).

$^1$H NMR (500 MHz, CDCl$_3$): δ = 7.42–7.34 (m, 1H, ArH), 7.34–7.14 (m, 8H, ArH), 4.03 (s, 2H, SCH$_2$), 3.75 (s, 2H, CH$_2$), 3.69 (s, 3H, OCH$_3$) ppm; $^{13}$C NMR (126 MHz, CDCl$_3$): δ = 172.0 (C=O), 137.5 (ArC), 136.0 (ArC), 135.9 (ArC), 132.5 (ArC), 130.7 (ArC), 129.0 (ArC), 128.6 (ArC), 128.0 (ArC), 127.5 (ArC), 127.3 (ArC), 52.2 (OCH$_3$), 40.2, 39.5 ppm; IR (neat): ν = 3061w, 2949w, 1732s, 1433m, 1339m, 1213w, 1155s, 739s cm$^{-1}$; HRMS (ES): Exact mass calculated for C$_{16}$H$_{16}$O$_2$S [M]$^+$: 272.0871, found 272.0867.
Methyl 2-(2-(benzylthio)phenyl) acetate 224:

A solution of 223 (115 mg, 0.42 mmol) in dry acetonitrile (4 mL) was cooled down to 0 °C before the addition of p-ABSA (121 mg, 1.2 equiv.) and DBU (75 µL, 1.2 equiv.) and stirred for 16 hours at room temperature under nitrogen and monitored by TLC (n-hexane/ethyl acetate, 9:1). The mixture was quenched with a saturated aqueous solution of NH₄Cl (10 mL) and the product was extracted with CH₂Cl₂ (3 × 5 mL). The combined organic layers were washed with water, brine, dried over MgSO₄ and concentrated under reduced pressure (20 °C water bath). The crude was purified by flash column chromatography to afford 224 as a yellow oil (51 mg, 0.17 mmol, 40% yield).

1H NMR (500 MHz, CDCl₃): δ = 7.45–7.38 (m, 1H, ArH), 7.39–7.34 (m, 1H, ArH), 7.30–7.16 (m, 7H, ArH), 4.08 (s, 2H, SCH₂), 3.81 (s, 3H, OCH₃) ppm; 13C NMR (126 MHz, CDCl₃): δ = 166.6 (C=O), 137.4 (ArC), 136.9 (ArC), 132.1 (ArC), 131.0 (ArC), 129.4 (ArC), 129.0 (ArC), 128.7 (ArC), 128.6 (ArC), 127.4 (ArC), 127.2 (ArC), 127.1 (ArC), 126.1 (ArC), 52.3 (OCH₃), 39.3 (SCH₂) ppm (C=N₂ not observed); IR (neat): ν = 2951w, 2089s, 1693s, 1433s, 1344m, 1286s, 1153s, 1078m, 1028s, 914w, 754s cm⁻¹; HRMS (ES): Exact mass calculated for C₁₆H₁₄N₂O₂S[M⁺]: 298.0775, found 298.0776.

5.3.2 Synthesis of α-Aryl Esters

General Procedure 17:

Ethyl 2-diazopropanoate 107 (0.3 mmol) was dissolved in CDCl₃ (0.5 mL) and the triarylborane 106a–e (0.1 mmol) was added under nitrogen and the reaction was performed for 1 hour at room temperature. A strong gas development was observed for 15–30 minutes, meanwhile the colour changed from orange to pale yellow. The reaction was monitored by NMR spectroscopy then it was quenched with 1 M aqueous solution
of NaOH (1 mL). The aqueous phase was extracted with CHCl₃ (3 × 1 mL). The combined organic layers were filtrated over SiO₂ plug and dried in vacuo, affording the products 182a–e as a colourless oil.

Ethyl 2-phenylpropanoate 182a:

Performed according to General Procedure 17 on a 0.3 mmol scale of 107 and 0.1 mmol of 106a; 182a (16 mg, 0.092 mmol, 30% yield) was obtained as a volatile colourless oil.

1H NMR (500 MHz, CDCl₃): δ = 7.30–7.24 (m, 4H, ArH), 7.22–7.18 (m, 1H, ArH), 4.13–4.02 (m, 2H, OC₂H₂), 3.66 (q, J = 7.2 Hz, 1H, CH₃), 1.45 (d, J = 7.2 Hz, 3H, CHC₂H₃), 1.16 (t, J = 7.1 Hz, 3H, OCH₂C₂H₅) ppm; 13C NMR (126 MHz, CDCl₃): δ = 174.7 (C=O), 140.8 (ArC–CH), 128.7 (2 × ArC), 127.6 (2 × ArC), 127.2 (ArC), 60.8 (OCH₂), 45.7 (CH), 18.7 (CH₃), 14.3 (CH₃) ppm. The spectroscopic data are in agreement with the literature.

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Ethyl 2-(4-fluorophenyl)propanoate 182b:

Performed according to General Procedure 17 on a 0.3 mmol scale of 107 and 0.1 mmol of 106b; 182b (20 mg, 0.11 mmol, 37% yield) was obtained as a volatile colourless oil.

1H NMR (500 MHz, CDCl₃): δ = 7.30–7.24 (m, 2H, ArH), 7.01–6.96 (m, 2H, ArH), 4.18–4.04 (m, 2H, OC₂H₂), 3.96 (q, J = 7.2 Hz, 1H, CH₃), 1.48 (d, J = 7.2 Hz, 3H, CH₃), 1.21 (t, J = 7.1 Hz, 3H, OCH₂C₂H₅) ppm; 13C NMR (126 MHz, CDCl₃): δ = 174.6 (C=O), 162.1 (d, J = 245.2 Hz, ArC–F), 136.5 (d, J = 8.3 Hz, ArC–CH), 129.2 (d, J = 8.0 Hz, 2 × ArC), 115.5 (d, J = 21.4 Hz, 2 × ArC), 61.0 (OCH₂), 44.9 (CH), 18.8 (CH₃), 14.3 (CH₃) ppm; 19F NMR (471 MHz, CDCl₃): δ = −115.9 (s) ppm. The spectroscopic data are in agreement with the literature. 32

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Ethyl 2-(2,4-difluorophenyl)propanoate 182c:

Performed according to General Procedure 17 on a 0.35 mmol scale of 107 and 0.1 mmol of 106c; 182c (34 mg, 0.16 mmol, 45% yield) was obtained as a volatile colourless oil.

1H NMR (500 MHz, CDCl₃): δ = 7.30–7.23 (m, 1H, ArH), 6.89–6.73 (m, 2H, ArH), 4.20–4.09 (m, 2H, OCH₂), 3.96 (q, J = 7.2 Hz, 1H, CH₃), 1.48 (d, J = 7.2 Hz, 3H, CHCH₂), 1.21 (t, J = 7.1 Hz, 3H, OCH₂CH₃) ppm; 13C NMR (126 MHz, CDCl₃): δ = 173.8 (C=O), 162.3 (dd, J = 200.2, 12.0 Hz, ArC–F), 160.3 (dd, J = 201.0, 12.0 Hz,
ArC–F), 129.6 (dd, J = 9.6, 5.7 Hz, ArC), 124.0 (dd, J = 15.1, 3.9 Hz, ArC), 111.5 (dd, J = 21.1, 3.7 Hz, ArC), 105.9–101.8 (m, ArC), 61.2 (OCH₂), 38.1 (d, J = 2.3 Hz, CH), 17.7 (CH₃), 14.2 (CH₃) ppm; ¹⁹F NMR (376 MHz, CDCl₃): δ = −112.1 (d, J = 6.9 Hz, 1F), −114.0 (d, J = 6.9 Hz, 1F) ppm; IR (neat): ν = 2916w, 1734s, 1618w, 1506s, 1194m, 964s cm⁻¹. HRMS (EI): Exact mass calculated for C₁₁H₁₂F₂O₂ [M⁺]: 214.0805, found 214.0807.

Ethyl 2-(pentafluorophenyl)propanoate 182d:

Performed according to General Procedure 17 on a 0.35 mmol scale of 107 and 0.1 mmol of 106d; 182d (64 mg, 0.25 mmol, 80% yield) was obtained as a colourless oil.

¹H NMR (500 MHz, CDCl₃): δ = 4.30–4.10 (m, 2H, CH₂), 4.05 (q, J = 7.3 Hz, 1H, CH), 1.54 (d, J = 7.4 Hz, 3H, CH₃), 1.23 (t, J = 7.1 Hz, 3H, OCH₂CH₃) ppm; ¹³C NMR (126 MHz, CDCl₃): δ = 171.3 (C=O), 145.4 (d, J = 247.3 Hz, 2 × ArC–F), 140.5 (d, J = 247.5 Hz, ArC–F), 137.7 (d, J = 252.4 Hz, 2 × ArC–F), 115.1 (dt, J = 17.0, 4.2 Hz, ArC–CH), 61.8 (OCH₂), 35.0 (CH), 16.3 (CH₃), 14.2 (CH₃) ppm; ¹⁹F NMR (376 MHz, CDCl₃): δ = −143.1 (dd, J = 22.0, 7.0 Hz, 2F), −156.3 (t, J = 20.7 Hz, 1F), −162.4 (dt, J = 21.1, 6.8 Hz, 2F, m-F) ppm; IR (neat): ν = 2960w, 2926w, 2854w, 1739m, 1521m, 1504s, 1261s, 1012s, 970s, 800s cm⁻¹; HRMS (EI): Exact mass calculated for C₁₁H₁₀F₅O₂ [M⁺]: 268.0523, found 268.0520.

Ethyl 2-(3,4,5-trifluorophenyl)propanoate 182e:

Performed according to General Procedure 17 on a 0.35 mmol scale of 107 and 0.1 mmol of 106e; 182e (44 mg, 0.19 mmol, 89% yield) was obtained as a colourless oil.

¹H NMR (500 MHz, CDCl₃): δ = 7.03–6.78 (m, 2H, ArH), 4.21–4.06 (m, 2H, OCH₂), 3.63 (q, J = 7.2 Hz, 1H, CH), 1.46 (d, J = 7.2 Hz, 3H, CH₃), 1.22 (t, J = 7.1 Hz, 3H, OCH₂CH₃) ppm; ¹³C NMR (126 MHz, CDCl₃): δ = 173.4 (C=O), 150.9 (ddd, J = 249.8, 9.9, 4.1 Hz, 2 × ArC–F), 139.0 (dt, J = 250.0, 15.6 Hz, ArC–F), 136.8 (td, J = 7.4, 4.7 Hz, 2 × ArC), 112.0–111.7 (m, ArC–CH), 61.4 (OCH₂), 44.9 (CH), 18.5 (CH₃), 14.2 (CH₃) ppm; ¹⁹F NMR (376 MHz, CDCl₃): δ = −134.2 (d, J = 21.4 Hz, 2F), −162.5 (t, J = 20.5 Hz, 1F) ppm; IR (neat): ν = 2986w, 1732s, 1620m, 1530s, 1447m, 1348m, 1329m, 1236m, 1211m, 1179s, 1038s, 945w, 860m, 797m, 771m cm⁻¹; HRMS (ES): Exact mass calculated for C₁₁H₁₀F₃O₂ [M–H]⁻: 231.0633, found 231.0644.
**General Procedure 18:**

The α-aryl-α-diazoacetates 165 or 179a–d (0.1 mmol) was dissolved in CDCl₃ (0.5 mL) and the triarylborane 106d–f (0.1 mmol) was added under nitrogen and the reaction was performed for 12 hours at room temperature. A strong gas development was observed for 1 hour, meanwhile the colour changed from orange to pale yellow. The reaction was monitored by NMR spectroscopy then it was quenched with 1 M aqueous solution of NaOH (1 mL). The aqueous phase was extracted with CHCl₃ (3 × 1 mL). The combined organic layers were filtrated over SiO₂ plug and the crude where purified by column chromatography, affording the products 182f–o.

**Methyl 2-Phenyl-2-(3,4,5-trifluorophenyl)acetate 182f:**

Performed according to **General Procedure 18** on a 0.12 mmol scale of 165 and 0.12 mmol of 106e; 182f (28 mg, 0.096 mmol, 80% yield) was obtained as a colourless oil.

$^1$H NMR (500 MHz, CDCl₃): $\delta = 7.39–7.25$ (m, 5H, ArH), 6.98–6.91 (m, 2H, ArH), 4.93 (s, 1H, CH), 3.76 (s, 3H, OCH₃) ppm; $^{13}$C NMR (126 MHz, CDCl₃): $\delta = 172.0$ (C=O), 151.2 (ddd, $J = 250.0$, 9.6, 4.2 Hz, 2 × ArC–F), 139.2 (td, $J = 252.0$, 15.3 Hz, ArC–F), 137.3 (ArC), 135.1–134.8 (m, ArC), 129.2 (2 × ArC), 128.5 (2 × ArC), 128.1 (ArC), 113.2–112.9 (m, 2 × ArC), 56.0 (CH), 52.8 (OCH₃) ppm; $^{19}$F NMR (376 MHz, CDCl₃): $\delta = −133.9$ (d, $J = 20.5$ Hz, 2F), $−162.0$ (t, $J = 20.3$ Hz, 1F) ppm; IR (neat): $\nu = 2955$w, 2924w, 2851w, 1735s, 1618m, 1528s, 1449m, 1435m, 1155s, 1043s, 698s cm$^{-1}$; HRMS (ASAP): Exact mass calculated for C₁₅H₁₁F₃O₂ [M]+: 280.0711, found 280.0713.
Methyl 2-phenyl-2-(pentafluorophenyl)acetate 182g:

Performed according to General Procedure 18 on a 0.12 mmol scale of 165 and 0.12 mmol of 106d; 182g (27 mg, 0.087 mmol, 73% yield) was obtained as a colourless oil.

\[ \text{1H NMR (500 MHz, CDCl}_3\text{: } \delta = 7.41-7.26 \text{ (m, 5H, ArH), 5.29 (s, 1H, C-H), 3.80 (s, 3H, OC}_3\text{H}_3\text{ ppm; } \text{13C NMR (126 MHz, CDCl}_3\text{: } \delta = 170.01 (C=O), 135.6 (ArC), 129.0 (2 } \times \text{ ArC), 128.9-128.8 (m, 2 } \times \text{ ArC), 128.2 (ArC), 53.2 (OCH}_3\text{), 46.2 (CH ppm (ArC-F not observed); } \text{19F NMR (471 MHz CDCl}_3\text{: } \delta = -140.9 \text{ (dd, } J = 21.7, 6.7 \text{ Hz, 2F), } -155.0 \text{ (t, } J = 20.9 \text{ Hz, 1F), } -161.5 \text{ (dt, } J = 21.0, 6.7 \text{ Hz, 2F) ppm; IR (neat): } \nu = 2957w, 1748s, 1522s, 1500s, 1300m, 1265s, 1205s, 1121s, 908s, 729s, 698s \text{ cm}^{-1}; \text{ HRMS (EI): Exact mass calculated for C}_{15}\text{H}_{9}\text{F}_5\text{O}_2^{[M+]}: 316.0523, found 316.0522.} \]

Methyl 2-(2-bromophenyl)-2-(3,4,5-trifluorophenyl)acetate 182h:

Performed according to General Procedure 18 on a 0.11 mmol scale of 179a and 0.12 mmol of 106e; 182h (31 mg, 0.86 mmol, 79% yield) was obtained as a colourless oil.

\[ \text{1H NMR (500 MHz, CDCl}_3\text{: } \delta = 7.61 \text{ (dd, } J = 7.9, 1.2 \text{ Hz, 1H, ArH), 7.39-7.27} \text{ (m, 2H, ArH), 7.19 (dd, } J = 8.0, 6.7, 2.3 \text{ Hz, 1H, ArH), 6.92 (dd, } J = 8.4, 6.5 \text{ Hz, 2H, ArH}, 5.42 \text{ (s, 1H, C-H), 3.77 (s, 3H, OCH}_3\text{) ppm; } \text{13C NMR (126 MHz, CDCl}_3\text{: } \delta = 171.5 (C=O), 151.2 \text{ (dd, } J = 250.0, 9.6, 5.7 \text{ Hz, 2 } \times \text{ ArC-F), 139.3} \text{ (dt, } J = 252.2, 15.2 \text{ Hz, ArC-F), 136.8} \text{ (ArC), 133.6} \text{ (ArC), 133.6-133.4 (m, ArC), 129.7} \text{ (ArC), 129.6} \text{ (ArC), 128.1} \text{ (ArC), 125.1} \text{ (ArC), 113.6-113.3 (m, 2 } \times \text{ ArC), 55.2 (CH), 53.0 (OCH}_3\text{) ppm; } \text{19F NMR (376 MHz CDCl}_3\text{: } \delta = -133.7 (d, } J = 20.5 \text{ Hz, 2F), } -162.5 \text{ (t, } J = 20.6 \text{ Hz, 1F); IR (neat): } \nu = 2957w, 2924w, 2851w, 1740s, 1620w, 1530s, 1449m, 1435m, 1348s, 1163s, 1043s, 1020s, 800.5, 735s \text{ cm}^{-1}; \text{ HRMS (ASAP): Exact mass calculated for C}_{15}\text{H}_{11}\text{BrF}_3\text{O}_2^{[M+H]^+: 358.9895, found 358.9883.} \]

Methyl 2-(2-bromophenyl)-2-(pentafluorophenyl) acetate 182i:

Performed according to General Procedure 18 on a 0.11 mmol scale of 179a and 0.12 mmol of 106d; 182i (46 mg, 0.12 mmol, 99% yield) was obtained as a colourless oil.

\[ \text{1H NMR (500 MHz, CDCl}_3\text{: } \delta = 7.60 \text{ (dd, } J = 8.0, 1.2 \text{ Hz 1H, ArH), 7.66-7.53} \text{ (m, 1H, ArH), 7.24-7.15} \text{ (m, 2H, ArH), 5.74} \text{ (s, 1H, C-H), 3.80 (s, 3H, OCH}_3\text{) ppm; } \text{13C NMR (126 MHz, CDCl}_3\text{: } \delta = 168.6 (C=O), 145.5 \text{ (d, } J = \]
Methyl 2-(4-trifluoromethylphenyl)-2-(3,4,5-trifluorophenyl)acetate 182j:

Performed according to General Procedure 18 on a 0.12 mmol scale of 179b and 0.12 mmol of 106e; 182j (37 mg, 0.11 mmol, 89% yield) was obtained as a colourless oil. 

$^1$H NMR (500 MHz, CDCl$_3$): δ = 7.62 (d, $J$ = 8.2 Hz, 2H, ArH), 7.41 (d, $J$ = 8.2 Hz, 2H, ArH), 6.94 (dd, $J$ = 8.3, 6.5 Hz, 2H, ArH), 4.98 (s, 1H, CH), 3.78 (s, 3H, OCH$_3$) ppm; $^{13}$C NMR (126 MHz, CDCl$_3$): δ = 171.3 (C=O), 151.3 (ddd, $J$ = 251.0, 9.6, 4.2 Hz, 2 × ArC–F), 141.1 (ArC), 139.4 (td, $J$ = 252.6, 15.2 Hz, ArC–F), 134.5–133.5 (m, ArC), 130.4 (q, $J$ = 32.7 Hz, ArC–CF$_3$), 128.9 (2 × ArC), 126.1 (q, $J$ = 3.7 Hz, 2 × ArC), 124.0 (q, $J$ = 272.2 Hz, CF$_3$), 113.2–112.9 (m, ArC), 55.7 (CH), 53.0 (OCH$_3$) ppm; $^{19}$F NMR (376 MHz, CDCl$_3$): δ = −62.7 (s, 3F), −133.2 (d, $J$ = 20.5 Hz, 2F), −161.2 (t, $J$ = 20.5 Hz, 1F) ppm; IR (neat) ν = 2955w, 1743s, 1522s, 1472m, 1435m, 1206m, 1123s cm$^{-1}$; HRMS (EI): Exact mass calculated for C$_{15}$H$_{11}$BrF$_3$O$_2$ [M+H]$^+$: 393.9628, found 393.9635.

Methyl 2-(4-trifluoromethylphenyl)-2-(pentafluorophenyl)acetate 182k:

Performed according to General Procedure 18 on a 0.12 mmol scale of 179b and 0.12 mmol of 106d; 182k (33 mg, 0.087 mmol, 73% yield) was obtained as a colourless oil.

$^1$H NMR (500 MHz, CDCl$_3$): δ = 7.61 (d, $J$ = 8.4 Hz, 2H, ArH), 7.43 (d, $J$ = 8.2 Hz, 2H, ArH), 5.33 (s, 1H, CH), 3.81 (s, 3H, OCH$_3$) ppm; $^{13}$C NMR (126 MHz, CDCl$_3$): δ = 169.4 (C=O), 144.9 (d, $J$ = 248.1 Hz, 2 × ArC–F), 139.4 (ArC), 137.8 (d, $J$ = 268.9 Hz, 2 × ArC–F), 130.6 (q, $J$ = 31.2 Hz, ArC–CF$_3$), 129.4 (2 × ArC), 126.0 (q, $J$ = 4.1 Hz, 2 × ArC), 124.0 (q, $J$ = 272.2 Hz, CF$_3$), 123.6 (ArC), 53.4 (OCH$_3$), 45.7 (CH) ppm, (1 × ArC not observed); $^{19}$F NMR (376 MHz, CDCl$_3$): δ = −62.78 (s, 3F), −140.9 (dd, $J$ = 20.0, 6.0 Hz, 2F), −153.86 (t, $J$ = 20.9 Hz, 1F), −160.8 (dt, $J$ = 21.6, 6.6 Hz, 2F); IR (neat) ν = 2957w, 2926w, 2855w, 1749w, 1531m, 1325m, 1263s, 1167m cm$^{-1}$; HRMS (ASAP): Exact mass calculated for C$_{16}$H$_{10}$F$_6$O$_2$ [M]: 348.0585, found 348.0593.
Methyl 2-(4-methoxyphenyl)-2-(pentafluorophenyl)acetate 182m:

Performed according to General Procedure 18 on a 0.05 mmol scale of 179c and 0.05 mmol of 106d; 182m (14 mg, 0.042 mmol, 83% yield) was obtained as a colourless oil.

\[\delta = 7.25-7.17 (m, 2H, ArH), 6.90-6.84 (m, 2H, ArH), 5.23 (s, 1H, CH), 3.79 (s, 6H, 2 \times OCH_3) \] ppm; \[\delta = 170.4 (C=O), 159.4 (ArC–O), 144.9 (d, J = 243.6 Hz, 2 \times ArC–F), 140.7 (d, J = 254.0 Hz, ArC–F), 137.8 (d, J = 252.1 Hz, 2 \times ArC–F), 130.4 (ArC), 130.0 (2 \times ArC), 127.7 (ArC), 114.4 (2 \times ArC), 114.2 (ArC), 55.4 (OCH_3), 53.1 (OCH_3), 45.4 (CH) ppm; \[\delta = -141.3 (d, J = 18.4 Hz, 2F), -155.3 (t, J = 20.9 Hz, 1F), -161.5 (t, J = 19.6 Hz, 2F) \] ppm; IR (neat): \[\nu = 2916w, 2849w, 1748m, 1514s, 1502s, 1252m, 1207m, 1180m, 1119m, 997m, 974m, 908w \text{ cm}^{-1} \}; HRMS (ASAP): Exact mass calculated for C_{16}H_{14}F_5O_2 [M+H]^+: 347.0706, found 347.0699.
Methyl 2-(naphthalen-1-yl)-2-(3,4,5-trifluorophenyl)acetate **182n**:

Performed according to *General Procedure 18* on a 0.12 mmol scale of **179d** and 0.12 mmol of **106e**; **182n** (35 mg, 0.11 mmol, 88% yield) was obtained as a colourless oil.

\[
\begin{align*}
\text{1H NMR (500 MHz, CDCl} & \text{3)}: \quad \delta = 7.92–7.82 \text{ (m, 3H, ArH), 7.56–7.44 (m, 3H, ArH), 7.01–6.88 (m, 2H, ArH),} \\
& \quad 5.70 \text{ (s, 1H, CH\text{)}, 3.78 \text{ (s, 3H, OCH} \text{3}) \text{ ppm; } ^{13}\text{C NMR (126 MHz, CDCl} \text{3):} \\
& \quad \delta = 172.4 \text{ (C=O), 151.3 (d, J = 240.2 Hz, 2 x ArC–F), 134.5–134.4 (m, ArC), 134.3 (ArC),} \\
& \quad 132.9 \text{ (ArC), 131.3 (ArC), 129.3 (ArC), 129.1 (ArC), 127.1 (ArC), 126.2 (2 x ArC), 125.6} \\
& \quad \text{(ArC), 123.0 (ArC), 114.4–111.7 (m, 2 x ArC), 52.8 (OCH} \text{3), 52.5 (CH) ppm (1 x ArC–F not observed);} \\
& \quad ^{19}\text{F NMR (376 MHz, CDCl} \text{3):} \quad \delta = -133.8 \text{ (d, J = 20.5 Hz, 2F), -161.7 (t, J = 20.5 Hz, 1F) ppm; IR (neat):} \\
& \quad \nu = 3055\text{w, 2954w, 2854w, 1740m, 1620w, 1530s, 1449w, 1435w, 1263s, 1045s cm}^{-1}; \text{ HRMS (ASAP):} \text{ Exact mass calculated for C}_{19}\text{H}_{13}\text{F}_{3}\text{O}_{2} [\text{M}]^{+}: 330.0868, \text{ found 330.0868.}
\end{align*}
\]

Methyl 2-(naphthalen-1-yl)-2-(pentafluorophenyl)acetate **182o**:

Performed according to *General Procedure 18* on a 0.12 mmol scale of **179d** and 0.12 mmol of **106d**; **182o** (27 mg, 0.075 mmol, 63% yield) was obtained as a colourless oil.

\[
\begin{align*}
\text{1H NMR (500 MHz, CDCl} & \text{3):} \quad \delta = 8.00–7.77 \text{ (m, 3H, ArH), 7.70–7.30} \\
& \quad \text{(m, 4H, ArH), 6.08 (s, 1H, CH\text{), 3.82 (s, 3H, OCH} \text{3}) \text{ ppm; } ^{13}\text{C NMR (126 MHz, CDCl} \text{3):} \\
& \quad \delta = 170.6 \text{ (C=O), 145.5 (d, J = 236.5 Hz, 2 x ArC–F), 134.1} \\
& \quad \text{(ArC), 131.5 (ArC), 131.0 (ArC), 129.4 (ArC), 129.2 (ArC), 128.4 (ArC),} \\
& \quad 127.2 \text{(ArC), 126.8 (t, J = 3.0 Hz, ArC), 126.1 (ArC), 125.4 (ArC), 122.2 (ArC), 113.0} \\
& \quad \text{(ArC), 53.3 (OCH} \text{3), 43.0 (CH) ppm; } ^{19}\text{F NMR (376 MHz, CDCl} \text{3):} \quad \delta = -140.0 \text{ (dd, J = 18.5 Hz, 2F),} \\
& \quad -154.5 \text{ (t, J = 20.8 Hz, 1F), -161.5 (t, J = 19.8 Hz, 2F) ppm; IR (neat):} \\
& \quad \nu = 3053\text{w, 2954w, 2848w, 1742m, 1654w, 1522s, 1501s, 1468w, 1435w, 1263s, 1045s cm}^{-1}; \text{ HRMS (EI):} \text{ Exact mass calculated for C}_{19}\text{H}_{11}\text{F}_{5}\text{O}_{2} [\text{M}]^{+}: 366.0679, \text{ found 366.0686.}
\end{align*}
\]
Methyl 2-(3,4-dichlorophenyl)-2-(4-methoxyphenyl)acetate 182p:

Performed according to General Procedure 18 on a 0.08 mmol scale of 179c and 0.08 mmol of 106f; 182p (24 mg, 0.074 mmol, 92% yield) was obtained as a colourless oil.

\[
\begin{align*}
\text{MeO} & \quad \text{O} \\
\text{Cl} & \quad \text{O} \\
\text{Cl} & \quad \\
\end{align*}
\]

\[^{1}H\text{ NMR (500 MHz CDCl}_3\text{)}: \delta = 7.38 \ (t, \ J = 5.6 \text{ Hz, 2H, ArH}),
7.23–7.18 \ (m, 2H, ArH), \ 7.14 \ (dd, \ J = 8.3, 2.1 \text{ Hz, 1H, ArH}),\]
6.89–6.85 \ (m, 2H, ArH), 4.91 \ (s, \ 1H, \ CH), 3.80 \ (s, \ 3H, \ OCH\text{3}),\]
3.75 \ (s, \ 3H, \ OCH\text{3}) ppm;

\[^{13}C\text{ NMR (126 MHz, CDCl}_3\text{)}: \delta = 172.5 \ (C=O), \ 159.2 \ (ArC–O), \ 139.3 \ (ArC), \ 132.7 \ (ArC), \ 131.6 \ (ArC), \ 130.6 \ (ArC), \ 130.6 \ (ArC), \ 129.7 \ (ArC), \ 129.6 \ (2 \times \ ArC), \ 128.0 \ (ArC), \ 114.4 \ (2 \times \ ArC), \ 55.4, \ 55.3, \ 52.7 \text{ ppm}; Spectroscopic data are in accordance with the literature.}^{33}\]

\[(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl2-(3,4,5-trifluorophenyl)propanoate 182q:

Performed according to General Procedure 18 on a 0.11 mmol scale of 179h and 0.11 mmol of 106e; 182q (36 mg, 0.11 mmol, 96% yield, 1.1:1 d.r.) was obtained as a colourless oil.

\[
\begin{align*}
\text{F} & \quad \text{O} \\
\text{F} & \quad \text{F} \\
\text{F} & \quad \text{F} \\
\text{Cl} & \quad \text{O} \\
\end{align*}
\]

\[^{1}H\text{ NMR (500 MHz CDCl}_3\text{)}: \delta = 7.00–6.81 \ (m, 4H, ArH), \ 4.77–4.52 \ (m, 2H, OCH\text{H}), \ 3.75–3.45 \ (m, 2H, CH\text{H}), \ 2.02–1.93 \ (m, 1H), \ 1.88–1.80 \ (m, 1H), \ 1.79–1.59 \ (m, 6H), \ 1.51–1.40 \ (m, 8H), \ 1.41–1.26 \ (m, 2H), \ 1.13–0.80 \ (m, 15H), \ 0.77 \ (d, \ J = 7.0 \text{ Hz, 3H, CH}\text{3}), \ 0.73 \ (d, \ J = 7.0 \text{ Hz, 3H, CH}\text{3}), \ 0.59 \ (d, \ J = 7.0 \text{ Hz, 3H, CH}\text{3}) \text{ ppm}; ^{13}C\text{ NMR (126 MHz, CDCl}_3\text{)}: \delta = 173.0 \ (C=O), \ 172.9 \ (C=O), \ 151.0 \ (d, \ J = 255.3 \text{ Hz, 2} \times \text{ArC–F}), \ 112.5–110.4 \ (m, 2 \times \text{ArC}), \ 75.3 \ (OCH\text{3}), \ 75.2 \ (OCH\text{3}), \ 47.2, \ 47.1, \ 45.3, \ 45.2, \ 40.9, \ 40.6, \ 34.3, \ 34.3, \ 31.5, \ 31.5, \ 26.5, \ 26.2, \ 23.5, \ 23.4, \ 22.1, \ 22.1, \ 20.8, \ 20.7, \ 18.4, \ 18.3, \ 16.4, \ 16.1 \ \text{ppm (1} \times \text{ArC–F not observed); ^{19}F\text{ NMR (376 MHz, CDCl}_3\text{)}: \delta = -134.4 \ (d, \ J = 20.4 \text{ Hz, 4F}), \ -162.6 \ (t, \ J = 20.4 \text{ Hz, 2F}) \text{ ppm; IR (neat): \nu = 2957w, 2872w, 1728s, 1530s, 1449s, 1348m, 1175s, 1038s, 856m, 797m cm}^{-1}; \text{HRMS (ASAP): Exact mass calculated for C}_{19}H_{24}F_{3}O_{2} \ [\text{M–H}]^{+}: 341.1728, found 341.1728.} \]
(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl 2-(pentafluorophenyl)propanoate 182r:

Performed according to General Procedure 18 on a 0.06 mmol scale of 179h and 0.06 mmol of 106d; 182r (22 mg, 0.058 mmol, 94% yield, 1.2:1 d.r.) was obtained as a colourless oil.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta = 4.74$ (td, $J = 10.9, 4.4$ Hz, 1.16H, OCH$_2$), 4.67 (td, $J = 10.9, 4.4$ Hz, 1H, OCH$_2$), 4.16–3.82 (m, 2.12H), 2.09–2.00 (m, 1H), 1.98–1.92 (m, 1.2H), 1.84–1.58 (m, 6.3H), 1.54–1.44 (m, 10.4H), 1.36–1.21 (m, 2.4H), 1.12–0.73 (m, 23H), 0.70 (d, $J = 7.0$ Hz, 3H, CH$_3$) ppm; $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta =$ 170.9 (C=O), 76.1 (OCH$_2$), 75.9 (OCH$_2$), 47.0, 47.0, 40.7, 40.4, 35.2, 34.3, 31.5, 31.5, 26.5, 26.2, 23.7, 23.3, 22.1, 20.8, 16.5, 16.3, 16.1, 16.0 ppm (ArC not observed); $^{19}$F NMR (376 MHz, CDCl$_3$): $\delta =$ −142.5 (d, $J =$ 19.0 Hz, 2F), −142.8 (d, $J =$ 18.6 Hz, 2.3F), −154.6–157.3 (m, 2.16F), −160.5–166.5 (m, 4.6F) ppm; IR (neat): $\nu = 2957$w, 2872w, 1740m, 1521m, 1503s, 1456m, 1207m, 968s, 740m cm$^{-1}$; HRMS (ASAP): Exact mass calculated for C$_{19}$H$_{23}$F$_5$O$_2$ [M−H]$^+$: 377.1540, found 377.1536.

(1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl 2-(2-bromophenyl)-2-(3,4,5-trifluoro-phenyl)acetate 182s:

Performed according to General Procedure 18 on a 0.07 mmol scale of 179i and 0.07 mmol of 106e; 182s (32 mg, 0.067 mmol, 96% yield, 1.3:1 d.r.) was obtained as a colourless oil.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta =$ 7.60 (d, $J = 8.0$ Hz, 2.3H, ArH), 7.35–7.21 (m, 4.6H, ArH), 7.21–7.15 (m, 2.3H, ArH), 6.97–6.86 (m, 4.6H, ArH), 5.38 (s, 1.3H, CH), 5.34 (s, 1H, CH$_2$), 4.80–4.66 (m, 2.3H, OCH$_2$), 2.06–1.98 (m, 2.3H), 1.71–1.57 (m, 6.9H), 1.53–1.43 (m, 2.3H), 1.39–1.30 (m, 2.3H), 1.10–0.79 (m, 18H), 0.78 (d, $J =$ 7.0 Hz, 3H, CH$_3$), 0.70 (d, $J =$ 7.0 Hz, 3.9H, CH$_3$), 0.65 (d, $J =$ 7.0 Hz, 3H, CH$_3$) ppm; $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta =$ 170.6 (C=O), 170.5 (C=O), 151.3 (d, $J = 249.8$ Hz, 2 $\times$ ArC–F), 139.2 (d, $J = 252.3$ Hz, ArC–F), 137.1 (ArC), 137.0 (ArC), 134.0–133.7 (m, ArC), 133.5 (ArC), 133.4 (ArC), 129.8 (ArC), 129.7 (ArC), 129.6 (ArC), 129.5 (ArC), 127.9 (ArC), 127.8 (ArC), 125.2 (ArC), 125.1 (ArC), 113.6–113.0 (m, 2 $\times$ ArC), 76.3 (OCH), 76.2 (OCH$_2$), 55.8, 55.7, 47.0, 46.9, 40.6, 40.5, 34.2, 31.6, 31.5, 26.2, 25.9, 23.4, 23.3, 22.1, 20.8, 20.7, 16.2, 16.1 ppm; $^{19}$F NMR (376 MHz, CDCl$_3$): $\delta = −133.8$ (d, $J =$ 20.6 Hz, 2.6F), −134.0 (d, $J =$ 20.7 Hz, 2F), −161.6 (t, $J =$ 20.8 Hz, 1.3F), −161.8 (t, $J =$ 20.5 Hz, 1F) ppm; IR (neat): $\nu = 2955$w, 2926w, 2870w, 1732m, 1527s, 1447m, 1348w, 1310w, 1279w, 1171s, 1045s, 739s cm$^{-1}$;
HRMS (ES): Exact mass calculated for C_{24}H_{26}BrF_{3}O_{2} [M–H]−: 481.0990, found 481.1009.

\((1R,2S,5R)-2\text{-isopropyl-5-methylcyclohexyl-2-(bromophenyl)-2-(pentafluorophenyl)}\text{ acetate 182t:}\)

Performed according to General Procedure 18 on a 0.10 mmol scale of 179i and 0.10 mmol of 106d; 182t (10 mg, 0.019 mmol, 19% yield, 1.15:1 d.r.) was obtained as a colourless oil.

\(^1\)H NMR (500 MHz, CDCl\(_3\)): δ = 7.63–7.55 (m, 2.25H, ArH), 7.33–7.15 (m, 4.7H, ArH), 5.78–5.51 (m, 2.25H, C\(_\text{H}\)), 4.95–4.59 (m, 2.25H, OCH\(_2\)), 2.22–2.02 (m, 2.25H), 1.84–1.61 (m, 6.7H), 1.51–1.43 (m, 2.25H), 1.33–1.25 (m, 2.25H), 1.10–0.70 (m, 27H) ppm; \(^{13}\)C NMR (126 MHz, CDCl\(_3\)): δ = 168.6 (C=O), 168.5 (C=O), 135.0 (ArC), 134.9 (ArC), 133.2 (ArC), 130.0 (dt, J = 5.1, 2.8 Hz, ArC), 129.7 (ArC), 129.6 (ArC), 127.7 (ArC), 127.6 (ArC), 125.3 (ArC), 125.1 (ArC), 77.0 (CH) 46.9, 46.8, 40.3, 40.3, 34.2, 34.2, 31.5, 31.5, 29.9, 26.2, 26.1, 23.4, 23.2, 22.1, 20.8, 20.7, 16.2, 16.1 (ArC–F not observed) ppm; \(^{19}\)F NMR (376 MHz, CDCl\(_3\)): δ = −139.1 (d, J = 18.4 Hz, 2F), −139.3 (d, J = 18.1 Hz, 2F), −154.28 (d, J = 21.1 Hz, 2.25F), −161.40–−162.02 (m, 4.5F) ppm; IR (neat): 2957w, 2926w, 2872w, 1734m, 1522m, 1503s, 1215m, 999m, 953m, cm\(^{-1}\); HRMS (ES): Exact mass calculated for C_{24}H_{26}BrF_{3}O_{2} [M–H]−: 517.0802, found 517.0798.

\((1R,2S,5R)-2\text{-isopropyl-5-methylcyclohexyl-2-(4-(trifluoromethyl)phenyl)-2-(3,4,5-trifluorophenyl)}\text{ acetate 182u:}\)

Performed according to General Procedure 18 on a 0.13 mmol scale of 179j and 0.13 mmol of 106e; 182u (56 mg, 0.12 mmol, 91% yield, 1.2:1 d.r.) was obtained as a colourless oil.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): δ = 7.73–7.56 (m, 4.4H, ArH), 7.47–7.31 (m, 4.4H, ArH), 6.00–6.88 (m, 4.4H, ArH), 4.95 (s, 1.2H, CH\(_3\)), 4.94 (s, 1H, CH\(_3\)), 4.81–4.68 (m, 2.2H, OCH\(_3\)), 2.06–1.92 (m, 2.2H), 1.74–1.30 (m, 12.5H), 1.12–0.74 (m, 20H), 0.68 (d, J = 7.0 Hz, 3.4H, CH\(_3\)), 0.62 (d, J = 6.9 Hz, 3H, CH\(_3\)) ppm; \(^{13}\)C NMR (126 MHz, CDCl\(_3\)): δ = 170.4 (C=O), 151.3 (ArC), 139.3 (dt, J = 252.6, 15.3 Hz, ArC–F), 139.3 (dt, J = 252.6, 15.3 Hz, ArC–F), 134.4–134.1 (m, ArC), 130.4 (q, J = 32.8 Hz, ArC–CF\(_3\)), 130.3 (q, J = 32.8 Hz, ArC–CF\(_3\)), 130.0 (2 × ArC), 129.9 (2 × ArC), 129.9–129.6 (m, 2 × ArC), 124.0 (q, J = 272.2 Hz, CF\(_3\)), 124.1 (q, J = 272.2 Hz, CF\(_3\)), 118.6–118.2 (m, ArC), 113.5–112.7 (m, 2 × ArC), 76.4 (OCH\(_3\)), 56.2, 47.1, 47.07, 40.8, 40.7, 34.2, 31.6, 31.6, 26.3,
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26.2, 23.4, 23.4, 22.1, 20.7, 20.7, 16.2, 16.1 ppm; $^{19}$F NMR (376 MHz, CDCl$_3$): $\delta = -62.6$–$-62.7$ (m, 6.6F), $-133.3$ (d, $J = 20.6$ Hz, 2.4F), $-133.5$ (d, $J = 20.5$ Hz, 2F), $-161.3$ (t, $J = 20.5$ Hz, 1.2F), 161.4 (t, $J = 20.4$ Hz, 1F) ppm; IR (neat): $\nu = 2959$w, 2930w, 2872w, 1734m, 1620m, 1530s, 1449m, 1325s, 1166s, 1128s, 1068s, 1047s, 1018m, 907s, 729s cm$^{-1}$; HRMS (ES): Exact mass calculated for C$_{25}$H$_{25}$F$_6$O$_2$ [M–H]$^-$: 471.1759, found 471.1772.

(1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl 2-(pentafluorophenyl)-2-(4-(trifluoromethyl)phenyl)acetate 182v:

Performed according to General Procedure 18 on a 0.13 mmol scale of 179j and 0.13 mmol of 106d; 182v (54 mg, 0.11 mmol, 82% yield, 1.1:1 d.r.) was obtained as a colourless oil.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta = 7.61$ (dd, $J = 8.4, 2.4$ Hz, 4H, Ar$H$), 7.64–7.58 (m, 4H, Ar$H$), 5.30 (s, 1H, C$H$), 5.29 (s, 1H, C$I$), 4.87–4.73 (m, 6H, Ar$H$), 1.74–1.54 (m, 6H), 1.52–1.43 (m, 2H), 1.33–1.25 (m, 2H), 1.11–0.68 (m, 24H) ppm; $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta = 168.4$ (C=O), 145.0 (d, $J = 248.5$ Hz, 2 × Ar$C$–F), 140.97 (d, $J = 253.9$ Hz, Ar$C$–F), 139.7 (Ar$C$), 139.6 (Ar$C$), 137.9 (d, $J = 252.4$ Hz, 2 × Ar$C$–F), 131.1–129.7 (m, Ar$C$), 129.4 (2 × Ar$C$), 129.3 (2 × Ar$C$), 128.4, 125.9 (q, $J = 3.8$ Hz, 2 × Ar$C$), 124.0 (q, $J = 272.2$ Hz, CF$_3$), 113.6–112.9 (m, Ar$C$), 77.2 (OCH), 77.1 (OCH), 46.9, 46.9, 46.2, 46.2, 40.5, 40.4, 34.2, 34.2, 31.5, 26.4, 26.3, 23.5, 22.1, 20.8, 20.7, 16.3, 16.0 ppm; $^{19}$F NMR (376 MHz, CDCl$_3$): $\delta = -62.7$–$-62.8$ (m, 6F), $-140.2$ (dd, $J = 18.2$ Hz, 2F), $-140.5$ (dd, $J = 18.3$ Hz, 2F), $-154.1$ (t, $J = 20.9$ Hz, 2F), $-161.0$–$-161.3$ (m, 4F) ppm; IR (neat): $\nu = 2958$w, 2872w, 1734m, 1530s, 1449m, 1325s, 1166s, 1128s, 1068s, 1047s, 1018m, 907s, 729s cm$^{-1}$; HRMS (ES): Exact mass calculated for C$_{25}$H$_{23}$F$_6$O$_2$ [M–H]$^-$: 507.1570, found 507.1574.

Methyl 2-(2-(benzylthio)phenyl)-2-(3,4,5-trifluorophenyl)acetate 182w:

Performed according to General Procedure 18 on a 0.083 mmol scale of 224 and 0.083 mmol of 106e; 182w (12 mg, 0.032 mmol, 38% yield) was obtained as a colourless oil after 72 h.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta = 7.48–7.41$ (m, 1H, Ar$H$), 7.29–7.19 (m, 6H, Ar$H$), 7.18–7.11 (m, 2H, Ar$H$), 6.76 (dd, $J = 8.4, 6.6$ Hz, 2H, Ar$H$), 5.56 (s, 1H, C$I$), 4.02 (d, $J = 12.8$ Hz, 1H, $1 \times$ S$CH_2$), 3.99 (d, $J = 12.9$ Hz, 1H, $1 \times$ S$CH_2$), 3.72 (s, 3H, OCH$_3$) ppm; $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta = 172.0$ (C=O), 151.0
(ddd, J = 250, 10.0, 4.1 Hz, 2 × ArC–F), 138.9 (dt, J = 252, 15.3 Hz, ArC–F), 138.8 (ArC), 134.3 (ArC), 132.9 (ArC), 128.8 (ArC), 128.5 (ArC), 128.5 (ArC), 128.4 (ArC), 127.7 (ArC), 127.4 (ArC), 113.7–112.2 (m, 2 × ArC), 52.7 (OCH3), 40.5 (SCH2) ppm; 19F NMR with 1H coupling (471 MHz, CDCl3, 298 K) δ = −134.1 (dd, J = 20.7, 8.6 Hz, 2F), −162.1 (tt, J = 20.6, 6.4 Hz, 1F) ppm; IR (neat): ν = 3030w, 2953w, 1736s, 1618m, 1528s, 1448m, 1435m, 1348m, 1163m, 1045s, 698s cm−1; HRMS (ES): Exact mass calculated for C21H23F3O2S [M−H]−: 401.0823, found 401.0826.

Methyl 2-(2-(benzyloxy)phenyl)-2-phenylacetate 182x:

Performed according to General Procedure 18 on a 0.1 mmol scale of 184a and 0.1 mmol of 106a; 182x (16 mg, 0.048 mmol, 48% yield) was obtained as a colourless oil after 7 days.

1H NMR (500 MHz, CDCl3): δ = 7.28–7.17 (m, 9 H, ArH), 7.17–7.08 (m, 2H, ArH), 7.36–7.08 (m, 1H, ArH), 6.90 (d, J = 7.0, 1H, ArH, ArH), 6.87–6.75 (m, 2H, ArH), 5.24 (s, 1H, C=CH2), 4.98 (s, 2H, OCH2), 3.50 (s, 3H, OCH3) ppm; 13C NMR (126 MHz, CDCl3): δ = 173.5 (C=O), 156.1 (ArC–O), 137.6 (ArC), 137.0 (ArC), 129.3 (ArC), 128.6 (ArC), 128.6 (ArC), 128.2 (ArC), 128.0 (ArC), 127.4 (ArC), 127.4 (ArC), 120.9 (ArC), 111.7 (ArC), 70.2 (OCH2), 52.2, 51.3 ppm; HRMS (ES): Exact mass calculated for C22H21O3 [M+H]+: 333.1487, found 333.1487.

Methyl 2-(2-(hexyloxy)phenyl)-2-(3,4,5-trifluorophenyl)acetate 182y:

Performed according to General Procedure 18 on a 0.1 mmol scale of 184k and 0.1 mmol of 106e; 182y (22 mg, 0.059 mmol, 59% yield) was obtained as a colourless oil after 24 h.

1H NMR (500 MHz, CDCl3): δ = 7.30–7.24 (m, 1H, ArH), 7.10 (d, J = 7.5 Hz, 1H, ArH), 6.97–6.90 (m, 3H, ArH), 6.87 (d, J = 8.2 Hz, 1H, ArH), 5.22 (s, 1H, CH2), 4.01–3.89 (m, 2H, OCH2), 3.73 (s, 3H, OCH3), 1.78–1.68 (m, 2H), 1.39 (dd, J = 14.2, 6.5 Hz, 2H), 1.37–1.29 (m, 4H), 0.90 (t, J = 6.3 Hz, 3H, CH3) ppm; 13C NMR (126 MHz, CDCl3): δ = 172.5 (C=O), 156.2 (ArC–O), 151.1 (ddd, J = 249.0, 10.0, 4.1 Hz, 2 × ArC–F), 139.1 (d, J = 251.0 Hz, ArC–F), 134.6–134.4 (m, ArC), 129.2 (ArC), 128.7 (ArC), 126.3 (ArC), 120.7 (ArC), 113.6–113.2 (m, ArC), 111.6 (m, ArC), 68.2 (OCH2), 52.6, 50.3, 31.7, 29.3, 25.9, 22.7, 14.1 ppm; 19F NMR (376 MHz, CDCl3): δ = −134.6 (d, J = 20.7 Hz, 2F), −162.5 (t, J = 20.5 Hz, 1F) ppm; IR (neat): ν = 2955m, 2932m, 2860m, 1742s, 1618m, 1599m, 1528s, 1493s, 1449s, 1348m, 1244m, 1043s,
750s, 675s cm\(^{-1}\); HRMS (EI): Exact mass calculated for C\(_{21}\)H\(_{23}\)F\(_3\)O\(_3\) [M]\(^+\): 380.1599, found 380.1591.

Methyl (E)-2-(2-(benzylideneamino)phenyl)-2-(3,4,5-trifluorophenyl)acetate 216:

Performed according to General Procedure 18 on a 0.1 mmol scale of 153a and 0.1 mmol of 106e; 216 (20 mg, 0.053 mmol, 53% yield) was obtained as a colourless oil after 12 hours at 50 °C.

\(^1\text{H} \text{NMR (500 MHz, CDCl}_3\): } \delta = 8.39 \text{ (s, 1H, N=CH), 7.89 (d, } J = 7.3 \text{ Hz, 1H, ArH), 7.55–7.38 (m, 2H, ArH), 7.39–7.33 (m, 3H, ArH), 7.32–7.20 (m, 1H, ArH), 7.09 (d, } J = 7.8 \text{ Hz, 2H, ArH), 6.99 (t, } J = 7.4 \text{ Hz, 1H, ArH), 5.52 (s, 1H, CH), 3.67 (s, 3H, OCH}_3\) ppm; \(^{13}\text{C} \text{NMR (126 MHz, CDCl}_3\): } \delta = 172.5 \text{ (C=O), 160.5 (ArC–N), 151.1 (ddd, } J = 250, 10.0, 4.0 \text{ Hz, 2 × ArC–F), 140.2 (ArC), 139.2 (dt, } J = 251.2, 15.3 \text{ Hz, ArC–F), 136.1, 135.2–134.3 (m, ArC), 132.6 (ArC), 131.9 (ArC), 129.1 (ArC), 129.1 (ArC), 129.0 (ArC), 128.5 (ArC), 126.7 (ArC), 118.0 (ArC), 114.1–112.9 (m, 2 × ArC), 52.6, 51.6 ppm; \(^{19}\text{F} \text{NMR with } ^1\text{H} \text{ coupling (471 MHz, CDCl}_3\): } \delta = -133.0–-138.4 \text{ (m, 2F), -162.5 (ddd, } J = 20.6, 13.5, 6.4 \text{ Hz, 1F) ppm; IR (neat): } \nu = 3017\text{m, 1738s, 1612m, 1529s, 1472s, 1447s, 1364m, 1229s, 1043s cm}^{-1}; \text{ HRMS (ES): Exact mass calculated for C}_{22}\text{H}_{17}\text{NO}_{2}\text{F}_{3} [M+H]^+: 384.1211, found 384.1211.

5.3.3 Synthesis of Cyclised Products

5.3.3.1 Synthesis on Indole 214 and Indoline 215

The diazo compound 213 (0.1 mmol) was dissolved in dry CDCl\(_3\) and borane 106e (0.1 mmol) was added. The reaction was performed under nitrogen and gas evolution was observed. After 30 minutes the reaction was quenched with aqueous solution of NaOH (0.1 M) and the crude was filtered over SiO\(_2\) plug then purified by preparative TLC affording indole 214 and indoline 215 in 23% and 42% yields, respectively.
Methyl 2-phenyl-1H-indole-3-carboxylate 214:

The minor product 214 (6 mg, 0.023 mmol, 23% yield) was afforded as a colourless solid.

\[
\begin{align*}
\text{C} & \quad \text{O} \\
\text{CONMe}_2 & \quad \text{Ph}
\end{align*}
\]

\(^1H\) NMR (500 MHz, CDCl\(_3\)): \(\delta = 8.49\) (s, 1H, N\(H\)), 8.22 (d, \(J = 6.6\) Hz, 1H, Ar\(H\)), 7.67 (d, \(J = 6.5\) Hz, 2H, Ar\(H\)), 7.47 (d, \(J = 5.6\) Hz, 3H, Ar\(H\)), 7.40 (d, \(J = 6.5\) Hz, 1H, Ar\(H\)), 7.29 (d, \(J = 5.4\) Hz, 2H, Ar\(H\)), 3.85 (s, 3H, OC\(H_3\)) ppm;

\(^{13}C\) NMR (126 MHz, CDCl\(_3\)): \(\delta = 165.9\) (C=O), 144.7 (Ar\(C–N\)), 135.2 (Ar\(C\)), 132.1 (Ar\(C\)), 129.4 (Ar\(C\)), 128.4 (Ar\(C\)), 127.7 (Ar\(C\)), 123.4 (Ar\(C\)), 122.4 (Ar\(C\)), 122.3 (Ar\(C\)), 111.1 (Ar\(C\)), 104.7 (Ar\(C\)), 51.0 (O\(C\)H\(_3\)) ppm. The spectroscopic data are in agreement with the literature.\(^{25}\)

Methyl 2-phenyl-3-(3,4,5-trifluorophenyl)indoline-3-carboxylate 215:

The major product 215 (16 mg, 0.042 mmol, 42% yield) was afforded as a colourless oil.

\[
\begin{align*}
\text{MeO}_2\text{C} & \quad \text{Ph} \\
\text{F} & \quad \text{F}
\end{align*}
\]

\(^1H\) NMR (500 MHz, CDCl\(_3\)): \(\delta = 7.28\) (d, \(J = 7.5\) Hz, 1H, Ar\(H\)), 7.22–7.12 (m, 6H, Ar\(H\)), 7.12–7.06 (m, 2H, Ar\(H\)), 6.81 (t, \(J = 7.3\) Hz, 1H, Ar\(H\)), 6.69 (d, \(J = 7.8\) Hz, 1H, Ar\(H\)), 4.99 (s, 1H, CH\(_3\)), 4.11 (s, 1H, N\(H\)), 3.18 (s, 3H, OC\(H_3\)) ppm;

\(^{13}C\) NMR (126 MHz, CDCl\(_3\)): \(\delta = 170.6\) (C=O), 151.0 (ddd, \(J = 249.2, 9.8, 4.1\) Hz, \(2 \times \text{ArC–F}\)), 150.4 (Ar\(C–N\)), 140.4 (Ar\(C\)), 139.7–139.5 (m, (Ar\(C\)), 139.1 (dt, \(J = 230.6, 15.5\) Hz, Ar–F), 129.7 (Ar\(C\)), 128.7 (Ar\(C\)), 125.8 (Ar\(C\)), 127.8 (Ar\(C\)), 127.7 (Ar\(C\)), 119.9 (Ar\(C\)), 111.7–111.3 (m, \(2 \times \text{ArC}\)), 74.4 (N–C\(H\)), 66.6 (C–CO\(_2\)Me), 52.1 (O\(C\)H\(_3\)) ppm; \(^{19}F\) NMR (376 MHz, CDCl\(_3\)): \(\delta = -133.8\) (d, \(J = 20.8\) Hz, 2F), -161.8 (t, \(J = 20.8\) Hz, 1F) ppm; IR (neat): \(\nu = 3364\)w, 3032w, 2951w, 1732s, 1525s, 1431s, 1259s, 1238s, 1045s, 1028s, 736s cm\(^{-1}\); HRMS (ES): Exact mass calculated for C\(_{22}\)H\(_{17}\)NO\(_2\)F\(_3\) [M+H]\(^+\): 384.1211, found 384.1209.

5.3.3.2 Synthesis of Lactones 185 and Thiolactone 225

**General Procedure 19:** The diazo compound \(184a–j\) or \(224\) (0.1 mmol) was dissolved in dry CDCl\(_3\) and borane 106 (0.1 mmol) was added. The reaction was performed under
nitrogen and gas evolution was observed. The reaction was then quenched with aqueous solution of NaOH (0.1 M), the crude was filtered over SiO₂ plug and purified by column chromatography to afford the final lactone 185 or thiolactone 225 as solids or oils.

3-Benzyl-3-(3,4,5-trifluorophenyl)benzofuran-2(3H)-one 185a:

Performed according to General Procedure 19 on a 0.1 mmol scale of 184a and 0.1 mmol of 106e; 185a (26 mg, 0.079 mmol, 79% yield) was obtained after 24 hours at room temperature as a colourless solid, m.p.: 110–112 °C.

¹H NMR (400 MHz, CDCl₃): δ = 7.34–7.27 (m, 1H, ArH), 7.26–7.03 (m, 7H, ArH), 6.96 (d, J = 7.9 Hz, 1H, ArH), 6.84–6.79 (m, 2H, ArH), 3.59 (d, J = 13.2 Hz, 1H, 1 × CH₂), 3.42 (d, J = 13.2 Hz, 1H, 1 × CH₂) ppm; ¹³C NMR (101 MHz, CDCl₃): δ = 176.5 (C=O), 153.1 (ArC–O), 151.3 (ddd, J = 251.0, 9.9, 4.1 Hz, 2 × ArC–F), 139.58 (dt, J = 254, 15.3 Hz, ArC-F), 134.8–134.6 (m, ArC), 133.9 (ArC), 130.1 (ArC), 130.0 (ArC), 128.3 (ArC), 127.6 (ArC), 127.5 (ArC), 126.0 (ArC), 124.5 (ArC), 112.4–111.7 (m, 2 × ArC), 111.3 (ArC), 56.6 (C), 45.5 (CH₂) ppm; ¹⁹F NMR (376 MHz, CDCl₃): δ = −132.5 (d, J = 20.6 Hz), −160.2 (t, J = 20.6 Hz) ppm; IR (neat): ν = 1790s, 1620m, 1531s, 1462s, 1435s, 1354m, 1292w, 1225m, 1120s, 1051s, 887m, 752s, 698s cm⁻¹; HRMS (ASAP): Exact mass calculated for C₂₁H₁₄F₃O₂ [M+H]⁺: 355.0946, found 355.0948; NCH₂¹D: Varian Polaris Silica (254 × 4.6 mm, 5μm), n-hexane/propan-2-ol: 99.9:0.1, 1.0 mL·min⁻¹, 20 °C, 210 and 254 nm, retention time 200a = 4.1 min; ¹D: YMC Chiral Amylose-C (254 × 4.6 mm, 5μm), n-hexane/propan-2-ol: 90:10, 1.0 mL·min⁻¹, 20 °C, 254 nm, retention time minor isomer = 4.8 min, retention time major isomer = 5.3 min.

Figure 5.15: ¹D HPLC chromatograms for the enantiomers of 185a.
Figure 5.16: ²D HPLC chromatograms for the enantiomers of 185a. From the top: racemic mixture and 44% ee mixture.

3-Benzyl-3-(pentafluorophenyl)benzofuran-2(3H)-one 185b:

Performed according to General Procedure 19 on a 0.1 mmol scale of 184a and 0.1 mmol of 106d; 185b (30 mg, 0.077 mmol, 77% yield) was obtained after 7 days at room temperature as a colourless solid, m.p.: 148–150 °C.

¹H NMR (400 MHz, CDCl₃): δ = 7.33–7.25 (m, 2H, ArH), 7.23–7.13 (m, 2H, ArH), 7.07 (t, J = 7.5 Hz, 2H, ArH), 6.84 (d, J = 7.9 Hz, 1H, ArH), 6.73 (d, J = 7.4 Hz, 2H, ArH), 3.97 (dt, J = 12.8, 2.4 Hz, 1H, 1 × CH₂), 3.73 (d, J = 12.5 Hz, 1H, 1 × CH₂) ppm; ¹³C NMR (126 MHz, CDCl₃): δ = 175.2 (C=O), 153.1 (ArC–O), 146.0 (d, J = 250.0 Hz, 2 × ArC–F), 141.1 (d, J = 257.0 Hz, ArC–F), 138.2 (d, J = 254.1 Hz, 2 × ArC–F), 132.7 (ArC), 130.5 (ArC), 130.2 (ArC), 128.8 (ArC), 128.2 (ArC), 127.8 (ArC), 124.9 (ArC), 123.8 (ArC), 114.0–113.3 (m, 2 × ArC), 111.1 (ArC), 54.5 (C), 42.1 (t, J = 7.2 Hz, CH₂) ppm; ¹⁹F NMR (376 MHz, CDCl₃): δ = −36.2 (d, J = 18.8 Hz, 2F), −152.8 (t, J = 20.9 Hz, 1F), −160.4 (t, J = 20.8 Hz, 2F) ppm; IR (neat): ν = 1807s, 1653w, 1524s, 1485s, 1464s, 1116.8s, 1061s,
1011s, 966s, 885m, 754s, 704s, 577m cm⁻¹; HRMS (EI): Exact mass calculated for C₂₁H₁₁F₅O₂ [M⁺]: 390.0679, found: 390.0676.

3-Benzyl-3-phenylbenzofuran-2(3H)-one 185c:

Performed according to General Procedure 19 on a 0.1 mmol scale of 184a and 0.1 mmol of 106a; 185c (6.3 mg, 0.021 mmol, 21% yield) was obtained after 14 days at room temperature as a colourless solid, m.p.: 118–120 °C.

¹H NMR (400 MHz, CDCl₃): δ = 7.55–7.51 (m, 2H, ArH), 7.41–7.36 (m, 2H, ArH), 7.36–7.32 (m, 1H, ArH), 7.29–7.26 (m, 1H, ArH), 7.25–7.16 (m, 3H, ArH), 7.14–7.04 (m, 3H, ArH), 6.94 (ddd, J = 7.9, 1.1, 0.6 Hz, 1H, ArH), 6.87 (dd, J = 8.0, 1.5 Hz, 2H, ArH), 3.74 (d, J = 13.1 Hz, 1H, C×CH₂), 3.53 (d, J = 13.1 Hz, 1H, C×CH₂) ppm; ¹³C NMR (126 MHz, CDCl₃): δ = 177.7 (C=O), 153.2 (ArC–O), 138.6 (ArC), 134.9 (ArC), 130.2 (ArC), 129.3 (ArC), 129.0 (ArC), 128.2 (ArC), 128.1 (ArC), 127.3 (ArC), 127.2 (ArC), 126.1 (ArC), 124.0 (ArC), 111.0 (ArC), 57.6 (C), 45.1 (CH₂) ppm; IR (neat): ν = 3030w, 2928w, 2851w, 1788s, 1618w, 1495m, 1460, 1292w, 1231m, 1063s, 951m, 881m cm⁻¹; HRMS (EI): Exact mass calculated for C₂₁H₁₆O₂ [M⁺]: 300.1150, found 300.1151.

3-(4-(Trifluoromethyl)benzyl)-3-(3,4,5-trifluorophenyl)benzofuran-2(3H)-one 185d:

Performed according to General Procedure 19 on a 0.1 mmol scale of 184b and 0.1 mmol of 106e; 185d (24 mg, 0.054 mmol, 54% yield) was obtained after 24 hours at 50 °C as a colourless solid, m.p.: 118–120 °C.

¹H NMR (400 MHz, CDCl₃): δ = 7.39–7.32 (m, 3H, ArH), 7.32–7.14 (m, 4H, ArH), 7.00 (d, J = 8.0 Hz, 1H, ArH), 6.96 (d, J = 8.1 Hz, 2H, ArH), 3.68 (d, J = 13.2 Hz, 1H, C×CH₂), 3.47 (d, J = 13.2 Hz, 1H, C×CH₂) ppm; ¹³C NMR (126 MHz, CDCl₃): δ = 176.2 (C=O), 153.1 (ArC–O), 151.4 (ddd, J = 251.1, 9.9, 4.2 Hz, 2 × ArC–F), 139.7 (dt, J = 254.0, 15.2 Hz, ArC–F), 138.1–137.9 (m, ArC), 134.4–134.2 (m, ArC), 130.4 (2 × ArC), 129.9 (q, J = 32.6 Hz, ArC–CF₃), 127.2 (ArC), 125.7 (ArC), 125.29 (q, J = 3.7 Hz, 2 × ArC), 124.7 (ArC), 123.9 (q, J = 272.3 Hz, CF₃), 112.1–111.8 (2 × ArC), 111.7 (ArC), 56.4 (C), 45.1 (CH₂) ppm; ¹⁹F NMR (376 MHz, CDCl₃): δ = −62.7 (s, 3F), −132.1 (d, J = 20.4 Hz, 2F), −159.7 (t, J = 20.4 Hz, 1F) ppm; IR (neat): ν = 2922w, 1792s, 1620m, 1531s, 1466m, 1313s, 1109s, 1068s, 1045s, 1016s, 872m, 839m, 752s, 625s cm⁻¹; HRMS (ASAP): Exact mass calculated for C₂₂H₁₅O₂F₆ [M+H⁺]: 423.0820, found 423.0828.
3-((4-(Trifluoromethyl)benzyl)-3-(pentafluorophenyl)benzofuran-2(3H)-one 185e:

Performed according to General Procedure 19 on a 0.1 mmol scale of 84b and 0.1 mmol of 106d; 185e (33 mg, 0.072 mmol, 72% yield) was obtained after 24 hours at 50 °C as a colourless solid, m.p.: 128–130 °C.

\[ \text{H NMR (400 MHz, CDCl}_3\text{): } \delta = 7.37–7.29 (m, 4H, ArH), 7.25–7.19 (m, 1H, ArH), 6.89–6.83 (m, 3H, ArH), 4.02 (dt, J = 12.8, 2.2 Hz, 1H, 1 × CH₂), 3.77 (d, J = 12.8, 1H, 1 × CH₂) ppm; \]
\[ \text{C NMR (126 MHz, CDCl}_3\text{): } \delta = 174.9 (C=O), 153.0 (ArC–O), 146.0 (d, J = 250.0 Hz, 2 × ArC–F), 141.3 (d, J = 257.1 Hz, ArC–F), 138.3 (d, J = 254.3 Hz, 2 × ArC–F) 136.9 (ArC), 130.9 (ArC), 130.6 (ArC), 130.1 (q, J = 32.5 Hz, ArC–CF₃), 128.2 (ArC), 125.1 (ArC), 125.1 (q, J = 3.8 Hz, 2 × ArC), 124.4 (q, J = 272.2 Hz, CF₃), 113.3 (m, ArC), 111.4 (ArC), 54.2 (C), 41.8 (t, J = 7.3 Hz, CH₂) ppm; \]
\[ \text{F NMR (376 MHz, CDCl}_3\text{): } \delta = -62.7 (s, 3F), -136.4 (d, J = 18.9 Hz, 2F), -152.4 (t, J = 21.1 Hz, 1F), -160.07 (t, J = 21.4 Hz, 2F) ppm; \]
\[ \text{IR (neat): } \nu = 2924w, 2853w, 1803s, 1738m, 1531m, 1485s, 1331s, 1221m, 1119s, 970s, 885, 856m, 748s, 675m cm}^{-1} \]; HRMS (ASAP): Exact mass calculated for C_{22}H_{10}O_{2}F_8 [M+H]^+: 459.0631, found 459.0629.

3-((4-(Trifluoromethyl)benzyl)-3-Benzylbenzofuran-2(3H)-one 185f:

Performed according to General Procedure 19 on a 0.1 mmol scale of 184b and 0.1 mmol of 106a; 185f (9.6 mg, 0.026 mmol, 26% yield) was obtained after 24 hours at 50 °C as a colourless solid, m.p.: 112–114 °C.

\[ \text{H NMR (400 MHz, CDCl}_3\text{): } \delta = 7.55–7.49 (m, 2H, ArH), 7.44–7.27 (m, 6H, ArH), 7.25–7.19 (m, 2H, ArH), 7.01–6.93 (m, 3H, ArH), 3.79 (d, J = 13.2 Hz, 1H, 1 × CH₂), 3.58 (d, J = 13.1 Hz, 1H, 1 × CH₂) ppm; \]
\[ \text{C NMR (101 MHz, CDCl}_3\text{): } \delta = 177.3 (C=O), 153.1 (ArC–O), 138.1 (ArC), 130.6 (ArC), 129.7 (ArC), 129.1 (ArC), 128.7 (ArC), 128.4 (ArC), 127.1 (ArC), 125.9 (ArC), 125.1 (q, J = 3.5 Hz, ArC), 124.3 (ArC), 111.3 (ArC), 57.3 (C), 44.7 (CH₂) ppm; \]
\[ \text{IR (neat): } \nu = 3059w, 2918w, 2853w, 1798s, 1618w, 1599m, 1462m, 1323s, 1122s, 1111s, 1064s, 879m, 844m, 754s cm}^{-1} \]; HRMS (ASAP): Exact mass calculated for C_{22}H_{15}O_{2}F_3 [M]^+: 369.1102, found 369.1102.
3-(4-Methoxybenzyl)-3-(3,4,5-trifluorophenyl)benzofuran-2(3H)-one **185g**: 

Performed according to General Procedure 19 on a 0.1 mmol scale of **184c** and 0.1 mmol of **106e**; **185g** (35 mg, 0.091 mmol, 91% yield) was obtained after 16 hours at room temperature as a colourless solid, m.p.: 98–102 °C.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.31$ (dd, $J = 7.7$, 1.4 Hz, 1H, ArH), 7.28–7.14 (m, 4H, ArH), 6.98 (d, $J = 8.0$ Hz, 1H, ArH), 6.75–6.70 (m, 2H, ArH), 6.64–6.59 (m, 2H, ArH), 3.70 (s, 3H, OCH$_3$), 3.53 (d, $J = 13.3$ Hz, 1H, 1 × CH$_2$), 3.37 (d, $J = 13.3$ Hz, 1H, 1 × CH$_2$) ppm; $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta = 176.6$ (C=O), 159.0 (ArC–O), 153.2 (ArC–O), 151.3 (dd, $J = 251.0$, 9.9, 4.1 Hz, 2 × ArC–F), 139.5 (dt, $J = 254.2$, 15.3 Hz, ArC–F), 135.1–134.5 (m, ArC), 131.2 (ArC), 130.0 (ArC), 127.6 (ArC), 126.0 (ArC), 125.9 (ArC), 124.4 (ArC), 113.7 (ArC), 112.2–111.8 (m, 2 × ArC), 111.4 (ArC), 56.7 (C), 44.9 (C) ppm; $^{19}$F NMR (376 MHz, CDCl$_3$): $\delta = -132.6$ (d, $J = 20.3$ Hz, 2F), -160.3 (t, $J = 20.3$ Hz, 1F) ppm; IR (neat): $\nu = 3076$w, 2951w, 2835w, 1792s, 1616m, 1528s, 1462w, 1431m, 1248s, 1178m, 1119m, 1036s, 752s cm$^{-1}$; HRMS (EI): Exact mass calculated for C$_{22}$H$_{15}$O$_3$F$_3$ [M]$^+$: 384.0973, found 384.0971.

3-(4-(Trifluoromethyl)benzyl)-3-benzylbenzofuran-2(3H)-one **185i**: 

Performed according to General Procedure 19 on a 0.1 mmol scale of **184c** and 0.1 mmol of **106a**; **185i** (18 mg, 0.054 mmol, 54% yield) was obtained after 72 hours at room temperature as a colourless solid, m.p.: 112–114 °C.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta = 7.52$ (d, $J = 7.4$ Hz, 2H, ArH), 7.35–7.27 (m, 2H, ArH), 7.25–7.17 (m, 2H, ArH), 6.96 (d, $J = 8.0$ Hz, 1H, ArH), 6.77 (d, $J = 8.5$ Hz, 2H, ArH), 6.61 (d, $J = 8.6$ Hz, 2H, ArH), 3.71 (s, 3H, OCH$_3$), 3.67 (d, $J = 13.3$ Hz, 1H, 1 × CH$_2$), 3.48 (d, $J = 13.3$ Hz, 1H, 1 × CH$_2$) ppm; $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta = 177.7$ (C=O), 158.7 (ArC–O), 153.2 (ArC–O), 138.6 (ArC), 131.2 (ArC), 129.4 (ArC), 129.2 (ArC), 129.0 (ArC), 128.1 (ArC), 127.2 (ArC), 126.9 (ArC), 126.0 (ArC), 124.0 (ArC), 113.5 (ArC), 111.0 (ArC), 57.7 (C), 55.2 (OCH$_3$), 44.3 (CH$_2$) ppm; IR (neat): $\nu = 3017$w, 2928w, 2841w, 1794w, 1794s, 1610m, 1512m, 1460m, 1246s, 1246s, 1068s, 1026s, 760s, 694s cm$^{-1}$; HRMS (ES): Exact mass calculated for C$_{22}$H$_{17}$O$_3$ [M−H]$^+$: 329.1178, found 329.1188.
3-(4-Methylbenzyl)-3-(3,4,5-trifluorophenyl)benzofuran-2(3H)-one 185j:

Performed according to General Procedure 19 on a 0.1 mmol scale of 184d and 0.1 mmol of 106e; 185j (32 mg, 0.087 mmol, 87% yield) was obtained after 24 hours at room temperature as a colourless solid, m.p.: 94–96 °C.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.33$ (dt, $J = 7.9, 1.6$ Hz, 1H, ArH), 7.26–7.17 (m, 4H, ArH), 6.99 (d, $J = 8.0$ Hz, 1H, ArH), 6.90 (d, $J = 7.9$ Hz, 2H, ArH), 6.71 (d, $J = 8.0$ Hz, 2H, ArH), 3.55 (d, $J = 13.2$ Hz, 1H, 1 × CH$_2$), 3.40 (d, $J = 13.2$ Hz, 1H, 1 × CH$_2$), 2.23 (s, 3H, CH$_3$) ppm; $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta = 176.6$ (C=O), 153.2 (ArC–O), 151.3 (ddd, $J = 251.1, 9.9, 4.2$ Hz, 2 × ArC–F), 139.5 (dt, $J = 253.4, 15.3$ Hz, ArC–F), 137.3 (ArC), 135.1–134.4 (m, ArC), 130.8 (ArC), 130.0 (ArC), 129.9 (ArC), 129.0 (ArC), 127.6 (ArC), 126.0 (ArC), 124.4 (ArC), 112.5–111.9 (m, 2 × ArC), 111.4 (ArC), 56.6 (C), 45.2 (CH$_2$), 21.1 (CH$_3$) ppm; $^{19}$F NMR (376 MHz, CDCl$_3$): $\delta = −132.6$ (d, $J = 19.9$ Hz, 2F), −160.3 (t, $J = 20.2$ Hz, 1F) ppm; IR (neat) $\nu = 3075$w, 3036w, 1794s, 1705s, 1618s, 1528s, 1464s, 1337m, 1234s, 885s, 829m, 814m, 752s, 586s, 475s cm$^{-1}$; HRMS (EI): Exact mass calculated for C$_{22}$H$_{15}$F$_3$O$_2$ [M]: 368.1024, found 368.1027.

3-(4-Methylbenzyl)-3-(pentafluorophenyl)benzofuran-2(3H)-one 185k:

Performed according to General Procedure 19 on a 0.1 mmol scale of 184d and 0.1 mmol of 106d; 185k (25 mg, 0.063 mmol, 63% yield) was obtained after 24 hours at 50 °C as a colourless solid, m.p.: 124–126 °C.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta = 7.32–7.25$ (m, 2H, ArH), 7.23–7.16 (m, 1H, ArH), 6.89–6.83 (m, 3H, ArH), 6.60 (d, $J = 8.0$ Hz, 2H, ArH), 3.92 (d, $J = 12.9$ Hz, 1H, 1 × CH$_2$), 3.68 (d, $J = 12.9$ Hz, 1H, 1 × CH$_2$), 2.23 (s, 3H, CH$_3$) ppm; $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta = 175.3$ (C=O), 153.1 (ArC–O), 146.0 (d, $J = 243.3$ Hz, 2 × ArC–F), 141.1 (d, $J = 257.1$ Hz, ArC–F), 138.1 (d, $J = 247.0$ Hz, 2 × ArC–F), 137.5 (ArC), 130.4 (ArC), 130.2 (ArC), 129.6 (ArC), 129.0 (ArC), 129.9 (ArC), 124.8 (ArC), 123.8 (ArC), 113.9–113.6 (m, ArC), 111.1 (ArC), 54.6 (C), 41.8 (t, $J = 7.2$ Hz, CH$_2$), 21.2 (CH$_3$) ppm; $^{19}$F NMR (376 MHz, CDCl$_3$): $\delta = −136.1$ (d, $J = 19.4$ Hz, 2F), −153.0 (t, $J = 21.1$ Hz, 1F), −160.4 (t, $J = 21.4$ Hz, 2F) ppm; IR (neat) $\nu = 2924$w, 1803s, 1526s, 1487s, 1119s, 968s, 883s, 739s, 615m, 573s, cm$^{-1}$; HRMS (ASAP): Exact mass calculated for C$_{22}$H$_{14}$O$_2$F$_5$ [M+H]: 405.0914, found 405.0911.
3-(4-Bromobenzyl)-3-(3,4,5-trifluorophenyl)benzofuran-2(3H)-one 185l:

Performed according to General Procedure 19 on a 0.1 mmol scale of 184e and 0.1 mmol of 106e; 185l (32 mg, 0.074 mmol, 74% yield) was obtained after 24 hours at room temperature as a colourless oil.

\[
\begin{align*}
\text{Br} & \quad \text{F} \\
\text{F} & \quad \text{O} \\
\text{O} & \quad \text{F}
\end{align*}
\]

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 7.35 \text{ (ddd, } J = 8.1, 7.5, 1.6 \text{ Hz, } 1\text{H, ArH}), 7.30 - 7.14 \text{ (m, } 6\text{H, ArH}), 6.74 - 6.61 \text{ (m, } 2\text{H, ArH}), 3.57 \text{ (d, } J = 13.2 \text{ Hz, } 1\text{H, } 1 \times \text{CH}_2\) \(\text{ppm; } ^{13}\text{C NMR (126 MHz, CDCl}_3\): } \delta = 176.3 \text{ (C=O), 153.1 (ArC–O), 151.4 (ddd, } J = 251.0, 9.9, 4.1 \text{ Hz, } 2 \times \text{ArC–F), 139.6 (dt, } J = 254.1, 15.3 \text{ Hz, ArC–F), 135.4–133.7 \text{ (m, ArC), 132.9 (ArC), 131.8 (ArC), 131.5 (ArC), 130.3 (ArC), 127.1 (ArC), 125.8 (ArC), 124.6 (ArC), 121.9 (ArC), 112.2–111.7 \text{ (m, } 2 \times \text{ArC), 111.7 (ArC) 56.4 (C), 44.8 (CH}_2\) \text{ppm; } ^{19}\text{F NMR (376 MHz, CDCl}_3\): } \delta = -132.2 \text{ (d, } J = 20.7 \text{ Hz, } 2\text{F), –159.9 (t, } J = 20.7 \text{ Hz, } 1\text{F) ppm; IR (neat): } \nu = 3080\text{w, 2924\text{w, 1798s, 1529s, 1047s, 1011s, 754s cm}^{-1}}\)\]

HRMS (ES): Exact mass calculated for C\(_{21}\)H\(_{11}\)F\(_3\)O\(_2\)Br [M–H]\(^-\): 430.9895, found 430.9903.

3-(4-Bromobenzyl)-3-(pentafluorophenyl)benzofuran-2(3H)-one 185l:

Performed according to General Procedure 19 on a 0.1 mmol scale of 184e and 0.1 mmol of 106d; 185l (34 mg, 0.073 mmol, 73% yield) was obtained after 24 hours at 50 °C as a colourless solid, m.p.: 116–118 °C.

\[
\begin{align*}
\text{Br} & \quad \text{F} \\
\text{F} & \quad \text{O} \\
\text{O} & \quad \text{F}
\end{align*}
\]

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 7.33–7.27 \text{ (m, } 2\text{H, ArH}), 7.23–7.17 \text{ (m, } 3\text{H, ArH}), 6.89 \text{ (d, } J = 8.1 \text{ Hz, 1H, ArH), 6.60 (d, } J = 8.4 \text{ Hz, 2H, ArH), 3.93 (dt, } J = 10.8, 2.1 \text{ Hz, } 1\text{H, } 1 \times \text{CH}_2\) \(\text{ppm; } ^{13}\text{C NMR (101 MHz, CDCl}_3\): } \delta = 175.0 \text{ (C=O), 153.0 (ArC–O), 146.0 (d, } J = 250.1 \text{ Hz, } 2 \times \text{ArC–F), 141.23 (d, } J = 262.4 \text{ Hz, ArC–F), 138.2 (d, } J = 253.0 \text{ Hz, } 2 \times \text{ArC–F), 132.2 (ArC), 131.7 (ArC), 131.4 (ArC), 130.5 \text{ (ArC), 128.4 (ArC), 125.0 (ArC), 123.7 (ArC), 122.2 (ArC), 113.8–113.1 \text{ (m, ArC), 111.4 \text{ (ArC), 54.2 (C), 41.5 (m, } \text{CH}_2\) \text{ppm; } ^{19}\text{F NMR (376 MHz, CDCl}_3\): } \delta = -136.3 \text{ (d, } J = 18.6 \text{ Hz, } 2\text{F), –152.5 (t, } J = 21.0 \text{ Hz, } 1\text{F), –160.2 (t, } J = 21.2 \text{ Hz, } 2\text{F) ppm; IR (neat): } \nu = 3090\text{w, 2924w, 1798s, 1529s, 1232m, 1047s, 1011s, 754s cm}^{-1}}\)\]

HRMS (EI): Exact mass calculated for C\(_{21}\)H\(_{11}\)F\(_5\)O\(_2\)Br [M]⁺: 467.9784, found 467.9767.
3-(2-Methylbenzyl)-3-(3,4,5-trifluorophenyl)benzofuran-2(3H)-one 185n:

Performed according to General Procedure 19 on a 0.1 mmol scale of 184f and 0.1 mmol of 106e; 185n (29 mg, 0.078 mmol, 78% yield) was obtained after 24 hours at room temperature as a colourless solid, m.p.: 82–84 °C.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 7.34 (td, $J$ = 8.0, 1.3 Hz, 1H, ArH), 7.24–7.17 (m, 2H, ArH), 7.14 (td, $J$ = 7.6, 0.9 Hz, 1H, ArH), 7.09–6.98 (m, 3H, ArH), 6.92–6.82 (m, 2H, ArH), 6.53 (d, $J$ = 7.5 Hz, 1H, ArH), 3.57 (d, $J$ = 13.9 Hz, 1H, 1 × CH$_2$), 3.49 (d, $J$ = 13.9 Hz, 1H, 1 × CH$_2$) ppm; $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ = 176.8 (C=O), 153.1 (ArC–O), 151.2 (ddd, $J$ = 251.2, 9.9, 4.1 Hz, 2 × ArC–F), 139.5 (dt, $J$ = 254.0, 15.3 Hz, ArC–F), 137.5 (ArC), 134.5 (m, ArC), 134.6 (ArC), 134.5 (ArC), 134.5 (ArC), 134.5 (ArC), 134.5 (ArC), 134.4 (ArC), 132.5 (ArC), 130.8 (ArC), 130.1 (ArC), 129.7 (ArC), 127.8 (ArC), 127.2 (ArC), 126.4 (ArC), 125.8 (ArC), 124.3 (ArC), 113.3–111.8 (m, 2 × ArC), 111.4 (ArC), 55.5 (C), 41.6 (CH$_2$), 20.0 (CH$_3$) ppm; $^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ = −132.6 (d, $J$ = 20.6 Hz, 2F), −160.2 (t, $J$ = 20.6 Hz, 1F) ppm; IR (neat): $\nu$ = 3086w, 2924w, 2854w, 1794s, 1620m, 1526m, 1458m, 1435m, 1346m, 1232m, 760s cm$^{-1}$; HRMS (ASAP): Exact mass calculated for C$_{22}$H$_{16}$O$_2$F$_3$[M+H]$^+$: 369.1102, found 369.1103.

3-(2-Methylbenzyl)-3-(pentafluorophenyl)benzofuran-2(3H)-one 185o:

Performed according to General Procedure 19 on a 0.1 mmol scale of 184f and 0.1 mmol of 106d; 185o (24 mg, 0.059 mmol, 59% yield) was obtained after 24 hours at 50 °C as a colourless oil.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 7.36–7.28 (m, 2H, ArH), 7.20 (t, $J$ = 7.5 Hz, 1H, ArH), 7.10–7.00 (m, 2H, ArH), 6.91 (d, $J$ = 8.0 Hz, 1H, ArH), 6.83 (t, $J$ = 7.2 Hz, 1H, ArH), 6.43 (d, $J$ = 7.7 Hz, 1H, ArH), 3.97 (d, $J$ = 13.5 Hz, 1H, 1 × CH$_2$), 3.89 (d, $J$ = 13.4 Hz, 1H, 1 × CH$_2$) ppm; $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ = 175.4 (C=O), 153.2 (ArC–O), 146.0 (d, $J$ = 246.0 Hz, 2 × ArC–F), 141.1 (d, $J$ = 257.2 Hz, ArC–F), 138.3 (d, $J$ = 253.0 Hz, 2 × ArC–F), 137.8 (ArC), 131.4 (ArC), 130.9 (ArC), 130.4 (ArC), 130.3 (ArC), 129.1 (ArC), 127.9 (ArC), 125.5 (ArC), 124.8 (ArC), 124.2 (ArC), 114.4–114.0 (m, ArC), 111.2 (ArC), 54.3 (C), 37.9 (t, $J$ = 7.1 Hz, CH$_3$), 20.0 (CH$_3$) ppm; $^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ = −135.8 (d, $J$ = 18.6 Hz, 2F), −153.0 (t, $J$ = 21.0 Hz, 1F), −160.37 (t, $J$ = 20.9 Hz, 2F) ppm; IR (neat): $\nu$ = 3086w, 1807s, 1524s, 1487s, 1464s, 1121s, 968s, 883m, 677m, 478m cm$^{-1}$; HRMS (ASAP): Exact mass calculated for C$_{22}$H$_{14}$O$_2$F$_5$[M+H]$^+$: 405.0914, found 405.0909.
3-(2-Phenylbenzyl)-3-(3,4,5-trifluorophenyl)benzofuran-2(3H)-one 185p:

Performed according to General Procedure 19 on a 0.1 mmol scale of 184g and 0.1 mmol of 106e; 185p (39 mg, 0.09 mmol, 91%) was obtained after 24 hours at room temperature as a colourless oil.

1H NMR (400 MHz, CDCl3) δ = 7.35–7.27 (m, 4H, ArH), 7.15 (td, J = 7.6, 1.6 Hz, 1H, ArH), 7.10–6.95 (m, 6H, ArH), 6.95–6.88 (m, 2H, ArH), 6.42 (dd, J = 7.6, 1.3 Hz, 1H, ArH), 3.84 (d, J = 13.9 Hz, 1H, 1×CH2), 3.61 (d, J = 13.9 Hz, 1H, 1×CH2) ppm; 13C NMR (101 MHz, CDCl3): δ = 176.8 (C=O), 153.0 (ArC–O), 151.1 (ddd, J = 250.1, 9.9, 4.1 Hz, 2×ArC–F), 143.3 (ArC), 140.9 (ArC), 139.5 (d, J = 253.2 Hz, ArC–F), 134.8–134.5 (m, ArC), 131.9 (ArC), 130.9 (ArC), 129.8 (ArC), 129.7 (ArC), 128.2 (ArC), 127.6 (ArC), 127.4 (ArC), 127.2 (ArC), 126.8 (ArC), 126.7 (ArC), 124.3 (ArC), 112.2–111.8 (m, 2×ArC), 111.0 (ArC), 55.9 (C), 41.1 (CH2) ppm; 19F NMR (376 MHz, CDCl3): δ = −132.7 (d, J = 20.7 Hz, 2F), −160.5 (t, J = 20.7 Hz, 1F) ppm; IR (neat): ν = 3059w, 2926w, 1800s, 1618m, 1528s, 1462m, 1435, 1232m, 1121m, 1045s, 750s, 704s cm−1; HRMS (ASAP): Exact mass calculated for C27H18F3O2 [M+H]+: 431.1259, found 431.1257.

3-(2-Phenylbenzyl)-3-(pentafluorophenyl)benzofuran-2(3H)-one 185q:

Performed according to General Procedure 19 on a 0.1 mmol scale of 184g and 0.1 mmol of 106d; 185q (24 mg, 0.052 mmol, 52% yield) was obtained after 24 hours at 50 ºC as a colourless oil.

1H NMR (500 MHz, CDCl3, 298 K) δ = 7.41–7.28 (m, 3H, ArH), 7.12 (t, J = 7.4 Hz, 1H, ArH), 7.07–6.97 (m, 4H, ArH), 6.90 (t, J = 7.6 Hz, 1H, ArH), 6.86 (d, J = 8.1 Hz, 1H, ArH), 6.57 (d, J = 7.5 Hz, 1H, ArH), 4.50 (d, J = 13.4 Hz, 1H, 1×CH2), 3.85 (d, J = 13.4 Hz, 1H, 1×CH2) ppm; 13C NMR (126 MHz, CDCl3): δ = 175.4 (C=O), 152.8 (ArC–O), 145.8 (d, J = 250.1 Hz, 2×ArC–F), 143.6 (ArC), 140.1 (ArC), 140.9 (d, J = 256.4 Hz, ArC–F), 138.1 (d, J = 254.3 Hz, 2×ArC–F), 131.0 (ArC), 131.0 (ArC), 130.3 (ArC), 130.0 (ArC), 129.7 (ArC), 128.4 (ArC), 128.2 (ArC), 127.8 (ArC), 127.2 (ArC), 127.0 (ArC), 125.0 (ArC), 124.2 (ArC), 114.7–113.9 (m, ArC), 110.7 (ArC), 54.3 (C), 36.9 (t, J = 7.4 Hz, CH2) ppm; 19F NMR (376 MHz, CDCl3): δ = −136.0 (d, J = 19.6 Hz, 2F), −153.3 (t, J = 21.1 Hz, 1F), −160.5 (t, J = 21.0, 2F) ppm; IR (neat): ν = 3059w, 2926w, 1800s, 1618m, 1528s, 1462m, 1435, 1232m, 1121m, 1045s, 750s, 704s cm−1; HRMS (EI): Exact mass calculated for C27H18F5O2 [M+H]+: 467.1070, found 467.1069.
3-Allyl-3-(3,4,5-trifluorophenyl)benzofuran-2(3H)-one 185r:

Performed according to General Procedure 19 on a 0.1 mmol scale of 184h and 0.1 mmol of 106e; 185r (17 mg, 0.057 mmol, 57% yield) was obtained after 24 hours at room temperature as a pale-yellow oil.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta = 7.42$ (t, $J = 7.6$ Hz, 1H, Ar$H_1$), 7.34–7.28 (m, 1H, Ar$H_1$), 7.26 (d, $J = 9.0$ Hz, 1H, Ar$H_1$), 7.20 (d, $J = 8.1$ Hz, 1H, Ar$H_1$), 7.08 (dd, $J = 8.1$, 6.7 Hz, 2H, Ar$H_2, H_3$), 5.47–5.27 (m, 1H), 5.14–5.00 (m, 2H), 3.04–2.90 (m, 2H) ppm; $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta = 176.4$ (C=O), 153.2 (Ar$C–O$), 151.4 (ddd, $J = 251.0$, 9.9, 4.1 Hz, 2 $\times$ Ar$C–F$), 139.5 (dt, $J = 253.1$, 15.2 Hz, ArC–F), 134.4 (td, $J = 7.1$, 4.5 Hz), 130.4, 130.1, 128.0, 125.5, 124.8, 121.5, 112.0–111.6 (m, 2 $\times$ ArC), 111.6 (ArC), 54.8 (C$_2$H), 43.5 (C$_3$H$_2$) ppm; $^{19}$F NMR (376 MHz, CDCl$_3$): $\delta = -132.6$ (d, $J = 20.1$ Hz, 2F), $-160.3$ (t, $J = 20.4$ Hz, 1F) ppm; IR (neat): $\nu = 3068$w, 2954w, 1802s, 1529s, 1229s, 754s cm$^{-1}$; HRMS (ES): Exact mass calculated for C$_{17}$H$_{10}$F$_3$O$_2$ [M–H]$^-$: 303.0633, found 303.0644.

3-Allyl-3-(pentafluorophenyl)benzofuran-2(3H)-one 185s:

Performed according to General Procedure 19 on a 0.1 mmol scale of 184h and 0.1 mmol of 106d; 185s (20 mg, 0.060 mmol, 60% yield) was obtained after 24 hours at 50 °C as a pale-yellow oil.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta = 7.39$–7.31 (m, 1H, Ar$H_1$), 7.19–7.12 (m, 3H, Ar$H_1$), 5.51–5.39 (m, 1H, Ar$H_1$), 5.14–5.07 (m, 2H), 3.28 (dd, $J = 13.2$, 6.2 Hz, 1H, 1 $\times$ CH$_2$), 3.20 (dd, $J = 13.2$, 8.0 Hz, 1H, 1 $\times$ CH$_2$) ppm; $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta = 175.2$ (C=O), 152.9 (ArC–O), 145.9 (d, $J = 250.2$ Hz, 2 $\times$ ArC–F), 141.1 (d, $J = 256.1$ Hz, ArC–F), 138.2 (d, $J = 254.0$ Hz, 2 $\times$ ArC–F), 130.1 (ArC), 129.6 (ArC), 129.1 (ArC), 125.1 (ArC), 123.5 (ArC), 122.2 (ArC), 114.2–112.6 (m, ArC), 111.2 (ArC), 52.6 (C), 40.8 (t, $J = 6.5$ Hz, CH$_2$) ppm; $^{19}$F NMR (376 MHz, CDCl$_3$): $\delta = -132.6$ (d, $J = 20.1$ Hz, 2F), $-160.3$ (t, $J = 20.4$ Hz, 1F) ppm; IR (neat): $\nu = 2922$w, 1807s, 1524s, 1487s, 1463s, 1487s, 1053s, 968s, 883s, 752s cm$^{-1}$; HRMS (EI): Exact mass calculated for C$_{17}$H$_{10}$F$_5$O$_2$ [M]: 340.0523, found 340.0522.

3-Cinnamyl-3-(3,4,5-trifluorophenyl)benzofuran-2(3H)-one 185t:

Performed according to General Procedure 19 on a 0.1 mmol scale of 184i and 0.1 mmol of 106e; 185t (20 mg, 0.060 mmol, 60% yield) was obtained after 24 hours at 50 °C as a pale-yellow oil.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta = 7.39$–7.31 (m, 1H, Ar$H_1$), 7.19–7.12 (m, 3H, Ar$H_1$), 5.51–5.39 (m, 1H, Ar$H_1$), 5.14–5.07 (m, 2H), 3.28 (dd, $J = 13.2$, 6.2 Hz, 1H, 1 $\times$ CH$_2$), 3.20 (dd, $J = 13.2$, 8.0 Hz, 1H, 1 $\times$ CH$_2$) ppm; $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta = 175.2$ (C=O), 152.9 (ArC–O), 145.9 (d, $J = 250.2$ Hz, 2 $\times$ ArC–F), 141.1 (d, $J = 256.1$ Hz, ArC–F), 138.2 (d, $J = 254.0$ Hz, 2 $\times$ ArC–F), 130.1 (ArC), 129.6 (ArC), 129.1 (ArC), 125.1 (ArC), 123.5 (ArC), 122.2 (ArC), 114.2–112.6 (m, ArC), 111.2 (ArC), 52.6 (C), 40.8 (t, $J = 6.5$ Hz, CH$_2$) ppm; $^{19}$F NMR (376 MHz, CDCl$_3$): $\delta = -136.7$ (d, $J = 19.7$ Hz, 2F), $-152.9$ (t, $J = 20.9$ Hz, 1F), $-160.4$ (t, $J = 20.8$ Hz, 2F) ppm; IR (neat): $\nu = 2922$w, 1807s, 1524s, 1487s, 1463s, 1291m, 1053s, 968s, 883s, 752s cm$^{-1}$; HRMS (EI): Exact mass calculated for C$_{17}$H$_{10}$F$_5$O$_2$ [M]: 340.0523, found 340.0522.

3-Cinnamyl-3-(3,4,5-trifluorophenyl)benzofuran-2(3H)-one 185t:

Performed according to General Procedure 19 on a 0.1 mmol scale of 184i and 0.1 mmol of 106e; 185t (20 mg, 0.053 mmol, 53% yield) was obtained after 24 hours at room temperature as a colourless oil.


1H NMR (500 MHz, CDCl3): δ = 7.42 (t, J = 7.7 Hz, 1H, ArH), 7.33 (d, J = 7.4 Hz, 1H, ArH), 7.31–7.10 (m, 9H, ArH), 6.40 (d, J = 15.7 Hz, 1H, CH), 5.80–5.65 (m, 1H, CH), 3.21–3.06 (m, 2H, CH2) ppm; 13C NMR (126 MHz, CDCl3): δ = 176.4 (C=O), 153.2 (ArC–O), 151.4 (ddd, J = 251.0, 9.9, 4.1 Hz, 2 × ArC–F), 139.6 (dd, J = 254.1, 17.1 Hz, ArC–F), 136.5, 136.2, 134.7–134.0, 130.2, 128.7, 128.0, 126.4, 125.6, 124.9, 121.4, 112.0–111.8 (m, 2 × ArC), 111.6 (ArC), 55.1 (C), 42.9 (CH2) ppm; 19F NMR (376 MHz, CDCl3): δ = −132.5 (d, J = 20.8 Hz, 2F), −160.2 (t, J = 20.7 Hz) ppm; IR (neat): ν = 3030w, 1801s, 1618m, 1464s, 1232s, 1047s, 885m, 692s cm−1; HRMS (ES): Exact mass calculated for C23H14F3O2 [M−H]−: 379.0946, found 379.0953.

5-Bromo-3-(4-methylbenzyl)-3-(3,4,5-trifluorophenyl)benzofuran-2(3H)-one 185v:

1H NMR (400 MHz, CDCl3): δ = 7.45 (dd, J = 8.6, 2.1 Hz, 1H, ArH), 7.30 (d, J = 2.1 Hz, 1H, ArH), 7.22–7.11 (m, 2H, CH), 6.94 (d, J = 7.9 Hz, 2H, ArH), 6.88 (d, J = 8.6 Hz, 1H, ArH), 6.71 (d, J = 8.0 Hz, 2H, ArH), 3.56 (d, J = 13.2 Hz, 1H, 1 × CH2), 3.38 (d, J = 13.2 Hz, 1H, 1 × CH2), 2.24 (s, 3H, CH3) ppm; 13C NMR (126 MHz, CDCl3): δ = 175.8 (C=O),
152.5 (ArC–O), 151.4 (ddd, \( J = 251.2, 9.9, 4.1 \) Hz, 2 × ArC–F), 139.7 (dt, \( J = 254.1, 15.2 \) Hz, ArC–F), 137.6, 134.1 (td, \( J = 7.0, 4.6 \) Hz, ArC), 133.0 (ArC), 130.2 (ArC), 130.1 (ArC), 130.0 (ArC), 129.9 (ArC), 129.2 (ArC), 128.9 (ArC), 117.0 (ArC), 113.0 (ArC), 112.4–111.4 (m, 2 × ArC), 56.9 (C), 45.0 (C\( \text{H}_2 \)), 21.1 (C\( \text{H}_3 \)) ppm; \(^{19}\text{F} \) NMR (376 MHz, CDCl\( _3 \)): \( \delta = -132.0 \) (d, \( J = 20.7 \) Hz, 2F), -159.6 (t, \( J = 20.7 \) Hz, 1F) ppm; IR (neat): \( \nu = 2918 \text{w}, 1809 \text{s}, 1618 \text{m}, 1526 \text{m}, 1462 \text{m}, 1433 \text{m}, 1132 \text{m}, 1053 \text{s}, 814 \text{s} \) cm\(^{-1} \); HRMS (ES): Exact mass calculated for C\( _{22} \)H\( _{13} \)O\( _2 \)F\( _3 \)Br \([M-H]^-\): 415.0757, found 415.0764.

3-Benzyl-3-(3,4,5-trifluorophenyl)benzo[b]thiophen-2(3H)-one \( 225 \):

Performed according to General Procedure 19 on a 0.083 mmol scale of \( 224 \) and 0.083 mmol of \( 106e \); \( 225 \) (17 mg, 0.046 mmol, 55% yield) was obtained after 72 hours at room temperature as a colorless solid, m.p.: 88–92 °C.

\(^1\text{H} \) NMR (500 MHz, CDCl\( _3 \)): \( \delta = 7.36–7.29 \) (m, 2H, ArH), 7.25–7.20 (m, 1H, ArH), 7.20–7.15 (m, 1H, ArH), 7.14–7.09 (m, 1H, ArH), 7.03–6.95 (m, 2H, ArH), 3.83 (d, \( J = 12.9 \) Hz, 1H, 1 × C\( \text{H}_2 \)), 3.36 (d, \( J = 12.9 \) Hz, 1H, 1 × C\( \text{H}_2 \)) ppm; \(^{13}\text{C} \) NMR (126 MHz, CDCl\( _3 \)): \( \delta = 206.2 \) (C=O), 152.3 (ArC–O), 151.3 (ddd, \( J = 250.1, 9.8, 4.1 \) Hz, 2 × ArC–F), 139.3 (dt, \( J = 254.0, 15.4 \) Hz, ArC–F), 138.5 (ArC), 136.7 (td, \( J = 6.9, 4.6 \) Hz, ArC), 138.4 (ArC), 138.4 (ArC), 136.7 (ArC), 136.7 (ArC), 136.0 (ArC), 133.9 (ArC), 130.3 (ArC), 129.4 (ArC), 128.1 (ArC), 127.3 (ArC), 126.9 (ArC), 126.7 (ArC), 123.4 (ArC), 112.3–111.9 (m, 2 × ArC), 67.7 (C), 44.8 (C\( \text{H}_2 \)) ppm; \(^{19}\text{F} \) NMR (376 MHz, CDCl\( _3 \)): \( \delta = -132.9 \) (d, \( J = 20.8 \) Hz, 2F), -160.5 (t, \( J = 20.8 \) Hz, 1F) ppm; IR (neat): \( \nu = 3032 \text{w}, 2926 \text{w}, 1703 \text{s}, 1618 \text{w}, 1529 \text{s}, 1435 \text{m}, 1344 \text{w}, 1244 \text{w}, 1051 \text{s} \) cm\(^{-1} \); HRMS (ES): Exact mass calculated for C\( _{22} \)H\( _{15} \)O\( _3 \)F\( _3 \)[M–H]\(^-\): 369.0561, found 369.0565.

5.3.4 Characterisation of Phenol Side Product 230

Methyl 2-(2-hydroxyphenyl)-2-(perfluorophenyl)-3-phenylpropanoate \( 230b \):

Compound \( 230b \) was obtained as a side product after reaction of \( 184b \) (1 equiv.) and \( 106d \) (1 equiv.) at room temperature as a colorless oil (12 mg, 0.54 mmol, 52% yield).

\(^1\text{H} \) NMR (500 MHz, CDCl\( _3 \)): \( \delta = 7.49 \) (dd, \( J = 8.1, 1.3 \) Hz, 1H, ArH), 7.33 (d, \( J = 8.1 \) Hz, 2H, ArH), 7.28–7.22 (m, 1H, ArH), 7.03–6.99 (m, 1H, ArH),
6.99–6.95 (m, 3H, ArH + OH), 6.90 (dd, J = 8.1, 1.3 Hz, 1H, ArH), 4.30 (d, J = 13.4 Hz, 1H, 1 × CH₂), 3.80 (s, 3H, OCH₃), 3.35 (d, J = 13.4 Hz, 1H, 1 × CH₂) ppm; ¹³C NMR (126 MHz, CDCl₃): δ = 172.7 (C=O), 155.0 (ArC–O), 145.2 (d, J = 255.0 Hz, 2 × ArC–F), 140.4 (d, J = 265.1 Hz, ArC–F), 139.6 (ArC), 137.5 (d, J = 246.0 Hz, 2 × ArC–F), 130.8 (ArC), 130.1 (ArC), 129.7 (q, J = 32.6 Hz, ArC–CF₃), 126.4 (ArC), 125.4 (ArC), 124.8 (q, J = 3.7 Hz, 2 × ArC), 121.6 (ArC), 120.0 (ArC), 113.7 (ArC), 54.8 (C), 54.1 (OCH₃), 40.8 (CH₂) ppm; ¹⁹F not ¹H-decoupled (471 MHz, CDCl₃): δ = −62.7 (s, 3F), −134.9 (d, J = 15.4 Hz, 2F), −153.7 (t, J = 21.3 Hz, 1F), −161.9 (qd, J = 22.0, 6.6 Hz, 2F) ppm; IR (neat): ν = 3333w, 1703m, 1489s, 1122s, 995s, 739s cm⁻¹; HRMS (ES): Exact mass calculated for C₂₃H₁₄O₃F₈ [M+H]⁺: 490.0815, found 490.0811.

Methyl 2-(2-hydroxyphenyl)-2-(perfluorophenyl)-3-phenylpropanoate 230c:

Compound 230c was obtained as a side product after reaction of 184c (1 equiv.) and 106a (1 equiv.) as a colourless oil which was not stable during analysis and decomposing into 185i.

¹H NMR (500 MHz, CDCl₃): δ = 7.53 (t, J = 7.7 Hz, 2H, ArH), 7.41–7.14 (m, 7H, ArH), 7.01 (t, J = 7.6 Hz, 1H, ArH), 6.96 (d, J = 7.7 Hz, 2H, ArH), 6.86 (dd, J = 8.0, 1.0 Hz, 1H, ArH), 6.77 (d, J = 8.6 Hz, 1H, ArH), 6.54 (d, J = 8.7 Hz, 1H, ArH), 6.51 (d, J = 8.7 Hz, 2H, ArH), 6.51 (d, J = 8.7 Hz, 2H, ArH), 6.27 (s, 1H, OH), 4.08 (d, J = 12.9 Hz, 1H, 1 × CH₂), 3.80 (s, 3H, OCH₃), 3.73 (s, 3H, OCH₃), 3.20 (d, J = 12.9 Hz, 1H, 1 × CH₂) ppm; IR (neat): ν = 3404m, 2951m, 2835m, 1800m, 1732s, 1705s, 1610s, 1512s, 1462, 1454, 1246, 1034m, 1034, 754 cm⁻¹; HRMS (ES): Exact mass calculated for C₂₃H₂₁O₄ [M−H]⁻: 361.1440, found 361.1444.
5.4  Experimental Data for Chapter 4:  
Synthesis of N,O-acetals in a Flow Microreactor

5.4.1  Synthesis of Starting Materials

[1,1'-Biphenyl]-2-carboxylic acid 287a:

Grounded KOH (6 g, 110 mmol) was dispersed into 50 mL of xylene and the temperature was raised to 85 °C. A solution of 9-fluorenone 286 (10 g, 55 mmol) in 50 mL of xylene was added dropwise over 30 minutes and the reaction was stirred for a further 5 hours at 160 °C. Water was added, and the phases separated. The organic phase was further washed with 1 M KOH aqueous solution (50 mL). The combined aqueous layers were acidified with 1 M HCl aqueous solution until pH = 2. The desired product 287a (8 g, 40 mmol, 72% yield) was afforded as a colourless solid after filtration and used for the next step without further purification; m.p.: 114–116 °C (Lit. 114.3 °C).34

\[ ^1H \text{ NMR (500 MHz, CDCl}_3): \delta = 8.11–7.79 (m, 1H, ArH), 7.57 (td, J = 7.6, 1.4 Hz, 1H, ArH), 7.47–7.29 m, 7H, ArH) \text{ ppm; } ^{13}C \text{ NMR (126 MHz, CDCl}_3): \delta = 173.5 (C=O), 143.5 (ArC), 141.1 (ArC), 132.2 (ArC), 131.3 (ArC), 130.8 (ArC), 129.4 (ArC), 128.6 (2 × ArC), 128.2 (2 × ArC), 127.5 (ArC), 127.3 (ArC) \text{ ppm.} \] The spectroscopic data are in agreement with the literature.34

General Procedure 20:

The desired biphenylic acid 287 (2 mmol) was dissolved in 5 mL of dry toluene. Thionyl chloride (4 mmol) and 1 drop of DMF were added. The mixture was stirred for 6 hours at
60 °C under N₂. Subsequently, the solvent and excess of thionyl chloride were removed under reduced pressure. The desired acyl chloride 288 was dissolved dry CH₂Cl₂ (1 mL) and added dropwise to an ice-cold solution of pyrrolidine 289 (2.2 mmol) and triethylamine (2.6 mmol) in dry CH₂Cl₂ (1 mL). The reaction was stirred at room temperature overnight then was diluted with CH₂Cl₂ and washed with 1 M HCl aqueous solution. The collected organic layers were washed with brine, dried over MgSO₄ and concentrated under reduced pressure to afford the desired amides 293a–b which were used for the Shono oxidation without further purification.

[1,1'-Biphenyl]-2-yl(pyrrolidin-1-yl)methanone 293a:

Performed according to General Procedure 20 on a 5.8 mmol scale of 288a; 293a (1.0 g, 4.0 mmol, 68% yield) was obtained as a colourless oil.

¹H NMR (500 MHz, CDCl₃): δ = 7.57–7.42 (m, 2H, ArH), 7.42–7.23 (m, 7H, ArH), 3.37 (br. s, 2H, C₂H₂), 2.71 (br. s, 2H, C₂H₂), 1.60 (br. s, 2H, C₂H₂), 1.42 (br. s, 2H, C₂H₂) ppm; ¹³C NMR (126 MHz, CDCl₃): δ = 169.8 (C=O), 140.0 (ArC), 138.3 (ArC), 136.9 (ArC), 129.5 (ArC), 129.4 (ArC), 128.5 (2 × ArC), 128.4 (2 × ArC), 127.7 (ArC), 127.6 (ArC), 127.2 (ArC), 47.5 (CH₂), 45.4 (CH₂), 25.6 (CH₂), 24.2 (CH₂) ppm. The spectroscopic data are in agreement with the literature.

[1,1'-Biphenyl]-2-yl(pyrrolidin-1-yl)methanone 293b:

Performed according to General Procedure 20 on a 2.0 mmol scale of 288b; 293b (396 mg, 1.4 mmol, 71% yield) was obtained as a colourless oil.

¹H NMR (500 MHz, CDCl₃): δ = 7.47–7.28 (m, 6H, ArH), 6.98 (td, J = 7.5, 1.0 Hz, 1H, ArH), 6.94 (d, J = 8.2 Hz, 1H, ArH), 3.77 (s, 3H, OCH₃), 3.36 (t, J = 7.0 Hz, 2H, CH₂), 2.98 (t, J = 6.7 Hz, 2H, CH₂), 1.75–1.47 (m, 4H, 2 × CH₂) ppm; ¹³C NMR (126 MHz, CDCl₃): δ = 169.7 (C=O), 156.3 (ArC–O), 137.9 (ArC), 135.5 (ArC), 131.6 (ArC), 131.3 (ArC), 129.2 (ArC), 128.6 (ArC), 127.5 (ArC), 127.1 (ArC), 120.7 (ArC), 110.8 (ArC), 55.6 (OCH₃), 47.9 (CH₂), 45.4 (CH₂), 25.9 (CH₂), 24.5 (CH₂) ppm.
General Procedure 21:

The carboxylic acid 287 (5 g, 17 mmol) was dissolved in 20 mL of dry toluene. Thionyl chloride (2.4 mL, 34 mmol) and 5 drops of DMF were added. The mixture was stirred for 6 hours at 60 °C under N₂ then the solvent and excess of thionyl chloride was removed under reduced pressure. The desired acyl chloride 288 was dissolved in dry THF (15 mL) and added dropwise to an ice-cold solution of L-amino acid (17 mmol) and KOH (2 g, 34 mmol). The solution was stirred at room temperature overnight. Once the reaction was completed, THF was removed under reduced pressure and the residue was partitioned into NaHCO₃ saturated aqueous solution (20 mL) and EtOAc (20 mL). The aqueous layer was acidified with HCl 1 M aqueous solution and the white precipitate was extracted with EtOAc (3 × 20 mL). The collected organic layers were washed with brine, dried over MgSO₄ and concentrated under reduced pressure and recrystallised from Et₂O and petroleum ether if needed. The products (S)-284a–f were isolated as colourless solids.

([1,1'-Biphenyl]-2-carbonyl)-L-proline (S)-284a:

Performed according to General Procedure 21 on a 8.5 mmol scale of 288a; (S)-284a (2.2 g, 7.5 mmol, 88% yield) was obtained as colourless crystals, m.p: 162–164 °C; [α]D²⁰ = –83.5° (c 0.93, MeOH).

¹H NMR (500 MHz, CDCl₃): δ = 7.63–7.33 (m, 9H, ArH), 4.46 (s, 1H, N–CH), 2.88 (s, 2H, CH₂), 2.34–2.10 (m, 1H, 1 × CH₂), 1.75–1.51 (m, 2H, CH₂), 1.35 (s, 1H, 1 × CH₂) ppm; ¹³C NMR (126 MHz, CDCl₃): δ = 173.6 (C=O), 171.5 (C=O), 139.4 (ArC), 134.4 (ArC), 130.6 (ArC), 129.8 (ArC), 128.9 (ArC), 128.5 (2 × ArC), 128.3 (2 × ArC), 128.1 (ArC), 127.6 (ArC), 60.4 (N–CH), 49.0 (N–CH₂), 27.3 (CH₂), 24.3 (CH₂) ppm; The spectroscopic data are in agreement with the literature.37
(2'-Methoxy-[1,1'-biphenyl]-2-carbonyl)-L-proline (S)-284b:

Performed according to General Procedure 21 on a 2.2 mmol scale of 288b; (S)-284b (672 mg, 2.1 mmol, 94% yield) was obtained as a colourless solid, m.p.: 68–70 °C; \([\alpha]_D^{20}\) = −78.0° (c 0.59, MeOH).

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 7.54–7.48 \text{ (m, } 1\text{H, Ar}H\)), 7.48–7.38 (m, 3H, ArH), 7.35 (ddd, \(J = 8.3, 7.5, 1.8 \text{ Hz, } 1\text{H, Ar}H\)), 7.31–7.17 (m, 1H, ArH), 7.02 (td, \(J = 7.5, 1.0 \text{ Hz, } 1\text{H, Ar}H\)), 6.95 (d, \(J = 8.3 \text{ Hz, } 1\text{H, Ar}H\)), 4.51 (br. s, 1H, N–C\(_H\)), 3.74 (s, 3H, OCH\(_3\)), 3.26 (br. s, 1H, 1×C\(_H_2\)), 3.11 (br. s, 1H, 1×C\(_H_2\)), 2.43 (br. s, 1H, 1×C\(_H_2\)) ppm;

\(^13\)C NMR (126 MHz, CDCl\(_3\)): \(\delta = 173.8 \text{ (C}=O), 171.1 \text{ (C}=O), 156.0 \text{ (Ar}=O), 134.9 \text{ (ArC), 131.6 (ArC), 131.3 (ArC), 130.2 (ArC), 129.9 (ArC), 128.2 (ArC), 127.5 (ArC), 127.0 (ArC), 121.0 (ArC), 110.9 (ArC), 60.5 (N–CH), 55.5 (N–CH), 49.6 (OCH\(_3\)), 27.1 (CH\(_2\)), 24.7 (CH\(_2\)) \text{ ppm; IR (neat): } \nu = 3439\text{w, 2949m, 1730s, 1591s, 1448s, 1421s, 1022s cm}^{-1};\) HRMS (ES): Exact mass calculated for C\(_{19}\)H\(_{20}\)NO\(_4\) [M+H]\(^+\) 326.1392; found 326.1404.

([1,1'-Biphenyl]-2-carbonyl)-L-alanine (S)-284c:

Performed according to General Procedure 21 on a 5.0 mmol scale of 288a; (S)-284c (1.3 g, 4.3 mmol, 86% yield) was obtained as a colourless solid, m.p.: 120–124 °C; \([\alpha]_D^{20}\) = −8.5 (c 1.4, MeOH).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 7.74 \text{ (dd, } J = 7.6, 1.2 \text{ Hz, } 1\text{H, Ar}H\)), 7.51 (td, \(J = 7.5, 1.5 \text{ Hz, } 1\text{H, Ar}H\)), 7.47–7.41 (m, 2H, ArH), 7.41–7.32 (m, 5H, ArH), 5.72 (d, \(J = 6.7 \text{ Hz, } 1\text{H, NH}\)), 4.49 (quin, \(J = 7.1 \text{ Hz, } 1\text{H, CH–CH}_3\)), 1.10 (d, \(J = 7.2 \text{ Hz, } 3\text{H, } CH_3\)) ppm; \(^13\)C NMR (101 MHz, CDCl\(_3\)): \(\delta = 175.9 \text{ (C}=O), 169.7 \text{ (C}=O), 140.2 \text{ (ArC), 140.1 (ArC), 134.3 (ArC), 130.9 (ArC), 130.5 (ArC), 129.2 (ArC), 128.9 (2 × ArC), 128.8 (2 × ArC), 128.1 (ArC), 127.9 (ArC), 48.7 (NCH), 17.3 (CH\(_3\)) \text{ ppm; IR (neat): } \nu = 3271\text{m, 3057m, 1718s, 1618s, 1518s, 1448s, 744s, 698s cm}^{-1};\) HRMS (ES): Exact mass calculated for C\(_{16}\)H\(_{15}\)NO\(_3\)Na [M+Na]\(^+\) 292.0950; found 292.0960.
([1,1'-Biphenyl]-2-carbonyl)-L-valine (S)-284d:

Performed according to General Procedure 21 on a 5.0 mmol scale of 288a; (S)-284d (1.1 g, 3.7 mmol, 74% yield) was obtained as a colourless solid, m.p.: 160–164 °C; \([\alpha]_D^{20} = -6.0^\circ (c 0.66, \text{MeOH})\).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 7.75–7.69 (m, 1H, \text{Ar} H), 7.49 (dt, J = 7.5, 3.8 Hz, 1H, \text{Ar} H), 7.45–7.30 (m, 7H, \text{Ar} H), 5.84 (d, J = 8.2 Hz, 1H, \text{N} H), 4.49 (dd, J = 8.3, 4.6 Hz, 1H, CH), 0.71 (d, J = 6.9 Hz, 3H, CH\(_3\)), 0.65 (d, J = 6.9 Hz, 3H, CH\(_3\)) ppm; \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta = 175.9 \ (\text{C}=\text{O}), 169.8 \ (\text{C}=\text{O}), 140.3 \ (\text{Ar} C), 139.9 \ (\text{Ar} C), 134.9 \ (\text{Ar} C), 130.6 \ (\text{Ar} C), 130.5 \ (\text{Ar} C), 129.1 \ (2 \times \text{Ar} C), 128.9 \ (2 \times \text{Ar} C), 128.6 \ (\text{Ar} C), 128.1 \ (\text{Ar} C), 127.8 \ (\text{Ar} C), 57.8 \ (\text{N} CH), 30.8 \ (\text{CH}), 18.8 \ (\text{CH}_3), 17.5 \ (\text{CH}_3)\) ppm. The spectroscopic data are in agreement with the literature.\(^38\)

([1,1'-Biphenyl]-2-carbonyl)-L-leucine (S)-284e:

Performed according to General Procedure 21 on a 10 mmol scale of 288a; (S)-284e (2.3 g, 7.4 mmol, 74% yield) was obtained as a colourless solid, m.p.: 90–94 °C; \([\alpha]_D^{20} = -17.7^\circ (c 1.1, \text{MeOH})\).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 7.74–7.71 (m, 1H, \text{Ar} H), 7.49 (dt, J = 7.5, 1.5 Hz, 1H, \text{Ar} H), 7.44–7.33 (m, 7H, \text{Ar} H), 5.67 (d, J = 7.7 Hz, 1H, NH), 4.50 (ddd, J = 9.2, 7.8, 5.2 Hz, 1H, CH), 1.53–1.35 (m, 1H, CH), 1.35–1.06 (m, 2H, CH\(_2\)), 0.79 (dd, J = 6.5, 4.1 Hz, 6H, 2\times CH\(_3\)) ppm; \(^{13}\)C NMR (126 MHz, CDCl\(_3\)): \(\delta = 176.5 \ (\text{C}=\text{O}), 169.9 \ (\text{C}=\text{O}), 140.3 \ (\text{Ar} C), 140.0 \ (\text{Ar} C), 134.6 \ (\text{Ar} C), 130.7 \ (\text{Ar} C), 130.5 \ (\text{Ar} C), 129.2 \ (\text{Ar} C), 128.9 \ (\text{Ar} C), 128.0 \ (4 \times \text{Ar} C), 127.8 \ (\text{Ar} C), 51.3 \ (\text{N} CH), 40.8, 24.5, 22.9, 21.9 ppm; IR (neat): v = 3306m, 2957m, 1705s, 1636s, 1510s, 1244s cm\(^{-1}\); HRMS (ES): Exact mass calculated for C\(_{19}\)H\(_{21}\)NO\(_3\)Na [M+Na]\(^+\) 334.1419; found 334.1430.

([1,1'-Biphenyl]-2-carbonyl)-L-phenylalanine (S)-284f:

Performed according to General Procedure 21 on a 8.5 mmol scale of 288a; (S)-284f (2.0 g, 5.8 mmol, 68% yield) was obtained as a colourless solid, m.p.: 134–136 °C; \([\alpha]_D^{20} = +1.8^\circ (c 1.1, \text{MeOH})\).

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 7.61 \ (d, J = 7.6 Hz, 1H, \text{Ar} H), 7.48 \ (t, J = 7.5 Hz, 1H, \text{Ar} H), 7.42–7.30 (m, 7H, \text{Ar} H), 7.24–7.15 (m, 3H, \text{Ar} H), 6.94–6.77 (m, 2H, \text{Ar} H), 5.83 \ (d, J = 7.3 Hz, 1H, NH), 4.85 \ (q, J = 6.3 Hz, 1H, NCH),
3.17–2.74 (m, 2H, CH₂) ppm; ¹³C NMR (126 MHz, CDCl₃): δ = 175.1 (C=O), 169.8 (C=O), 140.0 (ArC), 135.5 (ArC), 134.5 (ArC), 130.8 (ArC), 130.7 (ArC), 130.6 (ArC), 129.3 (2 × ArC), 129.0 (2 × ArC), 128.9 (ArC), 128.8 (2 × ArC), 128.8 (2 × ArC), 128.1 (ArC), 127.3 (ArC), 53.6 (NCH), 37.2 (CH₂) ppm. The spectroscopic data are in agreement with the literature.³⁷

Benzoyl-L-proline (S)-259:

Performed according to General Procedure 21 on a 10 mmol scale of benzyol chloride; (S)-259 (1.8 g, 8.2 mmol, 82% yield) was obtained as a colourless solid, m.p.: 146–148 °C; [α]₂₀°: −94.0° (c 1.0, MeOH).

¹H NMR (500 MHz, CDCl₃): δ = 9.04 (s, 1H, CO₂H), 7.57–7.52 (m, 2H, ArH), 7.50–7.37 (m, 3H, ArH), 4.73 (dd, J = 7.7, 5.9 Hz, 1H, 1 × CH₂), 3.63–3.49 (m, 2H, C₂H₂), 2.41–2.20 (m, 2H, CH₂), 2.10–1.95 (m, 1H, 1 × CH₂), 1.95–1.85 (m, 1H, 1 × CH₂) ppm; ¹³C NMR (126 MHz, CDCl₃): δ = 174.7 (C=O), 171.2 (C=O), 135.5 (ArC), 130.7 (ArC), 128.5 (2 × ArC), 127.4 (2 × ArC), 59.8 (NCH), 50.5 (NCH₂), 28.8 (CH₂), 25.3 (CH₂) ppm; The spectroscopic data are in agreement with the literature.³⁷

5.4.2 Synthesis of N,O-acetals

5.4.2.1 Enantioselective Synthesis

General Procedure 22:

The amino acid derivative (S)-259 or (S)-284 was dissolved in methanol (0.012–0.05 M) and pumped through the ion electrochemical microreactor at 0.2 mL·min⁻¹. Platinum was used as the cathode, graphite or glassy carbon as the anode (spacer: 0.5 mm; working electrode surface: 12 cm²). The current was fixed at 16–32 mA (2 F·mol⁻¹), and the temperature was maintained at −10 °C. The solution was collected over 90 minutes and the solvent was evaporated under reduced pressure. The desired N,O-acetals 260 or 285 were obtained after column chromatography (n-hexane/ethyl acetate, 8:2) as colourless oil or solid depending on the substrate.
(2-Methoxypyrrolidin-1-yl)(phenyl)methanone 260:

Performed according to General Procedure 22 on a 0.013 M methanol solution of (S)-259 using glassy carbon as anode; 260 (7.6 mg, 3.2 mM, 25% yield, 0% ee) was afforded as a colourless oil as a 1:1.5 mixture of rotamers.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 7.74–7.47 (m, 2H, ArH), 7.52–7.35 (m, 3H, ArH), 5.76 (s, 0.4H, NCH$_3$), 4.73 (s, 0.6H, NCH$_3$), 3.77–3.58 (m, 1.6H), 3.49 (s, 1.2H), 3.30 (s, 0.4H), 3.06 (s, 1.8H), 2.27–1.64 (m, 4H) ppm; $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ = 171.5 (C=O), 171.0 (C=O), 136.7 (ArC), 130.1 (ArC), 128.2 (ArC), 127.4 (ArC), 127.2 (ArC), 90.1, 87.5, 56.4, 54.1, 48.6, 45.5, 31.3, 30.6, 23.5, 21.0 ppm; HPLC analysis: $^1$D Varian Si-5 µm (250 × 4.6 mm) n-hexane/isopropanol 9:1 (v/v), 1.0 mL•min$^{-1}$, $\lambda$ = 254 nm, retention time 260 = 6.1 min; $^2$D DAICEL Chiralcel OB-H (250 × 4.6 mm, 5 µm), n-hexane/isopropanol 7:3 (v/v), 1.0 mL•min$^{-1}$, $\lambda$ = 254 nm, overall retention time major isomer = 12.4 min, retention time minor isomer = 14.0 min. The spectroscopic data are in agreement with the literature.39

Figure 5.17: HPLC chromatograms for the enantiomers of 260. From the top: $^1$D dimension and $^2$D for the racemic mixture.
(R)-[1,1'-Biphenyl]-2-yl(2-methoxypyrrrolidin-1-yl)methanone (R)-285a:

Performed according to General Procedure 22 on a 0.05 M methanol solution of (S)-284a using glassy carbon as anode; (R)-285a (102.8 mg, 0.026 M, 52% yield, 58% ee) was afforded as a colourless oil as a 1:2 mixture of rotamers; [α]D20 : −16.3° (c 1.7, CH₂Cl₂).

1H NMR (500 MHz, CDCl₃): δ = 7.62–7.30 (m, 9H, ArH), 5.46 (br. s, 0.4H, NC₃H), 4.31 (d, J = 4.1 Hz, 0.6H, NCH), 3.52 (ddd, J = 11.9, 9.4, 2.5 Hz, 0.7H), 3.40–3.29 (m, 1.7H), 2.78 (s, 2.2 H, OCH₃), 1.89–1.46 (m, 4H) ppm; 13C NMR (126 MHz): δ = 171.5 (C=O), 170.6 (C=O), 139.9 (ArC), 139.9 (ArC), 138.4 (ArC), 136.6 (ArC), 136.1 (ArC), 129.7 (ArC), 129.6 (ArC), 129.3 (ArC), 129.2 (ArC), 128.7 (ArC), 128.6 (ArC), 128.5 (ArC), 127.8 (ArC), 127.7 (ArC), 127.6 (ArC), 126.9 (ArC), 89.8 (NCH), 87.1 (NCH), 56.6 (OCH₃), 54.6 (OCH₃), 46.6 (NCH₂), 44.4 (NCH₂), 31.2, 22.5, 21.0 ppm; HPLC analysis (85:15 e.r.): ¹D Varian Si-5 µm (250 x 4.6 mm) n-hexane/isopropanol 9:1 (v/v), 1.0 mL•min⁻¹, λ = 254 nm, retention time 285a = 5.5 min; ²D DAICEL Chiralcel OD-H (250 x 4.6 mm, 5 µm), n-hexane/isopropanol 9:1 (v/v), 1.0 mL•min⁻¹, λ = 254 nm, retention time (R)-285a = 11.2 min, retention time (S)-285a = 13.1 min. The spectroscopic data are in agreement with the literature.⁴⁰

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Figure 5.18: ¹D HPLC chromatograms for 285a.

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Figure 5.19: ²D HPLC chromatograms for the enantiomers of 285a (racemic).
Figure 5.20: 2D HPLC chromatograms for the enantiomers of 285a (70% ee).

(R)-(2'-Methoxy-[1,1'-biphenyl]-2-yl)(2-methoxypyrrolidin-1-yl)methanone (R)-285b:

Performed according to General Procedure 22 on a 0.013 M methanol solution of (S)-284b using glassy carbon as anode; (R)-285b (15.9 mg, 3.6 mM, 28% yield, 50% ee) was afforded as a colourless oil as a 1:1.5 mixture of rotamers; \([\alpha]_D^{20} : -5.3^\circ\) (c 0.38, CH₂Cl₂).

1H NMR (500 MHz, CDCl₃): \(\delta = 7.60–7.23\) (m, 6H, ArH), 7.02–6.86 (m, 1H, 2H, ArH), 5.48 (d, \(J = 4.9\) Hz, 0.4H, NCH₂), 4.54 (d, \(J = 4.4\) Hz, 0.6H, NCH₂), 3.85–3.62 (m, 3H, OCH₃), 3.56–3.05 (m, 3.2H), 2.85 (s, 1.8H), 1.99–1.47 (m, 4H) ppm;

13C NMR (126 MHz, CDCl₃): \(\delta = 171.4\) (C=O), 170.6 (C=O), 156.2 (ArC–O), 156.2 (ArC–O), 137.3 (ArC), 136.9 (ArC), 135.7 (ArC), 135.3 (ArC), 131.6 (ArC), 131.5 (ArC), 131.4 (ArC), 131.1 (ArC), 129.4 (ArC), 129.3 (ArC), 128.8 (ArC), 128.8 (ArC), 128.7 (ArC), 128.6 (ArC), 127.4 (ArC), 127.3 (ArC), 126.7 (ArC), 120.8 (ArC), 120.7 (ArC), 110.9 (ArC), 110.8 (ArC), 89.8 (CH), 86.9 (CH), 56.3, 55.5, 55.4, 54.8, 47.0, 44.5, 31.7, 31.4, 22.9, 21.1 ppm; IR (neat): \(\nu = 3061\)w, 2926m, 2853w, 1632s, 1402s, 1254s, 1080s, 908m, 750s, 729s cm⁻¹; HRMS (ES): Exact mass calculated for C₁₉H₂₁NO₃Na \([M+Na]^+\) 334.1419; found 334.1410; HPLC analysis (75:25 e.r.): 1D Varian Si-5 \(\mu\)m (250 \(\times\) 4.6 mm) n-hexane/isopropanol 9:1 (v/v), 1.0 mL•min⁻¹, \(\lambda = 254\) nm, retention time 285b = 6.3 min; 2D YMC Chiral Amylose-C (250 \(\times\) 4.6 mm, 5 \(\mu\)m), n-hexane/isopropanol 85:15 (v/v), 1.0 mL•min⁻¹, \(\lambda = 254\) nm, overall retention time major isomer = 13.4 min, retention time minor isomer = 14.2 min. The HPLC chromatograms are reported in literature.⁴¹
(R)-[1,1'-Biphenyl]-2-yl(2-ethoxypyrrolidin-1-yl)methanone (R)-**285**c:

Performed according to *General Procedure 22* on a 0.013 M ethanol solution of (R)-**284a** using graphite as anode; (R)-**285**c (27.6 mg, 6.9 mM, 53% yield, 23% ee) was afforded as a 1:2.3 mixture of rotamers; \([\alpha]_D^{20} = -7.6^\circ\) (c 0.53, CH<sub>2</sub>Cl<sub>2</sub>).

**1H NMR** (500 MHz, CDCl<sub>3</sub>): \(\delta = 7.66–7.27\) (m, 9H, ArH), 5.55 (br. s, 0.3H, NC<sub>H</sub>), 4.40 (br. s, 0.7H, NC<sub>H</sub>), 3.70–3.43 (m, 1.1H), 3.41–3.21 (m, 0.7H), 3.09–2.90 (m, 1H), 2.87–2.68 (m, 1H), 1.98–1.35 (m, 4H), 1.10 (br. s, 0.9H), 0.84 (t, \(J = 7.0\) Hz, 2.1H, 3H) ppm; \(^{13}\)C NMR (126 MHz, CDCl<sub>3</sub>): \(\delta = 171.4\) (C=O), 170.6 (C=O), 140.0 (ArC), 140.0 (ArC), 138.5 (ArC), 136.8 (ArC), 136.3 (ArC), 129.8 (ArC), 129.7 (ArC), 129.4 (ArC), 129.2 (ArC), 128.8 (ArC), 128.7 (ArC), 128.7 (ArC), 128.5 (ArC), 127.8 (ArC), 127.7 (ArC), 127.6 (ArC), 127.0 (ArC), 88.3 (NCH), 85.7 (NCH), 64.4 (OCH<sub>2</sub>), 62.5 (OCH<sub>2</sub>), 46.4, 44.6, 31.9, 31.7, 22.6, 21.2, 15.5, 14.8 ppm; IR (neat): \(v = 3055\)w, 2974m, 2882w, 1630s, 1402s, 1070s, 733s, 700s cm<sup>-1</sup>; HRMS (ES): Exact mass calculated for C<sub>19</sub>H<sub>21</sub>NO<sub>2</sub>Na [M+Na]<sup>+</sup> 318.1470; found 318.1456; HPLC analysis (80:20 e.r.):

1D Varian Si-5 \(\mu\)m (250 \times 4.6 mm) n-hexane/isopropanol 9:1 (v/v), 1.0 mL•min<sup>-1</sup>, \(\lambda = 254\) nm, retention time **285**c = 4.9 min; 2D DAICEL Chiralcel OD-H (250 \times 4.6 mm, 5 \(\mu\)m), n-hexane/isopropanol 9:1 (v/v), 1.0 mL•min<sup>-1</sup>, \(\lambda = 254\) nm, overall retention time major isomer = 9.9 min, retention time minor isomer = 11.3 min. The HPLC chromatograms are reported in literature.<sup>41</sup>

(R)-[1,1'-Biphenyl]-2-yl(2-isopropoxypyrrolidin-1-yl)methanone (R)-**285**d:

Performed according to *General Procedure 22* on a 0.013 M propan-2-ol solution of (S)-**284a** using graphite as anode; (R)-**285**d (22.6 mg, 5.2 mM, 40% yield, 42% ee) was afforded as a colourless oil as a 1:2 mixture of rotamers; \([\alpha]_D^{20} = -22.7^\circ\) (c 0.26, CH<sub>2</sub>Cl<sub>2</sub>).

**1H NMR** (500 MHz, CDCl<sub>3</sub>): \(\delta = 7.61–7.30\) (m, 9H, ArH), 5.62 (br. s, 0.3H, NCH), 4.46 (br. s, 0.7H, NCH<sub>H</sub>), 3.97 (br. s, 0.3H), 3.66–3.50 (m, 0.7H), 3.27 (d, \(J = 9.4\) Hz, 0.7H), 3.07 (hept, \(J = 6.1\) Hz, 0.7H), 2.93 (s, 0.2H), 2.87–2.70 (m, 0.3H), 1.97–1.29 (m, 4H), 1.23–0.46 (m, 6H, 2 \times C<sub>H</sub>); ppm; \(^{13}\)C NMR (126 MHz, CDCl<sub>3</sub>): \(\delta = 170.3\) (C=O), 139.9 (ArC), 36.3 (ArC), 129.6 (ArC), 129.2 (ArC), 128.7 (ArC), 128.6 (ArC), 128.5 (ArC), 128.5 (ArC), 127.7 (ArC), 127.6 (ArC), 127.6 (ArC), 126.9 (ArC), 85.8 (NCH), 67.6 (OCH<sub>2</sub>), 46.4, 44.5, 32.3, 32.1, 23.4, 22.5, 22.1, 21.5, 21.0 ppm; IR (neat): \(v = 2970\)m, 1736s, 1616s, 1416s, 741s, 700s cm<sup>-1</sup>; HRMS (ES): Exact mass calculated for C<sub>20</sub>H<sub>23</sub>NO<sub>2</sub>Na [M+Na]<sup>+</sup> 332.1626; found 332.1631; HPLC analysis (84:16 e.r.):
Micol Santi  Experimental Part

1D Varian Si-5 μm (250 × 4.6 mm) n-hexane/isopropanol 9:1 (v/v), 1.0 mL•min⁻¹, λ = 254 nm, retention time 285d = 4.7 min; 2D DAICEL Chiralcel OD-H (250 × 4.6 mm, 5 μm), n-hexane/isopropanol 9:1 (v/v), 1.0 mL•min⁻¹, λ = 254 nm, overall retention time major isomer = 9.2 min, retention time minor isomer = 10.5 min. The HPLC chromatograms are reported in literature.41

(R)-N-(1-Methoxyethyl)-[1,1'-biphenyl]-2-carboxamide (R)-285e:

Performed according to General Procedure 22 on a 0.05 M methanol solution of (S)-284c using glassy carbon as anode; (R)-285e (39.1 mg, 0.012 M, 23% yield, 8% ee) was afforded as a colourless solid, m.p.: 82–84 °C; [α]D 20: +2.9° (c 0.69, CH₂Cl₂).

1H NMR (500 MHz, CDCl₃): δ = 7.73 (ddd, J = 7.6, 1.5, 0.4 Hz, 1H, ArH), 7.54–7.47 (m, 1H, ArH), 7.46–7.33 (m, 7H, ArH), 5.36 (d, J = 9.1 Hz, 1H NH), 5.18 (dq, J = 9.5, 5.9 Hz, 1H, NH), 3.19 (s, 3H, OCH₃), 0.91 (d, J = 5.9 Hz, 3H, CH₃) ppm;

13C NMR (126 MHz, CDCl₃): δ = 169.5 (C=O), 140.3 (ArC), 139.6 (ArC), 135.5 (ArC), 130.5 (ArC), 130.4 (ArC), 129.0 (ArC), 128.9 (2 × ArC), 128.8 (2 × ArC), 128.1 (ArC), 127.8 (ArC), 78.2 (NCH), 55.7 (OCH₃), 21.0 (CH₃) ppm; IR (neat): ν = 3289m, 3059w, 2984m, 2932m, 1647s, 1508s, 1088s, 910s, 729s, 698s cm⁻¹; HRMS (EI): Exact mass calculated for C₁₆H₁₇NO₂ [M]+ 255.1259; found 255.1252.

HPLC analysis (55:43 e.r.):

1D Varian Si-5 μm (250 × 4.6 mm) n-hexane/isopropanol 9:1 (v/v), 1.0 mL•min⁻¹, λ = 254 nm, retention time 267e = 5.0 min; 2D YMC Chiral Amylose-C (250 × 4.6 mm, 5 μm), n-hexane/isopropanol 85:15 (v/v), 1.0 mL•min⁻¹, λ = 254 nm, overall retention time major isomer = 10.9 min, retention time minor isomer = 13.7 min. The HPLC chromatograms are reported in literature.41

(R)-N-(1-Methoxy-2-methylpropyl)-[1,1'-biphenyl]-2-carboxamide (R)-285f:

Performed according to General Procedure 22 on a 0.05 M methanol solution of (S)-284d using glassy carbon as anode; (R)-285f (70.2 mg, 0.035 M, 69% yield, 7% ee) was afforded as a colourless solid, m.p.: 98–100 °C; [α]D 20: +23.5° (c 0.17, MeOH).

1H NMR (500 MHz, CDCl₃): δ = 7.72 (ddd, J = 7.6, 1.5, 0.5 Hz, 1H, ArH), 7.49 (td, J = 7.5, 1.5 Hz, 1H, ArH), 7.46–7.39 (m, 5H, ArH), 7.39–7.33 (m, 2H, ArH), 5.48 (d, J = 9.7 Hz, 1H, NH), 4.89 (dd, J = 9.8, 5.1 Hz, 1H, NH), 3.18 (s, 3H, OCH₃), 1.58–1.48 (m, 1H, CH) 0.66 (d, J = 6.9 Hz, 3H, CH₃), 0.64 (d, J = 6.8 Hz, 3H, CH₃) ppm;

13C NMR (126 MHz, CDCl₃): δ = 170.0 (C=O), 140.5 (ArC), 139.6 (ArC), 135.8 (ArC),
Experimental Part

Micol Santi

130.6 (ArC), 130.3 (ArC), 128.9 (2 × ArC), 128.9 (2 × ArC), 128.8 (ArC), 128.1 (ArC), 127.8 (ArC), 85.3 (NCH), 56.3 (OCH3), 32.8(CH), 17.1 (CH3), 17.0 (CH3) ppm; IR (neat): v = 3280m, 3057w, 2958m, 2924m, 1647s, 1502s, 1146m, 1088s, 744s, 698s cm⁻¹;
HRMS (ES): Exact mass calculated for C18H21NO2Na [M+Na]⁺ 306.1470; found 306.1472; HPLC analysis (53:46 e.r.): ¹D Varian Si-5 µm (250 × 4.6 mm) n-hexane/isopropanol 9:1 (v/v), 1.0 mL·min⁻¹, λ = 254 nm, retention time 285f = 4.0 min;
²D YMC Chiral Amylose-C (250 × 4.6 mm, 5 µm), n-hexane/isopropanol 85:15 (v/v), 1.0 mL·min⁻¹, λ = 254 nm, overall retention time major isomer = 9.6 min, retention time minor isomer = 11.6 min. The HPLC chromatograms are reported in literature.⁴¹

(R)-N-(1-Methoxy-3-methylbutyl)-[1,1'-biphenyl]-2-carboxamide (R)-285g:

Performed according to General Procedure 22 on a 0.05 M methanol solution of (S)-284e using glassy carbon as anode; (R)-285g (26.7 mg, 6.9 mM, 14% yield, 14% ee) was afforded as a colourless solid, m.p.: 86–88 °C; [α]D²⁰: +4.0° (c 0.50, CH2Cl2).

¹H NMR (500 MHz, CDCl3): δ = 7.70 (ddd, J = 7.6, 1.5, 0.5 Hz, 1H, ArH), 7.49 (td, J = 7.5, 1.5 Hz, 1H, ArH), 7.45–7.40 (m, 5H, ArH), 7.39–7.34 (m, 2H, ArH), 5.38 (d, J = 9.4 Hz, 1H, NH), 5.11 (ddd, J = 9.7, 7.1, 6.0 Hz, 1H, NCH), 3.21 (s, 3H, OCH3), 1.38 (tq, J = 13.1, 6.5 Hz, 1H, 1 × CH₂), 1.19 (dt, J = 14.1, 7.1 Hz, 1H, 1 × CH₂), 0.93 (ddd, J = 7.8, 6.9, 3.2 Hz, 1H, CH₂), 0.81 (dd, J = 6.6, 0.9 Hz, 6H, 2 × CH₃) ppm; ¹³C NMR (126 MHz, CDCl3): δ = 169.8 (C=O), 140.4 (ArC), 139.6 (ArC), 135.7 (ArC), 130.5 (ArC), 130.4 (ArC), 128.9 (2 × ArC), 128.9 (2 × ArC), 128.7 (ArC), 128.0 (ArC), 127.8 (ArC), 80.2 (NCH), 56.0 (OCH3), 44.2, 24.3, 22.8, 22.5 ppm; IR (neat): v = 3283m, 2955m, 1665s, 1508s, 1366m, 1148m, 1148m, 1095m, 1061m, 735s, 698s cm⁻¹;
HRMS (ES): Exact mass calculated for C19H23NO2Na [M+Na]⁺ 320.1626; found 320.1629; HPLC analysis (57:43 e.r.): ¹D Varian Si-5 µm (250 × 4.6 mm) n-hexane/isopropanol 9:1 (v/v), 1.0 mL·min⁻¹, λ = 254 nm, retention time 285g = 4.0 min;
²D YMC Chiral Amylose-C (250 × 4.6 mm, 5 µm), n-hexane/isopropanol 85:15 (v/v), 1.0 mL·min⁻¹, λ = 254 nm, overall retention time major isomer = 8.9 min, retention time minor isomer = 11.6 min. The HPLC chromatograms are reported in literature.⁴¹
(R)-N-(1-Methoxy-3-methylbutyl)-[1,1’-biphenyl]-2-carboxamide (R)-285h:

Performed according to General Procedure 22 on a 0.05 M methanol solution of (S)-284f using glassy carbon as anode; (R)-285h (47.4 mg, 0.033 M, 67% yield, 12% ee) was afforded as a colourless solid, m.p.: 118–120 °C; [α]_D^{20} +4.2° (c 0.95, CH₂Cl₂).

1H NMR (500 MHz, CDCl₃): δ = 7.58 (ddd, J = 7.6, 1.4, 0.4 Hz, 1H, ArH), 7.48 (td, J = 7.5, 1.4 Hz, 1H, ArH), 7.45–7.34 (m, 7H, ArH), 7.26–7.18 (m, 3H, ArH), 7.01–6.94 (m, 2H, ArH), 5.50 (d, J = 9.5 Hz, 1H, NCH), 5.36 (ddd, J = 9.6, 6.4, 4.5 Hz, 1H, NCCH), 3.17 (s, 3H, OC₃H₃), 2.65 (dd, J = 14.0, 4.4 Hz, 1H, 1×CH₂), 2.54 (dd, J = 14.0, 6.3 Hz, 1H, 1×CH₂) ppm; 13C NMR (126 MHz, CDCl₃): δ = 169.9 (C=O), 140.3 (ArC), 139.5 (ArC), 135.9 (ArC), 135.7 (ArC), 130.5 (ArC), 130.4 (ArC), 129.8 (2×ArC), 128.8 (2×ArC), 128.7 (ArC), 128.4 (ArC), 128.1 (ArC), 127.7 (ArC), 126.8 (ArC), 81.2 (NCH), 56.2 (OCH₃), 41.2 (CH₂) ppm; IR (neat): ν = 3227m, 3055m, 3022m, 2955m, 2928m, 1641s, 1530s, 1099s, 1067s, 862s, 742s, 696s cm⁻¹; HRMS (ES): Exact mass calculated for C₂₁H₁₈NO [M−OMe+H]⁺ 300.1388; found 300.1377; HPLC analysis (55:44 e.r.): ¹D Varian Si-5 μm (250 × 4.6 mm) n-hexane/isopropanol 9:1 (v/v), 1.0 mL·min⁻¹, λ = 254 nm, retention time 285h = 4.4 min; ²D YMC Chiral Amylose-C (250 × 4.6 mm, 5 μm), n-hexane/isopropanol 85:15 (v/v), 1.0 mL·min⁻¹, λ = 254 nm, overall retention time major isomer = 11.7 min, retention time minor isomer = 14.8 min. The HPLC chromatograms are reported in literature.⁴¹

6H-Benzoc[c]chromen-6-one 294:

Afforded as a side product. Colourless solid, m.p.: 84–86 °C.

¹H NMR (500 MHz, CDCl₃): δ = 8.41 (ddd, J = 7.9, 1.4, 0.6 Hz, 1H, ArH), 8.18–8.09 (m, 1H, ArH), 8.08 (dd, J = 7.9, 1.5 Hz, 1H, ArH), 7.84 (ddd, J = 8.1, 7.3, 1.4 Hz, 1H, ArH), 7.66–7.50 (m, 1H, ArH), 7.52–7.44 (m, 1H, ArH), 7.36 (dddd, J = 9.2, 8.0, 4.2, 0.8 Hz, 2H, ArH) ppm; ¹³C NMR (126 MHz, CDCl₃): δ = 161.4 (C=O), 151.4 (ArC−O), 135.0, 134.9, 130.7, 130.6, 129.0, 124.7, 122.9, 121.8, 121.4, 118.2, 118.0 ppm. The spectroscopic data are in agreement with the literature.⁴²

5.4.2.2 Synthesis of Racemates:

Rac-285a,b,c and d were synthesised via Shono oxidation from 293a–b following the procedure reported in literature.³⁵

Rac-285e–h were obtained via non-Kolbe reaction starting from achiral 284c–f.
5.4.3 DoE-assisted Optimisation

For the electrochemical step, an Ion Electrochemical reactor design by Vapourtec was used combined to a R-Series modular system. The solution was pumped using a Chemyx Fusion 200 syringe pump and the reactor was powered up by an Aim-tti bench power supply (300 Watt). The offline or online analysis was performed using an Agilent 1290 Infinity 2DLC system. The DoE was performed using Design Expert.⁹

Table 5.3: 'D-HPLC calibration curve of the product 285a.

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<th>Area Int Std (mAU)</th>
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General HPLC protocol: Varian Si 250 × 4.6 mm, 5 µm pore size, i-PrOH / n-hexane 1:9, 1 mL·min⁻¹, 20 °C, λ = 254 nm; Int Std = internal standard (α,α,α-trifluorotoluene as internal standard).
Table 5.4: Real and coded values (+1 = higher level, −1 = lower level, 0 = central point) for the independent variables (k) and responses.

<table>
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<th>Factor (k)</th>
<th>Type</th>
<th>Unit</th>
<th>−1</th>
<th>0</th>
<th>+1</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: (S)-284a</td>
<td>Numeric</td>
<td>mM</td>
<td>6.25</td>
<td>9.37</td>
<td>12.5</td>
</tr>
<tr>
<td>B: Anode</td>
<td>Categoric</td>
<td>graphite</td>
<td>−</td>
<td>−</td>
<td>glassy C</td>
</tr>
<tr>
<td>C: Flow rate</td>
<td>Numeric</td>
<td>mL•min⁻¹</td>
<td>0.1</td>
<td>0.15</td>
<td>0.2</td>
</tr>
<tr>
<td>D: Charge</td>
<td>Numeric</td>
<td>F•mol⁻¹</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>E: Temperature</td>
<td>Numeric</td>
<td>°C</td>
<td>−10</td>
<td>5</td>
<td>20</td>
</tr>
</tbody>
</table>

Responses: 285a yield (%)<sup>a</sup> 285a ee (%)<sup>b</sup>

<sup>a</sup>Yield determined by <sup>1</sup>H NMR by HPLC using α,α,α-trifluorotoluene as internal standard; <sup>b</sup>Determined by chiral HPLC.

Table 5.5: Experimental Matrix of the FFD 2⁵⁻¹ in coded values and factor generator E = A•B•C•D

<table>
<thead>
<tr>
<th>Std</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E = A•B•C•D</th>
</tr>
</thead>
<tbody>
<tr>
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<td>−1</td>
<td>−1</td>
<td>−1</td>
<td>+1</td>
</tr>
<tr>
<td>2</td>
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<td>−1</td>
<td>−1</td>
<td>−1</td>
<td>−1</td>
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<td>+1</td>
<td>−1</td>
<td>−1</td>
<td>−1</td>
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<td>−1</td>
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<td>level 1</td>
<td>0</td>
<td>0</td>
<td>0 - level 1</td>
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<tr>
<td>18</td>
<td>0</td>
<td>level 2</td>
<td>0</td>
<td>0</td>
<td>0 - level 2</td>
</tr>
</tbody>
</table>

Table 5.4 entries 1 and 3 gave lower yield and ee% than expected, that were very influential according to the Cook’s distance and other diagnostic plot, leading to a complex model with several significant terms and anomalous diagnostic plots.
Figure 5.21: Cook’s distance plot (yield).

Figure 5.22: Residuals vs predicted diagnostic plot; “funnel” shape.
Figure 5.23: Half-normal plots for yield% and ee% considering all experiments.

After several repeats of the experiments and a careful evaluation, it was decided to not include the two experiments (Table 5.4 entries 1 and 3) as they were leading into a less interesting part of the chemical space (low yield and low ee). The ANOVA is reported in literature.41
Figure 5.24: Half-normal plots for yield% and ee% without Std 1 and 3.
5.4.4 Cyclic Voltammetry

![Graph showing cyclic voltammograms](image)

**Figure 5.25:** Oxidative cyclic voltammograms of the model substrate 285a (5 mM) recorded in 0.1 M $n$-Bu$_4$NCIO$_4$/MeOH electrolyte at 20 mV/s scan rate (top) and solvent background (bottom). Working electrode: glassy carbon electrode tip (3 mm diameter); Counter electrode: platinum wire; Reference electrode: Ag/AgCl in 3 M NaCl.

$E_{p^{ox}} = +2.05$ V
References

9. The software can be found at: https://www.statease.com/software/design-expert. A copy of the design files (.dxpx) was submitted to Cardiff University together with this manuscript.
Appendix A: Glossary of DoE Terminology

Herein a glossary of terminologies and definitions regarding Design of Experiment is reported.¹

**2-Level Design**: It is a set of experiments where all the factors are set at one of two levels (low = −1; high = +1).

**Alias (Aliasing)**: When the estimate of an effect also includes the influence of one or more other effects (e.g.: high order interactions), and they cannot be separated and assigned. The effects are said to be “aliased”.

**Analysis of Variance (ANOVA)**: A mathematical process that measures whether a factor contributes significantly to the variance of a response and which amount of variance is due to pure error.

**Axial Point**: In a Central Composite Design (CCD) are those points that distance from the centre of a cube to a star portion of the design. The star portion of the design consists of an additional set of points arranged at equal distances from the centre of the cube on radii that pass through the centre point in the face of the cube. They afford an estimate of the experimental error variance to the entity of the curvature.

**Balanced Design**: An experimental design where all points have the same number of observations.

**Blocking**: It is achieved by restricting randomisation by blocking the experiments into homogenous groups. The reason for blocking is to isolate a systematic effect (nuisance) and prevent it from obscuring the main effects (e.g.: blocks can be created when it is necessary to include new batches of raw material, different laboratories, etc…). The runs must be randomised within the blocks.

**Central Composite Design (CCD)**: A 3-level design that starts with a 2-level factorial and some centre points. Used typically for quantitative factors and designed to estimate all the main effects plus the desired quadratics and two-factor interactions (2FI).

**Central Point**: Are design points at which all the continuous factors are run halfway between their high and low levels. The centre points can be used to check for curvature in screening designs as well as to add additional runs to experiments (Repeats) to estimate pure error.
**Coded Value:** It is generated by transforming the scale of measurement for a factor so that the high value becomes +1 and the low value becomes −1. Coding is a simple linear transformation of the original measurement scale. The coded values are used for convenience of computation and comparison of effects between different factors.

**Confounding:** Confusing two or more factors so their main effects cannot be separated (see Aliasing). Confounding designs naturally arise when full factorial designs have to be run in blocks and the block size is too small. They also occur whenever a fractional factorial design is chosen instead of a full factorial design.

**Contour Plot:** A plot that represents a two-dimensional grid surface similar to a topographical map. In experimental design, the contours represent the estimated level of the response variable.

**Curvature:** The degree of curving for a line or surface.

**Design:** A set of experimental runs which allows you to fit a particular model and estimate the desired effects.

**Design Matrix:** It is a compact representation of the experiments to run, which shows the factors level combinations and associated response values in a table.

**Design of Experiment (DoE):** It is a statistical technique that allows you to run the minimum number of experiments to optimise your product or process. It is defined by a list of experiments to run in order to fit the mathematical model.

**Design Points:** An intended experimental run.

**Diagnostic Plot:** is a scatterplot of the prediction errors (residuals) against the predicted values and is used to see if the predictions can be improved by fixing problems in your data.

**Effect:** It is the change in the average of the responses between two factor-level combinations or two experimental settings. For a factor A with two levels, scaled so that low = −1 and high = +1, the effect of A is estimated by subtracting the average response when A is −1 from the average response when A = +1 and dividing the result by 2. It gives an estimate of how changing the settings of a factor changes the response. The effect of a single factor is also called a *Main Effect*.

**Error:** Unexplained variation in a collection of observations.

**F-Ratio:** A ratio of the variance explained by a factor to the unexplained variance. If there is no effect, the associated *p*-value is close to 1.
**Factor:** It is a parameter (input) which is deliberately varied in an experiment in order to determine its effect on one or more responses (output). Some factors cannot be controlled by the experimenter but may affect the responses. If their effect is significant, these uncontrolled factors should be measured and used in the data analysis. The inputs can be:

**Numerical:** Are quantitative variables which can be:
- **Continuous:** Are numerical variables in which infinite number of values between two given point are accepted.
- **Discrete:** Are numerical variables that have a countable number of values within the limits.

**Categoric:** Are qualitative variables which contain a finite number of categories or distinct groups, which may not have a logical order (e.g. material types, solvent types).

**Face-Centered Design (FCD):** A central composite design (CCD) with three levels and with axial points at the centre of the faces of the factorial cube instead of the curve.

**Factor Range:** It is the range of values within the highest and the lowest levels.

**Factorial Generator:** Equations that indicate the columns that must be multiplied to produce the last columns in a Fractional Factorial Design (FFD).

**Factorial Point:** Are the points are the extremes, used to estimate the coefficients of the linear and the interaction terms.

**Fractional Factorial Design (FFD):** Differs from a Full Factorial Design (FD) as the FFD does not specify all the combinations of the factors. Instead, the operator uses a subset of a FD (number of experiments = $2^{k-n}$, with $k$ being the number of factor and $n$ the number of Factorial Generator).

**Full Factorial (FD):** A design that combines the levels for each factor with all the levels for every other factor (number of experiments = $2^k$, with $k$ being the number of factors).

**Graphical Optimisation:** It is used to simultaneously optimised multiple responses by overlapping the contour plots of every response. The area in which the optimal criteria for each response is satisfied (Sweet Spot) is usually highlighted.

**Half-Normal Plot:** It is a graphical tool that uses ordered estimated effects to assess which factors are important (larger than the noise) and which are unimportant. Large effects appear on the right side of the plot.
**Hard-to-Change (HTC):** Are factors that are hard to change quickly and might restrict the randomisation.

**Interaction Effect:** Occurs when a change in the response depends on the combination of multiple factors levels. An interaction involving two factors is known as a two-factor interaction (2FI), three factors as a three-factor interaction (etc).

**Lack of Fit Error:** Error that occurs when the analysis omits one or more important terms or factors from the process model.

**Main Effect:** A measure that estimates the influence of a single factor on a response when the factor is changed from one level to another.

**Model:** Mathematical relationship which relates changes in a measured response to changes in one or more factors.

**Noise:** Any unexplained or random variability in the response.

**Normal distribution:** The “bell-shaped” curve distribution used to calculate probabilities of events that tend to occur around a mean value and trail off with decreasing likelihood (Gaussian Distribution).

**Normal Plot:** It is a graphical tool that uses ordered estimated effects to assess which factors are important (larger than the noise) and which are unimportant. A default plot is shown in which it is assumed there are no significant parameters, hence all the points fall on a straight line. Any points that fall away from the line indicate real effects.

**Nuisance Variable:** Factors that are not included or cannot be controlled in a design that will can distort the results, if not held constant or controlled through randomisation.

**One factor at a time (OFAT):** A method where one factor is changed while all the others are kept constant. The method ignores the possibility of interactions.

**One variable at a time (OVAT):** synonym of OFAT

**Orthogonality:** A design where the correlation between factors is zero which means that all estimates can be obtained independently of one another.

**Outlier:** It is a data point that does not fit the model.

**p-Value:** The probability value or p-value is the probability of obtaining test results at least as extreme as the results actually observed during the test, assuming that the null hypothesis is correct (p-value > 0.05 are statistically insignificant; p-value < 0.05 are statistically significant).
**Pareto Chart:** A graph that shows the amount of influence each factor has on the response in order of decreasing influence.

**Pure Error:** The sums of squares from replicated environmental runs. Pure error provides an opportunity to test for lack-of-fit in the fitted model.

**Randomisation:** A system of using random numbers to evenly spread the effects of factors not included in an experiment (nuisance variables). Randomisation is necessary for conclusions to be correct, unambiguous and defensible.

**Repeat:** Performing the same treatment combination more than once.

**Replicate:** Is a duplicate set of complete runs from the complete design.

**Resolution:** Measure of the degree of confounding. Low-resolution designs are highly confounded and can only give limited information about the system under investigation.

**Response:** It is the property of the system that is being measured (output). For example, yield, purity, ee%.

**Response Surface Methodology (RSM):** A DoE that fully explores the process window and models the responses. Note: These designs are most effective when there are less than 5 factors. Quadratic models are used for response surface designs and at least three levels of every factor are needed in the design.

**Run:** A set of experimental conditions in which each of the factors is held at a specific level.

**Screening Experiments:** A screening experiment is used to identify the significant few factors that contribute the most to response variation.

**Sweet Spot:** In a graphical optimisation is the area in which the optimal criteria for each response is satisfied.

**Treatment Combination:** It is a set of factors and their levels; in other words, it is an entry of the design matrix.

**Variable:** Synonym of Factor

---

## Appendix B: Kinetic Data Table for 185a Formation

<table>
<thead>
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<th>Entry</th>
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<th>227 (%)</th>
<th>228 (%)</th>
<th>185a (%)</th>
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Kinetic study for the formation of lactone 185a. The reaction between 184a (0.05 mmol) and 106e (0.05 mmol) was run and in situ ¹H NMR (500 MHz, CDCl₃) spectra were measured at different time intervals using mesitylene as the internal standard; Ar = 3,4,5-F₃C₆H₂.