Applications of Hypervalent Iodine Reagents: From Enantioselective Copper-Catalysed Arylation-Semipinacol Cascade to Methionine Functionalisation for Peptide Macrocyclisation

Daniel Hartoyo Lukamto

A dissertation submitted in partial fulfilment of the requirements for the award of the degree of

Doctor of Philosophy

University of Cambridge

April 2018
Declaration

This thesis is submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy. It describes work carried out in the Department of Chemistry from May 2014 to April 2018. This dissertation is the result of my own work and includes nothing that is the outcome of work done in collaboration except as declared in the Preface and specified in the text.

It is not substantially the same as any that I have submitted, or, is being concurrently submitted for a degree or diploma or other qualification at the University of Cambridge or any other University or similar institution except as declared in the Preface and specified in the text. I further state that no substantial part of my dissertation has already been submitted, or, is being concurrently submitted for any such degree, diploma or other qualification at the University of Cambridge or any other University or similar institution except as declared in the Preface and specified in the text.

Daniel Hartoyo Lukamto

Date: 13 April 2018
Statement of Length

This thesis does not exceed the prescribed word limit of 60,000 as set by the Degree Committee for the faculty of Physics and Chemistry.

Daniel Hartoyo Lukamto

Date: 13 April 2018
Acknowledgements

First and foremost, I would like to thank my parents for their unwavering support throughout the course of my study. Without them, I would never be where I am today.

In Cambridge, I’ve met and interacted with some of the world’s best scientists and aspiring scientists, and it has been a great pleasure to be inspired by their brilliant minds. My PhD supervisor, Professor Matthew J. Gaunt – one of the leaders in chemistry, has not only provided me with the opportunity to study under his tutelage but has also taught me valuable life lessons. In particular, leadership as exemplified by his actions. Watching him lead the group through several events (2014-2018) such as lab moves, various scientific discussions, people management and other ad hoc activities, has provided me with insights that I will carry through the rest of my career. His support for my scientific learning and thirst for discovery has not only made my PhD journey insightful and transformational, but more importantly, fun.

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Last but not least, I would like to thank whoever I’ve missed here for their support – in one way or another – that have made this learning journey enjoyable. Cambridge has enabled my pursuit for scientific discovery to couple with the pursuit of love. As Stephen Hawking once said, science is not only a disciple of reason but, also, one of romance and passion.
Abstract

The unifying theme of this thesis is the exploitation of the reactivity of aryliodonium salts as electrophile transfer reagents. In the first part of the thesis, diaryliodonium salts are employed as arylation reagents for the enantioselective copper-catalysed arylation-semipinacol rearrangement (SPR) of various tertiary allylic alcohols. This cascade reaction is a rare example of asymmetrically activating SPR using carbon electrophiles. Different substrate classes – including dihydropyran, indene and dihydronaphthalene moieties – are converted to enantioenriched β-aryl spirocyclic ketones in excellent yields and enantioselectivities, and often as a single diastereomer. These are in turn useful functional handles for transformations into other moieties, including further rearrangements via Baeyer-Villiger oxidation.

Part 1

In the second part of this thesis, a two-step process for the macrocyclisation of native peptides via a non-natural linkage is developed. This study exploits previous work conducted in the group on the use of aryliodonium salts as methionine-selective diazoacetate transfer reagents. The functionalised methionine is in turn used for an intramolecular rhodium-catalysed insertion into tryptophan. Eventual translation onto solid-phase enables facile access into various macrocyclic peptides.
Abbreviations

(+) dextrorotary
(-) levorotary
9-BBN 9-borabicyclo[3.3.1]nonane
°C degree Celsius
[α]₀ absolute rotation
Å Angstrom
λ lambda, wavelength unit
δ chemical shift
Ac acetyl
Acac acetylacetone
AIBN azobisisobutyronitrile
Ala alanine
APCI atmospheric-pressure chemical ionisation
Aq aqueous
Ar aromatic group
Arg arginine
Asp aspartic acid
Asn asparagine
Atm atmospheres
b.p. boiling point
BINAP 2,2’-bis(diphenylphosphino)-1,1’-binaphthyl
BINOL 1,1’-bi-2-naphthol
Bn benzyl
Boc tert-butyloxy carbonyl
BOP (benzotriazol-1-yl)oxytris(dimethylamino)phosphonium hexafluorophosphate
BOX bis(oxazoline)
bpy 2,2’-bipyridine
br broad
Bu butyl
Bz benzoyl
CDI carbonyldiimidazole
CoA coenzyme A
Cod 1,5-cyclooctadiene
COSY ¹H correlation spectroscopy (NMR)
Cp cyclopentadienyl
CPME cyclopentylmethyl ether
CPP cell penetrating peptides
Cy cyclohexyl
cm⁻¹ wavenumbers
d day(s)
d doublet
δ chemical shift (NMR)
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
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<tr>
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<td>dibenzylideneacetone</td>
</tr>
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<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
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<td>DCM</td>
<td>dichloromethane</td>
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<td>2,3-dichloro-5,6-dicyano-1,4-benzoquinone</td>
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<td>d.e.</td>
<td>diastereomeric excess</td>
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<td>diethylene glycol</td>
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<td>density functional theory</td>
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<td>IUPAC</td>
<td>International Union of Pure and Applied Chemistry</td>
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<td>p-</td>
<td>para-</td>
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<td>PMB</td>
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<td>PMP</td>
<td>para-methoxy-phenyl</td>
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<tr>
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<td>proline</td>
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<td>room temperature</td>
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<td>secondary</td>
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<td>S_Ar</td>
<td>electrophilic aromatic substitution</td>
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<td>SEM</td>
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<td>solid-phase peptide synthesis</td>
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<td>SPR</td>
<td>semipinacol rearrangement</td>
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<td>TBAF</td>
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<td>TCBC</td>
<td>2,4,6-trichlorobenzoyl chloride</td>
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<td>Tf/triflic</td>
<td>trifluoromethanesulfonfonyl</td>
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<td>trifluoroacetic acid</td>
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<tr>
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<tr>
<td>Trp</td>
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<tr>
<td>TS</td>
<td>transition state</td>
</tr>
<tr>
<td>UV</td>
<td>ultraviolet</td>
</tr>
<tr>
<td>X</td>
<td>unspecified electronegative atom</td>
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<td>(Z)</td>
<td>zusammen</td>
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1. Background

1.1 Hypervalent Compounds – History and Definition

The chemistry of hypervalent compounds has attracted attention from both organic and inorganic chemists in recent times. The idea of hypervalent organic compounds, however, was founded almost a century ago from the visions of H. Staudinger and G. Wittig in the early twentieth century as a direct challenge to the valence theory. The standard octet rule – stating that main group elements would combine in such a way that each atom has eight electrons in its valence orbital – was, at the time, thought to be conserved. To challenge this theory, Staudinger and Wittig attempted to develop methods for the preparation of nitrogen and phosphorus compounds bearing five covalent bonds, which would certainly violate the beliefs of most chemists of that period.¹

Staudinger first unsuccessfully attempted to realise the idea of preparing molecules that deviated from the octet rule by having expanded octets, in 1919.² It wasn’t until 1949 that Wittig successfully prepared Ph₅P,³ followed by Ph₃Sb and Ph₄Te, both in 1952, all of which formally exceed the valence octet.⁴⁻⁵ Wittig, however, did not use the term hypervalency. Neither did he determine the structures of the compounds. It was not until 1969, in a review article by J. I. Musher, that the concept of hypervalency was established. This landmark work later laid the theoretical basis for hypervalent compounds.⁶

Musher classified hypervalent molecules and ions as those formed from elements in Groups V–VIII of the periodic table in any other valences than their lowest stable valence of 3, 2, 1, and 0, respectively.⁶ The term “hypervalent” was used since they involve donor atoms that exceed the number of valence allowed by the traditional Lewis-Langmuir theory. For standardisation, hypervalent compounds can be classified using the Martin–Arduengo designation, N–X–L, where bonding about the hypervalent donor atom X is described by the number of valence electrons (N) formally assigned to it and the number of ligands (L) bonded to it.⁷
1.2 Hypervalent Iodine Compounds

Hypervalent iodine compounds are versatile, mild, environmentally benign, and selective reagents in organic chemistry.\textsuperscript{8} In general, they can be classified into two distinct categories: $\lambda^3$-iodanes and $\lambda^5$-iodanes (Figure 1), where $\lambda$ denotes non-standard bonding. $\lambda^5$-iodanes, such as Dess–Martin reagent (12–I–5, 1) and IBX (10–I–4, 2), and $\lambda^3$-iodanes bearing two heteroatom ligands, such as PIDA (10–I–3, L = OAc, 3), have found widespread use as oxidative reagents.\textsuperscript{9–11} These iodanes, however, fall beyond the scope of this thesis and will not be discussed further. $\lambda^3$-iodanes bearing two carbon ligands, such as 4, on the other hand, are of importance in this thesis.

![Figure 1: Selected examples of common iodanes in organic synthesis.](image)

1.3 $\lambda^3$-Iodanes and Iodonium Salts

For hypervalent species, bonding can be explained through MO diagrams involving a three-centre-four-electron bond (3c–4e), initially proposed in 1951 by Pimentel, which built on the ideas developed by Rundle.\textsuperscript{12–14} In a typical example of a 3c–4e bond, one bonding pair of the donor atom is delocalised to its two ligands, resulting in a distribution of electron density located mostly on the ligands, leaving a net charge of $\delta^+$ on the hypervalent iodine. Such a 3c–4e bond – or hypervalent bond – is strongly polarised, making it longer and weaker than normal covalent bonds.\textsuperscript{15} In $\lambda^3$-iodanes, interaction between the filled 5p orbital of the donor iodine and the half-filled unhybridised orbitals of two ligands, trans to each other in the molecule, forms three MOs: bonding, non-bonding and anti-bonding (Figure 2).\textsuperscript{16}
Figure 2: MO diagram of PhI-X₂, where X is an electronegative atom.

The hypervalent bond is highly polarised as the HOMO corresponds to the non-bonding MO – bearing a node at the central iodine atom. Due to the requirements for efficient orbital overlap, the more electronegative ligands, X, tend to occupy the axial positions, while the less electronegative carbon ligand is situated in the equatorial position. This gives the final geometry of the λ³-iodane as a distorted trigonal bipyramidal or T-shaped.¹⁷

λ³-iodanes that have a single X ligand of significantly greater electronegativity than the other ligands exhibit greater ionic character, owing to the longer bond length between the central iodine and “counterion”.¹¹ For this reason, diaryl-λ³-iodanes are frequently referred to as diaryliodonium salts, and can be represented as 8-I-2 (6), instead of 10-I-3 (5, Figure 3). However, these “salts” are not simple ionic compounds as they still exhibit hypervalent-bonding characteristics; X-ray crystallographic studies have determined that in solid state,¹⁸ a T-shaped geometry is adopted by these iodonium salts. Hence, these reagents exhibit characters of both hypervalent and ionic bonding. This, coupled with polarisation along the hypervalent bond, makes these iodonium salts highly electrophilic and reactive.

Figure 3: Diaryliodonium salts representations.
1.4 General reactivity of aryl-\(\lambda^3\)-iodanes

The susceptibility of aryl-\(\lambda^3\)-iodanes to attacks by nucleophiles, as well as the favourable reduction of the hypervalent iodine centre to normal valence, are essential to their reactivities.\(^{19}\) The ability of aryl-\(\lambda^3\)-iodanes to undergo this reactivity mode can be rationalised by nucleofugality – the tendency of an atom or group to part with the bonding electron pair – of the ArI group. For example, PhI is estimated to have a leaving group ability of \(10^6\) times greater than triflate, making PhI a “hypernucleofuge”.\(^{19}\) Within this class of aryl-\(\lambda^3\)-iodanes, however, diaryliodonium salts represent the most well-investigated class.\(^{10,20}\) Diaryliodonium salts of the general formula Ar(R)IX, where R = transferring aryl and X = [OTf]\(^-\), [BF\(_4\)]\(^-\), or other anions, are useful electrophilic aryl transfer reagents. Their reactivities can be classified into (i) reactions with nucleophiles, and (ii) cross coupling reactions.

For reactions with nucleophiles, the mechanism was proposed to involve both ligand exchange (Scheme 1a), and ligand coupling (Scheme 1b).\(^{21}\) Initial attack by the nucleophile goes through an associative mechanism to 7, followed by isomerisation (8) and eventual elimination of the ligand to trigonal bipyramidal 10-I-3 intermediate 9 (Scheme 1a). However, since coupling between the apical and equatorial positions of a trigonal bipyramid is symmetry forbidden,\(^{22}\) the intermediate 9 undergoes Berry pseudorotation to 10.\(^{23-24}\) Ligand coupling, or reductive elimination, can then proceed in the same plane through a square pyramid structure (Scheme 1b). However, the exact mechanism of ligand coupling in hypervalent iodine compounds is not well understood.
Over the past four decades cross-coupling reactions catalysed by transition metals, notably palladium and nickel, have emerged as essential transformations in the formation of aryl-carbon bonds.\(^{25}\) In these processes, the first step is often an oxidative addition of a metal complex to an aryl halide (or pseudohalide). Since the oxidative addition step is often rate-limiting, significant optimisation of the metal source and ancillary ligands can be required to achieve acceptable rates for this process. In the 1980s, Yamazaki and Ochiai reported that diaryliodonium salts can be used in place of an aryl halide in a Pd-catalysed alkoxycarbonylation reaction.\(^{26,27}\) Since these reports, numerous studies had been documented and reviewed by Sanford in 2007.\(^{28}\) One example is the application of diaryliodonium salt 11 in the Suzuki-Miyaura reaction for the cross coupling of phenylboronic acid 12 to afford 13 in 98% yield (Scheme 2a).

![Scheme 2: Selected examples of Pd-catalysed cross-coupling reactions with diaryliodonium salts.](image)

Often, the use of diaryliodonium salts convey significant advantages over conventional aryl halides, such as lower temperatures and higher rates of reaction. This was proposed to be a consequence of the exceptional leaving ability of the ArI moiety, which facilitated oxidative addition to transition metal complexes.\(^{29}\) Another explanation proposed was that cationic metal species were generated when non-coordinating counterions (such as \([\text{BF}_4^-]\) in 11) were employed on the diaryliodonium salt, which are often more reactive than their neutral counterparts.\(^{29}\) Due to the milder conditions that can be utilised, diaryliodonium salts are often effective cross-coupling partners for temperature-sensitive transformations, such as the arylation of allylic carbonate 14 to afford product
15 in 97% yield (Scheme 2b, right arrow). On the other hand, the use of conventional aryl iodide as the coupling partner under the requisite higher temperature, led to the ring-opening of the carbonate and afforded the undesired allylic alcohol 16 (Scheme 2b, left arrow).

1.5 Preparations and use of diaryliodonium salts in chemical synthesis

Symmetrical or unsymmetrical diaryliodonium salts can be prepared by arylating \( \lambda^3 \)-iodanes with a nucleophilic reagent, such as arylborates, arylstannanes, or arylsilanes, and various procedures for their efficient preparation have been published by the groups of Kita, Kitamura and Olofsson (Scheme 3).\(^{30-33}\) Various commercially available oxidising agents, such as mCPBA (Scheme 3a)\(^{33}\) and potassium persulfate (Scheme 3b)\(^{32}\) can also be used to oxidise iodoarenes to form various diaryliodonium salts after coupling of the intermediates with simple arenes. Even highly sterically hindered arenes, such as mesitylene, 17, could be converted into their respective diaryliodonium salts with Koser’s reagent, [PhI(OH)OTs], as the starting aryl-\( \lambda^3 \)-iodane (Scheme 3c)\(^{31}\) In addition, the counterions of these diaryliodonium salts could be simply exchanged in organic/aqueous biphasic systems with the sodium salts of the desired counterion.\(^{34}\)

![Scheme 3: Selected synthesis of diaryliodonium salts.](image-url)
In this section, selected transformations involving diaryliodonium salts will be introduced. This includes (1) arylation of heteroatom nucleophiles, (2) α-arylation of carbonyl compounds, and (3) metal-catalysed cross-coupling reactions.

### 1.5.1 Arylation of Heteroatom Nucleophiles

The arylation of heteroatom nucleophiles by means of diaryliodonium salts has been known since 1953, when Beringer achieved the phenylation of various organic and inorganic bases such as alkoxides, phenoxides, benzoates, nitrites, sulfonamides, amines, sulfites, sulfinates, and cyanides. The reactions were mostly performed in water under reflux for several hours. A decade after Beringer’s study, Crowder reported the synthesis of diaryl ethers via a similar method; refluxing ditolyliodonium bromide in water with sodium hydroxide and phenol to obtain 1-methyl-4-phenoxybenzene in 86% yield. Both simple and substituted phenoxides gave diaryl ethers in 63–86% yields (Scheme 4).

![Scheme 4: Arylation of sodium phenoxides.](image)

In 2007, Carroll and Wood reported a high-yielding synthesis route to diarylamines (between 72–92% yield for both simple and substituted anilines), in which the influence of anion and other chemoselectivity issues were also discussed. Sterically bulky 2,4,6-trimethyl-N-phenylaniline 23, for example, was prepared in 72% yield from diphenyliodonium triflate 21 and 2,4,6-trimethylaniline 22 (Scheme 5). This exceptional reactivity could be further fine-tuned by changing the electronic nature of the aryl groups on the iodonium salts, or by swapping their counterions.
Most of the work done on the arylation of thioethers and thiols had required a metal catalyst to perform such reactions efficiently.\textsuperscript{20} An example in 2014 from the group of Ciufolini, however, showed that a metal-free reaction was possible. They used diaryl thioethers as nucleophiles to generate various triaryl sulfonium species with different diaryliodonium salts, simply by heating. In one example, bis(4-methoxyphenyl) sulfide \textsuperscript{24} is reacted with diaryliodonium triflate \textsuperscript{21} to generate triaryl sulfonium \textsuperscript{25} in 87\% yield (Scheme 6). In this work, other chalcogens, such as selenides and tellurides, were also found to work well.\textsuperscript{38}

![Scheme 6: Arylation of diaryl thioethers.](image)

### 1.5.2 \textit{α}-Arylation of carbonyl nucleophiles

The \textit{α}-arylation of carbonyls with diaryliodonium salts has been known since the 1960s, starting with a report by Beringer and co-workers. In their study, the phenylation of diketone \textsuperscript{26} by diphenyliodonium chloride \textsuperscript{27} was achieved in 22\% and 23\% yield of both the mono- and di-arylated products \textsuperscript{28a} and \textsuperscript{28b}, respectively (Scheme 7).\textsuperscript{39}

![Scheme 7: First reported \textit{α}-arylation of carbonyls.](image)

Since then, several reports have emerged with more efficient processes, allowing even a multigram-scale synthesis of \textit{α}-arylated ketones.\textsuperscript{40} In 1991, Chen and Koser demonstrated the first arylation of silyl enol ethers using diphenyliodonium fluoride. Either mono- or di-phenylated ketones were produced in up to 88\% yield, with cyclic substrates performing better than acyclic analogues.\textsuperscript{41} Later, Rawal and co-workers found that the use of unsymmetrical diaryliodonium salts, such as \textsuperscript{29}, allowed the transfer of the more electron-deficient aryl group to carbonyls (Scheme 8).\textsuperscript{42} This finding
was in line with what Beringer had previously observed, and was again reaffirmed by Oh et al. in their highly efficient arylation of malonates. This selectivity based on the electronics of the transferring aryl group had aroused interest in several research groups at the time. Eventually, steric effects were also investigated – Olofsson studied both ortho- and anti-ortho-effects of the transferring aryl groups. While the most electron-deficient aryl groups were generally transferred, there were cases where an ortho-substituent would overrule this effect, and cases where they do not – termed anti-ortho-effect. The mechanisms for these aryl transfer selectivity by unsymmetrical diaryliodonium salts are summarised in a recent review in 2017 by Stuart.

Scheme 8: Transfer of electron-deficient aryl in unsymmetrical iodonium salts.

In 1999, Ochiai and co-workers reported the first asymmetric arylation using chiral diaryliodonium salts. The authors used chiral BINAP-based diaryliodonium salts, such as 30, under a tert-butanol/tert-butoxide basic system to enable the arylation of β-ketoester 31 to α-quaternary ketone 32 in up to 53% e.e. (Scheme 9a). Although modest in enantioselectivity, this was a rare example where the enantio induction was imparted by the diaryliodonium salt itself.

Scheme 9: (a) Enantioselective α-arylation of β-ketoesters with chiral diaryliodonium salt, and (b) enantioselective arylation of ketones with diaryliodonium salt and chiral base.
An alternative approach to enantio induction came from Aggarwal and Olofsson in 2005, who used chiral base 33 to desymmetrise ketone 34, prior to arylation by diaryliodonium salt 35, giving moderate yield but excellent enantioselectivity (94% e.e.) and complete diastereoselectivity of the arylated ketone 36 (Scheme 9b). A more recent development in the use of diaryliodonium salts as aryl transfer reagents, however, was the introduction of metal-catalysed processes. This was especially useful in enantioselective induction, as chiral ligands could be employed in catalytic amounts with minimal wastage of chiral materials.

1.5.3 Metal-Catalysed Cross-Coupling Reactions

As described in Section 1.4, the excellent leaving group ability of aryl iodides imparts to diaryliodonium salts their exceptional ability to perform as cross-coupling partners for transition metals. The use of metal catalysts, in this case, would enhance the electrophilicity of the transferring aryl groups (Figure 4). In this section, the use of arenes and heteroarenes, alkynes, and alkenes as nucleophilic cross-coupling partners are discussed.

![Figure 4: Generating enhanced aryl-electrophile equivalents with metal catalysts.](image)

### 1.5.3a Arenes and Heteroarenes

Biaryls received significant attention during the early studies of metal-catalysed cross coupling reactions with diaryliodonium salts. Most notable was the focus on controlling the regioselectivity for arylation on relatively simple arenes and heteroaromatics. In 2005, Sanford and co-workers reported that diaryliodonium salts such as 11 could be used as effective arylating agents in a Pd-catalysed ortho-arylation of 2-arylpyridines, such as 37, and aniline derivatives, such as 39, to products 38 (88% yield) and 40 (75% yield), respectively (Scheme 10a). In their study, the reaction was proposed to proceed via a Pd(II)/Pd(IV) catalytic cycle in which a cyclometallated Pd(II) complex was oxidised to Pd(IV) by the iodonium salt, before reductive elimination to afford the observed products 38 and 40.
Mechanistic studies carried out by Sanford and co-workers on their ortho-arylation of 2-arylpyridine 37, eventually revealed that the reaction proceeded through a rate-limiting oxidation of Pd(II)-dimer 42 by diaryliodonium salt 11, to Pd(IV)-Pd(II) dimer 43 (Scheme 10b).49 This is in contrast to many Pd-catalysed C-H functionalisation reactions in which cyclopalladation is rate-limiting. Whilst high-valent Pd-dimer 43 is depicted in Scheme 10b as Pd(IV) attached to a bridging Pd(II) complex, it is also possible that interaction between the two metal centres occurs. In this case, the species may be considered to be a Pd(III)-Pd(III) dimer, which Ritter and co-workers had demonstrated to be the case in a related transformation.50
Pd(II)-catalysed C-H activation processes for the arylation of indoles were also thoroughly investigated by Sanford and co-workers.\textsuperscript{51} In 2006, the group developed a C-2 selective arylation of indoles using diaryliodonium salt 11. The reaction proceeded with complete selectivity on free indole 45 to afford arylated indole 46 under room temperature, and without the need for strong bases (Scheme 11). In their study, no competing N-H or C-3 arylation were observed and proposed an initial metallation on indole C-3, followed by rapid migration to C-2 before reductive elimination to 46.\textsuperscript{51}

\begin{equation}
\text{Scheme 11: Pd-catalysed C-2 selective arylation of indoles with diaryliodonium salt.}
\end{equation}

In 2008, Gaunt and co-workers began studies on a complementary site-selective copper-catalysed arylation of indoles. The authors found that by changing the substituents on the indole nitrogen, they could alter the site of arylation. While alkylated and free N-H indoles gave the C-3 arylated indole 47, N-acetylindoles gave the C-2 arylated indole 48. This was proposed to happen via an acetyl-assisted migration of the substrate-Cu(III)-aryl complex from C-3 to C-2 (complex 49, Figure 5a).\textsuperscript{52} Pioneering work on meta-selective copper-catalysed C-H bond activation/arylation by Gaunt in 2009 also paved the way for controlling the chemo- and regio-selectivity of copper-catalysed arylation. With just 10 mol\% Cu(OTf)\textsubscript{2} in DCE, a broad scope of meta-substituted biaryls such as 51 could be prepared from anilide 50 (Figure 5b).\textsuperscript{53} The mechanisms for these reactions were proposed to involve a Cu(III)-aryl intermediate complex. In their studies, the authors suggested that the Cu(II) starting catalyst undergoes an auto-reduction to Cu(I), prior to an oxidative addition step by the diaryliodonium salt to afford Cu(III).\textsuperscript{53} It is interesting to note the complementarity of these metal-catalysed arylations; while copper(II) triflate catalysed the meta-selective arylation to biaryl 51 (Figure 5b, right), the palladium(II) variant catalysed the formation of ortho-substituted biaryl product 52 (Figure 5b, left).\textsuperscript{53} Since these reports, the arylation of arenes and heteroarenes using diaryliodonium salts continued to develop and other transition metals, such as nickel, were also studied.\textsuperscript{54} Palladium and copper, however, remained the most studied.\textsuperscript{55-57}
The arylation of alkynes with diaryliodonium salts has received considerable attention. A good example on the early work on this was a copper-catalysed Sonogashira-type coupling developed by Kang and co-workers in 2001. Using only 10 mol% CuI, the group achieved arylation on various terminal alkynes in 57-85% yields (Scheme 12a). Later, in 2008, Zhu and co-workers implemented this transformation in a Pd/Ag-catalysed system (Scheme 12b). In these examples, the more electron-rich aryl groups were selectively transferred, if unsymmetrical iodonium salts were employed.

**Scheme 12:** (a) Cu- and (b) Pd/Ag catalysed Sonogashira reaction with diaryliodonium salts.
In 2006, Xue et al. reported the first reductive arylation of terminal alkynes by employing indium trichloride and NaBH₄ with diaryliodonium salts. In this study, a wide range of aromatic alkynes was tolerated, providing (E)-alkenes as the major product.²⁶

Then in 2013, both the Liu and Gaunt groups, independently developed various copper-catalysed reactions with iodonium salts that targeted internal alkynes.⁶¹-⁶³ During this time, the Gaunt group applied copper-catalysed reductive arylation of alkynes to the arylicative Meyer-Schuster rearrangement of substituted propargylic alcohols, such as 53. Trisubstituted enone product 54 was selectively formed as the (E)-isomer when diphenyliodonium triflate 21 was used (Scheme 13).⁶⁴ In their study, various arenes were also transferred using unsymmetrical mesityl(aryl)iodonium salts. However, efficient transformations were only observed for comparatively electron-rich aryl groups.⁶⁴

![Scheme 13: Cu-catalysed arylicative Meyer-Schuster rearrangement of propargylic alcohols to enones.](image)

Gaunt and co-workers later proposed that the mechanism for the arylation of alkynes involved a vinyl cation equivalent, and a second study by the same group in 2013 successfully trapped this highly electrophilic intermediate using a neighbouring aromatic-nucleophile, in a Friedel’s-Craft-type process.⁶³ Arylation of alkyne 55 with Cu(III)-aryl complex, generated from the activation of unsymmetrical diaryliodonium salt 56 with Cu(I), afforded product 57 in 83% yield (Scheme 14). In another study by Gaunt et al., these vinyl cation-like intermediates were further exploited through carbocation-induced hydride shifts; to translocate the positive charge into remote positions, before finally reacting with an intramolecular aromatic-nucleophile trap.⁶⁵

![Scheme 14: Exploiting vinyl cations generated from arylation of alkynes via an aryl nucleophile trap.](image)
1.5.3c Alkenes

In 2007, Zhu and co-workers, described an efficient process of arylation of acrylic acid 58 into trans-cinnamic acids 59, in excellent yields and under aqueous conditions, by utilising diphenyliodonium chloride 27 (Scheme 15a). The authors discovered that when unsymmetrical diaryliodonium salts were used, the more electron-rich aryl group was selectively transferred in this Heck-type process. In 2009, Szabó and co-workers further developed this transformation for the arylation of allylic acetates 60 and other electron-rich alkenes, with diaryliodonium salts such as 61. The process employed palladium-pincer complex 63 to provide highly functionalised allylic product 62 in high yields (Scheme 15b). A PdII/PdIV catalytic cycle was proposed for these transformations.

\[
\begin{align*}
&\text{a) } \\
&\text{b) }
\end{align*}
\]

Scheme 15: Heck-type arylations using diaryliodonium salts.

In 2012, the Gaunt group advanced this strategy for copper-catalysed systems. Interestingly, these Cu-catalysed processes demonstrated complementary selectivity to Pd-catalysed systems. For example, while the Pd-catalysed Heck reaction on dihydropyran gave the α-arylated product, the corresponding Cu-catalysed process gave exclusively the β-arylated product. This process was demonstrated to convert simple alkenes such as 64 into arylated compounds 65a/b, in 72% yield and 3.5:1 selectivity over the two positional isomers, with 5.5:1 and 3:1 preference for (E)-alkenes for 65a and 65b, respectively (Scheme 16). More importantly, this process was demonstrated to generate a carbocation-like intermediate 66, which led to the development of a number of tandem and cascade reactions following this arylation step (Scheme 16, right).
One of these tandem reactions studied by Gaunt et. al. was the semipinacol rearrangement (SPR) of tertiary allylic alcohols. In their study, the authors used the arylation event to trigger SPR in allylic alcohols 67 and 68. The process efficiently furnished β-aryl ketones 69 and 70 via a C-C bond migration to the postulated carbocation-like intermediate (Scheme 17). This was the first example of copper-catalysed arylation-driven SPR.

These original studies by Gaunt et. al. have shown that copper-catalysed arylation of alkenes represents a strategically important bond-forming process, that display similar and complementary reactivity to Pd-catalysed Heck reactions. An important advance in metal-catalysed processes on alkenes, is the development of their enantioselective variants. While the enantioselective Heck-type arylation of alkenes has seen much development, the enantioselective Cu-catalysed variant remains under-developed.
1.6 Enantioselective copper-catalysed arylations with diaryliodonium salts

The groups of Gaunt and MacMillan have completed pioneering work in the field of enantioselective arylation of alkenes with diaryliodonium salts. In 2011, Gaunt and co-workers used a chiral copper(II)-bisoxazoline complex 71 and diaryliodonium salt 73 to perform an enantioselective arylation of silylated N-acyloxazolidinones, such as 72, affording α-aryl carbonyl 74 in excellent 94% yield and 92% e.e. (Scheme 18). In this study, the authors observed that to achieve high enantio-induction, it was imperative that the substrate possessed the ability to bind with the chiral copper catalyst in a bidentate fashion. For example, between copper complex 71 and N-acyloxazolidinones 72 to form the intermediate complex 75 (Scheme 18, bottom).

Scheme 18: Enantioselective arylation of N-acyloxazolidinone via 2-point binding with catalyst.

Following this work, in 2015, Gaunt and co-workers reported that the same chiral copper-bisoxazoline complex 71 was able to achieve the efficient enantioselective arylation of allylic amides, such as 76. In this study, modulation of the electronics of the transferring aryl group effected a regiodivergent synthesis of either the endo-oxazine (78, Scheme 19a), when electron-rich diaryliodonium salts (77) were employed, or the β-β'-diaryl enamide (80, Scheme 19b), when electron-deficient diaryliodonium salts (79) were employed – both starting from the same allylic amide 76. Factors controlling this regiodivergence, however, were not clearly understood.
In 2012, MacMillan and co-workers were successful in the preparation of aryl pyrroloindolines via an enantioselective copper-catalysed arylation-cyclisation cascade, utilising chiral Cu(I)-bisoxazoline complex 83 (Scheme 20).\textsuperscript{75} In their study, arylation on indole 81 was postulated to generate a carbocation-like intermediate, which was subsequently trapped by an acetamide group appended to the C-3 position of indole 81. Cyclisation of this acetamide then led to the dearomatisation of the indole to form pyrroloindolines 84. Employing diaryliodonium hexafluoroarsenate 82, pyrroloindolines 84 was afforded in excellent 96\% yield and 99\% e.e. (Scheme 20).\textsuperscript{75}

Following this work, MacMillan and co-workers reported the enantioselective $\alpha$-arylation of aldehydes (Scheme 21). In this reaction, aldehyde 85 was converted into the nucleophilic enamine intermediate by utilising chiral amine catalyst 86. Employing diaryliodonium triflate 73 as the aryl transfer reagent, chiral $\alpha$-aryl aldehyde product 87 was afforded in excellent 90\% yield and 92\% e.e. (Scheme 21).
Aside from carbon nucleophiles, in 2016, Gaunt and co-workers reported the arylation of secondary phosphine oxides to chiral tertiary phosphine oxides. The ability to synthesise P-chiral tertiary phosphine oxides, such as 91, meant access into P-chiral phosphines, a well-known ligand class for various transition-metal catalysed complexes (Scheme 22). In this work, the authors were able to perform enantioselective arylation reactions on secondary phosphine oxide 88, by employing copper-PyBOX complex 90 and diaryliodonium hexafluorophosphate 89, to afford tertiary phosphine oxide 91 in excellent 96% yield and 96% e.e. (Scheme 22).
1.7 Proposed applications of iodonium salts

Chemical synthesis plays a central role in providing solutions to problems in most areas of our lives. However, to meet these challenges posed by nature and society, novel reactions to access functional molecules must be continuously developed. Studies towards the use of iodonium salts to achieve this will be described in this thesis.

The first part of the thesis comprises a study of the use of tertiary allylic alcohols as nucleophilic partners for cross-coupling with diaryliodonium salts – to generate a new quaternary stereocentre via an enantioselective copper-catalysed arylation that triggers a second semipinacol step, in a diastereoselective and enantioselective fashion (Figure 6a). This contribution would be an important advance as enantioselective carbon electrophile activation of SPR through a C-C bond formation is rare.

The second part of the thesis describes the exploitation of a diazoacetate-transfer iodonium salt reagent that selectively targets the nucleophilic thioether functionality on methionine (Met) in peptides – previously developed in our group by M. Taylor, J. Nelson and M. J. Gaunt – to couple with a second-step Rh(II)-catalysed insertion towards the synthesis of macrocyclic peptides. This contribution would expand existing chemical strategies available for peptide macrocyclisation via a non-natural linkage.

![Figure 6](image_url):

(a) Enantioselective copper-catalysed arylation-driven semipinacol rearrangement (Section 2), and (b) novel solid-phase peptide macrocyclisation strategy (Section 3).
2. Enantioselective Copper-Catalysed Arylation-Driven Semipinacol Rearrangement (SPR) of Tertiary Allylic Alcohols

2.1 Quaternary stereocentres

During the late twentieth century, chemists have succeeded in developing many powerful methods for directly forming a single three-dimensional configuration of carbon stereocentres having one hydrogen substituent. On the other hand, the construction of a single configuration of stereogenic carbon centres having four different carbon or heteroatom-carbon substituents is still a daunting challenge for chemical synthesis. One of the difficulties in making a quaternary stereocentre is the congested nature of the substituents around the central carbon atom. This imposes a high steric barrier that must be overcome during the transformations. Furthermore, performing these carbon-carbon bond formations in a diastereoselective and enantioselective manner is crucial as the biological effect of such molecules depends directly on their stereochemistry. Enantiomerically enriched stereocentres are thus important in natural products and drug molecules.

2.2 Semipinacol Rearrangements to access quaternary stereocentres

Semipinacol rearrangement (SPR) processes have been shown to be efficient in constructing quaternary stereocentres. The SPR reaction was first described in 1923 by M. Tiffeneau, and originally referred exclusively to the 1,2-migration of tertiary-secondary 1,2-diols towards the secondary centre. Its original meaning has since evolved to include all reactions resembling the Pinacol rearrangement (Scheme 23).

![Scheme 23: General meaning of the semipinacol rearrangement (SPR).](image)

Mechanistically, it can be described as all related processes where an electrophilic carbon centre, including carbocations, generated in the reaction is vicinal to an oxygen-containing carbon and can induce the 1,2-migration of a C-C or C-H bond to generate a carbonyl group. The most practical feature of the semipinacol rearrangement is that a variety of methods can be used to generate these electrophilic carbon centres.
One such approach is the use of a leaving group to generate an electrophilic carbon centre. The 1,2-migration step is facilitated by the loss of the leaving group under either acidic or basic conditions (Scheme 24a). Another method is the use of epoxides, where the electrophilic carbon corresponds to either carbon atoms in the oxirane, and an acid-catalysed ring opening of the epoxide drives the 1,2-migration step (Scheme 24b). A third method is the use of a carbonyl or imine carbon as the electrophilic centre – also known as the *acyloin rearrangement*, where α-hydroxy ketones or imines are used (Scheme 24c). The last method, and one that has dramatically enhanced the scope of the generic transformation, is the use of allylic alcohols and their derivatives; in this method, reacting the alkene with an electrophile generates the requisite carbocation, required to drive the 1,2-migration step in the SPR (Scheme 24d).

Scheme 24: Common methods used to introduce electrophilic carbon centre in SPR systems.

The use of electrophiles to activate allylic alcohols towards SPR, in both intermolecular and intramolecular processes, has developed into an active field of research. Of note are the advances in the use of Brønsted acids, Lewis acids, halonium ions and selenium ions for the activation of allylic alcohols. However, to the best of our knowledge, intermolecular processes using carbon electrophiles in a C-C bond forming process to activate SPR in a catalytic enantioselective manner was rare.
While intramolecular activation of allylic alcohols with carbon electrophiles has been developed extensively, especially by the Overman group,\textsuperscript{79} in reactions now widely known as the Prins-pinacol rearrangement,\textsuperscript{81-84} the intermolecular variant has been poorly developed. This is especially true in the case of enantioselective induction in SPR. In this section, the different types of electrophiles used in the development of enantioselective SPRs will be introduced.

### 2.2 Enantioselective SPR of allylic alcohols

Since its emergence, the SPR has seen much development in catalytic enantioselective transformations. For allylic alcohols, notable seminal examples include alkene activation \textit{via} halogenation,\textsuperscript{85-86} epoxidation,\textsuperscript{87-88} Brønsted acid,\textsuperscript{89} palladium,\textsuperscript{90-91} gold,\textsuperscript{92-93} and palladium/Brønsted acid catalysis.\textsuperscript{94}

#### 2.2.1 Enantioselective tandem halogenation-SPR

In 2005, Tu and co-workers reported the first successful example of a quinine-promoted fluorination-SPR. In their studies, the authors obtained modest yields and enantioselectivities for a variety of allylic alcohols, using a combination of quinine and Selectfluor as promoter and F\textsuperscript{+} reagent, respectively. Secondary allylic alcohols, such as 92, were activated towards fluorination-driven SPR, generating a quaternary all-carbon stereocentre, a tertiary carbon bearing the new fluorine atom, and a new aldehyde functional group (93) in 50% yield and 71% e.e. (Scheme 25a). In this reaction, the authors attributed the generation of 94 as the active chiral fluorinating agent.\textsuperscript{95}

\begin{center}
\begin{tikzpicture}
\node[draw] (92) at (0,0) {\Huge 92};
\node[draw] (93) at (3,0) {\Huge 93};
\node[draw] (94) at (3,1) {\Huge 94};
\node[draw] (95) at (0,-2) {\Huge 95};
\node[draw] (96) at (3,-2) {\Huge 96};
\node[draw] (97) at (3,-3) {\Huge 97};
\draw[->] (92) -- (93) node[midway,anchor=south] {\Huge quinine (1.4 eq.) Selectfluor(1.4 eq.) K\textsubscript{2}CO\textsubscript{3} (0.6 eq.) MeCN, rt};
\draw[->] (95) -- (96) node[midway,anchor=south] {\Huge (DHQD)\textsubscript{2}PYR (0.2 eq.) NFSI (1.2 eq.) K\textsubscript{2}CO\textsubscript{3} (0.6 eq.) DCE, -10 °C};
\end{tikzpicture}
\end{center}

\textbf{Scheme 25:} Examples of (a) quinine-promoted enantioselective fluorination-SPR for secondary allylic alcohol, and (b) organocatalytic enantioselective fluorination-SPR for tertiary allylic alcohol.
Ensuing studies by the same group also showed that a more electron-rich alkene, such as 95, could be employed in the presence of a catalytic bis-quinine derivative and NFSI to generate 97 as the chiral fluorinating agent. This was an improvement from previous work with quinine as the reaction was catalytic and enantioselectivities were enhanced up to 93% e.e. for product 96, although yields remained modest (56%, Scheme 25b).\textsuperscript{96}

In 2013, Alexakis and co-workers further developed the enantioselective fluorination-SPR on allylic alcohols. Using catalytic amounts of chiral phosphoric acid 98, the authors were able to show an anionic phase-transfer catalysis mechanism, with enantio-induction achieved through an asymmetric-counterion-directed strategy.\textsuperscript{85} In their study, β-fluoro spiroketone 100 was obtained from its allylic alcohol precursor 99, in excellent 85% yield and 92% e.e. (Scheme 26). In this study, the authors found that while expansions of cyclopropanol and cyclobutanol rings were efficient, the expansion of larger cyclopentanol rings proceeded with only modest enantioselectivities.\textsuperscript{85} Furthermore, without chiral phosphoric acid 98, the reaction produced a racemic compound with 1:1 d.r., indicating that both enantio- and diastereoselectivity were catalyst-controlled. This observation was different from that which Tu and co-workers reported in their enantioselective fluorination study (Scheme 25), in which diastereoselectivities were almost always substrate dependent.\textsuperscript{96}

\begin{center}
\includegraphics[width=\textwidth]{Scheme26.png}
\end{center}

\textbf{Scheme 26:} Chiral phosphoric acid-catalysed fluorination-SPR.

Aside from fluorination, Tu and co-workers have also developed other enantioselective halogenation-induced SPR processes, including chlorination and bromination.\textsuperscript{97} In this work, the authors employed the same electron-rich dihydropyran substrates (95) and bis-quinine derivatives as promoters. Both bromination-SPR product 101 (92% yield and 98% e.e., Scheme 27a) and chlorination-SPR product 102 (67% yield and 96% e.e., Scheme 27b) were successfully obtained.\textsuperscript{97}
Scheme 27: Studies on catalytic enantioselective (a) bromination-SPR, and (b) chlorination-SPR.

As the final halogenation-SPR process in this section, Alexakis and co-workers reported the first successful enantioselective iodination-SPR process, using 103 as the I⁺ source. The iodination-SPR reaction with chiral phosphoric acids afforded a single diastereomer regardless of the steric bulk of the catalyst used, in contrast to their previous work on fluorination-SPR. In this transformation, the expansion of allylic alcohols such as allylic cyclobutanol 104, catalysed by chiral phosphoric acid 106, to its iodinated spirocycle ketone product 105 was achieved in 76% yield, >20:1 d.r. and 90% e.e. (Scheme 28). 86

Scheme 28: Chiral phosphoric acid-catalysed iodination-SPR.

2.2.2 Enantioselective tandem epoxidation-SPR

In 1994, Fukumoto and co-workers developed an enantioselective tandem epoxidation-SPR of cyclopropylidene alcohols in the total synthesis of (-)-Debromoaplysin and (-)-Aplysin. 88 In their study, the authors observed a substituent effect on the enantioselectivity of the product ketone, owing to the bulky ortho-OTBS substituent in 107. While overlap of the π-system with the developing carbocation might induce epimerisation, the bulky -OTBS group prevented this, thus affording β-hydroxymethyl cyclobutanone 108 in excellent 98% yield and 95% e.e. (Scheme 29). 88
Scheme 29: Enantioselective epoxidation-SPR in the synthesis of (−)-Debromoaplysin and (−)-Aplysin.

Later, in 2011, Tu and co-workers further developed this transformation into a more general process for converting vinylogous α-ketol substrates into chiral spirocycles. The authors subjected α,β-enones with β-tertiary allylic alcohol, such as 109, to epoxidation with hydrogen peroxide and organocatalyst quinine analogue 111 in H₂O/dioxane solvent. Chiral spirocycle 110 was afforded in high yield (70%) and excellent enantioselectivity (93% e.e., Scheme 30).98

Scheme 30: Organocatalytic tandem epoxidation-SPR of vinylogous α-ketols.

2.2.3 Enantioselective tandem Brønsted acid protonation-SPR

BINOL-derived phosphoric acids represents one of the most commonly used chiral Brønsted acid catalyst class.99 In 2009, Tu and co-workers became the first to use this in a tandem protonation-SPR strategy for the synthesis of various enantioenriched spiroethers. In their work, the authors used chiral phosphoric acid 106 to achieve the enantioselective Brønsted acid-promoted SPR of allylic cyclobutanols bearing dihydropyran moieties, such as 112, to afford spiroether ketone 113 in excellent 90% yield and 98% e.e. (Scheme 31).89 Tu et. al. attributed this excellent enantioselectivity to a double hydrogen-bonding interaction between the substrates and catalyst 106.

Scheme 31: Phosphoric acid-catalysed SPR of allylic alcohol.
In 2012, Rainey and co-workers achieved a related transformation – an oxidative-SPR – on indene-type allylic cyclobutanols, such as 114, using both chiral phosphoric acid 106 and palladium(II) acetate. Indene 114 was heated with 106, Pd(OAc)$_2$ and benzoquinone (BQ) to afford indene spirocyclic compound 115 in modest 59% yield, but excellent 97% e.e. (Scheme 32).$^{94}$ Deuterium labelling studies performed suggested that the allylic proton on the indene moiety was abstracted to form acetic acid during the reaction, which might implicate a cationic allyl complex 116 in the SPR process (Scheme 32).

Scheme 32: Chiral phosphoric acid and Pd$^{II}$-catalysed oxidative-SPR.

Following this work, Tu and co-workers studied the intramolecular Nazarov 4π-conrotatory electrocyclisation of dienones, such as 117. This process, reported in 2015, employed chiral Brønsted acid 118 to generate a pentadienyl cationic intermediate 119, which in turn drove the SPR cascade. The final spirocyclic diketone product 120 was afforded in excellent 87% yield, 97% e.e., and as a single diastereomer (Scheme 33).$^{100}$ In this study, up to four contiguous stereocentres were generated.

Scheme 33: Organocatalytic enantioselective tandem Nazarov cyclisation-SPR of dienones.

### 2.2.4 Enantioselective chiral metal complex-catalysed SPR

As Rainey and co-workers had alluded to in their SPR process with Pd(II) and chiral phosphoric acid 106,$^{94}$ Pd complexes could induce SPRs. Thus, it stands to reason that a Pd complex bearing chiral ligands may influence the enantioselectivity process. In 2001, Trost and co-workers used chiral bisphosphine ligand 121 to perform an enantioselective SPR of allylic cycloalkanols, such as 122, catalysed by Pd(0). The substituent carbonate
ester group was eliminated in the process to generate the requisite cationic allyl palladium intermediate to drive the SPR, yielding the chiral \( \alpha \)-alkyl-\( \alpha \)-vinyl cycloketone product 123 in quantitative yield and excellent 92\% e.e. (Scheme 34). In their study, various chiral cyclobutanones and cyclopentanones were obtained in moderate to excellent yields (52-99\%) and enantioselectivities (69-93\% e.e.).\(^{91}\)

![Scheme 34: Pd\(^0\)-catalysed asymmetric SPR of allylic alcohols with chiral ligand.](image)

Besides palladium, gold had also seen some development in the field of enantioselective SPR of allylic alcohols. In 2008, Toste and co-workers described the first Au(I)-catalysed SPR of an allylic alcohol towards the total synthesis of Ventricosene. Although racemic, the process exploited a gold complex formed by Au(I) promoted alkyne activation.\(^{92}\) The following year, Toste et al. reported the first enantioselective gold complex-catalysed SPR. Chiral gold-phosphine complex 124 was used to activate allenyl alcohol 125 towards SPR, yielding \( \alpha \)-vinyl cyclobutanone 126 in high yield (76\%) and excellent enantioselectivity (91\% e.e., Scheme 35).\(^{93}\)

![Scheme 35: Enantioselective Au(I)-phosphine complex-catalysed SPR.](image)
2.3 Carbon electrophiles in catalytic enantioselective SPR

Although catalytic enantioselective SPR has progressed in the use of different electrophiles for alkene activation, carbon electrophiles are under-utilised. The generation of a C-C bond to activate alkenes enantioselectively, for example, is rare. In 2013, Tu and co-workers reported the first use of an external carbon electrophile, but with only one example showing enantioselective induction by a Cu(II)-BOX complex 127. In their study, ethyl 2,3-oxoacetate was activated with complex 127, which in turn induced allylic alcohol 128 towards an enantioselective SPR process. Following a cascade of intramolecular reactions, the transformation eventually led to the formation of complex tricyclic diastereomeric products 129a and 129b in 91% e.e. and 82% e.e., respectively (Scheme 36).\textsuperscript{101}

Scheme 36: Only example of enantioselective SPR activated by a carbon electrophile.
2.4 Asymmetric arylation-driven SPR of simple tertiary allylic alcohols

Gaunt and co-workers had previously achieved the arylation-induced semipinacol cascade reaction for simple allylic alcohol 67 and 68 to afford 69 and 70 in 74% and 71% yield, respectively, under copper catalysis (Scheme 15, Section 1). Building on this work – and coupled with the different enantioselective electrophilic arylation strategies developed in our group – we sought to discover if these initial arylation-driven SPR studies could be performed enantioselectively.

![Scheme 15: First arylation-semipinacol rearrangement reaction to produce racemic products.](image)

2.4.1 Substrate scope and reaction parameters

The initial substrates for asymmetric reactions were synthesised as shown in Scheme 37 from their respective ketones and Grignard reagents, using standard conditions for the 1,2-addition to carbonyls.

![Scheme 37: Initial substrate scope tested for asymmetric reactions.](image)

Achiral reactions of simple allylic alcohol substrates 68 and 130 with CuCl and diphenyliodonium triflate 21 were first performed to obtain their respective products 70 and 131 as racemic standards for chiral HPLC analysis. The reactions for substrate 130, with a phenyl substituent on the α-allylic alcohol position, gave product 131 with a 98% yield. This was more efficient that the same reaction with substrate 68, with a methyl substituent on the α-allylic alcohol position instead, which gave product 70 in 77% yield. This may be attributed to resonance stabilisation of the carbocation-like transition state by the phenyl ring (Scheme 38, right). These reactions were subsequently screened using chiral copper(II)-bis(oxazoline) (BOX) complexes as catalysts in our first attempt to induce enantioselectivity for 70 and 131. Initial catalysts tested are shown in Figure 7.
Results for substrates 68 and 130 are tabulated in Table 1. Initial screening of reactions with complexes 132 and 133 in 1,2-dichloroethane (DCE) at 50 °C gave no enantioselectivity (Table 1, entries 1-2). Furthermore, yields for both reaction products 70 and 131 were lower than with CuCl, with 70 suffering a drastic drop in yield from 77% to 7% (entries 1 and 2). Analysis of the multiple side products generated from reactions with 68 indicated a possible O-arylation as the major side product formed although isolation of this side product proved unsuccessful.

Previous studies in our group demonstrated that the iodonium salt counterion can greatly influence reactivity and selectivity of transition metal-mediated arylation processes. The effect of varying counterions on the reaction outcome was accordingly investigated (Table 1, entries 3-5 and 8). The first counteranion to be tested was hexafluorophosphate (PF₆⁻), an inert non-coordinating ligand (entries 3-5). The initial rationale for using a non-coordinating counteranion was to induce closer interaction between the substrates and the copper(II)-BOX, by freeing up coordination sites around copper. Initial results showed a small increase in e.e. from 0% to 9% (entry 3). However, the use of the PF₆⁻ counteranion also caused a loss in chemoselectivity. Arylated side-product 134 was observed, formed from the loss of proton instead of the desired SPR pathway. Higher reaction temperatures favoured formation of the SPR product, but with a decrease in enantioselectivity: increasing the temperature from 25 °C to 50 °C caused yields to increase from 2% to 37%, but e.e. to decrease from 18% to 9% (entries 3-5). From this result, it was clear that low temperatures favoured higher enantioselectivity.
Table 1: Initial screen of catalysts, iodonium counteranions and conditions

<table>
<thead>
<tr>
<th>#</th>
<th>substrate</th>
<th>solvent</th>
<th>X$^{-}$</th>
<th>temp</th>
<th>catalyst</th>
<th>product</th>
<th>yield</th>
<th>e.e.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>68</td>
<td>DCE</td>
<td>OTf</td>
<td>50 °C</td>
<td>133</td>
<td>70</td>
<td>7%</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>130</td>
<td>DCE</td>
<td>OTf</td>
<td>50 °C</td>
<td>133</td>
<td>131</td>
<td>90%</td>
<td>0%</td>
</tr>
<tr>
<td>3</td>
<td>130</td>
<td>DCE</td>
<td>PF$_6$</td>
<td>50 °C</td>
<td>133</td>
<td>131 (134)</td>
<td>37% (33%)</td>
<td>9%</td>
</tr>
<tr>
<td>4</td>
<td>130</td>
<td>DCE</td>
<td>PF$_6$</td>
<td>70 °C</td>
<td>133</td>
<td>131 (134)</td>
<td>70% (10%)</td>
<td>6%</td>
</tr>
<tr>
<td>5</td>
<td>130</td>
<td>PhMe</td>
<td>PF$_6$</td>
<td>25 °C</td>
<td>133</td>
<td>131 (134)</td>
<td>2% (8%)$^{b}$</td>
<td>18%</td>
</tr>
<tr>
<td>6</td>
<td>130</td>
<td>CH$_2$Cl$_2$</td>
<td>PF$_6$</td>
<td>70 °C$^{a}$</td>
<td>133</td>
<td>131 (134)</td>
<td>20% (17%)</td>
<td>6%</td>
</tr>
<tr>
<td>7</td>
<td>130</td>
<td>CH$_2$Cl$_2$</td>
<td>PF$_6$</td>
<td>25 °C</td>
<td>133</td>
<td>131 (134)</td>
<td>12% (45%)</td>
<td>33%</td>
</tr>
<tr>
<td>8</td>
<td>130</td>
<td>CH$_2$Cl$_2$</td>
<td>BF$_4$</td>
<td>25 °C</td>
<td>133</td>
<td>131 (134)</td>
<td>23% (30%)</td>
<td>18%</td>
</tr>
<tr>
<td>9</td>
<td>130</td>
<td>CH$_2$Cl$_2$</td>
<td>PF$_6$</td>
<td>25 °C</td>
<td>132</td>
<td>131 (134)</td>
<td>N.R.</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>130</td>
<td>CH$_2$Cl$_2$</td>
<td>PF$_6$</td>
<td>50 °C</td>
<td>132</td>
<td>131 (134)</td>
<td>35% (13%)</td>
<td>0%</td>
</tr>
</tbody>
</table>

Notes: (a) reaction in toluene required higher temperatures (70 °C) due to poor solubility of iodonium salts; (b) reaction did not reach completion (c) reactions were run for 24 h

Solvent effects had a clear influence on reactivity and enantioselectivity (Table 1, entries 4-7). Results for 131 in CH$_2$Cl$_2$ were much better (12% yield, 33% e.e.) than in DCE (2% yield, 18% e.e.) for the same reaction conditions, while performing the reaction in toluene gave worse results (20% yield, 6% e.e.) than in DCE (70% yield, 6% e.e.) for the same reaction conditions (entries 4-7). Another non-coordinating counteranion, tetrafluoroborate (BF$_4$), for the iodonium salt was also tested, but did not fare as well as PF$_6$ (entry 8). Changing the catalyst from Cu(II)-BOX complex 133 to 132 gave no reaction at low temperatures and no enantioselectivity at higher temperatures (entries 9-10). Chemoselectivity was also an issue, as the major product was the arylated side-product 134. Furthermore, as a control, treating the crude mixture with trifluoroacetic acid (TFA) converts 134 to racemic product 131, indicating that acid-mediated achiral background reaction could be a problem and that the choice of base could be important. Therefore, the effect of the choice of base on the reaction was considered (Table 2).
Table 2: Base screening for reactions of 68 and 130

![Chemical structure](image)

<table>
<thead>
<tr>
<th>#</th>
<th>substrate</th>
<th>base</th>
<th>X</th>
<th>catalyst</th>
<th>product</th>
<th>yield</th>
<th>e.e.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>130</td>
<td>None</td>
<td>PF₆</td>
<td>133</td>
<td>-</td>
<td>0%</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>130</td>
<td>DTBP</td>
<td>PF₆</td>
<td>133</td>
<td>131 (134)</td>
<td>12% (45%)</td>
<td>33%</td>
</tr>
<tr>
<td>3</td>
<td>130</td>
<td>K₂CO₃</td>
<td>PF₆</td>
<td>133</td>
<td>131 (134)</td>
<td>5% (5%)</td>
<td>4%</td>
</tr>
<tr>
<td>4</td>
<td>130</td>
<td>Cs₂CO₃</td>
<td>PF₆</td>
<td>133</td>
<td>131 (134)</td>
<td>N.R.</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>130</td>
<td>Li₂CO₃</td>
<td>PF₆</td>
<td>133</td>
<td>131 (134)</td>
<td>4% (6%)</td>
<td>4%</td>
</tr>
<tr>
<td>6</td>
<td>130</td>
<td>Na₂CO₃</td>
<td>PF₆</td>
<td>133</td>
<td>131 (134)</td>
<td>25% (7%)</td>
<td>26%</td>
</tr>
<tr>
<td>7</td>
<td>130</td>
<td>Na₃PO₄</td>
<td>PF₆</td>
<td>133</td>
<td>131 (134)</td>
<td>31% (26%)</td>
<td>23%</td>
</tr>
<tr>
<td>8</td>
<td>130</td>
<td>Na₃PO₄</td>
<td>BF₄</td>
<td>133</td>
<td>131 (134)</td>
<td>5% (22%)</td>
<td>30%</td>
</tr>
<tr>
<td>9</td>
<td>130</td>
<td>Na₃PO₄</td>
<td>AsF₆</td>
<td>133</td>
<td>131 (134)</td>
<td>24% (28%)</td>
<td>29%</td>
</tr>
<tr>
<td>10</td>
<td>130</td>
<td>Na₂CO₃</td>
<td>SbF₆</td>
<td>133</td>
<td>131 (134)</td>
<td>13% (0%)</td>
<td>29%</td>
</tr>
<tr>
<td>11</td>
<td>68</td>
<td>Na₂CO₃</td>
<td>PF₆</td>
<td>133</td>
<td>70</td>
<td>32%</td>
<td>52%</td>
</tr>
<tr>
<td>12</td>
<td>68</td>
<td>Na₂CO₃</td>
<td>PF₆</td>
<td>133</td>
<td>70</td>
<td>41%</td>
<td>52%</td>
</tr>
</tbody>
</table>

Note: (a) no reaction observed without base added; (b) reaction was performed at 30 °C, instead of 25 °C.

Di-tert-butylpyridine (DTBP) was the initial choice of base as it is non-nucleophilic (Table 2, entry 2), precluding unwanted side reactions such as arylation of the nucleophilic bases, or deactivation of the copper catalyst through base ligation. Furthermore, previous work conducted in the group had found DTBP to be an efficient base for arylation of alkenes. Results from the base screen showed that Na₃PO₄ (31% yield, 23% e.e. for 131) and Na₂CO₃ (25% yield, 26% e.e. for 131, and 41% yield, 52% e.e. for 70) were the best performing bases among the others tested (entries 6-7 and 11-12). Other carbonate bases gave much poorer results at 0-5% yield and 0-4% e.e. (entries 3-5). With the best performing bases, other counterions for the diaryliodonium salts were also tested, but no improvements in yield and enantioselectivity were observed (entries 8-10). A full scope is shown in Appendix 2 (Table S1).
Although asymmetric arylation-driven SPR was achievable (for example, 52% e.e. was achieved for product 70), stereocontrol was still insufficient. Since changing the conditions did little to improve either chemoselectivity or enantioselectivity, other cyclic substrates were investigated. We rationalised that tethering the alkene moiety in 130 back onto the aromatic substituent in the substrate could help achieve better stereocontrol due to reduced backbone flexibility. Thus, dihydronaphthalene substrates 137 and 138, with rigid alkene moieties, were synthesised from their vinyl bromide precursors 135 and 136, respectively (Scheme 39).

Reactions on substrates 137 and 138 generated two stereocentres in a single cascade process – one chiral all-carbon quaternary stereocentre, and one chiral tertiary stereocentre. Initial tests on achiral reactions with CuCl and diphenyliodonium triflate yielded an interesting result, where some diastereoselectivity (28% d.e.) was achieved for 137 to 139 (Table 3, entries 1-2) and near perfect diastereoselectivity (97% d.e.) for 138 to 140 (Table 3, entries 8-9).

Unlike for acyclic substrate 130, DTBP was found to be the optimal base for promoting arylation-driven SPR for dihydronaphthalene substrates 137 (entries 3-5) and 138 (entries 10-12). Eventually, it was found that lowering the temperature, concentration and catalyst loading resulted in the best results for 137 (14% yield, >20:1 d.r., 68% e.e. for product 139, entries 6-7) and 138 (12% yield, >20:1 d.r., 73% e.e. for product 140, entries 13-14). Details of the full study can be found in Appendix 2 (Table S2). Whilst reactivities were poor for these systems, higher enantioselectivity was achieved for reactions with cyclic substrates 137 (68% e.e.) and 138 (73% e.e.), than with acyclic substrates 68 (52% e.e.) and 130 (26% e.e.). Furthermore, it was observed that lower temperatures (30 °C) resulted in reduced side-product formation and better enantioselectivity, although with incomplete conversions.
Similar counteranion effects were observed for 137 and 138, as with previous acyclic substrates 35 and 90. The diaryliodonium triflate salts gave no enantioselectivities, but enantiomeric excesses were, however, observed for diphenyliodonium salts with non-coordinating counteranions. In particular, PF₆ salts gave superior enantioselectivities (up to 73% e.e.). Other counteranions such as hexafluoroarsenate (AsF₆) and hexafluoroantimonate (SbF₆) were also tested but gave poorer enantioselectivity (entries...
Therefore, it was imperative that iodonium hexafluorophosphate salts made from the triflate precursors should be strictly triflate free. It was observed that even small amounts of triflate impurities in iodonium salts (1%) were enough to cause a drop in e.e. (68% to 65% e.e in reaction for dihydronaphthalene substrate 137 to tetralin spirocyclic ketone product 139, table 4, entries 1-2). This phenomenon was further evaluated by performing reactions with dihydronaphthalene substrate 137, doped with triflate salts (Table 4, entries 3-5). It was found that addition of external triflate salts drastically reduced enantioselectivity of the reactions from 68% to 42% e.e. with 10 mol% NaOTf added (entry 3) and 38% e.e. with 10 mol% Mg(OTf)$_2$ added (entry 4). With LiOTf added, the reaction stopped working under the conditions used (entry 5). One explanation for this effect is that the presence of a more coordinating triflate counteranion might compete with the substrate for binding to the copper complex. Other reasons include nucleophilic attack by the triflate into electrophilic sites, such as the carbocation-like intermediate generated, as the reaction progresses.

**Table 4: Triflate doping screening**

<table>
<thead>
<tr>
<th>#</th>
<th>substrate</th>
<th>$M(OTf)_n$</th>
<th>$X$</th>
<th>product</th>
<th>yield</th>
<th>d.r.</th>
<th>e.e.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>137</td>
<td>none</td>
<td>PF$_6$</td>
<td>139</td>
<td>14%</td>
<td>&gt;20:1</td>
<td>68%</td>
</tr>
<tr>
<td>2</td>
<td>137</td>
<td>none</td>
<td>PF$_6$ (+ 1% OTf)</td>
<td>139</td>
<td>14%</td>
<td>&gt;20:1</td>
<td>65%</td>
</tr>
<tr>
<td>3</td>
<td>137</td>
<td>NaOTf</td>
<td>PF$_6$</td>
<td>139</td>
<td>10%</td>
<td>&gt;20:1</td>
<td>42%</td>
</tr>
<tr>
<td>4</td>
<td>137</td>
<td>Mg(OTf)$_2$</td>
<td>PF$_6$</td>
<td>139</td>
<td>10%</td>
<td>&gt;20:1</td>
<td>38%</td>
</tr>
<tr>
<td>5</td>
<td>137</td>
<td>LiOTf</td>
<td>PF$_6$</td>
<td>-</td>
<td>0%</td>
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</tbody>
</table>
At 0 °C, reactions were much more selective for the desired product, although conversions were poorer and reaction rates were significantly slower. We rationalised that a more reactive substrate bearing a more electron-rich alkene moiety could help expedite the reaction at low temperatures. Thus, *para*-methoxy-dihydronaphthalene substrate 142 and dihydropyran substrates 73 and 90 were synthesised. These substrate types contain more nucleophilic alkenes due to resonance-driven electron donation from alkoxy groups (Scheme 40).

These new substrates (73, 90 and 142) were initially used in the reaction with an achiral CuCl catalyst at 30 °C. While previous substrates reacted well under these conditions, these new more reactive substrates formed multiple side products in the achiral reaction with CuCl. Dihydropyran 73 gave none of the desired product 143 (Scheme 41), while dihydronaphthalene 142 (Table 5, entry 1) and dihydropyran 90 (Table 6, entry 1) had unexpectedly low yields for their respective products in the reaction with CuCl. Although the achiral reactions were unsuccessful, substrates 142 and 90 were tested against catalyst complex 133. Pleasingly, the enantioselective reactions worked much better than the achiral variants – giving excellent yields, enantioselectivity and diastereoselectivity for products 144a/b (up to 63% yield, 5:1 d.r. and 90% e.e., Table 5, entries 2-3) and 145 (up to 94% yield, >20:1 d.r. and 91% e.e., Table 6, entries 2-4).

**Scheme 40:** New reactive substrates.

**Scheme 41:** Unsuccessful racemic arylation of dihydropyran 73.
Table 5: Reaction studies for dihyronaphthalene-type substrate 142

```
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<th>catalyst</th>
<th>product</th>
<th>yield</th>
<th>d.r.</th>
<th>e.e.</th>
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<td>133</td>
<td>144a/b</td>
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<td>5:1</td>
<td>90%</td>
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</tbody>
</table>
```

Note: (a) unless otherwise stated, e.e. for either diastereomers were the same; (a) Reagents were added at 0 °C before slow warming to 10 °C to start the reaction.

Table 6: Reaction studies for dihydropyran-type substrate 90

```
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<th>temp.</th>
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<th>product</th>
<th>yield</th>
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<th>e.e.</th>
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<td>Na₃PO₄</td>
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<td>48 h</td>
<td>133</td>
<td>145</td>
<td>85%</td>
<td>&gt;20:1</td>
<td>85%</td>
</tr>
<tr>
<td>4</td>
<td>90</td>
<td>DTBP</td>
<td>5 °C</td>
<td>48 h</td>
<td>133</td>
<td>145</td>
<td>94%</td>
<td>&gt;20:1</td>
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<td>80%</td>
</tr>
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Note: (a) diphenyliodonium triflate salt was used, instead of 146.

Table 7: Copper salts with (+)Ph-BOX screening

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<th>yield</th>
<th>d.r.</th>
<th>e.e.</th>
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<td>145</td>
<td>94%</td>
<td>&gt;20:1</td>
<td>91%</td>
</tr>
<tr>
<td>2</td>
<td>90</td>
<td>CuPF₆</td>
<td>5 °C</td>
<td>48 h</td>
<td>145</td>
<td>67%</td>
<td>&gt;20:1</td>
<td>76%</td>
</tr>
<tr>
<td>3</td>
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<td>5 °C</td>
<td>48 h</td>
<td>145</td>
<td>82%</td>
<td>&gt;20:1</td>
<td>81%</td>
</tr>
<tr>
<td>4</td>
<td>90</td>
<td>CuCl₂</td>
<td>5 °C</td>
<td>48 h</td>
<td>145</td>
<td>63%</td>
<td>&gt;20:1</td>
<td>70%</td>
</tr>
</tbody>
</table>
```

Note: CuXₙ-(+)-Ph-BOX catalyst complexes were used for all reactions, instead of 93.
Reactions of copper-BOX complex 133 with dihydropyran 90 proved to be robust and effective, giving excellent yields (94%), with complete diastereoselectivity (>20:1) and excellent enantioselectivity (91% e.e.), when DTBP was used as the base (Table 6, entry 4). It was also observed that fluctuations in temperatures significantly affected the enantioselectivities in these reactions; higher temperatures lowered e.e. from 91% at 5 °C to 79% at 30 °C (Table 6, entries 4-7). For these new reactions with dihydropyran substrate 90, different copper sources were also tested to determine the most suitable counterion for the catalyst (+)Ph-BOX complex (Table 7, entries 2-4). Despite our previous results on triflate salt doping in Table 4, it was found that the Cu(OTf)2 with (+)Ph-BOX complex was still better than CuPF6 (Table 7, entry 2) or CuCl (entry 3), indicating that a highly electronegative ligand on the copper is still a design prerequisite. Reports of other copper-BOX catalysed reactions on alkenes also indicated the importance of these electronegative ligands.103-104

This work on dihydropyran substrate 90 demonstrated that the chiral bis(oxazoline) ligand was necessary not just to achieve enantioselectivity, but also for the overall reaction itself. Chemoselectivity and reactivity were enhanced through the use of the bis(oxazoline) ligand, which influences the electronic effects and coordination sites of the copper in the reaction. For this to occur, the reaction intermediate copper-complex would require four- to five-coordination sites around the copper species. A five-coordination complex with the substrate, for example, is possible if the hydroxyl group on the allylic alcohol takes part in coordination in a bidentate fashion. This substrate-catalyst bidentate feature was also found to be important in previous studies done by our group,53,73 as well as in MacMillan’s group – who used a pendant carbonyl group to facilitate the formation of a square-pyramidal Cu(III) complex.75 This chelating effect of the substrate to the copper, through both the hydroxyl group and alkene, could perhaps contribute to the high diastereoselectivity displayed in the achiral reaction with CuCl (Figure 8a). The absolute configuration of the major enantiomer of product 145 was studied under X-ray crystallography (Figure 8b), and the major enantiomer was found to be (5R,10R)-10-phenyl-6-oxaspiro[4.5]decan-1-one.
Figure 8: (a) Possible initial binding to 90 by Cu(III)-aryl complex; (b) absolute configuration of 145 as determined by X-ray crystallography.

2.4.2 Mechanistic discussion for Cu(II)-BOX-catalysed arylation-driven SPR

Since electron-rich substrates, para-methoxy-dihyronaphthalene 99 and dihydropyran 101, were shown to have increased selectivity and reactivity, it is possible that a carbocation-like intermediate could be in play. Previous work conducted in our group has established this for arylation with copper and diaryliodonium salt on alkenes.\textsuperscript{68} Furthermore, the observed diastereoselectivity for reactions with dihyronaphthalene-type substrates 137, 138, and 142, and dihydropyran substrate 90 might be due to substrate chelation in the intermediate via the alcohol functionality and alkene, where the newly generated ketone functionality faces the same side as the newly introduced aryl group. Thus, an initial oxidative addition of Cu(I) into diaryliodonium salt to generate a square planar copper(III)-aryl complex 147, followed by either a coordination to alkene to form complex 148a via a formal alkoxide directing group, or direct insertion into the alkene through the formation of a cyclic organometallic complex 148b, is proposed (Scheme 42).

Scheme 42: Proposed initial generation of Cu(III) complex.
To differentiate between these two possible initial intermediates, a control reaction was performed using trimethylsilyl (TMS)-protected alcohol 149. Previous optimum condition employed for simple acyclic substrate 68 was able to generate the arylated ketone product 70 in 41% yield and 52% e.e., while the TMS-protected variant 149 afforded just 5% yield and 26% e.e. of the same product 70 (Scheme 43). This result might implicate the importance of the hydroxyl group in the reactivity, possibly through an initial coordination to copper, such as in intermediate 148a. Furthermore, since the phenylation process of the terminal double bond in substrate 68 did not generate a stereocentre, the observed enantioselectivity for product 70 could only be induced by the catalyst during the SPR step. This might indicate that the involvement of a formal carbocation in the SPR process is not the only pathway in operation, and that the copper complex may be involved in the rearrangement step.

**Scheme 43:** Control reaction with TMS-protected alcohol.

Subsequently, this highly electrophilic complex 148a could undergo three possible reaction pathways. In the first pathway, insertion of the Cu(III)-Ar bond to the ligated alkene (syn-carbocupration) generates a Cu(III)-alkyl intermediate 150a. The generation of this species places the required partial positive charge adjacent to the tertiary alcohol, thus triggering the stereoselective 1,2-migration of one of the two C-C bonds on the tertiary alcohol and completing the arylation-driven SPR process to afford spirocyclic β-aryl ketone product 145 (A, Scheme 44).
Scheme 44: Reaction pathway A; insertion of the Cu(III)-Ar bond into alkene prior to SPR.

In the second possible pathway, initiation of the process via SPR may also occur. An electrophilic attack on the alkene is coupled to the SPR step to generate a Cu(III)-alkyl intermediate, 150b. This high valent copper complex then reductively eliminates to transfer an aryl group on the β-position of the newly formed ketone, with the concomitant regeneration of the active Cu(I) catalyst (B, Scheme 45).

Scheme 45: Reaction pathway B; SPR preceding arylation.

In the third possible pathway, electrophilic attack by the alkene was postulated to proceed first, transferring the aryl group and generating carbenium intermediate 150c. This is then proceeded by SPR to complete the arylative SPR process (C, Scheme 46).

Scheme 46: Reaction pathway C; alkene arylation to generate a carbenium intermediate prior to SPR.
Although further study is needed to elucidate the exact reaction mechanism, the stereochemical outcome may be rationalised by the participation of the copper complex in the SPR step, as postulated in reaction pathway A and B (Scheme 44 and 45).

**Figure 9:** Proposed mechanistic cycle for copper(II)-(+) BOX-catalysed arylation-driven SPR cascade.

In all three possible pathways, chelation of the substrate to the copper(III)-aryl species in intermediate 148a, with the copper complex sitting on one face of the molecule, would react to generate the corresponding intermediates 150a-c. In pathways A and B,
precluding racemisation of the C-Cu bond, this would bring both the transferring aryl group and the newly-formed carbonyl group on the same face of the molecule (Scheme 44 and 45). This might explain the high diastereoselectivity observed in the reaction. However, the generation of arylated alkene side-product 134 – previously observed during our optimisation study with substrate 130 – suggests that the arylation event should precede the SPR process and indicates pathway A to intermediate 150a to be more likely. Nevertheless, pathway C could also be in operation and should not be ruled out – generating either configuration about the spirocyclic chiral carbon centre via carbenium intermediate 150c. A proposed full mechanism is summarised (Figure 9), with absolute configuration rationalised (Figure 10).

The approach by the highly electrophilic copper(III)-aryl-(+)-BOX complex onto the electron-rich alkene via the Re face to form (R,R)-148a is favoured, as approach from the Si face goes through a higher energy steric clash with the phenyl substituent on the oxazoline ring (Figure 10). This allows the attack and complexation on the substrate to go through a square pyramidal complex, which then favours the subsequent cascade reactions discussed in pathways A to C (Schemes 44-46).

Figure 10: Rationalisation of the preferred facial selectivity for R,R configuration on intermediate 148a.
2.4.3 Substrate scope

Following our studies on electron-rich substrates, the scope was first studied with the best performing dihydropyran-type substrates. In addition, the products of these dihydropyran substrates would enable access into functionalised tetrahydropyran (THP) rings, which are important building blocks for many natural products. The preparation of spirocyclic THPs have been described in numerous studies involving SPRs, further highlighting its importance. Hence, initial attempts focused on varying both the size of and the substituents on the migrating allylic carbinol (Figure 11).

The first substrate tested was dihydropyran 151a/b, which possessed a symmetrical ethyl ester appendage on the allylic carbinol moiety. This cyclic compound could generate either isomer of the ester appendage as a chiral centre during our arylation-driven SPR reaction. Its substrate synthesis, however, favoured the cis diastereomer over the trans isomer (13:1 d.r., inseparable mixture, Scheme 47a). Applying 151a/b into our arylation-driven SPR reaction then afforded us 156a in excellent yield (92%), complete diastereoselectivity (>20:1), and good enantioselectivity (80% e.e.). As expected, both starting isomers were converted equally, yielding the respective products (156a/b) in 13:1 ratio with diphenyliodonium hexafluorophosphate 146 as the aryl source (Scheme 47b).

Scheme 47: (a) Synthesis of meso compound 151a/b, and (b) its arylation-driven SPR to 156a/b.
Arylative-SPRs on oxetane-containing dihydropyran 152 and the azetidine-containing dihydropyran 153 were next investigated. These substrates would allow entry into spirocycles with heteroatoms in the expanded ring, as well as further functionalisations, especially on the Boc-protected azetidine in 153. Arylation-driven SPR on both substrates 152 and 153, afforded, in high yields, complete diastereoselectivity and high enantiomeric excess, the corresponding spirocyclic tetrahydrofuranone 157 (77% yield, >20:1 d.r., 83% e.e.) and pyrrolidinone 158 (86% yield, >20:1 d.r., 85% e.e., Scheme 48).

Scheme 48: Arylation-drive SPR to generate spirocyclic tetrahydrofuranone 118 and pyrrolidinone 119.

Besides pendant groups and substitutions on the cyclic carbinol moiety, larger ring sizes were also investigated. Dihydropyran substrates 154 and 155 underwent smooth arylative SPR to form the [5,5] spirocyclic ketones 159 (96% yield, >20:1 d.r., 92% e.e.) and 160 (85% yield, >20:1 d.r., 99% e.e.), respectively (Scheme 49). These 6-membered rings spirocycles were obtained with surprisingly higher enantioselectivities, with 160 giving 99% e.e. However, 160 required three equivalents of both diphenyliodonium hexafluorophosphate 146 and base DTBP to complete the reaction (Scheme 49).

Scheme 49: Arylation-drive SPR to generate [5,5] spirocycles 159 and 160.
X-ray crystallography was performed on product 160 to determine its absolute configuration (Figure 12). Whilst initial arylation was successful, the subsequent dihydropyran substrates bearing larger sized rings (161 and 162), O-TMS protected alcohol (163), and allylic isopropanol 164 were unsuccessful in the SPR process (Figure 13). However, of these new dihydropyran substrates, 161, 162 and 164 did undergo arylation (Scheme 50). This was rationalised to be due to the thermodynamic requirement of the ring-expansion to be at least energetically more favourable in preference to the deprotonation of the newly arylated tertiary carbon. Strain energies of cycloalkanes are a good gauge of the ability of these substrates to perform arylative SPR. While expansion from 4- to 5-membered cycloalkane releases -20.1 kcal/mol of ΔH, and 5- to 6-membered expansion releases -6.1 kcal/mol of ΔH, ring expansions from 6- to 7-membered (161) and 7- to 8-membered (162) cycloalkanes require gains in enthalpy.\(^{107}\) The SPR process is thus disfavoured for these substrates, following the arylation event. While dihydropyran 161, 162 and 164 gave the unsaturated arylated products 165 (71% yield), 166 (89% yield) and 167 (82% yield), respectively, dihydropyran 163 did not take part in the arylation event and was completely unreactive (Scheme 50). This could be due to either the requirement of the initial binding to the alcohol moiety in a formal copper-alkoxide bond, or the steric bulk imposed by the O-TMS group around the alkene.

**Figure 13:** Unsuccessful dihydropyran-type substrates tested
Scheme 50: Unsuccessful SPR reactions for substrates 122-125.

Thus, with the use of these dihydropyran-type scaffolds, optimum yield, d.r. and e.e. were observed for the corresponding β-aryl spirocyclic THP products, and these are summarised below (Figure 14).

Figure 14: Summary of dihydropyran-type substrate scope to form β-aryl spirocyclic THP products.
Since reactivity of the alkene was important in achieving high yield and stereoselectivities of the reaction, the next step was to design other substrate types with activated alkenes. Indene was thus chosen as a motif of interest due to its reactivity on the alkene. Furthermore, reactions with indene-type substrates would allow facile access into functionalised indane-type structures, which are prevalent in different anti-pathogenic natural products. Another substrate class to investigate was the para-methoxy-dihydronaphthalene-type systems, which were found to work well in our initial attempt with 142, giving tetralin-type products (144a/b, 63% yield, 5:1 d.r., 90% e.e.) that are also prevalent in different natural products and drug molecules. Both indene (168-170) and dihydronaphthalene-type (171) substrate analogues have subsequently been investigated (Figure 15).

![Figure 15: Indene and dihydronaphthalene-type substrates](image)

The arylation-driven SPR of indene 168 proceeded with a modest 3:1 d.r. Gratifyingly, however, both yield and enantioselectivity were excellent (172a/b, 97% yield and 90% e.e., Scheme 51a). X-ray crystallography of the minor diastereomer 172b revealed that this loss of diastereoselectivity arose from the choice of the migrating C-C bond in the ring-expansion SPR step (Figure 16). The cyclobutanol ring in this system now lacks facial selectivity. Increasing the size of this allylic cyclic carbinol returns the high facial selectivity (Scheme 51b). The related 5-membered cyclopentanol ring in substrates 169 and 170, induced higher diastereoselectivities of >20:1 d.r., with excellent yields and enantioselectivities for spirocyclic indane products 173 (98% yield, 91% e.e.) and 174 (96% yield, 95% e.e.), respectively (Scheme 51b and 51c). This effect of increasing diastereoselectivity due to increasing allylic cycloalkanol size was also observed when comparing the reaction products, spirocyclic tetralin 144a/b and 175, from dihydronaphthalene substrates 142 and 171, respectively, where d.r. increased from 5:1 in 144a/b to >20:1 in 175 (63% yield, 84% e.e., Scheme 51d). Another interesting aspect observed was when electron density of the alkene increased from indene substrate 169 to 170, enantioselectivity was also observed to increase, albeit by a small amount.
(Scheme 51c). This supports the observation made previously during optimisation in Section 2.4.1. X-ray crystallography on tetralin product 175 confirmed that the absolute configurations in these new substrate types were similar to that of the THP product.

Scheme 51: Arylation-driven SPR for indene- and dihydronaphthalene-type substrates

Figure 16: X-ray crystallography for minor diastereomer 172b (left), and tetralin product 175 (right).
Substrates were also designed bearing heteroaromatic indole, benzofuran, and benzothiophene functionalities (Figure 17). Subjecting these substrates to the arylation-driven SPR, if successful, would also add to the existing arsenal of heteroaromatics dearomatisation reactions, useful in various total synthesis strategies. These substrates were prepared via lithiation on the C-H bond vicinal to the heteroatom directing group. The most nucleophilic carbon on these heteroaromatic systems is the C-3 carbon, due to resonance donation from the heteroatom (Figure 17). Furthermore, previous work on the enantioselective copper-catalysed arylation-cyclisation cascade with indole-based substrates, by MacMillan and co-workers, showed that arylation via copper-catalysed activation of the diaryliodonium salt almost always happened on the C-3 position of the indole. Thus, tertiary allylic alcohols bearing scaffolds of N-methyl indole 176 were subjected to the arylative SPR conditions, completing the heteroaromatics scope with scaffolds of benzofuran 177 and benzothiophene 178. Unfortunately, the arylative-SPRs of these heteroaromatic substrates were unsuccessful under the conditions used. Trace amounts of O-arylation on the alcohol (179) were, however, observed (Figure 17).

![Figure 17: Heteroaromatic substrates synthesised and tested.](image)

Thus, for these different aromatic scaffold classes studied, optimum yields, d.r. and e.e. were observed for the indene and dihydronaphthalene-type substrate classes, affording us the corresponding β-aryl spirocyclic indane and tetralin products as summarised in Figure 18.
After a number of cyclic allylic alcohol substrate classes – namely the dihydropyran, indene and dihydronaphthalene classes – we attempted the transformation again on new acyclic substrates to probe the limits of the reaction. From the established substrate scope, electron-rich substrates consistently performed better in both reactivity and enantioselectivity. Hence, substrates 180 and 181 were synthesised, possessing an O-activated alkene (Scheme 52). It is notable that during the synthesis of 180, starting from a mixture of cis- and trans-alkenes, only the trans-alkene product 180 was formed, as indicated by NOESY 2D-NMR and 1-D NOE NMR measurements.

Subjecting these activated acyclic substrates into the reaction showed that while 180 worked moderately well, giving 62% yield, 2.6:1 d.r., and 78% e.e. of cyclopentanone product 182, substrate 181 surprisingly gave no enantioselectivity even though the yield for cyclopentanone 183 was quantitative (Scheme 53). This intriguing stark difference in enantio-control could not be explained simply by the absence of a substituent on the 2-
position of the alkene, as our initial simple acyclic substrates tested, 68 and 130, gave modest enantioselectivity for their products (52% e.e. and 26% e.e., respectively). One possible explanation is that the O-iso-butyl (-OCH(CH₃)₂) substituent in 181 has a much smaller steric bulk compared to the methyl (-CH₃) group in 68 around the alkene, due to the longer C-O bond length.¹¹² On the other hand, substrate 180, with a much lower steric bulk than 181 on the 1-position of the alkene still generated high enantioselectivity (78% e.e.). This was attributed to the presence of the ethyl substituent on the 2-position of the alkene in 180 – which might indicate that for these acyclic substrates, while steric bulk on both the 1- and 2-positions on the alkene are required to generate enantioselectivity, the 2-position is much more important in determining stereo-control.

**Scheme 53:** Arylation-driven SPR on activated acyclic substrates.
2.4.4 Diaryliodonium salt scope

The tolerance of the reaction towards a range of transferring aryl groups was next investigated (Table 8). Symmetrical and unsymmetrical diaryliodonium salts were prepared and used, specifically: Mes(Ph)IPF$_6$ (184), Mes(Tol)IPF$_6$ (185), Mes(Ar-i-Bu)IPF$_6$ (186), Mes(ArCl)IPF$_6$ (187) and (ArCl)$_2$IPF$_6$ (188, Figure 19).

![Figure 19: Diaryliodonium salts used to probe aryl transfer reagent scope.](image)

In general, with the exception of phenyl transfer reagents, other aryl transfer reagents used displayed lower reactivity and, in some cases, resulted in lower enantioselективivity when employed with dihydropyran substrate 90 (Table 8, entries 1-5). For example, while the transfer of phenyl groups gave 94% e.e. (entry 2), the transfer of para-tolyl, para-iso-butyl and para-chloro aryl groups gave just 82%, 80% and 81% e.e., respectively, and required higher temperatures (10 °C) for the reaction to proceed (entries 3-5). Furthermore, the reactions utilising relatively electron-rich diaryliodonium salts 185 and 186, were observed to proceed much faster (entries 3-4), indicating the importance of electronic effects.

<table>
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<td>91%</td>
</tr>
<tr>
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<td>145</td>
<td>5 °C</td>
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<td>&gt;20:1</td>
<td>94%</td>
</tr>
<tr>
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</tr>
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</tbody>
</table>
In the substrate scope, the larger allylic cyclopentanol substrates – namely the dihydropyran, indene and dihydronaphthalene scaffolds – were much more robust in their reactions; optimum diastereoselectivities (up to >20:1 d.r.) and enantioselectivities (up to 99% e.e.) were achieved at room temperature. Using indene substrate 169, the transfer of the same para-substituted aryl groups used in the study with 90 – tosyl (185), iso-butyl (186), chloro (188) – was first probed. Pleasingly, these diaryliodonium salts were found to perform better with substrate 169, giving indane spirocyclic products 192 (97% yield, 90% e.e.), 193 (99% yield, 91% e.e.) and 194 (99% yield, 94% e.e.), all in excellent yields, e.e. and as a single diastereomer (Scheme 54).

Next, other para-substituted halo-aryl groups, namely bromo (195), and fluoro (196), followed by other electron withdrawing groups, ethyl ester (197) and trifluoromethyl (198) and electron-donating para-methoxy groups (199), were transferred (Scheme 54). Pleasingly, all these diaryliodonium salts were found to work well, giving spirocyclic indane products 200 (91% yield, 90% e.e.), 201 (99% yield, 92% e.e.), 202 (96% yield, 92% e.e.), 203 (94% yield, 93% e.e.) and 204 (81% yield, 62% e.e.), respectively, and as a single diastereomer (Scheme 54). It is worthwhile to note that between the same transferring aryl for both symmetrical and unsymmetrical diaryliodonium salts, only the better of the two are shown, although differences were minimal.

Scheme 54: Scope for para-substituted aryl transfer groups with 169. All reactions gave >20:1 d.r.
The scope of aryl transfer was also investigated for dihydropyran substrate 154. Using diaryliodonium salts 185, 186 and 188, spirocyclic THP products 205-207 were afforded in excellent yields (82-91%) and enantioselectivities (90-92% e.e.), and as a single diastereomer (Scheme 55).

Scheme 55: Scope for para-substituted aryl transfer groups with 154. All reactions gave >20:1 d.r.

After establishing that the reaction worked well with para-substituted aryl transfer reagents on both the indene and dihydropyran-type substrates, meta-substituted aryl transfer reagents were next investigated. Bromo- (208), fluoro- (209), ethyl ester- (210), trifluoromethyl- (211), trifluoromethoxy- (212), and dichloro-aryl (213), as well as 2-naphthyl (214) were all used in the reaction with substrate 169 to generate the corresponding spirocyclic indane products 215-221 (Scheme 56). Delightfully, various meta-substituted aryl groups, as well as 2-naphthyl, were successfully transferred, giving 85-99% yields, >20:1 d.r., and 90-99% e.e., indicating the generality of this method for these aromatic groups.

Next, ortho-tolyl (223) and the ortho-fluoro aryl (222) groups were attempted. The bis(2-fluorophenyl)iodonium hexafluorophosphate salt (222) worked well with substrate 169, but required heating at 50 °C for 48 h in a sealed microwave vial in CH2Cl2 to obtain indane spirocycle 224 in good yield and high e.e. (Scheme 57). The mesityl(ortho-tolyl)iodonium hexafluorophosphate salt (223), on the other hand, was unsuccessful in transferring the bulkier ortho-tolyl group to substrate 169.
Scheme 56: Transfer of meta-substituted aryl and 2-naphthalene groups. All reactions gave >20:1 d.r.

Fortunately, trying the more reactive dihydropyran-type substrate 154 enabled the transfer of the ortho-tolyl group, again requiring heating at 50 °C for 48 h to obtain the spirocyclic THP product 225 in good yield and high e.e. (Scheme 57). Lastly, X-ray diffraction of single crystals of 194 and 215 confirmed that the absolute configuration (R,R) remained unchanged with the transfer of these halo-aryl groups (Figure 20).

Scheme 57: Transfer of ortho-substituted aryl groups. All reactions gave >20:1 d.r.
The transfer of heteroaromatic groups, such as pyridines, were also attempted. However, initial tests revealed that the bis(2-chloro-pyridine)iodonium salt (226) was unreactive under the conditions used for either the dihydropyran (154) or indene-type (169) substrates (Scheme 58a). This was probably due to the association of the pyridine to the copper catalyst. In addition, attempts at transferring thiophene by employing bis(thiophenes)iodonium hexafluorophosphate salt afforded just trace amounts of the product with 0% e.e.

However, a recent study by J. Zhu and co-workers, reported after this study was published, demonstrated the successful preparation of β-thiophene spirocycle ketone 227 with 71% yield, 3.1:1 d.r., and 89% e.e., when Cu(II)-BOX 228 and mesityl(thiophenes)iodonium hexafluoroarsenate 229 were utilised (Scheme 58b). To the best of our knowledge, this was the only heteroaromatic group that was successfully transferred for this arylative SPR transformation.

**Scheme 58:** Transfer of (a) 2-chloropyridine, unsuccessfully, and (b) thiophene by J. Zhu et. al.\textsuperscript{113}
Overall, the diarylodonium salt scope is summarised in Figure 21 below.

Figure 21: Summary of diarylodonium salt scope. All reactions gave >20:1 d.r.
2.4.5 Transformations of β-aryl-α,α'-spirocyclic ketones

The products generated from the arylative SPR methodology demonstrated here contain β-aryl-α,α'-spirocyclic ketones with rigid scaffolds and spatially defined functionalities, both of which could be exploited to build into small molecule biological probes. The molecules obtained from this arylation-driven SPR were subsequently revealed to work as platforms for further diversification, including (i) hydride reduction, (ii) reductive amination, and (iii) other rearrangement reactions.

β-aryl-α,α'-spirocyclic ketone 194, was selected as a model substrate and recrystallised to enantiopurity from hexane. A racemic version of ketone 194 was prepared and subjected to analogous conditions as the enantiopure version, to study the effects of the proceeding transformations on retention of chirality of the products, by chiral HPLC. Since the system has a carbonyl group, a hydride reduction was first performed to generate the corresponding alcohol. Initial attempts at using lithium aluminium hydride formed the desired alcohol product 230 in 80% yield and 10:1 d.r., indicating a large preference for the (S)-α,α'-spirocyclic alcohol. Approach from the Re face was probably shielded by the β-aryl group introduced from our arylative SPR process (Scheme 59, bottom). Repeating this reaction with two equivalents of the bulkier L-selectride furnished 98% yield of the desired alcohol with complete diastereoselectivity, and retention of enantiopurity as measured by chiral HPLC (Scheme 59).

Scheme 59: Hydride reduction with L-selectride on spirocyclic indane 194.
Amines are prevalent in natural products as well as medicinal molecules. Chiral amines, in particular, have been prevalent as pharmacophores for defining new drugs. Thus, the second transformation performed was a reductive amination to transform the ketone, generated in the SPR process, into a secondary amine. Using TiCl₄/Et₃N as the Lewis acid/base combination, m-Br-C₆H₄CH₂NH₂ as the source of amine, and NaBH₄ as a reductant, β-aryl-α,α'-spirocyclic ketone 194 was converted into the corresponding secondary amine 232, in 91% yield as a single diastereomer, and with retention of enantiopurity (Scheme 60).

Next, a second rearrangement was attempted. This was first tested with the Beckmann rearrangement, which would provide the spirocyclic ε-caprolactam product from the corresponding spirocyclic ketone-derived oxime. Studies to generate spirocyclic oxime 233 from ketone 194 were conducted, and the most efficient method was found to be the use of large excess (5.0 eq.) of hydroxylamine hydrochloride, with 1.1 equivalents of DABCO in methanol at room temperature for 12 h, affording spirocyclic oxime 233 in quantitative yields (Scheme 61a). Although application of the Beckmann rearrangement was observed to form ε-caprolactam product 234, isolation of this proved challenging. Spirocyclic ε-caprolactam 234 was unstable to purification methods on silica, alumina or LC columns, even under basic conditions. This could possibly be due to the labile tertiary benzylic C-H bond. Undesired product 235 was observed instead, formed from the loss of the tertiary benzylic proton and subsequent E2 elimination and dehydration (Scheme 61b).
Scheme 61: (a) Oxime 194 formation from 160 in preparation for (b) Beckmann rearrangement.

A related transformation to the Beckmann rearrangement, the Baeyer-Villiger oxidation, was next attempted by utilising mCPBA. Attack of the perbenzoate ion onto the ketone would generate a hemiketal with a δ+ perbenzoate oxygen. Since both carbon atoms adjacent to the hemiketal are different, the one that can most stabilise a developing positive charge – the quaternary spirocyclic carbon – would migrate to the δ+ perbenzoate oxygen, stereospecifically generating a highly strained spirocyclic ε-caprolactone product 236 (Scheme 62). Delightfully, the Baeyer Villiger oxidation worked to give 236 in 99% yield as a single diastereomer, with complete retention of chirality. To unequivocally show the stereoretention of the chiral centres, X-ray crystallography data on this spirocyclic ε-caprolactone 236 was obtained (Figure 22).

Scheme 62: Baeyer-Villiger oxidation of spirocyclic ketone 194 to spirocyclic ε-caprolactone 236.
Figure 22: X-ray crystal structure of 236 showing complete stereoretention

Since transformations of indane-type compound 194 were successful, the Baeyer-Villiger transformation was next applied to THP-type compound 160. Ring-expansion via the Baeyer-Villiger oxidation would enable access into chiral spiroketals, a useful moiety found in various insect pheromones as well as being an interesting synthetic challenge.\textsuperscript{116} Initial attempts, using excess mCPBA as for 194, successfully afforded spiroketal product 237. However, purification of spiroketal 237 was challenging as the product was sensitive to both Brønsted and Lewis acids. Purification on basified silica or alumina was unsuccessful as the product readily decomposed on the column. It was only after changing the inorganic base used to sodium carbonate instead of lithium carbonate, and using just 1.1 equivalents of mCPBA, that the reaction could be completed in quantitative yields and with complete diastereoselectivity (Scheme 63). The reaction mixture was immediately washed with saturated aqueous sodium metabisulfite to remove any remaining mCPBA, and the crude product obtained was sufficiently pure for NMR, HRMS and IR analysis. It was, however, too unstable to survive in the chiral HPLC column, and could not be analysed in this way.

\[
\text{Scheme 63: Baeyer-Villiger oxidation on tetrahydropyran-type ketone 160 to spiroacetal 237.}
\]

Hence, the ketone functional group generated from the arylation-driven SPR process can be stereoselectively transformed into various reactive groups. This functional handle was converted with ease into spirocyclic alcohol (230), amine (232) and caprolactones (236 and 237), although more work still needs to be done to optimise the reaction for caprolactams (234).
3. Non-Natural Peptide Macrocyclisation Enabled by Methionine-to-Tryptophan Linkage

3.1 Macroyclic peptides - Background

Macrocyclic peptides have huge potential as lead compounds for pharmaceuticals or as vehicles for cellular payload delivery due to improved properties in comparison to their linear counterparts: better bioavailability, through higher peptidase resistance; better cellular uptake efficiency; and better efficacy as drugs. This is especially important since the emergence of protein-protein interactions (PPIs) as promising targets for new therapeutics. By modifying features such as ring shape, size and functional groups, the rational design of macrocyclic peptide-based drugs and cellular vehicles is possible.

As pharmaceuticals, the United States Food and Drug Administration (FDA) has approved more than fifty macrocyclic peptides. The increasing rate of approval stems from the fact that peptide-based drugs display higher specificity and lower toxicity than small molecule drugs. Furthermore, the inclusion of unnatural amino acids and functional groups have generated novel lead compounds for therapeutics. In 2018, over forty macrocyclic peptides are in clinical use.

![Pasireotide](Image)

**Pasireotide**: trade name: Signifor; approved 2014

![Lanreotide](Image)

**Lanreotide**: trade name: Somatuline; approved 2007

**Figure 23**: Some FDA approved native macrocyclic peptide and analogues as drugs.

Most current macrocyclic peptide-based therapeutics are derived from natural products, such as pasireotide, a somatostatin analogue for the treatment of Cushing’s disease, and lanreotide, a long-lasting somatostatin analogue for the treatment of acromegaly and symptoms of endocrine tumours (Figure 23). However, recent synthetic advances have enabled the synthesis of unnatural macrocyclic peptides that interact with targets for which nature does not offer solutions.
One important aspect relevant to the ability for macrocyclic peptides to both act as drugs for cellular targets and as vehicles for cellular delivery, is their ability to penetrate the cell membrane. This may be performed either passively,\textsuperscript{124} or through endocytosis.\textsuperscript{125-127}

3.2 Macro cyclic peptides as cell-penetrating peptides (CPP)

Cell penetrating peptides (CPPs) are in general short peptides, not exceeding 30 residues, which have the ability to traverse cell membranes with little toxicity, without the need for chiral recognition by membrane receptors. The first observation of CPPs was in the late 1980, when the trans-activator of transcription (Tat) protein of the human immunodeficiency virus (HIV) was discovered to be an efficient CPP.\textsuperscript{128-129}

3.2.1 Structural requirements for CPP

Interactions between CPPs and the plasma membrane are regulated by (i) the positive charge density (Figure 24), (ii) the presence of hydrophobic and aromatic groups (Figure 25), and (iii) secondary structure through macrocyclisation (Figure 26).

3.2.1a Positive charge density

Long-range electrostatic attraction is believed to be the first interaction between a positively-charged CPP and the negatively charged polysaccharides and lipids on the plasma membrane (Figure 24). This crucial initial interaction was proven for different CPPs, where a significant reduction in cellular uptake was observed if any of the basic residues on a CPP were replaced.\textsuperscript{130-131}

![Figure 24: Electrostatic interaction between positively-charged CPP and negatively charged membrane.](image)

3.2.1b Hydrophobicity and tryptophan (Trp)

Hydrophobic residues were also shown to assist CPP as they enhance peptide translocation across the cell membrane (Figure 25).\textsuperscript{132-133} However, too much hydrophobicity may result in less efficient internalisation, as CPPs become stuck in the plasma membrane.\textsuperscript{134}
Among hydrophobic residues, aromatic residues play a role beyond simple hydrophobicity. Tryptophan (Trp), in particular was calculated to possess favourable free energies of insertion into lipid bilayers. In addition, it was demonstrated that Trp is involved in membrane destabilisation during translocation, and was a crucial residue for many CPPs. Norden and co-workers observed that simply increasing the number of Trp could enhance cellular uptake. Binding of Trp to membranes was postulated to be mediated by hydrophobic and π-anion interactions.

3.2.1c Macrocyclisation

One of the most successful recent approaches to the development of CPPs is through macrocyclisation to induce secondary structure stabilisation. In 2013, Pei and co-workers compared known endocytosis-promoting linear CPP motifs to their macrocyclic counterparts, and discovered that the latter bind to membranes with much higher affinity (Figure 26).

It was postulated that while the binding of flexible linear peptides to membranes causes a loss of entropy, the binding of macrocyclic peptides is conformationally constrained and thus reduces entropic loss (Figure 26).
Strategies used for peptide macrocyclisation vary but can in general be classified into three distinct categories: (i) head-to-tail coupling, (ii) side-to-head or -tail coupling, and (iii) side-to-side coupling. These are briefly described in the next section.

3.3 Synthetic strategies for peptide macrocyclisation

The first category is a straightforward head-to-tail macrocyclisation (Figure 27). Various chemical coupling reagents have been developed for this strategy, and are typically employed to form native amide linkages in a macrolactamisation reaction. Other chemical methods have also been developed to form unnatural linkages, such as the 1,2,3-triazole heterocyclic group in azide-alkyne cycloadditions.

![Figure 27: Head-to-tail coupling.](image)

The second category is the native side-chain to head/tail macrocyclisation strategy, usually linking the -CO$_2$H side chain of aspartic acid (Asp) or glutamic acid (Glu) with the N-terminus, or the -NH$_2$ side chain of lysine (Lys) residue with the C-terminus. If the side chains of alcohol-containing residues are used to couple with the C-terminus instead, then macrolactonisation can occur (Figure 28).

![Figure 28: Side-to-head or -tail coupling showing Macrolactonisation.](image)
The third category is the native side-chain to side-chain macrocyclisation strategy, of which the most commonly used is the disulfide bond formation from two cysteine residues (Figure 29). Other forms of macrolactonisation or macrolactamisation can also occur from carboxylic acid/alcohol or carboxylic acid/amine coupling, respectively, from the relevant side-chain residues. However, for these types of macrocyclisation, significant conformational elements must be considered. Sterically encumbered sites of macrocyclisation, for example, can severely impact reactivity and yield.\textsuperscript{146}

\textbf{Figure 29:} Side-to-side coupling showing disulfide bridge formation.

Chemical transformations developed for these macrocyclisation strategies include, but are not limited to, (i) macrolactamisation, (ii) native chemical ligation, (iii) macrolactonisation, (iii) Ugi-type multicomponent reaction, (v) reversible imine formation, as well as (vi) various peptide stapling strategies.
3.3.1 Macrolactamisation reactions

One of the earliest examples of the macrolactamisation approach using conventional coupling reagent, in a head-to-tail fashion, is the total synthesis of cyclosporin A 241 (Scheme 64).\textsuperscript{154} Isolated from the fungus \textit{Toiyocladium inflatum gams}, it is a cyclic undecapeptide, recognised as a reversible inhibitor for the transcription of cytokines with several N-methylated amide bonds and novel amino acid, (2S,3R,4R,6E)-3-hydroxy-4-methyl-2-methylamino-6-octenoate (MeBmt).\textsuperscript{153}

\textbf{Scheme 64:} First total synthesis of cyclosporin A.\textsuperscript{153}

First synthesised in 1984 by R. M. Wenger, the total synthesis began with the preparation of fragment 238, containing MeBmt (Scheme 64). This was then coupled to 239, using a peptide coupling reagent, BOP, in the presence of N-methyl morpholine (MeMorph) to give linear peptide 240 in 73% yield. Deprotection of both termini revealed the unprotected undecapeptide, which was coupled over two days using BOP to afford cyclosporine A (241) in 30% yield (Scheme 64).\textsuperscript{153}
Thirty years later, Danishefsky and co-workers employed a thioacid/isonitrile coupling strategy in the total synthesis of Cyclosporin A; various thioacids, such as leucine-derived 242, were smoothly coupled with isonitriles, such as valine-derived 243, to afford intermediate N-thioformyl amides (244). Reduction of this subsequently afforded N-methylated peptide fragment 245 (Scheme 65). This coupling process was repeated until the final cyclosporine molecule was afforded in 0.3% overall yield over 29 steps.\(^{155}\)

![Scheme 65: Isonitrile coupling for fragment synthesis towards the total synthesis of cyclosporine.](image)

Various chemical coupling reagents, such as TBTU, have since been developed for efficient amide bond formation.\(^ {146}\) By utilising orthogonal protection strategies, macrocyclic peptides have been prepared using traditional coupling reagents on solid-phase.\(^ {151}\) In one example, head-to-tail macrocyclisation – in the synthesis of cell-membrane integrin-binding macrocyclic tetrapeptides – was achieved on solid-phase peptide synthesis (SPPS) starting with Asp that is bound on the solid support by its side chain (Scheme 66).\(^ {152}\) Orthogonal protection of the C-terminus with O-allyl and the N-terminus with Fmoc, in resin-bound tetrapeptide 246, facilitated their selective deprotection and eventual macrocyclisation with TBTU to macrocyclic tetrapeptide 247 in 65% overall yield (Scheme 66).\(^ {152}\)

![Scheme 66: Macrocyclisation using orthogonal protection strategy on SPPS.](image)
3.3.2 Native chemical ligation for macrocyclisation

One of the biggest factors for the successful study of various biologically important peptides, such as \( \alpha \)-defensins (Figure 30), is their accessibility by chemical synthesis. Isolated from the rhesus macaque (\textit{Macaca mulata}) in 1999, \( \alpha \)-defensins 1 (RTD-1) is a disulfide-rich macrocyclic 18 residues peptide that plays a key role in mammalian immune system against microbes (Figure 30).\textsuperscript{156} Targeting cell membranes rather than specific enzymes,\textsuperscript{157} these macrocyclic peptides utilise their positively charged surface to interact with the anionic phospholipid head groups.\textsuperscript{158-159}

![Figure 30: RTD 1; General structure of \( \alpha \)-defensins (right). Picture from M. E. Selsted \textit{et. al}.\textsuperscript{160}](image)

Early syntheses enlisted Fmoc chemistry on SPPS, followed by oxidation of the cysteine (Cys) groups to bring the C- and N-termini into close proximity for chemical coupling. Although successful, racemisation of Cys residues during macrocyclisation was a pertinent problem.\textsuperscript{156} It was only after the development of native chemical ligation by Kent and co-workers in 1994 that this problem was solved.\textsuperscript{161} This strategy involves an exchange between a thioester and the free thiol of Cys. Macrocyclisation is achieved by an irreversible S-to-N acyl transfer, which releases Cys as a free thiol (Figure 31).\textsuperscript{162}

![Figure 31: Native chemical ligation in the chemical synthesis of \( \alpha \)-defensins.](image)
3.3.3 Macrolactonisation reactions

In 2012, Jolliffe and co-workers synthesised the cyclic peptide core of the antifungal and antibiotic cyclic depsipeptide, LI-F04a, using a modified Yamaguchi macrolactonisation strategy. Alternative approaches, such as the Corey–Nicolaou macrolactonisation, resulted in epimerisation of the C-terminal amino acid (Scheme 67). Enlisting Fmoc chemistry on solid-phase peptide synthesis (SPPS), the authors prepared the starting linear peptide 248. Yamaguchi reagent, TCBC, was employed under basic conditions to generate a reactive mixed anhydride intermediate 249, which upon reaction with N-terminal Thr, afforded macrocycle 250 in 58% yield and 11.5:1 d.r. (Scheme 67).\(^1\)

\[\text{Scheme 67: Synthesis of macrocyclic core of antifungal and antibiotic LI-F04a.}\]

3.3.4 Ugi multicomponent reactions for peptide macrocyclisation

In 2015, Rivera and co-workers developed the Ugi multicomponent reaction on peptides. In their study, the authors achieved macrocyclisation by linking Lys with Asp or Glu three or four residues away.\(^2\) In one of the systems studied, linear protected peptide 251 was reacted with isocyanide 252 in the presence of paraformaldehyde and triethylamine, to give the macrocyclic peptide 253 in 62% yield (Scheme 68).\(^2\) In this reaction, paraformaldehyde generated a reactive imine with Lys, which underwent nucleophilic addition by isocyanide 252 to form a reactive nitrilium ion intermediate. A second nucleophilic addition by the carboxylate (Glu or Asp) then induced a Mumm rearrangement to the desired macrocyclic peptide 253 (Scheme 68).
In 2016, Yudin and co-workers further developed this into a modified Ugi-multicomponent reaction that forms an oxadiazole graft in the macrocyclisation of short peptides. In their synthesis, the authors combined free linear pentapeptide 254 with aldehyde 255 and (N-isocyanimino)triphenylphosphorane 256 (Scheme 69).
Reactions of these compounds in a 1:1 mixture of DCE and acetonitrile, stirring at 50 °C over 12 h, afforded the final oxadiazole-containing macrocyclic pentapeptide 257 in 68% yield (Scheme 69).\textsuperscript{124} These macrocyclic peptides were not only shown to be conformationally rigid, but also to contain multiple intramolecular hydrogen bonds, which resulted in higher passive membrane permeability than even cyclosporine – a well-known membrane-permeable macrocyclic peptide.\textsuperscript{124} Structural analyses from NMR and X-ray crystallography revealed that the stabilisation comes from a type II β-turn, an important class of secondary structure in biologically active peptides. Yudin and co-workers also confirmed that both the oxadiazole and proline residue contributed to the formation and stabilisation of the turn motif. Indeed, for peptides with more than four residues, proline was required in the sequence to ensure macrocyclisation.\textsuperscript{124}

### 3.3.5 Macrocyclisation through reversible imine formation

Given their potential as therapeutics, there is a huge need for the development of facile methodologies to not only synthesise native cyclic peptides quickly and efficiently, but also to access diverse analogues. In 2017, Baran and co-workers reported the macrocyclisation of peptides, using a thermodynamic approach to access native macrocyclic peptides via the generation of imines (Scheme 70).

![Scheme 70](image)

**Scheme 70:** Facile synthesis of macrocyclic peptide natural products and structural analogues.

Using SPPS to prepare linear amino aldehyde precursors of type 258 and using various nucleophilic imine traps to generate 259, they were able to synthesise analogues of scytonemide A 260 and koranimine 261, as well as natural product sanguinamide A 262
(Scheme 70). From NMR and circular dichroism (CD) studies, Baran and co-workers showed that substrate preorganisation was not required for macrocyclisation. They have also exemplified this through the macrocyclisation of random sequences.\textsuperscript{164}

### 3.3.5 Peptide stapling strategies

Many protein or peptide stapling strategies can be considered to be forms of side-chain to side-chain macrocyclisation of larger peptides or proteins. These stapling approaches commonly relied on established techniques such as nucleophilic substitutions,\textsuperscript{165} olefin metathesis,\textsuperscript{166} and click reactions (azide-alkyne cycloadditions),\textsuperscript{167} and was traditionally performed to induce or stabilise secondary structures in peptide sequences.\textsuperscript{168}

The groups of S. J. Korsmeyer and G. L. Verdine, for example, showed that the stapling of \textit{de novo} synthesised BH3 peptides – an $\alpha$-helical peptide involved in the regulation of cell apoptosis – \textit{via} alkene metathesis with first generation Grubbs catalyst 264 through the incorporation of unnatural amino acid 263, caused an increase in the proportion of sustained $\alpha$-helical configurations from 15.7\% to 87.5\% (Figure 32a).\textsuperscript{169} The macrocyclisation of these peptides not only enhanced serum stability, but also cell permeability as well as efficiently activating apoptosis in leukaemia cells.\textsuperscript{169} Another more recent advance is the use of perfluoroaromatic 265 in perfluoroaryl-cysteine $\text{SN}_\text{Ar}$ chemistry to generate macrocycles of transportan-10 (TP-10) 266, for the efficient crossing of the blood-brain barrier (BBB, Figure 32b).\textsuperscript{170}

![Figure 32: Peptide stapling to improve (a) drug efficacy and cellular uptake efficiency for the apoptosis of leukaemia cells,\textsuperscript{169} and (b) penetration of the blood brain barrier (BBB) to deliver payloads.\textsuperscript{170}](image-url)
3.5 Methionine (Met) as entry into macrocyclisation strategy

Most native peptide macrocyclisation approaches have focused on the use of polar reactive functional groups, such as (i) amines on Lys or the N-terminus, (ii) carboxylic acids on Asp, Glu and the C-terminus, or (iii) alcohols on serine (Ser) and threonine (Thr). To employ these reactive functional groups in peptide backbone macrocyclisation, elaborate protection and deprotection steps were usually required in the synthesis. Traditionally unreactive residues such as methionine (Met), on the other hand, is rarely used for backbone macrocyclisation of peptides.

While macrocyclisation strategies that target unnatural functional groups exist, many require the installation of unnatural amino acids. Hence, the development of a chemical method that targets the native sulfide moiety in Met, by first functionalising it with a reactive group to influence a second ring-closing step – generating a non-natural linkage – would be a distinct macrocyclisation strategy. There are few methods available for functionalising Met, and can be classified into (i) oxidants, or (ii) electrophiles.

3.5.1 Functionalising Met with oxidants

The use of Met as a target for oxidants was studied in 2017 by C. J. Chang and co-workers. The authors used oxaziridines as oxidants to form sulfimide (S=N) linkages, enabling a selective functionalisation of Met. These stable sulfimide conjugates were then used for further functionalisation to attach payloads such as drug molecules (Scheme 71). In this work, the authors described the functionalisation of Met with a sulfimide link, carrying an alkyne substituent that reacts with an azide in a ‘click’ reaction.

![Scheme 71: Bio-conjugation process that specifically functionalise Met into sulfimides.](image-url)
3.5.2 Functionalising Met with electrophiles

Besides being an oxidation target, Met had also been employed as a mild nucleophile. In studies carried out as early as 1976, it was found that benzyl bromide **268** was able to alkylate Met **269** selectively at acidic pH, with faster reaction kinetics than other nucleophilic residues to form sulfonium **270** (Scheme 72a).

![Scheme 72: Thioether as nucleophiles in (a) Met, and (b) Met-containing polypeptides.](image)

Preference for sulfide was rationalised by benzyl bromide having an ion-pair intermediate, which was selective towards polarisable S-nucleophiles as compared to N- or O-nucleophiles.\(^{173}\) It was not until 2012 that J. R. Kramer and T. J. Deming exploited this mode of reactivity to prepare sulfonium polymers **273** and **274** using various alkyl halides on polypeptides **271** and **272**, respectively (Scheme 72b).\(^{174-175}\)

![Scheme 73: Recent alkylation/dealkylation strategy for peptide macrocyclisation targeting Met residues.](image)

In 2018, Z. Li et al. employed this Met alkylation strategy in the macrocyclisation of unprotected peptides. By targeting two Met residues on peptide **275** using a bis-brominated-benzyl or allyl reagent **276** the authors were able to form a bis-sulfonium macrocyclic peptide **277** (Scheme 73). In their biological assay study, these Met-sulfonium macrocyclic peptides were found to be efficient CPPs. Furthermore, the authors demonstrated that the conjugates were also removable via the addition of glutathione, recovering the original bis-methionine peptide **275**.\(^{145}\)
3.5.3 Functionalising Met with α-aryliodonio diazoacetate salt

In 1994, Weiss and co-workers described the first synthesis and use of α-aryliodonio diazoacetate salt 278, an aryl-\(\lambda^3\)-iodane, as a diazoacetate transfer reagent (Scheme 74). Reaction of phenyliodonium diacetate 276 with ethyl diazoacetate 277 afforded iodonium salt 278 in 84\% yield. The unique electrophilic reactivity of aryl-\(\lambda^3\)-iodane 278 permitted the transfer of its diazoacetate group onto nucleophiles such as dimethylsulfide, furnishing sulfonium diazoacetate salt 279 in 90\% yield (Scheme 74). In their study, other nucleophiles such as pyridine, tertiary amines, triphenylarsine and triphenylstibine were also found to work well.\(^\text{176}\)

\[
\begin{align*}
\text{AcO} & \quad \text{I} \quad \text{AcO} \\
\text{O} & \quad \text{N} \\
\text{TMS-OTf} & \quad \text{CHCl}_2
\end{align*}
\]

\(276\)

\[
\begin{align*}
\text{N}_2 & \quad \text{OEt} \\
\text{OTf} & \quad \text{N}_2 \\
\text{Me} \quad \text{Me} \quad \text{S} \\
\text{Me} \quad \text{Me}
\end{align*}
\]

\(278, 84\%\)

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

\(279, 90\%\)

\(\text{\textbf{Scheme 74}}\): Synthesis of α-aryliodonio diazoacetate salt 278, a diazoacetate transfer reagent.

The Gaunt group has since developed this class of compounds into a methionine-selective labelling tool. They were interested in this class of iodonium salts for two reasons: (i) the ability to tailor for a selective bioconjugation method through fine tuning of the substituents and counterion on the polarisable I(III) atom, and (ii) the ability to develop a distinct bioconjugation method that delivers a high-energy diazo-conjugate with ‘on-protein’ reactivity. Both of these attributes served as the basis for their work on the design of novel bio-compatible transformations for diverse protein constructs (unpublished work).

Through iterative optimisation from previously reported aryl-\(\lambda^3\)-iodane 278, Gaunt \textit{et al.} designed a reagent for the chemoselective transfer of diazoacetate onto Met (Scheme 75). While the progenitor iodonium salt 278 reacted with Met poorly, giving Met-conjugate 280 in 27\% yield with oxidation side-products (Scheme 75a), the optimised iodonium salt 281, with a 2,4-difluorophenyl motif and a BF\(_4\) counteranion, afforded Met-conjugate 280 in quantitative yield (Scheme 75b).
Scheme 75: Novel bioconjugation using hypervalent iodine species by Gaunt et al. demonstrating (a) progenitor iodonium salt in reaction with Met, (b) improved variant of iodonium salt for Met-selective labelling, and (c) Met-selective labelling with improved iodonium salt in a peptide.

More importantly, the authors demonstrated that iodonium salt 281 specifically targets Met in peptides such as exenatide 282 to form its diazoacetate-conjugates 283 (Scheme 75c). A key breakthrough in their discovery was the use of a low concentration of thiourea (20 mM), which dramatically improved reactivity and kinetics – affording >90% conversion of exenatide 282 to its conjugate 283 in less than 2 minutes. Further improvements were made through the addition of TEMPO, a reactive oxygen species scavenger, to reduce oxidation side-products, as well as the addition of formic acid (5 mM, pH 3) to reduce non-specific labelling.

The successful transfer of a high energy diazo moiety onto Met opened up opportunities for the coupling of this reactive functional group to known diazo chemistries. In particular, three methods were considered: (i) photolysis to free carbene, (ii) single electron transfer (SET) chemistry, and (ii) metallocarbenoid insertion chemistry.
The first possible method is the generation of a highly reactive free singlet or triplet carbene, through photolysis of the diazo group (path 1, Scheme 76). The second possible method is the use of a reducing agent, such as in a photocatalytic process with Hantzsch ester derivative 285, that Gaunt et al. demonstrated in their unpublished work with exenatide to form alkylated construct 286 (path 2, Scheme 76). The third possible method is the generation of a metallocarbenoid, which would be structurally-related to singlet carbenes and possess similar reactivity (path 3, Scheme 76). However, unlike free carbenes, metallocarbenoids usually react in a more selective manner. In the work presented here, we will exploit these diazoacetate groups on Met to form metallocarbenoids for peptide macrocyclisation (path 3, Scheme 76). One possibility for an intramolecular insertion target for ‘on-peptide’ metallocarbenoids generated this way, is the indole ring on tryptophan (Trp).
3.6 Tryptophan (Trp) as macrocyclisation target for non-natural linkage

As a component of CPP, Trp has been shown to promote cellular penetration of macrocyclic peptides. Furthermore, the electron-rich indole ring of Trp appeals as a viable target for our planned electron-poor metallocarbenoid; both N-H and C-H insertion reactivities on indoles have been demonstrated to work with different types of carbenes, such as donor-acceptor carbenoids, and acceptor-acceptor carbenoids, in reports that span different salts of transition metals, including but not limited to copper, ruthenium, and rhodium.

Relevant to our study is the discovery of tryptophan labelling with Rh-carbenoids by Francis and co-workers in 2009. The authors employed metallocarbenoids via diazo that specifically targeted the indoles of tryptophan in melittin (Scheme 77).

In their studies, Francis and co-workers explained that the products were a mixture of positional isomers owing to both N-H (289a) and C-H (289b) insertions. However, no peptide or protein products were isolated to determine their structures.

\[ \text{Scheme 77: Trp-selective modification of melittin, a honey bee venom peptide.} \]
3.7 Project outline and goal

We were interested in developing a distinct peptide macrocyclisation strategy that would employ the Gaunt group’s Met-selective reaction with aryliodonium salt 281 as the first step, to install a diazo functional group onto a peptide that contains both Met and Trp residues. In our design considerations, the generation of a cationic sulfonium group on Met after the first step diazoacetate transfer, would in principle initiate an intramolecular cationic-\(\pi\) interaction with the indole of Trp. Several studies have documented cationic-\(\pi\) interactions between Trp and basic residues in protein structures, following a series of pioneering work done by D. A. Dougherty and co-workers.\(^{186-188}\) In our study, this stabilising interaction would potentially bring both Met and Trp residues into close proximity on a peptide for macrocyclisation (step 1, Figure 33).

Activating this reactive diazo functional group with a rhodium salt would subsequently induce a Trp-selective metallocarbenoid insertion into the indole ring (step 2, Figure 33). Furthermore, as the methodology generates a positively charged sulfonium group, and the peptide would contain Trp as the Rh-carbenoid insertion target, both of these fit the requirement for an efficient macrocyclic peptide-based CPP.

![Figure 33](image-url) Planned reactions for a distinct macrocyclisation strategy.

As part of our overall goal of developing a technology that provides facile access to macrocyclic peptides through a distinct but practical macrocyclisation strategy, the platform for this methodology would be integrated with current SPPS technology.
3.8 Towards step-wise non-natural peptide macrocyclisation enabled by methionine-to-tryptophan linkage

In order to investigate the potential of this chemistry in peptidic systems, a simple pentapeptide was employed as the model substrate with the sequence Trp-Gly-Pro-Gly-Met (290, Scheme 78). In our macrocyclisation reaction design plan, initial nucleophilic attack of the methionine sulfide group onto iodonium salt 281 would generate the sulfonium diazoacetate conjugate 291, with the diazo group flanked by both electron-withdrawing ester and cationic sulfonium groups (Scheme 78). As carbenoids formed from acceptor-acceptor compounds are known to have high electrophilicity and are more prone to side reactions,179 the conditions used should be strictly controlled. Subsequent generation of metallocarbenoid 292 from the diazo moiety would lead to the intramolecular insertion and macrocyclisation into the indole ring of Trp, affording 293a/b. In this two-step design plan, both steps were individually optimised.

Scheme 78: Reaction design plan on achieving macrocyclisation via Rh-metallocarbenoid 292.
3.8.1 Model pentapeptide substrate

The model system was designed to contain both Met and Trp on either end. Employing solution-phase synthesis, N-Boc-protected proline (294) was first coupled to ethyl ester glycine (295) using DCC and HOBt, to form dipeptide 296 in 87% yield. Dipeptide 296 was deprotected on the N-terminus (297) and coupled to Boc-protected glycine (298) using EDC and HOBt, to form tripeptide 299 in 69% yield. The N-terminus was again deprotected (300) and coupled to Boc-protected Met (301) to form tetrapeptide 302 in 52% yield. Final deprotection of the C-terminus (303) and coupling to methyl ester protected Trp (304) afforded the desired pentapeptide 290 in 70% yield (Scheme 78). As shown by NOESY and NOE NMR calculations, both Met and Trp residues are in close proximity in space, probably due to the β-turn imparted by the central proline (Pro) residue (Scheme 79). The glycine (Gly) residues flanking Pro were incorporated to allow some degree of backbone flexibility. As part of this model pentapeptide design, having Trp and Met on either end of the peptide would enable diazoacetate transfer to occur on Met and intramolecular insertion to occur on Trp (Scheme 78).

Scheme 79: Solution-phase synthesis of terminally-protected pentapeptide 290.
3.8.2 First-step Met-selective installation of diazoacetate

Before conditions were screened, determination of the stability of diazoacetate conjugate 291 was required. Although previous studies within our group ascertained that these diazoacetate conjugates are tolerant to a variety of biological conditions, the stability on such synthetic peptide conjugate 291 are unknown. Hence, solvents and additives were screened in the first Met-selective installation of diazoacetate (Table 9).

In dichloromethane, complete oxidation of the conjugate 305 was observed when a large excess of iodonium salt 281 was utilised (10.0 equivalents, entry 1) – understanding its stability to a large excess of iodonium salt reagent is important when translating to solid-phase later. Swapping solvents to acetonitrile gave 15% product ratio of the desired conjugate 291, but still 85% of the oxidised conjugate 305 (entry 2). Oxidations of both Met and Trp are known to occur in biological systems, such as in monoclonal antibody (mAb) molecules. Trp, for example, could be oxidised to the indolin-2-one (306) or to the indol-6-ol (307, Scheme 80a). A control reaction between amino acid Trp 308 and iodonium salt 281 demonstrated that the oxidation was not due to non-selective iodonium salt reaction with Trp (Scheme 80b).

\[
\begin{align*}
\text{Scheme 80:} & \quad \text{(a) Trp oxidation in biological systems, and (b) control between Trp and iodonium salt 255.} \\
\end{align*}
\]

In a previous optimisation work on protein labelling from our group, the addition of TEMPO, an efficient radical and reactive oxygen scavenger, was observed to suppress oxidation. In this work, TEMPO was used as an initial attempt to suppress oxidation products, giving 80% of the desired conjugate (entry 3).
**Table 9:** Ethyl diazoacetate conjugation of linear pentapeptide 290 study

<table>
<thead>
<tr>
<th>#</th>
<th>Solvent</th>
<th>Peptide</th>
<th>Iodonium Salt</th>
<th>TEMPO</th>
<th>291:305</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₂Cl₂</td>
<td>0.5 mM</td>
<td>50 mM</td>
<td>-</td>
<td>1.99</td>
</tr>
<tr>
<td>2</td>
<td>MeCN</td>
<td>0.5 mM</td>
<td>50 mM</td>
<td>-</td>
<td>3:17</td>
</tr>
<tr>
<td>3</td>
<td>MeCN</td>
<td>0.5 mM</td>
<td>50 mM</td>
<td>10 mM</td>
<td>4:1</td>
</tr>
<tr>
<td>4</td>
<td>MeCN&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.5 mM</td>
<td>0.6 mM</td>
<td>0.65 mM</td>
<td>99:1</td>
</tr>
</tbody>
</table>

Note: Amounts of 291 and 305 are shown as product ratios. Conversions are complete for all entries; (a) dry and degassed acetonitrile.

With dry and degassed acetonitrile as the solvent, the reaction was less prone to give oxidised products, giving the optimised condition for conversion of pentapeptide 290 to diazo conjugate 291 with 1.2 equivalents of iodonium salt 281 (entry 4).

### 3.8.3 Second-step Trp-selective insertion of Rh-carbenoid

Following the first step, the conjugate was purified and subjected for metallocarbenoid insertion. Various solvents were screened (Table 10). Surprisingly, the second step reaction with dirhodium(II) tetraacetate, Rh₂(OAc)₄, worked in 3% product ratio for 293a/b on the first attempt in MeCN/H₂O, as studied on LC-MS (entry 1).
The main side product seemed to be the hydrolysis of the Met-conjugate 291 to return the starting pentapeptide 290, as well as solvent insertion side-products (310 and 311, Scheme 81). Efforts with other water/solvent combinations were unsuccessful (entries 2-3), except with trifluoroethanol (TFE), which afforded 13% product ratio (entry 4). Repeating this without water afforded the desired insertion product 293a/b in 70% product ratio (entry 5). Trying other Rh salts gave poorer results (entries 6-7). The use of dry TFE improved the results to 79% product ratio (entry 8). Swapping the solvent to dry hexafluoroisopropanol (HFIP) afforded an optimised 85% for Rh₂OAc₄ and 88% for dirhodium tetraoctanoate (Rh₂(oct)₄, entries 9-10). Full screen in Appendix 2 (Table S4).

Table 10: Rh-catalysed insertions of pentapeptide diazo-conjugate 291

<table>
<thead>
<tr>
<th>#</th>
<th>Solvent (0.5 mM)</th>
<th>[Rh] (0.05 mM)</th>
<th>Purifieda</th>
<th>Conv. 291?</th>
<th>293a/b</th>
<th>310</th>
<th>311</th>
<th>290</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeCN/H₂O</td>
<td>Rh₂(OAc)₄</td>
<td>Yes</td>
<td>50%</td>
<td>3%</td>
<td>18%</td>
<td>12%</td>
<td>17%</td>
</tr>
<tr>
<td>2</td>
<td>IPA/H₂O</td>
<td>Rh₂(OAc)₄</td>
<td>Yes</td>
<td>50%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>50%</td>
</tr>
<tr>
<td>3</td>
<td>EtOH/H₂O</td>
<td>Rh₂(OAc)₄</td>
<td>Yes</td>
<td>74%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>74%</td>
</tr>
<tr>
<td>4</td>
<td>TFE/H₂O</td>
<td>Rh₂(OAc)₄</td>
<td>Yes</td>
<td>80%</td>
<td>13%</td>
<td>-</td>
<td>-</td>
<td>67%</td>
</tr>
<tr>
<td>5</td>
<td>TFE</td>
<td>Rh₂(OAc)₄</td>
<td>Yes</td>
<td>88%</td>
<td>70%</td>
<td>-</td>
<td>-</td>
<td>18%</td>
</tr>
<tr>
<td>6</td>
<td>TFE</td>
<td>Rh₂(oct)₄</td>
<td>Yes</td>
<td>92%</td>
<td>71%</td>
<td>-</td>
<td>-</td>
<td>21%</td>
</tr>
<tr>
<td>7</td>
<td>TFE</td>
<td>Rh₂(esp)₄</td>
<td>Yes</td>
<td>76%</td>
<td>41%</td>
<td>-</td>
<td>-</td>
<td>35%</td>
</tr>
<tr>
<td>8</td>
<td>TFE (dry)</td>
<td>Rh₂(OAc)₄</td>
<td>Yes</td>
<td>96%</td>
<td>79%</td>
<td>-</td>
<td>-</td>
<td>11%</td>
</tr>
<tr>
<td>9</td>
<td>HFIP (dry)</td>
<td>Rh₂(OAc)₄</td>
<td>Yes</td>
<td>96%</td>
<td>85%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>HFIP (dry)</td>
<td>Rh₂(oct)₄</td>
<td>Yes</td>
<td>97%</td>
<td>88%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>HFIP (dry)</td>
<td>Rh₂(oct)₄</td>
<td>Noa</td>
<td>99%</td>
<td>90%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Note: (a) “No” for this meant that the reaction was performed in one pot from starting peptide.
Next, a one-pot Rh-carbenoid insertion after conjugation was devised. This was attempted by replacing the acetonitrile solvent from the first step conjugation with HFIP for the second step insertion. Refilling the reaction flask with a suspension of the rhodium catalyst in HFIP and stirring for 30 minutes then afforded the highest product ratio of 90% for insertion product 293a/b (Table 10, entry 12). While both Rh₂(OAc)₄ and Rh₂(oct)₄ gave similar reactivity, the latter performed slightly better perhaps due to better solubility. This reaction was repeated using 100 mg scale of the starting pentapeptide 290 (Scheme 82). The product macrocyclic peptides 293a/b were purified on HPLC (90% yield). Comparisons of NMR, HRMS and tandem ms-ms fragment analysis were next made with starting peptide 290 and intermediate conjugate 291.

**Scheme 82:** Reaction with crude LC-MS shown (middle and bottom), using atmospheric pressure chemical ionisation (APCI) method. LC-MS trace shown indicated the product ion peak at 1.8 min. Selective ion monitoring (SIM) channel is shown (bottom), scanning at m/z 745 for the product macrocyclic peptide 293a/b. Pure compound (red solution, bottom right) shown in 3 mL NMR tube, dissolved in CD₂Cl₂.
3.8.3a Analysis of starting linear peptide tandem ms-ms spectra

The starting linear peptide 290 was subjected to collision activated dissociation (CAD) analysis (Figure 34). The selected parent ion for CAD was [M+H]^+ m/z 661.2908. Initial fragmentation was the facile loss of Boc group, giving pentapeptide ion [M+H]^+ m/z 561.2383 as the major ion peak. Subsequent fragmentations included two pathways: (i) the loss of Met residue from the N-terminus, via an amide bond cleavage, to form tetrapeptide fragment y4 ion [M+H]^+ m/z 430.2050, or (ii) the loss Trp residue from the C-terminus, via an amide bond cleavage, to form tetrapeptide fragment b4 ion [M+H]^+ m/z 343.1383.

From the first fragmentation pathway involving y-ions, following the loss of Met, the adjacent Gly residue is lost to afford tripeptide fragment y3 ion [M+H]^+ m/z 373.1803. Ensuing this was the loss of Pro residue to afford dipeptide fragment y2 ion [M+H]^+ m/z 276.1355, and finally the loss of the following Gly residue to obtain methyl ester protected amino acid Trp as the final y1 ion [M+H]^+ m/z 219.1141 (Figure 34).

From the second fragmentation pathway, the loss of Trp residue from the C-terminus was followed by the subsequent loss of Gly residue to form the tripeptide fragment b3 ion [M+H]^+ m/z 286.1226. Ensuing this, the loss of Pro residue afforded the final b-ion found in this spectrum, the dipeptide fragment b2 ion [M+H]^+ m/z 189.0698 (Figure 34).
Figure 34: Tandem ms-ms spectrum of starting linear peptide 290 using collisionally activated dissociation (CAD) on 10-25 eV energy ramp.
3.8.3b Analysis of diazo conjugate tandem ms-ms spectra

Next, fragmentation patterns of the diazo conjugate 291 (Figure 35) and the starting linear peptide 290 (Figure 34), were compared. For diazo conjugate 291, the selected parent ion for CAD was [M]+ m/z 773.3406, with the diazoacetate conjugate attached to the cationic sulfonium group.

Initial fragmentations included two pathways: (i) The loss of N₂ molecule to give pentapeptide fragment ion [M]+ m/z 745.3383, followed by the loss of the Boc protecting group from this to give pentapeptide fragment ion [M]+ m/z 645.2819, or (ii) the loss of cationic sulfonium-conjugate fragment, S(Me)C(N₂)CO₂Et, to give pentapeptide fragment ion [M+H]+ m/z 614.3088. This second fragmentation pathway of the sulfonium-conjugate through the cleavage of weak C-S⁺ bond was conserved in other sulfonium-containing peptides, as studied extensively by Simpson and co-workers.192

Following the fragmentation of the sulfonium-conjugate, in this second pathway, the loss of the Boc group proceeded in two steps: the loss of tert-butyl to give pentapeptide fragment ion [M+H]+ m/z 557.2426, followed by the loss of CO₂ to give pentapeptide fragment ion [M+H]+ m/z 513.2493. Subsequent first amide bond cleavage from both these fragmentation pathways led to the overall loss of Met residue to afford tetrapeptide fragment y₄ ion [M+H]+ m/z 430.2134 (Figure 35).

Ensuing this loss of Met, together with the Boc and diazoacetate-conjugate groups appended to it, the loss of the adjacent Gly residue then afforded the tripeptide fragment [M+H]+ m/z 373.1882 as the y₃ ion. Further amide bond cleavage from this through the loss of Pro residue then provided the dipeptide fragment y₂ ion [M+H]+ m/z 276.1355, before the final amide bond cleavage to leave behind methyl ester protected amino acid Trp, as the fragment y₁ ion with [M+H]+ m/z 219.1141 (Figure 35).

Thus, the tandem ms-ms analysis of diazo intermediate 291 indicated that the diazoacetate-conjugate from the first step reaction between iodonium salt 281 and starting peptide 290 was affixed on the Met residue. This fragmentation pattern was next compared to that for the product macrocyclic peptide 293a/b.
Figure 35: Tandem ms-ms spectrum of intermediate diazo peptide conjugate 291 using collisionally activated dissociation (CAD) on 10-25 eV energy ramp.
3.8.3c Analysis of macrocyclic peptide product tandem ms-ms spectra

In the product spectrum for 293a/b (Figure 37), the parent molecular ion is positively charged due to the sulfonium cation, giving \([M]^+\) m/z 745.3216. This ion was selected for CAD with 15-40 eV energy ramp; the first fragment loss was the Boc protecting group, giving fragment ion \([M]^+\) m/z 645.2715.

The second fragment loss was observed to be the Met residue, from the N-terminus via amide bond cleavage, giving tetrapeptide fragment \(y_4\) ion \([M+H]^+\) m/z 514.2275. The peptide had, at this point, lost the sulfonium cation as indicated by the \(y_4\) ion on the spectrum (Figure 37). Following this, the third fragment loss found was that of the adjacent Gly residue, giving tripeptide fragment \(y_3\) ion \([M+H]^+\) m/z 457.2053. Subsequent loss of middle residue Pro gave the dipeptide fragment \(y_2\) ion \([M+H]^+\) m/z 360.1530. The final fragmentation of the Gly residue then afforded the single methyl ester protected amino acid Trp, with the ethyl ester-conjugate attached, as fragment \(y_1\) ion \([M+H]^+\) m/z 303.1324. This result suggested the successful insertion of the diazoacetate conjugate on Met into the Trp residue, with an associated loss of the diazo moiety to generate the requisite Rh-carbenoid (Figure 37).

In summary, sequence analysis of macrocyclic peptide product 293a/b reveals an initial bond-cleavage at the weak C-S+ bond, followed by a loss of Met (\(y_4\)), Gly (\(y_3\)), Pro (\(y_2\)), and Gly (\(y_1\)), in that order, finally leaving the molecular ion Trp with the ethyl ester-conjugate (\(y_1\)) at \([M+H]^+\) m/z 303.1324. Tandem ms-ms on sulfonium-containing peptides were studied by Simpson and co-workers, whose work confirmed an initial C-S+ bond cleavage, followed by amide bond cleavages (Figure 36). Tandem ms-ms on sulfonium-containing peptides with high CAD (>22 eV) thus resulted in an energy-resolved “pseudo” multistage ms-ms or MS3 analysis.\(^{192}\)

Figure 36: Fragmentation on tandem ms-ms.
Figure 37: Tandem ms-ms spectrum of product macrocyclic peptide 293a/b using collisionally activated dissociation (CAD) on 15-40 eV energy ramp.

Final Y+ ion: [M+H]+

Found m/z 303.1324

Required m/z 303.1339

Sequence: Boc-Met-Gly-Pro-Gly-TP-Rome

CO2Et
3.8.3d NMR analysis

The NMR spectra of product 293a/b was compared to that of the starting peptide 290 and diazo intermediate 291. Although the spectrum was challenging to deconvolute, some important information was obtained. From the product spectrum, four isomers were found: two isomers corresponding to N-H or C-H insertion on the indole ring of Trp, as well as diastereomers from each. This is depicted in the DEPT-135 $^{13}$C-NMR spectra (Figure 38). New C-H peaks were also found: at $^{13}$C $\delta$: 70.1 ppm, $^1$H $\delta$: 4.58-4.36 ppm (293a) and at $^{13}$C $\delta$: 52.8 ppm, $^1$H $\delta$: 3.6-3.2 ppm (293b, see experimental section 5), attributed to the new CH from insertion of metallocarbenoid into Trp.

![DEPT-135 spectra](image)

Starting peptide 290 | Diazo conjugate intermediate 291

---

**Figure 38:** DEPT-135 experiment in CD$_2$Cl$_2$ showing only indole aryl region for starting linear peptide 290 (top left), diazo intermediate 291 (top right), and product macrocyclic peptides 293a/b (bottom).
3.8.4 Translation of solution-phase macrocyclisation onto solid-phase on-bead synthesis

For this macrocyclisation methodology to be easily adopted, integration into the current SPPS platform is essential. In SPPS, although various resins are available for use, the rink amide 4-methylbenzhydrylamine (MBHA) resin was chosen as it is one of the most widely used. To translate the two-step conjugation-macrocyclisation process developed in solution-phase onto solid-phase, and to integrate them into this SPPS system meant two considerations: (i) First, that the reaction monitoring has to be developed to study the efficiency of both the conjugation and macrocyclisation, and (ii) second, that the methodology has to work on the resin materials taken directly from the SPPS system.

For the first consideration, a milder method of cleavage from resin is needed. Fortunately, a recent study by Stetsenko and co-workers in 2016, devised an alternative acidic method of using 0.1 M HCl in HFIP to cleave peptides off rink amide MBHA resins, as well as the deprotection of various acid-labile groups common to Fmoc-SPPS synthesis. This cleavage method was adopted into our methodology, with addition of some known additives to prevent side-reactions during cleavage. For the second consideration, a co-solvent system is required to swell the beads and improve reaction efficiency for both the conjugation and macrocyclisation steps.

Resin-bound linear peptide 312 was initially subjected to the conditions developed from solution-phase. Employing the macrocyclisation process would then afford resin-bound product 314, which was cleaved from the resin to afford free macrocyclic peptide 315a/b in modest 40% conversion and 54% product ratio (Scheme 83a). Unlike in solution-phase, where 1.1 equivalents of iodonium salt 281 was used, in solid-phase reaction a large excess of iodonium salt 281 (4.0 equivalents) was required (Scheme 83a). Furthermore, acetonitrile was observed to shrink the resin and possibly retard the reaction. Thus, solvent optimisation for this solid-phase synthesis began with co-solvents known for their swelling properties on rink amide MBHA resins. To perform this co-solvent screening, however, the reaction needed to be brought forward to the second step, as the first step pentapeptide conjugate (313) was found to be unstable during cleavage from the resin. Keeping the second step constant, the effects of each co-solvent were studied.
Scheme 83: Solid-phase two-step conjugation-macrocyclisation using (a) optimised solution-phase conditions, and (b) re-optimised for solid-phase conditions. Conversions were calculated based on total ion count (TIC) of unaltered free starting pentapeptide (m/z 545) against the total TIC for all peaks related to the peptide. Product ratios were calculated based on the TIC of the product peak (m/z 630) against the TIC calculated for all peaks related to the peptide, minus that of the starting peptide. Note: Product peptides cleaved from rink amide resin would possess an amide group (-CONH₂) on the C-terminal.
Almost all the co-solvents tested, including THF, DMF and DMSO, were found to deactivate the conjugation step. Only benzyl cyanide (PhCH₂CN) was found to be a suitable co-solvent. It was observed that 33% v/v of PhCH₂CN in acetonitrile was sufficient to swell the resin beads. Similarly, the best results required both PhCH₂CN and acetonitrile to be distilled and degassed to give excellent conversions of the linear pentapeptide to its corresponding diazo-conjugate (313) on-bead and eventually to the free macrocyclic peptide (315a/b), after cleavage from the resin (Scheme 83b). It is notable that operating with PhCH₂CN alone as the solvent causes conversion to drop to 60%. Finally, to optimise the second step Rh-carbenoid generation and insertion, solubility of the dirhodium octanoate [Rh₂(oct)₄] salt was improved via addition of 20% v/v CH₂Cl₂. Delightfully, this first modification worked well to afford macrocyclic product 315a/b with complete conversion and high product ratio (Scheme 83b). The reaction set-up is shown (Figure 39).

Figure 39: Current reaction set-up for inert solid-phase macrocyclisation of peptides.

In this set-up, the resin-bound peptide and a magnetic stir-bar were first loaded into a plastic syringe, fitted with a chemically-resistant filter and Teflon tap at the bottom. The top of the syringe was sealed with a septum and a nitrogen line is attached via a needle
through the septum to ensure inert atmosphere (picture 1, Figure 39). The initial solvents used for conjugation were PhCH$_2$CN:MeCN in 1:2 ratio with iodonium salt 281. Vigorous stirring for 1 h was applied by placing the set-up atop a magnetic stir-plate (picture 1). The reacting solution was drained into a container through the bottom of the syringe, washed, and the resin swelled with CH$_2$Cl$_2$ (picture 2). The resins were then subjected to a solution of Rh$_2$(oct)$_4$ in CH$_2$Cl$_2$:HFIP 1:4 solvent ratio to effect macrocyclisation (picture 3). Prior to cleavage, the reaction solution was drained, washed and swelled with CH$_2$Cl$_2$ again.

Following this set-up under the current optimised condition for starting peptide 312, attempts to isolate macrocyclic peptide 315a/b were, however, unsuccessful as the product was observed to oxidise and decompose quickly. To improve its stability, the N-terminus was extended by a Gly residue (316), as the free amine was suspected to play a role in its decomposition, post-cleavage from resin. Subjecting linear hexapeptide 316 to the reaction afforded the macrocyclic peptide product 317a/b in reasonable stability for isolation (Scheme 84). However, oxidation was still observed to occur over time.

**Scheme 84:** Extending the N-terminus by a Gly residue to improve stability.
To study this oxidation reaction on $^{19}$F NMR, a new iodonium salt reagent was synthesised; 3,5-bis(trifluoromethyl)benzyl α-aryliodonio diazoacetate salt 318 (Scheme 85). While attempts to study the reaction with $^{19}$F NMR were unsuccessful due to difficulty in the deconvolution of the fluorine NMR peaks, we were delighted to find that the new benzyl ester conjugate from 318 instead provided better stability for conversion of 312 to the product 324a/b (Scheme 86).

![Scheme 85](image)

**Scheme 85**: New iodonium salt reagent 318; (a) reaction of 318 with fully protected Boc-Met-OMe, and (b) reaction of 281 with fully protected Boc-Met-OMe.

Iodonium salt 318 was tested on protected Met 319 and compared to previously used iodonium salt 281 (Scheme 85a and 85b). The reaction on protected Met 319 resulted in some deprotection of the Boc group on Met conjugate 320, giving 20% yield of free amine 321 in the reaction (Scheme 85a). On the other hand, the reaction with iodonium salt 281 leaves the Boc group intact with 98% yield of the respective Met conjugate 322 (Scheme 85b). This might indicate a stronger electrophilicity and enhanced Lewis acidity of iodonium salt 318, possibly due to inductive effects of the -CF$_3$ groups on the hypervalent iodine centre. Fortunately, the deprotection of the Boc group was not a problem since it would be removed during the resin cleavage step.
Previous reactions with iodonium salt 281 required the reagent to be used in 4.0 equivalents on solid-phase synthesis. On the other hand, iodonium salt 318 only required 2.4 equivalents for conjugation on resin-bound pentapeptide 312 (Scheme 86). More importantly, however, was that the new conjugate from reaction with iodonium salt 318 was more resistant to oxidation, and that TEMPO was not required in the first step reaction to resin-bound conjugate 323 (Scheme 86). Simply using distilled and degassed solvents was enough to ensure elimination of oxidation side-reactions, further simplifying this methodology. Subsequent generation of the Rh-carbenoid in the second step then effected the insertion into Trp, giving macrocyclic peptide 324a/b in 79% product ratio, post-cleavage from resin.
3.8.5 Peptide scope

To probe the reactivity and scope of the macrocyclisation, various residues were added and substituted into the starting linear peptide sequence. The succeeding two-step conjugation-macrocyclisation reaction on these elongated peptides would then form “pinched” macrocyclic peptides. Such a system might be useful for designing short stapled peptides that could carry specific sequences on either end, which could in turn be designed to form site-specific interactions with proteins or receptors on cells.

In this study, the effects of changing chain flexibility, sterics, and the use of other residues were probed. These sequences were first modelled on a peptide structure prediction software, Pep-Fold 3.\(^{195}\) Developed by Tuffery and co-workers, Pep-Fold 3 works by assembling the peptide fragments using a greedy algorithm driven by a coarse-grained force field.\(^{196-198}\) Using this information, sequences were studied to identify those with Met and Trp having close associations in space, between 4-7 Å. The first peptide attempted had just one extra Gly residue on the N-terminus following Met (\(325a/b\)) and was found to afford similar results as that observed for \(324a/b\), affording 90\% conversion and 79\% product ratio (Scheme 87).

The second peptide attempted, however, performed poorly with a significant drop in conversion and product ratio to 80\% and 22\%, respectively, for \(326a/b\) (Scheme 87). As this peptide contained twice the amount of Gly residues in the macrocycle, this might indicate sensitivity of the reaction to chain flexibility. For the third peptide tested (\(327a/b\)), alanine (Ala) were used in place of Gly residues in the sequence. Disappointingly, the reaction fared poorly with a low conversion and product ratio of 86\% and 10\%, respectively. Increasing the chain flexibility of this structure by adding Gly residues in the sequence (\(328a/b\)), led to a significant drop in conversions (from 86\% to 51\%) and product ratios (from 10\% to 7\%), again highlighting the sensitivity of the reaction to increased chain flexibility (Scheme 87).
**Scheme 87**: Two-step conjugation-macrocyclisation on resin-bound peptide substrates. Starting linear sequence reads from C-to-N-terminus. Analysed by tandem ms-ms.

Key: G = Gly, W = Trp, P = Pro, P* = D-Pro, F = phenylalanine (Phe), T = threonine (Thr), M = Met.
Next, a stronger turn motif was tested using D-Pro-L-Pro template (329a/b). This turn motif is commonly used to induce β-hairpin conformations in cyclic protein mimetics.\textsuperscript{199} The reaction, however, gave similarly poor 60\% conversion and 15\% product ratio. One possibility for this is the rigid structure of the D-Pro-L-Pro template, which allowed less conformational flexibility for cyclisation (Scheme 87).

The final substrate tested in this series contained Phe and Thr residues in the peptide sequence (330a/b). Although seemingly hindered, this sequence was found to be optimised on Pep-Fold 3. Furthermore, the linear sequence “Thr-Phe-Pro-Phe” was found to possess a very strong βVI turn-inducing element in previous studies.\textsuperscript{147} The results for the reaction, however, afforded disappointingly low 58\% conversion and 14\% product ratio for 330a/b (Scheme 87).

In the model system, Trp and Met were both on the C- and N-terminus, respectively. However, in most of these peptide sequences (326-330a/b, Scheme 86), Met and Trp were both capped with Gly residues. Since these were the reacting residues in the peptide sequence, placing them at either end of the sequences might be essential for reactivity. Hence, new sequences were tested, using Trp and Met on C- and N-terminus, respectively (331-335, Scheme 88). In this new series of resin-bound linear peptides, the residues Trp-Phe-Pro-R-Met were kept constant in the sequence, where R indicates the variable residue; Lys (331), Glu (332), Asp (333), Asn (334), and Thr (335). While conversions for these substrates were higher, between 79-90\%, product ratios were still low (between 16-21\%, Scheme 88). These results indicated that the methodology was still under-developed for sequences apart from our initial model pentapeptide.
**Scheme 88:** Two-step conjugation-macrocyclisation on resin-bound peptide substrates. Starting linear sequence reads from C-to-N-terminus. Analysed by tandem ms-ms.

Key: W = Trp, P = Pro, F = Phe, T = Thr, K = lysine (Lys), E = glutamic acid (Glu), D = aspartic acid (Asp), N = asparagine (Asn), M = Met.
As a control, an intermolecular variant of the insertion between methionine-conjugate and tryptophan 308 was performed (Scheme 89). It was found that the reaction worked to give 337a/b in 7% yield. The product was, however, unstable to isolation. Tandem ms-ms of the product was performed to show that the product contained both Met-conjugate and Trp-conjugate fragments (in experimental). The major side-product appeared to be an insertion within Met itself (336, Scheme 89), as shown in the LC-MS trace for m/z 546 (Figure 40). Attempts to isolate this was, however, unsuccessful.

Scheme 89: Intermolecular control reaction between 271 and 296.

Figure 40: LC-MS spectra showing desired product m/z 864 and major side-product m/z 546.
3.9 Future study

In dirhodium complexes, the axial sites are where catalysis occur (Figure 41); while one axial site on dirhodium complexes reacts with diazo compounds to form Rh-carbenoids, the other is used as an electrophilic sink.\(^{200}\) Furthermore, there is mounting evidence that the reactive site is a cationic Rh(III) after formation of the requisite Rh-carbenoid, while the unreacted site is an anionic Rh(I), (complex 338, Figure 41).\(^{200-201}\) Rhodium catalyst with two L-type ligands that bind weakly on the axial positions, through essentially \(\sigma\)-interactions with the Rh\(_2\)(II) centre, have been known to exist for dirhodium tetracarboxylate complexes.\(^{201}\) It was postulated that this weak axial binding was due to the large \(\text{trans}\)- influence of the Rh-Rh bond.\(^{202}\)

![Figure 41: Nakamura’s model for Rh insertion, showing cationic Rh(III) and anionic Rh(I) generation.](image)

Thus, with the appropriate choice of axially-coordinating ligand, the Rh-carbenoid species may be stabilised by an electronegative group to allow for a more selective reactivity.\(^{203}\) The choice of ligands, however, was crucial. Afonso and co-workers showed in 2008 that when strongly \(\sigma\)-donating ligands, such as N-heterocyclic carbenes (NHCs), are used, the Rh-Rh metallic bond weakens to the point of breakage through donation
of electron density into the Rh-Rh σ*-bond. Later in 2010, Afonso and co-workers circumvented this problem by using sterically bulky NHC axial ligands to confer protection around one of the Rh atoms while at the same time activating the other Rh atom towards the desired reaction. Using the appropriate axial ligand, T. Z. Ball and co-workers also managed to successfully perform cyclopropanation on styrene 339 using diazo 340, to form cyclopropane 341 in quantitative yield and 97% e.e (Scheme 90). In their study, the use of histidine’s imidazole side-chain to bind dirhodium tetracarboxylate on the axial position (342) was essential for efficient cyclopropanation.

Scheme 90: Axially-bound histidine on dirhodium complex improved cyclopropanation reactions.

Consequently, the use of an axial ligand to improve the reactivity of our second step Rh-carbenoid towards X-H insertion into Trp could be explored in this project. As an initial test, ⁴BuNHOH, the same ligand that Francis and co-workers used to affect insertions of Rh-carbenoids into Trp, was employed in our solid-phase reaction using resin-bound pentapeptide 312 and iodonium salt reagent 318 to form 324a/b (Scheme 91). However, a lower product ratio was instead observed with the use of this additive.

Scheme 91: Reaction with tert-butyl-hydroxylamine hydrochloride additive on model peptide 312.
Another area that could be explored is the use of other metal catalysts to activate the diazo moiety towards the generation of metallocarbenoids, in the macrocyclisation step. Although our initial efforts have been focused on rhodium, other metals such as copper, ruthenium and iridium salts could be screened for the desired reactivity.\textsuperscript{179} Furthermore, the transferring diazoacetate groups currently employed on iodonium salts \textbf{281} and \textbf{318} may not be the best candidate for the generation of metallocarbenoids. Other reactive variants of diazoacetate could be tested, such as the use of a less electron withdrawing vicinal amide group instead of the current ester group employed. The electronic effects of different substituents on the diazoacetate group could also be probed for reactivity.

A key challenge in the synthesis of these macrocyclic peptides on solid-phase synthesis was the stability of the product macrocycles. One study that is currently on-going in the group is the de-methylation of the sulfonium group on functionalised Met (Scheme 92). The removal of the methyl group would potentially solve two problems: (i) removing chirality from the sulfur atom to eliminate one possibility of affording diastereomers, and (ii) stabilising the final macrocycle. However, this would also remove the positive charge from the macrocyclic peptide and potentially affect its ability to function as an effective CPP.

\begin{center}
\textbf{Scheme 92}: De-methylation process development.
\end{center}
4. Conclusions and Future Outlook

4.1 Enantioselective arylation-driven semipinacol rearrangement (SPR) with diaryliodonium salts

Hypervalent aryl-\(\lambda^3\)-iodanes have demonstrated themselves to be useful electrophiles in the transformation of various nucleophilic molecules. The transfer of aryls onto alkenes with diaryliodonium salts, for example, has seen unprecedented development owing to the ease of preparation, low toxicity, bench top stability and remarkable arylation activity of these diaryl-\(\lambda^3\)-iodanes.\(^{206}\)

In this thesis, section 2.5 describes the work on asymmetric arylation-driven semipinacol rearrangement (SPR) of simple tertiary allylic alcohols. The substrate scope was established, enabling enantioselective arylation on dihydropyran (6 examples, 77–96% yield, >20:1 d.r. and 80–99% e.e.), indenes (3 examples, 96–98% yield, 3:1 to >20:1 d.r. and 90–95% e.e.), and dihydronaphthalenes (2 examples, 63% yield, 5:1 to >20:1 d.r. and 84–90% e.e.). Preliminary results also demonstrated moderate success in the use of acyclic substrates (143, 62% yield, 2.6:1 d.r. and 78% e.e.). Development of bulkier ligands could be useful in the advancement of enantioselective arylation-driven SPR of acyclic allylic alcohol substrates, affording improved utility of the reaction.

The diaryliodonium salt scope was also established, transferring aryl groups with \(para\)-substitutions (8 examples on indene class of substrates and 3 examples on dihydropyran class of substrates, 81–99% yield, >20:1 d.r. and 62–94% e.e.); \(meta\)-substitutions (5 examples on indene class of substrates, 85–99% yield, >20:1 d.r. and 90–92% e.e.); \(ortho\)-substitutions (1 example on indene 185, 61% yield, >20:1 d.r., 86% e.e. and 1 example on dihydropyran 186, 63% yield, >20:1 d.r. and 87% e.e.); as well as 3,4-dichlorophenyl (181, 94% yield, >20:1 d.r. and 99% e.e.) and 2-naphthalene (182, 71% yield, >20:1 d.r. and 90% e.e.). However, as explained in section 2.4.4, heteroaromatics were found to be unsuitable for transfer in our system. Other important advancements in enantioselective transformations of nucleophilic carbon or heteroatom molecules with diaryliodonium salts will continue to be developed as this field matures. This growing interest in diaryliodonium salts will hopefully accelerate research into the chemistry of other related electrophilic carbon-transfer aryliodonium salts.
4.2 Future work on macrocyclisation of peptides

The development of cell penetrating peptides (CPP) using our macrocyclic peptide scaffold is underway and holds great potential for both synthetic chemistry and biology. Relevant to our work, sulfonium-containing macrocyclic peptides were demonstrated to be efficient CPPs. In addition, the use of Trp as a component of macrocyclic peptides was shown to improve cell-penetrating properties by triggering endocytosis mechanism in cells.

In our study, the exploitation of the diazo functionality, transferred chemoselectively onto Met by aryliodonium salts 281 and 318, through the generation of Rh-carbenoids was demonstrated to target Trp in the macrocyclisation process. Although the chemoselective insertion of diazo compounds into Trp on a peptide was previously reported to work with rhodium catalysts, the work presented here described the union of two processes, separately developed for functionalising Met and Trp, into a distinct macrocyclisation strategy. Furthermore, on-going work to translate this process onto current SPPS methods would improve the utility of our methodology, and accelerate research into the development of new therapeutics or drug delivery.
5. Experimental Procedures

5.1 General Experimental

All proton nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AM 400 (400 MHz) or an Advance 500 (500 MHz) spectrometer. Chemical shifts for $^1$H NMR were measured to the nearest 0.01 ppm and reported relative to the residual solvent peak CD$_2$Cl$_2$ / CDCl$_3$ / C$_6$D$_6$ / (CD$_3$)$_2$SO / CD$_3$CN ($^1$H δ = 5.32 / 7.26 / 7.16 / 2.50 / 1.94 ppm), with the coupling constants ($J$) given to the nearest 0.1 Hz. Multiplicity was reported according to the conventions: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, s = sextet, h = heptaplet, m = multiplet, br = broad. All $^{13}$C NMR spectra were recorded on a Bruker AM 400 (100 MHz) or an Advance 500 (125 MHz) spectrometer. Chemical shifts for $^{13}$C NMR were measured to the nearest 0.1 ppm and reported relative to CD$_2$Cl$_2$ / CDCl$_3$ / C$_6$D$_6$ / (CD$_3$)$_2$SO / CD$_3$CN ($^{13}$C δ = 53.8 / 77.0 / 128.1 / 39.5 / 118.26 ppm). All $^{19}$F NMR spectra were recorded on Advance 500 (376.5 MHz) spectrometer in CD$_2$Cl$_2$ / CDCl$_3$ / C$_6$D$_6$ / (CD$_3$)$_2$SO / CD$_3$CN uncorrected and reported to the nearest 0.1 ppm. Unless noted otherwise, $^{19}$F NMR spectra are $^1$H decoupled. Infra-red spectra were recorded on a Perkin Elmer Spectrum One FT infra-red spectrophotometer sampling accessory, scanning from 4000-600 cm$^{-1}$. IR absorption maxima ($\nu_{\text{max}}$) are reported in wavenumbers (cm$^{-1}$) with characteristic peaks identified and their signal strengths indicated according to the conventions: s = strong, m = medium, w = weak. High resolution mass spectra (HRMS) were made on a Micromass Q-TOF spectrometer using EI (electron impact) or ES (electrospray ionisation) techniques by the EPSRC mass spectrometry service (Swansea). Melting points (m.p.) were recorded using a Gallenkamp hot stage apparatus and are reported uncorrected. Optical rotations were measured in either CHCl$_3$ or C$_6$H$_6$ on a Perkin Elmer 343 Polarimeter using a sodium lamp (λ 589 nm, D-line); [α]$^{\text{Temp}}$D values are reported in degrees cm$^2$ g$^{-1}$ and concentration in g 100 mL$^{-1}$. X-ray crystallography was performed on a Nonius Kappa CCD at the Cambridge University Chemistry X-Ray Laboratory, by Dr. Andrew Bond (adb29@cam.ac.uk). Elemental analysis was acquired using Thermo Scientific iCAP 7000 series Inductively Coupled Plasma-Optical Emission Spectroscopy (ICP-OES) at the
Cambridge University Chemistry Technical Services. All yields are reported as isolated yields, unless otherwise stated.

**Chromatography:** Analytical thin layer chromatography (TLC) was performed using pre-coated Merck glass backed silica gel plates (Silicagel 60 F254). Visualisation was by ultraviolet fluorescence (λ = 254 nm) and/or staining with cerium ammonium molybdate (CAM). Column chromatography was carried out on Merck Kieselgel 60 (230-400 mesh) or aluminium oxide 60 (basic, 70-230 mesh). Chiral high-performance liquid chromatography (HPLC) analysis to determine enantiomeric excess (e.e.) was performed on Shimadzu XR-LC apparatus with chiralpak (IA, IB, IC and AD-H) or chiralcel OD columns in a mixed solvent system of n-hexane and iso-propanol. HPLC purification was done on HP Agilent 1100 apparatus, fitted with a semi-preparative reverse-phase C-18 column. Tandem mass-spectrometry (ms-ms) was done in the Cambridge University Chemistry Mass Spectrometry Laboratory’s Waters Xevo G2-S bench top Quardrupole Time-of-Flight (QTOF), using ES techniques for soft ionisation. All reactions were monitored by TLC or LCMS (Shimadzu LCMS 2020, method: 5-95% B over 3.5 min, then hold 0.5 min, then 95-5% B over 0.5 min, hold 0.5 min, 0.7 mL/min) as appropriate.

**Solvents and reagents:** Solvents were distilled using standard techniques. Tetrahydrofuran was distilled over lithium aluminium hydride; dichloromethane and hexafluoroisopropanol (HFIP) was distilled over calcium hydride; trifluoroethanol (TFE) was distilled over calcium sulfate / sodium bicarbonate. Commercial Cu(OTf)$_2$ was dried under high vacuum at 100°C and stored under nitrogen. Diaryliodonium triflate and tetrafluoroborate sources were prepared following the procedures by Olofsson. All other reagents were used as supplied or purified as necessary.
5.2 General procedures:

Available iodonium salt precursors

The Gaunt laboratory maintains a stock of diaryliodonium triflates as reagents. Several of these iodonium salts were used during these studies (Figure 42). Full experimental procedures for the synthesis all these diaryliodonium triflates used in this study have been reported by our laboratory and are not given within this document. I am grateful to previous members of the Gaunt group for this resource.

Figure 42: Gaunt group stockpile of iodonium salts used in this study.
The appropriate diaryliodonium triflate or tetrafluoroborate salt (2.0 mmol) was dissolved in dichloromethane (4 mL) and mixed with a saturated aqueous solution of sodium hexafluorophosphate (8 mL), stirred for 12 h. The aqueous layer was extracted with dichloromethane, solvent removed in vacuo and dried. The crude was washed with diethyl ether 3x, and once with chloroform to give a white crystalline solid. Successful counterion exchange was monitored and confirmed using $^{19}$F NMR.

Copper(II) triflate complex (133) solution [0.1 M, (R,R)-93]

Copper(II) triflate, (180 mg, 0.5 mmol, 1.0 eq.) and 4 Å molecular sieves were weighed out carefully in a glove box and added into a microwave tube and sealed. Separately, the ligand, (+)-2,2′-Isopropylidenebis[(4R)-4-phenyl-2-oxazoline], (184 mg, 0.55 mmol, 1.1 eq.) was weighed out in a glove box and added into another microwave tube and sealed. The ligand was subsequently dissolved in anhydrous dichloromethane (5 mL) and mixed with the copper(II) triflate to generate a 0.1 M solution.
Section 2: Enantioselective Cu-catalysed arylative SPR of allylic alcohols

General procedure A: Allylic tertiary alcohol from 3,4-dihydro-2H-pyran

To a solution of 3,4-dihydro-2H-pyran (1.5 eq.) in anhydrous tetrahydrofuran at 0 °C was added n-butyllithium (1.25 eq., 2.5 M in hexane) over 10 min. The mixture was allowed to warm to rt and stirred for a further 3 h, before it was cooled again to −78 °C. The appropriate ketone (1.0 eq.) was then added dropwise or portion-wise into the solution over 15 min. The reaction was warmed to 25 °C and stirred for 2 h before quenching with saturated NaHCO₃ (aq.). The aqueous layer was extracted with diethyl ether 3x, washed once with brine, dried (MgSO₄), and concentrated in vacuo. Purification by flash chromatography afforded the desired product.

General procedure B: Allylic tertiary alcohol from indene

To a solution of indene (1.0 eq.) in anhydrous diethyl ether (0.6 M) at −78 °C was added n-butyllithium (1.0 eq., 2.5 M in hexane) dropwise over 10 min. The mixture was allowed to warm to 25 °C and stirred for 6 h, before it was cooled again to −78 °C. The appropriate ketone (1.0 eq.) was added, and the solution warmed to 25 °C with stirring for 6 h, before quenching with water, extracting with diethyl ether 3x, washing once with brine, drying (MgSO₄), and concentrating in vacuo. Purification by flash chromatography afforded the desired product.
General procedure C: Vinylic bromide from tetralone derivatives

To a solution of triphenyl phosphite (1.1 eq.) in anhydrous dichloromethane (0.37 M) at −78 °C was added bromine (1.2 eq.). Anhydrous triethylamine (1.3 eq.) was added, followed by the appropriate tetralone derivative (1.0 eq.). The mixture was stirred for 18 h at 25 °C before refluxing for 2 h. The solution was then cooled to 25 °C and quenched with 10 % (w/w) aqueous Na₂SO₃ before extracting with dichloromethane 3x, washing once with brine, drying (MgSO₄), and concentrating in vacuo. Purification by flash chromatography afforded the desired product.

General procedure D: Allylic tertiary alcohol from vinylic bromide

To a solution of vinylic bromide (1.0 eq.), prepared from general procedure C, in anhydrous tetrahydrofuran (0.43 M) at −78 °C was added tert-butyllithium (2.0 eq., 1.7 M in pentane) dropwise over 20 min with stirring at −78 °C for 30 min. The appropriate ketone (1.0 eq.) was added dropwise over 20 min and stirred for 30 min at −78 °C. The mixture was warmed to 25 °C and stirred for another 1 h, before quenching with water, extracting with dichloromethane 3x, washing once with brine, drying (MgSO₄), and concentrating in vacuo. Purification by flash chromatography afforded the desired product.
**General procedure E: Racemic CuCl-catalysed arylation**

To a solution of the appropriate substrate (1.0 eq.), diaryliodonium triflate salt (2.0 eq.) and anhydrous CuCl (0.1 eq.) in anhydrous dichloromethane (0.13 M) at 25 °C was added the appropriate base (2.0 eq.). The mixture was heated to the appropriate temperature for a specified amount of time, before quenching with saturated NaHCO₃ (aq.), extracting with dichloromethane 3x, drying (MgSO₄) and concentrating *in vacuo*. Purification by flash chromatography afforded the desired product as a racemic mixture.

**General procedure F: Enantioselective copper-catalysed arylation**

To a solution of the appropriate substrate (1.0 eq.) in anhydrous dichloromethane (0.13 M) at a specified temperature was added 2,6-di-tert-butylpyridine or the appropriate base (2.0 or 3.0 equiv.), copper(II) (+)-2,2'-Isopropylidenebis[(4R)-4-phenyl-2-oxazoline] triflate solution (133, 0.05 or 0.10 equiv.) and diaryliodonium salt (2.0 or 3.0 equiv.) as a solution or suspension in dichloromethane. The mixture was subjected to the appropriate reacting temperature for a specified time until completion or otherwise stated, before quenching with saturated NaHCO₃ (aq.), extracting with dichloromethane 3x, drying (MgSO₄) and concentrating *in vacuo*. Purification by flash chromatography afforded the desired product.
General procedure G: Arylation using mixed 1:1 (+/-)-BOX-ligands

To a solution of the appropriate substrate (1.0 eq.) in anhydrous dichloromethane at a specified temperature was added 2,6-di-tert-butylpyridine (2.0 or 3.0 eq.), copper(II) (+/-)-2,2'-Isopropylidenebis[(4R)-4-phenyl-2-oxazoline] triflate solution (0.10 eq.) – prepared using a 1:1 equivalent ratio of both enantiomers (+/-) of 2,2'-Isopropylidenebis(4-phenyl-2-oxazoline) ligand – and diaryliodonium salt (2.0 or 3.0 eq.) as a solution or suspension in dichloromethane. The mixture was subjected to the appropriate reacting temperature for a specified time, before quenching with saturated NaHCO₃ (aq.), extracting with dichloromethane 3x, drying (MgSO₄), and concentrating in vacuo. Purification by flash chromatography afforded the desired product.
5.4 Preparation of Iodonium Salts

mesityl(phenyl)iodonium hexafluorophosphate, 184

General procedure 1 was performed on 2.0 mmol of mesityl(phenyl)iodonium triflate to yield the title compound as a white powder (749 mg, 1.6 mmol, 80%). $^1$H NMR (400 MHz, DMSO-$d_6$) δ_H 8.00 (d, J = 7.6 Hz, 2H, H2), 7.63 (t, J = 7.6 Hz, 1H, H4), 7.50 (t, J = 7.6 Hz, 2H, H3), 7.21 (s, 2H, H5), 2.61 (s, 6H, H6), 2.28 (s, 3H, H10); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ_C 143.1 (C8), 141.6 (2C, C6), 134.5 (2C, C2), 131.9 (2C, C3), 131.8 (C4), 129.8 (2C, C7), 122.5 (C1), 114.5 (C3), 26.3 (2C, C9), 20.5 (C10); $^{19}$F NMR (376.5 MHz, DMSO-$d_6$) δ_F −71.0 (d, $^1$J_F-P = 711.5 Hz, PF6); $^{31}$P NMR (162 MHz, DMSO-$d_6$) δ_P −144.2 (h, $^1$J_P-F = 709.0 Hz, PF6). Data in accordance with literature.$^{74}$

mesityl(p-tolyl)iodonium hexafluorophosphate, 185

General procedure 1 was performed on 2.0 mmol of mesityl(p-tolyl)iodonium triflate to yield the title compound as a white powder (733 mg, 1.5 mmol, 76%). $^1$H NMR (400 MHz, DMSO-$d_6$) δ_H 7.86 (d, J = 8.0 Hz, 2H, H2), 7.31 (d, J = 8.0 Hz, 2H, H3), 7.20 (s, 2H, H7), 2.59 (s, 6H, H6), 2.31 (s, 3H, H11), 2.28 (s, 3H, H10); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ_C 143.1 (C8), 142.3 (C4), 141.4 (2C, C6), 134.6 (2C, C2), 132.5 (2C, C3), 129.7 (2C, C7), 122.7 (C1), 110.8 (C5), 26.3 (2C, C9), 20.8 (C10), 20.5 (C11); $^{19}$F NMR (376.5 MHz, DMSO-$d_6$) δ_F −70.2 (d, $^1$J_F-P = 714.5 Hz, PF6); $^{31}$P NMR (162 MHz, DMSO-$d_6$) δ_P −144.2 (h, $^1$J_P-F = 709.0 Hz, PF6). Data in accordance with literature.$^{74}$
mesityl(4-isobutylphenyl)iodonium hexafluorophosphate, 186

General procedure 1 was performed on 2.0 mmol of mesityl(4-isobutylphenyl)iodonium triflate to yield the title compound as a white powder (818 mg, 1.6 mmol, 78%). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta_H$ 7.88 (d, $J = 8.0$ Hz, 2H, H$_2$), 7.30 (d, $J = 8.0$ Hz, 2H, H$_3$), 7.21 (s, 2H, H$_7$), 2.60 (s, 6H, H$_6$), 2.50-2.47 (m, 2H, H$_{11}$), 2.30 (s, 3H, H$_{10}$), 1.80 (m, 1H, H$_{12}$), 0.83 (d, $J = 6.7$ Hz, 6H, H$_{13}$); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta_C$ 146.0 (C$_6$), 143.5 (C$_4$), 142.1 (2C, C$_2$), 134.9 (2C, C$_2$), 132.9 (2C, C$_3$), 130.1 (2C, C$_7$), 123.1 (C$_1$), 111.5 (C$_5$), 44.3 (C$_{11}$), 29.9 (C$_{12}$), 26.7 (2C, C$_9$), 22.3 (2C, C$_{13}$), 21.0 (C$_{10}$); $^{19}$F NMR (376.5 MHz, DMSO-$d_6$) $\delta_F$ (-70.1 (d, $^1J_{F-P} = 714.4$ Hz, PF$_6$); $^{31}$P NMR (162 MHz, DMSO-$d_6$) $\delta_P$ -144.2 (h, $^1J_{P-F} = 709.0$ Hz, PF$_6$). Data in accordance with literature.$^{74}$

bis(4-chlorophenyl)iodonium hexafluorophosphate, 187

General procedure 1 was performed on 2.0 mmol of bis(4-chlorophenyl)iodonium triflate to yield the title compound as a white powder (854 mg, 1.7 mmol, 85%). IR (thin film) $\nu_{\text{max}}$/cm$^{-1}$ 1390, 1262, 1173, 1085, 1025, 997; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta_H$ 8.27-8.24 (m, 4H, H$_2$), 7.65-7.62 (m, 4H, H$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta_C$ 139.8 (4C, C$_2$), 136.9 (2C, C$_4$), 132.5 (4C, C$_3$), 111.3 (2C, C$_1$); $^{19}$F NMR (376.5 MHz, DMSO-$d_6$) $\delta_F$ -71.1 (d, $^1J_{F-P} = 711.0$ Hz, PF$_6$); $^{31}$P NMR (162 MHz, DMSO-$d_6$) $\delta_P$ -144.3 (h, $^1J_{P-F} = 710.0$ Hz, PF$_6$); mp 175-177 °C; m/z HRMS (NSI) found [M + PF$_6$]$^+$ 348.9043 C$_{12}$H$_8$$^{35}$Cl$_2$I requires 348.9042.
mesityl(4-bromophenyl)iodonium hexafluorophosphate, 195

General procedure 1 was performed on 2.0 mmol of mesityl(4-bromophenyl)iodonium triflate to yield the title compound as a white powder (777 mg, 1.4 mmol, 71%). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta_H$ 7.88 (d, $J = 8.4$ Hz, 2H, $H_2$), 7.71 (d, $J = 8.4$ Hz, 2H, $H_3$), 7.22 (s, 2H, $H_7$), 2.60 (s, 6H, $H_9$), 2.31 (s, 3H, $H_{10}$); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta_C$ 143.2 (C8), 141.6 (2C, C6), 136.3 (2C, C2), 134.6 (2C, C3), 130.0 (2C, C7), 125.8 (C4), 122.6 (C1), 113.0 (C5), 26.3 (2C, C9), 20.5 (C10); $^{19}$F NMR (376.5 MHz, DMSO-$d_6$) $\delta_F$ −70.0 (d, $^3$J$_{F-P} = 711.6$ Hz, PF$_6$); $^{31}$P NMR (162 MHz, DMSO-$d_6$) $\delta_P$ −144.2 (h, $^3$J$_{P-F} = 710.0$ Hz, PF$_6$). Data in accordance with literature. $^{24}$

bis(4-fluorophenyl)iodonium hexafluorophosphate, 196

General procedure 1 was performed on 2.0 mmol of bis(4-fluorophenyl)iodonium triflate to yield the title compound as a white powder (841 mg, 1.8 mmol, 91%). IR (thin film) $\nu_{\text{max}}$/cm$^{-1}$ 1735, 1473, 1370, 1230, 759; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta_H$ 8.32 (d, $J = 8.9$ Hz, 4H, $H_2$), 7.42 (d, $J = 8.9$ Hz, 4H, $H_3$); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta_C$ 164.0 (d, $^1$J$_{C-F} = 251.5$ Hz, 2C, C4), 137.9 (d, $^3$J$_{C-F} = 9.2$ Hz, 4C, C2), 119.2 (d, $^2$J$_{C-F} = 22.8$ Hz, 4C, C3), 111.2 (2C, C1); $^{19}$F NMR (376.5 MHz, CD$_2$Cl$_2$) $\delta_F$ −70.9 (d, $^3$J$_{F-P} = 712.8$ Hz, PF$_6$), −104.3 (Ph-F); $^{31}$P NMR (162 MHz, DMSO-$d_6$) $\delta_P$ −144.3 (h, $^3$J$_{P-F} = 710.0$ Hz, PF$_6$); mp 163-164$^\circ$C; m/z HRMS (NSI) found [M − PF$_6$]$^+$ 316.9630 C$_{12}$H$_8$F$_2$I requires 316.9633.
mesityl(4-(ethoxycarbonyl)phenyl)iodonium hexafluorophosphate, 197

General procedure 1 was performed on 2.0 mmol of mesityl(4-(ethoxycarbonyl)phenyl)iodonium triflate to yield the title compound as a white powder (962 mg, 1.8 mmol, 89%). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta_H$ 8.08 (d, $J$ = 8.6 Hz, 2H, H$_2$), 7.99 (d, $J$ = 8.6 Hz, 2H, H$_3$), 7.24 (s, 2H, H$_7$), 4.31 (q, $J$ = 7.0 Hz, 2H, H$_{12}$), 2.60 (s, 6H, H$_9$), 2.30 (s, 3H, H$_{10}$), 1.30 (t, $J$ = 7.0 Hz, 3H, H$_{13}$); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta_c$ 164.5 (C$_{11}$), 143.4 (C$_6$), 141.7 (2C, C$_5$), 134.6 (2C, C$_3$), 132.7 (2C, C$_2$), 132.0 (C$_4$), 130.0 (2C, C$_1$), 122.7 (C$_1$), 119.2 (C$_3$), 61.5 (C$_{12}$), 26.4 (2C, C$_9$), 20.5 (C$_{10}$), 14.0 (C$_{13}$); $^{19}$F NMR (376.5 MHz, DMSO-$d_6$) $\delta_F$ -70.1 (d, $^1$J$_{F-P}$ = 711.1 Hz, PF$_6$); $^{31}$P NMR (162 MHz, DMSO-$d_6$) $\delta_P$ -144.3 (h, $^1$J$_{P-F}$ = 710.0 Hz, PF$_6$). Data in accordance with literature.$^{74}$

mesityl(4-(trifluoromethyl)phenyl)iodonium hexafluorophosphate, 198

General procedure 1 was performed on 2.0 mmol of mesityl(4-(trifluoromethyl)phenyl)iodonium triflate to yield the title compound as a white powder (962 mg, 1.8 mmol, 89%). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta_H$ 8.15 (d, $J$ = 8.3 Hz, 2H, H$_2$), 7.87 (d, $J$ = 8.3 Hz, 2H, H$_3$), 7.25 (s, 2H, H$_7$), 2.60 (s, 6H, H$_9$), 2.30 (s, 3H, H$_{10}$); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta_c$ 143.5 (C$_8$), 141.7 (2C, C$_5$), 135.1 (C$_4$), 131.8 (q, $^2$J$_{C-F}$ = 32.5 Hz, 1C, C$_4$), 129.9 (2C, C$_7$), 128.3 (q, $^3$J$_{C-F}$ = 4.0 Hz, 2C, C$_3$), 123.4 (q, $^3$J$_{C-F}$ = 274.5 Hz, 1C, C$_{11}$), 122.6 (C$_5$), 118.8 (q, $^3$J$_{C-F}$ = 1.4 Hz, 2C, C$_2$), 26.3 (2C, C$_9$), 20.5 (C$_{10}$); $^{19}$F NMR (376.5 MHz, DMSO-$d_6$) $\delta_F$ -62.7 (CF$_3$), −71.1 (d, $^1$J$_{F-P}$ = 711.1 Hz, PF$_6$); $^{31}$P NMR (162 MHz, DMSO-$d_6$) $\delta_P$ -144.2 (h, $^1$J$_{P-F}$ = 709.0 Hz, PF$_6$). Data in accordance with literature.$^{74}$
bis(4-methoxyphenyl)iodonium hexafluorophosphate, 199

General procedure 1 was performed on 2.0 mmol of Bis(4-methoxyphenyl)iodonium triflate to yield the title compound as a pale brown powder (828 mg, 1.5 mmol, 87%). IR (thin film) \( \nu_{\text{max}} / \text{cm}^{-1} \) 2231, 1311, 1305, 1100, 1021, 797; \(^1\text{H NMR} \) (400 MHz, DMSO-\( d_6 \)) \( \delta_H \) 8.14-8.10 (m, 4H, H\(_2\)), 7.08-7.04 (m, 4H, H\(_3\)), 3.79 (s, 6H, H\(_5\)); \(^{13}\text{C NMR} \) (100 MHz, DMSO-\( d_6 \)) \( \delta_c \) 161.9 (2C, C\(_2\)), 136.9 (4C, C\(_2\)), 117.3 (4C, C\(_3\)), 106.0 (2C, C\(_1\)), 55.7 (2C, C\(_5\)); \(^{19}\text{F NMR} \) (376.5 MHz, DMSO-\( d_6 \)) \( \delta_F \) -71.1 (d, \( J_{F-P} = 711.5 \text{ Hz, PF}_6 \)); \(^{31}\text{P NMR} \) (162 MHz, DMSO-\( d_6 \)) \( \delta_P \) -144.3 (h, \( J_{P-F} = 710.0 \text{ Hz, PF}_6 \)); \( \text{mp} \) 160-161 °C; m/z HRMS (NSI) found [M – PF\(_6\)]\(^+\) 341.0031 C\(_{14}\)H\(_{10}\)IO\(_2\) requires 341.0033.

mesityl(3-bromophenyl)iodonium hexafluorophosphate, 208

General procedure 1 was performed on 2.0 mmol of mesityl(3-bromophenyl)iodonium triflate to yield the title compound as a white powder (1.09 g, 1.8 mmol, 91%). \(^1\text{H NMR} \) (400 MHz, DMSO-\( d_6 \)) \( \delta_H \) 8.27 (t, \( J = 1.7 \text{ Hz, 1H, H}_{11} \)), 7.88 (ddd, \( J = 7.9, 1.7, 0.8 \text{ Hz, 1H, H}_4 \)), 7.82 (ddd, \( J = 7.9, 1.7, 0.8 \text{ Hz, 1H, H}_2 \)), 7.44 (t, \( J = 7.9 \text{ Hz, 1H, H}_3 \)), 7.23 (s, 2H, H\(_7\)), 2.61 (s, 6H, H\(_5\)), 2.31 (s, 3H, H\(_{10} \)); \(^{13}\text{C NMR} \) (100 MHz, DMSO-\( d_6 \)) \( \delta_c \) 143.4 (C\(_8\)), 141.6 (C\(_6\)), 136.1 (C\(_2\)), 134.8 (C\(_{11}\)), 133.5 (C\(_4\)), 133.0 (C\(_3\)), 129.9 (C\(_7\)), 123.4 (C\(_{12}\)), 122.6 (C\(_1\)), 115.0 (C\(_5\)), 26.4 (2C, C\(_9\)), 20.5 (C\(_{10}\)); \(^{19}\text{F NMR} \) (376.5 MHz, DMSO-\( d_6 \)) \( \delta_F \) -71.1 (d, \( J_{F-P} = 711.4 \text{ Hz, PF}_6 \)); \(^{31}\text{P NMR} \) (162 MHz, DMSO-\( d_6 \)) \( \delta_P \) -144.3 (h, \( J_{P-F} = 710.0 \text{ Hz, PF}_6 \)). Data in accordance with literature.\(^7\)
mesityl(3-fluorophenyl)iodonium hexafluorophosphate, 209

General procedure 1 was performed on 2.0 mmol of mesityl(3-fluorophenyl)iodonium triflate to yield the title compound as a white powder (1.09 g, 1.8 mmol, 91%). IR (thin film) ν\textsubscript{max}/cm\textsuperscript{-1} 1730, 1470, 1360, 1228, 751; \textsuperscript{1}H NMR (400 MHz, DMSO-d\textsubscript{6}) δ\textsubscript{H} 7.99 (dt, J = 7.9, 2.0 Hz, 1H, H\textsubscript{2}), 7.76 (dt, J = 7.9, 1.2 Hz, 1H, H\textsubscript{4}), 7.59-7.48 (m, 2H, H\textsubscript{3} and H\textsubscript{11}), 7.24 (s, 2H, H\textsubscript{1}), 2.60 (s, 6H, H\textsubscript{6}), 2.31 (s, 3H, H\textsubscript{10}); \textsuperscript{13}C NMR (100 MHz, DMSO-d\textsubscript{6}) δ\textsubscript{C} 162.1 (d, J\textsubscript{C-F} = 252.4 Hz, 1C, C\textsubscript{12}), 143.4 (C\textsubscript{8}), 141.7 (2C, C\textsubscript{6}), 133.5 (d, J\textsubscript{C-F} = 7.9 Hz, 1C, C\textsubscript{3}), 130.6 (d, J\textsubscript{C-F} = 3.2 Hz, 1C, C\textsubscript{2}), 129.9 (2C, C\textsubscript{7}), 122.7 (C\textsubscript{5}), 121.7 (d, J\textsubscript{C-F} = 24.7 Hz, 1C, C\textsubscript{11}), 119.2 (d, J\textsubscript{C-F} = 21.0 Hz, 1C, C\textsubscript{4}), 113.9 (d, J\textsubscript{C-F} = 7.5 Hz, 1C, C\textsubscript{1}), 26.3 (2C, C\textsubscript{0}), 20.5 (C\textsubscript{10}); \textsuperscript{19}F NMR (376.5 MHz, DMSO-d\textsubscript{6}) δ\textsubscript{F} -71.1 (d, J\textsubscript{F-P} = 711.1 Hz, PF\textsubscript{6}), -108.5 (Ph-F); \textsuperscript{31}P NMR (162 MHz, DMSO-d\textsubscript{6}) δ\textsubscript{P} -144.3 (h, J\textsubscript{P-F} = 710.0 Hz, PF\textsubscript{6}); mp 155-156 °C; m/z HRMS (NSI) found [M – PF\textsubscript{6}]\textsuperscript{+} 341.0195 C\textsubscript{15}H\textsubscript{13}FI requires 341.0197.

mesityl(3-(ethoxycarbonyl)phenyl)iodonium hexafluorophosphate, 210

General procedure 1 was performed on 2.0 mmol of mesityl(3-(ethoxycarbonyl)phenyl)iodonium triflate to yield the title compound as a white powder (918 mg, 1.7 mmol, 85%). \textsuperscript{1}H NMR (400 MHz, DMSO-d\textsubscript{6}) δ\textsubscript{H} 8.47 (t, J = 1.7 Hz, 1H, H\textsubscript{11}), 8.15 (dt, J = 7.5, 1.2 Hz, 1H, H\textsubscript{4}), 8.61 (ddd, J = 8.1, 1.7, 0.9 Hz, 1H, H\textsubscript{2}), 7.63 (t, J = 8.1 Hz, 1H, H\textsubscript{3}), 7.25 (s, 2H, H\textsubscript{1}), 4.33 (q, J = 7.0 Hz, 2H, H\textsubscript{14}), 2.59 (s, 6H, H\textsubscript{6}), 2.31 (s, 3H, H\textsubscript{10}), 1.31 (t, J = 7.0 Hz, 3H, H\textsubscript{15}); \textsuperscript{13}C NMR (100 MHz, DMSO-d\textsubscript{6}) δ\textsubscript{C} 163.9 (C\textsubscript{13}), 143.3 (C\textsubscript{8}), 141.8 (2C, C\textsubscript{6}), 138.1 (C\textsubscript{12}), 134.3 (C\textsubscript{2}), 132.7 (C\textsubscript{3}), 132.4 (C\textsubscript{4}), 131.9 (C\textsubscript{11}), 130.0(C\textsubscript{7}), 122.5 (C\textsubscript{1}), 114.4 (C\textsubscript{5}), 61.5 (C\textsubscript{14}), 26.3 (2C, C\textsubscript{0}), 20.5 (C\textsubscript{10}), 14.0 (C\textsubscript{15}); \textsuperscript{19}F NMR (376.5 MHz, DMSO-d\textsubscript{6}) δ\textsubscript{F} -70.1 (d, J\textsubscript{F-P} = 711.1 Hz, PF\textsubscript{6}); \textsuperscript{31}P NMR (162 MHz, DMSO-d\textsubscript{6}) δ\textsubscript{P} -144.2 (h, J\textsubscript{P-F} = 710.0 Hz, PF\textsubscript{6}). Data in accordance with literature.\textsuperscript{74}
mesityl(3-(trifluoromethyl)phenyl)iodonium hexafluorophosphate, 211

General procedure 1 was performed on 2.0 mmol of mesityl(3-(trifluoromethyl)phenyl)iodonium triflate to yield the title compound as a white powder (962 mg, 1.8 mmol, 89%). $^1$H NMR (400 MHz, DMSO-$d_6$) δ_H 8.48 (s, 1H, H$_{11}$), 8.10 (d, J = 8.1 Hz, 1H, H$_2$), 8.01 (d, J = 7.9 Hz, 1H, H$_4$), 7.40 (t, J = 8.1 Hz, 1H, H$_3$), 7.23 (s, 2H, H$_1$), 2.61 (s, 6H, H$_6$), 2.30 (s, 3H, H$_{10}$); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ_C 143.5 (C$_8$), 141.9 (2C, C$_6$), 138.2 (C$_3$), 132.9 (C$_2$), 131.5 (q, $^3$J$_{C-F}$ = 32.9 Hz, 1C, C$_{12}$), 131.0 (q, $^3$J$_{C-F}$ = 3.8 Hz, 1C, C$_{11}$), 129.9 (2C, C$_7$), 128.6 (q, $^3$J$_{C-F}$ = 3.5 Hz, 1C, C$_4$), 123.0 (q, $^3$J$_{C-F}$ = 273.3 Hz, 1C, C$_{13}$), 122.6 (C$_5$), 114.8 (C$_1$), 26.3 (2C, C$_9$), 20.5 (C$_{10}$); $^{19}$F NMR (376.5 MHz, DMSO-$d_6$) δ_F −61.3 (CF$_3$), −70.2 (d, $^1$J$_{F-P}$ = 711.2 Hz, PF$_6$); $^{31}$P NMR (162 MHz, DMSO-$d_6$) δ_P −144.2 (h, $^1$J$_{P-F}$ = 709.0 Hz, PF$_6$). Data in accordance with literature.$^{74}$

bis(3-(trifluoromethoxy)phenyl)iodonium hexafluorophosphate, 212

General procedure 1 was performed on 2.0 mmol of mesityl(3-(trifluoromethoxy)phenyl)iodonium triflate to yield the title compound as a white powder (828 mg, 1.5 mmol, 75%). IR (thin film) $\nu_{max}/\text{cm}^{-1}$ 2247, 1320, 1301, 1107, 1051, 791; $^1$H NMR (400 MHz, DMSO-$d_6$) δ_H 8.48 (s, 2H, H$_3$), 8.34-8.31 (m, 2H, H$_3$), 7.71 (d, J = 4.7 Hz, 4H, H$_2$ and H$_4$); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ_C 148.6 (2C, C$_6$), 134.4 (2C, C$_3$), 133.6 (2C, C$_2$), 127.7 (2C, C$_5$), 125.2 (2C, C$_4$), 119.8 (q, $^1$J$_{C-F}$ = 257.0 Hz, 2C, OCF$_3$), 116.9 (2C, C$_1$); $^{19}$F NMR (376.5 MHz, DMSO-$d_6$) δ_F −58.1 (OCF$_3$), −71.1 (d, $^1$J$_{F-P}$ = 711.1 Hz, PF$_6$); $^{31}$P NMR (162 MHz, DMSO-$d_6$) δ_P −144.3 (h, $^1$J$_{P-F}$ = 710.0 Hz, PF$_6$); mp 167-168 °C; m/z HRMS (NSI) found [M − PF$_6$]$^+$ 448.9455 C$_{14}$H$_8$F$_6$IO$_2$ requires 448.9468.
mesityl(3,4-dichlorophenyl)iodonium hexafluorophosphate, 213

General procedure 1 was performed on 2.0 mmol of mesityl(3,4-dichlorophenyl)iodonium triflate to yield the title compound as a white powder (999 mg, 1.9 mmol, 93%). $^1$H NMR (400 MHz, DMSO-$d_6$) δH 8.35 (d, $J$ = 2.1 Hz, 1H, H$_1$), 7.84 (dd, $J$ = 8.5, 2.1 Hz, 1H, H$_3$), 7.75 (d, $J$ = 8.5 Hz, 1H, H$_2$), 7.23 (s, 2H, H$_7$), 2.60 (s, 6H, H$_9$), 2.31 (s, 3H, H$_{10}$); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δC 143.6 (C$_8$), 141.9 (2C, C$_6$), 135.8 (C$_{11}$), 135.4 (C$_2$), 134.3 (C$_{12}$), 133.6 (C$_4$), 133.5 (C$_3$), 130.0 (2C, C$_7$), 122.9 (C$_2$), 112.5 (C$_1$), 26.3 (2C, C$_9$), 20.5 (C$_{10}$); $^{19}$F NMR (376.5 MHz, DMSO-$d_6$) δF −71.1 (d, $^1$J$_{F,P}$ = 711.4 Hz, PF$_6$); $^{31}$P NMR (162 MHz, DMSO-$d_6$) δP −144.3 (h, $^1$J$_{P,F}$ = 710.0 Hz, PF$_6$). Data in accordance with literature.$^{74}$

mesityl(naphthalen-2-yl)iodonium hexafluorophosphate, 214

General procedure 1 was performed on 2.0 mmol of mesityl(naphthalen-2-yl)iodonium triflate to yield the title compound as a white powder (821 mg, 1.6 mmol, 78%). $^1$H NMR (400 MHz, DMSO-$d_6$) δH 8.80 (s, 1H, H$_2$), 7.96-7.81 (m, 4H, H$_{13-16}$), 7.68-7.71 (m, 2H, H$_{11-12}$), 7.21 (s, 2H, H$_7$), 2.69 (s, 6H, H$_9$), 2.31 (s, 3H, H$_{10}$); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δC 143.1 (C$_8$), 141.6 (2C, C$_6$), 135.6 (C$_2$), 133.9 (C$_3$), 133.3 (C$_4$), 131.5 (C$_{12}$), 129.8 (2C, C$_7$), 129.7 (C$_{11}$), 128.7 (C$_{14}$), 128.1 (C$_{16}$), 128.0 (C$_{13}$), 127.9 (C$_{15}$), 122.7 (C$_5$), 111.4 (C$_1$), 20.3 (2C, C$_9$), 20.1 (C$_{10}$); $^{19}$F NMR (376.5 MHz, DMSO-$d_6$) δF −73.2 (d, $^1$J$_{F,P}$ = 710.0 Hz, PF$_6$); $^{31}$P NMR (162 MHz, DMSO-$d_6$) δP −144.2 (h, $^1$J$_{P,F}$ = 709.0 Hz, PF$_6$). Data in accordance with literature.$^{74}$
bis(2-fluorophenyl)iodonium hexafluorophosphate, 222

General procedure 1 was performed on 2.0 mmol of bis(2-fluorophenyl)iodonium triflate to yield the title compound as a white powder (826 mg, 1.7 mmol, 85%). IR (thin film) \( \nu_{\text{max}}/\text{cm}^{-1} \) 3010, 1730, 1476, 1375, 1228, 950, 751; \(^1\text{H NMR} \) (400 MHz, DMSO-\( d_6 \)) \( \delta \)H 8.54-8.50 (m, 2H, H5), 7.91-7.85 (m, 2H, H4), 7.65-7.61 (m, 2H, H6), 7.50-7.46 (m, 2H, H3); \(^{13}\text{C NMR} \) (100 MHz, DMSO-\( d_6 \)) \( \delta \)C 159.0 (d, \( J_{\text{C-F}} \) = 250.0 Hz, 2C, C2), 137.1 (2C, C1), 136.0 (d, \( J_{\text{C-F}} \) = 7.9 Hz, 2C, C5), 127.8 (2C, C6), 117.1 (d, \( J_{\text{C-F}} \) = 22.2 Hz, 2C, C3), 104.0 (d, \( J_{\text{C-F}} \) = 25.2 Hz, 2C, C1); \(^{19}\text{F NMR} \) (376.5 MHz, CD2Cl2) \( \delta \)F −73.5 (d, \( J_{\text{F-P}} \) = 708.5 Hz, PF6), −98.3 (Ph-F); \(^{31}\text{P NMR} \) (162 MHz, DMSO-\( d_6 \)) \( \delta \)P −144.3 (h, \( J_{\text{P-F}} \) = 710.0 Hz, PF6); \text{mp} \ 154-156 °C; \text{m/z} \text{ HRMS (NSI) found [M −PF}_6]^+ \ 316.9632 \text{C}_{12}\text{H}_8\text{F}_2\text{I requires 316.9633.}

mesityl(2-methylphenyl)iodonium hexafluorophosphate, 223

General procedure 1 was performed on 2.0 mmol of Mesityl(2-methylphenyl)iodonium triflate to yield the title compound as a white powder (878 mg, 1.8 mmol, 91%). \(^1\text{H NMR} \) (400 MHz, DMSO-\( d_6 \)) \( \delta \)H 7.95 (d, \( J = 8.1 \) Hz, 1H, H11), 7.58-7.55 (m, 2H, H4,12), 7.27-7.20 (m, 3H, H3,7), 2.57-2.56 (m, 9H, H9,13), 2.30 (s, 3H, H10); \(^{13}\text{C NMR} \) (100 MHz, DMSO-\( d_6 \)) \( \delta \)C 143.4 (C8), 142.1 (C2), 141.0 (2C, C9), 137.1 (C11), 134.0 (C12), 132.9 (C3), 132.2 (C4), 130.4 (2C, C7), 122.2 (C1), 119.0 (C5), 26.6 (2C, C14), 24.8 (C13), 20.9 (C10); \(^{19}\text{F NMR} \) (376.5 MHz, DMSO-\( d_6 \)) \( \delta \)F −70.1 (d, \( J_{\text{F-P}} \) = 714.3 Hz, PF6); \(^{31}\text{P NMR} \) (162 MHz, DMSO-\( d_6 \)) \( \delta \)P −144.2 (h, \( J_{\text{P-F}} \) = 709.0 Hz, PF6). Data in accordance with literature.\(^{74}\)
5.5 Synthesis of Substrates

1-(prop-1-en-2-yl)cyclobut-1-en-2-yl)cyclobutan-1-ol (68)

To a solution of cyclobutanone (701 mg, 10.0 mmol) in anhydrous tetrahydrofuran (8 mL) at −40 °C was added isopropenylmagnesium bromide (30 mL, 0.5 M solution in tetrahydrofuran) under N₂ (g). The reaction was warmed to 25 °C and stirred for 2 h before quenching with water (20 mL), extracting with diethyl ether 3x, drying (MgSO₄), and concentrating in vacuo. Purification by column chromatography (5-30 % diethyl ether / hexane) afforded the desired compound as a yellow oil (841 mg, 7.5 mmol, 75 %).

Rf 0.3 (20% diethyl ether / hexane); IR (thin film) νmax/cm⁻¹ 3415, 2987, 1451, 1250, 1055, 892; ¹H NMR (400 MHz, CDCl₃) δH 4.99 (bs, 1H, H₁), 4.87 (bs, 1H, H₁), 2.36-2.30 (m, 2H, H₄,6), 2.10-2.02 (m, 2H, H₄,6), 1.93-1.83 (m, 1H, H₅), 1.80 (bs, 3H, H₈), 1.68 (s, 1H, OH₇), 1.62-1.51 (m, 1H, H₃); ¹³C NMR (100 MHz, CDCl₃) δc 147.8 (C₂), 109.2 (C₁), 77.9 (C₃), 34.3 (2C, C₄,6), 17.7 (C₈), 12.7 (C₅). Data in accordance with literature.⁶⁸
trimethyl(1-(prop-1-en-2-yl)cyclobutoxy)silane (149, TMS-protected 68)

To a solution of 68 (100 mg, 0.89 mmol) in anhydrous dichloromethane (10 mL) at 0 °C was added triethylamine (0.5 mL, 3.57 mmol) and trimethylsilyl trifluoromethanesulfonate (0.32 mL, 1.78 mmol). The reaction was warmed to 25 °C and stirred for 1 h before quenching with water (20 mL), extracting with dichloromethane 3x, drying (MgSO₄), and concentrating in vacuo. Purification by column chromatography (0-2 % diethyl ether / hexane) afforded the desired compound as a yellow oil (154 mg, 0.84 mmol, 94 %).

Rₜ0.85 (20% diethyl ether / hexane); IR (thin film) ν max/cm⁻¹ 2923, 1442, 1256, 1153, 1019, 840; ¹H NMR (400 MHz, CD₂Cl₂) δH 4.99 (s, 1H, H₁), 4.86 (s, 1H, H₁), 2.29-2.23 (m, 2H, H₄,₆), 2.18-2.10 (m, 2H, H₄,₆), 1.75 (s, 3H, H₈), 1.73-1.67 (m, 1H, H₅), 1.51-1.40 (m, 1H, H₃), 0.09 (s, 9H, H₇); ¹³C NMR (100 MHz, CD₂Cl₂) δc 148.4 (C₂), 109.4 (C₁), 79.3 (C₃), 35.8 (2C, C₄,₆), 17.8 (C₈), 13.5 (C₉), 1.7 (C₇); m/z HRMS (NSI) found [M+H]+ 185.1361 C₁₀H₂₁OSi requires 185.1362.
1-(1-phenylvinyl)cyclobutan-1-ol (130)

To magnesium turnings (402 mg, 16.6 mmol) in anhydrous tetrahydrofuran (0.5 mL) were added iodine crystals (20 mg, 0.07 mmol) and the resulting suspension stirred for 30 minutes. α-Bromostyrene (1.0 g, 5.46 mmol) in tetrahydrofuran (1 mL) was added dropwise, and the mixture refluxed for 2 h, before being cooled to −40 °C. A solution of cyclobutanone (255 mg, 3.64 mmol) in tetrahydrofuran (2 mL) was added to the suspension, and the solution warmed to 25 °C with stirring for 15 minutes, before quenching with saturated aqueous ammonium chloride, extracting with dichloromethane 3x, drying (MgSO₄), and concentrating in vacuo. The product was purified by column chromatography (5-40 % diethyl ether / hexane) to afford the desired compound as a pale-yellow oil (613 mg, 3.52 mmol, 97%).

**Rf** 0.45 (40% diethyl ether / hexane); **IR** (thin film) ν<sub>max</sub>/cm<sup>−1</sup> 3380, 2984, 1626, 1573, 1493, 1249, 1116, 904; **¹H NMR** (400 MHz, CDCl₃) δ<sub>H</sub> 7.49-7.46 (m, 2H, H₁₀), 7.35-7.26 (m, 3H, H₉,₁₁), 5.37 (dd, J = 1.0, 9.5 Hz, 2H, H₁), 2.52-2.44 (m, 2H, H₄,₆), 2.29-2.20 (m, 2H, H₄,₆), 2.06-1.93 (m, 1H, H₃), 1.91 (bs, 1H, OH₇), 1.69-1.58 (m, 1H, H₃); **¹³C NMR** (100 MHz, CDCl₃) δ<sub>c</sub> 152.4 (C₂), 139.1 (C₅), 128.1 (2C, C₁₀), 127.6 (C₁₁), 127.5 (2C, C₅), 112.8 (C₁), 78.0 (C₃), 35.8 (2C, C₄,₆), 13.4 (C₅); **m/z HRMS** (APCI) found [M + NH₄]<sup>+</sup> 192.1381 C₁₂H₁₆ON requires 192.1383.
According to the general procedure B, to a solution of triphenyl phosphite (6.8 g, 22.0 mmol) in anhydrous dichloromethane (60 mL) was added bromine (3.8 g, 24.0 mmol). Anhydrous triethylamine (3.6 mL, 26.0 mmol) was added, followed by α-tetralone (2.9 g, 20.0 mmol). Purification by column chromatography (100 % hexane) afforded the desired compound as a light-yellow oil (3.6 g, 17.2 mmol, 86%).

$R_f$ 0.6 (1% ethyl acetate/hexane); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2941, 2821, 1679, 1658, 1436, 1059, 766; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$H 7.59 (d, $J = 7.5$ Hz, 1H, H$_7$), 7.30-7.22 (2H, m, H$_{8,9}$), 7.14 (d, $J = 7.5$ Hz, 1H, H$_6$), 6.49 (t, $J = 4.4$ Hz, 1H, H$_2$), 2.89 (t, $J = 8.0$ Hz, 2H, H$_4$), 2.45-2.38 (2H, m, H$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$C 136.3 (C$_5$), 133.0 (C$_{10}$), 130.7 (C$_7$), 128.3 (C$_6$), 127.2 (C$_9$), 126.8 (C$_8$), 126.5 (C$_2$), 121.4 (C$_1$), 27.6 (C$_4$), 25.4 (C$_3$). Data in accordance with literature.$^{85}$
According to general procedure C, to a solution of 135 (3.6 g, 17.0 mmol) in anhydrous tetrahydrofuran (40 mL) was added tert-butyllithium (1.7 M in pentane, 20 mL, 34.0 mmol) followed by cyclobutanone (1.2 g, 17.0 mmol). Purification by column chromatography (1-10% diethyl ether / hexane) afforded the desired compound as a white solid (3.0 g, 15.0 mmol, 89%).

\( \text{Rf} 0.25 \) (20% diethyl ether / hexane); \( \text{IR (thin film)} \ \nu_{\text{max}}/\text{cm}^{-1} 3224, 2969, 1450, 1406, 1250, 1076, 892; \) \( \text{\textsuperscript{1}H NMR} \ (500 \text{MHz, CD}_2\text{Cl}_2) \ \delta_H 7.51 \) (dd, \( J = 5.0, 5.0 \text{ Hz, 1H}, \text{H}_7)), 7.19-7.12 (m, 3H, H_{6,8,9}), 6.20 (t, \( J = 5.0 \text{ Hz, 1H}, \text{H}_2)), 2.75 (t, \( J = 8.0 \text{ Hz, 2H}, \text{H}_4)), 2.56-2.50 (m, 2H, H_{12,14}), 2.35-2.27 (m, 4H, H_{3,12,14}), 2.17 (bs, 1H, OH_{15}), 2.01-1.92 (m, 1H, H_{13}), 1.65-1.57 (m, 1H, H_{13}); \( \text{\textsuperscript{13}C NMR} \ (125 \text{MHz, CD}_2\text{Cl}_2) \ \delta_C 139.8 \) (C_1), 137.8 (C_5), 132.6 (C_{10}), 128.0 (C_7), 126.8 (C_6), 126.1 (C_8), 125.6 (C_9), 125.5 (C_2), 77.6 (C_{11}), 36.1 (2C, C_{12,14}), 28.4 (C_4), 23.4 (C_3), 14.1 (C_{13}); \( m/z \) HRMS (NSI) found [M + Na]^+ 223.1094 \( \text{C}_{14}\text{H}_{16}\text{ONa} \) requires 223.1093. Data in accordance with literature.\textsuperscript{85}
4-bromo-6,8-dimethyl-1,2-dihydronaphthalene (136)

According to the general procedure B, to a solution of triphenyl phosphite (1.7 g, 5.5 mmol) in anhydrous dichloromethane (15 mL) was added bromine (0.96 g, 6.0 mmol), anhydrous triethylamine (0.66 g, 6.5 mmol), and 5,7-dimethyl-1-tetralone (0.91 mL, 5 mmol). Purification by column chromatography (100 % hexane) afforded the desired compound as a colourless oil (1.0 g, 4.2 mmol, 84%).

Rf 0.5 (100% hexane); IR (thin film) νmax/cm⁻¹ 2941, 2830, 1684, 1473, 1437, 1320, 1042, 856, 766; ¹H NMR (400 MHz, CDCl₃) δH 7.27 (s, 1H, H₉), 6.91 (s, 1H, H₇), 6.43 (t, J = 4.8 Hz, 1H, H₂), 2.74 (t, J = 8.2 Hz, 2H, H₄), 2.37-2.32 (m containing 1s at 2.32 ppm, 5H, H₃, H₁₂), 2.25 (s, 3H, H₁₁); ¹³C NMR (100 MHz, CDCl₃) δc 135.4 (C₅), 134.5 (C₈), 132.7 (C₆), 131.6 (C₁₀), 131.1 (C₇), 130.2 (C₂), 125.4 (C₃), 121.9 (C₁), 25.3 (C₄), 23.2 (C₃), 21.0 (C₁₂), 19.4 (C₁₁); m/z HRMS (NSI) found [M + H]⁺ 237.0278 C₁₂H₁₄Br requires 237.0279.
1-(5,7-dimethyl-3,4-dihydronaphthalen-1-yl)cyclobutan-1-ol (138)

According to the general procedure C, to a solution of 136 (0.50 g, 2.11 mmol) in anhydrous tetrahydrofuran (5 mL) was added tert-butyllithium (1.7 M in pentane, 2.5 mL, 4.22 mmol) followed by cyclobutanone (0.15 g, 2.11 mmol). Purification by column chromatography (1-10% diethyl ether / hexane), followed by recrystallisation from hexane, afforded the desired compound as a white crystal (0.45 g, 1.98 mmol, 94%).

Rf 0.25 (20% diethyl ether / hexane); IR (thin film) ν_{max}/cm^{-1} 3380, 2938, 1604, 1473, 1427, 1248, 1116, 834; $^{1}$H NMR (500 MHz, CD$_2$Cl$_2$) δ$_H$ 7.18 (s, 1H, H$_9$), 6.86 (s, 1H, H$_7$), 6.17 (t, $J$ = 4.8 Hz, 1H, H$_2$), 2.64 (t, $J$ = 8.0 Hz, 2H, H$_4$), 2.55-2.48 (m, 2H, H$_{14,15}$), 2.33-2.22 (m containing 2s at 2.26 and 2.27 ppm, 10H, H$_{3,11,12,14,15}$), 2.11 (bs, 1H, OH$_{17}$), 1.99-1.91 (m, 1H, H$_{16}$), 1.63-1.55 (m, 1H, H$_{16}$); $^{13}$C NMR (125 MHz, CD$_2$Cl$_2$) δ$_C$ 140.3 (C$_1$), 135.2 (C$_{10}$), 134.7 (C$_5$), 133.1 (C$_8$), 132.3 (C$_6$), 129.8 (C$_7$), 125.2 (C$_9$), 124.2 (C$_2$), 78.0 (C$_{13}$), 36.3 (2C, C$_{14,15}$), 23.8 (C$_4$), 23.4 (C$_3$), 21.4 (C$_{12}$), 20.0 (C$_{11}$), 14.2 (C$_{16}$); mp 45-47 °C; m/z HRMS (APCI) found [M + NH$_4$]$^+$ 246.1851 C$_{16}$H$_{24}$ON requires 246.1852.
According to the general procedure C, to a solution of triphenyl phosphite (6.8 g, 22.0 mmol) in anhydrous dichloromethane (60 mL) was added bromine (3.8 g, 24.0 mmol), anhydrous triethylamine (3.72 mL, 26.0 mmol), and 6-methoxy-1-tetralone (3.5 g, 20.0 mmol). Purification by column chromatography (100 % hexane) afforded the desired compound as a colourless oil (3.4 g, 14.2 mmol, 71%).

\( R_f \) 0.25 (100% hexane); \( \text{IR (thin film)} \ \nu_{\max}/\text{cm}^{-1} \) 2988, 2901, 1603 (m, C=C), 1566, 1494, 1250, 1123, 1038, 810, 670; \( \text{\textsuperscript{1}H NMR (400 MHz, CD}_2\text{Cl}_2) \ \delta_H \) 7.54 (d, \( J = 8.4 \) Hz, 1H, \( H_9 \)), 6.80 (dd, \( J = 8.4, 2.7 \) Hz, 1H, \( H_8 \)), 6.74 (d, \( J = 2.7 \) Hz, 1H, \( H_6 \)), 6.35 (t, \( J = 4.8 \) Hz, 1H, \( H_2 \)), 3.84 (s, 3H, \( H_{11} \)), 2.85 (t, \( J = 8.0 \) Hz, 2H, \( H_4 \)), 2.40-2.35 (m, 2H, \( H_3 \)); \( \text{\textsuperscript{13}C NMR (100 MHz, CD}_2\text{Cl}_2) \ \delta_c \) 160.0 (C7), 138.5 (C5), 128.4 (C9), 128.1 (C10), 126.4 (C2), 121.2 (C1), 113.9 (C6), 111.3 (C8), 55.5 (C11), 28.4 (C4), 25.8 (C3); \( m/z \) HRMS (NSI) found \([M + H]^+ \) 240.1198 C\(_{11}\)H\(_{12}\)\textsuperscript{79}BrO requires 240.1197.
According to the general procedure D, to a solution of 141 (3.5 g, 14.8 mmol) in anhydrous tetrahydrofuran (36 mL) was added tert-butyllithium (1.7 M in pentane, 17.7 mL, 30.0 mmol), followed by cyclobutanone (1.05 g, 15.0 mmol). Purification by column chromatography (1-10% diethyl ether / hexane), and recrystallisation from hexane, afforded the desired compound as a white crystal (3.10 g, 13.5 mmol, 91%).

**Rf** 0.3 (20% diethyl ether / hexane); **IR** (thin film) ν<sub>max</sub>/cm<sup>-1</sup> 3381 (s, br, OH), 2935, 2832, 1606 (m, C=C), 1568, 1496, 1427, 1302, 1245, 1102, 832; **<sup>1</sup>H NMR** (500 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ<sub>H</sub> 7.44 (d, J = 8.6 Hz, 1H, H<sub>9</sub>), 6.74 (d, J = 3.0 Hz, 1H, H<sub>6</sub>), 6.70 (dd, J = 8.6, 3.0 Hz, 1H, H<sub>8</sub>), 6.06 (t, J = 4.7 Hz, 1H, H<sub>2</sub>), 3.79 (s, 3H, H<sub>11</sub>), 2.71 (t, J = 8.0 Hz, 2H, H<sub>4</sub>), 2.54-2.48 (m, 2H, H<sub>3</sub>), 2.32-2.24 (m, 5H, H<sub>13,14,16</sub>), 1.99-1.91 (m, 1H, H<sub>15</sub>), 1.64-1.55 (m, 1H, H<sub>15</sub>); **<sup>13</sup>C NMR** (125 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ<sub>C</sub> 158.6 (C<sub>7</sub>), 139.8 (C<sub>1</sub>), 139.6 (C<sub>2</sub>), 127.0 (C<sub>10</sub>), 125.7 (C<sub>9</sub>), 123.0 (C<sub>2</sub>), 114.1 (C<sub>6</sub>), 110.9 (C<sub>8</sub>), 77.7 (C<sub>12</sub>), 55.5 (C<sub>11</sub>), 36.1 (2C, C<sub>13,14</sub>), 29.1 (C<sub>4</sub>), 23.5 (C<sub>3</sub>), 14.2 (C<sub>13</sub>); **mp** 108-110 °C; **m/z** HRMS (NSI) found [M + Na]<sup>+</sup> 253.1200 C<sub>15</sub>H<sub>18</sub>O<sub>2</sub>Na requires 253.1199.
(3,4-dihydro-2H-pyran-6-yl)diphenylmethanol (73)

According to general procedure A, to a solution of 3,4-dihydro-2H-pyran (1.26 g, 15.0 mmol) in anhydrous tetrahydrofuran (13 mL) was added n-butyllithium (2.5 M in hexane, 6.0 mL, 15.0 mmol), followed by benzophenone (2.72 g, 14.9 mmol) as a solution in tetrahydrofuran (7 mL). The reaction was warmed to 25 °C and stirred for 2 h. Purification by column chromatography (1-10% diethyl ether / hexane) afforded the desired compound as a white solid (3.8 g, 14.3 mmol, 95%).

Rf0.4 (20% diethyl ether / hexane); IR (thin film) ν max/cm⁻¹ 3452, 2987, 1665, 1446, 1394, 1232, 1057, 891; ¹H NMR (500 MHz, CD₂Cl₂) δH 7.46-7.44 (m, 4H, H₈), 7.37-7.29 (m, 6H, H₉,₁₀), 4.45 (t, J = 4.0 Hz, 1H, H₂), 4.09 (t, J = 5.0 Hz, 2H, H₅), 3.54 (s, 1H, OH₁₁), 2.10 (dt, J = 3.0, 3.5, 2H, 4.0 Hz, H₃) 1.91-1.86 (qn, J = 5.3, 6.3 Hz, 2H, H₄); ¹³C NMR (125 MHz, CD₂Cl₂) δc 156.0 (2C, C₁), 145.0 (C₇), 128.1 (4C, C₉), 128.0 (4C, C₈), 127.5 (2C, C₁₀), 101.7 (C₂), 80.9 (C₆), 67.1 (C₅), 22.5 (C₃), 20.6 (C₄); m/z HRMS (NSI) found [M + H]⁺ 267.1379 C₁₈H₁₉O₂ requires 267.1380. Data in accordance with literature.⁹⁷
According to general procedure A, to a solution of 3,4-dihydro-2H-pyran (2.52 g, 30.0 mmol) in anhydrous tetrahydrofuran (50 mL) was added n-butyllithium (2.5 M in hexane, 10.0 mL, 25.0 mmol), followed by cyclobutanone (1.40 g, 20.0 mmol). Purification by column chromatography (1-10% diethyl ether / hexane) afforded the desired compound as a colourless oil (1.52 g, 9.86 mmol, 49%).

R<sub>f</sub> 0.3 (20% diethyl ether / hexane); IR (thin film) ν<sub>max</sub>/cm<sup>-1</sup> 3405 (s, br, OH), 2991, 1670 (m, C=C), 1451, 1407, 1250, 1065, 892; <sup>1</sup>H NMR (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ<sub>H</sub> 4.88 (t, J = 4.0 Hz, 1H, H<sub>2</sub>), 4.02 (t, J = 5.2 Hz, 2H, H<sub>3</sub>), 2.45 (bs, 1H, OH<sub>10</sub>), 2.31-2.25 (m, 2H, H<sub>7,8</sub>), 2.08-1.99 (m, 4H, H<sub>3,7,8</sub>), 1.83-1.73 (m, 3H, H<sub>4,9</sub>) 1.62-1.51 (m, 1H, H<sub>9</sub>); <sup>13</sup>C NMR (100 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ<sub>C</sub> 156.1 (C<sub>1</sub>), 94.4 (C<sub>2</sub>), 75.4 (C<sub>6</sub>), 66.8 (C<sub>5</sub>), 34.3 (2C, C<sub>7,8</sub>), 22.7 (C<sub>3</sub>), 20.3 (C<sub>4</sub>), 13.2 (C<sub>9</sub>); m/z HRMS (NSI) found [M + H]<sup>+</sup> 155.1063 C<sub>9</sub>H<sub>15</sub>O<sub>2</sub> requires 155.1067. Data in accordance with literature. <sup>89</sup>
methyl 3-(3,4-dihydro-2H-pyran-6-yl)-3-hydroxycyclobutane-1-carboxylate (151a/b)

According to general procedure A, to a solution of 3,4-dihydro-2H-pyran (2.52 g, 30.0 mmol) in anhydrous tetrahydrofuran (50 mL) was added n-butyllithium (2.5 M in hexane, 10.0 mL, 25.0 mmol), followed by methyl 3-oxocyclobutane-1-carboxylate (2.56 g, 20.0 mmol). Purification by column chromatography (1-10% diethyl ether / hexane) afforded the desired compounds as viscous colourless oils, and as an inseparable mixture of diastereomers (2.33 g, 11.0 mmol, 13:1 d.r., 55%).

Rf 0.6 (100% diethyl ether); IR (thin film) νmax/cm⁻¹ 3676 (s, br, OH), 3459 (s, br, OH), 2953, 1733, 1671 (m, C=C), 1437, 1407, 1361, 1249, 1224, 1204, 1169, 1078, 918; ¹H NMR (400 MHz, C₆D₆) δH 4.88 (t, J = 3.8 Hz, 1H, 151a, H₂), 4.83 (t, J = 3.8 Hz, 1H, 151b, H₂), 3.71 (t, J = 5.2 Hz, 2H, 151a/b, H₃), 3.54 (bs, 1H, 151a/b, OH₁₂), 3.35 (s, 3H, 151a/b, H₁₁), 2.90-2.75 (m, 1H, 151a/b, H₉), 2.69-2.64 (m, 2H, 151a, H₇,8), 2.68-2.53 (m, 2H, 151b, H₇,8), 2.58-2.53 (m, 2H, 151a, H₇,8), 2.33-2.27 (m, 2H, 151b, H₇,8), 1.81-1.77 (m, 2H, 151a/b, H₃), 1.47-1.41 (m, 2H, 151a/b, H₄); ¹³C NMR (100 MHz, C₆D₆) δC 176.0 (1C, 151a, C₁₀), 175.5 (1C, 151b, C₁₀), 156.4 (1C, 151b, C₁), 156.0 (1C, 151a, C₁), 94.6 (1C, 151b, C₂), 94.4 (1C, 151a, C₂), 73.5 (1C, 151b, C₆), 71.3 (1C, 151a, C₆), 66.4 (1C, 151a, C₅), 66.3 (1C, 151b, C₅), 51.5 (1C, 151a, C₁₁), 51.3 (1C, 151b, C₁₁), 38.9 (2C, 151a, C₇,8), 37.2 (2C, 151b, C₇,8), 32.0 (1C, 151a, C₉), 30.0 (1C, 151b, C₉), 22.6 (1C, 151a, C₃), 22.5 (1C, 151b, C₃), 20.2 (2C, 151a/b, C₄); m/z HRMS (NSI) found [M + H]⁺ 213.1122 C₁₁H₁₇O₄ requires 213.1121.
According to general procedure A, to a solution of 3,4-dihydro-2H-pyran (2.52 g, 30.0 mmol) in anhydrous tetrahydrofuran (50 mL) was added n-butyllithium (2.5 M in hexane, 10.0 mL, 25.0 mmol), followed by 3-oxetanone (1.44 g, 20.0 mmol). Purification by column chromatography (1-10% diethyl ether / hexane), and recrystallisation from hexane, afforded the desired compound as a white crystal (1.41 g, 9.01 mmol, 45%).

Rf 0.40 (100% diethyl ether); IR (thin film) νmax/cm⁻¹ 3347 (s, br, OH), 2945, 2876, 1674 (m, C=C), 1449, 1293, 1221, 1181, 1074, 971; ¹H NMR (400 MHz, C₆D₆) δH 4.91 (t, J = 3.9 Hz, 1H, H₂), 4.89 (d, J = 6.2 Hz, 2H, H₇,8), 4.63 (d, J = 6.5 Hz, 2H, H₇,8), 3.71 (bs, 1H, OH₉), 3.68 (t, J = 5.2 Hz, 2H, H₅), 1.74 (td, J = 6.5, 3.9 Hz, 2H, H₃), 1.39 (dt, J = 10.6, 6.2 Hz, 2H, H₄); ¹³C NMR (100 MHz, C₆D₆) δc 153.4 (C₁), 95.6 (C₂), 81.9 (C₆), 74.7 (2C, C₇,8), 66.4 (C₃), 22.3 (C₃), 20.0 (C₄); mp 28-29 °C; m/z HRMS (NSI) found [M + H]⁺ 157.0856 C₈H₁₃O₃ requires 157.0859.
tert-butyl 3-(3,4-dihydro-2H-pyran-6-yl)-3-hydroxyazetidine-1-carboxylate (153)

According to general procedure A, to a solution of 3,4-dihydro-2H-pyran (2.52 g, 30.0 mmol) in anhydrous tetrahydrofuran (50 mL) was added n-butyllithium (2.5 M in hexane, 10.0 mL, 25.0 mmol), followed by 1-boc-3-azetidinone (3.42 g, 20.0 mmol). Purification by column chromatography (1-10% diethyl ether / hexane), and recrystallisation from hexane, afforded the desired compound as a white crystal (2.40 g, 9.4 mmol, 47%).

Rf 0.50 (100% diethyl ether); IR (thin film) νmax/cm⁻¹ 3375 (s, br, OH), 2976, 2879, 1671 (m, C=C), 1419, 1366, 1220, 1157, 1117, 1063, 918; ¹H NMR (400 MHz, C₆D₆) δ H 4.80 (t, J = 3.8 Hz, 1H, H₂), 4.33 (d, J = 8.1 Hz, 2H, H₇,8), 3.96 (d, J = 8.9 Hz, 2H, H₇,8), 3.58 (t, J = 5.1 Hz, 2H, H₃), 2.67 (bs, 1H, H₀), 1.67 (td, J = 6.5, 3.8 Hz, 2H, H₃), 1.43 (s, 9H, H₁₂), 1.34-1.27 (m, 2H, H₃); ¹³C NMR (100 MHz, C₆D₆) δ C 156.6 (C₁), 153.8 (C₁₀), 95.6 (C₂), 79.2 (C₁₁), 70.0 (C₆), 66.3 (C₅), 61.5 (2C, C₇,8), 28.5 (3C, C₁₂), 22.4 (C₃), 20.0 (C₄); mp 90-91 °C; m/z HRMS (NSI) found [M + Na]^+ 278.1360 C₁₃H₂₁NO₄Na requires 278.1363.
According to general procedure A, to a solution of 3,4-dihydro-2H-pyran (2.52 g, 30.0 mmol) in anhydrous tetrahydrofuran (50 mL) was added n-butyllithium (2.5 M in hexane, 10.0 mL, 25.0 mmol), followed by cyclopentanone (1.68 g, 20.0 mmol). Purification by column chromatography (1-10% diethyl ether / hexane) afforded the desired compound as a colourless oil (2.09 g, 12.42 mmol, 62%).

R<sub>f</sub> 0.35 (20% diethyl ether / hexane); IR (thin film) ν<sub>max</sub>/cm<sup>-1</sup> 3410 (s, br, OH), 2946, 2871, 1671 (m, C=C), 1449, 1436, 1283, 1215, 1064, 918; <sup>1</sup>H NMR (400 MHz, C<sub>6</sub>D<sub>6</sub>) δ<sub>H</sub> 4.85 (t, J = 4.0 Hz, 1H, H<sub>2</sub>), 3.69 (t, J = 5.2 Hz, 2H, H<sub>3</sub>), 2.04-1.96 (m, 2H, H<sub>5</sub>), 1.92-1.87 (m, 2H, H<sub>4</sub>), 1.81 (dt, J = 6.4, 3.8 Hz, 2H, H<sub>7,8</sub>), 1.74-1.68 (m, 2H, H<sub>7,8</sub>), 1.64-1.61 (m, 2H, H<sub>9,10</sub>), 1.50 (bs, 1H, OH<sub>11</sub>), 1.46-1.40 (dt, J = 10.5, 6.4 Hz, 2H, H<sub>9,10</sub>); <sup>13</sup>C NMR (100 MHz, C<sub>6</sub>D<sub>6</sub>) δ<sub>c</sub> 158.0 (C<sub>1</sub>), 93.3 (C<sub>2</sub>), 82.0 (C<sub>6</sub>), 66.3 (C<sub>5</sub>), 38.9 (2C, C<sub>7,8</sub>), 24.5 (2C, C<sub>9,10</sub>), 22.8 (C<sub>3</sub>), 20.3<sub>s</sub> (C<sub>4</sub>); m/z HRMS (NSI) found [M + H]<sup>+</sup> 169.1222 C<sub>10</sub>H<sub>17</sub>O<sub>2</sub> requires 169.1223.
According to general procedure A, to a solution of 3,4-dihydro-2H-pyran (2.52 g, 30.0 mmol) in anhydrous tetrahydrofuran (50 mL) was added n-butyllithium (2.5 M in hexane, 10.0 mL, 25.0 mmol), followed by 2-indanone (2.64 g, 20.0 mmol). Purification by column chromatography (1-10% diethyl ether / hexane), and recrystallisation from hexane, afforded the desired compound as a white crystal (1.51 g, 7.0 mmol, 35%).

R_f 0.40 (20% diethyl ether / hexane); IR (thin film) ν_max/cm⁻¹ 3335 (s, br, OH), 2920, 2866, 2844, 1671 (m, C=C), 1584, 1483, 1384, 1292, 1226, 1168, 1088, 1065, 918; ¹H NMR (400 MHz, C₆D₆) δ_H 7.08 (s, 4H, H₁₀,₁₁), 4.95 (t, J = 3.8 Hz, 1H, H₂), 3.67 (t, J = 5.2 Hz, 2H, H₃), 3.46 (d, J = 16.3 Hz, 2H, H₇,₈), 2.90 (d, J = 16.3 Hz, 2H, H₇,₈), 1.89 (bs, 1H, OH₁₂), 1.78 (td, J = 6.5, 3.8 Hz, 2H, H₃), 1.44-1.38 (m, 2H, H₄); ¹³C NMR (100 MHz, C₆D₆) δ_C 156.6 (C₁), 141.8 (2C, C₉), 126.7 (2C, C₁₀), 125.1 (2C, C₁₁), 94.5 (C₂), 81.9 (C₆), 66.3 (C₃), 46.2 (2C, C₇,₈), 22.6 (C₃), 20.2 (C₄); mp 69-70 °C; m/z HRMS (NSI) found [M + Na]^+ 239.1041 C₁₄H₁₆O₂Na requires 239.1043.
1-(3,4-dihydro-2H-pyran-6-yl)cyclohexan-1-ol (161)

According to general procedure A, to a solution of 3,4-dihydro-2H-pyran (2.52 g, 30.0 mmol) in anhydrous tetrahydrofuran (50 mL) was added n-butyllithium (2.5 M in hexane, 10.0 mL, 25.0 mmol), followed by cyclohexanone (1.96 g, 20.0 mmol). Purification by column chromatography (1-10% diethyl ether / hexane) afforded the desired compound as a colourless oil (1.46 g, 8.01 mmol, 40%).

Rf 0.40 (20% diethyl ether / hexane); IR (thin film) νmax/cm⁻¹ 3450 (s, br, OH), 2932, 2856, 1671 (m, C=C), 1432, 1332, 1213, 1032, 907; ¹H NMR (400 MHz, CDCl₃) δH 4.79 (t, J = 3.8 Hz, 1H, H₂), 3.99 (t, J = 5.1 Hz, 2H, H₃), 2.06-2.02 (m, 2H, H₃), 1.89 (bs, 1H, OH₁₂), 1.82-1.76 (m, 2H, H₄), 1.70-1.55 (m, 8H, H₇-₁₀), 1.51-1.48 (m, 1H, H₁₁), 1.28-1.19 (m, 1H, H₁₁); ¹³C NMR (100 MHz, C₆D₆) δc 158.3 (C₁), 93.7 (C₂), 72.0 (C₆), 66.3 (C₅), 35.1 (2C, C₇,₈), 25.71 (2C, C₉,₁₀), 22.38 (C₃), 21.87 (C₁₁), 19.94 (C₄); Data in accordance with literature.²⁰⁹
According to general procedure A, to a solution of 3,4-dihydro-2H-pyran (2.52 g, 30.0 mmol) in anhydrous tetrahydrofuran (50 mL) was added n-butyllithium (2.5 M in hexane, 10.0 mL, 25.0 mmol), followed by cycloheptanone (2.24 g, 20.0 mmol). Purification by column chromatography (1-10% diethyl ether / hexane) afforded the desired compound as a white solid (1.26 g, 6.41 mmol, 32%).

Rf 0.40 (20% diethyl ether / hexane); IR (thin film) νmax/cm⁻¹ 3352 (s, br, OH), 2920, 2845, 1670 (m, C=C), 1443, 1139, 1070, 919; ¹H NMR (400 MHz, CD₂Cl₂) δ(H) 4.77 (t, J = 3.8 Hz, 1H, H₂), 3.97 (t, J = 5.2 Hz, 2H, H₃), 2.02 (dt, J = 6.4, 3.9 Hz, 2H, H₄), 1.98 (bs, 1H, OH₁₃), 1.86 (ddd, J = 14.0, 10.1, 1.3 Hz, 2H, H₅), 1.80-1.74 (m, 2H, H₇,₈), 1.68-1.62 (m, 4H, H₇,₁₀), 1.60-1.55 (m, 2H, H₉,₁₀), 1.52-1.41 (m, 4H, H₁₁,₁₂); ¹³C NMR (100 MHz, CDCl₃) δ(159.1 (C₁), 93.1 (C₂), 75.9 (C₆), 66.3 (C₅), 39.1 (2C, C₇,₈), 29.6 (2C, C₁₁,₁₂), 22.4 (2C, C₉,₁₀), 22.4 (C₃), 20.0 (C₄). Data in accordance with literature.
((1-(3,4-dihydro-2H-pyran-6-yl)cyclohexyl)oxy)trimethylsilane (163)

To a solution of 1-(3,4-dihydro-2H-pyran-6-yl)cyclohexan-1-ol (130, 0.18 g, 1.0 mmol) in anhydrous dichloromethane (2 mL) at 25 °C was added 2,6-lutidine (0.6 mL, 5.0 mmol) and trimethylsilyl triflate (0.42 mL, 2.0 mmol). The mixture was stirred for 6 h before quenching with water, extracting with dichloromethane 3x, washing once with brine, drying (MgSO₄), and concentrating in vacuo. Purification by column chromatography (0-1% diethyl ether / hexane) afforded the desired compound as a colourless oil (0.23 g, 0.91 mmol, 91%).

Rf 0.50 (hexane); IR (thin film) νmax/cm⁻¹ 2811, 1653 (m, C=C), 1433, 1124, 1074, 910; ¹H NMR (400 MHz, CDCl₃) δH 4.74 (t, J = 3.8 Hz, 1H, H₂), 3.98 (t, J = 5.2 Hz, 2H, H₅), 2.04 (dt, J = 6.4, 3.9 Hz, 2H, H₃), 1.80-1.70 (m, 4H, H₄, H₇-₈), 1.62-1.49 (m, 5H, H₉-₁₁), 1.45-1.41 (m, 2H, H₉-₁₀), 1.27-1.18 (m, 1H, H₁₁), 0.10 (s, 9H, H₁₂); ¹³C NMR (100 MHz, CDCl₃) δC 157.7 (C₁), 95.0 (C₂), 75.1 (C₆), 66.0 (C₅), 36.4 (2C, C₇-₈), 26.2 (C₁₁), 22.4 (2C, C₉-₁₀), 22.3 (C₃), 20.4 (C₄), 2.4 (3C, C₁₂); m/z HRMS (NSI) found [M + H]⁺ 255.1779 C₁₄H₂₇O₂Si requires 255.1780.
2-(3,4-dihydro-2H-pyran-6-yl)propan-2-ol (164)

According to general procedure A, to a solution of 3,4-dihydro-2H-pyran (2.52 g, 30.0 mmol) in anhydrous tetrahydrofuran (50 mL) was added n-butyllithium (2.5 M in hexane, 10.0 mL, 25.0 mmol), followed by acetone (2.84 g, 20.0 mmol). Purification by column chromatography (1-10% diethyl ether / hexane) afforded the desired compound as a colourless oil (1.71 g, 12.0 mmol, 60%).

Rf 0.3 (20% diethyl ether / hexane); IR (thin film) νmax/cm⁻¹ 3331 (s, br, OH), 2911, 2830, 1651 (m, C=C), 1431, 1145, 1068, 901; ¹H NMR (400 MHz, CD₂Cl₂) δH 4.77 (t, J = 3.8 Hz, 1H, H₄), 3.99 (t, J = 5.1 Hz, 2H, H₃), 2.11 (bs, 1H, OH₈), 2.02 (dt, J = 6.4, 3.8 Hz, 2H, H₅), 1.80-1.74 (m, 2H, H₆), 1.28 (s, 6H, H₇); ¹³C NMR (100 MHz, CDCl₃) δc 159.0 (C₁), 93.0 (C₂), 71.2 (C₃), 66.8 (C₄), 28.0 (2C, C₇), 22.8 (C₅), 20.3 (C₆). m/z HRMS (NSI) found [M + H]⁺ 143.1071 C₈H₁₅O₂ requires 143.1072.
1-(1H-inden-3-yl)cyclobutan-1-ol (168)

According to general procedure B, to a solution of indene (3.485 g, 30.0 mmol) in anhydrous diethyl ether (50 mL) was added n-butyllithium (2.5 M in hexane, 12.0 mL, 30.0 mmol), followed by cyclobutanone (2.10 g, 30.0 mmol). Purification by column chromatography (1-10% diethyl ether / hexane), and recrystallisation from hexane, afforded the desired compound as a white crystal (4.02 g, 21.6 mmol, 72%).

Rf 0.35 (20% diethyl ether / hexane); IR (thin film) νmax/cm⁻¹ 3282 (s, br, OH), 2973, 2941, 1606 (w, C=C), 1458, 1396, 1247, 1212, 1144, 1122, 966; ¹H NMR (400 MHz, C₆D₆) δH 7.73 (d, J = 7.5 Hz, 1H, H₇), 7.30 (d, J = 7.4 Hz, 1H, H₄), 7.23 (tt, J = 7.5, 0.5 Hz, 1H, H₆), 7.16-7.12 (m, 1H, H₅), 6.01 (t, J = 2.1 Hz, 1H, H₂), 3.03 (d, J = 2.1 Hz, 2H, H₃), 2.44-2.38 (m, 2H, H₁₁,₁₂), 2.27-2.20 (m, 2H, H₁₁,₁₂), 1.74-1.70 (m, 1H, H₁₃), 1.68 (bs, 1H, OH₁₄), 1.51-1.44 (m, 1H, H₁₃); ¹³C NMR (100 MHz, C₆D₆) δC 148.2 (C₈), 145.3 (C₉), 143.3 (C₁), 127.4 (C₅), 126.3 (C₆), 125.1 (C₂), 124.1 (C₄), 122.4 (C₇), 73.9 (C₁₀), 37.6 (C₃), 35.9 (2C, C₁₁,₁₂), 13.6 (C₁₃); mp 97-98 °C; m/z HRMS (NSI) found [M + Na]⁺ 209.0938 C₁₃H₁₄ONa requires 209.0937.
1-(1H-inden-3-yl)cyclopentan-1-ol (169)

According to general procedure B, to a solution of indene (3.48 g, 30.0 mmol) in anhydrous diethyl ether (50 mL) was added n-butyllithium (2.5 M in hexane, 12.0 mL, 30.0 mmol), followed by cyclopentanone (2.52 g, 30.0 mmol). Purification by column chromatography (1-10% diethyl ether / hexane) in both silica gel and basic aluminium oxide, sequentially, followed by recrystallisation from hexane, afforded the desired compound as a white crystal (3.91 g, 19.5 mmol, 65%).

**Rf** 0.40 (20% diethyl ether / hexane); **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3317 (s, br, OH), 2961, 2961, 2873, 1606 (w, C=C), 1572, 1457, 1388, 1250, 1194, 995; **$^1$H NMR** (400 MHz, C$_6$D$_6$) $\delta_H$ 7.72 (d, $J = 7.6$ Hz, 1H, H$_7$), 7.30 (d, $J = 7.4$ Hz, 1H, H$_4$), 7.24 (t, $J = 7.4$ Hz, 1H, H$_6$), 7.15-7.12 (m, 1H, H$_3$), 6.07 (t, $J = 2.1$ Hz, 1H, H$_2$), 3.03 (d, $J = 2.1$ Hz, 2H, H$_3$), 2.04-1.84 (m, 6H, H$_{11-14}$), 1.66-1.55 (m, 2H, H$_{13,14}$), 1.35 (bs, 1H, OH$_{15}$); **$^{13}$C NMR** (100 MHz, C$_6$D$_6$) $\delta_c$ 150.4 (C$_8$), 145.5 (C$_9$), 144.0 (C$_1$), 126.8 (C$_3$), 126.3 (C$_6$), 124.9 (C$_2$), 124.1 (C$_4$), 122.5 (C$_7$), 81.1 (C$_{10}$), 40.0 (2C, C$_{11,12}$), 37.5 (C$_3$), 24.3 (2C, C$_{13,14}$); **mp** 60-61 °C; **m/z** HRMS (NSI) found [M + Na]$^+$ 223.1093 C$_{14}$H$_{16}$ONa requires 223.1093.
1-(5,6-dimethoxy-1H-inden-3-yl)cyclopentan-1-ol (170)

According to general procedure B, to a solution of 5,6-dimethoxy-indene (5.29 g, 30.0 mmol) in anhydrous diethyl ether (50 mL) was added n-butyllithium (2.5 M in hexane, 12.0 mL, 30.0 mmol), followed by cyclopentanone (2.52 g, 30.0 mmol). Purification by column chromatography (10-40% diethyl ether / hexane) afforded the desired compound as a yellow solid (0.39 g, 1.5 mmol, 5%).

Rf 0.55 (100% diethyl ether); IR (thin film) νmax/cm⁻¹ 3509 (s, br, OH), 2945, 2869, 2832, 1704, 1607 (w, C=C), 1572, 1490, 1465, 1413, 1316, 1274, 1208, 1185, 1110, 1064, 1029, 978; ¹H NMR (400 MHz, CD₂Cl₂) δH 7.20 (s, 1H, H₇), 7.05 (s, 1H, H₄), 6.27 (t, J = 2.0 Hz, 1H, H₂), 3.85 (s, 3H, H₁₆), 3.84 (s, 3H, H₁₇), 3.28 (d, J = 1.7 Hz, 2H, H₃), 2.14-2.07 (m, 2H, H₁₁,₁₂), 2.00-1.94 (m, 4H, H₁₁₋₁₄), 1.80-1.76 (m, 2H, H₁₃₋₁₄), 1.64 (bs, 1H, H₁₅); ¹³C NMR (100 MHz, CD₂Cl₂) δC 149.8 (C₅), 148.4 (C₆), 147.8 (C₈), 138.2 (C₉), 136.7 (C₁), 126.0 (C₂), 108.7 (C₄), 106.6 (C₇), 81.5 (C₁₀), 56.6 (C₁₆), 56.5 (C₁₇), 39.9 (2C, C₁₁,₁₂), 37.7 (C₃), 24.2 (C₁₃₋₁₄); mp 55-56 °C; m/z HRMS (NSI) found [M + H]+ 261.1487 C₁₆H₂₁O₃ requires 261.1485.
1-(6-methoxy-3,4-dihydonaphthalen-1-yl)cyclopentan-1-ol (171)

According to the general procedure D, a solution of 4-bromo-7-methoxy-1,2-dihydonaphthalene (3.5 g, 14.8 mmol) in anhydrous tetrahydrofuran (36 mL) was added tert-butyllithium (1.7 M in pentane, 17.7 mL, 30.0 mmol), followed by cyclopentanone (1.26 g, 15.0 mmol). Purification by column chromatography (1-10% diethyl ether / hexane), and recrystallisation from hexane, afforded the desired compound as a white crystal (3.26 g, 13.2 mmol, 88%).

Rf 0.4 (20% diethyl ether / hexane); IR (thin film) νmax/cm⁻¹ 3404 (s, br, OH), 2939, 2872, 2832, 1607 (m, C=C), 1567, 1493, 1428, 1301, 1247, 1220, 1141, 1103, 1040, 995; ¹H NMR (400 MHz, CD₂Cl₂) δH 8.14 (d, J = 8.5 Hz, 1H, H₉), 6.78 (d, J = 2.6 Hz, 1H, H₆), 6.73 (dd, J = 8.5, 2.6 Hz, 1H, H₈), 5.86 (t, J = 4.8 Hz, 1H, H₂), 3.38 (s, 3H, H₁₁), 2.52 (t, J = 7.8 Hz, 2H, H₄), 2.05-2.00 (m, 2H, H₃), 1.96-1.83 (m, 6H, H₁₃-₁₆), 1.62-1.54 (m, 2H, H₁₅,₁₆), 1.05 (bs, 1H, H₁₇); ¹³C NMR (100 MHz, CD₂Cl₂) δC 158.8 (C₇), 142.0 (C₁), 139.6 (C₅), 128.8 (C₁₀), 127.7 (C₉), 121.8 (C₂), 114.1 (C₆), 111.0 (C₈), 83.6 (C₁₂), 54.7 (C₁₁), 39.7 (2C, C₁₃,₁₄), 29.6 (C₄), 23.9 (2C, C₁₅,₁₆), 23.5 (C₃); mp 62-63 °C; m/z HRMS (NSI) found [M + Na]⁺ 267.1355 C₁₆H₂₀O₂Na requires 267.1356.
According to general procedure B, to a solution of N-methylindole (3.94 g, 30.0 mmol) in anhydrous diethyl ether (50 mL) was added n-butyllithium (2.5 M in hexane, 12.0 mL, 30.0 mmol), followed by cyclobutanone (2.10 g, 30.0 mmol). Purification by column chromatography (1-10% diethyl ether / hexane) afforded the desired compound as a white solid (5.01 g, 24.9 mmol, 83%).

Rf 0.30 (20% diethyl ether / hexane); IR (thin film) νmax/cm⁻¹ 3430 (s, br, OH), 1628 (w, C=C), 1456, 1100; ¹H NMR (400 MHz, CD₂Cl₂) δH 7.56 (d, J = 7.4 Hz, 1H, H₅), 7.31 (d, J = 8.5 Hz, 1H, H₆), 7.19 (t, J = 7.5 Hz, 1H, H₄), 7.06 (t, J = 7.4 Hz, 1H, H₃), 6.49 (s, 1H, H₁), 3.78 (s, 3H, H₁₄), 2.71-2.65 (m, 2H, H₁₀,₁₁), 2.47-2.40 (m, 2H, H₁₀,₁₁), 2.16 (bs, 1H, OH₁₃), 1.99-1.92 (m, 1H, H₁₂), 1.77-1.65 (m, 1H, H₁₂); ¹³C NMR (100 MHz, CD₂Cl₂) δc 143.1 (C₂), 139.2 (C₈), 127.3 (C₇), 122.0 (C₄), 120.9 (C₆), 119.7 (C₅), 109.4 (C₃), 99.0 (C₁), 73.1 (C₉), 36.6 (2C, C₁₀,₁₁), 31.3 (C₁₄), 13.7 (C₁₂); mp 112-113 °C. Data in accordance with literature.¹¹¹
According to general procedure B, to a solution of benzofuran (0.35 g, 3.0 mmol) in anhydrous diethyl ether (50 mL) was added n-butyllithium (2.5 M in hexane, 1.2 mL, 3.0 mmol), followed by cyclobutanone (0.21 g, 3.0 mmol). Purification by column chromatography (1-10% diethyl ether / hexane) afforded the desired compound as a yellow solid (0.40 g, 2.13 mmol, 71%).

Rf 0.30 (20% diethyl ether / hexane); IR (thin film) νmax/cm⁻¹ 3429 (s, br, OH), 1614 (w, C=C), 1448, 1126; H NMR (400 MHz, CD₂Cl₂) δH 7.57 (d, J = 7.6 Hz, 1H, H₃), 7.47 (d, J = 7.9 Hz, 1H, H₆), 7.27 (t, J = 7.9 Hz, 1H, H₅), 7.22 (t, J = 7.6 Hz, 1H, H₄), 6.69 (s, 1H, H₁), 2.65-2.58 (m, 2H, H₁₀₁₁), 2.47 (s, 1H, OH₁₃), 2.42-2.34 (m, 2H, H₁₀₁₁), 2.00-1.90 (m, 1H, H₁₂), 1.85-1.73 (m, 1H, H₁₂); C NMR (100 MHz, CD₂Cl₂) δC 161.5 (C₂), 155.5 (C₈), 128.7 (C₇), 124.5 (C₄), 123.1 (C₅), 121.4 (C₆), 111.4 (C₃), 101.7 (C₁), 73.0 (C₉), 36.0 (2C, C₁₀₁₁), 13.2 (C₁₂); mp 47-48 ºC. Data in accordance with literature.²¹⁰
According to general procedure B, to a solution of benzothiophene (0.40 g, 3.0 mmol) in anhydrous diethyl ether (50 mL) was added n-butyllithium (2.5 M in hexane, 1.2 mL, 3.0 mmol), followed by cyclobutanone (0.21 g, 3.0 mmol). Purification by column chromatography (1-10% diethyl ether / hexane) afforded the desired compound as a white solid (0.43 g, 2.11 mmol, 70%).

\( R_f 0.30 \) (20% diethyl ether / hexane); \( \text{IR (thin film)} \upsilon_{\text{max}}/\text{cm}^{-1} \) 3244 (s, br, OH), 2960, 1448, 1126; \( \text{\textsuperscript{1}H NMR} \) (400 MHz, CD\textsubscript{2}Cl\textsubscript{2}) \( \delta_H \) 7.82 (d, \( J = 7.7 \text{ Hz} \), 1H, H\textsubscript{3}), 7.74 (d, \( J = 7.4 \text{ Hz} \), 1H, H\textsubscript{6}), 7.35 (dt, \( J = 7.4, 1.1 \text{ Hz} \), 1H, H\textsubscript{5}), 7.30 (dt, \( J = 7.7, 1.3 \text{ Hz} \), 1H, H\textsubscript{4}), 7.28 (s, 1H, H\textsubscript{1}), 2.64-2.57 (m, 2H, H\textsubscript{10,11}), 2.49-2.41 (m, 3H, H\textsubscript{10,11} and OH\textsubscript{13}), 2.03-1.94 (m, 1H, H\textsubscript{12}), 1.88-1.79 (m, 1H, H\textsubscript{12}); \( \text{\textsuperscript{13}C NMR} \) (100 MHz, CD\textsubscript{2}Cl\textsubscript{2}) \( \delta_c \) 152.8 (C\textsubscript{2}), 140.2 (C\textsubscript{8}), 140.0 (C\textsubscript{7}), 124.7 (C\textsubscript{4}), 124.5 (C\textsubscript{5}), 123.8 (C\textsubscript{6}), 122.7 (C\textsubscript{3}), 119.3 (C\textsubscript{1}), 75.5 (C\textsubscript{9}), 38.7 (2C, C\textsubscript{10,11}), 13.2 (C\textsubscript{12}).

\( \text{mp} \) 53-54 °C. Data in accordance with literature.\textsuperscript{210}
According to general procedure A, to a solution of (E/Z)-1-butenyl ethyl ether (5.00 g, 50.0 mmol, mixture of cis/trans) in anhydrous tetrahydrofuran (83 mL) was added n-butyllithium (2.5 M in hexane, 20.5 mL, 50.0 mmol), followed by cyclobutanone (3.51 g, 50.0 mmol). Purification by column chromatography (1-10% diethyl ether / hexane) afforded the desired compound as a colourless oil (2.55 g, 15.0 mmol, 30%).

Rf 0.45 (20% diethyl ether / hexane); IR (thin film) νmax/cm⁻¹ 3381 (s, br, OH), 2972, 2902, 1651 (w, C=C), 1453, 1406, 1394, 1250, 1197, 1146, 1066, 899; ¹H NMR (400 MHz, CD₂Cl₂) δH 4.32 (t, J = 7.6 Hz, 1H, H₂), 3.62 (q, J = 6.8 Hz, 2H, H₅), 2.57-2.50 (m, 2H, H₃), 2.15-2.05 (m, 5H, OH₁₁, H₈,₉), 2.03-1.92 (m, 1H, H₁₀), 1.69-1.59 (m, 1H, H₁₀), 1.27 (t, J = 7.0 Hz, 3H, H₆), 0.97 (t, J = 8.0 Hz, 3H, H₄); ¹³C NMR (100 MHz, CD₂Cl₂) δC 157.5 (C₁), 101.2 (C₂), 77.5 (C₇), 62.3 (C₃), 35.3 (2C, C₈,₉), 19.2 (C₅), 15.6 (C₆), 14.5 (C₄), 14.4 (C₁₀); m/z HRMS (TOF-MS) found [M]+ 170.1306 C₁₀H₁₈O₂ requires 170.1307.
NOESY spectra of 180:

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{O} \\
\text{OH} & \\
\end{align*}
\]

NOE: 5.4%
1-(1-iso-butoxyvinyl)cyclobutan-1-ol (181)

According to general procedure A, to a solution of 2-methyl-1-(vinyloxy)propane (5.00 g, 50.0 mmol) in anhydrous tetrahydrofuran (83 mL) was added n-butyllithium (2.5 M in hexane, 20.5 mL, 50.0 mmol), followed by cyclobutanone (3.51 g, 50.0 mmol). Purification by column chromatography (1-10% diethyl ether / hexane) afforded the desired compound as a colourless oil (3.83 g, 22.5 mmol, 45%).

Rf 0.40 (20% diethyl ether / hexane); IR (thin film) νmax/cm⁻¹ 3374 (s, br, OH), 2910, 1651 (w, C=C), 1401, 911; ¹H NMR (400 MHz, CDCl₃) δH 4.14 (d, J = 2.5 Hz, 1H, H₁), 3.88 (d, J = 2.5 Hz, 1H, H₂), 3.38 (d, J = 6.5 Hz, 2H, H₃), 2.41 (s, 1H, OH₁₀), 2.29-2.23 (m, 2H, H₇,₈), 2.07-1.99 (m, 2H, H₇,₈), 1.95-1.89 (m, 1H, H₀), 1.79-1.70 (m, 1H, H₀), 1.60-1.49 (m, 1H, H₄), 0.87 (d, J = 6.7 Hz, 6H, H₅); ¹³C NMR (100 MHz, CDCl₃) δC 164.9 (C₁), 79.2 (C₂), 75.9 (C₆), 74.1 (C₃), 34.6 (2C, C₇,₈), 28.1 (C₄), 19.5 (2C, C₅), 13.1 (C₀); m/z HRMS (NSI) found [M + H]⁺ 171.1380 C₁₀H₁₉O₂ requires 171.1385.
5.6 Enantioselective arylation-SPR products:

2-benzyl-2-methylcyclopentan-1-one (70)

According to general procedure F, to a mixture of 68 (28.0 mg, 0.25 mmol) in anhydrous dichloromethane (8 mL) at 25 °C was added Na₂CO₃ (53 mg, 0.50 mmol), copper(II) (+)-2,2'-isopropylidenebis[(4R)-4-phenyl-2-oxazoline] triflate solution (0.1 M in dichloromethane, 0.25 mL, 0.025 mmol), and diphenyliodonium hexafluorophosphate (213 mg, 0.50 mmol), with stirring for 24 h at 30 °C. Purification by column chromatography (0-4% diethyl ether / hexane) afforded the desired compound as a yellow oil (19.3 mg, 0.103 mmol, 41%). Racemic 70 were prepared according to general procedure E: 68 (56.0 mg, 0.50 mmol), 2,6-di-tert-butylpyridine (0.225 mL, 1.0 mmol), diphenyliodonium triflate (430.2 mg, 1.0 mmol) and CuCl (5.0 mg, 0.050 mmol) were reacted in anhydrous dichloromethane (4 mL) to obtain the desired compound as a yellow oil, and as racemic mixtures (72.1 mg, 0.383 mmol, 77%).

Rᵣ 0.6 (20% diethyl ether / hexane); IR (thin film) νmax/cm⁻¹ 2972, 1733 (s, C=O), 1453, 1394, 1251, 1058, 892, 703; ¹H NMR (400 MHz, CDCl₃) δH 7.31-7.21 (m, 3H, H₅,₆), 7.14 (d, J = 7.2 Hz, 2H, H₈), 2.89 (d, J = 13.2 Hz, 1H, H₂), 2.62 (d, J = 13.2 Hz, 1H, H₂), 2.32 (ddd, J = 19.0, 8.0, 5.0 Hz, 1H, H₉), 2.12-1.95 (m, 2H, H₀,₁), 1.87-1.71 (m, 2H, H₈), 1.69-1.61 (m, 1H, H₇), 1.05 (3H, s, H₁₁); ¹³C NMR (100 MHz, CDCl₃) δC 223.3 (C₁₀), 138.0 (C₃), 130.2 (2C, C₅), 128.1 (2C, C₄), 126.4 (C₆), 49.7 (C₁), 42.6 (C₂), 38.0 (C₀), 34.6 (C₇), 22.7 (C₁₁), 18.6 (C₈); m/z HRMS (NSI) found [M+H]+ 189.1272 C₁₃H₁₇O requires 189.1274. [α]D⁰ +48.7 (c = 0.67, CHCl₃); e.e. 52% from Chiral HPLC. Chiralpak IA. Hexane / isopropanol 99:1; 1.0 mL/min. tᵣ 7.0 minutes (major), 8.3 minutes (minor). Data in accordance with literature.⁶₈
2-benzyl-2-phenylcyclopentan-1-one (131)

According to general procedure F, to a mixture of 130 (43.6 mg, 0.25 mmol) in anhydrous dichloromethane (8 mL) at 25 °C was added Na₃PO₄ (82 mg, 0.50 mmol), copper(II) (+)-2,2′-Isopropylidenebis[(4R)-4-phenyl-2-oxazoline] triflate solution (0.1 M in dichloromethane, 0.25 mL, 0.025 mmol), and diphenyliodonium hexafluorophosphate (213 mg, 0.50 mmol), with stirring for 24 h at 30 °C. Purification by column chromatography (0-4% diethyl ether / hexane) afforded the desired compound as a white solid (19.4 mg, 0.08 mmol, 31%). Racemic 131 were prepared according to general procedure E: 130 (87.1 mg, 0.50 mmol), 2,6-di-tert-butylpyridine (0.225 mL, 1.0 mmol), diphenyliodonium triflate (430.2 mg, 1.0 mmol) and CuCl (5.0 mg, 0.050 mmol) were reacted in anhydrous dichloromethane (4 mL) to obtain the desired compound as a colourless oil, and as racemic mixtures (123.0 mg, 0.491 mmol, 98%).

Rᵣ 0.45 (20% diethyl ether / hexane); IR (thin film) ν_max/cm⁻¹ 2961, 1732 (s, C=O), 1600, 1495, 1454, 1152, 1079, 934, 754, 699; ¹H NMR (400 MHz, CD₂Cl₂) δ_H 7.36-7.30 (m, 4H, H₁₂,₁₃), 7.27-7.23 (m, 1H, H₁₄), 7.17-7.12 (m, 3H, H₅,₆), 6.86-6.83 (m, 2H, H₉), 3.08 (d, J = 13.5 Hz, 1H, H₂), 3.04 (d, J = 13.5 Hz, 1H, H₂), 2.48-2.43 (m, 1H, H₇), 2.32-2.25 (m, 1H, H₉), 2.20-2.13 (m, 1H, H₀), 2.10-2.03 (m, 1H, H₇), 1.86-1.78 (m, 1H, H₈), 1.77-1.69 (m, 1H, H₈); ¹³C NMR (100 MHz, CD₂Cl₂) δ_c 219.0 (C₁₀), 139.8 (C₁₁), 138.1 (C₃), 130.5 (2C, C₄), 128.7 (2C, C₁₃), 128.1 (2C, C₅), 127.5 (2C, C₁₂), 127.2 (C₁₄), 126.6 (C₆), 58.3 (C₁), 45.2 (C₉), 37.9 (C₇), 33.2 (C₂), 18.8 (C₈); mp 44-46 °C; m/z HRMS (NSI) found [M+NH₄]⁺ 268.1697 C₁₈H₂₅ON requires 268.1696. [α]D²⁰ +18.8 (c = 1.00, CHCl₃); e.e. 23% from Chiral HPLC. Chiralpak IA. Hexane / isopropanol 99:1; 1.0 mL/min. tᵣ 8.0 minutes (minor), 9.2 minutes (major).
**2'-phenyl-3',4'-dihydro-2'H-spirocyclopentane-1,1'-naphthalen]-2-one (139)**

According to general procedure F, to a solution of **137** (50.1 mg, 0.25 mmol) in anhydrous dichloromethane (8 mL) at 0 °C was added 2,6-di-tert-butylpyridine (0.112 mL, 0.50 mmol), copper(II) (+)-2,2'-Isopropylidenedibis[(4R)-4-phenyl-2-oxazoline] triflate solution (0.1 M in dichloromethane, 0.125 mL, 0.0125 mmol), and diphenyliodonium hexafluorophosphate (213 mg, 0.50 mmol), with stirring for 24 h at 0 °C. Purification by column chromatography (0-4% diethyl ether / hexane) afforded the desired compound as a white solid (9.7 mg, 0.035 mmol, 14%). Racemic **139** were prepared according to general procedure E: **137** (0.1 g, 0.50 mmol), 2,6-di-tert-butylpyridine (0.225 mL, 1.0 mmol), diphenyliodonium triflate (430.2 mg, 1.0 mmol) and CuCl (5.0 mg, 0.050 mmol) were reacted in anhydrous dichloromethane (4 mL) to obtain the desired compounds as a white powder, and as racemic mixtures of inseparable diastereomers **139** (129.1 mg, 0.467 mmol, 91% yield, 2:1 d.r.).

**Rf**0.5 (20% diethyl ether / hexane); **IR** (thin film) ν<sub>max</sub>/cm<sup>-1</sup> 2972, 1729 (s, C=O), 1601, 1492, 1406, 1250, 1057, 892; **<sup>1</sup>H NMR** (500 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ<sub>H</sub> 7.32-7.19 (m, 5H, H<sub>12-14</sub>), 7.18-7.05 (m, 4H, H<sub>5-8</sub>), 3.02-2.95 (m, 3H, H<sub>2,3</sub>), 2.76-2.65 (m, 1H, H<sub>4</sub>), 2.59-2.47 (m, 2H, H<sub>15</sub>), 2.24-2.14 (m, 1H, H<sub>17</sub>), 1.88-1.76 (m, 3H, H<sub>4,16,17</sub>), 1.22-1.10 (m, 1H, H<sub>16</sub>); **<sup>13</sup>C NMR** (125 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ<sub>C</sub> 221.4 (C<sub>18</sub>), 142.6 (C<sub>0</sub>), 140.9 (C<sub>11</sub>), 137.8 (C<sub>10</sub>), 129.3 (2C, C<sub>13</sub>), 128.9 (2C, C<sub>12</sub>), 128.3 (C<sub>5</sub>), 127.4 (C<sub>14</sub>), 126.9 (C<sub>6</sub>), 126.2 (C<sub>7</sub>), 126.1 (C<sub>8</sub>), 56.0 (C<sub>1</sub>), 51.7 (C<sub>2</sub>), 39.8 (C<sub>17</sub>), 39.3 (C<sub>15</sub>), 30.1 (C<sub>3</sub>), 26.3 (C<sub>4</sub>), 19.3 (C<sub>16</sub>); **mp** 64-66 °C; **m/z** HRMS (NSI) found [M+NH<sub>4</sub>]<sup>+</sup> 294.1855 C<sub>20</sub>H<sub>24</sub>ON requires 294.1852. [α]<sup>20</sup><sub>D</sub> -105.0 (c = 0.40, CHCl<sub>3</sub>). **d.e.** 99%, according to NMR; e.e. 68%, from chiral HPLC. Chiralpak IA. Hexane / isopropanol 99:1; 1.0 mL/min. **t<sub>R</sub>** 8.7 minutes (major), 17.3 minutes (minor), no peaks from 13.6 and 25.2 minutes.
5',7'-dimethyl-2'-phenyl-3',4'-dihydro-2'H-spiro[cyclopentane-1,1'-naphthalen]-2-one (140)

According to general procedure F, to a solution of 138 (76.1 mg, 0.25 mmol) in anhydrous dichloromethane (8 mL) at 0 °C was added 2,6-di-tert-butylypyridine (0.112 mL, 0.50 mmol), copper(II) (+)-2,2'-Isopropylidenebis[(4R)-4-phenyl-2-oxazoline] triflate solution (0.1 M in dichloromethane, 0.125 mL, 0.0125 mmol), and diphenyliodonium hexafluorophosphate (213 mg, 0.50 mmol), with stirring for 24 h at 0 °C. Purification by column chromatography (0-4% diethyl ether / hexane) afforded the desired compound as white solid (9.1 mg, 0.030 mmol, 12%). Racemic 140 were prepared according to general procedure E: 138 (114.2 mg, 0.50 mmol), 2,6-di-tert-butylypyridine (0.225 mL, 1.0 mmol), diphenyliodonium triflate (430.2 mg, 1.0 mmol) and CuCl (5.0 mg, 0.050 mmol) were reacted in anhydrous dichloromethane (4 mL) to obtain the desired compound as a white solid, and as racemic mixtures (42.6 mg, 0.140 mmol, 28%).

Rf 0.55 (20% diethyl ether / hexane); IR (thin film) νmax/cm−1 2925, 1724 (s, C=O), 1602, 1579, 1454, 1154, 1129, 853, 755; 1H NMR (500 MHz, CD2Cl2) δH 7.30-7.22 (m, 5H, H12-14), 6.90 (s, 1H, H6), 6.75 (s, 1H, H8), 2.97 (d, J = 9.8 Hz, 1H, H2), 2.87 (d, J = 12.8 Hz, 1H, H4), 2.74-2.65 (m, 2H, H3,4), 2.57-2.47 (m, 2H, H15), 2.38-2.04 (m containing 1bs at 2.26 ppm, 7H, H17,19,20), 1.96-1.89 (m, 1H, H3), 1.86-1.81 (m, 2H, H16,17), 1.19-1.10 (m, 1H, H16); 13C NMR (125 MHz, CD2Cl2) δc 222.2 (C18), 143.3 (C9), 141.1 (C3), 136.7 (C11), 135.3 (C7), 133.6 (C10), 129.2 (2C, C13), 129.1 (2C, C12), 126.7 (C8), 127.2 (C8), 126.1 (C14), 56.5 (C1), 51.6 (C2), 40.3 (C17), 40.1 (C15), 27.3 (C3), 26.5 (C4), 21.1 (C20), 20.0 (C19), 19.7 (C16); mp 126-128 °C; m/z HRMS (NSI) found [M+NH4+] 322.2166 C22H28ON requires 322.2165. [α]D20 −92.2 (c = 0.60, CHCl3). d.e. 99%, according to NMR; e.e. 73%, from chiral HPLC. Chiralpak IC. Hexane / isopropanol 99.3:0.7; 1.0 mL/min. tR 21.5 minutes (major), 23.1 minutes (minor).
According to general procedure F, to a solution of 142 (76.6 mg, 0.25 mmol) in anhydrous dichloromethane (8 mL) at 0 °C was added 2,6-di-tert-butylpyridine (0.112 mL, 0.50 mmol), copper(II) (+)-2,2′-Isopropylidenebis[(4R)-4-phenyl-2-oxazoline] triflate solution (0.1 M in dichloromethane, 0.25 mL, 0.025 mmol), and diphenyliodonium hexafluorophosphate (213 mg, 0.50 mmol), with stirring at 10 °C for 18 h. Purification by column chromatography (0–4% diethyl ether / hexane) afforded the desired compound as white solid 144b (14.1 mg, 0.046 mmol, 18%), and colourless viscous oil 144a (21.1 mg, 0.069 mmol, 28%). Racemic 144a/b were prepared according to general procedure E: 142 (153.2 mg, 0.50 mmol), 2,6-di-tert-butylpyridine (0.225 mL, 1.0 mmol), diphenyliodonium tetrafluoroborate (394.0 mg, 1.0 mmol) and CuCl (5.0 mg, 0.050 mmol) were reacted in anhydrous dichloromethane (4 mL) to obtain the desired compounds as white solids, and racemic mixtures of diastereomers 144b (1.0 mg, 0.003 mmol, 1%) and 144a (8.0 mg, 0.02 mmol, 8%).

144a: Rf 0.4 (20% diethyl ether / hexane); IR (thin film) νmax/cm⁻¹ 2944, 1703 (s, C=O), 1608, 1579, 1493, 1445, 1268, 1161, 1036, 804, 752, 702; ′H NMR (400 MHz, CD₂Cl₂) δH 7.51 (td, J = 7.5, 1.7 Hz, 2H, H₁₂), 7.37 (dt, J = 7.5, 1.7 Hz, 2H, H₁₃), 7.30 (tt, J = 7.5, 1.7 Hz, 1H, H₁₄), 6.69 (d, J = 2.4 Hz, 1H, H₅), 6.35 (dd, J = 8.4, 2.4 Hz, 1H, H₇), 5.85 (d, J = 8.4 Hz, 1H, H₆), 3.97 (dd, J = 8.8, 4.2 Hz, 1H, H₂), 3.70 (s, 3H, H₁₉), 2.94-2.85 (m, 1H, H₄), 2.82-2.75 (m, 1H, H₄), 2.37-2.12 (m, 4H, H₃,15,17), 2.02-1.90 (m, 2H, H₁₅,16), 1.86-1.74 (m, 2H, H₃,1₆); ′C NMR (100 MHz, CD₂Cl₂) δc 218.9 (C₁₈), 159.3 (C₆), 146.8 (C₁₁), 138.6 (C₁₀), 135.8 (C₉), 128.8 (C₂, C₁₃), 128.2 (2C, C₁₂), 127.4 (C₈), 126.1 (C₁₄), 111.7 (C₃), 109.6 (C₇), 61.9 (C₁), 55.5 (C₂), 51.9 (C₁₉), 38.4 (C₁₇), 32.3 (C₁₅), 29.4 (C₃), 28.3 (C₄), 18.8 (C₁₆); m/z HRMS (NSI) found [M+Na]+ 329.1510 C₂₁H₂₂O₂Na requires 329.1512; [α]D₂₀ –22.6 (c = 1.00, CHCl₃). d.e. 20%, according to NMR; e.e. 90%, from chiral HPLC. Chiralpak IA. Hexane / isopropanol 99.5:0.5; 1.0 mL/min. tR 13.8 minutes (minor), 15.7 minutes (major).
**144b:** Rf 0.45 (20% diethyl ether / hexane); **IR** (thin film) νmax/cm⁻¹ 2959, 1730, 1605, 1582, 1489, 1465, 1444, 1404, 1317, 1257, 1242, 1145, 808, 749, 699; **¹H NMR** (400 MHz, CD₂Cl₂) δH 7.52 (td, J = 7.5, 1.6 Hz, 2H, H₁₂), 7.35 (dt, J = 7.5, 1.6 Hz, 2H, H₁³), 7.26 (tt, J = 7.5, 1.6 Hz, 1H, H₁₄), 6.95 (d, J = 8.3 Hz, 1H, H₈), 6.73 (d, J = 2.3 Hz, 1H, H₅), 6.65 (dd, J = 8.3, 2.3 Hz, 1H, H₇), 3.96 (dd, J = 8.7, 4.8 Hz, 1H, H₂), 3.76 (s, 3H, H₁₉), 2.71-2.57 (m, 2H, H₄), 2.55-2.47 (m, 1H, H₁₅), 2.30-2.23 (1H, m, H₁₇), 2.10-2.00 (m, 1H, H₁₇), 1.85-1.68 (m, 4H, H₃,₁₅,₁₆), 1.66-1.58 (m, 1H, H₃); **¹³C NMR** (100 MHz, CD₂Cl₂) δC 219.7 (C₁₈), 159.5 (C₆), 147.8 (C₁₁), 138.9 (C₁₀), 135.0 (C₉), 128.8 (2C, C₁₃), 127.7 (2C, C₁₂), 127.2 (C₈), 126.1 (C₁₄), 112.4 (C₅), 110.0 (C₇), 61.8 (C₁), 55.6 (C₂), 51.8 (C₁₉), 38.6 (C₁₇), 31.7 (C₁₅), 28.9 (C₃), 28.2 (C₄), 19.0 (C₁₆); m/p 90-92 °C; m/z HRMS (NSI) found [M+Na⁺] 329.1514 C₂₁H₂₂O₂Na requires 329.1512; [α]²⁰D +2.6 (c = 1.00, CHCl₃). d.e. –20%, according to NMR; e.e. 82%, from chiral HPLC. Chiralpak IA. Hexane / isopropanol 99.5:0.5; 1.0 mL/min. tR 18.2 minutes (major), 20.6 minutes (minor).
(5R,10R)-10-phenyl-6-oxaspiro[4.5]decan-1-one (145)

According to general procedure F, to a solution of 90 (38.6 mg, 0.25 mmol) in anhydrous dichloromethane (6 mL) at 0 °C was added 2,6-di-tert-butylpyridine (0.112 mL, 0.50 mmol), copper(II) (+)-2,2’-Isopropylidenebis[(4R)-4-phenyl-2-oxazoline] trflate solution (0.1 M in dichloromethane, 0.25 mL, 0.025 mmol), and mesityl(phenyl)iodonium hexafluorophosphate (234.1 mg, 0.5 mmol) as a solution in dichloromethane (2 mL), with stirring for 48 h at 5 °C. Purification by column chromatography (0–4% diethyl ether / hexane) afforded the desired compound as a white solid (55.2 mg, 0.24 mmol, 96%). Slow cooling from hot saturated solution of 145 in hexane grew single crystals. Racemic 145 were prepared according to general procedure E: 90 (77.2 mg, 0.50 mmol), 2,6-di-tert-butylpyridine (0.225 mL, 1.0 mmol), diphenyliodonium trflate (430.2 mg, 1.0 mmol) and CuCl (5.0 mg, 0.050 mmol) were reacted in anhydrous dichloromethane (4 mL) to obtain the desired compound as a white solid, and as racemic mixtures (9.2 mg, 0.04 mmol, 8%).

Elemental analysis (%) calcd for C₁₅H₂₂O₂: C, 78.23; H, 7.88. Found: C, 78.12; H, 7.93. Rf 0.5 (20% diethyl ether / hexane); IR (thin film) ν max/cm⁻¹ 2958, 1732, 1603, 1493, 1453, 1404, 1378, 1154, 1072, 948, 761, 702; ¹H NMR (500 MHz, CD₂Cl₂) δ H 7.72–6.97 (m, 5H, H₇–H₉), 3.98–3.90 (m, 1H, H₃), 3.77–3.73 (m, 1H, H₅), 2.89 (dd, J = 13.1, 3.9 Hz, 1H, H₂), 2.71–2.63 (m, 1H, H₃), 2.30–2.21 (m, 1H, H₁₂), 1.96–1.88 (m, 1H, H₁₀), 1.86–1.62 (m, 6H, H₃, H₄, H₁₀–H₁₂), 1.39–1.27 (m, 1H, H₁₁); ¹³C NMR (125 MHz, CD₂Cl₂) δ C 216.4 (C₁₅), 141.9 (C₆), 129.8 (2C, C₈), 128.7 (2C, C₇), 127.1 (C₉), 80.2 (C₁), 63.3 (C₃), 48.1 (C₂), 39.4 (C₁₂), 37.2 (C₃), 26.9 (C₁₀), 26.1 (C₄), 18.3 (C₁₁); mp 44–46 °C; m/z HRMS (NSI) found [M+NH₄⁺]⁺ 248.1648 C₁₅H₂₂O₂ requires 248.1645. [α]D⁻²° –145.1 (c = 1.00, CHCl₃). d.e. >99%, according to NMR; e.e. 94%, from chiral HPLC. Chiralpak AD-H. Hexane / isopropanol 99.5:0.5; 1.0 mL/min. tR 7.0 minutes (minor), 7.5 minutes (major).
methyl (2S,5R,10R)-4-oxo-10-phenyl-6-oxaspiro[4.5]decane-2-carboxylate (156a)
methyl (2R,5R,10R)-4-oxo-10-phenyl-6-oxaspiro[4.5]decane-2-carboxylate (156b)

According to general procedure F, to a solution of inseparable diastereomeric mixtures of 151a/b (53.1 mg, 0.25 mmol, 13:1 d.r.) in anhydrous dichloromethane (6 mL) at 0 °C was added 2,6-di-tert-butylpyridine (0.112 mL, 0.50 mmol), copper(II) (+)-2,2'-Isopropylidenebis[(4R)-4-phenyl-2-oxazoline] trflate solution (0.1 M in dichloromethane, 0.250 mL, 0.025 mmol), and diphenyldonium hexafluorophosphate (213.0 mg, 0.5 mmol) as a solution in dichloromethane (2 mL), with stirring for 48 h at 25 °C. Purification by column chromatography (0-6% diethyl ether / hexane) afforded the desired compounds as white solid 156a (66.3 mg, 0.23 mmol, 92%), and viscous oil 156b (5.05 mg, 0.02 mmol, 7%). Racemic compounds 156a/b were synthesised according to general procedure G.

156a: Rf 0.35 (20% diethyl ether / hexane); IR (thin film) ν_max/cm⁻¹ 2955, 2877, 1733 (s, C=O), 1603, 1494, 1438, 1407, 1367, 1314, 1219, 1154, 1104, 1071, 1025, 950; ¹H NMR (500 MHz, C₆D₆) δ_H 7.21 (d, J = 7.8 Hz, 2H, H₇), 7.06 (t, J = 7.5 Hz, 2H, H₈), 6.96 (t, J = 7.5 Hz, 1H, H₉), 3.82 (t, J = 12.0 Hz, 1H, H₂), 3.64-3.60 (m, 1H, H₃), 3.21-3.14 (m, 1H, H₅), 3.11 (s, 3H, H₁₅), 2.92-2.78 (m, 1H, H₁₁), 2.73 (dd, J = 13.0, 3.2 Hz, 1H, H₁₂), 2.35 (ddd, J = 18.7, 8.0, 1.5 Hz, 1H, H₃), 2.24-2.04 (m, 3H, H₁₀₁₂), 1.56-1.47 (m, 2H, H₃₄), 1.38-1.35 (m, 1H₄); ¹³C NMR (125 MHz, C₆D₆) δ_C 210.7 (C₁₃), 173.9 (C₁₄), 141.2 (C₆), 130.0 (2C, C₈), 128.8 (2C, C₇), 127.4 (C₉), 81.4 (C₁), 63.3 (C₃), 51.3 (C₁₅), 48.1 (C₂), 41.9 (C₁₂), 40.2 (C₃), 36.9 (C₁₀), 26.7 (C₄), 25.9 (C₁₁); mp 54-55 °C; m/z HRMS (NSI) found [M + NH₄]⁺ 306.1701 C₁₇H₂₄O₄N requires 306.1700; [α]_D²⁰ −92.0 (c = 1.00, CHCl₃); d.e. >99%, according to NMR for starting diastereomer 151a; e.e. 80%, from chiral HPLC. Chiralpak AD-H, hexane / isopropanol 98:2, 1.0 mL/min, oven temperature: 30 °C, t_R 7.2 minutes (minor), 9.2 minutes (major).
156b: Rf 0.30 (20% diethyl ether / hexane); IR (thin film) ν_{max}/cm^{-1} 2953, 1733 (s, C=O), 1494, 1453, 1437, 1354, 1260, 1240, 1211, 1152, 1074, 1059, 1020, 941; \textsuperscript{1}H NMR (500 MHz, C\textsubscript{6}D\textsubscript{6}) δH 7.18-7.16 (m, 2H, H\textsubscript{7}), 7.06 (t, J = 7.4 Hz, 2H, H\textsubscript{8}), 7.01-6.97 (m, 1H, H\textsubscript{9}), 4.15-4.08 (m, 1H, H\textsubscript{2}), 3.63-3.59 (m, 1H, H\textsubscript{3}), 3.27 (s, 3H, H\textsubscript{15}), 2.85 (ddd, J = 18.8, 5.5, 1.1 Hz, 1H, H\textsubscript{3}), 2.77-2.67 (m, 2H, H\textsubscript{11,12}), 2.42-2.37 (m, 1H, H\textsubscript{12}), 2.17 (dd, J = 13.9, 8.3 Hz, 1H, H\textsubscript{10}), 1.97-1.90 (m, 1H, H\textsubscript{3}), 1.68 (dd, J = 18.8, 8.8 Hz, 1H, H\textsubscript{10}), 1.56-1.44 (m, 2H, H\textsubscript{3,4}), 1.38-1.33 (m, 1H, H\textsubscript{4}); \textsuperscript{13}C NMR (125 MHz, C\textsubscript{6}D\textsubscript{6}) δC 213.6 (C\textsubscript{13}), 173.8 (C\textsubscript{14}), 141.2 (C\textsubscript{6}), 129.7 (C\textsubscript{8}), 128.8 (2C, C\textsubscript{2}), 127.4 (C\textsubscript{9}), 80.5 (C\textsubscript{1}), 63.3 (C\textsubscript{3}), 51.5 (C\textsubscript{15}), 49.6 (C\textsubscript{2}), 40.9 (C\textsubscript{12}), 40.7 (C\textsubscript{3}), 36.3 (C\textsubscript{10}), 26.6 (C\textsubscript{4}), 25.8 (C\textsubscript{11}); m/z HRMS (NSI) found [M + H]^+ 289.1432 C\textsubscript{17}H\textsubscript{21}O\textsubscript{4} requires 289.1434; [α]\textsuperscript{25}D ≈ -49.4 (c = 1.00, CHCl\textsubscript{3}); d.e. >99%, according to NMR for starting diastereomer 151b; e.e. 80%, from chiral HPLC. Chiralpak AD-H, hexane / isopropanol 98:2, 1.0 mL/min, oven temperature: 30 °C, t\textsubscript{R} 11.2 minutes (minor), 12.0 minutes (major).
(5S,10R)-10-phenyl-2,6-dioxaspiro[4.5]decan-4-one (157)

According to general procedure F, to a solution of 152 (39.05 mg, 0.25 mmol) in anhydrous dichloromethane (6 mL) at 0 °C was added 2,6-di-tert-butylpyridine (0.112 mL, 0.50 mmol), copper(II) (+)-2,2'-isopropylidenebis[(4R)-4-phenyl-2-oxazoline] triflate solution (0.1 M in dichloromethane, 0.250 mL, 0.025 mmol), and diphenyliodonium hexafluorophosphate (213.0 mg, 0.5 mmol) as a solution in dichloromethane (2 mL), with stirring for 48 h at 10 °C. Purification by column chromatography (1-5% diethyl ether / hexane) afforded the desired compound as a colourless viscous oil (44.7 mg, 0.193 mmol, 77%). Racemic compound 157 was synthesised according to general procedure G.

Rr 0.45 (20% diethyl ether / hexane); IR (thin film) νmax/cm⁻¹ 2931, 2871, 1750 (s, C=O), 1603, 1584, 1493, 1454, 1234, 1202, 1071, 1053, 931; ¹H NMR (500 MHz, CDCl₃) δH 7.10-6.98 (m, 5H, H₇-9), 4.15 (td, J = 12.0, 2.7 Hz, 1H, H₆), 3.99-3.93 (m, 2H, H₁₁), 3.73 (d, J = 17.5 Hz, 1H, H₁₀), 3.65 (ddt, J = 11.7, 4.7, 1.6 Hz, 1H, H₃), 3.17 (d, J = 17.5 Hz, 1H, H₁₀), 2.70-2.58 (m, 2H, H₂,₃), 1.58-1.41 (m, 2H, H₃,₄), 1.38-1.30 (m, 1H, H₄); ¹³C NMR (125 MHz, CDCl₃) δc 213.6 (C₁₂), 140.4 (C₆), 129.4 (2C, C₈), 128.9 (2C, C₇), 128.6 (C₉), 78.0 (C₁), 77.2 (C₁₁), 72.2 (C₁₀), 63.4 (C₃), 46.9 (C₂), 26.4 (C₃), 26.0 (C₄); m/z HRMS (ESI-TOF) found [M + NH₄]^+ 250.1440 C₁₄H₂₀NO₃ requires 250.1443; [α]D²⁵ = -122.2 (c = 1.00, CHCl₃); [α]D 99%, according to NMR; e.e. 83%, from chiral HPLC. Chiralpak AD-H, hexane / isopropanol 99:1, 1.0 mL/min, oven temperature: 30 °C, tR 10.7 minutes (minor), 11.3 minutes (major).
**tert-b’utyl (5S,10R)-4-oxo-10-phenyl-6-oxa-2-azaspiro[4.5]decane-2-carboxylate (158)**

According to general procedure F, to a solution of 153 (63.83 mg, 0.25 mmol) in anhydrous dichloromethane (6 mL) at 0 °C was added 2,6-di-tert-butylpyridine (0.112 mL, 0.50 mmol), copper(II) (+)-2,2’-isopropylidenebis[(4R)-4-phenyl-2-oxazoline] triflate solution (0.1 M in dichloromethane, 0.250 mL, 0.025 mmol), and diphenyliodonium hexafluorophosphate (213.0 mg, 0.5 mmol) as a solution in dichloromethane (2 mL), with stirring for 48 h at 10 °C. Purification by column chromatography (2-6% diethyl ether / hexane) afforded the desired compound as a colourless viscous oil 158 (71.3 mg, 0.215 mmol, 86%). Racemic compound 158 was synthesised according to general procedure G.

\[ R_f 0.3 (20\% \text{ diethyl ether} / \text{hexane}); \text{IR (thin film) } \nu_{\text{max}}/\text{cm}^{-1} 2932, 2880, 1743 (s, C=O), 1698 (s, C=O), 1603, 1493, 1454, 1407, 1366, 1220, 1152, 1083, 1071, 772; \text{^1H NMR} (500 MHz, DMSO-}d_6, 25 ^\circ\text{C, rotamers} \delta_H 7.30-7.21 (m, 5H, H_7-9), 4.10-3.97 (m, 1H, H_5), 3.83-3.79 (m, 1H), 3.75-3.68 (m, 2H), 3.50-3.35 (m, 1H), 3.14 (dd, J = 19.9, 5.8 Hz, 1H), 3.05 (dd, J = 12.8, 3.1 Hz, 1H), 2.43-2.33 (m, 1H, H_3), 1.74-1.66 (m, 3H, H_3,4), 1.35 (s, 4H, H_13), 1.25 (s, 5H, H_13); \text{^1H NMR} (500 MHz, DMSO-}d_6, 90 ^\circ\text{C} \delta_H 7.30-7.21 (m, 5H, H_7-9), 4.07 (td, J = 11.2, 4.7 Hz, 1H, H_5), 3.84-3.81 (m, 1H, H_3), 3.74 (d, J = 12.3 Hz, 1H, H_11), 3.73 (d, J = 19.6 Hz, 1H, H_10), 3.48 (d, J = 12.3 Hz, 1H, H_11), 3.18 (d, J = 19.6 Hz, 1H, H_10), 3.04 (dd, J = 12.8, 3.6 Hz, 1H, H_2), 2.47-2.36 (m, 1H, H_1), 1.79-1.70 (m, 3H, H_3,4), 1.33 (s, 9H, H_15); \text{^13C NMR} (125 MHz, C_6D_6, 25 ^\circ\text{C, rotamers}) \delta_c 210.0, 208.8, 153.5, 153.4, 140.1, 140.0, 129.4, 129.4, 128.9, 128.8, 127.6, 127.5, 80.2, 79.9, 79.5, 79.3, 63.7, 55.5, 55.0, 54.0, 53.7, 47.8, 28.4, 28.3, 26.4, 26.3, 26.0, 25.8; \text{^13C NMR} (125 MHz, DMSO-}d_6, 90 ^\circ\text{C} \delta_c 209.2 (C_{12}), 152.4 (C_{13}), 139.0 (C_6), 128.1 (2C, C_8), 127.8 (2C, C_7), 126.6 (C_9), 79.0 (C_1), 78.7 (C_{14}), 62.6 (C_5), 54.2 (C_{11}), 52.8 (C_{10}), 46.6 (C_2), 27.5 (3C, C_{15}), 24.9 (C_3), 24.9 (C_4); m/z HRMS (NSI) found [M + Na]^+ 354.1676 C_{19}H_{25}NO_4Na requires 354.1676; [\alpha]^{25}D +31.0 (c = 1.00, CHCl_3); \text{d.e. } >99\%, \text{according to NMR}; \text{e.e. } 85\%, \text{from chiral HPLC. Chiralpak AD-H, hexane / isopropanol 90:10, 1.0 mL/min, oven temperature: 30 °C, t_R 5.6 minutes (major), 6.0 minutes (minor).}
According to general procedure F, to a solution of 154 (420.6 mg, 2.5 mmol) in anhydrous dichloromethane (60 mL) at 0 °C was added 2,6-di-tert-butylpyridine (1.12 mL, 5.0 mmol), copper(II) (+)-2,2'-Isopropylidenebis[(4R)-4-phenyl-2-oxazoline] triflate solution (0.1 M in dichloromethane, 2.5 mL, 0.25 mmol), and diphenyliodonium hexafluorophosphate (2.13 g, 5.0 mmol) as a solution in dichloromethane (20 mL). The solution as stirred for 36 h at 25 °C. Purification by column chromatography (0-4% diethyl ether / hexane) afforded the desired compound as a white solid (586.4 mg, 2.4 mmol, 96%). Racemic 159 were prepared according to general procedure E: 154 (84.2 mg, 0.50 mmol), 2,6-di-tert-butylpyridine (0.225 mL, 1.0 mmol), diphenyliodonium triflate (430.2 mg, 1.0 mmol) and CuCl (5.0 mg, 0.050 mmol) were reacted in anhydrous dichloromethane (4 mL) to obtain the desired product as a white solid, and as racemic mixtures (6.1 mg, 0.025 mmol, 5%).

Rf 0.6 (20% diethyl ether / hexane); IR (thin film) νmax/cm⁻¹ 2932, 2861, 1714 (s, C=O), 1602, 1493, 1451, 1434, 1256, 1210, 1113, 1093, 1073, 1047, 979; ¹H NMR (500 MHz, C₆D₆) δH 7.60-7.57 (m, 2H, H₂), 7.19 (t, J = 7.4 Hz, 2H, H₈), 7.07 (tt, J = 7.4, 1.3 Hz, 1H, H₀), 3.64 (m, 1H, H₅), 3.20 (td, J = 12.1, 2.6 Hz, 1H, H₅), 2.75 (m, 1H, H₁₁), 2.54 (dd, J = 12.8, 3.4 Hz, 1H, H₂), 2.44 (td, J = 13.5, 6.3, 1H, H₁₃), 2.01-1.96 (m, 1H, H₁₃), 1.95-1.83 (m, 2H, H₃₄), 1.67-1.48 (m, 3H, H₅₁₂), 1.45-1.39 (m, 1H, H₁₀), 1.37-1.31 (m, 1H, H₁₂), 1.16-1.08 (m, 1H, H₅), 0.98-0.84 (m, 1H, H₁₀); ¹³C NMR (125 MHz, C₆D₆) δc 210.0 (C₁₄), 142.1 (C₆), 131.3 (C₅), 128.1 (C₇), 126.8 (C₉), 81.6 (C₁), 63.8 (C₃), 52.9 (C₂), 40.3 (C₁₃), 39.4 (C₅), 27.1 (C₁₂), 26.8 (C₁₀), 26.5 (C₁₁), 20.2 (C₄); mp 42-43 °C; m/z HRMS (NSI) found [M + Na]⁺ 267.1354 C₁₆H₂₉O₂Na requires 267.1356; [α]D²⁶ = -25.3 (c = 1.00, CHCl₃); d.e. >99%, according to NMR; e.e. 92%, from chiral HPLC. Chiralpak AD-H, hexane / isopropanol 99.7:0.3, 1.0 mL/min, oven temperature: 30 °C, tR 7.1 minutes (minor), 8.9 minutes (major).
(2R,3'R)-3'-phenyl-1,3',4,4',5',6'-hexahydro-3H-spiro[naphthalene-2,2'-pyran]-3-one (160)

According to general procedure F, to a solution of 155 (540.7 mg, 2.5 mmol) in anhydrous dichloromethane (60 mL) at 0 °C was added 2,6-di-tert-butylpyridine (1.68 mL, 7.5 mmol), copper(II) (+)-2,2'-Isopropylidenebis[(4R)-4-phenyl-2-oxazoline] triflate solution (0.1 M in dichloromethane, 2.5 mL, 0.25 mmol), and diphenyldiodonium hexafluorophosphate (3.2 g, 7.5 mmol) as a solution in dichloromethane (20 mL), with stirring for 48 h at 25 °C. Purification by column chromatography (0-4% diethyl ether / hexane) afforded the desired compound as a white solid (622.8 mg, 2.13 mmol, 85%). Slow cooling from hot saturated solution of 160 in hexane grew single crystals. X-Ray crystal structure is deposited in the Cambridge Crystallographic Data Centre CCDC 1539188. Racemic compound 160 was synthesised according to general procedure G.

Elemental analysis (%) calcld for C_{20}H_{20}O_{2}: C, 82.16; H, 6.90. Found: C, 82.06; H, 6.85. Rs 0.5 (20% diethyl ether / hexane); IR (thin film) ν_{max}/cm^{-1} 2930, 2872, 1713 (s, C=O), 1602, 1494, 1454, 1292, 1212, 1157, 1115, 1074, 1046, 961; ^1H NMR (500 MHz, CD_{6}) δ_{H} 7.37-7.35 (m, 2H, H7), 7.14-7.10 (m, 2H, H8), 7.04 (tt, J = 7.4, 1.6 Hz, 1H, H9), 7.00-6.95 (m, 2H, H12,13), 6.94-6.90 (m, 1H, H14), 6.61 (d, J = 7.5 Hz, 1H, H11), 3.73 (td, J = 11.8, 3.0 Hz, 1H, H3), 3.52 (ddt, J = 11.8, 4.6, 1.6 Hz, 1H, H5), 3.35 (d, J = 18.8 Hz, 1H, H10), 3.12 (d, J = 15.8 Hz, 1H, H17), 2.90 (d, J = 18.8 Hz, 1H, H10), 2.83 (d, J = 15.8 Hz, 1H, H17), 2.85-2.68 (m, 1H, H3), 2.70 (dd, J = 12.5, 3.3 Hz, 1H, H2), 1.66-1.61 (m, 1H, H3), 1.55-1.44 (m, 1H, H4), 1.41-1.34 (m, 1H, H3); ^13C NMR (125 MHz, CD_{6}) δ_{C} 206.3 (C_{18}), 141.5 (C_{6}), 134.8 (C_{16}), 132.7 (C_{15}), 130.4 (2C, C_{7}), 128.7 (C_{9}), 128.5 (2C, C_{8}), 127.3 (C_{11}), 127.2 (C_{12}), 126.8 (C_{13}), 126.6 (C_{14}), 77.7 (C_{1}), 63.7 (C_{5}), 51.4 (C_{2}), 45.9 (C_{17}), 42.5 (C_{10}), 26.5 (C_{3}), 26.5 (C_{4}); mp 100-101 °C; m/z HRMS (NSI) found [M + Na]^+ 315.1354 C_{20}H_{20}O_{2}Na requires 315.1356; [α] D -37.2 (c = 1.00, CHCl_{3}); d.e. >99%, according to NMR; e.e. 99%, from chiral HPLC. Chiralpak AD-H, hexane / isopropanol 98:2, 1.0 mL/min, oven temperature: 30 °C, t_R 9.9 minutes (minor), 17.8 minutes (major).
(1S,2'R)-2'-phenyl-2',3'-dihydrospiro[cyclopentane-1,1'-inden]-2-one (172a)

(1R,2'R)-2'-phenyl-2',3'-dihydrospiro[cyclopentane-1,1'-inden]-2-one (172b)

According to general procedure F, to a solution of 168 (46.6 mg, 0.25 mmol) in anhydrous dichloromethane (6 mL) at 0 °C was added 2,6-di-tert-butylpyridine (0.112 mL, 0.50 mmol), copper(II) (+)-2,2'-Isopropylidenebis[(4R)-4-phenyl-2-oxazoline] trflate solution (0.1 M in dichloromethane, 0.25 mL, 0.025 mmol), and diphenyliodonium hexafluorophosphate (213.0 mg, 0.5 mmol) as a solution in dichloromethane (2 mL), with stirring for 48 h at 10 °C. Purification by column chromatography (0-4% diethyl ether / hexane) afforded the desired diastereomeric compounds as colourless viscous oil 172a (47.9 mg, 0.183 mmol, 73%) and white solid 172b (15.9 mg, 0.061 mmol, 24%). Slow cooling from hot saturated solution of 172b in hexane grew single crystals. X-Ray crystal structure is deposited in the Cambridge Crystallographic Data Centre CCDC 1539186. Racemic compounds 172a/b were synthesised according to general procedure G.

172a: Rr 0.55 (20% diethyl ether / hexane); IR (thin film) v_{max}/cm^{-1} 2956, 2886, 1729 (s, C=O), 1603, 1584, 1479, 1455, 1403, 1270, 1220, 1124, 772; ^1H NMR (500 MHz, C_{6}D_{6}) δ_{H} 7.30-7.28 (m, 2H, H_{4,7}), 7.15-7.09 (m, 5H, H_{6,11-12}), 7.05 (tt, J = 7.2, 1.3 Hz, 1H, H_{13}), 6.89-6.85 (m, 1H, H_{9}), 3.74 (dd, J = 15.1, 11.4 Hz, 1H, H_{3}), 3.21 (dd, J = 11.4, 7.6 Hz, 1H, H_{2}), 2.86 (dd, J = 15.1, 7.6 Hz, 1H, H_{3}), 2.16-2.09 (m, 1H, H_{14}), 2.02-1.95 (m, 1H, H_{14}), 1.79-1.71 (m, 1H, H_{16}), 1.49-1.36 (m, 2H, H_{15,16}), 1.32-1.21 (m, 1H, H_{15}); ^13C NMR (125 MHz, C_{6}D_{6}) δ_{C} 217.1 (C_{17}), 146.4 (C_{9}), 144.6 (C_{8}), 140.0 (C_{10}), 129.7 (2C, C_{12}), 128.6 (2C, C_{11}), 127.5 (C_{4}), 127.4 (C_{13}), 127.0 (C_{7}), 125.0 (C_{5}), 122.7 (C_{3}), 65.3 (C_{1}), 59.2 (C_{2}), 38.6 (C_{16}), 38.3 (C_{3}), 35.7 (C_{14}), 20.0 (C_{15}); m/z HRMS (ESI-TOF) found [M + H]^+ 263.1436 C_{19}H_{19}O requires 263.1436; [α]^{26}D -184.9 (c = 1.00, CHCl_{3}); d.e. 50%, according to NMR; e.e. 90%.
from chiral HPLC. Chiralpak IA, hexane / isopropanol 99:1, 1.0 mL/min, oven temperature: 30 °C, t<sub>R</sub> 9.5 minutes (major), 12.0 minutes (minor).

172b: Elemental analysis (%) calcd for C<sub>19</sub>H<sub>10</sub>O: C, 86.99; H, 6.92. Found: C, 86.97; H, 6.94. R<sub>f</sub> 0.5 (20% diethyl ether / hexane); IR (thin film) ν<sub>max</sub>/cm<sup>-1</sup> 2980, 2919, 2877, 1720 (s, C=O), 1494, 1480, 1455, 1273, 1219, 1140, 1106, 772; <sup>1</sup>H NMR (500 MHz, C<sub>6</sub>D<sub>6</sub>) δ<sub>H</sub> 7.36-6.96 (m, 8H, H<sub>4,6-7,11-13</sub>), 6.80 (d, J = 7.3 Hz, 1H, H<sub>5</sub>), 4.01 (t, J = 8.0 Hz, 1H, H<sub>2</sub>), 3.21 (dd, J = 15.5, 8.0 Hz, 1H, H<sub>3</sub>), 3.04 (dd, J = 15.5, 8.0 Hz, 1H, H<sub>3</sub>), 2.04 (ddd, J = 18.5, 8.8, 6.4 Hz, 1H, H<sub>10</sub>), 1.88 (ddd, J = 18.5, 8.8, 7.0 Hz, 1H, H<sub>16</sub>), 1.69 (dt, J = 13.3, 7.3, 1H, H<sub>14</sub>), 1.60-1.54 (m, 1H, H<sub>14</sub>), 1.41-1.34 (m, 1H, H<sub>15</sub>), 1.16-1.06 (m, 1H, H<sub>15</sub>); <sup>13</sup>C NMR (125 MHz, C<sub>6</sub>D<sub>6</sub>) δ<sub>C</sub> 218.5 (C<sub>17</sub>), 147.3 (C<sub>5</sub>), 143.5 (C<sub>8</sub>), 141.7 (C<sub>10</sub>), 128.7 (C<sub>12</sub>), 128.6 (C<sub>11</sub>), 127.5 (C<sub>4</sub>), 127.2 (C<sub>13</sub>), 127.1 (C<sub>7</sub>), 124.9 (C<sub>6</sub>), 123.3 (C<sub>3</sub>), 66.0 (C<sub>1</sub>), 52.8 (C<sub>2</sub>), 38.0 (C<sub>16</sub>), 37.5 (C<sub>3</sub>), 32.7 (C<sub>14</sub>), 19.1 (C<sub>13</sub>); mp 70-71 °C; m/z HRMS (ESI-TOF) found [M + H]<sup>+</sup> 263.1436 C<sub>19</sub>H<sub>10</sub>O requires 263.1436; [α]<sup>26</sup> <sub>D</sub> +52.2 (c = 1.00, CHCl<sub>3</sub>); d.e. -50%, according to NMR; e.e. 97%, from chiral HPLC. Chiralpak AD-H, hexane / isopropanol 98:2, 1.0 mL/min, oven temperature: 30 °C, t<sub>R</sub> 9.4 minutes (minor), 12.7 minutes (major).
(1S,2'R)-2'-phenyl-2',3'-dihydrospiro[cyclohexane-1,1'-inden]-2-one (173)

According to general procedure F, to a solution of 169 (500.7 mg, 2.5 mmol) in anhydrous dichloromethane (60 mL) at 0 °C was added 2,6-di-tert-butylpyridine (1.12 mL, 5.0 mmol), copper(II) (+)-2,2'-Isopropylidenedi(4R)-4-phenyl-2-oxazoline] triflate solution (0.1 M in dichloromethane, 2.5 mL, 0.25 mmol), and diphenyliodonium hexafluorophosphate (2.13 g, 5.0 mmol) as a solution in dichloromethane (20 mL), with stirring for 48 h at 25 °C. Purification by column chromatography (0-4% diethyl ether / hexane) afforded the desired compound as a white solid (677.1 mg, 2.45 mmol, 98%). Slow cooling from hot saturated solution of 173 in hexane grew single crystals. X-Ray crystal structure is deposited in the Cambridge Crystallographic Data Centre CCDC 1539184. Racemic compound 173 was synthesised according to general procedure G.

Elemental analysis (%) calcd for C_{20}H_{20}O: C, 86.92; H, 7.29. Found: C, 86.90; H, 7.34. Rf 0.6 (20% diethyl ether / hexane); IR (thin film) ν max/cm⁻¹ 2934, 2862, 1707 (s, C=O), 1602, 1494, 1480, 1455, 1310, 1220, 1125, 772; ¹H NMR (500 MHz, C₆D₆) δ_H 7.54 (d, J = 7.4 Hz, 1H, H₄), 7.24 (t, J = 7.4 Hz, 1H, H₃), 7.18-7.14 (m, 1H, H₆), 7.09 (d, J = 7.4 Hz, 1H, H₇), 7.02-6.98 (m, 2H, H₁₂), 6.96-6.92 (m, 3H, H₁₁,13), 3.43 (dd, J = 8.1, 3.2 Hz, 1H, H₂), 3.24 (dd, J = 16.0, 8.1 Hz, 1H, H₅), 2.92 (dd, J = 16.0, 3.2 Hz, 1H, H₃), 2.11-2.05 (m, 1H, H₁₇), 1.86-1.78 (m, 2H, H₁₅,17), 1.68-1.60 (m, 1H, H₁₃), 1.60-1.45 (m, 2H, H₁₄,16), 1.39-1.28 (m, 2H, H₁₄,16); ¹³C NMR (125 MHz, C₆D₆) δ_C 208.6 (C₁₈), 146.8 (C₉), 143.6 (C₈), 142.4 (C₁₀), 128.6 (2C, C₁₁), 128.56 (2C, C₁₂), 127.6 (C₆), 127.2 (C₃), 126.9 (C₅), 126.7 (C₄), 124.6 (C₇), 67.8 (C₁), 53.4 (C₂), 42.2 (C₁₇), 41.5 (C₃), 40.4 (C₁₅), 27.6 (C₁₆), 23.1 (C₁₄); mp 75-76 °C; m/z HRMS (ESI-TOF) found [M + H]⁺ 277.1588 C_{20}H_{21}O requires 277.1592; [α]^{26}_{D} +112.3 (c = 1.00, CHCl₃); d.e. >99%, according to NMR; e.e. 91%, from chiral HPLC. Chiralpak IA, hexane / isopropanol 99:1, 1.0 mL/min, oven temperature: 30 °C, tᵣ 8.9 minutes (minor), 11.3 minutes (major).
According to general procedure F, to a solution of 170 (65.1 mg, 0.25 mmol) in anhydrous dichloromethane (6 mL) at 0 °C was added 2,6-di-tert-butylpyridine (0.112 mL, 0.50 mmol), copper(II) (+)-2,2'-Isopropylidenebis[(4R)-4-phenyl-2-oxazoline] triflate solution (0.1 M in dichloromethane, 0.25 mL, 0.025 mmol), and diphenyliodonium hexafluorophosphate (213.1 mg, 0.50 mmol) as a solution in dichloromethane (2 mL), with stirring for 48 h at 25 °C. Purification by column chromatography (5-20% diethyl ether / hexane) afforded the desired compound as a white solid (81.1 mg, 0.24 mmol, 96%). Racemic compound 174 was synthesised according to general procedure G.

Rf 0.2 (20% diethyl ether / hexane); IR (thin film) νmax/cm⁻¹ 2934, 2862, 1705 (s, C=O), 1604, 1496, 1464, 1453, 1341, 1302, 1273, 1243, 1211, 1187, 1103, 1079, 1017, 972; ¹H NMR (500 MHz, C₆D₆) δH 7.17 (s, 1H, H₇), 7.13-7.05 (m, 2H, H₁₁), 7.03-6.97 (m, 3H, H₁₂,1₃), 6.57 (s, 1H, H₄), 3.57 (s, 3H, H₂₀), 3.54 (dd, J = 8.1, 2.5 Hz, 1H, H₂), 3.47 (s, 3H, H₁₉), 3.32 (dd, J = 15.8, 8.1 Hz, 1H, H₃), 2.88 (dd, J = 15.8, 2.5 Hz, 1H, H₃), 2.19-2.05 (m, 1H, H₁₇), 1.94-1.86 (m, 2H, H₁₄,1₇), 1.72 (td, J = 13.4, 3.5 Hz, 1H, H₁₄), 1.65-1.54 (m, 2H, H₁₅,1₆), 1.44-1.40 (m, 2H, H₁₅,1₆); ¹³C NMR (125 MHz, C₆D₆) δC 209.3 (C₁₈), 150.3 (C₅), 149.6 (C₆), 144.0 (C₁₀), 138.6 (C₀), 133.7 (C₈), 128.6 (2C, C₁₁/₁₂), 128.5 (2C, C₁₁/₁₂), 127.2 (C₁₃), 110.7 (C₄), 108.6 (C₇), 68.0 (C₁), 56.0 (C₂₀), 55.8 (C₁₉), 53.4 (C₂), 42.5 (C₁₇), 41.9 (C₃), 40.4 (C₁₅), 27.9 (C₁₆), 23.3 (C₁₄); mp 132-133 °C; m/z HRMS (NSI) found [M + H]+ 337.1801 C₂₂H₂₅O₃ requires 337.1798; [α]D +79.9 (c = 1.00, CHCl₃); d.e. >99%, according to NMR; e.e. 95%, from chiral HPLC. Chiralpak IA, hexane / isopropanol 85:15, 1.0 mL/min, oven temperature: 30 °C, tR 10.7 minutes (major), 12.4 minutes (minor).
(1S,2'R)-6'-methoxy-2'-phenyl-3',4'-dihydro-2'H-spiro[cyclohexane-1,1'-naphthalen]-2-one (175)

According to general procedure F, to a solution of 171 (61.1 mg, 0.25 mmol) in anhydrous dichloromethane (6 mL) at 0 °C was added 2,6-di-tert-butylpyridine (0.168 mL, 0.75 mmol), copper(II) (+)-2,2'-Isopropylidenebis[(4R)-4-phenyl-2-oxazoline] trflate solution (0.1 M in dichloromethane, 0.25 mL, 0.025 mmol), and diphenyliodonium hexafluorophosphate (319.6 mg, 0.75 mmol) as a solution in dichloromethane (2 mL), with stirring for 48 h at 25 °C. Purification by column chromatography (0-4% diethyl ether / hexane) afforded the desired compound as a white solid (50.5 mg, 0.16 mmol, 63%). Slow cooling from hot saturated solution of 175 in hexane grew single crystals. X-Ray crystal structure is deposited in the Cambridge Crystallographic Data Centre CCDC 1539187. Racemic compound 175 was synthesised according to general procedure G.

Elemental analysis (%) calcd for C_{22}H_{24}O_{2}: C, 82.46; H, 7.55. Found: C, 82.45; H, 7.57. R{\text{f}} 0.5 (20% diethyl ether / hexane); IR (thin film) v{\text{max}}/cm^{-1} 2933, 2860, 1707 (s, C=O), 1609, 1575, 1500, 1464, 1450, 1285, 1263, 1238, 1119, 1040, 756; \text{^1H NMR} (500 MHz, C_{6}D_{6}) \text{δ} \text{H} 7.39 (d, J = 8.8 Hz, 1H, H_{8}), 7.09-7.06 (m, 2H, H_{12}), 7.01-6.91 (m, 4H, H_{7,13,14}), 6.64 (d, J = 2.6 Hz, 1H, H_{5}), 3.51 (t, J = 3.8 Hz, 1H, H_{2}), 3.40 (s, 3H, H_{29}), 2.73-2.64 (m, 1H, H_{4}), 2.35-2.30 (m, 1H, H_{4}), 2.16-2.04 (m, 4H, H_{3,17,18}), 1.76 (dt, J = 13.8, 4.3 Hz, 1H, H_{18}), 1.65-1.53 (m, 3H, H_{3,15,16}), 1.48-1.40 (m, 1H, H_{16}), 1.29-1.26 (m, 1H, H_{15}); \text{^13C NMR} (125 MHz, C_{6}D_{6}) \text{Δ} \text{C} 209.4 (C_{19}), 158.3 (C_{6}), 141.4 (C_{11}), 138.4 (C_{10}), 133.2 (C_{8}), 131.8 (C_{9}), 130.1 (2C, C_{13}), 128.6 (2C, C_{12}), 126.9 (C_{14}), 113.3 (C_{3}), 112.6 (C_{7}), 56.6 (C_{1}), 54.8 (C_{20}), 44.5 (C_{2}), 43.8 (C_{18}), 41.1 (C_{17}), 28.0 (C_{15}), 26.4 (C_{3}), 25.6 (C_{4}), 22.2 (C_{13}); mp 124-125 °C; m/z HRMS (NSI) found [M + Na]^+ 343.1665 C_{22}H_{24}O_{2}Na requires 343.1669; [α]^{27}\text{D} +81.3 (c = 1.00, CHCl_{3}); d.e. >99%, according to NMR; e.e. 84%, from chiral HPLC. Chiralpak IA, hexane / isopropanol 99:1, 1.0 mL/min, oven temperature: 30 °C, t{\text{R}} 15.3 minutes (minor), 26.9 minutes (major).
(R)-2-ethoxy-2-((S)-1-phenylpropyl)cyclopentan-1-one (182a) / (S)-2-ethoxy-2-((S)-1-phenylpropyl)cyclopentan-1-one (182b)

According to general procedure F, to a solution of 180 (42.6 mg, 0.25 mmol) in anhydrous dichloromethane (6 mL) at 0 °C was added 2,6-Di-tert-butylpyridine (0.112 mL, 0.5 mmol), copper(II) (+) -2,2'-Isopropylidenebis[(4R)-4-phenyl-2-oxazoline] triflate solution (0.1 M in dichloromethane, 0.25 mL, 0.025 mmol), and diphenyliodonium hexafluorophosphate (213 mg, 0.5 mmol) as a solution in dichloromethane (2 mL), with stirring for 48 h at 25 °C. Purification by column chromatography (0-4% diethyl ether / hexane) afforded the desired diastereomeric compounds as colourless oils 182a (27.7 mg, 0.112 mmol, 45%), and 182b (10.5 mg, 0.043 mmol, 17%). Racemic compounds 182a/b were synthesised according to general procedure G.

182a: [α]D^27 0.7 (20% diethyl ether / hexane); IR (thin film) ν_max/cm⁻¹ 2970, 2935, 1878, 1740 (s, C=O), 1493, 1467, 1453, 1404, 1390, 1186, 1163, 1110, 1059, 701; ^1H NMR (500 MHz, CDCl₃) δ_H 7.28-7.16 (m, 5H, H₄₋₆), 3.48-3.41 (m, 2H, H₁₁), 3.04 (dd, J = 12.2, 3.2, 1H, H₂), 2.18-2.11 (m, 1H, H₂), 1.98-1.71 (m, 6H, H₇₋₁₃), 1.60-1.53 (m, 1H, H₁₃), 1.16 (t, J = 6.9 Hz, 3H, H₁₂), 0.76 (t, J = 7.4 Hz, 3H, H₁₄); ^13C NMR (125 MHz, CDCl₃) δ_c 216.1 (C₁₀), 139.0 (C₃), 130.6 (2C, C₅), 128.2 (2C, C₄), 126.7 (C₅), 85.3 (C₁), 58.6 (C₁₁), 47.5 (C₂), 37.2 (C₆), 30.4 (C₇), 20.4 (C₁₃), 17.8 (C₈), 15.8 (C₁₂), 12.4 (C₁₄); m/z HRMS (NSI) found [M + H]^⁺ 247.1703 C₁₆H₂₃O₂ requires 247.1698; [α]D^27 0.0 -52.4 (c = 1.00, CHCl₃); d.e. 44%, according to NMR; e.e. 78%, from chiral HPLC. Chiralpak IA, hexane / isopropanol 99.7:0.3, 1.0 mL/min, oven temperature: 30 °C, t_R 5.14 minutes (minor), 5.73 minutes (major).
**182b:** \( R_f 0.65 \) (20% diethyl ether / hexane); **IR** (thin film) \( \nu_{\text{max}}/\text{cm}^{-1} \) 2968, 2933, 2875, 1736 (s, C=O), 1496, 1453, 1390, 1269, 1182, 1165, 1138, 1109, 1060, 964, 699; **\(^1\)H NMR** (500 MHz, CDCl\(_3\) \( \delta_{\text{H}} \) 7.31-7.20 (m, 5H, H\(_{4-6}\)), 3.52-3.45 (m, 1H, H\(_{11}\)), 3.28-3.20 (m, 1H, H\(_{11}\)), 3.10 (dd, \( J = 11.5, 2.8 \) Hz, 1H, H\(_2\)), 2.41-2.33 (m, 1H, H\(_9\)), 1.96-1.88 (m, 1H, H\(_7\)), 1.70-1.56 (m, 2H, H\(_{8,13}\)), 0.95 (t, \( J = 7.0 \) Hz, 3H, H\(_{12}\)), 0.72 (t, \( J = 7.3 \) Hz, 3H, H\(_{14}\)); **\(^{13}\)C NMR** (125 MHz, CDCl\(_3\) \( \delta_{\text{C}} \) 216.4 (C\(_{10}\)), 140.4 (C\(_5\)), 129.4 (2C, C\(_5\)), 128.3 (2C, C\(_4\)), 126.7 (C\(_6\)), 84.9 (C\(_1\)), 58.6 (C\(_{11}\)), 48.1 (C\(_2\)), 37.7 (C\(_9\)), 32.1 (C\(_7\)), 24.3 (C\(_{13}\)), 17.9 (C\(_3\)), 15.6 (C\(_{12}\)), 12.7 (C\(_{14}\)) \( m/z \) HRMS (NSI) found [M + NH\(_4\)]\(^+\) 264.1963 C\(_{16}\)H\(_{23}\)O\(_2\) requires 264.1964; \([\alpha]_{D}^{20} +17.6 \) (c = 0.50, CHCl\(_3\)); d.e. \(-44\)%, according to NMR; e.e. \( 80\)% from chiral HPLC. Chiralpak IC, hexane / isopropanol 99.5:0.5, 1.0 mL/min, oven temperature: 30 °C, \( t_R \) 6.4 minutes (major), 6.8 minutes (minor).
5.7 Unsuccessful enantioselective arylation-SPR products:

2-benzyl-2-isobutoxycyclopentan-1-one (183)

According to general procedure F, to a solution of 181 (42.6 mg, 0.25 mmol) in anhydrous dichloromethane (6 mL) at 0 °C was added 2,6-Di-tert-butylpyridine (0.112 mL, 0.5 mmol), copper(II) (+)-2,2'-Isopropylidenebis[(4R)-4-phenyl-2-oxazoline] triflate solution (0.1 M in dichloromethane, 0.25 mL, 0.025 mmol), and diphenyliodonium hexafluorophosphate (213 mg, 0.5 mmol) in dichloromethane (2 mL), with stirring for 48 h at 25 °C. Purification by column chromatography (0-4% diethyl ether / hexane) afforded a colourless oil (61.6 mg, 0.25 mmol, quant.).

Rf 0.5 (10% diethyl ether / hexane); IR (thin film) νmax/cm⁻¹ 2921, 1732 (s, C=O), 1462, 1365, 1156, 921; ¹H NMR (500 MHz, CD₆D₆) δH 7.18-7.12 (m, 5H, H₄-₅), 7.06 (tt, J = 6.8, 2.5 Hz, 1H, H₆), 3.28 (dd, J = 8.8, 6.1 Hz, 1H, H₁₁), 3.13 (dd, J = 8.8, 6.1 Hz, 1H, H₁₁), 2.91 (apparent q, J = 12.5 Hz, 2H, H₂), 2.05-1.96 (m, 1H, H₉), 1.80-1.60 (m, 4H, H₇-₉), 1.49-1.39 (m, 1H, H₇), 1.21-1.15 (m, 1H, H₁₂), 0.87-0.83 (m, 6H, H₁₃, rotamers); ¹³C NMR (125 MHz, CD₆D₆) δc 214.1 (C₁₀), 137.5 (C₃), 130.7 (2C, C₅), 128.5 (2C, C₄), 126.7 (C₂), 82.7 (C₁), 70.0 (C₁₁), 37.2 (C₂), 36.4 (C₉), 33.5 (C₇), 29.3 (C₁₂), 19.5 (C₁₃, rotamer), 19.4 (C₁₃, rotamer), 17.9 (C₈); m/z HRMS (NSI) found [M + H]⁺ 247.1695 C₁₆H₂₃O₂ requires 247.1693; [α]D 0.0 (c = 1.00, CHCl₃); e.e. 0%, from chiral HPLC. Chiralpak IA, hexane / isopropanol 99.7:0.3, 1.0 mL/min, oven temperature: 30 °C, tR 6.54 minutes (minor), 7.26 minutes (major).
1-(5-phenyl-3,4-dihydro-2H-pyran-6-yl)cyclohexan-1-ol (165)

According to general procedure F, to a solution of 161 (455.7 mg, 2.5 mmol) in anhydrous dichloromethane (60 mL) at 0 °C was added 2,6-di-tert-butylpyridine (1.12 mL, 5.0 mmol), copper(II) (+)-2,2'-Isopropylidenebis[(4R)-4-phenyl-2-oxazoline] triflate solution (0.1 M in dichloromethane, 2.5 mL, 0.25 mmol), and diphenyliodonium hexafluorophosphate (2.13 g, 5.0 mmol) as a solution in dichloromethane (20 mL), with stirring for 48 h at 10 °C. Purification by column chromatography (0-4% diethyl ether / hexane) afforded 165 as a yellow oil (459.7 mg, 1.78 mmol, 71%).

\( R_f 0.5 \) (20% diethyl ether / hexane); \( IR \) (thin film) \( \nu_{\text{max}}/\text{cm}^{-1} \) 3512 (s, br, OH), 2912, 2716, 1482, 1214, 916; \( ^1H \text{NMR} \) (500 MHz, CD\(_2\)Cl\(_2\)) \( \delta_H \) 7.35-7.29 (m, 2H, H\(_8\)), 7.23 (tt, \( J = 7.4, 2.1 \text{ Hz}, 1H, H_9 \)), 7.20-7.18 (m, 2H, H\(_7\)), 4.00 (t, \( J = 5.1 \text{ Hz}, 2H, H_5 \)), 2.20 (t, \( J = 6.5 \text{ Hz}, 2H, H_3 \)), 1.94-1.89 (m, 2H, H\(_4\)), 1.69-1.63 (m, 2H, H\(_{11,15}\)), 1.55-1.46 (m, 5H, H\(_{11,12,13,14,15}\)), 1.40-1.35 (m, 3H, H\(_{12,14}, \text{OH}_{16}\)), 1.11-1.01 (m, 1H, H\(_{13}\)); \( ^{13}C \text{NMR} \) (125 MHz, CD\(_2\)Cl\(_2\)) \( \delta_C \) 154.6 (C\(_1\)), 143.6 (C\(_6\)), 129.8 (2C, C\(_8\)), 128.5 (2C, C\(_7\)), 126.6 (C\(_9\)), 109.8 (C\(_2\)), 74.8 (C\(_{10}\)), 66.1 (C\(_3\)), 36.9 (2C, C\(_{11,15}\)), 31.2 (C\(_3\)), 25.9 (C\(_{13}\)), 23.7 (C\(_4\)), 21.9 (C\(_{12,14}\)); \( m/z \) HRMS (NSI) found [M + H]^+ 259.1688 C\(_{17}\)H\(_{23}\)O\(_2\) requires 259.1698.

1-(5-phenyl-3,4-dihydro-2H-pyran-6-yl)cycloheptan-1-ol (166)

According to general procedure F, to a solution of 162 (490.7 mg, 2.5 mmol) in anhydrous dichloromethane (60 mL) at 0 °C was added 2,6-di-tert-butylpyridine (1.12 mL, 5.0 mmol), copper(II) (±)-2,2'-Isopropylidenebis[(4R)-4-phenyl-2-oxazoline] triflate solution (0.1 M in dichloromethane, 2.5 mL, 0.25 mmol), and diphenyliodonium hexafluorophosphate (2.13 g, 5.0 mmol) as a solution in dichloromethane (20 mL), with stirring for 48 h at 10 °C. Purification by column chromatography (0-4% diethyl ether / hexane) afforded 166 as a colourless oil (606.1 mg, 2.23 mmol, 89%).

Rf 0.6 (20% diethyl ether / hexane); IR (thin film) νmax/cm−1 3312 (s, br, OH), 2842, 1452, 1220, 910; 1H NMR (500 MHz, CD2Cl2) δH 7.33-7.29 (m, 2H, H8), 7.24-7.18 (m, 3H, H7,9), 4.00 (t, J = 5.2 Hz, 2H, H5), 2.19 (t, J = 6.7 Hz, 2H, H3), 1.99-1.93 (m, 2H, H4), 1.92-1.88 (m, 2H, H11,12), 1.62-1.49 (m, 6H, H11,12,13,14,15,16), 1.46-1.40 (m, 4H, H13,14,15,16), 1.29 (bs, 1H, OH17); 13C NMR (125 MHz, CD2Cl2) δc 156.4 (C1), 143.5 (C6), 129.9 (2C, C8), 128.6 (2C, C7), 126.6 (C9), 108.5 (C2), 78.1 (C10), 66.1 (C5), 41.8 (2C, C11,12), 31.1 (C3), 29.8 (2C, C13,14), 23.6 (C4), 23.0 (C15,16); m/z HRMS (NSI) found [M + H]+ 273.1861 C18H25O2 requires 273.1855.
2-(5-phenyl-3,4-dihydro-2H-pyran-6-yl)propan-2-ol (167)

According to general procedure F, to a solution of 164 (355.5 mg, 2.5 mmol) in anhydrous dichloromethane (60 mL) at 0 °C was added 2,6-di-tert-butylpyridine (1.12 mL, 5.0 mmol), copper(II) (+)-2,2’-Isopropylidenebis[(4R)-4-phenyl-2-oxazoline] triflate solution (0.1 M in dichloromethane, 2.5 mL, 0.25 mmol), and diphenyliodonium hexafluorophosphate (2.13 g, 5.0 mmol) as a solution in dichloromethane (20 mL), with stirring for 48 h at 10 °C. Purification by column chromatography (0-4% diethyl ether / hexane) afforded 167 as a yellow oil (447.5 mg, 2.05 mmol, 82%).

Rf 0.6 (20% diethyl ether / hexane); IR (thin film) νmax/cm⁻¹ 3331 (s, br, OH), 2821, 1432, 1218, 906; ¹H NMR (500 MHz, CD₂Cl₂) δH 7.31 (t, J = 7.4 Hz, 2H, H₈), 7.25-7.22 (m, 1H, H₉), 7.20-7.18 (m, 2H, H₇), 4.03 (t, J = 5.1 Hz, 2H, H₅), 2.21 (t, J = 6.6 Hz, 2H, H₃), 2.15 (bs, 1H, OH₁₂), 1.93 (apparent quint, J = 5.3 Hz, 2H, H₄), 1.17 (s, 6H, H₁₁); ¹³C NMR (125 MHz, CD₂Cl₂) δC 153.9 (C₁), 143.3 (C₆), 129.8 (2C, C₈), 128.6 (2C, C₇), 126.8 (C₉), 109.5 (C₂), 73.2 (C₁₀), 66.3 (C₃), 30.8 (C₅), 30.0 (2C, C₁₁), 23.6 (C₄); m/z HRMS (NSI) found [M + H]^+ 219.1376 C₁₄H₁₉O₂ requires 219.1385.
5.8 Enantioselective arylation-SPR products (aryl scope):

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(5R,10R)-10-(p\text{-tolyl})-6\text{-oxaspiro[4.5]decan-1-one} \ (189)
\]

According to general procedure F, to a solution of 90 (38.6 mg, 0.25 mmol) in anhydrous dichloromethane (6 mL) at 0 ºC was added 2,6-di-tert-butylpyridine (0.112 mL, 0.50 mmol), copper(II) (+)-2,2'-Isopropylidenebis[(4R)-4-phenyl-2-oxazoline] triflate solution (0.1 M in dichloromethane, 0.25 mL, 0.025 mmol), and mesityl(p-tolyl)iodonium hexafluorophosphate (185, 241.1 mg, 0.50 mmol) as a solution in dichloromethane (2 mL), with stirring at 10 ºC for 8 h. Purification by column chromatography (0-4% diethyl ether / hexane) afforded the desired compound as a white solid (58.6 mg, 0.24 mmol, 96%). Racemic 189 were prepared according to general procedure E: 90 (38.6 mg, 0.25 mmol), 2,6-di-tert-butylpyridine (0.112 mL, 0.5 mmol), mesityl(p-tolyl)iodonium tetrafluoroborate (212.0 mg, 0.5 mmol) and CuCl (2.5 mg, 0.025 mmol) were reacted in anhydrous dichloromethane (4 mL) to obtain the desired compound as a white solid, and as racemic mixtures (6 mg, 0.025 mmol, 10%).

Rf 0.55 (20% diethyl ether / hexane); IR (thin film) ν\text{max}/cm\textsuperscript{-1} 2971, 1732 (s, C=O), 1515, 1465, 1405, 1250, 1079, 809; \textsuperscript{1}H NMR (400 MHz, CD\textsubscript{2}Cl\textsubscript{2}) δ\textsubscript{H} 7.09 (dd, J = 14.4, 8.2 Hz, 4H, H\textsubscript{7,8}), 3.99-3.89 (m, 1H, H\textsubscript{5}), 3.77-3.72 (m, 1H, H\textsubscript{3}), 2.85 (dd, J = 13.0, 3.8 Hz, 1H, H\textsubscript{2}), 2.69-2.59 (m, 1H, H\textsubscript{6}), 2.29-2.21 (m, 4H, H\textsubscript{12,14}), 1.97-1.87 (m, 1H, H\textsubscript{10}), 1.85-1.71 (m, 5H, H\textsubscript{4,10,11,12}), 1.68-1.63 (m, 1H, H\textsubscript{3}), 1.39-1.28 (m, 1H, H\textsubscript{11}); \textsuperscript{13}C NMR (100 MHz, CD\textsubscript{2}Cl\textsubscript{2}) δ\textsubscript{c} 216.5 (C\textsubscript{13}), 138.7 (C\textsubscript{9}), 136.7 (C\textsubscript{8}), 129.6 (2C, C\textsubscript{9}), 129.3 (2C, C\textsubscript{7}), 80.3 (C\textsubscript{1}), 63.3 (C\textsubscript{5}), 48.6 (C\textsubscript{2}), 39.4 (C\textsubscript{12}), 37.2 (C\textsubscript{3}), 26.9 (C\textsubscript{10}), 26.2 (C\textsubscript{4}), 21.1 (C\textsubscript{14}), 18.3 (C\textsubscript{11}); mp 48-50 ºC; m/z HRMS (NSI) found [M + H]\textsuperscript{+} 245.1538 C\textsubscript{16}H\textsubscript{21}O\textsubscript{2} requires 245.1536. [α]\textsubscript{D}\textsuperscript{20} = -140.6 (c = 1.00, CHCl\textsubscript{3}). d.e. >99%, according to NMR; e.e. 82%, from chiral HPLC. Chiralpak IC. Hexane / isopropanol 99.7:0.3; 1.0 mL/min. t\textsubscript{R} 11.0 minutes (major), 12.0 minutes (minor).
According to general procedure F, to a solution of 90 (38.6 mg, 0.25 mmol) in anhydrous dichloromethane (6 mL) at 0 °C was added 2,6-di-tert-butylpyridine (0.112 mL, 0.50 mmol), copper(II) (±)-2,2'-Isopropylidenebis[(4R)-4-phenyl-2-oxazoline] triflate solution (0.1 M in dichloromethane, 0.25 mL, 0.025 mmol), and (4-isobutylphenyl)(mesityl)iodonium hexafluorophosphate (186, 241.1 mg, 0.50 mmol) as a solution in dichloromethane (2 mL), with stirring at 10 °C for 8 h. Purification by column chromatography (0-4% diethyl ether / hexane) afforded the desired compound as a pale yellow oil (70.9 mg, 0.25 mmol, 99%). Racemic 190 were prepared according to general procedure E: 90 (38.6 mg, 0.25 mmol), 2,6-di-tert-butylpyridine (0.112 mL, 0.5 mmol), (4-isobutylphenyl)(mesityl)iodonium trifluoromethanesulfonate (264.2 mg, 0.5 mmol) and CuCl (2.5 mg, 0.025 mmol) were reacted in anhydrous dichloromethane (4 mL) to obtain the desired compound as a yellow oil, and as racemic mixtures (5.7 mg, 0.02 mmol, 8%).

Rf 0.6 (20% diethyl ether / hexane); IR (thin film) νmax/cm⁻¹ 2969, 1733 (s, C=O), 1513, 1465, 1405, 1383, 1250, 1154, 1075, 1016, 948; ¹H NMR (400 MHz, CD₂Cl₂) δH 7.12 (d, J = 8.1 Hz, 2H, H₂), 7.04 (d, J = 8.1 Hz, 2H, H₆), 4.01-3.91 (m, 1H, H₃), 3.76-3.72 (m, 1H, H₃), 2.85 (dd, J = 13.0, 3.8 Hz, 1H, H₂), 2.71-2.57 (m, 1H, H₃), 2.43 (d, J = 7.2 Hz, 2H, H₁₄), 2.28-2.19 (m, 1H, H₁₂), 2.00-1.91 (m, 1H, H₁₀), 1.86-1.72 (m, 6H, H₄,10,11,12,15), 1.70-1.63 (1H, m, H₃), 1.35-1.25 (m, 1H, H₁₁), 0.88 (d, J = 6.6 Hz, 6H, H₁₆); ¹³C NMR (100 MHz, CD₂Cl₂) δC 216.7 (C₁₃), 140.6 (C₉), 138.9 (C₆), 129.4₃ (2C, C₈), 129.4 (2C, C₇), 80.3 (C₁), 63.4 (C₅), 48.8 (C₂), 45.3 (C₁₄), 39.5 (C₁₂), 37.3 (C₃), 30.6 (C₁₅), 26.9 (C₁₀), 26.2 (C₄), 22.5₂ (C₁₆, rotamer), 22.4₀ (C₁₆, rotamer), 18.3 (C₁₁); m/z HRMS (NSI) found [M + H]+ 287.2009 C₁₉H₂₇O₂ requires 287.2011. [α]²⁰D −111.3 (c = 1.00, CHCl₃). d.e. >99%, according to NMR; e.e. 80%, from chiral HPLC. Chiralpak AD-H. Hexane / isopropanol 99.8:0.2; 0.5 mL/min. tR 16.4 minutes (major), 17.3 minutes (minor).
According to general procedure F, to a solution of 90 (38.6 mg, 0.25 mmol) in anhydrous dichloromethane (6 mL) at 0 °C was added 2,6-di-tert-butylpyridine (0.112 mL, 0.50 mmol), copper(II) (+)-2,2’-Isopropylidenebis[(4R)-4-phenyl-2-oxazoline] triflate solution (0.1 M in dichloromethane, 0.25 mL, 0.025 mmol), and bis(4-chlorophenyl)iodonium hexafluorophosphate (188, 247.5 mg, 0.375 mmol) as a suspension in dichloromethane (2 mL). The mixture was stirred at 20 °C for 5 h. Purification by column chromatography (0-4% diethyl ether / hexane) afforded the desired compound as a white solid (63.5 mg, 0.24 mmol, 96%). Racemic 191 were prepared according to general procedure E: 90 (38.6 mg, 0.25 mmol), 2,6-di-tert-butylpyridine (0.112 mL, 0.5 mmol), (bis(4-chlorophenyl)iodonium tetrafluoroborate (218.4 mg, 0.5 mmol) and CuCl (2.5 mg, 0.025 mmol) were reacted in anhydrous dichloromethane (4 mL) to obtain the desired compound as a white solid, and as racemic mixtures (18 mg, 0.07 mmol, 28%).

**R**ₐ 0.45 (20% diethyl ether / hexane); IR (thin film) ν max/cm⁻¹ 2971, 1732, 1595, 1492, 1409, 1250, 1154, 1079, 1014, 828; **¹H NMR** (400 MHz, CD₂Cl₂) δH 7.24 (d, J = 8.5 Hz, 2H, H₃), 7.18 (d, J = 8.5 Hz, 2H, H₅), 3.93-3.83 (m, 1H, H₃), 3.77-3.72 (m, 1H, H₅), 2.88 (dd, J = 13.1, 3.9 Hz, 1H, H₂), 2.69-2.58 (m, 1H, H₃), 2.30-2.20 (m, 1H, H₁₂), 1.90-1.71 (m, 6H, H₄,10,11,12), 1.69-1.63 (m, 1H, H₃), 1.47-1.34 (m, 1H, H₁₁); **¹³C NMR** (100 MHz, CD₂Cl₂) δc 216.0 (C₁₃), 140.5 (C₆), 132.7 (C₉), 131.3 (2C, C₇), 128.7 (2C, C₈), 80.1 (C₁), 63.4 (C₅), 48.2 (C₂), 39.3 (C₁₂), 37.0 (C₃), 26.7 (C₁₀), 26.0 (C₄), 18.3 (C₁₁); **mp** 62-64 °C; **m/z HRMS** (NSI) found [M + Na]+ 287.0811 C₁₃H₁₇ClO₂Na requires 287.0815. [α]²⁰ D -135.6 (c = 1.00, CHCl₃). **d.e.** >99%, according to NMR; **e.e.** 81%, from chiral HPLC. Chiralpak IC. Hexane / isopropanol 99.8:0.2; 0.5 mL/min. **t**ᵣ 29.1 minutes (major), 31.4 minutes (minor).
(1S,2'R)-2'- (p-tolyl)-2',3'-dihydrospiro[cyclohexane-1,1'-inden]-2-one (192)

According to general procedure F, to a solution of 169 (50.1 mg, 0.25 mmol) in anhydrous dichloromethane (6 mL) at 0 °C was added 2,6-di-tert-butylpyridine (0.168 mL, 0.75 mmol), copper(II) (+)-2,2'-Isopropylidenebis[(4R)-4-phenyl-2-oxazoline] triflate solution (0.1 M in dichloromethane, 0.25 mL, 0.025 mmol), and mesityl(p-tolyl)iodonium hexafluorophosphate (185, 361.6 mg, 0.75 mmol) as a solution in dichloromethane (2 mL), with stirring for 48 h at 25 °C. Purification by column chromatography (0-4% diethyl ether / hexane) afforded the desired compound as a white solid (70.4 mg, 0.24 mmol, 97%). Racemic compound 192 was synthesised according to general procedure G.

R<sub>t</sub>0.55 (20% diethyl ether / hexane); IR (thin film) ν<sub>max</sub>/cm<sup>-1</sup> 2933, 2861, 1708 (s, C=O), 1514, 1479, 1448, 1338, 1309, 1218, 1125, 749; <sup>1</sup>H NMR (500 MHz, C<sub>6</sub>D<sub>6</sub>) δ<sub>H</sub> 7.55 (d, J = 7.6 Hz, 1H, H<sub>2</sub>), 7.24 (t, J = 7.4 Hz, 1H, H<sub>3</sub>), 7.19-7.15 (m, 1H, H<sub>6</sub>), 7.10 (d, J = 7.4 Hz, 1H, H<sub>1</sub>), 6.95 (d, J = 8.0 Hz, 2H, H<sub>12</sub>), 6.80 (d, J = 8.0 Hz, 2H, H<sub>11</sub>), 3.45 (dd, J = 8.0, 3.2 Hz, 1H, H<sub>2</sub>), 3.27 (dd, J = 16.1, 8.0 Hz, 1H, H<sub>3</sub>), 2.97 (dd, J = 16.1, 3.2 Hz, 1H, H<sub>3</sub>), 2.14-2.09 (m, 1H, H<sub>17</sub>), 1.99 (s, 3H, H<sub>19</sub>), 1.89 (td, J = 13.5, 6.0 Hz, 1H, H<sub>17</sub>), 1.85-1.81 (m, 1H, H<sub>15</sub>), 1.66 (td, J = 12.7, 3.8 Hz, 1H, H<sub>14</sub>), 1.63-1.55 (m, 1H, H<sub>15</sub>), 1.53-1.47 (m, 1H, H<sub>16</sub>), 1.41-1.29 (m, 2H, H<sub>14,15</sub>); <sup>13</sup>C NMR (125 MHz, C<sub>6</sub>D<sub>6</sub>) δ<sub>C</sub> 208.7 (C<sub>18</sub>), 146.9 (C<sub>9</sub>), 142.5 (C<sub>8</sub>), 140.6 (C<sub>10</sub>), 136.6 (C<sub>13</sub>), 129.3 (2C, C<sub>12</sub>), 128.5 (2C, C<sub>11</sub>), 127.6 (C<sub>6</sub>), 126.9 (C<sub>5</sub>), 126.7 (C<sub>4</sub>), 124.6 (C<sub>7</sub>), 67.8 (C<sub>1</sub>), 53.2 (C<sub>2</sub>), 42.3 (C<sub>17</sub>), 41.5 (C<sub>3</sub>), 40.5 (C<sub>15</sub>), 27.6 (C<sub>16</sub>), 23.1 (C<sub>14</sub>), 21.0 (C<sub>19</sub>); mp 61-62 °C; m/z HRMS (ESI-TOF) found [M + H]<sup>+</sup> 291.1747 C<sub>21</sub>H<sub>23</sub>O requires 291.1749; [α]<sub>d</sub><sup>28</sup> +85.1 (c = 1.00, CHCl<sub>3</sub>); d.e. 99%, according to NMR; d.e. 90%, from chiral HPLC. Chiralpak IA, hexane / isopropanol 99:1, 1.0 mL/min, oven temperature: 30 °C, t<sub>r</sub> 9.0 minutes (minor), 13.1 minutes (major).
(1S,2′R)-2′-(4-isobutylphenyl)-2′,3′-dihydrospiro[cyclohexane-1,1′-inden]-2-one (193)

According to general procedure F, to a solution of 169 (50.1 mg, 0.25 mmol) in anhydrous dichloromethane (6 mL) at 0 °C was added 2,6-di-tert-butylpyridine (0.168 mL, 0.75 mmol), copper(II) (+)-2,2′-Isopropylidenebis[(4R)-4-phenyl-2-oxazoline] triflate solution (0.1 M in dichloromethane, 0.25 mL, 0.025 mmol), and mesityl(p-isobutylphenyl)iodonium hexafluorophosphate (186, 393.2 mg, 0.75 mmol) as a solution in dichloromethane (2 mL), with stirring for 48 h at 25 °C. Purification by column chromatography (0-4% diethyl ether / hexane) afforded the desired compound as a colourless viscous oil (82.3 mg, 0.25 mmol, 99%). Racemic compound 193 was synthesised according to general procedure G.

Rf 0.60 (20% diethyl ether / hexane); IR (thin film) v max/cm⁻¹ 2930, 2866, 1709 (s, C=O), 1512, 1480, 1458, 1422, 1311, 1125, 751; ¹H NMR (500 MHz, C₆D₆) δ H 7.55 (d, J = 7.1 Hz, 1H, H₄), 7.24 (t, J = 7.5 Hz, 1H, H₅), 7.19-7.17 (m, 1H, H₆), 7.10 (d, J = 7.5 Hz, 1H, H₇), 7.01 (d, J = 8.1 Hz, 2H, H₁₂), 6.83 (d, J = 8.1 Hz, 2H, H₁₁), 3.47 (dd, J = 8.2, 3.3 Hz, 1H, H₂), 3.27 (dd, J = 16.0, 8.2 Hz, 1H, H₃), 2.99 (dd, J = 16.0, 3.3 Hz, 1H, H₄), 2.24 (d, J = 7.3 Hz, 2H, H₁₉), 2.14-2.08 (m, 1H, H₁₇), 1.92-1.82 (m, 2H, H₁₅,₁₇), 1.71-1.62 (m, 2H, H₁₄,₁₅), 1.61-1.47 (m, 2H, H₁₄,₁₆), 1.40-1.30 (m, 2H, H₁₆,₂₀), 0.78 (d, J = 5.8 Hz, 3H, H₂₁), 0.76 (d, J = 5.8 Hz, 3H, H₂₁); ¹³C NMR (125 MHz, C₆D₆) δ C 208.7 (C₁₈), 146.9 (C₉), 142.5 (C₃), 140.9 (C₁₀), 140.4 (C₁₃), 129.4 (2C, C₁₂), 128.4 (2C, C₁₁), 127.6 (C₆), 126.9 (C₅), 126.7 (C₄), 124.6 (C₇), 67.8 (C₁), 53.3 (C₂), 45.2 (C₁₀), 42.2 (C₁₇), 41.6 (C₃), 40.5 (C₁₃), 30.3 (C₂₀), 27.6 (C₁₆), 23.1 (C₁₄), 22.4 (2C, C₂¹); m/z HRMS (ESI-TOF) found [M + H]⁺ 333.2216 C₂₄H₂₉O requires 333.2218; [α]D 29 +71.4 (c = 1.00, CHCl₃); d.e. 99%, according to NMR; e.e. 91%, from chiral HPLC. Chiralpak IA, hexane / isopropanol 99:1, 1.0 mL/min, oven temperature: 30 °C, tR 7.1 minutes (minor), 16.5 minutes (major).
(1S,2'R)-2'-(4-chlorophenyl)-2',3'-dihydrospiro[cyclohexane-1,1'-inden]-2-one (194)

According to general procedure F, to a solution of 169 (500.7 mg, 2.5 mmol) in anhydrous dichloromethane (60 mL) at 0 °C was added 2,6-di-tert-butylpyridine (1.12 mL, 5.0 mmol), copper(II) (+)-2,2'-Isopropylidenedibis[(4R)-4-phenyl-2-oxazoline] triflate solution (0.1 M in dichloromethane, 2.5 mL, 0.25 mmol), and bis(4-chlorophenyl)iodonium hexafluorophosphate (188, 2.47 g, 5.0 mmol) as a solution in dichloromethane (20 mL). The mixture was stirred for 48 h at 25 °C. Purification by column chromatography (0-4% diethyl ether / hexane) afforded the desired compound as a white solid (769.0 mg, 0.25 mmol, 99%). Slow cooling from hot saturated solution of 194 in hexane grew single crystals. X-Ray crystal structure is deposited in the Cambridge Crystallographic Data Centre CCDC 1539189. Racemic compound 194 was synthesised according to general procedure G.

Elemental analysis (%) calcd for C_{20}H_{19}ClO: C, 77.29; H, 6.16. Found: C, 77.29; H, 6.17; Rr 0.45 (20% diethyl ether / hexane); IR (thin film) v_{max}/cm\(^{-1}\) 2934, 1706 (s, C=O), 1544, 1491, 1447, 1411, 1220, 1125, 1080, 1015, 758; \(^{1}H\) NMR (500 MHz, C\(_{6}\)D\(_{6}\)) \(\delta_{H}\) 7.49 (d, \(J = 7.5\ Hz, 1H, H_{4}\)), 7.21 (t, \(J = 7.4\ Hz, 1H, H_{3}\)), 7.17-7.13 (m, 1H, H\(_{6}\)), 7.07 (d, \(J = 7.4\ Hz, 1H, H_{7}\)), 6.91-6.88 (m, 2H, H\(_{11}\)), 6.76-6.73 (m, 2H, H\(_{12}\)), 3.29 (dd, \(J = 8.2, 2.8\ Hz, 1H, H_{2}\)), 3.18 (dd, \(J = 16.0, 8.2\ Hz, 1H, H_{3}\)), 2.78 (dd, \(J = 16.0, 2.8\ Hz, 1H, H_{3}\)), 2.09-2.04 (m, 1H, H\(_{17}\)), 1.79-1.66 (m, 2H, H\(_{15,17}\)), 1.63-1.56 (m, 1H, H\(_{15}\)), 1.53-1.42 (m, 2H, H\(_{14,16}\)), 1.40-1.28 (m, 2H, H\(_{14,16}\)); \(^{13}C\) NMR (125 MHz, C\(_{6}\)D\(_{6}\)) \(\delta_{C}\) 208.4 (C\(_{18}\)), 146.5 (C\(_{9}\)), 142.0 (C\(_{8}\)), 141.9 (C\(_{10}\)), 132.9 (C\(_{13}\)), 130.0 (2C, C\(_{12}\)), 128.7 (2C, C\(_{11}\)), 127.7 (C\(_{6}\)), 127.0 (C\(_{5}\)), 126.7 (C\(_{4}\)), 124.7 (C\(_{7}\)), 67.7 (C\(_{1}\)), 52.5 (C\(_{2}\)), 42.2 (C\(_{17}\)), 41.2 (C\(_{3}\)), 40.1 (C\(_{15}\)), 27.5 (C\(_{16}\)), 23.1 (C\(_{14}\)); mp 115-116 °C; m/z HRMS (ESI-TOF) found [M + H]\(^{+}\) 311.1202 C\(_{20}\)H\(_{20}\)ClO requires 311.1203; [\(\alpha\)]\(^{27}\)D +140.9 (c = 1.00, CHCl\(_{3}\); d.e. 99%, according to NMR; e.e. 94%, from chiral HPLC. Chiralpak IA, hexane / isopropanol 99:1, 1.0 mL/min, oven temperature: 30 °C, t\(_{R}\) 10.1 minutes (minor), 13.1 minutes (major).
(1S,2'R)-2'-(4-bromophenyl)-2',3'-dihydrospiro[cyclohexane-1,1'-inden]-2-one (200)

According to general procedure F, to a solution of 169 (50.1 mg, 0.25 mmol) in anhydrous dichloromethane (6 mL) at 0 °C was added 2,6-di-tert-butylpyridine (0.168 mL, 0.75 mmol), copper(II) (+)-2,2'-Isopropylidenebis[(4R)-4-phenyl-2-oxazoline] triflate solution (0.1 M in dichloromethane, 0.25 mL, 0.025 mmol), and mesityl(4-bromophenyl)iodonium hexafluorophosphate (195, 410.3 mg, 0.75 mmol) as a solution in dichloromethane (2 mL), with stirring for 48 h at 35 °C. Purification by column chromatography (1-5% diethyl ether / hexane) afforded the desired compound as a white solid (80.8 mg, 0.23 mmol, 91%). Racemic compound 200 was synthesised according to general procedure G.

Rf 0.45 (20% diethyl ether / hexane); IR (thin film) νmax/cm⁻¹ 2935, 2862, 1707 (s, C=O), 1482, 1408, 1220, 1126, 1073, 1011, 772; ¹H NMR (500 MHz, C₆D₆) δH 7.50 (d, J = 7.6 Hz, 1H, H₄), 7.22 (t, J = 7.5 Hz, 1H, H₃), 7.15-7.13 (m, 1H, H₆), 7.07-7.03 (m, 3H, H7,11), 6.69-6.65 (m, 2H, H12), 3.24 (dd, J = 8.1, 2.8 Hz, 1H, H2), 3.16 (dd, J = 15.8, 8.1 Hz, 1H, H3), 2.77 (dd, J = 15.8, 2.8 Hz, 1H, H3), 2.09-2.03 (m, 1H, H17), 1.77-1.64 (m, 2H, H15,17), 1.62-1.54 (m, 1H, H15), 1.49-1.38 (m, 2H, H14,16), 1.36-1.25 (m, 2H, H14,16); ¹³C NMR (125 MHz, C₆D₆) δC 208.3 (C18), 146.5 (C9), 142.4 (C3), 142.0 (C10), 131.7 (2C, C11), 130.3 (2C, C12), 127.7 (C8), 127.0 (C5), 126.7 (C4), 124.7 (C7), 121.2 (C13), 67.6 (C1), 52.6 (C2), 42.2 (C17), 41.2 (C3), 40.1 (C15), 27.4 (C16), 23.1 (C14); mp 95-96 °C; m/z HRMS (NSI) found [M + Na]+ 377.0512 C₂₀H₁₉⁷⁹BrONa requires 377.0511; [α]₂⁵D +103.8 (c = 1.00, CHCl₃); d.e. >99%, according to NMR; e.e. 90%, from chiral HPLC. Chiralpak IA, hexane / isopropanol 99:1, 1.0 mL/min, oven temperature: 30 °C, tR 10.2 minutes (minor), 13.5 minutes (major).
According to general procedure F, to a solution of 169 (50.1 mg, 0.25 mmol) in anhydrous dichloromethane (6 mL) at 0 °C was added 2,6-di-tert-butylpyridine (0.112 mL, 0.50 mmol), copper(II) (+)-2,2′-Isopropylidenebis[(4R)-4-phenyl-2-oxazoline] triflate solution (0.1 M in dichloromethane, 0.25 mL, 0.025 mmol), and bis(4-fluorophenyl)iodonium hexafluorophosphate (196, 231.0 mg, 0.50 mmol) as a solution in dichloromethane (2 mL), with stirring for 36 h at 30 °C. Purification by column chromatography (1-5% diethyl ether / hexane) afforded the desired compound as a white solid (72.9 mg, 0.25 mmol, 99%). Racemic compound 201 was synthesised according to general procedure G.

Rf 0.5 (20% diethyl ether / hexane); IR (thin film) νmax/cm⁻¹ 2935, 2863, 1707 (s, C=O), 1603, 1508, 1479, 1457, 1449, 1338, 1223, 1161, 1125, 751; ¹H NMR (500 MHz, C₆D₆) δH 7.51 (d, J = 7.4 Hz, 1H, H₄), 7.23 (t, J = 7.5 Hz, 1H, H₅), 7.18-7.14 (m, 1H, H₆), 7.08 (d, J = 7.4 Hz, 1H, Hₗ), 6.81-6.76 (m, 2H, H₁₁), 6.62-6.56 (m, 2H, H₁₂), 3.31 (dd, J = 8.1, 3.0 Hz, 1H, H₂), 3.19 (dd, J = 16.1, 8.1 Hz, 1H, H₃), 2.81 (dd, J = 16.1, 3.0 Hz, 1H, H₄), 2.11-2.06 (m, 1H, H₁₇), 1.79-1.68 (m, 2H, H₁₅,₁₆), 1.64-1.56 (m, 1H, H₁₃), 1.53-1.41 (m, 2H, H₁₄,₁₆), 1.38-1.27 (m, 2H, H₁₄,₁₆); ¹³C NMR (125 MHz, C₆D₆) δC 208.4 (C₁₈), 162.3 (d, 1J_C-F = 242.0 Hz, 1C, C₁₃), 146.5 (C₉), 142.1 (C₈), 139.1 (d, 4J_C-F 3.2 Hz, 1C, C₁₀), 130.1 (d, 3J_C-F = 7.8 Hz, 2C, C₁₁), 127.7 (C₆), 127.6 (C₅), 126.7 (C₄), 124.7 (C₇), 115.3 (d, 2J_C-F = 21.1 Hz, 2C, C₁₂), 67.7 (C₁), 52.4 (C₂), 42.2 (C₁₇), 41.2 (C₃), 40.3 (C₁₅), 27.5 (C₁₆), 23.1 (C₁₄); ¹⁹F NMR (376.5 MHz, C₆D₆) δF −115.4 (Ph-F); mp 85-86 °C; m/z HRMS (ESI-TOF) found [M + H]⁺ 295.1498 C₂₀H₂₀FO requires 295.1498; [α]D²⁵ +113.8 (c = 1.00, CHCl₃); d.e. >99%, according to NMR; e.e. 92%, from chiral HPLC. Chiralpak IA, hexane / isopropanol 99:1, 1.0 mL/min, oven temperature: 30 °C, tR 9.2 minutes (minor), 11.4 minutes (major).
ethyl 4-((1S,2'R)-2-oxo-2',3'-dihydrospiro[cyclohexane-1,1'-inden]-2'-yl)benzoate (202)

According to general procedure F, to a solution of 169 (50.1 mg, 0.25 mmol) in anhydrous dichloromethane (6 mL) at 0 °C was added 2,6-di-tert-butylpyridine (0.168 mL, 0.75 mmol), copper(II) (+)-2,2'-Isopropylidenediethane[(4R)-4-phenyl-2-oxazoline] trflate solution (0.1 M in dichloromethane, 0.25 mL, 0.025 mmol), and mesityl[(ethoxycarbonyl)phenyl]iodonium hexafluorophosphate (197, 405.2 mg, 0.75 mmol) as a solution in dichloromethane (2 mL), with stirring for 48 h at 35 °C. Purification by column chromatography (1-5% diethyl ether / hexane) afforded the desired compound as a white solid (83.6 mg, 0.24 mmol, 96%). Racemic compound 202 was synthesised according to general procedure G.

Rf 0.30 (20% diethyl ether / hexane); IR (thin film) νmax/cm⁻¹ 2935, 2864, 1708 (s, C=O), 1610 (m, C=O), 1573, 1478, 1447, 1420, 1367, 1311, 1272, 1183, 1124, 1103, 751; ¹H NMR (500 MHz, C₆D₆) δH 7.92 (dt, J = 8.4, 1.8 Hz, 2H, H₁₂), 7.51 (d, J = 7.5 Hz, 1H, H₄), 7.23 (t, J = 7.5 Hz, 1H, H₅), 7.18-7.14 (m, 1H, H₆). 7.07 (d, J = 7.5 Hz, 1H, H₇), 6.96 (dt, J = 8.4, 1.8 Hz, 2H, H₁₁), 4.06 (dq, J = 7.1, 1.3 Hz, 2H, H₂₀), 3.36 (dd, J = 8.1, 3.0 Hz, 1H, H₂), 3.19 (dd, J = 16.1, 8.1 Hz, 1H, H₃), 2.83 (dd, J = 16.1, 3.0 Hz, 1H, H₃), 2.09-2.04 (m, 1H, Hₙ), 1.80-1.68 (m, 2H, H₁₅₋₁₇), 1.64-1.57 (m, 1H, H₁₅), 1.53-1.42 (m, 2H, H₁₄₋₁₆), 1.39-1.29 (m, 2H, H₁₄₋₁₆), 0.96 (t, J = 7.1 Hz, 3H, H₂₁); ¹³C NMR (125 MHz, C₆D₆) δC 208.3 (C₈), 166.0 (C₁₀), 148.4 (C₁₃), 146.5 (C₉), 142.0 (C₈), 130.0 (C₂, C₁₂), 129.9 (C₂, C₁₁), 128.6 (C₁₀), 127.8 (C₆), 127.0 (C₃), 126.7 (C₄), 124.7 (C₇), 67.9 (C₁), 60.7 (C₂₀), 53.1 (C₂), 42.2 (C₁₇), 41.4 (C₃), 40.0 (C₁₅), 27.5 (C₁₆), 23.1 (C₁₄), 14.2 (C₂₁); mp 90-91 °C; m/z HRMS (NSI) found [M + Na]⁺ 371.1611 C₂₃H₂₄O₃Na requires 371.1609; [α]D²⁵ +94.8 (c = 1.00, CHCl₃); d.e. >99%, according to NMR; e.e. 92%, from chiral HPLC. Chiralpak IA, hexane / isopropanol 95:5, 1.0 mL/min, oven temperature: 30 °C, tᵣ 9.3 minutes (minor), 14.2 minutes (major).
(1S,2'R)-2'-(4-(trifluoromethyl)phenyl)-2',3'-dihydrospiro[cyclohexane-1,1'-inden]-2-one (203)

According to general procedure F, to a solution of 169 (50.1 mg, 0.25 mmol) in anhydrous dichloromethane (6 mL) at 0 °C was added 2,6-di-tert-butylpyridine (0.168 mL, 0.75 mmol), copper(II) (+)-2,2'-isopropylidenebis[(4R)-4-phenyl-2-oxazoline] triflate solution (0.1 M in dichloromethane, 0.25 mL, 0.025 mmol), and mesityl(4-trifluoromethyl)phenyl)iodonium hexafluorophosphate (198, 402.1 mg, 0.75 mmol) as a solution in dichloromethane (2 mL), with stirring for 48 h at 35 °C. Purification by column chromatography (1-5% diethyl ether / hexane) afforded the desired compound as a white solid (80.9 mg, 0.24 mmol, 94%). Racemic compound 203 was synthesised according to general procedure G.

Rf 0.40 (20% diethyl ether / hexane); IR (thin film) νmax/cm⁻¹ 2937, 2860, 1708 (s, C=O), 1619, 1479, 1458, 1421, 1323, 1163, 1111, 1067, 1017, 753; ¹H NMR (500 MHz, C₆D₆) δH 7.52 (d, J = 7.5 Hz, 1H, H₄), 7.24 (t, J = 7.5 Hz, 1H, H₅), 7.19-7.15 (m, 1H, H₆), 7.12 (d, J = 8.1 Hz, 2H, H₁₂), 7.07 (d, J = 7.4 Hz, 1H, H₇), 6.84 (d, J = 8.1 Hz, 2H, H₁₁), 3.29 (dd, J = 8.1, 2.8 Hz, 1H, H₂), 3.15 (dd, J = 16.0, 8.1 Hz, 1H, H₃), 2.73 (dd, J = 16.0, 2.8 Hz, 1H, H₃), 2.05-1.99 (m, 1H, H₁₇), 1.74 (ddd, J = 13.9, 6.2, 3.5 Hz, 1H, H₁₇), 1.66-1.53 (m, 2H, H₁₅), 1.49-1.40 (m, 2H, H₁₄,₁₆). ¹³C NMR (125 MHz, C₆D₆) δC 208.1 (C₁₈), 147.4 (C₉), 146.4 (C₁₀), 141.8 (C₈), 129.3 (q, ²J_C−F = 32.5 Hz, 1C, C₁₃), 128.9 (2C, C₁₁), 128.5 (C₆), 127.1 (C₅), 126.7 (C₄), 125.5 (q, ³J_C−F = 3.8 Hz, 2C, C₁₂), 124.9 (q, ¹J_C−F = 272.2 Hz, 1C, C₁₉), 124.7 (C₇), 67.7 (C₁), 52.7 (C₂), 42.1 (C₁₇), 41.2 (C₃), 39.9 (C₁₃), 27.4 (C₁₆), 23.1 (C₁₄); ¹⁹F NMR (376.5 MHz, C₆D₆) δF −62.2 (CF₃); mp 106-107 °C; m/z HRMS (ESI-TOF) found [M + H]+ 345.1470 C₂₁H₂₀F₃O requires 345.1466; [α]D +98.9 (c = 1.00, CHCl₃); d.e. >99%, according to NMR; e.e. 93%, from chiral HPLC. Chiralpak IA, hexane / isopropanol 99:1, 1.0 mL/min, oven temperature: 30 °C, tR 8.2 minutes (minor), 11.2 minutes (major).
(1S,2'R)-2'-(4-methoxyphenyl)-2',3'-dihydrospiro[cyclohexane-1,1'-inden]-2-one (204)

According to general procedure F, to a solution of 169 (50.1 mg, 0.25 mmol) in anhydrous dichloromethane (6 mL) at 0 °C was added 2,6-di-tert-butylpyridine (0.112 mL, 0.50 mmol), copper(II) (+)-2,2'-Isopropylidenebis[(4R)-4-phenyl-2-oxazoline] triflate solution (0.1 M in dichloromethane, 0.25 mL, 0.025 mmol), and bis(4-methoxyphenyl)iodonium hexafluorophosphate (199, 243.1 mg, 0.50 mmol) as a solution in dichloromethane (2 mL), with stirring for 48 h at 25 °C. Purification by column chromatography (1-5% diethyl ether / hexane) afforded the desired compound as a colourless oil (62.0 mg, 0.20 mmol, 81%). Racemic compound 204 was synthesised according to general procedure G.

$R_f$ 0.30 (20% diethyl ether / hexane); IR (thin film) $\nu_{\text{max}}$ cm$^{-1}$ 2925, 2853, 1708 (s, C=O), 1611, 1582, 1511, 1480, 1457, 1248, 1180, 1125, 1092, 1032, 801, 752; $^1$H NMR (500 MHz, CD$_2$Cl$_2$) $\delta$H 7.56 (d, $J = 7.5$ Hz, 1H, H$_6$), 7.25 (t, $J = 7.5$ Hz, 1H, H$_5$), 7.19 (dd, $J = 7.5$, 1.5 Hz, 1H, H$_6$), 7.12 (d, $J = 7.5$ Hz, 1H, H$_7$), 6.95-6.91 (m, 2H, H$_{11}$), 6.58-6.54 (m, 2H, H$_{12}$), 3.43 (dd, $J = 8.1$, 3.2 Hz, 1H, H$_2$), 3.27 (dd, $J = 16.0$, 8.1 Hz, 1H, H$_3$), 3.19 (s, 3H, H$_{19}$), 2.95 (dd, $J = 16.0$, 3.2 Hz, 1H, H$_3$), 2.16-2.10 (m, 1H, H$_{17}$), 1.93-1.81 (m, 2H, H$_{15,17}$), 1.70-1.49 (m, 3H, H$_{14,15,16}$), 1.42-1.34 (m, 2H, H$_{14,16}$); $^{13}$C NMR (125 MHz, CD$_2$Cl$_2$) $\delta$C 208.8 (C$_{18}$), 159.1 (C$_{13}$), 146.9 (C$_6$), 142.5 (C$_8$), 135.4 (C$_{10}$), 129.6 (2C, C$_{11}$), 127.6 (C$_6$), 126.9 (C$_3$), 126.7 (C$_4$), 124.7 (C$_7$), 114.0 (2C, C$_{12}$), 67.7 (C$_1$), 54.6 (C$_{19}$), 52.7 (C$_2$), 42.3 (C$_{17}$), 41.4 (C$_3$), 40.6 (C$_{15}$), 27.6 (C$_{16}$), 23.2 (C$_{14}$); $m/z$ HRMS (NSI) found [M + Na]$^+$ 329.1506 C$_{21}$H$_{22}$O$_2$Na requires 329.1512; $[\alpha]_D^{25}$ +45.2 (c = 1.00, CHCl$_3$); d.e. 99%, according to NMR; e.e. 62%, from chiral HPLC. Chiralpak IA, hexane / isopropanol 98:2, 1.0 mL/min, oven temperature: 30 °C, $t_R$ 10.2 minutes (minor), 14.6 minutes (major).
(1S,2'R)-2'-(3-bromophenyl)-2',3'-dihydrospiro[cyclohexane-1,1'-inden]-2-one (215)

According to general procedure F, to a solution of 169 (50.1 mg, 0.25 mmol) in anhydrous dichloromethane (6 mL) at 0 °C was added 2,6-di-tert-butylpyridine (0.168 mL, 0.75 mmol), copper(II) (+)-2,2'-Isopropylidenebis[(4R)-4-phenyl-2-oxazoline] trflate solution (0.1 M in dichloromethane), 0.25 mL, 0.025 mmol), and mesityl(3-bromophenyl)iodonium hexafluorophosphate (208, 410.3 mg, 0.75 mmol) as a solution in dichloromethane (2 mL), with stirring for 48 h at 35 °C. Purification by column chromatography (1-5% diethyl ether / hexane) afforded the desired compound as a white solid (87.9 mg, 0.25 mmol, 99%). Slow cooling from hot saturated solution of 215 in hexane grew single crystals. X-Ray crystal structure is deposited in the Cambridge Crystallographic Data Centre CCDC 1539190. Racemic compound 215 was synthesised according to general procedure G.

Elemental analysis (％) calcd for C_{20}H_{19}BrO: C, 67.62; H, 5.39. Found: C, 67.60; H, 5.42; Rf 0.45 (20% diethyl ether / hexane); IR (thin film) ν_{max}/cm^{-1} 2936, 2861, 1707 (s, C=O), 1592, 1564, 1475, 1427, 1338, 1217, 1125, 1074, 749; ¹H NMR (500 MHz, C₆D₆) δ_H 7.49 (d, J = 7.4 Hz, 1H, H₆), 7.29 (d, J = 1.8 Hz, 1H, H₁₃), 7.20 (t, J = 7.4 Hz, 1H, H₃), 7.13 (dd, J = 7.4, 1.3 Hz, 1H, H₈), 7.07-7.04 (m, 2H, H₇,₁₁), 6.81 (dt, J = 7.9, 1.2 Hz, 1H, H₁₂), 6.51 (t, J = 7.9 Hz, 1H, H₁₉), 3.22 (dd, J = 8.1, 2.8 Hz, 1H, H₂), 3.13 (dd, J = 15.8, 8.1 Hz, 1H, H₃), 2.77 (dd, J = 15.8, 2.8 Hz, 1H, H₃), 2.07-2.02 (m, 1H, H₁₇), 1.76-1.68 (m, 2H, H₁₅,₁₇), 1.59-1.51 (m, 1H, H₁₅), 1.42-1.38 (m, 2H, H₁₄,₁₆), 1.33-1.25 (m, 2H, H₁₄,₁₆); ¹³C NMR (125 MHz, C₆D₆) δ_C 208.3 (C₁₈), 146.4 (C₉), 145.9 (C₈), 141.9 (C₁₀), 131.9 (C₁₉), 130.5 (C₁₁), 130.5 (C₁₃), 127.7 (C₆), 127.0 (C₅), 126.8 (C₁₂), 126.6 (C₄), 124.7 (C₇), 122.3 (C₂₀), 67.6 (C₁), 52.7 (C₂), 42.2 (C₁₇), 41.2 (C₈), 40.0 (C₁₅), 27.4 (C₁₆), 23.1 (C₁₄); mp 99-100 °C; m/z HRMS (ESI-TOF) found [M + H]^+ 355.0695 C₂₀H₂₀⁷BrO requires 355.0698; [α]^{25}_D +90.0 (c = 1.00, CHCl₃); d.e. >99%, according to NMR; e.e. 90%, from chiral HPLC. Chiralpak IA, hexane / isopropanol 99:1, 1.0 mL/min, oven temperature: 30 °C, t_R 9.1 minutes (minor), 11.9 minutes (major).
(1S,2'R)-2'-(3-fluorophenyl)-2',3'-dihydrospiro[cyclohexane-1,1'-inden]-2-one (216)

According to general procedure F, to a solution of 169 (50.1 mg, 0.25 mmol) in anhydrous dichloromethane (6 mL) at 0 °C was added 2,6-di-tert-butylpyridine (0.168 mL, 0.75 mmol), copper(II) (+)-2,2'-isopropylidenebis([4R]-4-phenyl-2-oxazoline) trflate solution (0.1 M in dichloromethane, 0.25 mL, 0.025 mmol), and mesityl(3-fluorophenyl)iodonium hexafluorophosphate (209, 364.6 mg, 0.75 mmol) as a solution in dichloromethane (2 mL), with stirring for 48 h at 35 °C. Purification by column chromatography (1-5% diethyl ether / hexane) afforded the desired compound as a white solid (73.5 mg, 0.25 mmol, 99%). Racemic compound 216 was synthesised according to general procedure G.

Rf 0.5 (20% diethyl ether / hexane); IR (thin film) ν max/cm⁻¹ 2933, 2864, 1706 (s, C=O), 1616, 1586, 1485, 1450, 1339, 1310, 1270, 1248, 1126, 753; ¹H NMR (500 MHz, C₆D₆) δ H 7.50 (d, J = 7.5 Hz, 1H, H₄), 7.20 (t, J = 7.5 Hz, 1H, H₃), 7.16-7.11 (m, 1H, H₅), 7.05 (d, J = 7.4 Hz, 1H, H₇), 6.82-6.79 (m, 1H, H₂), 6.70-6.66 (m, 2H, H₁₁,₁₃), 6.64-6.58 (m, 1H, H₁₉), 3.30 (dd, J = 8.1, 3.0 Hz, 1H, H₂), 3.16 (dd, J = 16.0, 8.1 Hz, 1H, H₃), 2.82 (dd, J = 16.0, 3.0 Hz, 1H, H₅), 2.10-2.04 (m, 1H, H₁₇), 1.80-1.72 (m, 2H, H₁₅,₁₇), 1.62-1.55 (m, 1H, H₁₅), 1.50-1.40 (m, 2H, H₁₄,₁₆), 1.36-1.29 (m, 2H, H₁₄,₁₆); ¹³C NMR (125 MHz, C₆D₆) δ C 208.3 (C₁₈), 162.9 (d, ³JC=F = 245.4 Hz, 1C, C₂₀), 146.4 (C₉), 146.1 (d, ³JC=F = 6.9 Hz, 1C, C₁₀), 141.9 (C₈), 130.3 (d, ³JC=F = 8.2 Hz, 1C, C₁₂), 127.7 (C₆), 127.0 (C₅), 126.6 (C₄), 124.7 (C₇), 124.0 (d, ⁴JC=F = 2.9 Hz, 1C, C₁₁), 115.7 (d, ³JC=F = 21.5 Hz, 1C, C₁₉), 114.0 (d, ³JC=F = 20.7 Hz, 1C, C₁₃), 67.7 (C₁), 52.95 (d, ⁴JC=F = 2.5 Hz, 1C, C₂), 42.2 (C₁₇), 41.1 (C₃), 40.0 (C₁₅), 27.5 (C₁₆), 23.1 (C₁₄); ¹⁹F NMR (376.5 MHz, C₆D₆) δ F = -112.9 (Ph-F); mp 102-103 °C; m/z HRMS (NSI) found [M + Na]⁺ 317.1310 C₂₀H₁₉FONa requires 317.1312; [α]D ³₅ +109.8 (c = 1.00, CHCl₃); d.e. >99%, according to NMR; e.e. 92%, from chiral HPLC. Chiralpak IA, hexane / isopropanol 99:1, 1.0 mL/min, oven temperature: 30 °C, tₚ 9.0 minutes (minor), 11.0 minutes (major).
ethyl 3-((1S,2'R)-2-oxo-2',3'-dihydrospiro[cyclohexane-1,1'-inden]-2'-yl)benzoate (217)

According to general procedure F, to a solution of 169 (50.1 mg, 0.25 mmol) in anhydrous dichloromethane (6 mL) at 0 °C was added 2,6-di-tert-butylpyridine (0.168 mL, 0.75 mmol), copper(II) (+)-2,2'-Isopropylidenebis[(4R)-4-phenyl-2-oxazoline] triflate solution (0.1 M in dichloromethane, 0.25 mL, 0.025 mmol), and mesityl(3-ethoxycarbonyl)phenyl)iodonium hexafluorophosphate (210, 405.2 mg, 0.75 mmol) as a solution in dichloromethane (2 mL), with stirring for 48 h at 30 °C. Purification by column chromatography (1-5% diethyl ether / hexane) afforded the desired compound as a white solid (86.2 mg, 0.25 mmol, 99%). Racemic compound 217 was synthesised according to general procedure G.

Rf 0.30 (20% diethyl ether / hexane); IR (thin film) νmax/cm⁻¹: 2937, 2865, 1711 (s, C=O), 1605 (m, C=O), 1585, 1478, 1445, 1367, 1281, 1195, 1125, 1108, 1085, 1025, 755; ¹H NMR (500 MHz, C₆D₆) δH 8.14 (t, J = 1.7 Hz, 1H, H₁₉), 7.91 (dt, J = 7.8, 1.4 Hz, 1H, H₁₃), 7.51 (d, J = 7.4 Hz, 1H, H₆), 7.22 (t, J = 7.4 Hz, 1H, H₃), 7.17-7.15 (m, 1H, H₆), 7.14-7.11 (m, 1H, H₁₁), 7.07 (d, J = 7.4 Hz, 1H, H₇), 6.80 (t, J = 7.8 Hz, 1H, H₁₂), 4.17-4.05 (m, 2H, H₂₂), 3.45 (dd, J = 8.1, 2.8 Hz, 1H, H₂), 3.21 (dd, J = 16.1, 8.1 Hz, 1H, H₃), 2.85 (dd, J = 16.1, 2.8 Hz, 1H, H₅), 2.08-2.02 (m, 1H, H₁₇), 1.83-1.74 (m, 2H, H₁₅,₁₇), 1.61-1.54 (m, 1H, H₁₅), 1.50-1.38 (m, 2H, H₁₄,₁₆), 1.34-1.26 (m, 2H, H₁₄,₁₆), 1.00 (t, J = 7.1 Hz, 3H, H₂₃); ¹³C NMR (125 MHz, C₆D₆) δc 208.5 (C₈), 166.3 (C₂₁), 146.6 (C₉), 143.9 (C₈), 142.1 (C₁₀), 132.4 (C₁₁), 130.9 (C₂₀), 130.2 (C₁₉), 129.1 (C₁₂), 128.5 (C₁₃), 127.7 (C₆), 127.0 (C₅), 126.7 (C₄), 124.7 (C₇), 67.7 (C₁), 60.9 (C₂₂), 52.9 (C₂), 42.3 (C₁₇), 41.2 (C₅), 40.1 (C₁₅), 27.5 (C₁₆), 23.1 (C₁₄), 14.3 (C₂₃); m.p 95-96 °C; m/z HRMS (NSI) found [M + Na]⁺ 371.1608 C₂₃H₂₄O₃Na requires 371.1618; [α]D +85.1 (c = 1.00, CHCl₃); d.e. 99%, according to NMR; d.e. 92%, from chiral HPLC. Chiralpak IA, hexane / isopropanol 95:5, 1.0 mL/min, oven temperature: 30 °C, tR 7.3 minutes (minor), 9.0 minutes (major).
(1S,2'R)-2’-(3-(trifluoromethyl)phenyl)-2',3'-dihydrospiro[cyclohexane-1,1'-inden]-2-one (218)

According to general procedure F, to a solution of 169 (50.1 mg, 0.25 mmol) in anhydrous dichloromethane (6 mL) at 0 °C was added 2,6-di-tert-butylpyridine (0.168 mL, 0.75 mmol), copper(II) (+)-2,2’-Isopropylidenebis[(4R)-4-phenyl-2-oxazoline] triflate solution (0.1 M in dichloromethane, 0.25 mL, 0.025 mmol), and mesityl(3-trifluoromethyl)phenyl]iodonium hexafluorophosphate (211, 402.1 mg, 0.75 mmol) as a solution in dichloromethane (2 mL), with stirring for 48 h at 30 °C. Purification by column chromatography (1-5% diethyl ether / hexane) afforded the desired compound as a white solid (85.2 mg, 0.25 mmol, 99%). Racemic compound 218 was synthesised according to general procedure G.

Rf 0.40 (20% diethyl ether / hexane); IR (thin film) νmax/cm⁻¹ 2932, 1853, 1708 (s, C=O), 1596, 1480, 1451, 1325, 1291, 1262, 1164, 1120, 1098, 1075. 752; ¹H NMR (500 MHz, C₆D₆) δH 7.48 (d, J = 7.4 Hz, 1H, H₃), 7.40 (s, 1H, H₁₉), 7.20 (t, J = 7.4 Hz, 1H, H₅), 7.16-7.14 (m, 1H, H₆), 7.12 (d, J = 7.1 Hz, 1H, H₁₁), 7.06 (d, J = 7.4 Hz, 1H, H₂), 7.02 (d, J = 8.0 Hz, 1H, H₁₃), 6.66 (t, J = 8.0 Hz, 1H, H₁₂), 3.29 (dd, J = 8.1, 2.9 Hz, 1H, H₂₂), 3.14 (dd, J = 16.1, 8.1 Hz, 1H, H₃), 2.74 (dd, J = 16.1, 2.9 Hz, 1H, H₃), 2.05-2.00 (m, 1H, H₁₇), 1.76-1.62 (m, 2H, H₁₅,₁₇), 1.59-1.51 (m, 1H, H₁₅), 1.46-1.36 (m, 2H, H₁₄,₁₆), 1.35-1.24 (m, 2H, H₁₄,₁₆); ¹³C NMR (125 MHz, C₆D₆) δc 208.3 (C₁₈), 146.4 (C₉), 144.4 (C₈), 141.8 (C₁₀), 131.5 (C₁₁), 130.4 (q, ²JCF = 31.9 Hz, 1C, C₂₀), 129.4 (C₁₂), 128.6 (C₆), 127.1 (C₅), 126.6 (C₄), 125.6 (q, ³JCF = 3.8 Hz, 1C, C₁₉), 125.0 (q, ¹JCF = 272.7 Hz, 1C, C₂₁), 124.7 (C₇), 124.0 (q, ³JCF = 3.8 Hz, 1C, C₁₃), 67.6 (C₁), 52.9 (C₂), 42.1 (C₁₇), 41.0 (C₃), 39.9 (C₁₅), 27.3 (C₁₆), 23.1 (C₁₄); ¹⁹F NMR (376.5 MHz, C₆D₆) δF −62.2 (CF₃); mp 109-110 °C; m/z HRMS (ESI-TOF) found [M + H]⁺ 345.1471 C₂₁H₂₀F₃O requires 345.1466; [α]²⁵_D +79.0 (c = 1.00, CHCl₃); d.e. 99%, according to NMR; e.e. 92%, from chiral HPLC. Chiralpak IA, hexane / isopropanol 99:1, 1.0 mL/min, oven temperature: 30 °C, tR 6.9 minutes (minor), 9.0 minutes (major).
(1S,2'R)-2'-(3-(trifluoromethoxy)phenyl)-2',3'-dihydrospirocyclohexane-1,1'-inden]-2-one (219)

According to general procedure F, to a solution of 169 (50.1 mg, 0.25 mmol) in anhydrous dichloromethane (6 mL) at 0 °C was added 2,6-di-tert-butylpyridine (0.168 mL, 0.75 mmol), copper(II) (+)-2,2'-Isopropylidenebis[(4R)-4-phenyl-2-oxazoline] triflate solution (0.1 M in dichloromethane, 0.25 mL, 0.025 mmol), and bis(3-trifluoromethoxy)phenyl)iodonium hexafluorophosphate (212, 445 mg, 0.75 mmol) as a solution in dichloromethane (2 mL), with stirring for 48 h at 40 °C. Purification by column chromatography (1-5% diethyl ether / hexane) afforded the desired compound as a colourless oil (76.6 mg, 0.21 mmol, 85%). Racemic compound 219 was synthesised according to general procedure G.

Rf 0.30 (20% diethyl ether / hexane); IR (thin film) νmax/cm⁻¹ 2931, 2854, 1709 (s, C=O), 1612, 1587, 1487, 1451, 1253, 1215, 1160, 1126, 751; ¹H NMR (500 MHz, C₆D₆) δH 7.47 (d, J = 7.5 Hz, 1H, H₄), 7.20 (t, J = 7.5 Hz, 1H, H₃), 7.13 (dd, J = 7.4, 1.2 Hz, 1H, H₆), 7.05 (d, J = 7.4 Hz, 1H, H₇), 6.95 (s, 1H, H₁₉), 6.79 (dt, J = 7.7, 1.3 Hz, 1H, H₁₃), 6.74-6.71 (m, 1H, H₁₁), 6.63 (t, J = 7.9 Hz, 1H, H₁₂), 3.25 (dd, J = 8.0, 3.1 Hz, 1H, H₂), 3.12 (dd, J = 16.1, 8.0 Hz, 1H, H₃), 2.77 (dd, J = 16.1, 3.1 Hz, 1H, H₃), 2.09-2.03 (m, 1H, H₁₇), 1.76-1.66 (m, 2H, H₁₅,₁₇), 1.60-1.53 (m, 1H, H₁₅), 1.47-1.40 (m, 2H, H₁₄,₁₆), 1.34-1.29 (m, 2H, H₁₄,₁₆); ¹³C NMR (125 MHz, C₆D₆) δC 208.2 (C₁₈), 149.2 (q, ²JCF = 1.7 Hz, 1C, C₂₀), 146.4 (C₉), 145.8 (C₈), 141.9 (C₁₀), 130.2 (C₁₂), 128.7 (C₆), 127.1 (C₅), 126.8 (C₁₃), 126.6 (C₄), 124.7 (C₇), 121.5 (C₁₉), 121.2 (q, ¹JCF = 256.5 Hz, 1C, C₂₁), 119.5 (C₁₁), 67.6 (C₁), 52.9 (C₂), 42.1 (C₁₇), 41.0 (C₃), 39.9 (C₁₅), 27.3 (C₁₆), 23.1 (C₁₄); ¹⁹F NMR (376.5 MHz, C₆D₆) δF = -57.6 (OCF₃); m/z HRMS (NSI) found [M + Na]⁺ 383.1230 C₂₁H₁₉F₃O₂Na requires 383.1229; [α]D²⁵ = +52.8 (c = 1.00, CHCl₃); d.e. >99%, according to NMR; e.e. 90%, from chiral HPLC. Chiralpak IA, hexane / isopropanol 99:1, 1.0 mL/min, oven temperature: 30 °C, tR 6.7 minutes (minor), 8.4 minutes (major).
(1S,2'R)-2'-(3,4-dichlorophenyl)-2',3'-dihydrospiro[cyclohexane-1',1'-inden]-2-one (220)

According to general procedure F, to a solution of 169 (500.7 mg, 2.5 mmol) in anhydrous dichloromethane (60 mL) at 0 °C was added 2,6-di-tert-butyldipyridine (1.68 mL, 7.5 mmol), copper(II) (−)-2,2'-Isopropylidenebis[(4R)-4-phenyl-2-oxazoline] triflate solution (0.1 M in dichloromethane, 2.5 mL, 0.25 mmol), and mesityl(3,4-dichlorophenyl)iodonium hexafluorophosphate (213, 4.03 g, 7.5 mmol) as a solution in dichloromethane (20 mL), with stirring for 48 h at 35 °C. Purification by column chromatography (1-5% diethyl ether / hexane) afforded the desired compound as a white solid (811.4 mg, 2.4 mmol, 94%). Racemic compound 220 was synthesised according to general procedure G.

Rf 0.40 (20% diethyl ether / hexane); IR (thin film) νmax/cm−1 2937, 1708 (s, C=O), 1589, 1558, 1471, 1403, 1338, 1311, 1262, 1216, 1127, 1030, 750; 1H NMR (500 MHz, C6D6) δH 7.45 (d, J = 7.3 Hz, 1H, H4), 7.19 (td, J = 7.3, 1.1 Hz, 1H, H3), 7.15-7.13 (m, 1H, H6), 7.12-7.11 (m, 1H, H12), 7.05 (d, J = 7.3 Hz, 1H, H7), 6.78-6.74 (m, 1H, H19), 6.59 (dd, J = 8.4, 2.1 Hz, 1H, H11), 3.17-3.08 (m, 2H, H2,3), 2.75-2.66 (m, 1H, H3), 2.07-2.01 (m, 1H, H17), 1.73-1.61 (m, 2H, H15,17), 1.57-1.50 (m, 1H, H15), 1.46-1.23 (m, 4H, H14,16); 13C NMR (125 MHz, C6D6) δC 208.2 (C18), 146.2 (C9), 143.7 (C8), 141.6 (C10), 132.2 (C20), 131.3 (C13), 130.8 (C12), 130.76 (C19), 128.6 (C11), 127.7 (C6), 127.2 (C3), 126.6 (C4), 124.7 (C7), 67.5 (C1), 52.2 (C2), 42.1 (C17), 40.9 (C3), 39.8 (C15), 27.3 (C16), 23.0 (C14); mp 117-118 °C; m/z HRMS (ESI-TOF) found [M + H]+ 345.0810 C20H19Cl3O requires 345.0813; [α]D 25 +116.3 (c = 1.00, CHCl3); d.e. >99%, according to NMR; e.e. 99%, from chiral HPLC. Chiralpak IA, hexane / isopropanol 99:1, 1.0 mL/min, oven temperature: 30 °C, tR 9.3 minutes (minor), 11.5 minutes (major).
(1S,2'R)-2'-(naphthalen-2-yl)-2',3'-dihydrospiro[cyclohexane-1,1'-inden]-2-one (221)

According to general procedure F, to a solution of 169 (50.1 mg, 0.25 mmol) in anhydrous dichloromethane (6 mL) at 0 °C was added 2,6-di-tert-butylpyridine (0.168 mL, 0.75 mmol), copper(II) (+)-2,2'-Isopropylidenebis[(4R)-4-phenyl-2-oxazoline] triflate solution (0.1 M in dichloromethane, 0.25 mL, 0.025 mmol), and mesityl(naphthalen-2-yl)phenyl)iodonium hexafluorophosphate (214, 388.7 mg, 0.75 mmol) as a solution in dichloromethane (2 mL), with stirring for 48 h at 35 °C. Purification by column chromatography (1-5% diethyl ether / hexane) afforded the desired compound as a white solid (57.9 mg, 0.18 mmol, 71%). Racemic compound 221 was synthesised according to general procedure G.

Rf 0.65 (20% diethyl ether / hexane); IR (thin film) ν max/cm⁻¹ 2929, 2859, 1705 (s, C=O), 1631, 1600, 1507, 1480, 1457, 1375, 1337, 1261, 1216, 1124, 1080, 1019, 745; ¹H NMR (500 MHz, CD₂Cl₂) δ H 7.76-7.73 (m, 2H, H₂1,24), 7.63-7.60 (m, 2H, H₁2,19), 7.46-7.39 (m, 2H, H₄,23), 7.33-7.29 (m, 4H, H₅,6,7,22), 7.04 (dd, J = 8.5, 1.8 Hz, 1H, H₁₁), 3.98 (dd, J = 8.2, 3.2 Hz, 1H, H₂), 3.63 (dd, J = 16.3, 8.2 Hz, 1H, H₃), 3.12 (dd, J = 16.3, 3.2 Hz, 1H, H₃), 2.25-2.20 (m, 1H, H₁₇), 2.09-1.86 (m, 6H, H₁₄,16,15,17), 1.78-1.70 (m, 1H, H₁₄); ¹³C NMR (125 MHz, CD₂Cl₂) δ C 210.9 (C₁₈), 146.7 (C₉), 142.8 (C₈), 141.2 (C₁₀), 133.5 (C₂₀), 132.9 (C₁₃), 128.3 (C₂₄), 127.9 (C₂₁), 127.87 (C₁₂), 127.7 (C₆), 127.3 (C₅), 126.9 (C₂₂), 126.5 (C₄), 126.4 (C₁₁), 126.2 (C₂₃), 126.0 (C₁₉), 124.8 (C₇), 68.3 (C₁), 42.7 (C₂), 41.9 (C₁₇), 40.5 (C₃), 30.5 (C₁₅), 27.7 (C₁₆), 23.2 (C₁₄); mp 177-178 °C; m/z HRMS (NSI) found [M + Na⁺] 349.1564 C₂₄H₂₃ONa requires 349.1563; [α]²⁵D +67.6 (c = 1.00, CHCl₃); d.e. 99%, according to NMR; e.e. 90%, from chiral HPLC. Chiralpak IA, hexane / isopropanol 98:2, 1.0 mL/min, oven temperature: 30 °C; tR 9.4 minutes (minor), 18.2 minutes (major).
(1S,2'S)-2'-(2-fluorophenyl)-2',3'-dihydrospiro[cyclohexane-1,1'-inden]-2-one (224)

According to general procedure F, to a solution of 169 (50.1 mg, 0.25 mmol) in anhydrous dichloromethane (6 mL) at 0 °C was added 2,6-di-tert-butylpyridine (0.168 mL, 0.75 mmol), copper(II) (+)-2,2'-Isopropylidenebis[(4R)-4-phenyl-2-oxazoline] triflate solution (0.1 M in dichloromethane, 0.25 mL, 0.025 mmol), and bis(2-fluorophenyl)iodonium hexafluorophosphate (222, 346.5 mg, 0.75 mmol) as a solution in dichloromethane (2 mL), with stirring for 48 h at 50 °C. Purification by column chromatography (1-5% diethyl ether / hexane) afforded the desired compound as a white solid (44.9 mg, 0.15 mmol, 61%). Racemic compound 224 was synthesised according to general procedure G.

Rf 0.45 (20% diethyl ether / hexane); IR (thin film) v\textsubscript{max}/cm\textsuperscript{-1} 2930, 1859, 1709 (s, C=O), 1583, 1491, 1455, 1338, 1311, 1292, 1260, 1226, 1126, 1095, 751; \textsuperscript{1}H NMR (500 MHz, C\textsubscript{6}D\textsubscript{6}) δ\textsubscript{H} 7.52 (d, J = 7.7 Hz, 1H, H\textsubscript{a}), 7.22 (t, J = 7.4 Hz, 1H, H\textsubscript{5}), 7.13 (dd, J = 7.4, 1.0 Hz, 1H, H\textsubscript{6}), 7.05 (d, J = 7.4 Hz, 1H, H\textsubscript{7}), 7.00 (td, J = 7.7, 1.6 Hz, 1H, H\textsubscript{13}), 6.81-6.76 (m, 1H, H\textsubscript{19}), 6.73-6.67 (m, 1H, H\textsubscript{11}), 6.49 (td, J = 7.7, 1.1 Hz, 1H, H\textsubscript{12}), 4.23 (dd, J = 8.3, 2.5 Hz, 1H, H\textsubscript{2}), 3.22 (dd, J = 16.2, 8.3 Hz, 1H, H\textsubscript{3}), 2.79 (dd, J = 16.2, 2.5 Hz, 1H, H\textsubscript{1}), 2.14-2.08 (m, 1H, H\textsubscript{17}), 1.96 (td, J = 13.5, 5.8 Hz, 1H, H\textsubscript{17}), 1.84-1.79 (m, 1H, H\textsubscript{15}), 1.75-1.64 (m, 1H, H\textsubscript{13}), 1.60 (dd, J = 13.1, 3.1 Hz, 1H, H\textsubscript{14}), 1.54-1.49 (m, 1H, H\textsubscript{16}), 1.37-1.33 (m, 2H, H\textsubscript{14,16}); \textsuperscript{13}C NMR (125 MHz, C\textsubscript{6}D\textsubscript{6}) δ\textsubscript{c} 208.6 (C\textsubscript{18}), 160.0 (d, \textsuperscript{3}J\textsubscript{C-F} = 242.8 Hz, 1C, C\textsubscript{20}), 146.6 (C\textsubscript{9}), 142.2 (C\textsubscript{8}), 130.5 (d, \textsuperscript{2}J\textsubscript{C-F} = 13.0 Hz, 1C, C\textsubscript{10}), 129.8 (d, \textsuperscript{4}J\textsubscript{C-F} = 3.3 Hz, 1C, C\textsubscript{12}), 128.6 (d, \textsuperscript{3}J\textsubscript{C-F} = 8.5 Hz, 1C, C\textsubscript{11}), 127.7 (C\textsubscript{5}), 127.0 (C\textsubscript{5}), 126.8 (C\textsubscript{4}), 124.9 (d, \textsuperscript{2}J\textsubscript{C-F} = 3.6 Hz, 1C, C\textsubscript{13}), 124.6 (C\textsubscript{7}), 114.9 (d, \textsuperscript{3}J\textsubscript{C-F} = 23.5 Hz, 1C, C\textsubscript{19}), 67.8 (C\textsubscript{1}), 42.4 (d, \textsuperscript{3}J\textsubscript{C-F} = 3.7 Hz, 1C, C\textsubscript{2}), 41.8 (C\textsubscript{17}), 41.6 (C\textsubscript{3}), 39.7 (C\textsubscript{15}), 27.7 (C\textsubscript{16}), 23.2 (C\textsubscript{14}); \textsuperscript{19}F NMR (376.5 MHz, C\textsubscript{6}D\textsubscript{6}) δ\textsubscript{F} -118.9 (Ph-F); mp 105-106 °C; m/z HRMS (ESI-TOF) found [M + H]\textsuperscript{+} 295.1498 C\textsubscript{20}H\textsubscript{20}FO requires 295.1498; [α]\textsuperscript{25}D +71.2 (c = 1.00, CHCl\textsubscript{3}); d.e. >99%, according to NMR; e.e. 86%, from chiral HPLC. Chiralpak IA, hexane / isopropanol 99:1, 1.0 mL/min, oven temperature: 30 °C, tr 7.3 minutes (minor), 9.8 minutes (major).
(5R,6R)-5-(p-tolyl)-1-oxaspiro[5.5]undecan-7-one (205)

According to general procedure F, to a solution of 154 (42.1 mg, 0.25 mmol) in anhydrous dichloromethane (6 mL) at 0 °C was added 2,6-di-tert-butylpyridine (0.112 mL, 0.50 mmol), copper(II) (+)-2,2’-Isopropylidenebis[(4R)-4-phenyl-2-oxazoline] triflate solution (0.1 M in dichloromethane, 0.25 mL, 0.025 mmol), and mesityl(p-tolyl)iodonium hexafluorophosphate (185, 234.1 mg, 0.5 mmol) as a solution in dichloromethane (2 mL), with stirring for 36 h at 25 °C. Purification by column chromatography (0-4% diethyl ether / hexane) afforded the desired compound as a white solid (53.0 mg, 0.21 mmol, 82%). Racemic 205 were prepared according to general procedure E: 154 (84.2 mg, 0.50 mmol), 2,6-di-tert-butylpyridine (0.225 mL, 1.0 mmol), mesityl(p-tolyl)iodonium triflate (466.2 mg, 1.0 mmol) and CuCl (5.0 mg, 0.050 mmol) were reacted in anhydrous dichloromethane (4 mL) to obtain the desired compound as a white solid, and as racemic mixtures (5.2 mg, 0.02 mmol, 4%).

Rf 0.65 (20% diethyl ether / hexane); IR (thin film) ν\text{max}/\text{cm}^{-1} 2933, 2861, 1708 (s, C=O), 1514, 1479, 1448, 1309, 1218, 1125, 749; ¹H NMR (500 MHz, C₆D₆) δₜ 7.53 (d, J = 8.1 Hz, 2H, H₇), 7.04 (d, J = 8.1 Hz, 2H, H₈), 3.65 (ddd, J = 11.8, 4.8, 1.7 Hz, 1H, H₉), 3.22 (td, J = 11.8, 2.6 Hz, 1H, H₅), 2.83-2.72 (m, 1H, H₁₁), 2.56 (dd, J = 12.8, 3.5 Hz, 1H, H₂), 2.45 (td, J = 13.5, 6.2 Hz, 1H, H₁₃), 2.13 (s, 3H, H₁₅), 2.04-1.98 (m, 1H, H₁₃), 1.96-1.86 (m, 2H, H₃,₄), 1.71-1.60 (m, 2H, H₃,₁₁), 1.59-1.50 (m, 1H, H₁₂), 1.47-1.40 (m, 1H, H₁₀), 1.38-1.32 (m, 1H, H₁₂), 1.18-1.10 (m, 1H, H₉), 1.00-0.86 (m, 1H, H₁₀); ¹³C NMR (125 MHz, C₆D₆) δₜ 210.0 (C₁₄), 139.1 (C₉), 136.0 (C₆), 131.2 (2C, C₈), 128.8 (2C, C₇), 81.7 (C₁), 63.8 (C₃), 52.5 (C₂), 40.4 (C₁₃), 39.5 (C₃), 27.1 (C₁₂), 26.8 (C₁₀), 26.6 (C₁₁), 21.0 (C₁₃), 20.2 (C₄); mp 68-69 °C; \text{m/z} HRMS (NSI) found [M + Na]⁺ 281.1511 C₁₇H₂₂O₂Na requires 281.1512; [α]₂⁵_D -17.8 (c = 1.00, CHCl₃); d.e. >99%, according to NMR; e.e. 92%, from chiral HPLC. Chiralpak AD-H, hexane / isopropanol 99.7:0.3, 1.0 mL/min, oven temperature: 30 °C, tₚ 7.2 minutes (minor), 8.9 minutes (major).
(5R,6R)-5-(4-isobutylphenyl)-1-oxaspiro[5.5]undecan-7-one (206)

According to general procedure F, to a solution of 154 (42.1 mg, 0.25 mmol) in anhydrous dichloromethane (6 mL) at 0 °C was added 2,6-di-tert-butylpyridine (0.112 mL, 0.50 mmol), copper(II) (+)-2,2'-Isopropylidenebis[(4R)-4-phenyl-2-oxazoline] triflate solution (0.1 M in dichloromethane, 0.25 mL, 0.025 mmol), and mesityl(p-isobutylphenyl)iodonium hexafluorophosphate (186, 262.1 mg, 0.5 mmol) as a solution in dichloromethane (2 mL), with stirring for 36 h at 25 °C. Purification by column chromatography (0-4% diethyl ether / hexane) afforded the desired compound as a colourless viscous oil (64.6 mg, 0.22 mmol, 86%). Racemic 205 were prepared according to general procedure E: 154 (84.2 mg, 0.50 mmol), 2,6-di-tert-butylpyridine (0.225 mL, 1.0 mmol), mesityl(p-isobutylphenyl)iodonium triflate (528.4 mg, 1.0 mmol) and CuCl (5.0 mg, 0.050 mmol) were reacted in anhydrous dichloromethane (4 mL) to obtain the desired compound as a white solid, and as racemic mixtures (9.0 mg, 0.03 mmol, 6%).

Rt 0.7 (20% diethyl ether / hexane); IR (thin film) v_max/cm⁻¹ 2953, 2929, 2867, 1717 (s, C=O), 1513, 1466, 1449, 1420, 1383, 1312, 1220, 1113, 1089, 1069, 980; ¹H NMR (500 MHz, C₆D₆) δ_H 7.57 (d, J = 8.1 Hz, 2H, H₁), 7.06 (d, J = 8.1 Hz, 2H, H₈), 3.66 (ddd, J = 11.9, 4.8, 1.7 Hz, 1H, H₃), 3.22 (td, J = 11.9, 2.6 Hz, 1H, H₅), 2.84-2.74 (m, 1H, H₁₁), 2.58 (dd, J = 12.8, 3.5 Hz, 1H, H₃), 2.45 (td, J = 13.5, 6.2 Hz, 1H, H₁₃), 2.35 (d, J = 7.2 Hz, 2H, H₁₅), 2.03-1.97 (m, 1H, H₁₁), 1.97-1.87 (m, 2H, H₃,₄), 1.83-1.73 (m, 1H, H₁₆), 1.71-1.61 (m, 2H, H₃,₁₁), 1.60-1.51 (m, 1H, H₁₂), 1.46-1.39 (m, 1H, H₁₀), 1.38-1.32 (m, 1H, H₁₂), 1.18-1.10 (m, 1H, H₄), 1.00-0.88 (m, 1H, H₁₀), 0.84 (d, J = 6.6 Hz, 6H, H₁₇); ¹³C NMR (125 MHz, C₆D₆) δ_C 210.1 (C₁₄), 140.0 (C₅), 139.5 (C₆), 131.1 (2C, C₈), 128.9 (2C, C₇), 81.7 (C₁), 63.8 (C₃), 52.6 (C₂), 45.3 (C₁₃), 40.4 (C₁₃), 39.5 (C₃), 30.4 (C₁₆), 27.2 (C₁₂), 26.7 (C₁₀), 26.6 (C₁₁), 22.6 (C₁₇), 20.2 (C₄); m/z HRMS (NSI) found [M + Na]^+ 323.1976 C₂₇H₂₈O₂Na requires 323.1982; [α]D²₈ = -12.7 (c = 1.00, CHCl₃); d.e. >99%, according to NMR; e.e. 90%, from chiral HPLC. Chiralpak AD-H, hexane / isopropanol 99:1, 1.0 mL/min, oven temperature: 30 °C, t_R 4.5 minutes (minor), 4.8 minutes (major).
(5R,6R)-5-(4-chlorophenyl)-1-oxaspiro[5.5]undecan-7-one (207)

According to general procedure F, to a solution of 154 (42.1 mg, 0.25 mmol) in anhydrous dichloromethane (6 mL) at 0 °C was added 2,6-di-tert-butylpyridine (0.112 mL, 0.50 mmol), copper(II) (+)-2,2'-Isopropylidenebis[(4R)-4-phenyl-2-oxazoline] triflate solution (0.1 M in dichloromethane, 0.25 mL, 0.025 mmol), and bis(4-chlorophenyl)iodonium hexafluorophosphate (188, 247.5 mg, 0.5 mmol) as a solution in dichloromethane (2 mL), with stirring for 36 h at 25 °C. Purification by column chromatography (1-5% diethyl ether / hexane) afforded the desired compound as a white solid (63.4 mg, 0.23 mmol, 91%). Racemic 205 were prepared according to general procedure E: 154 (84.2 mg, 0.50 mmol), 2,6-di-tert-butylpyridine (0.225 mL, 1.0 mmol), bis(4-chlorophenyl)iodonium triflate (499.1 mg, 1.0 mmol) and CuCl (5.0 mg, 0.050 mmol) were reacted in anhydrous dichloromethane (4 mL) to obtain the desired compound as a white solid, and as racemic mixtures (9.8 mg, 0.04 mmol, 7%).

\[ \text{Rr} 0.45 \text{ (20% diethyl ether / hexane); IR (thin film) } \nu_{\text{max}} / \text{cm}^{-1} \ 2930, 2859, 1716 \text{ (s, C=O), } 1595, 1492, 1448, 1411, 1265, 1220, 1108, 1084, 1069, 1049, 1016, 981; ^{1} \text{H NMR (500 MHz, C}_{6}\text{D}_{6}) \ \delta_{11} 7.31 \text{ (d, } J = 8.5 \text{ Hz, 2H, H}_{8}), 7.15 \text{ (d, } J = 8.5 \text{ Hz, 2H, H}_7), 3.63-3.58 \text{ (m, 1H, H}_5), 3.13 \text{ (td, } J = 11.8, 2.5 \text{ Hz, 1H, H}_5), 2.63-2.52 \text{ (m, 1H, H11), 2.46-2.35 \text{ (m, 2H, H2,13), 2.00-1.84 \text{ (m, 2H, H3,13), 1.75 \text{ (ddd, } J = 14.0, 6.4, 3.0 \text{ Hz, 1H, H3), 1.53-1.37 \text{ (m, 4H, H4,10,11,12), 1.32-1.26 \text{ (m, 1H, H12), 1.14-1.09 \text{ (m, 1H, H4), 1.01-0.87 \text{ (m, 1H, H10); } ^{13} \text{C NMR (125 MHz, C}_{6}\text{D}_{6}) \ \delta_{c} 210.2 \text{ (C}_{14}), 140.4 \text{ (C}_{6}), 132.7 \text{ (C}_9), 132.65 \text{ (2C, C}_7), 128.1 \text{ (2C, C}_8), 81.5 \text{ (C}_1), 63.8 \text{ (C}_5), 52.0 \text{ (C}_2), 40.2 \text{ (C}_{13}), 39.4 \text{ (C}_3), 27.0 \text{ (C}_{12}, 26.9 \text{ (C}_{10}, 26.3 \text{ (C}_{11}, 20.1 \text{ (C}_4); mp 78-79 \degree \text{C; m/z HRMS (NSI) found [M + Na]^+ 301.0966 C}_{16}H_{19}ClO_2Na requires 301.0966; [\alpha]^{25}_D -18.4 \text{ (c = 1.00, CHCl}_3); \ \text{d.e. >99\%, according to NMR; e.e. 90\%, from chiral HPLC. Chiralpak AD-H, hexane / isopropanol 99.7:0.3, 1.0 mL/min, oven temperature: 30 \degree \text{C, t} \text{R 8.6 minutes (minor), 10.3 minutes (major).}} \]
According to general procedure F, to a solution of 154 (42.1 mg, 0.25 mmol) in anhydrous dichloromethane (6 mL) at 0 °C was added 2,6-Di-tert-butylpyridine (0.168 mL, 0.75 mmol), copper(II) (+)-2,2′-Isopropylidenebis[(4R)-4-phenyl-2-oxazoline] triflate solution (0.1 M in dichloromethane, 0.25 mL, 0.025 mmol), and mesityl(o-tolyl)iodonium hexafluorophosphate (223, 361.6 mg, 0.75 mmol) as a solution in dichloromethane (2 mL), with stirring for 48 h at 50 °C. Purification by column chromatography (0-4% diethyl ether / hexane) afforded the desired compound as a colourless viscous oil (40.7 mg, 0.16 mmol, 63%). Racemic compound 225 was synthesised according to general procedure G.

Rr 0.5 (20% diethyl ether / hexane); IR (thin film) $\nu_{\text{max}}$/cm$^{-1}$ 2930, 2860, 1713 (s, C=O), 1604, 1489, 1449, 1377, 1261, 1167, 1112, 1069, 1044, 978; $^1$H NMR (500 MHz, C$_6$D$_6$) $\delta$H 8.23 (d, $J = 7.7$ Hz, 1H, H$_{13}$), 7.36-7.17 (m, 1H, H$_8$), 7.05 (dd, $J = 7.7$, 2.0 Hz, 1H, H$_7$), 7.02 (td, $J = 7.5$, 1.2 Hz, 1H, H$_9$), 3.66-3.61 (m, 1H, H$_3$), 3.37 (td, $J = 11.2$, 3.4, 1H, H$_5$), 3.04 (dd, $J = 11.2$, 3.8 Hz, 1H, H$_2$), 2.63-2.53 (m, 1H, H$_{11}$), 2.45 (td, $J = 13.1$, 6.1 Hz, 1H, H$_{13}$), 2.20 (s, 3H, H$_{17}$), 2.07-2.02 (m, 1H, H$_{13}$), 1.96-1.87 (m, 1H, H$_3$), 1.86-1.75 (m, 1H, H$_4$), 1.61-1.50 (m, 2H, H$_{3,11}$), 1.49-1.36 (m, 3H, H$_{10,12}$), 1.14-0.98 (m, 2H, H$_{4,10}$); $^{13}$C NMR (125 MHz, C$_6$D$_6$) $\delta$C 209.5 (C$_{14}$), 141.1 (C$_9$), 136.4 (C$_6$), 130.9 (C$_{13}$), 130.6 (C$_7$), 126.6 (C$_5$), 126.5 (C$_8$), 82.5 (C$_1$), 63.3 (C$_3$), 46.0 (C$_2$), 40.4 (C$_{13}$), 37.9 (C$_3$), 26.8 (C$_{12}$), 26.6 (C$_{10}$), 26.3 (C$_{11}$), 20.9 (C$_{17}$), 20.4 (C$_4$); m/z HRMS (NSI) found [M + Na]$^+$ 281.1511 C$_{17}$H$_{22}$O$_2$Na requires 281.1512; [α]$^{25}_D$ $-11.6$ (c = 1.00, CHCl$_3$); d.e. >99%, according to NMR; e.e. 87%, from chiral HPLC. Chiralpak AD-H, hexane / isopropanol 99.7:0.3, 1.0 mL/min, oven temperature: 30 °C, t$_R$ 8.8 minutes (minor), 10.9 minutes (major).
5.8 Transformations of aryalted products:

(1S,2S,2'R)-2'-{(4-chlorophenyl)-2',3'-dihydrospiro[cyclohexane-1,1'-inden]-2-ol (230)

To a solution of 194 (100 mg, 0.32 mmol, recrystallised to 99% e.e.) in anhydrous tetrahydrofuran (4 mL) was added L-selectride* (0.64 mL, 0.64 mmol, 1.0 M solution in tetrahydrofuran) dropwise at −78 °C. The mixture was allowed to warm to 25 °C and then stirred for 30 h at 30 °C. The reaction was quenched with methanol and concentrated in vacuo. Purification by column chromatography (2–6% diethyl ether / hexane) afforded the desired compound as a colourless viscous oil, and as a single diastereomer (98.5 mg, 0.31 mmol, 98%). Racemic 230 was prepared from racemic 194 in the same fashion.

Rf 0.40 (20% diethyl ether / hexane); IR (thin film) νmax/cm⁻¹ 3668 (s, OH), 2988, 2931, 2902, 1491, 1479, 1449, 1410, 1394, 1883, 1251, 1231, 1066, 1058, 1015, 759;¹H NMR (500 MHz, C₆D₆) δ 7.18-7.08 (m, 4H, H₁₁,₁₂), 6.96 (s, 4H, H₄₋₇), 3.62-3.60 (m, 1H, H₁₈), 3.22-3.13 (m, 2H, H₂₃), 2.88-2.81 (m, 1H, H₃), 1.83-1.79 (m, 1H, H₁₇), 1.68-1.60 (m, 2H, H₁₄,₁₆), 1.50-1.40 (m, 2H, H₁₄,₁₇), 1.37-1.23 (m, 3H, H₁₅,₁₆, OH₁₉), 0.87-0.84 (m, 1H, H₁₅);¹³C NMR (125 MHz, C₆D₆) δ C₈, 148.6 (C₈), 143.9 (C₉), 143.1 (C₁₀), 132.5 (C₁₃), 131.1 (2C, C₁₁), 128.4 (2C, C₁₂), 127.3 (C₄/5/6), 126.8 (C₄/5/6), 124.9 (C₄/5/6), 124.5 (C₇), 73.8 (C₁₈), 58.0 (C₁), 55.5 (C₂), 40.3 (C₃), 37.3 (C₁₇), 31.3 (C₁₄), 23.4 (C₁₆), 22.3 (C₁₅); m/z HRMS (NSI) found [M − 2H + Na]⁺ 333.1018 C₂₀H₁₉ClO₃Na requires 333.1017; [α]²⁵D +23.3 (c = 1.00, CHCl₃); d.e. >99%, according to NMR; e.e. 99%, from chiral HPLC. Chiralpak IA, hexane / isopropanol 95:5, 1.0 mL/min, oven temperature: 30 °C, tR 7.3 minutes (minor), 8.9 minutes (major).
(1S,2S,2'R)-N-(3-bromobenzyl)-2'-(4-chlorophenyl)-2',3'-dihydrospiro[cyclohexane-1,1'-inden]-2-amine (232)

To a solution of 194 (100 mg, 0.32 mmol, recrystallised to 99% e.e.) in anhydrous dichloromethane (4 mL) was added triethylamine (0.112 mL, 0.80 mmol), 3-bromobenzylamine (231, 0.089 mL, 0.70 mmol) and TiCl₄ (0.32 mL, 0.32 mmol, 1.0 M solution in dichloromethane), sequentially, dropwise at 0 °C. The mixture was warmed to 25 °C and stirred for 48 h at 40 °C. Sodium borohydride (13.3 mg, 0.35 mmol) was dissolved in ethanol (1 mL) and added into the mixture at – 78 °C. The solution was allowed to warm to 25 °C and stirring continued for another 24 h, before quenching with water and extracting in dichloromethane 3x. Purification by column chromatography (2-6% diethyl ether / hexane) afforded the desired compound as a pale-yellow viscous oil, and as a single diastereomcr (140.0 mg, 0.29 mmol, 91%). Racemic 232 was prepared from racemic 194 in the same fashion.

Rₛ0.50 (20% diethyl ether / hexane); IR (thin film) νₘₐₓ/cm⁻¹ 3675 (m, NH), 2988, 2972, 2923, 2902, 1595, 1569, 1491, 1475, 1456, 1409, 1394, 1382, 1242, 1230, 1067, 1057, 1028, 1015, 754; ¹H NMR (500 MHz, C₆D₆) δ H 7.16–7.04 (m, 10H, H11-12,21-23,25), 6.75 (t, J = 7.7 Hz, 1H, H6), 6.64 (d, J = 7.6 Hz, 1H, H7), 3.21–3.12 (m, 3H, H2,3,19), 2.94–2.86 (m, 2H, H3,19), 2.65–2.63 (m, 1H, H18), 1.66–1.38 (m, 6H, H14,15,16,17), 1.23–1.18 (m, 2H, H16,17), 0.62 (bs, 1H, NH₂); ¹³C NMR (125 MHz, C₆D₆) δ C 149.6 (C₈), 143.9 (C₉), 143.3 (C₂₀), 143.1 (C₁₀), 132.3 (C₃), 131.6 (C₂₁/22/23/25), 131.3 (2C, C₁₁), 130.0 (C₂₁/22/23/25), 129.9 (C₂₁/22/23/25), 128.2 (2C, C₁₂), 127.3 (C₄/5/6), 127.1 (C₄/5/6), 124.8 (C₄/5/6), 123.7 (C₂₁/22/23/25), 123.2 (C₄), 57.5 (C₁), 54.7 (C₂), 51.6 (C₁₉), 40.9 (C₃), 39.7 (C₁₈), 30.5 (C₁₄), 27.1 (C₁₇), 24.8 (C₁₆), 22.9 (C₁₅); m/z HRMS (NSI) found [M + H]⁺ 480.1077 C₂₇H₂₅N⁷⁹Br⁻Cl requires 480.1088; [α]₂₅⁰ –13.5 (c = 1.00, CHCl₃); d.e. >99%, according to NMR; e.e. 99%, from chiral HPLC. Chiralpak OD, hexane / isopropanol 99.7:0.3, 1.0 mL/min, oven temperature: 30 °C, tᵣ 11.4 minutes (minor), 24.4 minutes (major).
(1S,2R)-2-(4-chlorophenyl)-2,3-dihydrospiro[indene-1,2'-oxepan]-7'-one (236)

A sealed microwave vial was charged with 194 (100 mg, 0.32 mmol, recrystallised to 99% e.e.), 3-chloroperbenzoic acid (166 mg, 0.96 mmol) and Li₂CO₃ (236 mg, 3.2 mmol). Anhydrous benzene (6 mL) was then added at 0 °C while stirring. The mixture was warmed to 25 °C and stirred for 12 h at 25 °C. The solution was diluted in diethyl ether (20 mL) and washed with saturated Na₂SO₃ (aq) 5x, and once with brine. The solution was concentrated in vacuo and the desired product obtained without further purification as a white solid, and as a single diastereomer (104.6 mg, 0.32 mmol, 99%).¹ Slow cooling of hot saturated solution of 236 in hexane grew single crystals. X-Ray crystal structure is deposited in the Cambridge Crystallographic Data Centre CCDC 1539185. Racemic 236 was prepared from racemic 194 in the same fashion.

Elemental analysis (%) calcd for C₂₀H₁₉ClO₂: C, 73.50; H, 5.86. Found: C, 73.51; H, 5.89; Rᵣ 0.20 (20% diethyl ether / hexane); IR (thin film) νₘₐₓ/cm⁻¹ 2934, 1715 (s, C=O), 1486, 1445, 1346, 1330, 1305, 1282, 1232, 1179, 1171, 1148, 1097, 1062, 1025, 1015, 761;¹¹H NMR (500 MHz, C₆D₆) δ_H 7.43-7.40 (m, 1H, H₇), 7.15-7.10 (m, 2H, H₄,₆), 7.00-6.96 (m, 3H, H₅,₁₂), 6.89-6.87 (m, 2H, H₁₁), 3.28 (t, J = 5.9 Hz, 1H, H₂), 2.83 (d, J = 5.9 Hz, 2H, H₃), 2.35-2.29 (m, 1H, H₁₇), 1.94-1.87 (m, 1H, H₁₇), 1.83-1.75 (m, 1H, H₁₄), 1.56 (ddd, J = 15.2, 6.6, 3.1 Hz, 1H, H₁₄), 1.50-1.42 (m, 1H, H₁₅), 1.40-1.29 (m, 1H, H₁₅), 1.26-1.11 (m, 2H, H₁₆);¹³C NMR (125 MHz, C₆D₆) δ_C 172.2 (C₁₈), 147.3 (C₈), 140.3 (C₉), 138.8 (C₁₀), 133.4 (C₁₃), 131.0 (2C), 129.0 (C₆), 128.8 (2C), 127.5 (C₄), 125.2 (C₅), 123.8 (C₇), 90.8 (C₁), 53.9 (C₂), 39.6 (C₃), 38.3 (C₁₄), 36.6 (C₁₇), 24.8 (C₁₅), 22.6 (C₁₆); mp 134-135 °C; m/z HRMS (NSI) found [M + H]+ 327.1146 C₂₀H₁₉₃ClO₂ requires 327.1146, found [M + Na]+ 349.0964 C₂₀H₁₉₃ClO₂Na requires 349.0966; [α]²⁵D +3.6 (c = 1.00, CHCl₃); d.e. >99%, according to NMR; e.e. 99%, from chiral HPLC. Chiralpak IA, hexane / isopropanol 95:5, 1.0 mL/min, oven temperature: 30 °C, tᵣ 14.6 minutes (minor), 17.8 minutes (major).

¹ Product 236 is unstable in silica gel.
(2S,3'R)-3'-phenyl-1,3',4',5',6'-hexahydro-4H-spiro[benzo[d]oxepine-2,2'-pyran]-4-one (237)

A sealed microwave vial was charged with 160 (100 mg, 0.34 mmol), 3-chloroperbenzoic acid (65 mg, 0.38 mmol) and Na₂CO₃ (108 mg, 1.02 mmol). Anhydrous benzene (6 mL) was then added at 0 °C while stirring. The mixture was allowed to warm to 25 °C and stirring continued for 12 h at 25 °C. The solution was diluted in diethyl ether (20 mL) and washed with saturated Na₂SO₃ (aq) five times, and once with brine. The solution was concentrated in vacuo and the desired product obtained without further purification as a colourless viscous oil, and as a single diastereomer (103.8 mg, 0.34 mmol, 99%).

Rᵣ 0.20 (20% diethyl ether / hexane, 5% triethylamine); IR (thin film) ν max/cm⁻¹ 2927, 1735 (s, C=O), 1603, 1493, 1454, 1336, 1290, 1235, 1159, 1137, 1070, 1054, 701; ¹H NMR (500 MHz, C₅D₅) δ H 7.29-7.24 (m, 2H, H₈), 7.14-6.98 (m, 3H, H₇,12), 6.86-6.79 (m, 2H, H₉,13), 6.70-6.68 (m, 1H, H₁₁), 6.61-6.59 (m, 1H, H₁₄), 3.94-3.87 (m, 1H, H₅), 3.75 (d, J = 14.6 Hz, 1H, H₁₇), 3.42-3.37 (m, 1H, H₃), 3.35 (d, J = 14.6 Hz, 1H, H₁₇), 3.06 (d, J = 15.7 Hz, 1H, H₁₀), 2.94 (d, J = 15.7 Hz, 1H, H₁₀), 2.57 (dd, J = 12.9, 3.5 Hz, 1H, H₂), 2.33-2.22 (m, 1H, H₃), 1.52-1.41 (m, 2H, H₃,4), 1.22-1.17 (m, 1H, H₄); ¹³C NMR (125 MHz, C₅D₅) δ c 168.6 (C₁₈), 140.8 (C₆), 134.8 (C₁₆), 132.1 (C₁₅), 130.3 (C₁₄), 129.7 (2C, C₈), 128.8 (C₁₁), 128.5 (2C, C₇), 127.5 (C₁₄), 127.2 (C₁₂), 127.1 (C₁₃), 125.5 (C₉), 103.5 (C₁), 62.3 (C₅), 54.3 (C₂), 44.4 (C₁₀), 42.9 (C₁₇), 26.7 (C₃), 25.9 (C₄); m/z HRMS (NSI) found [M + Na]⁺ 331.1301 C₂₀H₂₀O₃Na requires 331.1305; [α]²⁵D ~57.4 (c = 1.00, CHCl₃); d.e. >99%, according to NMR.

² Compound 198 was extremely unstable in silica gel, Brønsted acids and strong Lewis acids. It is also unstable when left standing in air. Compound needs to be stored in anhydrous benzene at ~ 40 °C.
³ Compound 198 was unstable in the chiral HPLC column condition.
(1S,2'R,E)-2'- (4-chlorophenyl)-2',3'-dihydrospiro[cyclohexane-1,1'-inden]-2-one oxime (233)

A sealed microwave vial was charged with 194 (100 mg, 0.32 mmol, recrystallised to 99% e.e.), hydroxylamine hydrochloride (111.2 mg, 1.6 mmol) and DABCO (39.5 mg, 0.35 mmol). Methanol (6 mL) was then added at rt, and stirred for 12 h. The solution was subsequently concentrated in vacuo, diluted in dichloromethane (20 mL) and washed with saturated Na₂CO₃ (aq.) 3x, and once with brine. The organic phase was collected, concentrated in vacuo, and dried to give a white solid (104.6 mg, 0.32 mmol, 99%).

Elemental analysis (%) calcd for C₂₀H₂₀ClNO: C, 73.72; H, 6.19. Found: C, 73.70; H, 6.22; Rₖ 0.20 (20% diethyl ether / hexane); IR (thin film) ν_max/cm⁻¹ 3650, 2924, 1544, 1473, 1459, 1410, 1212, 1123, 1081, 1024, 907; ¹H NMR (500 MHz, C₆D₆) δ_H 8.97 (bs, 1H, OH₁⁹), 7.28 (d, J = 7.5 Hz, 1H, H₄), 7.25 (t, J = 7.5 Hz, 1H, H₅), 7.15-7.06 (m, 4H, H₆,7,11), 6.86-6.83 (m, 2H, H₁₂), 3.30-3.25 (m, 1H, H₁₃), 3.21 (dd, J = 8.2, 6.0 Hz, 1H, H₂), 3.05 (dd, J = 16.2, 7.9 Hz, 1H, H₅), 2.91 (dd, J = 16.2, 5.9 Hz, 1H, H₃), 1.73-1.62 (m, 2H, H₁₇), 1.38-1.27 (m, 3H, H₁₄,₁₆), 1.16-1.05 (m, 1H, H₁₆), 0.98-0.89 (m, 1H, H₁₅); ¹³C NMR (125 MHz, C₆D₆) δ_C 159.9 (C₁₈), 147.5 (C₉), 142.2 (C₈), 142.1 (C₁₀), 132.7 (C₁₃), 130.6 (2C, C₁₂), 128.6 (2C, C₁₁), 127.5 (C₆), 127.1 (C₅), 126.0 (C₄), 124.5 (C₇), 58.8 (C₁), 52.3 (C₂), 41.4 (C₁₇), 40.2 (C₃), 24.9 (C₁₃), 23.6 (C₁₆), 22.7 (C₁₄); mp 178-179 °C; m/z HRMS (ESI-TOF) found [M + H]^⁺ 325.1245 C₂₀H₂₀ClNO requires 325.1233; [α]°D +130.1 (c = 1.00, CHCl₃); d.e. 99%, according to NMR.
5.9 Synthesis of α-diazoesters:

3,5-bis(trifluoromethyl)benzyl 2-bromoacetate (318Br)

The synthesis of 318Br was achieved by adapting the procedure of Fukuyama, as follows: A round-bottomed flask was charged with NaHCO$_3$ (0.42 g, 5.0 mmol), (3,5-bis(trifluoromethyl)phenyl)methanol (0.24 g, 1.0 mmol) and acetonitrile (0.15 M of alcohol) under N$_2$ (g) atmosphere and cooled to 0 °C. To the solution was added bromoacetyl bromide (0.30 g, 0.13 mL, 1.5 mmol), with stirring for 1 h at 0 °C, before quenching with NaHCO$_3$ (aq), extracting with diethyl ether 3x, washing with NaHCO$_3$ (aq) 2x, drying (MgSO$_4$), and concentrating in vacuo to yield 318Br in sufficient purity for the next step (0.35 g, 0.95 mmol, 95%).

**IR (thin film)** $\nu_{\text{max}}$/cm$^{-1}$ 3098, 3041, 1639, 1598, 1484, 1368, 1270, 1142, 1014; **$^1$H NMR** (400 MHz, CDCl$_3$) $\delta_{\text{H}}$ 7.87 (s, 1H, H$_7$), 7.84 (s, 2H, H$_3$), 5.31 (s, 2H, H$_3$), 3.92 (s, 2H, H$_1$); **$^{13}$C NMR** (100 MHz, CDCl$_3$) $\delta_c$ 167.0 (C$_2$), 137.7 (C$_4$), 132.3 (q, $^2$J$_{C-F}$ = 33.7 Hz, 2C, C$_6$), 128.2 (app. d, $^3$J$_{C-F}$ = 2.9 Hz, 2C, C$_5$), 123.19 (1, $^1$J$_{C-F}$ = 273.0 Hz, 2C, C$_8$), 122.65 (app. qn, $^3$J$_{C-F}$ = 3.9, 1C, C$_7$), 66.1 (C$_3$), 25.3 (C$_1$); **$^{19}$F NMR** (376 MHz, CDCl$_3$) $\delta_F$ -64.6 (6F, CF$_3$); **m/z** HRMS (NSI) found [M + H]$^+$ 364.9620 C$_{11}$H$_{79}$BrF$_6$O$_2$ requires 364.9612;
The synthesis of 318N\(_2\) was achieved by adapting the procedure of Fukuyama\(^\text{211}\) as follows: A round-bottomed flask was charged with N,N’-ditosylhydrazine (0.51 g, 1.5 mmol), 318Br (0.37 g, 1.0 mmol) and tetrahydrofuran (0.2M of 318Br) under N\(_2\) (g) atmosphere and cooled to 0 °C. To the solution was added 1,8-diaza-[4.4.0]-bicyclo-undec-7-ene (0.34 g, 3.0 mmol), and the resulting mixture stirred for 1 h at 0 °C, before quenching with NaHCO\(_3\) (aq), extracting with diethyl ether 3x, washing once with brine, drying (MgSO\(_4\)), and concentrating in vacuo. Purification on column chromatography afforded the desired α-diazoacetate 318N\(_2\) (0.25 g, 0.81 mmol, 81\%).

\(\text{R}_f\) 0.60 (20% diethyl ether / hexane); IR (thin film) \(\nu_{\text{max}}/\text{cm}^{-1}\) 3124, 2952, 2771, 1652, 1421, 1389, 1325, 1275, 991; \(^1\text{H NMR}\) (400 MHz, CD\(_3\)CN) \(\delta_H\) 7.95–7.94 (m, 3H, H\(_{5,7}\)), 5.30 (s, 2H, H\(_3\)), 5.09 (bs, 1H, H\(_1\)); \(^{13}\text{C NMR}\) (100 MHz, CDCl\(_3\)) \(\delta_c\) 167.5 (C\(_2\)), 140.9 (C\(_4\)), 132.4 (q, \(^2\text{J}_{\text{C-F}} = 32.5\) Hz, 2C, C\(_6\)), 129.3 (q, \(^3\text{J}_{\text{C-F}} = 3.0\) Hz, 2C, C\(_5\)), 124.6 (q, \(^1\text{J}_{\text{C-F}} = 270.8\) Hz, 2C, C\(_8\)), 123.0 (app. hept, \(^3\text{J}_{\text{C-F}} = 3.9\) Hz, 1C, C\(_7\)), 65.4 (C\(_3\)), 47.3 (C\(_1\)); \(^{19}\text{F NMR}\) (376 MHz, CDCl\(_3\)) \(\delta_F\) −64.6 (6F, CF\(_3\)). mp 72 °C (decomp.); m/z HRMS (NSI) found [M + H]\(^+\) 313.0410 C\(_{11}\)H\(_7\)F\(_6\)N\(_2\)O\(_3\) requires 313.0412.
5.10 Synthesis of α-diazoester arylidonium salts:

(1-diazo-2-ethoxy-2-oxoethyl)(2,4-difluorophenyl)iodonium tetrafluoroborate (281)

To a solution of (2,4-difluorophenyl)-λ3-iodanediyi diacetate (0.94 g, 2.6 mmol) in dichloromethane (17 mL) at 0 °C under N₂ (g) atmosphere, was added boron trifluoride diethyl etherate (0.42 mL, 3.0 mmol), with stirring for 5 min before adding ethyl diazoacetate (0.41 mL, 87% purity, 3.0 mmol). Stirring was continued for 30 min at 0 °C. The solution was concentrated in vacuo and triturated using a sonicator (5 : 20 : 75 CH₂Cl₂ : 40-60 petroleum ether : diethyl ether, 20 mL) to afford the desired compound as a yellow powder (1.15 g, 2.61 mmol, 87% yield).

**IR (thin film) v max/cm⁻¹** 3086, 3065, 3037, 2988, 1698, 1682, 1598, 1587, 1474, 1426, 1371, 1270, 1192, 1155, 1117, 1056, 1041, 1001, 963, 876, 851, 822, 760, 732, 616; **¹H NMR** (500 MHz, CD₃CN) δ H 8.23 (app dt, J = 9.0, 6.4 Hz, 1H, H₆), 7.40 (app td, J = 9.0, 2.7 Hz, 1H, H₃), 7.25 (app td, J = 8.6, 2.5 Hz, 1H, H₃), 4.31 (q, J = 7.1 Hz, 2H, H₀), 1.28 (t, J = 7.1 Hz, 3H, H₁₀); **¹³C NMR** (125 MHz, CDCl₃) δ C 166.9 (dd, ¹³C-F = 258.0, 12.2 Hz, 1C, C₂), 161.3 (dd, ¹³C-F = 254.0, 14.0 Hz, 1C, C₄), 160.4 (C₃), 139.0 (d, ¹³C-F = 11.0 Hz, 1C, C₆), 115.4 (app dd, ²⁴J_C-F = 23.0, 2.8 Hz, 1C, C₃), 106.2 (app t, ²²J_C-F = 27.0 Hz, 1C, C₃), 96.5 (app dd, ²²J_C-F = 23.0 Hz, 1C, C₁), 64.3 (C₈), 41.3 (br s, C₇), 13.3 (C₁₀); **¹⁹F NMR** (376 MHz, CD₃CN) δ F -92.9 (d, J = 12.0 Hz), -100.0 (app d, J = 12 Hz), -151.3 – -151.6 (m, br, BF₄); **mp** 74 °C (decomp); **m/z** HRMS-(ESI)+ (m/z) Found [M – BF₄]: 352.9601 C₁₀H₈O₂N₂F₂I requires 352.9593.
To a solution of (2,4-difluorophenyl)-λ3-iodanediyl diacetate (0.94 g, 2.6 mmol) in dichloromethane (15 mL) at 0 °C under N₂ (g) atmosphere, was added boron trifluoride diethyl etherate (0.42 mL, 3.0 mmol), with stirring for 5 min before adding 3,5-bis(trifluoromethyl)benzyl 2-diazoacetate (318N₂, 0.93 g, 3.0 mmol) as a solution in dichloromethane (2 mL). Stirring was continued for 30 min at 0 °C. The solution was concentrated in vacuo and tritivated using a sonicator (5 : 20 : 75 CH₂Cl₂ : 40-60 petroleum ether : diethyl ether, 20 mL) to afford the desired compound as a light yellow powder (1.84 g, 2.88 mmol, 96% yield).

**IR** (thin film) ν max/cm⁻¹ 3060, 3015, 2975, 1681, 1588, 1470, 1370, 1181, 990; **¹H NMR** (500 MHz, CD3CN) δH 8.22 (app dt, J = 8.7, 6.5 Hz, 1H, H₆), 7.99 (bs, 1H, H₁₁), 7.95 (bs, 2H, H₁), 7.30 (app dt, J = 8.8, 2.5 Hz, 1H, H₅), 7.17 (app dt, J = 8.6, 2.4 Hz, 1H, H₃), 5.39 (s, 2H, H₀); **¹³C NMR** (125 MHz, CD3CN) δC 168.1 (dd, ¹³JC-F = 257.0, 12.4 Hz, 1C, C₂), 162.5 (dd, ¹³JC-F = 255.0, 13.4 Hz, 1C, C₄), 161.6 (C₆), 140.1 (d, ³JC-F = 9.8 Hz, 1C, C₆), 139.2 (C₁₀), 132.3 (q, ²JC-F = 33.4 Hz, 2C, C₁₂), 129.9 (app. q, ³JC-F = 2.8 Hz, 2C, C₁₁), 124.4 (q, ¹JC-F = 272.0 Hz, 2C, C₁₄), 123.5 (app. hept, ⁴JC-F = 3.8 Hz, 1C, C₁₃), 116.5 (dd, ²⁴JC-F = 23.3, 3.1 Hz, 1C, C₅), 107.2 (app. t, ²JC-F = 26.6 Hz, 1C, C₃), 97.8 (dd, ²⁴JC-F = 23.6, 4.2 Hz, 1C, C₅), 68.4 (C₈), 42.1 (br s, C₇); **¹⁹F NMR** (376 MHz, CD3CN) δF -64.3 (6F, CF₃), -92.1 (Ph-F), -97.6 (app d, J = 11.9 Hz, Ph-F), -146.5 – –146.6 (m, br, BF₄); **mp** 102 °C (decomp.); **m/z** HRMS-(ESI)+ (m/z) Found [M – BF₄]: 550.9501 C₁₇H₈O₂N₂F₃I requires 550.9503.
5.11 Synthesis of oligo-peptides:

**tert-butyl (S)-2-((2-ethoxy-2-oxoethyl)carbamoyl)pyrrolidine-1-carboxylate (296)**

To a solution of (tert-butoxycarbonyl)-L-proline (1.08 g, 5.0 mmol) in N,N-dimethylformamide (10 mL) at rt was added N,N'-dicyclohexylcarbodiimide (1.13 g, 5.5 mmol), 1-hydroxybenzotriazole (0.68 g, 5.0 mmol) and triethylamine (1.4 mL, 10.0 mmol), with stirring for 30 min before adding ethyl glycinate hydrochloride (0.70 g, 5.0 mmol). Stirring was continued for 2 h at 25 °C. The solution was poured into hexanes (20 mL) with shaking. The mixture was stored in the freezer overnight, and the urea co-product filtered. The remaining organic layer was washed with brine (3 x 100 mL), concentrated in vacuo and purified on column chromatography to afford the desired compound as a white solid (1.31 g, 4.4 mmol, 87% yield).

Rf 0.45 (10% methanol / dichloromethane); \(^1\)H NMR (500 MHz, CDCl\(_3\)) δ\(_H\) 6.50 (bs, 1H, NH\(_{13}\)), 4.33-4.27 (m, 1H, H\(_4\)), 4.20 (q, J = 7.2 Hz, 2H, H\(_6\)), 4.08 (dd, J = 18.4, 5.5 Hz, 1H, H\(_3\)), 3.97 (dd, J = 18.4, 6.2 Hz, 1H, H\(_5\)), 3.47-3.36 (m, 2H, H\(_1\)), 2.53-2.25 (m, 1H, H\(_3\)), 2.17-2.11 (m, 1H, H\(_2\)), 1.89 (m, 2H, H\(_{2,3}\)), 1.47 (s, 9H, H\(_9\)), 1.28 (t, J = 7.2 Hz, 3H, H\(_7\)); \(^1^3\)C NMR (125 MHz, CDCl\(_3\)) δ\(_C\) 169.4 (C\(_{11}\)), 162.3 (C\(_{10}\)), 155.4 (C\(_{12}\)), 80.0 (C\(_8\)), 61.0 (C\(_4\)), 53.3 (C\(_6\)), 46.8 (C\(_1\)), 41.0 (C\(_3\)), 36.2 (C\(_3\)), 31.1 (C\(_2\)), 28.1 (3C, C\(_9\)), 13.9 (C\(_7\)). Data in accordance with literature.\(^{212}\)
ethyl (tert-butoxycarbonyl)glycyl-L-prolylglycinate (299)

To a solution of 296 (1.19 g, 4.0 mmol) in dichloromethane (5 mL) at 25 °C was added trifluoroacetic acid (5 mL), with stirring for 3 h. The solution was then concentrated in vacuo, dried under high vacuum, precipitated with diethyl ether, dried again and placed in a round-bottom flask. To the flask was added N,N-dimethylformamide (40 mL), 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.84 g, 4.4 mmol), 1-hydroxybenzotriazole (0.54 g, 4.0 mmol), N,N-di-iso-propylethylamine (1.40 mL, 8.0 mmol), and (tert-butoxycarbonyl)glycine (0.70 g, 4.0 mmol), with stirring for 24 h at 25 °C. The solution was washed with brine (3x 100 mL), concentrated in vacuo and purified on column chromatography to afford the desired compound as a white solid (0.99 g, 2.76 mmol, 69% yield). Slow cooling of hot saturated solution of 299 in hexane grew single crystals.

Elemental analysis (%) calcd for C_{16}H_{27}N_{3}O_{6}: C, 53.77; H, 7.61. Found: C, 53.66; H, 7.72. \(R_f\) 0.40 (10% methanol / dichloromethane); IR (thin film) \(\nu_{\text{max}}/\text{cm}^{-1}\): 3302, 3103, 2897, 2974, 1656, 1637, 1518, 1408, 1325, 1232, 921; \(^1\text{H NMR}\) (500 MHz, C\(_6\)D\(_6\)) \(\delta_{H}\): 7.49 (bs, 0.5H, NH\(_{13}\)), 5.55 (bs, 0.5H, NH\(_{13}\)), 4.35-4.25 (m, 0.5H, H\(_{4}\)), 3.86-3.75 (m, 1.5H, H\(_{4,5}\)), 3.71-3.57 (m, 4H, H\(_{5,6,14}\)), 3.26 (q, \(J = 7.0\) Hz, 1H, H\(_{6}\)), 2.55 (app. t, \(J = 8.4\) Hz, 0.5H, H\(_{1}\)), 2.27-2.10 (m, 1H, H\(_{1}\)), 1.76-1.57 (m, 1H, H\(_{1,3}\)), 1.45-1.09 (m, 12.5H, H\(_{2,3,9}\)), 0.89-0.80 (m, 3H, H\(_{7}\)), 0.60 (bs, 1H, NH\(_{16}\)); \(^{13}\text{C NMR}\) (125 MHz, C\(_6\)D\(_6\)) \(\delta_c\): 170.5 (C\(_{11}\)), 169.3 (C\(_{10}\)), 168.5 (C\(_{12}\)), 155.6 (C\(_{15}\)), 65.5 (C\(_{8}\)), 60.5 (C\(_{4}\)), 59.5 (C\(_{6}\)), 45.3 (C\(_{1}\)), 43.1 (C\(_{14}\)), 41.0 (C\(_{5}\)), 28.1 (3C, C\(_{9}\)), 26.4 (C\(_{3}\)), 15.2 (C\(_{2}\)), 13.6 (C\(_{7}\)). mp 78-79°C (decomp.); m/z HRMS-(ESI)+ (m/z) Found [M + H]\(^+\): 358.1970, C\(_{16}\)H\(_{28}\)N\(_3\)O\(_6\) requires 358.1978.
ethyl (\textit{tert}-butoxycarbonyl)-L-methionylglycyl-L-prolylglycinate (302)

To a solution of 299 (0.71 g, 2.0 mmol) in dichloromethane (2 mL) at 25 °C was added trifluoroacetic acid (2 mL), with stirring for 3 h. The solution was then concentrated \textit{in vacuo}, dried under high vacuum, precipitated with diethyl ether, dried again and placed in a round-bottom flask. To the flask was added N,N-dimethylformamide (20 mL), 1-Ethyl-3-(3-diethylaminopropyl)carbodiimide hydrochloride (0.42 g, 2.2 mmol), 1-hydroxybenzotriazole (0.27 g, 2.0 mmol), N,N-di-\textit{iso}-propylethylamine (0.7 mL, 4.0 mmol), and (\textit{tert}-butoxycarbonyl)-L-methionine (0.50 g, 2.0 mmol), with stirring for 24 h at 25 °C. The solution was washed with brine (3x 100 mL), concentrated \textit{in vacuo} and purified on column chromatography to afford the desired compound as a white solid (0.508 g, 1.04 mmol, 52% yield).

\textbf{Rf} 0.30 (10% methanol / dichloromethane); \textbf{IR} (thin film) \textit{v}_{\text{max}}/\text{cm}^{-1} 3316, 3140, 3010, 2879, 1658, 1621, 1603, 1530, 1408, 1324, 1241, 923; \textbf{\textit{\textit{1H NMR}}} (500 MHz, CD$_3$CN) $\delta$H 7.35-7.18 (m, 2H, NH$_{13,16}$), 5.85-5.45 (m, 1H, NH$_{22}$), 4.41-4.40 (m, 1H, H$_{4}$), 4.21-4.19 (m, 1H, H$_{17}$), 4.12 (q, $J$ = 7.1 Hz, 2H, H$_{6}$), 4.03-3.86 (m, 3H, H$_{5,14}$), 3.81-3.72 (m, 1H, H$_{14}$), 3.62-3.44 (m, 2H, H$_{1}$), 2.58-2.46 (m, 2H, H$_{19}$), 2.06-1.78 (m with large s, 9H, H$_{2,3,18,20}$), 1.40 (s, 9H, H$_{9}$), 1.23-1.19 (m, 3H, H$_{3}$); \textbf{\textit{\textit{13C NMR}}} (125 MHz, CD$_3$CN) $\delta$C 173.2 (C$_{21}$), 173.1 (C$_{11}$), 170.7 (C$_{10}$), 168.7 (C$_{12}$), 156.6 (C$_{15}$), 80.1 (C$_{8}$), 61.8 (C$_{4}$), 61.3 (C$_{6}$), 47.2 (C$_{17}$), 42.7 (C$_{14}$), 41.7 (C$_{14}$), 32.7 (C$_{5}$), 30.8 (C$_{19}$), 30.0 (C$_{3}$), 28.6 (C$_{5}$), 25.2 (C$_{2}$), 23.0 (C$_{18}$), 15.3 (C$_{20}$), 14.5 (C$_{7}$); \textbf{mp} 75-76 °C; \textbf{m/z} HRMS-(ESI$^+$) (m/z) Found [M + H]$^+$: 489.2380, C$_{21}$H$_{37}$N$_{3}$O$_{3}$S requires 489.2383.
methyl (tert-butoxycarbonyl)-L-methionylglycyl-L-prolylglycyl-L-tryptophanate (290)

To a solution of 302 (0.49 g, 1.0 mmol) in tetrahydrofuran (2 mL) at 25 °C was added NaOH (aq., 40 mg, 1.0 mmol, in 0.1 mL H₂O), with stirring for 2 h. The solution was then concentrated in vacuo, precipitated with diethyl ether, dried and placed in a round-bottom flask. To the flask was added N,N-dimethylformamide (10 mL), 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.21 g, 1.1 mmol), 1-hydroxybenzotriazole (0.14 g, 1.0 mmol), N,N-di-iso-propylethylamine (0.35 mL, 2.0 mmol), and methyl L-tryptophanate hydrochloride (0.25 g, 1.0 mmol), with stirring for 24 h at 25 °C. The solution was washed with brine (3x 100 mL), concentrated in vacuo and purified on column chromatography to afford the desired compound as a white solid (0.46 g, 0.70 mmol, 70% yield).

Rᵣ 0.25 (20% methanol / dichloromethane); IR (thin film) νmax/cm⁻¹ 3168, 3146, 3015, 2955, 1681, 1637, 1638, 1501, 1434, 1325, 1240, 906; ¹H NMR (500 MHz, CD₃CN) δH 9.36 (bs, 1H, NH₂), 7.52 (d, J = 7.9 Hz, 1H, H₃₀), 7.37 (d, J = 7.9 Hz, 1H, H₃₂), 7.32 (t, J = 6.1 Hz, 1H, NH₁₃/₁₆), 7.25 (d, J = 7.5 Hz, 1H, NH₃₄), 7.14-7.09 (m, 2H, H₂₆,₃₃), 7.05 (t, J = 7.3 Hz, 1H, H₃₁), 5.79-5.56 (m, 1H, NH₂₂), 4.63 (app. dd, J = 13.2, 7.2 Hz, 1H, H₂₃), 4.32 (app. dd, J = 7.8, 3.8, 1H, H₄), 4.11-4.10 (m, 1H, H₁₇), 3.97-3.82 (m, 2H, H₁₄), 3.81-3.68 (m, 2H, H₃), 3.61 (s, 3H, H₇), 3.50-3.42 (m, 2H, H₁), 3.28 (dd, J = 14.7, 5.6 Hz, 1H, H₂₄), 3.18 (dd, J = 14.7, 7.2 Hz, 1H, H₂₄), 2.54-2.34 (m, 2H, H₁₉), 2.26-2.12 (m, 1H, NH₁₃/₁₆), 2.07-1.97 (m with s at 1.97 ppm, 5H, H₃₂,₂₀), 1.92-1.87 (m, 3H, H₂,₁₈), 1.79-1.55 (m, 1H, H₂), 1.40 (s, 9H, H₉); ¹H NMR (500 MHz, CD₂Cl₂) δH 9.08 (bs, 1H, NH₂₇), 7.50-7.48 (m, 1H, H₃₀), 7.38 (bs, 1H, NH), 7.34-7.31 (m, 2H, NH, H₃₂), 7.15-7.11 (m, 1H, H₃₁), 7.08-7.04 (m, 3H, NH, H₂₆,₃₃), 5.69-5.37 (m, 1H, NH₂₂), 4.79 (dd, J = 12.5, 6.7 Hz, 1H, H₂₃), 4.31 (bs, 1H, H₄),
4.18-4.16 (m, 1H, H_{17}), 3.93-3.79 (m, 2H, H_{5,14}), 3.74-3.61 (m, 5H, H_{5,7,14}), 3.51-3.39 (m, 1H, H_{1}), 3.34-3.19 (m, 3H, H_{1,24}), 2.39-2.37 (m, 2H, H_{19}), 2.04-1.86 (m, 8H, H_{2,3,18,20}), 1.69-1.59 (m, 1H, H_{18}), 1.43-1.35 (m, 9H, H_{9}); $^{13}$C NMR (125 MHz, CD$_3$CN) $\delta_c$ 173.3 (C_{11}), 173.2 (C_{10}), 172.9 (C_{21}), 170.2 (C_{6}), 169.1 (C_{12}), 156.6 (C_{15}), 137.3 (C_{28}), 128.3 (C_{29}), 125.1 (C_{26}), 122.5 (C_{33}), 120.0 (C_{31}), 119.1 (C_{30}), 112.5 (C_{32}), 110.5 (C_{25}), 80.2 (C_{8}), 61.8 (C_{4}), 54.6 (C_{17}), 54.3 (C_{23}), 52.8 (C_{7}), 47.4 (C_{1}), 43.4 (C_{5}), 42.7 (C_{14}), 32.6 (C_{18}), 30.7 (C_{19}), 29.9 (C_{3}), 28.6 (3C, C_{9}), 28.2 (C_{24}), 25.5 (C_{2}), 15.3 (C_{20}); $^{13}$C NMR (125 MHz, CD$_2$Cl$_2$) $\delta_c$ 172.8 (C_{11}), 172.6 (C_{10}), 172.5 (C_{21}), 169.7 (C_{6}), 168.5 (C_{12}), 156.1 (C_{15}), 136.5 (C_{28}), 127.7 (C_{29}), 124.5 (C_{26}), 122.2 (C_{33}), 119.7 (C_{31}), 118.6 (C_{30}), 111.9 (C_{32}), 109.8 (C_{25}), 80.4 (C_{8}), 61.1 (C_{4}), 54.0 (C_{17}), 53.8 (C_{23}), 52.8 (C_{7}), 47.0 (C_{1}), 43.3 (C_{5}), 42.3 (C_{14}), 32.5 (C_{18}), 30.4 (C_{19}), 29.2 (C_{3}), 28.5 (3C, C_{9}), 27.7 (C_{24}), 25.2 (C_{2}), 15.5 (C_{20}); mp 85 °C (decomp.); m/z HRMS-(ESI)+ (m/z) Found [M + H]$^+$: 661.3011, C$_{31}$H$_{48}$N$_{6}$O$_{8}$S requires 661.3020.

Figure 43: NOESY Spectra for 290; calc. H$_{31}$-H$_{17}$: > 1% NOE.
Figure 44: NOESY Spectra for 290; calc. H$_{32}$-H$_{30}$: 0.1% NOE

Figure 45: NOESY Spectra for 290; H$_{14}$-H$_{11}$: 0.1% NOE.
methyl (tert-butoxycarbonyl)-L-methioninate (319)

To a solution of methyl L-methioninate hydrochloride salt (0.20 g, 1.0 mmol) in acetonitrile (10 mL) at 25 °C was added di-tert-butyl dicarbonate (0.33 g, 1.5 mmol), with stirring for 5 min before adding 4-dimethylaminopyridine (0.12 g, 1.0 mmol). Stirring was continued for 24 h at 25 °C. The solution was concentrated in vacuo, diluted with dichloromethane (20 mL), washed once with NaHCO₃ (aq), extracted with dichloromethane, washed once with brine, dried (MgSO₄), and concentrated in vacuo. Purification on column chromatography afforded the desired compound as a colourless oil (0.24 g, 0.92 mmol, 92% yield).

R_f 0.50 (10% methanol / dichloromethane); ¹H NMR (500 MHz, CD3CN) δ_H 5.63-5.45 (m, 1H, NH₁₀), 4.24 (m, 1H, H₂), 3.67 (s, 3H, H₆), 2.52 (m, 2H, H₃), 2.06 (s, 3H, H₄), 2.02-1.97 (m, 1H, H₂), 1.91-1.82 (m, 1H, H₂), 1.40 (s, 9H, H₉); ¹³C NMR (125 MHz, CD3CN) δ_C 173.9 (C₅), 156.6 (C₇), 80.0 (C₈), 53.6 (C₁), 52.7 (C₆), 31.9 (C₂), 30.7 (C₃), 28.5 (3C, C₉), 15.3 (C₄). Data in accordance with literature.²¹³
methyl (tert-butoxycarbonyl)-L-tryptophanate (308)

To a solution of methyl L-tryptophanate hydrochloride (0.25 g, 1.0 mmol) in acetonitrile (10 mL) at 25 °C was added di-tert-butyl dicarbonate (0.33 g, 1.5 mmol), with stirring for 5 min before adding 4-dimethylaminopyridine (0.12 g, 1.0 mmol). Stirring was continued for 24 h at 25 °C. The solution was then concentrated in vacuo, diluted with dichloromethane (20 mL), washed with NaHCO₃ (aq), extracted with dichloromethane 3x, washed once with brine, dried (MgSO₄), and concentrated in vacuo. Purification on column chromatography afforded the desired compound as a white solid (0.24 g, 0.89 mmol, 89% yield).

Rf 0.40 (10% methanol / dichloromethane); ¹H NMR (500 MHz, CD₃CN) δH 9.17 (bs, 1H, NH₁₁), 7.53 (d, J = 7.7 Hz, 1H, H₈), 7.40 (d, J = 8.2 Hz, 1H, H₅), 7.14 (t, J = 7.1 Hz, 1H, H₆), 7.08 (s, 1H, H₄), 7.06 (t, J = 7.1 Hz, 1H, H₇), 5.47-5.10 (m, 1H, NH₁₇), 4.43 (app. dd, J = 7.2, 5.5 Hz, 1H, H₁), 3.64 (s, 3H, H₁₄), 3.24 (dd, J = 14.6, 5.5 Hz, 1H, H₂), 3.12 (dd, J = 14.6, 7.2 Hz, 1H, H₂), 1.37 (s, 9H, H₁₃); ¹³C NMR (125 MHz, CD₃CN) δc 173.8 (C₁₁), 156.3 (C₁₆), 137.4 (C₁₀), 128.5 (C₉), 124.6 (C₄), 122.6 (C₆), 120.0 (C₇), 119.3 (C₈), 112.4 (C₅), 110.8 (C₃), 80.0 (C₁₂), 55.5 (C₁), 52.7 (C₁₄), 28.5 (C₁₃), 28.3 (C₂). Data in accordance with literature.²¹⁴
5.11.1 Solid-phase peptide synthesis:

Peptide coupling was performed on MBHA rink amide resins. The steps were as follow:

1. Resins (0.2 mmol) were transferred to a coupling vessel (fitted with a porous filter), which is connected to a waste vessel and a vacuum pump.

2. Resins were washed with N,N-dimethylformamide (DMF) / MeOH / CH₂Cl₂ / DMF, sequentially (3 x 4 mL each time), ending with DMF. During these steps, the vacuum pump was used to pull the solvent through the porous filter and into the waste vessel.

3. Fmoc deprotection was performed by adding 4 mL of 20% piperidine, with N₂ (g) bubbling applied through the frit to agitate the solution for 1 h. Deprotection was verified using Kaiser test kits (positive). Washing steps were repeated.

5. The appropriate Fmoc-protected amino acid (4.0 eq.), coupling reagent 2-(6-Chloro-1-H-benzotriazole-1-yl)-1,1,3,3-tetramethylammonium hexafluorophosphate (HCTU, 4.0 eq.) and di-iso-propylethylamine (4.0 eq.) were dissolved in DMF (4 mL) and added into the coupling vessel, with N₂ (g) bubbling applied to agitate the solution for 1 h. Completion was verified using Kaiser test kits (negative). Longer coupling times (1–12 hours) were tolerated and are recommended for longer peptides.

6. Steps 2–5 were repeated until peptide sequence was completed. The final amino acid used in the sequence was Boc-protected instead, which would be removed during the global deprotection and resin cleavage step with acidic conditions. Washing steps were repeated. A small amount of resin was transferred to a glass vial and treated with 400 µL of trifluoroacetic acid (TFA) : H₂O : triisopropylsilane (TIPS) in 93:5:2 ratio, and the success of the peptide coupling was confirmed by LC-MS and HRMS analysis.
On-bead (resin) peptide substrate characterisation data:

Table 11: Solid-phase peptide synthesis (SPPS) of peptide substrates

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<tr>
<td>WFPTM</td>
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</table>

Notes: (a) Sequence is written from C- to N- terminus; (b) m/z was calculated using protonated species (peptide C-terminus is CONH₂); *(D)-amino acid residue.

Single letter amino acid residue key

5.12 Solution-phase two-step conjugation-macrocyclisation of peptides:

(6R)-6-((2-(S)-2-((2-(((R)-3-(1H-indol-3-yl)-1-methoxy-1-oxopropan-2-yl)amino)-2-oxoethyl)carbamoyl)pyrrolidin-1-yl)-2-oxoethyl)carbamoyl)-10-diazo-2,2,9-trimethyl-4,11-dioxo-3,12-dioxo-9-thia-5-azatetradecan-9-ium tetrafluoroborate (291)

Pentapeptide methyl (tert-butoxycarbonyl)-L-methionylglycyl-L-prolylglycyl-L-tryptophanate (290, 0.10 g, 0.15 mmol) and (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl (TEMPO, 0.03 g, 0.2 mmol) was charged into a microwave tube, and the tube evacuated and refilled with N₂ (g). Acetonitrile (1 mL, distilled and bubbled with N₂ (g) overnight) was added into the tube, followed by (1-diazo-2-ethoxy-2-oxoethyl)(2,4-difluorophenyl)iodonium tetrafluoroborate (281, 0.133 g, 0.30 mmol) as a solution in acetonitrile (1 mL) to give a final peptide concentration of 0.08 M, with stirring for 30 min. The solution was concentrated in vacuo, and triturated with diethyl ether 3x, to afford the desired compound as a yellow powder, and as an inseparable mixture of diastereomers (112 mg, 0.13₃ mmol, 99%).

IR (thin film) ν_max/cm⁻¹ 3353, 2981, 1652, 1521, 1456, 1368, 1256, 1159, 1019, 954, 708; ¹H NMR (500 MHz, CD₂Cl₂) δ_H 9.01 (bs, 1H, NH₂), 7.51-7.49 (m, 1.5H, NH₁₃,3₄,1₆,2₂, H₃₀), 7.38-7.29 (m, 1.5H, NH₁₃,3₄,1₆,2₂, H₃₂), 7.13-7.07 (m, 3.5H, NH₁₃,3₄,1₆,2₂, H₂₆,3₁,₃₃), 6.20 (bs, 0.5H, NH₁₃,3₄,1₆,2₂), 5.50-5.32 (m, 1H, H₂₃), 5.18 (bs, 0.5H, NH₁₃,3₄,1₆,2₂), 5.20-4.82 (m, 2H, H₁₉), 4.75-4.63 (m, 1H, H₁₇), 4.41-4.17 (m, 5H, H₁,4,5,1₄), 3.86-3.64 (m, 5H, H₅,7,₁₄), 3.44 (q, J = 7.0 Hz, 2H, H₁₇), 3.31-3.11 (m, 3H, H₁₈,2₄), 2.91-2.36 (m, 3H, H₂,₁₈), 2.24-2.08 (m, 2H, H₃), 1.97 (bs, 3.5H, NH₁₃,3₄,1₆,2₂, H₂₀), 1.44-1.26 (m, 10H, NH₁₃,3₄,1₆,2₂, H₉), 1.15 (t, J = 7.0 Hz, 3H, H₃₈); ¹³C NMR (125 MHz, CD₂Cl₂) δ: 182.2, 175.9, 173.4, 172.7, 172.6, 172.1, 171.5, 170.1, 169.1, 166.1, 165.6, 164.9, 156.0 (C₁₅a/b), 155.7 (C₁₅a/b), 142.9 (C₂₈a/b), 136.6 (C₂₈a/b), 226.
127.6 (C\textsubscript{29}), 124.6 (C\textsubscript{26}), 122.1 (C\textsubscript{33}), 119.6 (C\textsubscript{31}), 118.4 (C\textsubscript{30}), 112.0 (C\textsubscript{32}), 110.5 (C\textsubscript{35a/b}), 109.7 (C\textsubscript{35a/b}), 81.5 (C\textsubscript{8a/b}), 80.6 (C\textsubscript{8a/b}), 78.1 (C\textsubscript{19}), 74.2 (C\textsubscript{35}), 66.1 (C\textsubscript{27a/b}), 66.0 (C\textsubscript{27a/b}), 62.8 (C\textsubscript{1a/b}), 62.2 (C\textsubscript{1a/b}), 61.4 (br, C\textsubscript{4}), 53.6 (C\textsubscript{23}), 53.1 (C\textsubscript{17}), 52.9 (C\textsubscript{7a/b}), 50.4 (C\textsubscript{7a/b}), 47.0 (C\textsubscript{5a/b}), 45.4 (C\textsubscript{5a/b}), 43.0 (C\textsubscript{14a/b}), 41.6 (C\textsubscript{14a/b}), 30.3 (C\textsubscript{3a/b}), 29.9 (C\textsubscript{3a/b}), 29.6 (C\textsubscript{2a/b}), 29.3 (C\textsubscript{2a/b}), 28.4 (C\textsubscript{9a/b}), 28.3 (C\textsubscript{9a/b}), 28.0 (C\textsubscript{24a/b}), 27.7 (C\textsubscript{24a/b}), 24.9 (C\textsubscript{18a/b}), 24.2 (C\textsubscript{18a/b}), 15.5 (C\textsubscript{20}), 14.3 (C\textsubscript{38a/b}), 14.1 (C\textsubscript{38a/b}); \textsuperscript{19}F NMR (376 MHz, CD\textsubscript{2}Cl\textsubscript{2}) \( \delta \): -146.5 – -146.6 (m, br, BF\textsubscript{4}); mp 47-48 °C (decomp.); m/z HRMS-(ESI)+ (m/z) Found [M – BF\textsubscript{4}]\textsuperscript{+}: 773.3283, C\textsubscript{35}H\textsubscript{49}N\textsubscript{8}O\textsubscript{10}S requires 773.3292 (\( \delta \) = 1.16 ppm). Diazocarbon is marked in brown.

**Figure 46:** LC-MS of crude reaction for 291a/b with SIM showing at m/z 773.
Pentapeptide methyl (tert-butoxycarbonyl)-L-methionylglycyl-L-prolylglycyl-L-tryptophanate (290, 0.10 g, 0.15 mmol) and (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl (TEMPO, 0.03 g, 0.2 mmol) was charged into a microwave tube, and the tube evacuated and refilled with N₂ (g). Acetonitrile (1 mL, distilled and bubbled with N₂ (g) overnight) was added into tube, followed by (1-diazo-2-ethoxy-2-oxoethyl)(2,4-difluorophenyl)iodonium tetrafluoroborate (281, 0.133 g, 0.30 mmol), as a solution in acetonitrile (1 mL) to give a final peptide concentration of 0.08 M, with stirring for 30 min. The solvent was evaporated in vacuo into a liquid nitrogen trap, and the contents dried for 2 h under vacuum. A suspension of rhodium(II) octanoate dimer (Rh₂(oct)₄, 0.012 g, 0.015 mmol) in hexafluoroisopropanol (20 mL) was added, with stirring for 30 min. The solution was concentrated in vacuo, re-dissolved in CH₂Cl₂, washed with brine (3x, 50 mL), dried (MgSO₄), and filtered through a C-18 silica reverse-phase packed column to remove the rhodium catalyst. Purification on reversed-phase (RP) HPLC afforded the desired compounds as a red powder, and as an inseparable mixture of isomers: N-H (293a) and C-H (293b) insertion products in 2:1 ratio, as well as diastereomeric mixtures – racemic about the sulfonium chiral centre (112 mg, 0.135 mmol, 90%).

(92S,3S,14S,Z)-14-((tert-butoxycarbonyl)amino)-18-(ethoxycarbonyl)-3-(methoxycarbonyl)-17-methyl-5,8,10,13-tetraoxo-11H-17-thia-4,7,12-triaza-1(3,1)-indola-9(2,1)-pyrrolidinacyclooctadecaphan-17-ium tetrafluoroborate (293a)

(92S,3S,14S)-14-((tert-butoxycarbonyl)amino)-18-(ethoxycarbonyl)-3-(methoxycarbonyl)-17-methyl-5,8,10,13-tetraoxo-11H-17-thia-4,7,12-triaza-1(3,6)-indola-9(2,1)-pyrrolidinacyclooctadecaphan-17-ium tetrafluoroborate (293b)
IR (thin film) $\nu_{\text{max}}$/cm$^{-1}$ 3257, 3152, 3019, 2975, 1681, 1637, 1613, 1521, 1428, 1335, 1241, 980; $^1$H NMR (500 MHz, CD$_2$Cl$_2$) $\delta_H$ 9.48-9.41 (m, 0.5H, H$_{26b}$), 8.92-8.79 (m, 1.5H, NH$_{27b}$, H$_{30b,32b}$), 8.75-8.71 (m, 0.5H, H$_{31b}$), 7.92-7.85 (m, 1H, NH$_{22/16/3/13}$), 7.52-7.48 (m, 1H, H$_{31a}$), 7.43-7.40 (m, 1H, NH$_{22/16/3/13}$), 7.35-7.33 (m, 1.5H, H$_{26a}$, NH$_{22/16/3/13}$), 7.28-7.24 (m, 1H, NH$_{22/16/3/13}$), 7.22-7.19 (m, 1H, NH$_{22/16/3/13}$), 7.17-7.13 (m, 1.5H, H$_{32a}$, NH$_{22/16/3/13}$), 7.09-7.06 (m, 2H, H$_{33a,30a}$), 6.92 (s, 0.5H, NH$_{22/16/3/13}$), 5.95-5.91 (m, 0.5H, NH$_{22/16/3/13}$), 4.95-4.78 (m, 1.5H, H$_{23a/b}$), 4.58-4.36 (m, 5H, H$_{35a,37a/b}$), 4.32-4.14 (m, 3.5H, H$_{17a,4a,23b,17b}$), 4.04-3.87 (m, 4.5H), 3.84-3.64 (m, 9H, H$_{38a/b,7a/b}$), 3.6-3.2 (m, 8H, H$_{24a/b,35b}$), 2.43-2.40 (m, 2.5H), 2.13-2.04 (m, 7H), 2.02 (s, 1.5H, H$_{20b}$), 2.01-1.99 (m, 2H), 1.97 (s, 3H, H$_{20a}$), 1.46-1.42 (m, 13.5H, H$_{9a/b}$); $^{13}$C NMR (125 MHz, CD$_2$Cl$_2$) $\delta$: 172.7, 172.6, 172.4, 172.3, 172.1, 172.0, 171.9, 171.9, 169.6, 169.5, 169.3, 168.9, 168.7, 168.4, 156.1 (C$_{15b}$), 155.8 (C$_{15a}$), 143.3 (C$_{28b}$), 141.9 (C$_{29b}$), 140.3 (C$_{30b}$), 138.8(C$_{32b}$), 137.6 (C$_{31b}$), 136.6 (C$_{26b}$), 136.4 (C$_{28a}$), 127.7 (C$_{29a}$), 126.0 (C$_{33b}$), 124.6 (C$_{25b}$), 124.0 (C$_{26a}$), 122.1 (C$_{33a}$), 119.6 (C$_{31a}$), 118.6 (C$_{30a}$), 111.7 (C$_{32a}$), 110.0 (C$_{25a}$), 80.2 (C$_{8a/b}$), 79.9 (C$_{8a/b}$), 70.1 (C$_{35a}$), 62.9, 61.2, 61.0, 54.1, 53.9, 53.7, 53.5, 53.2, 52.9, 52.8 (C$_{35b}$), 52.7 (C$_{7a/b}$), 52.5 (C$_{7a/b}$), 47.2, 46.8, 43.5, 43.3, 42.5, 42.2, 32.6, 32.5, 30.2, 28.9, 28.8, 28.6, 28.3 (C$_{9a}$), 28.29 (C$_{9b}$), 27.7, 27.4, 25.2, 25.0, 15.3 (C$_{20a/b}$), 15.3 (C$_{20a/b}$), 14.4 (C$_{38a/b}$), 14.38 (C$_{38a/b}$); $^{19}$F NMR (376 MHz, CD$_2$Cl$_2$) $\delta$: -146.55 -- -146.6 (m, br, BF$_4$); mp 75 °C (decomp.); m/z HRMS-(ESI)+ (m/z) Found [M – BF$_4$]$^+$: 745.3243, C$_{35}$H$_{49}$N$_6$O$_{10}$S requires 745.3225 ($\delta$ = 2.41 ppm). Proton and carbon assignments were made as thoroughly as possible. New C-H bond from insertion is marked in brown.
Figure 47: RP-HPLC purification using isocratic-gradient run combinations (5% MeCN in H2O for 1.5 min, 5-25% MeCN for 0.5 min, 25% MeCN for 13 min, 25-95% MeCN for 1 min, 95% MeCN for 2 min), collecting at 13.0-14.1 min.

Figure 48: UV-Vis spectroscopy of 293a/b at 1.0 x 10^{-6} M showing tryptophan absorption at 351.50 nm and 279.50 nm, with a new weaker absorption peak at 450.00 nm.
Figure 49: DEPT-135 $^{13}$C NMR spectra in CD$_2$Cl$_2$ showing distinct indole region for isomers 293a/b.

Figure 50: HSQC experiment showing four isomers, two diastereomers each for 262a and 262b. H$_{23a/b}$ was the only isolated proton peak in the $^1$H NMR studied.
Figure 51: Starting peptide substrate 290 in HSQC NMR.

Figure 52: Products 293a/b in HSQC NMR.
**Figure 53:** HSQC NMR showing new ethyl conjugate -CH$_2$ (H$_{37}$), and H$_4$.

**Figure 54:** HSQC NMR showing new ethyl conjugate -CH$_3$ (H$_{38}$).
Figure 55: Starting peptide substrate 290 HSQC NMR showing H₄, H₁₇ and H₂₃.

Figure 56: Products 293a/b HSQC NMR showing new H35a and H37a/b.
Figure 57: Starting peptide substrate 290 HSQC NMR showing H7.

Figure 58: Products 293a/b HSQC NMR showing new H15b and H7a/b.
Figure 59: Starting peptide substrate 290 HMBC NMR showing Trp indole region.

Figure 60: Products 293a/b HMBC NMR showing Trp indole region.
Figure 61: Starting peptide substrate 290 HMBC NMR showing benzylic region.

Figure 62: Products 293a/b HMBC NMR showing benzylic region for H_{35a,35b}. 
Figure 63: Starting peptide substrate 290 HMBC NMR showing benzylic region.

Figure 64: Products 293a/b HMBC NMR showing benzylic region for H^{35}b.
Figure 65: Starting peptide substrate 290 HMBC NMR showing benzylic region.

Figure 66: Products 293a/b HMBC NMR showing benzylic region for H_{35a}. 
Figure 67: Starting peptide substrate 290 NOESY NMR showing indole region.

Figure 68: Products 293a/b NOESY NMR. Interactions are too complicated to deconvolute.
Figure 69: DEPT-135 experiment showing only indole aryl region for starting linear peptide 290 (top left), diazo intermediate 291 (top right), and product macrocyclic peptides 293a/b (bottom).
(6S)-10-diazo-6-(methoxycarbonyl)-2,2,9-trimethyl-4,11-dioxo-3,12-dioxa-9-thia-5-azatetradecan-9-iium (322)

To a solution of methyl (tert-butoxycarbonyl)-L-methioninate (319, 26 mg, 0.1 mmol) in dichloromethane (0.67 mL) under N2 (g) atmosphere was added (1-diazo-2-ethoxy-2-oxoethyl)(2,4-difluorophenyl)iodonium tetrafluoroborate (281, 49 mg, 0.11 mmol) as solution in dichloromethane (0.67 mL), with stirring for 15 min at 25 °C, before precipitation by addition of 40-60 petroleum ether and standing in a 4°C refrigerator. The supernatant was then decanted, and the residue dried in vacuo to afford the desired compound as a faint yellow residue, and as a 1:1 mixture of diastereomers (35 mg, 0.093 mmol, 93%).

**Rf** 0.10 (20% methanol / dichloromethane); **IR** (thin film) νmax/cm⁻¹ 3388, 2981, 2143, 1703, 1514 (br), 1512, 1367, 1271, 1161, 854, 739; **¹H NMR** (500 MHz, CD₃CN) δH 5.85 (br s, 1H, NH₄), 4.35 (q, J = 7.1 Hz, 2H, H₁2), 4.29-4.17 (m, 1H, H₁), 3.85-3.77 (m, 1H, H₃), 3.71 (s, 3H, H₆), 3.58-3.49 (m, 1H, H₃), 3.17 (s, 1.5 H, H₄), 3.16 (s, 1.5H, H₄), 2.42-2.38 (m, 1H, H₂), 2.20-2.08 (m, 1H, H₂), 1.42 (s, 9H, H₀), 1.32 (app. t, J = 7.1 Hz, 3H, H₁₃); **¹³C NMR** (125 MHz, CD₃CN) δc 172.3 (C₅), 161.1 (C₁₁), 161.0 (C₁₁'), 156.9 (C₇), 81.0 (C₈), 80.8 (C₈'), 64.7 (C₁), 53.3 (C₆), 53.3 (C₁₂), 53.0 (br, C₁₀), 52.9 (br, C₁₀'), 43.2 (br, C₄), 42.6 (br, C₃), 28.5 (3C, C₉), 27.6 (br, C₂), 27.5 (br, C₂'), 14.4 (C₁₃); **¹⁹F NMR** (376 MHz, CD₃CN) δF -146.5₅ − −146.6 (m, br, BF₄); **m/z** HRMS-(ESI)+ (m/z) Found [M]⁺: 376.1545, C₁₅H₂₆N₃O₆S requires 376.1537.
(8S)-1-(3,5-bis(trifluoromethyl)phenyl)-4-diazo-8-(methoxycarbonyl)-5,12,12-
trimethyl-3,10-dioxo-2,11-dioxo-5-thia-9-azatridecan-5-ium (320)

To a solution of methyl (tert-butoxycarbonyl)-L-methioninate (319, 26 mg, 0.1 mmol) in
dichloromethane (0.67 mL) under N₂ (g) atmosphere was added (1-diazo-2-(3,5-
bis(trifluoromethyl)benzyl)-2-oxoethyl)(2,4-difluorophenyl)iodonium
tetrafluoroborate (318, 70 mg, 0.11 mmol) as solution in dichloromethane (0.67 mL),
with stirring for 15 min at 25 °C, before precipitation by addition of 40-60 petroleum
ether and standing in a 4°C refrigerator. The supernatant was then decanted, and the
residue dried in vacuo to afford the desired compound as a faint yellow residue, and as
a 1:1 mixture of diastereomers (43.7 mg, 0.076 mmol, 76%).

Rf 0.15 (20% methanol / dichloromethane); IR (thin film) νmax/cm⁻¹ 3361, 2956, 2137,
1680, 1508 (br), 1351, 1265, 1052, 906; ¹H NMR (500 MHz, CD₃CN) δH 7.92 (bs, 3H,
H₁₄,₁₆), 5.66 (bs, 1H, NH₁₈), 5.43 (s, 2H, H₁₂), 4.35 (bs, 1H, H₁), 3.99-3.87 (m, 1H, H₃),
3.77-3.64 (m, 4H, H₃,₆), 3.32 (s, 3H, H₄), 2.49-2.38 (m, 1H, H₂), 2.31-2.18 (m, 1H, H₂),
1.41-1.40 (m, 9H, H₃O); ¹³C NMR (125 MHz, CD₃CN) δc 171.7 (C₅), 160.3 (C₁₁), 156.4 (C₇),
137.2 (C₁₃), 132.4 (app. q, ³J_C-F = 33.5 Hz, 2C, C₁₅), 129.4 (2C, C₁₄), 123.6 (2C, ¹J_C-F = 272.2
Hz, C₁₇), 123.3 (C₁₆), 81.1 (C₈), 67.6 (C₁₂), 67.5 (C₁₀), 53.2 (C₆), 52.6 (br, C₁), 52.4 (br, C₁⁻),
42.8 (br, C₃), 42.3 (br, C₃⁻), 28.3₁ (C₉), 28.3 (C₉⁻), 27.9 (C₂), 27.6 (C₂⁻), 26.9 (C₄), 26.6 (C₄⁻);
¹⁹F NMR (376 MHz, CD₂Cl₂) δF -64.3 (s, 6F, CF₃), -151.2 - -151.3 (m, br, BF₄); m/z
HRMS-(ESI)+ (m/z) Found [M⁺]: 574.1455, C₂₂H₂₆F₆N₅O₆S requires 574.1447.
5.13 Solid-phase two-step conjugation-macrocyclisation of peptides:

On-resin pentapeptide substrate (0.017 mmol) was charged into a reacting vessel (plastic syringe, fitted with a porous frit), under N₂ (g) atmosphere. The set-up is shown on the next page. Resins were washed sequentially with CH₂Cl₂ 3x, MeOH 3x, and benzyl cyanide (PhCH₂CN) 3x, leaving it to swell in PhCH₂CN for 1 min. PhCH₂CN (1 mL, distilled and bubbled with N₂ (g) overnight) was added into tube, followed by (1-diazo-2-(3,5-bis(trifluoromethyl)benzyl)-2-oxoethyl)(2,4-difluorophenyl)iodonium tetrafluoroborate \(318, 26 \text{ mg}, 0.041 \text{ mmol}\), or ethyl 2-diazo-2-((2,4-difluorophenyl)(tetrafluoro-\(\lambda^5\)-boraneyl)-\(\lambda^3\)-iodaneyl)acetate \(281, 30 \text{ mg}, 0.068 \text{ mmol}\) as a solution in acetonitrile (2 mL) to give a final solvent ratio of 2:1 acetonitrile to PhCH₂CN. The mixture was stirred vigorously for 1 h and the solution drained. The resins were rinsed with acetonitrile (3x 4 mL), CH₂Cl₂ (3x 4 mL), MeOH (3x 4 mL), and again with CH₂Cl₂ (3x 4 mL). A suspension of rhodium(II) octanoate dimer \(\text{Rh}_2\text{(octa)}_4, 3.0 \text{ mg}, 0.007 \text{ mmol}\) in CH₂Cl₂:HFIP (1:4, 5 mL) was added, with stirring for 2 h. The solution was drained, and the resin washed with dichloromethane (3x 4 mL), methanol (3x 4 mL) and again with dichloromethane (3x 4 mL). Cleavage of the peptide was done using 0.1 M HCl in HFIP with 5% v/v TIPS, 3% w/v dithiothreitol (DTT), 2% v/v thioanisole, with stirring for 1 h, under N₂ (g) atmosphere. \textbf{Note: stirring longer will cause degradation.} The mixture was filtered, and the filtrate collected and concentrated \textit{in vacuo} before precipitating with diethyl ether. Purification with reverse-phase C-18 semi-preparative column on HPLC afforded the desired products as mixed isomers.
Reaction set-up shown on the left. (1) Peptides on resins are loaded into the plastic syringe, fitted with a filter and Teflon tap at the bottom, and sealed with a septum at the top. A nitrogen line is attached via a needle through the septum to ensure inert atmosphere, (2) and to supply positive pressure when washing and draining solvents down the tap and into a collector, prior to (3) macrocyclisation. The final cleavage step was also done under inert atmosphere in this set-up.

### Table 12: Solid-phase two-step conjugation-macrocyclisation of peptides

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Notes: (a) Sequence is written from C- to N- terminus; (b) IS = iodonium salt reagent used for the first step conjugation prior to rhodium-catalysed insertion; (c) conversion was calculated using total ion count (TIC) of peaks on the LC-MS against starting peptide substrate ions, using soft ESI ionisation; (d) product ratio was calculated using TIC of product peptide ions over total converted peptide ions; (e) m/z was calculated using [M]+ species (peptide C-terminus is CONH2); *(D)-amino acid residue.

### Single letter amino acid residue key


LC-MS and Tandem ms-ms spectra are shown in section 5.13.2, and in Appendix.
5.13.1 Considerations in using total ion count (TIC) for calculations

For the calculation of product ratios using total ion count (TIC), it was imperative that the right ionisation method be used. To prevent fragmentation of the parent molecular ion, electrospray ionisation (ESI), a softest ionisation method was used for calculations. The harsher atmospheric pressure chemical ionisation (APCI) method, typically used for quick assays of organic compounds on LC-MS, uses reactions between ions and sample molecules carried by hot (450 °C) N_2 gas, and would thus cause fragmentation of the molecular ion peaks upon analysis, leading to errors in TIC calculations. Furthermore, since the desired product is already positively charged, harsh ionisation was not required.
5.13.2 LC-MS spectra and tandem ms-ms analysis for macrocyclic peptide products

Macrocyclic peptide 293a/b

293a/b: Description: Tandem ms-ms analysis of product 293a/b. Sequence analysis using y-ions, where the first bond cleavage happens on the weak C-S bond, followed by sequential loss of Boc, Met (y4), Gly (y3), Pro (y2), and Gly (y1), from the N-terminus, affording the final molecular y-ion as Trp(conjugate) with [M+H]+ m/z 303.1324. The corresponding b-ions were, however, suppressed.
**Macro cyclic peptide 317a/b**

317a/b: Description: Tandem ms-ms analysis of product 317a/b. Sequence analysis using y-ions, where the first bond cleavage happens on the weak C-S+ bond, followed by sequential loss of Gly-Met (y4), Gly (y3), Pro (y2), and Gly (y1), from the N-terminus, affording the final molecular y-ion as Trp(conjugate) with [M+H]+ m/z 288.1407. Further loss of -OEt from the conjugate was also observed to afford Trp(conjugate-OEt) with [M+H]+ m/z 243.1142. The corresponding b-ions were, however, suppressed.
**324a/b**: Description: Tandem ms-ms analysis of product 324a/b. Sequence analysis using y-ions, where the first bond cleavage happens on the weak C-S bond, followed by sequential loss of Met (y4), Gly (y3), Pro (y2), and Gly (y1), from the N-terminus, affording the final molecular y-ion as Trp(conjugate) with [M+H]^+ m/z 488.1498. The corresponding b-ions (blue) followed a sequential loss starting with Trp(conjugate) (b4), and Gly (b2), from the C-terminus, giving the final molecular b-ion Pro-Gly-Met with [M]^+ m/z 286.1295.
**Macrocyclic peptide 325a/b**

**325a/b**: Description: Tandem ms-ms analysis of product 325a/b. Sequence analysis using y-ions, where the first bond cleavage happens on the weak C-S bond, followed by sequential loss of Gly-Met (y4), Gly (y3), Pro (y2), and Gly (y1), from the N-terminus, affording the final molecular y-ion as Trp(conjugate) with [M+H]+ m/z 486.1235. Further loss through fragmentation of NH and CO were also observed (green arrows). The corresponding b-ions were, however, suppressed.
Macrocyclic peptide 326a/b

**326a/b**: Description: Tandem ms-ms analysis of product 326a/b. Sequence analysis using y-ions, where the first bond cleavage happens on the weak C-S bond, followed by sequential loss of Gly-Met (y6), Gly (y5), Gly (y4), Pro (y3), Gly (y2), and Gly (y1) from the N-terminus, affording the final molecular y-ion as Trp(conjugate)-Gly-Gly with [M+H]+ m/z 600.1683. The corresponding b-ions were, however, suppressed.
**327a/b**: Description: Tandem ms-ms analysis of product 327a/b. Sequence analysis using y-ions, where the first bond cleavage happens on the weak C-S bond, followed by sequential loss of Gly-Met (y4), Ala (y3), and Pro-Ala (y1), from the N-terminus, affording the final molecular y-ion as Trp(conjugate)-Gly-Gly with [M+H]+ m/z 600.1739. Further loss of Gly-Gly from this was observed, affording molecular ion Trp(conjugate) at [M+H]+ m/z 469.1035. The corresponding b-ions (blue) followed a sequential loss from the C-terminus starting with Trp(conjugate)-Gly-Gly (b4), Ala (b3), Pro (b2), and Ala (b1), affording the final molecular b-ion Met(+) with [M]+ m/z 286.1295.
**Macrocyclic peptide 328a/b**

**328a/b:** Description: Tandem.ms-ms analysis of product 328a/b. Sequence analysis using y-ions (black). Where first bond cleavage happens on the weak C-S bond, followed by sequential loss of Gly-Met (y6), Ala (y5), Gly (y4), Pro-Gly (y2), and Ala (y1), from the N-terminus, affording the final molecular y-ion Trp(conjugate)-Gly-Gly with [M+H]^+ m/z 600.1730. The corresponding b-ions (blue) followed a sequential loss from the C-terminus, starting with Trp(conjugate)-Gly-Gly (b6), Ala (b5), and Gly (b4), affording the final molecular b-ion Gly-Met(+) Ala-Gly-Pro with [M]^+ m/z 414.1875. No further molecular b-ions were found.
**Macro cyclic peptide 329a/b**

329a/b: Description: Tandem ms-ms analysis of product 329a/b. Sequence analysis using y-ions (black). Where first bond cleavage happens on the weak C-S bond, followed by sequential loss of Gly-Met (y5), Gly (y4), Pro (y3) and Pro-Gly (y1), from the N-terminus, affording the final molecular y-ion Trp(conjugate)-Gly-Gly with [M+H]+ m/z 600.1638. For the corresponding b-ions (blue), only loss of Trp(conjugate)-Gly-Gly (b5) from the C-terminus was found, affording the final molecular b-ion Gly-Met-Gly-Pro-Pro-Gly with [M]+ m/z 497.2200.
Macrocyclic peptide 330a/b

Description: Tandem ms-ms analysis of product 330a/b. Sequence analysis using y-ions (black). Where first bond cleavage happens on the weak C-S bond, followed by sequential loss of Gly-Met (y5), Thr (y4), Phe (y3), Pro (y2) and Phe (y1), from the N-terminus, affording the final molecular y-ion Trp(conjugate)-Gly-Gly with [M+H]^+ m/z 600.1663. The corresponding b-ions (blue) followed a sequential loss from the C-terminus, starting with Trp(conjugate)-Gly-Gly (b6), Phe-Pro-Phe (b2), and Thr (b1), affording the final molecular b-ion Gly-Met(+) with [M]^+ m/z 189.0685.
**Macrocyclic peptide 331a/b**

331a/b: Description: Tandem ms-ms analysis of product 331a/b. Sequence analysis using y-ions (black). Where first bond cleavage happens on the weak C-S\(^+\) bond, followed by sequential loss of Met (y4), Lys (y3), and Pro-Phe (y1), from the N-terminus, affording the final y-ion Trp(conjugate) with [M+H]\(^+\) m/z 486.1362. Another pathway for y-ions was observed: sequential loss of Lys-Met(conjugate) (y3), and Pro (y2), affording the final y-ion Phe-Trp at [M+H]\(^+\) m/z 351.1878. The corresponding b-ions (blue) followed a sequential loss from the C-terminus, starting with Trp(conjugate) (b4), and Phe-Pro (b2), giving the final b-ion Lys-Met(+) with [M]\(^+\) m/z 260.1462.
**332a/b:** Description: Tandem ms-ms analysis of product 332a/b. Sequence analysis using y-ions (black). Where first bond cleavage happens on the weak C-S bond, followed by sequential loss of Met (y4), Glu (y3), Pro (y2), and Phe (y1), from the N-terminus, affording the final y-ion Trp(conjugate) with [M+H]+ m/z 486.1362. Another pathway for y-ions was observed: loss of Glu-Met(conjugate) (y3), affording the final y-ion Pro-Phe-Trp at [M+H]+ m/z 448.2438. The corresponding b-ions (blue) followed a sequential loss from the C-terminus, starting with Trp(conjugate) (b4), Phe (b3), and Pro (b2), affording the final b-ion Glu-Met(+) with [M]+ m/z 261.0973.
Macrocyclic peptide 333a/b

333a/b: Description: Tandem ms-ms analysis of product 333a/b. Sequence analysis using y-ions (black). Where first bond cleavage happens on the weak C-S* bond, followed by sequential loss of Met (y4), Asp (y3), Pro (y2), and Phe (y1), from the N-terminus, affording the final y-ion Trp(conjugate) with [M+H]^+ m/z 486.1362. The corresponding b-ions (blue) followed a sequential loss from the C-terminus, starting with Trp(conjugate) (b4), Phe (b3), and Pro (b2), affording the final b-ion Asp-Met(+) with [M]^+ m/z 247.0779.
**334a/b**: Description: Tandem ms-ms analysis of product 334a/b. Sequence analysis using y-ions (black). Where first bond cleavage happens on the weak C-S bond, followed by sequential loss of Met-Asn (y3), Pro (y2), and Phe (y1), from the N-terminus, affording the final y-ion Trp(conjugate) with [M+H]+ m/z 486.1362. The corresponding b-ions (blue) followed a sequential loss from the C-terminus, starting with Trp(conjugate) (b4), Phe (b3), and Pro (b2), affording the final b-ion Asn-Met(+) with [M]+ m/z 246.0949. Another pathway for b-ions was observed: sequential loss of H2, Trp (b4), Phe (b3), Pro (b2), and Asn (b1), affording the final b-ion (+)Met(conjugate) with [M]+ m/z 414.1002.
335a/b: Description: Tandem ms-ms analysis of product 335a/b. Sequence analysis using y-ions (black). Where first bond cleavage happens on the weak C-S bond, followed by sequential loss of Met-Thr (y3), Pro (y2), and Phe (y1), from the N-terminus, affording the final y-ion Trp(conjugate) with [M+H]^+ m/z 486.1362. The corresponding b-ions (blue) followed a sequential loss from the C-terminus, starting with Trp(conjugate) (b4), and Phe (b3), affording the final b-ion Pro-Thr-Met(+) with [M]^+ m/z 330.1530. Another pathway for b-ions was observed: sequential loss of H2, Trp (b4), Phe (b3), Pro (b2), and Thr (b1), affording the final b-ion (+)Met(conjugate) with [M]^+ m/z 414.1002.
References

References

References

References

129. Green, M.; Loewenstein, P. M. Cell 1988, 55, 1179-1188.
References

References

References

6.0 Appendix 1: Publications
Enantioselective Copper-Catalyzed Arylation-Driven Semipinacol Rearrangement of Tertiary Allylic Alcohols with Diaryliodonium Salts

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Supporting Information

ABSTRACT: A copper-catalyzed enantioselective arylative semipinacol rearrangement of allylic alcohols using diaryliodonium salts is reported. Chiral Cu(II)-bisoxazoline catalysts initiate an electrophilic alkene arylation, triggering a 1,2-alkyl migration to afford a range of nonracemic spirocyclic ketones with high yields, diastereoselectivities.

The class of reactions described as semipinacol rearrangements (SPRs) have become cornerstone transformations in complex molecule synthesis. Described simply as a process in which a C−C or C−H bond attached to an oxygen-containing carbon atom undergoes a 1,2-migration to a vicinal electrophilic carbon center, SPRs are most easily defined by the nature of the electrophilic activation pathway. While the classical SPR involves activation of a leaving group, thereby generating the requisite electrophilic carbon, the use of allylic alcohols as substrates has dramatically expanded the efficacy of the generic transformation. Based on the availability of allylic alcohols, there has been burgeoning interest in the development of catalytic enantioselective variants of this type of SPR; notable seminal examples include alkene activation via halogenation and epoxidation, and Brønsted acid catalysis. Interestingly, catalytic enantioselective SPRs involving a C−C bond formation step as part of the alkene activation are rare (eq 1). We reasoned that the asymmetric introduction of a carbon-based electrophile as part of an SPR would generate synthetically useful ketone scaffolds displaying vicinal quaternary and aryl-containing tertiary stereogenic centers, which would be nontrivial to form by alternate means.

Our laboratory, and also that of MacMillan, has introduced the use of asymmetric copper-bisoxazoline complexes in combination with diaryliodonium salts to provide convenient access to catalytically generated chiral aromatic electrophile equivalents. The chiral Cu(III)-aryl intermediates (formed as part of this activation mode) undergo union with nucleophiles such as enol silanes and indoles, providing a means for enantioselective arylation of ketones with high enantioselectivities. Central to the success of these enantioselective arylation reactions has been the apparent necessity for the substrate to engage in two-point binding with the Cu(III)-aryl intermediate.

In an effort to demonstrate the wide-ranging applications of this enantioselective alkene arylation tactic, we speculated that allylic alcohols may participate in a bidentate coordination to the electrophilic Cu(III) species that could lead to an arylation-driven SPR. Our design plan for this process is shown in eq 2 and begins with binding of an allylic alcohol to the Cu(III)−Ar complex formed from the combination of allylic alcohol 1, diaryliodonium salt 2, and the Cu-complex of bisoxazoline ligand (R,R)−3. Insertion of the Cu(III)−Ar bond to the ligated alkene generates a Cu(III)−alkyl intermediate int-II. This species possesses the requisite partial positive charge adjacent to the carbinol to trigger the stereoselective 1,2-migration of one of the carbinol substituents and complete an arylation-driven SPR to nonracemic α,α'-disubstituted-β-arylketone 4.

To test this hypothesis, we selected allylic alcohol 1a, in combination with conditions first identified from our work on the arylation of enolsilanes. We found that reaction of 1a with...
diphenyliodonium triflate 2a, 2,6-di-tert-butylpyridine (DTBP) as base, and 10 mol % of Cu(OTf)$_2·(R,R)$-PhBox gave a low yield of racemic spirocyclic ketone 4a, as a single diastereomer (Table 1, entry 1). Changing the counteranion of salt 2 from OTf to BF$_4$ gave a 61% yield of 4a with an enantiomeric ratio (e.r.) of 70:30 (entry 2). Inspired by this, we found that further adjustment of the salt 2 to include a PF$_6$ counteranion resulted in a reaction that gave a 95% yield of 4a in 92.5:7.5 e.r. (entry 3). Lowering the temperature of the reaction to 5 °C further increased the e.r. of 4a without compromising the yield of the reaction (entry 4). Systematic investigation of other parameters revealed that changing the solvent away from dichloromethane (see Supporting Information), using inorganic bases in place of DTBP, and changing the Cu-catalyst all had a deleterious effect on both the yield and e.r. of the product (entries 4−7). Optimal conditions for the reaction were found to involve treatment of 1a with 2 equiv of (Mes)PhI−PF$_6$ 2c, 2 equiv of DTBP, and 5 mol % of catalyst (R,R)-3-Cu(OTf)$_2$ in a 0.3 M solution of dichloromethane at 5 °C for 48 h, which gave a single diastereomer of spirocyclic ketone 4a in 96% yield and an e.r. of 97:3.

With an optimal set of reaction conditions in hand, we next explored the scope of the enantioselective arylative SPR. First, the substituents directly appended to the allylic carbinol were varied. We found that a variety of cyclobutyl-derived allylic alcohols could be successfully employed as substrates (Table 2, 1a−d). Particularly interesting was arylative SPR of oxetane and azetidine-containing substrates, which formed the single diasteroisomers of the corresponding spirocyclic tetrahydrofuranone and pyrrolidinone in good yield and high e.r. (4c−d).

A cyclopentyl- and indane-derived system also underwent smooth arylative SPR to form the 6−6 spiroketones in excellent yields and diastereoselectivities and with 96:4 and 99.5:0.5 e.r. respectively (4e−f).

In changing the tetrahydrofuran ring, we found that the indene- and tetrahydronapthalene framework worked well with both cyclobutyl and cyclopentyl carbinol substituents (1g−k) to form the corresponding products (4g−4k) in excellent yields and enantioselectivities. It was noticeable that for successful enantioselective arylative-SPR, the allylic alcohol substrate required inherent strain within the carbinol substituents; dimethyl or cyclohexyl derivatives did not undergo SPR. Importantly, spiroketone 5c was crystalline, enabling assignment of the absolute configuration using X-ray diffraction of a single crystal. Moreover, recrystallization upgraded the e.r. to >99.5:0.5.
Next, we explored the scope of the diaryliodonium salts that could be used in the catalytic enantioselective arylative SPR. First, using indene-derived allylic alcohol \(1h\), we found that a broad range of substituted aryl groups could be transferred as part of the reaction (Table 3, 5a−p). For example, arenes displaying electron-donating and -withdrawing substituents, useful functional handles for downstream transformations, extended arene systems, and even the ortho-substituted arenes were all successfully applied in the catalytic SPR process to form the indane-derived spiroketones in excellent yields, diastereoselectivities, and enantiomeric ratios. We also found that arylation of the tetrahydropyran-derived allylic alcohol \(1e\) was compatible with a number of diaryliodonium salts, delivering the desired products (6a−d) in high yields and e.r.

Table 3. Scope of Diaryliodonium Salt

<table>
<thead>
<tr>
<th>Diaryliodonium Salt</th>
<th>Product</th>
<th>Yield (%)</th>
<th>e.r.</th>
<th>R1</th>
<th>R2</th>
</tr>
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<tr>
<td>5a</td>
<td>77</td>
<td>97:3</td>
<td>R1</td>
<td>R2</td>
<td></td>
</tr>
<tr>
<td>5b</td>
<td>99</td>
<td>95:5:4.5</td>
<td>R1</td>
<td>R2</td>
<td></td>
</tr>
<tr>
<td>5c</td>
<td>99</td>
<td>97:3</td>
<td>R1</td>
<td>R2</td>
<td></td>
</tr>
<tr>
<td>5d</td>
<td>91</td>
<td>95:5</td>
<td>R1</td>
<td>R2</td>
<td></td>
</tr>
<tr>
<td>5e</td>
<td>99</td>
<td>96:4</td>
<td>R1</td>
<td>R2</td>
<td></td>
</tr>
<tr>
<td>5f</td>
<td>96</td>
<td>96:4</td>
<td>R1</td>
<td>R2</td>
<td></td>
</tr>
<tr>
<td>5g</td>
<td>94</td>
<td>95:5:2.5</td>
<td>R1</td>
<td>R2</td>
<td></td>
</tr>
<tr>
<td>5h</td>
<td>81</td>
<td>81:19</td>
<td>R1</td>
<td>R2</td>
<td></td>
</tr>
<tr>
<td>5i</td>
<td>99</td>
<td>95:5</td>
<td>R1</td>
<td>R2</td>
<td></td>
</tr>
<tr>
<td>5j</td>
<td>99</td>
<td>96:4</td>
<td>R1</td>
<td>R2</td>
<td></td>
</tr>
<tr>
<td>5k</td>
<td>99</td>
<td>96:4</td>
<td>R1</td>
<td>R2</td>
<td></td>
</tr>
<tr>
<td>5l</td>
<td>99</td>
<td>96:4</td>
<td>R1</td>
<td>R2</td>
<td></td>
</tr>
<tr>
<td>5m</td>
<td>85</td>
<td>95:5</td>
<td>R1</td>
<td>R2</td>
<td></td>
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<td>5n</td>
<td>94</td>
<td>95:5:0.5</td>
<td>R1</td>
<td>R2</td>
<td></td>
</tr>
<tr>
<td>5o</td>
<td>71</td>
<td>95:5</td>
<td>R1</td>
<td>R2</td>
<td></td>
</tr>
<tr>
<td>5p</td>
<td>61</td>
<td>93:70</td>
<td>R1</td>
<td>R2</td>
<td></td>
</tr>
<tr>
<td>5q</td>
<td>82</td>
<td>96:4</td>
<td>R1</td>
<td>R2</td>
<td></td>
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<tr>
<td>5r</td>
<td>63</td>
<td>93:5:0.5</td>
<td>R1</td>
<td>R2</td>
<td></td>
</tr>
</tbody>
</table>

*Reaction with symmetrical diaryliodonium salt.

The \(\beta\)-aryl-\(\alpha,\alpha'\)-spirocyclic ketone moiety presents an interesting rigid scaffold with spatially defined functionality that may be useful as a starting point in the design of small molecules to probe biological processes. Toward this, we performed a series of simple transformations to elaborate the novel scaffolds by increasing stereochemical complexity or functional diversity (Scheme 1). First, we found that the ketone could be reduced with \(\text{L-selectride}\) to give a single carbinol product 7. A two-step reductive amination protocol from 5c delivered secondary amine 8 in excellent yield and selectivity. Alternatively, Baeyer–Villiger oxidation with mCPBA transformed the cyclohexanone motif to a seven-membered ring spiro-lactone 9 in excellent yield. Finally, we found that a related oxidative ring expanding transformation on the tetrahydropyranyl-derived ketone 4f produced the spiroketal 10 in almost quantitative yield.

Finally, we conducted preliminary experiments to assess whether the enantioselective arylative SPR was compatible with acyclic allylic alcohol substrates. We were pleased to observe promising levels of enantioselectivity for simple cyclobutane-derived allylic alcohols 11a−b to form monocyclic ketones 12a−b. Although the selectivity is lower than that for the cyclic substrates shown in Tables 1 and 2, the results in Scheme 2 suggest that a more general array of allylic alcohols may be compatible with this enantioselective process; studies toward this ideal are ongoing.

In summary, we have developed an enantioselective Cu-catalyzed arylative SPR using diaryliodonium salts, which transforms allylic alcohols into spirocyclic ketones in high yield and enantiomeric ratios. The enantioenriched spirocyclic ketones display vincinal \(\alpha,\alpha'\)-quaternary and \(\beta\)-aryl tertiary centers, often as single diastereomers, and can undergo complexity-generating reactions to a variety of novel molecular scaffolds. This operationally simple process uses readily available starting materials and a commercial catalyst and...
bisoxazoline ligand, which we believe will be useful to practitioners of chemical synthesis.

**ASSOCIATED CONTENT**

1. Supporting Information
   The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b05340.

   Experimental procedures and characterization data for all compounds (PDF)
   Crystallographic data for 5c (ZIP)

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Notes
The authors declare no competing financial interest.

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7.0 Appendix 2: Optimisation Tables
Table S1: Base screening for reactions with substrates 68 and 130

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<th>#</th>
<th>substrate</th>
<th>base</th>
<th>−X</th>
<th>catalyst</th>
<th>product</th>
<th>yield</th>
<th>e.e.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>130</td>
<td>None</td>
<td>-</td>
<td>PF₆</td>
<td>133</td>
<td>0%</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>130</td>
<td>MS 4Å</td>
<td>-</td>
<td>PF₆</td>
<td>133</td>
<td>0%</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>130</td>
<td>iPr₂(Et)N</td>
<td>-</td>
<td>PF₆</td>
<td>133</td>
<td>0%</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>130</td>
<td>KHCO₃</td>
<td>-</td>
<td>PF₆</td>
<td>133</td>
<td>0%</td>
<td>-</td>
</tr>
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<td>5</td>
<td>130</td>
<td>NaHCO₃</td>
<td>-</td>
<td>PF₆</td>
<td>133</td>
<td>131 (134)</td>
<td>18% (15%)</td>
</tr>
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<td>6</td>
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<td>NaHCO₃ + 3Å MS</td>
<td>-</td>
<td>PF₆</td>
<td>133</td>
<td>131 (134)</td>
<td>19% (18%)</td>
</tr>
<tr>
<td>7</td>
<td>130</td>
<td>NaH₂PO₄ + 3Å MS</td>
<td>-</td>
<td>PF₆</td>
<td>133</td>
<td>131 (134)</td>
<td>3% (9%)</td>
</tr>
<tr>
<td>8</td>
<td>130</td>
<td>K₂CO₃</td>
<td>-</td>
<td>PF₆</td>
<td>133</td>
<td>131 (134)</td>
<td>5% (5%)</td>
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<tr>
<td>9</td>
<td>130</td>
<td>Cs₂CO₃</td>
<td>-</td>
<td>PF₆</td>
<td>133</td>
<td>131 (134)</td>
<td>N.R.</td>
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<td>10</td>
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<td>Li₂CO₃</td>
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<td>133</td>
<td>131 (134)</td>
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<td>133</td>
<td>-</td>
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<td>0%</td>
</tr>
<tr>
<td>13</td>
<td>130</td>
<td>Na₂CO₃</td>
<td>-</td>
<td>PF₆</td>
<td>133</td>
<td>131 (134)</td>
<td>25% (7%)</td>
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<td>130</td>
<td>Na₃PO₄</td>
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<td>Na₃PO₄</td>
<td>-</td>
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<td>Na₃PO₄</td>
<td>-</td>
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<td>SbF₆</td>
<td>133</td>
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<td>13% (0%)</td>
</tr>
<tr>
<td>19</td>
<td>68</td>
<td>Na₃PO₄</td>
<td>-</td>
<td>PF₆</td>
<td>133</td>
<td>70</td>
<td>3%</td>
</tr>
<tr>
<td>20</td>
<td>68</td>
<td>Na₂CO₃</td>
<td>-</td>
<td>PF₆</td>
<td>133</td>
<td>70</td>
<td>32%</td>
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<tr>
<td>21</td>
<td>68</td>
<td>Na₂CO₃</td>
<td>-</td>
<td>PF₆</td>
<td>133</td>
<td>70</td>
<td>41%ₗ</td>
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</table>

Notes: (a) reaction was performed at 30 °C, instead of 25 °C, to improve yield without sacrificing enantioselectivities.
Table S2: Reaction studies with substrates 137 and 138

<table>
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<tr>
<th>#</th>
<th>substrate</th>
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<th>catalyst</th>
<th>product</th>
<th>yield</th>
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<td>OTf</td>
<td>DTBP</td>
<td>70 °C</td>
<td>CuCl</td>
<td>139</td>
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<tr>
<td>2</td>
<td>137</td>
<td>OTf</td>
<td>DTBP</td>
<td>50 °C</td>
<td>133</td>
<td>139</td>
<td>96%</td>
<td>2:1</td>
<td>0%</td>
</tr>
<tr>
<td>3</td>
<td>137</td>
<td>PF6</td>
<td>DTBP</td>
<td>50 °C</td>
<td>133</td>
<td>-</td>
<td>0%</td>
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<td>-</td>
</tr>
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<td>4</td>
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<td>&gt;20:1</td>
<td>38%</td>
</tr>
<tr>
<td>5</td>
<td>137</td>
<td>PF6</td>
<td>Na3PO4</td>
<td>30 °C</td>
<td>133</td>
<td>139</td>
<td>15%</td>
<td>&gt;20:1</td>
<td>52%</td>
</tr>
<tr>
<td>6</td>
<td>137</td>
<td>PF6</td>
<td>Na2CO3</td>
<td>30 °C</td>
<td>133</td>
<td>139</td>
<td>1%</td>
<td>28%</td>
<td>64%b</td>
</tr>
<tr>
<td>7</td>
<td>137</td>
<td>PF6</td>
<td>DTBP</td>
<td>30 °C</td>
<td>133d</td>
<td>139</td>
<td>6%</td>
<td>&gt;20:1</td>
<td>57%</td>
</tr>
<tr>
<td>8</td>
<td>137</td>
<td>PF6</td>
<td>DTBP</td>
<td>0 °C</td>
<td>133d</td>
<td>139</td>
<td>14%</td>
<td>&gt;20:1</td>
<td>68%</td>
</tr>
<tr>
<td>9</td>
<td>138</td>
<td>OTf</td>
<td>DTBP</td>
<td>70 °C</td>
<td>CuCl</td>
<td>140</td>
<td>30%</td>
<td>&gt;20:1</td>
<td>0%</td>
</tr>
<tr>
<td>10</td>
<td>138</td>
<td>OTf</td>
<td>DTBP</td>
<td>50 °C</td>
<td>133</td>
<td>140</td>
<td>30%</td>
<td>&gt;20:1</td>
<td>0%</td>
</tr>
<tr>
<td>11</td>
<td>138</td>
<td>PF6</td>
<td>DTBP</td>
<td>50 °C</td>
<td>132</td>
<td>-</td>
<td>0%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>138</td>
<td>PF6</td>
<td>Na3PO4</td>
<td>30 °C</td>
<td>133</td>
<td>140</td>
<td>7%</td>
<td>&gt;20:1</td>
<td>70%</td>
</tr>
<tr>
<td>13</td>
<td>138</td>
<td>PF6</td>
<td>Na2CO3</td>
<td>30 °C</td>
<td>133</td>
<td>140</td>
<td>4%</td>
<td>&gt;20:1</td>
<td>70%</td>
</tr>
<tr>
<td>14</td>
<td>138</td>
<td>PF6</td>
<td>DTBP</td>
<td>30 °C</td>
<td>133</td>
<td>140</td>
<td>29%</td>
<td>&gt;20:1</td>
<td>58%</td>
</tr>
<tr>
<td>15</td>
<td>138</td>
<td>PF6</td>
<td>DTBP</td>
<td>30 °C</td>
<td>133d</td>
<td>140</td>
<td>8%</td>
<td>&gt;20:1</td>
<td>68%</td>
</tr>
<tr>
<td>16</td>
<td>138</td>
<td>PF6</td>
<td>DTBP</td>
<td>0 °C</td>
<td>133d</td>
<td>140</td>
<td>12%</td>
<td>&gt;20:1</td>
<td>73%</td>
</tr>
<tr>
<td>17</td>
<td>138</td>
<td>AsF6</td>
<td>Na2CO3</td>
<td>30 °C</td>
<td>133</td>
<td>140</td>
<td>5%</td>
<td>&gt;20:1</td>
<td>70%</td>
</tr>
<tr>
<td>18</td>
<td>138</td>
<td>SbF6</td>
<td>Na2CO3</td>
<td>30 °C</td>
<td>133</td>
<td>140</td>
<td>2%</td>
<td>&gt;20:1</td>
<td>66%</td>
</tr>
</tbody>
</table>

Note: Unless otherwise stated, reactions were run for 24 h at 0.125 M in CH2Cl2 and conversions were in general incomplete in a reasonable amount of time; (a) reaction was done in 2 h in 1,2-dichloroethane (DCE) instead of CH2Cl2; (b) other diastereomer has an e.e. of 94%; (c) conversion was complete; (d) 5 mol% of catalyst 133 was used instead and concentration of substrates were decreased to 0.03 M.
Table S3: Preliminary diaryliodonium salt reagent scope for substrate 90

![Chemical structure](image)

<table>
<thead>
<tr>
<th>#</th>
<th>Ar</th>
<th>product</th>
<th>temp.</th>
<th>time</th>
<th>yield</th>
<th>d.r.</th>
<th>e.e.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(Ph)$_2$, 146</td>
<td>145</td>
<td>5 °C</td>
<td>48 h</td>
<td>98%</td>
<td>&gt;20:1</td>
<td>91%</td>
</tr>
<tr>
<td>2</td>
<td>(Ph)$_2$, 146</td>
<td>145</td>
<td>10 °C</td>
<td>23 h</td>
<td>98%</td>
<td>&gt;20:1</td>
<td>85%</td>
</tr>
<tr>
<td>3</td>
<td>(Ph)$_2$, 146</td>
<td>145</td>
<td>20 °C</td>
<td>4 h</td>
<td>95%</td>
<td>&gt;20:1</td>
<td>84%</td>
</tr>
<tr>
<td>4</td>
<td>(Ph)$_2$, 146</td>
<td>145</td>
<td>30 °C</td>
<td>2 h</td>
<td>96%</td>
<td>&gt;20:1</td>
<td>80%</td>
</tr>
<tr>
<td>5</td>
<td>Mes(Ph), 184</td>
<td>145</td>
<td>5 °C</td>
<td>48 h</td>
<td>96%</td>
<td>&gt;20:1</td>
<td>94%</td>
</tr>
<tr>
<td>6</td>
<td>Mes(Ph), 184</td>
<td>145</td>
<td>10 °C</td>
<td>20 h</td>
<td>96%</td>
<td>&gt;20:1</td>
<td>80%</td>
</tr>
<tr>
<td>7</td>
<td>Mes(Ph), 184</td>
<td>145</td>
<td>20 °C</td>
<td>12 h</td>
<td>95%</td>
<td>&gt;20:1</td>
<td>78%</td>
</tr>
<tr>
<td>8</td>
<td>Mes(Ph), 184</td>
<td>145</td>
<td>30 °C</td>
<td>5 h</td>
<td>91%</td>
<td>&gt;20:1</td>
<td>78%</td>
</tr>
<tr>
<td>9</td>
<td>Mes(Tol), 185</td>
<td>189</td>
<td>10 °C</td>
<td>8 h</td>
<td>96%</td>
<td>&gt;20:1</td>
<td>82%</td>
</tr>
<tr>
<td>10</td>
<td>Mes(Tol), 185</td>
<td>189</td>
<td>20 °C</td>
<td>8 h</td>
<td>97%</td>
<td>&gt;20:1</td>
<td>81%</td>
</tr>
<tr>
<td>11</td>
<td>Mes(Tol), 185</td>
<td>189</td>
<td>30 °C</td>
<td>4 h</td>
<td>82%</td>
<td>&gt;20:1</td>
<td>79%</td>
</tr>
<tr>
<td>12</td>
<td>Mes(Ar-i-Bu), 186</td>
<td>190</td>
<td>10 °C</td>
<td>8 h</td>
<td>99%</td>
<td>&gt;20:1</td>
<td>80%</td>
</tr>
<tr>
<td>13</td>
<td>Mes(Ar-i-Bu), 186</td>
<td>190</td>
<td>20 °C</td>
<td>7 h</td>
<td>97%</td>
<td>&gt;20:1</td>
<td>78%</td>
</tr>
<tr>
<td>14</td>
<td>Mes(Ar-i-Bu), 186</td>
<td>190</td>
<td>30 °C</td>
<td>3 h</td>
<td>96%</td>
<td>&gt;20:1</td>
<td>76%</td>
</tr>
<tr>
<td>15</td>
<td>(ArCl)$_2$, 188</td>
<td>191</td>
<td>10 °C</td>
<td>48 h$^a$</td>
<td>80%$^a$</td>
<td>&gt;20:1</td>
<td>77%</td>
</tr>
<tr>
<td>16</td>
<td>(ArCl)$_2$, 188</td>
<td>191</td>
<td>20 °C</td>
<td>5 h</td>
<td>96%</td>
<td>&gt;20:1</td>
<td>81%</td>
</tr>
<tr>
<td>17</td>
<td>(ArCl)$_2$, 188</td>
<td>191</td>
<td>30 °C</td>
<td>5 h</td>
<td>98%</td>
<td>&gt;20:1</td>
<td>77%</td>
</tr>
<tr>
<td>18</td>
<td>Mes(ArCl), 187</td>
<td>191</td>
<td>10 °C</td>
<td>16 h</td>
<td>97%</td>
<td>&gt;20:1</td>
<td>64%</td>
</tr>
<tr>
<td>19</td>
<td>Mes(ArCl), 187</td>
<td>191</td>
<td>30 °C</td>
<td>6 h</td>
<td>97%</td>
<td>&gt;20:1</td>
<td>51%</td>
</tr>
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</table>

Note: (a) Conversion could not be completed in 48 h; low solubility of iodonium salt at this temperature.
Table S4: Rh-catalysed insertions of pentapeptide diazo-conjugate 256 into Trp

<table>
<thead>
<tr>
<th>#</th>
<th>Solvent(^a) (0.5 mM)</th>
<th>[Rh] (^b) (0.05 mM)</th>
<th>Purified(^b) 291?</th>
<th>Conv.(^a/b)</th>
<th>293</th>
<th>310</th>
<th>311</th>
<th>290</th>
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<tbody>
<tr>
<td>1</td>
<td>H(_2)O</td>
<td>Rh(_2)OAc(_4)</td>
<td>Yes</td>
<td>84%</td>
<td>10%</td>
<td>20%</td>
<td></td>
<td>54%</td>
</tr>
<tr>
<td>2</td>
<td>H(_2)O</td>
<td>Rh(_2) (CF(_3)CO(_2))(_4)</td>
<td>Yes</td>
<td>&lt;5%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>H(_2)O</td>
<td>Rh(_2)(esp)(_4)</td>
<td>Yes</td>
<td>90%</td>
<td></td>
<td></td>
<td></td>
<td>90%</td>
</tr>
<tr>
<td>4</td>
<td>H(_2)O</td>
<td>Rh(_2)(oct)(_4)</td>
<td>Yes</td>
<td>95%</td>
<td></td>
<td></td>
<td></td>
<td>95%</td>
</tr>
<tr>
<td>5</td>
<td>MeCN/H(_2)O</td>
<td>Rh(_2)OAc(_4)</td>
<td>Yes</td>
<td>50%</td>
<td>3%</td>
<td>18%</td>
<td>12%</td>
<td>17%</td>
</tr>
<tr>
<td>6</td>
<td>MeCN/H(_2)O</td>
<td>Rh(_2)OAc(_4)</td>
<td>No</td>
<td>70%</td>
<td>11%</td>
<td>32%</td>
<td>11%</td>
<td>16%</td>
</tr>
<tr>
<td>7</td>
<td>tBuOH/H(_2)O</td>
<td>Rh(_2)OAc(_4)</td>
<td>Yes</td>
<td>76%</td>
<td></td>
<td></td>
<td></td>
<td>76%</td>
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<tr>
<td>8</td>
<td>Acetone/H(_2)O</td>
<td>Rh(_2)OAc(_4)</td>
<td>Yes</td>
<td>&gt;95%</td>
<td></td>
<td></td>
<td></td>
<td>95%</td>
</tr>
<tr>
<td>9</td>
<td>DMSO/H(_2)O</td>
<td>Rh(_2)OAc(_4)</td>
<td>Yes</td>
<td>&gt;95%</td>
<td></td>
<td></td>
<td></td>
<td>95%</td>
</tr>
<tr>
<td>10</td>
<td>DMF/H(_2)O</td>
<td>Rh(_2)OAc(_4)</td>
<td>Yes</td>
<td>&gt;95%</td>
<td></td>
<td></td>
<td></td>
<td>95%</td>
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<tr>
<td>11</td>
<td>THF/H(_2)O</td>
<td>Rh(_2)OAc(_4)</td>
<td>Yes</td>
<td>&gt;95%</td>
<td></td>
<td></td>
<td></td>
<td>95%</td>
</tr>
<tr>
<td>12</td>
<td>(CH(_2)OH)(_2)/H(_2)O</td>
<td>Rh(_2)OAc(_4)</td>
<td>Yes</td>
<td>38%</td>
<td></td>
<td></td>
<td></td>
<td>38%</td>
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<tr>
<td>13</td>
<td>IPA/H(_2)O</td>
<td>Rh(_2)OAc(_4)</td>
<td>Yes</td>
<td>50%</td>
<td></td>
<td></td>
<td></td>
<td>50%</td>
</tr>
<tr>
<td>14</td>
<td>EtOH/H(_2)O</td>
<td>Rh(_2)OAc(_4)</td>
<td>Yes</td>
<td>74%</td>
<td></td>
<td></td>
<td></td>
<td>74%</td>
</tr>
<tr>
<td>15</td>
<td>MeOH/H(_2)O</td>
<td>Rh(_2)OAc(_4)</td>
<td>Yes</td>
<td>49%</td>
<td></td>
<td></td>
<td></td>
<td>49%</td>
</tr>
<tr>
<td>16</td>
<td>TFE/H(_2)O</td>
<td>Rh(_2)OAc(_4)</td>
<td>Yes</td>
<td>80%</td>
<td>13%</td>
<td></td>
<td></td>
<td>67%</td>
</tr>
<tr>
<td>17</td>
<td>TFE</td>
<td>Rh(_2)OAc(_4)</td>
<td>Yes</td>
<td>88%</td>
<td>70%</td>
<td></td>
<td></td>
<td>18%</td>
</tr>
<tr>
<td>18</td>
<td>TFE</td>
<td>Rh(_2)(oct)(_4)</td>
<td>Yes</td>
<td>92%</td>
<td>71%</td>
<td></td>
<td></td>
<td>21%</td>
</tr>
<tr>
<td>19</td>
<td>TFE</td>
<td>Rh(_2)(esp)(_4)</td>
<td>Yes</td>
<td>76%</td>
<td>41%</td>
<td></td>
<td></td>
<td>35%</td>
</tr>
<tr>
<td>20</td>
<td>TFE (dry)</td>
<td>Rh(_2)OAc(_4)</td>
<td>Yes</td>
<td>96%</td>
<td>79%</td>
<td></td>
<td></td>
<td>11%</td>
</tr>
<tr>
<td></td>
<td>Solvent (dry)</td>
<td>Rh Catalyst</td>
<td>Use Thiourea</td>
<td>Isolated Conversion (%)</td>
<td>Product Conversion (%)</td>
<td>Yield (mg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>----</td>
<td>---------------</td>
<td>-------------</td>
<td>---------------</td>
<td>--------------------------</td>
<td>------------------------</td>
<td>------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>TFE (dry)</td>
<td>Rh(_2)(oct)(_4)</td>
<td>Yes</td>
<td>97%</td>
<td>78%</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>HFIP (dry)</td>
<td>Rh(_2)OAc(_4)</td>
<td>Yes</td>
<td>96%</td>
<td>85%</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>HFIP (dry)</td>
<td>Rh(_2)(oct)(_4)</td>
<td>Yes</td>
<td>97%</td>
<td>88%</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>HFIP (dry)</td>
<td>Rh(_2)(oct)(_4)</td>
<td>No</td>
<td>99%</td>
<td>90%</td>
<td>-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: (a) IPA = isopropanol, TFE = trifluoroethanol, HFIP = hexafluoroisopropanol; (b) “No” for this meant that the reaction was performed in one pot and in situ without addition of thiourea by first evacuating the solvent from the previous step and replacing it with a solution of the Rh(II) catalyst in the desired solvent.
8.0 Appendix 3: NMR Spectra
MeOTMS

1H NMR
CDCl₃

149
$^1$H NMR
CDCl$_3$
190
$^{13}$C NMR
CDCl$_3$

135
$^1$H NMR
CD$_2$Cl$_2$
137
$^{13}$C NMR
CD$_2$CO$_2$
137
$^{13}$C NMR
CDCl$_3$
136
$^{13}$C NMR

$\text{CD}_2\text{Cl}_2$

138
$^1$H NMR
CD$_2$Cl$_2$
141
$^{13}$C NMR
CD$_2$Cl$_2$
141
$^1H$ NMR
CD$_2$Cl$_2$

142
\textsuperscript{1}H NMR
CD\textsubscript{2}Cl\textsubscript{2}
73
$^{13}$C NMR
CD$_2$Cl$_2$
73
$\text{C NMR}$
$\text{CD}_2\text{Cl}_2$
$90$
13C NMR
C₆D₆
151a
13:1 d.r.

13C NMR
C₆D₆
151b
The image displays a 13C NMR spectrum with the chemical structure of a compound. The carbon resonances are labeled with their respective ppm values, ranging from 220 to 20 ppm. The spectrum includes a peak at 156.63 ppm, 141.83 ppm, 128.30 ppm, 128.06 ppm, 127.82 ppm, 126.75 ppm, 125.09 ppm, 94.54 ppm, 81.86 ppm, 66.26 ppm, 46.15 ppm, 22.62 ppm, and 20.23 ppm. The structure includes a ring with double bonds and hydroxyl groups, labeled with carbon numbers from 1 to 11.
$^1$H NMR
CDCl$_3$
163
$^{1}H$ NMR
$CD_2Cl_2$

164
$^{13}$C NMR
CD$_2$Cl$_2$
164
$^{13}$C NMR
$C_6D_6$

169
$^{13}$C NMR
$C_6D_6$
171
$^{13}$C NMR

CD$_2$Cl$_2$

177
$\text{H NMR}$

$\text{CD}_2\text{Cl}_2$

178
$\text{OH}^{13}$

$^{13}$C NMR

CD$_2$Cl$_2$

178
Cryoprobe ATM TCI DRX500 1D Gradient NOESY

NOE NMR
C6D6
180

NOE: 5.4%
$^{13}$C NMR
CDCl$_3$
180
$^{1}\text{H NMR}$

CDCl$_3$

181
$\text{H NMR}$

$\text{CDCl}_3$

70
$^{13}$C NMR
CDCl$_3$
70
$^1$H NMR
CD$_2$Cl$_2$

131
$^{13}$C NMR
CD$_2$Cl$_2$
131
$\text{H NMR}$
$
\text{CD}_2\text{Cl}_2$

140
$^{13}$C NMR

CD$_2$Cl$_2$

148
$^{13}$C NMR

CD$_2$Cl$_2$

144a
$^{13}$C NMR
CD$_2$Cl$_2$
144b
$^1$H NMR
CD$_2$Cl$_2$
145

4.766
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0

2.9 ppm

9.05
8.98
2.87
2.83

1.000
0.999
0.980
1.011
1.010
1.077
6.125
1.117

1.333
1.351
1.354
1.358
1.368
1.393
1.395
1.396
1.402
1.409
1.409
1.411
1.417
1.419
1.426
1.429
1.433
1.447
1.454
1.457
1.464
1.469
1.497
1.500
1.510
1.512
1.517
1.519
1.526
1.533
1.545
1.547
1.550
1.552
1.558
1.565
1.570
1.572
1.577
1.580
1.584
1.588
1.595
1.602
1.607
1.610
1.612
1.617
1.625
1.628
1.633
1.642
1.648
1.653
1.656
1.662
1.668
1.682
1.692
1.698
1.703
1.707
1.713
1.716
1.727
1.733
1.735
1.744
1.747
1.754
1.765
1.781
1.791
1.796
1.810
1.820
1.826
1.830
1.832
1.845
1.876
1.897
1.907
1.915
2.065
2.863
3.139
3.205
$^{13}$C NMR
CD$_2$Cl$_2$

145
$^1$H NMR
C$_6$D$_6$
156b
$^1$H NMR, 25 °C
DMSO-d$_6$
158
$^1$H NMR, 90 °C
DMSO-d$_6$
158
$^{13}$C NMR, 25 °C
DMSO-$_2$$_6$
158
$^{13}$C NMR, 90 °C
DMSO-d$_6$
158
$^{13}$C NMR

$\text{C}_8\text{D}_8$

154
$^{1}H$ NMR

C$_6$D$_6$

172a
$^{13}$C NMR

C$_{6}$D$_{6}$

173
$^1$H NMR
CDCl$_3$
182a
$^{13}$C NMR
CDCl$_3$
182a
$\text{H NMR}$

$\text{CDCl}_3$

$182b$
$^{13}$C NMR

CDCl$_3$

182b
$^1$H NMR
CD$_2$Cl$_2$
165
$^1$H NMR  
CD$_2$Cl$_2$  
190
$^1$H NMR
CD$_2$Cl$_2$
191
$^{13}$C NMR
CD$_2$Cl$_2$
191
$^{1}H$ NMR
$C_6D_6$
192
$^1H$ NMR
C$_6$D$_6$
193
$^{13}$C NMR
$C_{6}D_{6}$
193
\[ ^1H \text{ NMR} \]
\[ C_6D_6 \]
\[ 200 \]
$^{13}$C NMR
$C_6D_6$
200
\textsuperscript{1}H NMR

$\text{C}_6\text{D}_6$

201
$^{19}$F NMR
$C_6D_6$
201
$^{13}$C NMR
$C_{6}D_{6}$
203
$^{19}$F NMR
Cl$_2$D$_6$
203
$^{13}$C NMR
$C_6D_6$
215
$^{19}$F NMR
$C_6D_6$
216
$^{13}$C NMR
$\text{C}_2\text{D}_6$
219
$^1$H NMR

$\text{CD}_3\text{OD}$

220
$^{13}$C NMR
CD$_2$Cl$_2$
221
$^{1}H$ NMR
$C_6D_6$
224
$^{13}$C NMR

$C_6D_6$

224
$^{13}$C NMR
C$_6$D$_6$
205
$^{13}$C NMR

C₆D₆

225
H NMR
C₆D₆
230
HN
Cl
Br

1H NMR
C₆D₆
232

6.8  6.7  6.6 ppm

8.0  7.5  7.0  6.5  6.0  5.5  5.0  4.5  4.0  3.5  3.0  2.5  2.0  1.5  1.0  0.5 ppm

6.734  6.650  6.631


10.682  1.030  0.979  3.001  2.002  1.000  1.091  1.956  3.397  2.011  1.026
$^1$H NMR

$C_6D_6$

236
$^{13}$C NMR
$C_6D_6$
236
$\text{BrO}_2\text{CF}_3 \text{CF}_3 \text{H NMR CDCl}_3 318\text{Br}$
$^{19}$F NMR
CDCl$_3$
318Br

$\text{Br} \quad \text{O} \quad \text{CF}_3$
\[ \text{CF}_3 \]

$\text{Br} \quad \text{O} \quad \text{CF}_3$
\[ \text{CF}_3 \]

$\text{Br} \quad \text{O} \quad \text{CF}_3$
\[ \text{CF}_3 \]

$\text{Br} \quad \text{O} \quad \text{CF}_3$
\[ \text{CF}_3 \]
$\text{H NMR} \quad \text{CD}_3\text{CN} \quad 318N_2$
$^{19}$F NMR
CD$_3$CN
318N$_2$
C NMR
CD$_3$CN
319
$^1$H NMR
$C_{6}D_{6}$
299
N H
O
O
Me
O
O
Me
Me
O
H
N
O
N
O
HN
HON
HN
Me

1H NMR
CD$_2$Cl$_2$
290
$^{13}$C NMR
CD$_2$CN
308
$^{1}H$ NMR
$CD_{2}Cl_{2}$
291
$^1$H NMR
CD$_2$Cl$_2$
293a/b
19F NMR
CD$_2$Cl$_2$
293a/b

293a

293b

2:1
$^{1}H$ NMR
$CD_3CN$
322
$\text{ONHS}$

$\text{Me}$

$\text{Me}$

$\text{Me}$

$\text{O}$

$\text{Me}$

$\text{Me}$

$\text{O}$

$\text{Me}$

$\text{O}$

$\text{Me}$

$\text{N$_2$}$

$\text{BF}_4$

$\text{CD$_3$CN}$

$\text{322}$

$^{19}\text{F NMR}$

$152.369$

$-152.422$

$0$ $-20$ $-40$ $-60$ $-80$ $-100$ $-120$ $-140$ $-160$ $-180$ $-200$ $-220$ ppm
$^{1}$H NMR
CD$_{2}$Cl$_{2}$
320
$^{13}$C NMR
CD$_2$Cl$_2$
320 ppm
9.0 Appendix 4

Raw Chiral HPLC Spectra

Products from arylative SPR of cyclic substrates

Racemic 70

Enantioenriched 70
Racemic 131

Enantioenriched 131

Racemic 139

Enantioenriched 139
Racemic 144a/b

Enantioenriched 144a

Enantioenriched 144b
Racemic 157

Enantioenriched 157

Racemic 158

Enantioenriched 158
Racemic 172a/b

Enantioenriched 172a

Enantioenriched 172b

172a

172b
Racemic 173

Enantioenriched 173

Racemic 174

Enantioenriched 174
Products from arylative SPR of acyclic substrates
Racemic 182a

Enantioenriched 182a

Me \( O \) \( Me \) 182a

Racemic 182b

Enantioenriched 182b

Me \( O \) \( Me \) 182b
Racemic 183

Unsuccessful enantioselective reaction for 183

Arylation scope
Racemic 189

Enantioenriched 189

Racemic 190

Enantioenriched 190
**Racemic 191**

**Enantioenriched 191**

**Racemic 192**

**Enantioenriched 192**
Racemic 193

Enantioenriched 193

Racemic 194

Enantioenriched 194
Racemic 202

Enantioenriched 202

Racemic 203

Enantioenriched 203
Racemic 204

Enantioenriched 204

Racemic 215

Enantioenriched 215
Racemic 216

Enantioenriched 216

Racemic 217

Enantioenriched 217

216

217
Racemic 218

Enantioenriched 218

Racemic 219

Enantioenriched 219
Racemic 224

Enantioenriched 224

Racemic 205

Enantioenriched 205
Transformation products
Racemic 230

Enantioenriched 230

Racemic 232

Enantioenriched 232
Racemic 236

Enantioenriched 236
10.0 Appendix 5

Tandem ms-ms spectral analysis
Final y1 ion:
\([M+H]^+\)

Found m/z 303.1324

Requires m/z 303.1339

Sequence:
Boc-Met-Gly-Pro-Gly-Trp-OMe

\(\text{CO}_2\text{Et}\)
Sequence:
Gly-Met-Gly-Pro-Gly-Trp

$\text{CO}_2\text{Et}$

$\text{y4 ion:}$
$[M+H]^+$
Found m/z 499.2304
Requires m/z 499.2300
Sequence:
Met-Gly-Pro-Gly-Trp

y3 ion:
[M+H]^+
Found m/z 642.2198
Requires m/z 642.2170
Sequence: Gly-Met-Gly-Pro-Gly-Trp

Final y1 ion: [M+H]^+
Found m/z 486.1235
Requires m/z 486.1252

CO₂CH₂Ph(CF₃)₂
Sequence:
Gly-Met-Gly-Gly-Pro-Gly-Trp-Gly-Gly

Final y1 ion:
[M+H]+
Found m/z 600.1683
Requires m/z 600.1676
**Sequence:**
Gly-Met-Ala-Pro-Ala-Trp-Gly-Gly

**y3 ion:**
\[\text{[M+H]}^+\]

*Found m/z 768.2612*
*Requires m/z 768.2575*
Sequence:
Gly-Met-Ala-Gly-Pro-Gly-Ala-Trp-Gly-Gly

CO₂CH₂Ph(CF₃)

γ⁵ ion:
[M+H]⁺
Found m/z 882.3038
Requires m/z 882.3004
Sequence:
Gly-Met-Gly-(D)Pro-Pro-Gly-Trp-Gly-Gly

CO₂CH₂Ph(CF₃)₂

Final y1 ion:
[M+H]⁺
Found m/z 600.1680
Requires m/z 600.1676
Sequence: Gly-Met-Thr-Phe-Pro-Phe-Trp-Gly-Gly

Final y1 ion: [M+H]^+

Found m/z 600.1663
Requires m/z 600.1676
Sequence: Met-Lys-Pro-Phe-Trp

y3 ion: [M+H]^+
Found m/z 730.2489
Requires m/z 730.2464
Sequence:

Met - Glu - Pro - Phe - Trp

y3 ion: [M+H]^+

Found m/z 730.2489
Requires m/z 730.2464
Sequence:
Met-Asp-Pro-Phe-Trp

CO$_2$CH$_2$Ph(CF$_3$)$_2$

y3 ion:
[M+H]$^+$

Found m/z 730.2489
Requires m/z 730.2464
Sequence:
Met-Asn-Pro-Phe-Trp

334a/b

**y3 ion:**
[M+H]^+
Found m/z 730.2489
Requires m/z 730.2464
Sequence:
Met-Thr-Pro-Phe-Trp
CO₂CH₂Ph(CF₃)₂

y₃ ion:
[M+H]⁺
Found m/z 730.2489
Requires m/z 730.2464
Sequence: 
Boc-Met(OMe)-Trp(OMe)-Boc

Final y1 ion: 
[M+H]+

Found m/z 501.1245
Requires m/z 501.1244