GENERATING COMPLEXITY BY REDUCTIVE ELECTRON TRANSFER: ASYMMETRIC STUDIES AND CYCLISATION CASCADES

A thesis submitted to The University of Manchester for the degree of Doctor of Philosophy
In the faculty of Engineering and Physical Sciences

2014

Sarah Lyons
School of Chemistry
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Abstract

The University of Manchester
School of Chemistry
Sarah Lyons
Doctor of Philosophy
2014

Generating complexity by reductive electron transfer:
Asymmetric studies and cyclisation cascades

Reductive electron transfer has been successfully utilized to facilitate the first enantioselective desymmetrisation of malonate derivatives. Selective monoreduction of cyclic 1,3-diesters through the combined use of SmI$_2$-Et$_3$N and chiral non-racemic diols has granted rapid access to enantioenriched β-hydroxy acids containing challenging quaternary centres – an abundant motif in many drug molecules.

Unique radical anions generated from the single electron reduction of cyclic 1,3-diesters have been exploited in cyclisation cascades. Capture of acyl-type radical anions by both alkene and alkyne acceptors have permitted the construction of complex bicyclic architectures in a single synthetic operation.

The reductive cyclisation cascade of lactones has also been demonstrated, using SmI$_2$-H$_2$O to achieve a challenging domino 5-exo-trig/6-exo-trig cyclisation event. This process generates highly decorated carbo[5.4.0]bicyclic scaffolds with complete diastereocntrol.
Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

Part of this work has been published in peer-reviewed journals.


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Acknowledgments

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### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
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<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>AD</td>
<td>asymmetric dihydroxylation</td>
</tr>
<tr>
<td>anal.</td>
<td>analysis (elemental)</td>
</tr>
<tr>
<td>aq.</td>
<td>aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>BINAPo</td>
<td>2,2'-bis(diphenylphosphinyl)-1,1'-binaphthalene</td>
</tr>
<tr>
<td>BINOL</td>
<td>1,1'-bi(2-naphthol)</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butyloxycarbonyl</td>
</tr>
<tr>
<td>BRSM</td>
<td>by recovered starting material</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
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<td>Bz</td>
<td>benzoyl</td>
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<td>calculated</td>
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<td>cat.</td>
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</tr>
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<td>carboxybenzyl</td>
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<td>c</td>
<td>cyclo</td>
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<td>DABCO</td>
<td>1,4-diazabicyclo[2.2.2]octane</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DCH</td>
<td>trans-(N,N^\prime)-dimethyl-1,2-cyclohexyldiamine</td>
</tr>
<tr>
<td>DHPEB</td>
<td>2,2'-di[((S)-2-hydroxy-2-phenylethoxy)-1,1'-binaphthyl</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>di-(iso)-butyaluminium hydride</td>
</tr>
<tr>
<td>diglycol</td>
<td>diethylene glycol</td>
</tr>
<tr>
<td>dimethylglycol</td>
<td>diethylene glycol dimethyl ether</td>
</tr>
<tr>
<td>DIPA</td>
<td>di-(iso)-propyl amine</td>
</tr>
<tr>
<td>DIPEA</td>
<td>(N,N)-di-(iso)-propylethylamine</td>
</tr>
<tr>
<td>DMF</td>
<td>(N,N)-dimethylformamide</td>
</tr>
<tr>
<td>DMP</td>
<td>Dess-Martin Periodinane</td>
</tr>
<tr>
<td>DMPU</td>
<td>(N,N)^\prime)-dimethylpropylene urea</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>dr</td>
<td>diastereomeric ratio</td>
</tr>
<tr>
<td>e</td>
<td>electron</td>
</tr>
<tr>
<td>ED</td>
<td>ethylenediamine</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>EG</td>
<td>ethylene glicol</td>
</tr>
<tr>
<td>EI</td>
<td>electrospray ionisation</td>
</tr>
<tr>
<td>eq.</td>
<td>equivalents</td>
</tr>
<tr>
<td>ES</td>
<td>electrospray</td>
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<td>ethyl</td>
</tr>
<tr>
<td>g</td>
<td>grams</td>
</tr>
<tr>
<td>GC</td>
<td>gas chromatography</td>
</tr>
<tr>
<td>Grubbs II</td>
<td>(1,3-bis(2,4,6-trimethylphenyl)-2 imidazolidinylidene) dichloro(phenylmethylene)(tricyclohexylphosphine)ruthenium</td>
</tr>
<tr>
<td>h</td>
<td>hour</td>
</tr>
<tr>
<td>HMPA</td>
<td>hexamethylphosphoramide</td>
</tr>
<tr>
<td>Hoveyda-Grubbs II</td>
<td>(1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene) dichloro(o-isoproxyphenylmethylene)ruthenium</td>
</tr>
<tr>
<td>HPLC</td>
<td>high pressure liquid chromatography</td>
</tr>
<tr>
<td>i</td>
<td>iso</td>
</tr>
<tr>
<td>im</td>
<td>imidazole</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium di-iso-propylamide</td>
</tr>
<tr>
<td>M</td>
<td>molar</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>MeOH</td>
<td>methanol</td>
</tr>
<tr>
<td>methyl diglycol</td>
<td>methylene glycol methyl ether</td>
</tr>
<tr>
<td>mg</td>
<td>milligram</td>
</tr>
<tr>
<td>min</td>
<td>minute</td>
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<tr>
<td>mL</td>
<td>milliliter</td>
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<td>mmol</td>
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</tr>
<tr>
<td>mol</td>
<td>mole</td>
</tr>
<tr>
<td>MOM</td>
<td>methoxymethane</td>
</tr>
<tr>
<td>mp.</td>
<td>melting point</td>
</tr>
<tr>
<td>Ms</td>
<td>methanesulfonyl</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectrum</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Nu</td>
<td>nucleophile</td>
</tr>
<tr>
<td>p</td>
<td>para</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>Pr</td>
<td>propyl</td>
</tr>
<tr>
<td>p-TsOH</td>
<td>para-toluenesulfonic acid</td>
</tr>
<tr>
<td>PFTB</td>
<td>perfluoro-\textit{t}-butanol</td>
</tr>
<tr>
<td>py</td>
<td>pyridine</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>sat.</td>
<td>saturated</td>
</tr>
<tr>
<td>SOMO</td>
<td>singly occupied molecular orbital</td>
</tr>
<tr>
<td>t</td>
<td>\textit{tert}</td>
</tr>
<tr>
<td>TADDOL</td>
<td>\textit{\alpha,\alpha,\alpha,\alpha}-tetraaryl-1,3-dioxolane-4,5-dimethanols</td>
</tr>
<tr>
<td>TBDPS</td>
<td>\textit{tert}-butyldiphenylsilyl</td>
</tr>
<tr>
<td>TBS</td>
<td>\textit{tert}-butyldimethylsilyl</td>
</tr>
<tr>
<td>TFE</td>
<td>trifluoroethanol</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TIP</td>
<td>2,4,6-tri-\textit{iso}-propylphenyl</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMEDA</td>
<td>\textit{N,N,N',N'}-tetramethylethylenediamine</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>TMU</td>
<td>trimethylurea</td>
</tr>
<tr>
<td>TPPA</td>
<td>tripyrrolidinophosphoric acid triamide</td>
</tr>
<tr>
<td>Ts</td>
<td>para-toluenesulfonyl</td>
</tr>
<tr>
<td>UV</td>
<td>ultraviolet</td>
</tr>
</tbody>
</table>
1. Introduction

1.1 Introduction to samarium diiodide

Samarium (II) iodide (SmI$_2$) has become one of the most important reducing reagents in the organic chemists’ toolbox due to its unique modes of reactivity. Since its initial introduction to organic synthesis by Kagan in 1977,$^1$$^2$ it has been used extensively in organic synthesis to perform a variety of transformations exclusive to the reagent. As a single electron transfer agent, it can mediate both radical and anionic processes permitting its use in a vast number of functional group interconversions and complex carbon-carbon bond forming events (Scheme 1).

The reagent is often highly chemo-, regio- and stereoselective, and its reactivity can be modulated through the use of various modifiers including metal additives, Lewis bases and proton donors. Coordination of additives to the metal centre thereby facilitates the fine-tuning of its reduction potential, reactivity and selectivity.

1.2 Tuning the reactivity of SmI$_2$

1.2.1 Metal additives

Within Kagan’s seminal report on the preparation and use of SmI$_2$, he described the use of catalytic ferric chloride (FeCl$_3$) to accelerate the coupling rate of alkyl iodides and ketones.$^2$ Metal salts have since been used as additives in reductive processes, with SmI$_2$-mediated reactions benefiting from enhanced reaction rates and selectivity. Flowers
first demonstrated the use of LiBr and LiCl in the SmI$_2$-mediated pinacol coupling of cyclohexanone, reporting a dramatic increase in the reaction rate. Further study showed that SmBr$_2$ and SmCl$_2$ were generated \textit{in situ} in these processes by displacement of iodide from the samarium centre, generating a reducing system of enhanced redox potential: the measured reduction potential of the SmI$_2$-LiBr combination was $-2.07$ V vs. Ag/AgNO$_3$. Other transition metal salts and complexes, commonly Fe(III) or Ni(II) derived, have also been used in conjunction with SmI$_2$. Amongst a variety of transition metal halides, Kagan found NiI$_2$ to be the superior inorganic additive and demonstrated its synthetic utility in a variety of transformations including epoxide opening and Barbier reactions. Subsequently, NiI$_2$ has been used extensively in SmI$_2$-mediated reactions such as conjugate addition of alkyl iodides to $\alpha,\beta$-unsaturated esters, amides and lactones, Grob fragmentation, coupling of acid chlorides with esters and alkyl halides with nitriles (Scheme 2).

![Scheme 2](image_url)

Its extensive use in SmI$_2$-mediated Barbier reactions has solicited the question as to its role in such transformations. A mechanistic investigation to determine the role of catalytic NiI$_2$ in the samarium-mediated Barbier reaction was recently reported by Flowers. Flowers discovered that upon mixing NiI$_2$ and SmI$_2$, Ni(II) was reduced to Ni(0) by the action of Sm(II) (Scheme 3). Subsequent oxidative addition of Ni(0) into the alkyl halide bond of then produces an organonickel species which can transmetallate to Sm(III) to yield, permitting Ni(II) to re-enter the catalytic cycle. Addition of the
resulting organosamarium 26 to ketone 27 with subsequent protonation of alkoxide 28 yields the Barbier product 29.\(^\text{82}\)

\[
\text{Scheme 3}
\]

The acceleration of various SmI\(_2\)-mediated reactions by inorganic additives such as NiI\(_2\) has greatly expanded the synthetic utility of SmI\(_2\). Furthermore, elucidating the mechanistic role of such additives can have a significant impact on the field, with the potential to optimize current processes or even develop new modes of reactivity.

### 1.2.2 Lewis bases

Lewis bases have been shown to accelerate a variety of functional group interconversions and bond-forming reactions, primarily by increasing the reduction potential of SmI\(_2\). One of the most extensively used additives is HMPA – upon addition of 4 equivalents of HMPA, the reduction potential of Sm(II) increases from -1.3 V to -2.1 V (vs. Ag/AgNO\(_3\)), permitting access to novel modes of reactivity inaccessible to SmI\(_2\) alone. Mechanistic studies have shown that coordination of HMPA to Sm(II) results in the displacement of iodide ligands to the outer coordination sphere thereby providing vacant sites for reactants to coordinate.\(^\text{13,14}\) The result is a more powerful and highly sterically hindered Sm(II) reductant. Inanaga first described the use of SmI\(_2\)-HMPA, using 2-propanol as a proton source in the coupling of carbonyl 30 and \(\alpha,\beta\)-unsaturated ester 31 yielding 32 (Table 1).\(^\text{15}\)
HMPA not only accelerated the coupling rate, reducing the reaction time from 4 hours to 1 minute, it also improved the yield of 33 significantly. Mikami subsequently used the chiral bis-phosphine oxide ligand (R)-BINAPO 36 in place of HMPA, to effect an asymmetric variant of this transformation. This demonstrated a rare example of an asymmetric ligand-controlled SmI$_2$-mediated reaction (Scheme 4).$^{16}$

Scheme 4

Samarium-mediated Barbier reactions have also been shown to benefit from the addition of HMPA – Krief and Laval employed HMPA in the Barbier addition of alkyl halide 37 to ketone 38, increasing the reaction rate and improving the yield of alcohol 39 (Table 2).$^{17}$ When HMPA was absent, reaction times were days and yields were low to moderate whereas in the presence of HMPA, reaction times were reduced to minutes and yields exceeded 90%.

### Table 1

<table>
<thead>
<tr>
<th>Additive</th>
<th>Time</th>
<th>Yield 32 (%)</th>
</tr>
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<tbody>
<tr>
<td>None</td>
<td>4 h</td>
<td>57</td>
</tr>
<tr>
<td>HMPA</td>
<td>1 min</td>
<td>89</td>
</tr>
</tbody>
</table>
Flowers has investigated the mechanistic role of HMPA in the selective reduction of alkyl halides over carbonyls in the SmI₂-mediated Barbier coupling. Experimental and computational studies found that coordination of HMPA to the alkyl halide results in an elongation of the carbon-halide bond, making its reduction by Sm(II) more facile. Pinacol formation is also hampered by the addition of HMPA, influencing the fate of radical anions post-electron-transfer; coordination to Sm(III) hinders bridging between ketyl radicals thereby preventing pinacol coupling.

Molander’s pioneering research on the SmI₂-HMPA intramolecular ketyl-olefin coupling has granted access to a variety of medium-sized rings such as 41, with cyclisation events often occurring with high diastereoselectivity (Scheme 5). HMPA was a necessary additive to generate persistent ketyl-radicals and hence facilitate cyclisation events, which do not occur in the absence of the additive. Reissig also described the intramolecular 8-endo-dig cyclisation of a ketone and an alkyne present in 42 using HMPA, isolating a single diastereoisomer of the benzannulated cyclooctenol product 43.

Table 2

<table>
<thead>
<tr>
<th>Additive</th>
<th>Reaction time</th>
<th>Yield 39 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1.5 days</td>
<td>27</td>
</tr>
<tr>
<td>HMPA</td>
<td>1 min</td>
<td>91</td>
</tr>
</tbody>
</table>

Scheme 5
Due to its innate toxicity, research has also focussed on employing Lewis bases that can provide comparable selectivity and reactivity to HMPA 44 but lack its harmful biological effects. Alternative Lewis basic additives used in samarium-mediated reductions include \(N,N'\)-dimethylpropyleneurea 45 (DMPU),\(^{23}\) tetramethylurea 46 (TMU), nitrogen donor solvents (\textit{vide infra}) and, more recently, tripyrrolidinophosphoric acid triamide 47 (TPPA) (Scheme 6).\(^{24}\) A large excess of additive is necessary in most of these cases though and thus far these alternative Lewis bases lack the generality of HMPA.

### Scheme 6

#### 1.2.3 Proton donors

Proton donors such as alcohols, glycols and water are frequently utilised co-solvents used for quenching alkoxides and carbanion intermediates generated \textit{in situ} in SmI\(_2\)-mediated reductions and reductive coupling processes. The choice of proton source can be of significant consequence, with the potential to influence the regio- and stereochemical outcome of a reaction. Keck elegantly demonstrated the importance of the proton source employed in the diastereoselective reduction of \(\beta\)-hydroxy ketone 48 (Table 3).\(^{25}\) Lower concentrations of MeOH and H\(_2\)O gave excellent yields obtaining diol 50 with good diastereoselectivity. Using a higher concentration of water eroded the diastereoselectivity significantly. This was the result of water competitively coordinating to the inner sphere of Sm(II) thereby inhibiting substrate binding. In contrast, this was not observed at higher concentrations of MeOH as it is a much weaker ligand for Sm(II).
A recent example demonstrating the high selectivity that can be achieved by using the mild SmI₂-MeOH conditions was published by the Eisai process group in the commercial synthesis of the anticancer drug Halaven® (Scheme 7). Chemoselective sulfone reduction of 51 yielded 52 in the presence of both a highly reactive aldehyde and vinyl iodide group – an in situ protection of the aldehyde by MeOH was thought to be involved. Furthermore, this reaction was successfully demonstrated on a 1.27 kg scale – the largest Sm(II)-mediated process reported to date.

Procter has demonstrated the effective use of proton donors in manipulating the reaction outcome of γ,δ-unsaturated ketone cyclisations, obtaining different cyclisation products by careful selection of the proton source used (Scheme 8).

### Table 3

<table>
<thead>
<tr>
<th>H⁺ source</th>
<th>H⁺ donor (eq)</th>
<th>Yield 50 (%)</th>
<th>Ratio (anti: syn)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H₂O</td>
<td>2</td>
<td>96</td>
<td>83:17</td>
</tr>
<tr>
<td>H₂O</td>
<td>10</td>
<td>88</td>
<td>50:50</td>
</tr>
<tr>
<td>MeOH</td>
<td>2</td>
<td>95</td>
<td>98:2</td>
</tr>
<tr>
<td>MeOH</td>
<td>10</td>
<td>99</td>
<td>&gt;99:1</td>
</tr>
</tbody>
</table>

Scheme 7

Procter has demonstrated the effective use of proton donors in manipulating the reaction outcome of γ,δ-unsaturated ketone cyclisations, obtaining different cyclisation products by careful selection of the proton source used (Scheme 8).
A solvent effect was observed upon switching from MeOH to $t$-BuOH obtaining either cyclopentanols 53 or cyclobutanols 55 respectively, isolating each as the sole product of cyclisation. Use of MeOH resulted in aldol spirocyclization, whilst $t$-BuOH affected a novel cyclobutanol-forming process. The alcohol dependence of the reaction was thought to be caused by different rates of protonation of radical-anion intermediate 57 (Scheme 9).

The anion intermediate 57 can be quenched rapidly by MeOH bound to samarium to give syn-cyclopentanols 53. In contrast, the rate of protonation by bulky $t$-BuOH is sufficiently slow to allow cyclisation to give syn-cyclobutanols 55. In both processes, a second reduction generates Sm(III)-enolates. With MeOH, the enolate 59 undergoes aldol cyclisation to generate cyclopentanols whilst with $t$-BuOH, protonation of the intermediate enolate 61 produces cyclobutanols that subsequently cyclise to give the bicyclic lactone 55. This is arguably the most dramatic co-solvent effect seen to date in the chemistry of SmI$_2$.

The oxophilic nature of SmI$_2$ means that oxygen-containing proton donors coordinate to the Sm(II) centre and are in close proximity to radical anions formed, facilitating subsequent protonation events through heterolytic cleavage of the O-H bond.
1.3 Introduction to SmI₂-H₂O

SmI₂ alone has a reduction potential of \(-1.3\) V (vs. Ag/AgNO₃) and can reduce aldehydes and ketones as well as sulfones, aryl halides and alkyl halides. Recently, Flowers has shown an enhancement in reduction potential to \(-1.9\) V (vs. Ag/AgNO₃) upon the addition of up to 500 equivalents of water. Mechanistic studies recently reported by Flowers uncovered the role of proton donors in accelerating SmI₂ reactions: water acts by displacing THF and iodine ligands from the inner sphere of the metal thereby providing open coordination sites to facilitate substrate binding, in a similar manner to HMPA.²⁸ Proton donors such as alcohols were shown to accelerate SmI₂ reactions at low concentrations though significantly larger quantities impede the rate of reduction by saturating the coordination sphere of samarium, preventing the substrate from interacting with the metal. At these concentrations, water does not exhibit such behaviour associated with a coordinatively saturated complex, achieving only a maximum rate of reduction.²⁹

Kagan’s seminal report on the preparation and use of SmI₂ also demonstrated the first use of water as an additive in facilitating the reduction of 2-octanone.² Following this report, Corey employed the SmI₂-H₂O reducing system to effect the diastereoselective ketone reduction of 62 in efforts toward the total synthesis of the biologically active diterpanoid atractylenin.³⁰ Chelation controlled reduction invoking the β-ester moiety favoured formation of an equatorial alcohol 63 (Scheme 10).

![Scheme 10](image)

In 1993, Kamochi published an extensive investigation on the reducing ability of the SmI₂-H₂O system, demonstrating the mild and selective reduction of aromatic carboxylic acids, esters, amides and nitriles (Scheme 11).³¹-³²
Reduction of these functionalities cannot be achieved using SmI\(_2\) alone, with the enhanced reactivity being attributed to an increase in the reducing potential of SmI\(_2\) by water.

In an effort to synthesize 2-deoxy sugars, Hanessian described the \(\alpha\)-deoxygenation of aldonolactones \(\text{72}\) using SmI\(_2\)-H\(_2\)O (Scheme 12).\(^{33}\)

Scheme 11

\[
\begin{align*}
\text{(R = H; 89\%) } & \quad \text{Sml}_2\text{-H}_2\text{O} & \quad \text{PhCN} & \quad \text{Sml}_2\text{-H}_2\text{O} \\
\text{64} & \quad \text{65} & \quad \text{66} & \quad \text{67}
\end{align*}
\]

\[
\begin{align*}
\text{(R = Me; 93\%)} & \quad \text{Ph-OH} & \quad \text{Ph-NH}_2 \\
\text{3 s, 94\%}} & \quad \text{68} & \quad \text{69}
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} & \quad \text{Ph} & \quad \text{Ph} \\
\text{NH}_2 & \quad \text{OH} & \quad \text{OH} & \quad \text{NH}_2 \\
\text{70} & \quad \text{71}
\end{align*}
\]

Scheme 11

Subsequent investigations by Khuong-Huu and Georg on the synthesis of new Taxol derivatives found that the natural Taxol precursor baccatin III \(\text{74}\) could selectively undergo \(\alpha\)-deacetylation and subsequent ketone reduction to yield \(\text{75}\) using SmI\(_2\)-H\(_2\)O.\(^{34-35}\)

Following \(\alpha\)-deacetylation, directed ketone reduction occurred \(\text{via}\) chelation to the
neighbouring hydroxyl moiety. This positioned samarium on the $\alpha$-face of the molecule thereby favouring delivery of the proton from the $\beta$-face.$^{36}$ Similarly, Curran described the demethoxylation of aromatic acetals and ketals$^{76}$.$^{37}$ The accessibility of these transformations was ascribed to the enhanced reduction potential of SmI$_2$ upon coordination of water.

In 2000, Mukaiyama demonstrated the SmI$_2$-H$_2$O mediated fragmentation of oxiranyl ketones. Sm(III) enolates produced in situ subsequently underwent intermolecular aldol reaction with an external aldehyde.$^{38}$ This methodology was extended further to intramolecular aldol cyclisations by introducing a pendant aldehyde to the oxiranyl ketones. Exposure of $\omega$-oxiranyl keto-octanal 78 to SmI$_2$-H$_2$O conditions generated polyoxygenated cyclooctanone 80 (Scheme 13).$^{39}$

![Scheme 13](image)

In the years following Kagan’s seminal publication describing both the preparation of SmI$_2$ and the first application of SmI$_2$-H$_2$O, there had been limited attention on exploring the scope of the SmI$_2$-H$_2$O reducing system. The last decade has seen a significant revolution in SmI$_2$-H$_2$O chemistry and resultanty it has become an essential addition to the organic chemist’s toolbox.

1.4 Modern uses of SmI$_2$-H$_2$O

1.4.1 Reductive coupling of C=N

Seminal reports by Imamoto described the first Sm(II)-mediated reductive-dimerisation of imines.$^{40}$ Treatment of aldimines with SmI$_2$-H$_2$O successfully afforded 1,2-diamines in moderate to good yield. In contrast, cross-coupling of ketimines could not be accomplished as the reduction rate of imines to the corresponding amine was faster than the desired coupling process. Unlike aldimines, ketimines were reported to effectively couple with aliphatic ketones.
Py and Vallée extended C=N cross-coupling to that of nitrones and carbonyl compounds granting access to N-hydroxy-β-amino alcohols (Scheme 14). A comprehensive substrate scope was demonstrated, isolating N-hydroxyamino alcohols such as 83 in excellent yield. Furthermore, use of an excess of SmI₂ provided direct access to β-amino alcohols 81 through successive N-O bond cleavage. The oxophilic nature of SmI₂ led the authors to propose that coordination of an aminoxyl radical to the carbonyl through Sm(III) elicited the diastereoselective coupling of 82.

Scheme 14

Subsequently, Py and Vallée reported the first intermolecular reductive coupling of nitrones 84 to α,β-unsaturated esters and alkynoates 85 (Scheme 15). Excellent diastereoselectivity was achieved using substituted α,β-unsaturated esters, methyl methacrylate and (E)-methyl crotonate as alkene acceptors.

Scheme 15
The necessary use of water as an additive was exemplified by its use in the intermolecular nitrone-alkynoate coupling. The presence of 8 equivalents of water effected an increase in yield to 71% in comparison to <10% when SmI$_2$ alone was used. The use of nitrones such as 89 containing a chiral auxiliary also resulted in asymmetric reductive coupling (Scheme 16).\textsuperscript{43}

Scheme 16

Nitrones 89 derived from isobutyraldehyde and enantiomerically pure 1-(2,4,6-triisopropylphenyl)ethylamine successfully underwent SmI$_2$-H$_2$O-mediated reductive coupling of with $\alpha,\beta$-unsaturated esters 88 and 90 to afford $\alpha$-amino acid derivatives 87 and 91 respectively in excellent diastereoselectivity and yield.

Py later demonstrated the SmI$_2$-H$_2$O mediated reductive coupling of 1-pyrroline N-oxide 93 with aromatic and aliphatic ketones 94 to generate an assortment of prolinol derivatives 96a-f which are important motifs used in the field of organocatalysis (Scheme 17). This provided a range of new racemic $\alpha,\alpha$-disubstituted prolinols, from which both enantiomers could be isolated by resolution of the intermediate N-hydroxy prolinol.\textsuperscript{44}
In 2012, Zhang utilized this methodology in the cross-coupling of chiral nitrone 97 and methyl 4-oxo-butanoate 98 en route to the polyoxygenated heterocyclic natural product (−)-8a-epi-swainsonine 100 (Scheme 18).\(^{45}\)

The prolinol derivative 99 was isolated in good yield as a mixture of diastereoisomers, which could be separated by downstream processing to allow access to both (−)-8a-epi-swainsonine and (−)-8,8a-di-epi-swainsonine.

1.4.2 Facilitating reactions of acyl equivalents

A prevalent issue associated with the addition of acyl radicals to olefins is the occurrence of decarbonylation prior to C-C bond formation.\(^{46}\) Significant efforts have therefore been made toward the development of novel acyl equivalents that are impervious to decarbonylation. Consequently, Skrydstrup reported the use of 4-pyridyl thioesters 101 as
a way of generating stable acyl radical equivalents in a Sm(II)-mediated coupling to acrylamides \textbf{102} and acrylates.\textsuperscript{47} Single-electron transfer to the thioester generated a thermodynamically stable acyl-type radical that could undergo coupling to an activated olefin (Scheme 19).

![Scheme 19](image)

C-S bond cleavage with successive decarbonylation was not observed under these conditions, allowing the thioester to act as a stable $\alpha$-amino acid acyl radical equivalent. Coupling occurred without epimerisation of the acidic $\alpha$-stereocentre permitting the mild synthesis of enantiomerically enriched 1,4-dicarbonyls \textbf{103} derived from amino acids.

In 2005, Skrydstrup proposed the use of oxazolidinones as precursors to stable acyl-type radicals using SmI$_2$-H$_2$O conditions (Scheme 20).\textsuperscript{48} A broad range of $N$-acyl oxazolidinones \textbf{104} were tolerated under the mild reductive conditions including substrates containing secondary, tertiary and heteroatom $\alpha$-substitution, with no decarbonylation products being detected. Acrylates \textbf{105} as well as acrylamides were shown to undergo reductive-coupling in good to excellent yield. Importantly, the use of water as an additive was vital for reactivity and other co-solvents or additives used in conjunction with SmI$_2$ led to decomposition products.

![Scheme 20](image)
In 2006, Skrydstrup and Flowers disclosed a mechanistic investigation of this reductive SmI$_2$-H$_2$O-mediated cross-coupling (Scheme 21). It was proposed that the coupling most likely proceeds by initial reduction of the acrylamide or acrylate with subsequent chelation-controlled addition to the N-acyl moiety. The highly reductive SmI$_2$-H$_2$O system was believed to facilitate carbonyl reduction by lowering the energy of the $\pi^*_{C=O}$ orbital sufficiently thereby favouring electron transfer. The Lewis acidity of SmI$_2$ was also shown to instigate rotation about the C-N bond of the N-acyl oxazolidinone from the $s$-trans 104a to an $s$-cis 104b conformation. Rotation is crucial for effective chelation between the carbonyl groups and hence reductive coupling.

![Scheme 21](image)

Subsequently, Skrydstrup reported the use of Evans’ chiral oxazolidine in the SmI$_2$-H$_2$O mediated coupling with acrylamides (Scheme 22). Cleavage of the auxiliary and C-C bond formation could be achieved simultaneously, providing enantiomerically pure $\delta$-ketoamide 111. An intramolecular 5-exo-trig cyclisation was also realised, affording $trans$-2,5-substituted cyclopentanone 113 with complete control of diastereoselectivity and high enantiomeric purity.

![Scheme 22](image)

Multiple stereocenters and functional groups were tolerated in these couplings. Intermediate samarium(III) enolates could also be intercepted by ketones to install an
additional α-substituent. Skrydstrup further demonstrated the value of this methodology in
the synthesis of aliskiren 117, currently used for the treatment of hypertension (Scheme
23). These couplings were previously found to be ineffective when employing the
corresponding 4-pyridyl thioesters.

Scheme 23

The successful coupling of a sterically encumbered N-acyl oxazolidinone 114 with the
methyl acrylate derivative 115 provided the carbon skeleton of aliskerin in 95% yield (by
recovered starting material) albeit with low diastereocontrol (5:4 dr).

1.4.3 Reductive transformations of lactones

In 2008, Procter described the first SmI$_2$-mediated reduction of lactones to synthesise a
variety of substituted diols; a transformation previously thought inaccessible to SmI$_2$. Lactones
were shown to be selectively reduced to the diol in the presence of acyclic esters
using SmI$_2$-H$_2$O (Scheme 24). Competition experiments also demonstrated the ring-size
discrimination of the SmI$_2$-H$_2$O reducing system, selectively reducing 6-membered
lactones over other ring-sizes.
It was postulated that the ring-size selectivity results from the favoured initial electron transfer to the carbonyl moiety. The ensuing ketyl radical anion possesses anomeric stabilisation from the antiperiplanar oxygen lone pairs; an effect that is most prevalent in 6-membered ring systems.\(^5\) This was evidenced by the calculated relative reaction energy for the first electron transfer, which was significantly lower for the 6-membered lactone than for 5- and 7-membered lactones (Scheme 25).

Additionally, 5- and 6-membered lactol intermediates that are generated during the lactone reduction were found to undergo rapid reduction to the corresponding diol upon exposure to SmI\(_2\)-H\(_2\)O. This provides further evidence that the ring-size selectivity arises from the favourability of the initial electron transfer from SmI\(_2\) to the carbonyl moiety. Furthermore, the conformationally locked lactone 2-oxabicyclo[2,2,2]octan-3-one 125, from which a radical anion intermediate cannot adopt the chair conformation necessary to achieve optimal electronic stabilisation, was not reduced by SmI\(_2\)-H\(_2\)O (Scheme 26).
Overall these observations suggest a complex mechanistic pathway initiated by single electron reduction of the lactone carbonyl. After the initial electron transfer, an anomerically stabilized radical anion $127$ is generated that is subsequently protonated to give $128$. A further reduction-protonation sequence then yields the hemi-acetal $130$, which is in equilibrium with the activated aldehyde $131$. Electron transfer to the aldehyde produces a second ketyl-radical anion $132$. A final series of electron transfer and protonation events then yields the diol $133$ (Scheme 27).

Radical anions generated from the initial electron transfer step have also been exploited in reductive cyclisations by trapping with a pendant alkene in the $\alpha$-position (Scheme 28). Ketyl-olefin couplings generated a wide variety of substituted cyclopentanones $136$ in good yield and high diastereoselectivity. The presence of an $\alpha$-ester in substrates $134$ prevented over-reduction by impeding collapse of the hemi-ketal intermediate $135$ generated from cyclisation.
Additionally, alkene tethers in the δ-position of the lactone could also undergo reductive cyclisation to afford highly decorated cycloheptanols 138 (Scheme 29). Lactones bearing a second alkyl group in the 5-position also underwent efficient cyclisation to afford hemi-ketals 139 after DMP oxidation.

Scheme 28

Scheme 29

**Kinetics and the role of H$_2$O**

Previous reports by Curran, Flowers, and Hoz proposed that the coordination of water to Sm(II) plays several key roles in SmI$_2$-H$_2$O mediated transformations. In all cases the addition of water was found to accelerate reductive processes through its coordination to SmI$_2$. Flowers’ use of UV-vis and conductance experiments showed that displacement of iodide and bulk solvent by H$_2$O from the inner coordination sphere of the metal accelerates Sm(II)-mediated processes. As a result, the proton donor is in close proximity to the reacting centre of the carbonyl, facilitating efficient protonation of radical anion intermediates.

A recent study by Procter and Szostak has provided further mechanistic insight into the role of water in the reduction of cyclic and acyclic esters by SmI$_2$. It was found that water assists electron transfer from Sm(II) by stabilising the intermediate radical anion rather than solely by promoting the first electron transfer step as previously thought.
Measurement of the kinetic isotope effect for the reduction of 5-decanolide gave a $k_H/k_D$ value of 1.33, suggesting that proton transfer is not involved in the rate-determining step.

The effect of water on the rate of reduction of ketyl radicals was investigated by exposing lactone 140 to SmI₂ and a range of water concentrations. This lactone can undergo either complete reduction to 141 or reductive cyclisation to 142 (Table 4). Increasing concentrations of water led to a linear decrease in the rate of reduction of the ketyl-radical generated from 141 thereby favouring 5-exo-trig cyclisation. Preferential cyclisation is observed at higher concentrations of water due to competitive coordination of water to the metal centre. Chemoselectivity between the 5-exo cyclisation and reduction could therefore be accomplished by modifying the concentration of water.

Table 4

<table>
<thead>
<tr>
<th>H₂O (eq)</th>
<th>141:142</th>
<th>Rate [10⁻⁷ × M⁻¹ s⁻¹]</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>&gt;98:2</td>
<td>&gt;21.3</td>
</tr>
<tr>
<td>100</td>
<td>&gt;98:2</td>
<td>&gt;21.3</td>
</tr>
<tr>
<td>400</td>
<td>94:6</td>
<td>7.21</td>
</tr>
<tr>
<td>800</td>
<td>77:23</td>
<td>1.60</td>
</tr>
<tr>
<td>1600</td>
<td>42:58</td>
<td>0.39</td>
</tr>
<tr>
<td>3200</td>
<td>30:70</td>
<td>0.28</td>
</tr>
<tr>
<td>6400</td>
<td>22:78</td>
<td>0.25</td>
</tr>
</tbody>
</table>

The mechanism of lactone reduction was also probed by exploiting new reactivity of SmI₂-H₂O with lactones bearing a radical-stabilising group at the position next to the ring oxygen. C-O bond scission was observed to give carboxylic acid products under specific reaction conditions. Phenyl-bearing lactones of different ring-size were exposed to SmI₂ under a range of water concentrations (Table 5).
Interestingly, 5-, 6- and 7-membered lactones underwent scission in good to high selectivity and yield depending on water concentration and ring-size. Previously it was shown that alkyl substituted 5- and 7-membered lactones did not undergo reduction to the diol under SmI$_2$-H$_2$O conditions. The new mechanistic probes described in Table 5 therefore show that even in 5- and 7-membered lactones the initial electron transfer occurs but that it is reversible. Thus, the first electron transfer cannot be the rate determining step of lactone reduction. The rate of radical anion reduction could be altered by varying the amount of H$_2$O used: lower water concentration facilitated reduction of the ketyl-radicals and hence selectivity for C-O bond fragmentation was reduced whilst at high water concentration C-O scission predominated.

1.4.4 Barbituric acid reductions

In 2013, Procter and Szostak demonstrated the first SmI$_2$-H$_2$O-mediated monoreduction of barbituric acid derivatives 146 to afford the corresponding hemi-aminals 147 (Scheme 30).}$^{60}$

<table>
<thead>
<tr>
<th>$n$</th>
<th>H$_2$O (eq)</th>
<th>144:145</th>
<th>Conv. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>200</td>
<td>41:59</td>
<td>35</td>
</tr>
<tr>
<td>0</td>
<td>800</td>
<td>77:23</td>
<td>9</td>
</tr>
<tr>
<td>1</td>
<td>200</td>
<td>34:66</td>
<td>96</td>
</tr>
<tr>
<td>1</td>
<td>800</td>
<td>72:28</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>200</td>
<td>96:4</td>
<td>&gt;98</td>
</tr>
<tr>
<td>2</td>
<td>800</td>
<td>99:1</td>
<td>&gt;98</td>
</tr>
</tbody>
</table>
Despite requiring a two-fold excess of SmI$_2$ to ensure complete conversion, no over-reduction was observed. Water was the additive of choice in this Sm(II)-mediated transformation as none of the desired products were generated when other additives, such as alcohols (MeOH, $t$-BuOH), Lewis bases (HMPA, Et$_3$N) or metal salts (LiCl), were used in its place. It was suggested that the imide reduction is favoured by anomeric stabilisation (cf. lactones) of the acyl-type radical produced. The stability of the hemi-aminal products toward dehydration under the Lewis acidic conditions was attributed to the $n_N\rightarrow\pi^*\text{C}=$O delocalisation in a conformationally locked system.

Acyl-type radical anions generated could also undergo effective 5-exo cyclisations onto both activated and unactivated radical acceptors in good yield and with full control of stereochemistry (Scheme 31).
This is the first time that SmI₂-H₂O mediated reductive cyclisations have yielded products with full diasterecontrol. Procter hypothesised that the radical anion generated from the initial electron transfer has an increased half-life due to stabilisation from n_N → SOMO delocalisation, which allows the pendant radical acceptor to adopt the lowest energy conformation prior to cyclisation.

Water has become a pivotal additive in Sm(II)-promoted transformations owing to its dual role in: (1) coordinating to SmI₂ affecting an increase in the reagent’s reduction potential from -1.3 V to -1.9 V (vs. Ag/AgNO₃) (2) acting as an efficient proton donor due to its close proximity to the developing radical anion. More specifically, the high affinity of water for samarium results in a SmI₂-H₂O complex that has a reduction potential comparable to HMPA itself.¹⁵ This highly effective reducing system has been used to expand the substrate scope of the reagent significantly to include the reduction of differentially substituted lactones, activated carboxylic acid derivatives and barbituric acids.

1.5 SmI₂-H₂O-amine reductions

SmI₂-H₂O reductions can be promoted by the addition of amines, whose Lewis basic nature enhances the reduction potential of the reagent. In 1995, Cabri first reported the use of SmI₂-H₂O in combination with amines to effect aryl-alkene cyclisations, obtaining results comparable to that when toxic HMPA was used (Table 6).¹⁵¹

<table>
<thead>
<tr>
<th>Lewis base</th>
<th>151:152</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMPA</td>
<td>48:52</td>
<td>68</td>
</tr>
<tr>
<td>DBU</td>
<td>32:68</td>
<td>70</td>
</tr>
<tr>
<td>Et₃N</td>
<td>30:70</td>
<td>61</td>
</tr>
</tbody>
</table>
Hilmersson subsequently discovered that the rate of Sm(II)-mediated ketone reduction could be enhanced dramatically by the combined use of SmI₂, water and an amine. The reduction of 3-heptanone 153 was instantaneous when SmI₂-H₂O was used in combination with either Et₃N or TMEDA, increasing the reaction rate 100 000 fold compared to when no additive was present (Scheme 32). This more benign reagent system increased the reaction rate by up to two orders of magnitude compared to when SmI₂-HMPA-alcohol combinations were used.

Scheme 32

It was hypothesized that a dimeric species [SmI₂(R₃N)₂(OH)₂]₂ existed in solution to which the ketone could coordinate (Scheme 33). Furthermore, the precipitation of insoluble Sm(III) salts was thought to drive the equilibrium toward formation of the product.

\[
R₂C=O + 2\text{SmI}_2 + 6\text{H}_2\text{O} + 4\text{R}_3\text{N} \xrightarrow{rt, <10 \text{ s}} \text{R}_2\text{CHOH} + 2\text{Sm(OH)}_3 + 4\text{R}_3\text{N} + \text{HI}
\]

Scheme 33

In 2003, Hilmersson reported further scope of the SmI₂-H₂O-amine system, describing the instantaneous reduction of α,β-unsaturated esters and imines. It has also proved an effective and mild method for the deprotection of allylic ethers 155, propargyl ethers 157 and tosyl groups 159 (Scheme 34).
The success of these transformations is attributed to the enhanced reduction potential of SmI₂ achieved by using water in combination with the Lewis basic amine additive. Other functional moieties found to be susceptible to SmI₂-H₂O-amine reduction include nitro groups, conjugated olefins and alkyl halides.

Diastereoselective intramolecular coupling of aryl iodides and pendant alkenes has been described by Hilmersson. 5-Exo and 6-exo cyclisations with alkene and alkyne acceptors were shown to proceed with complete diastereocontrol (Scheme 35).

Recently Hilmersson reported an unusual selective α-defluorination of polyfluorinated esters and amides. Monodefluorination of 164 was accomplished through the use of SmI₂-H₂O to yield 165, whilst the addition of an amine effected complete α-defluorination to give 163 (Scheme 36).
In 2011, Procter described the SmI$_2$-H$_2$O-Et$_3$N reduction of unactivated esters to their corresponding alcohols. This was further extended in 2012 to incorporate the reduction of unactivated carboxylic acids (Scheme 37). Prior to these reports it was believed that carboxylic acids and their derivatives lay outside the reducing power of SmI$_2$. The crucial use of amine additives in combination with SmI$_2$-H$_2$O permitted access to these transformations.

Scheme 36

![Scheme 36](image)

The addition of a Lewis basic amine also allows access to the reduction of lactone substrates previously shown to be inaccessible to SmI$_2$-H$_2$O alone; SmI$_2$-H$_2$O facilitates the selective reduction of 6-membered lactones over any other ring-sized lactone. In 2012, Procter reported the reduction of different ring-sized lactones, which was accomplished through the combined use of SmI$_2$-H$_2$O and Et$_3$N (Scheme 38).

Scheme 37

![Scheme 37](image)
Subsequently, Procter and Szostak demonstrated the first highly chemoselective reduction of primary, secondary and tertiary amides to alcohols, reporting >95:5 C-N/C-O bond cleavage selectivity (Scheme 38). To date, the vast majority of amide reduction methods proceed with C-O bond cleavage of the intermediate hemi-aminal to generate amines. This use of SmI$_2$ constitutes the first general method for the reduction of all types of amides that proceeds with excellent C-N bond cleavage under mild conditions. Furthermore, this method was shown to facilitate the reductive cleavage of enantioenriched amides derived from Myers and Evans auxiliaries, affording alcohols in good yield and excellent enantioselectivity (Scheme 39).

Control experiments using $\text{H}_2^{18}\text{O}$ showed that amide hydrolysis or hydrolysis of an iminium intermediate is not a predominant pathway. The high C-N/C-O bond cleavage selectivity was thought to be promoted by the coordination of Sm(III) to the Lewis basic nitrogen of the hemi-aminal intermediate, which would facilitate C-N bond cleavage.
This multicomponent reagent system has also been shown to reduce nitriles to primary amines, constituting a method orthogonal to hydride mediated transformation.\(^7^6\) Under the optimized conditions, reduction was effected in excellent yield, generating no products from reductive fragmentation, hydrolysis or ionic polymerization pathways, which demonstrated the mild reaction conditions involved with the use of the SmI\(_2\)-H\(_2\)O-Et\(_3\)N system.

### 1.6 Novel SmI\(_2\) additives

Other proton donors, have been used in SmI\(_2\)-mediated reductions to unearth new modes of reactivity. Ethers have been shown to have a high binding affinity for SmI\(_2\) and hence have been utilized in selected reductive transformations. Hilmersson found that multi-dentate alcohols facilitate reduction of 3-heptanone and that a correlation exists between the reduction rate and the number of ethereal oxygens present in the polydentate ether. It was discovered that extending the ether chain length by introducing additional ethereal groups increased the rate of reduction.\(^7^7\) The enhanced reduction rate was most prominent when using diglycol with SmI\(_2\), measuring a rate 70 times faster than that of methanol. Mechanistic investigations suggested the formation of a dimeric species 176 bridged by two hydroxyl groups (Scheme 40).

![Scheme 40](image)

A logical extension of this chemistry was to perform enantioselective reductive processes, using the polydentate ether as a scaffold to design a ligand with a chiral backbone. Takeuchi successfully demonstrated the enantioselective protonation of samarium enolates 180 using a multi-dentate, chiral polyether 182 (Scheme 41).\(^7^8\)
Flowers has also used various multi-dentate additives as proton donors to accelerate SmI$_2$-promoted reductions.\textsuperscript{28} Diglycol 186 was shown to enhance the reduction rate of benzyl bromide 183 to toluene 184 (Scheme 42). This acceleration was less than that observed when water was employed. In contrast to water, a large excess of diglycol was shown to saturate the coordination sphere of the reductant, thereby preventing coordination of the substrate to Sm(II) and inhibiting reduction.

The reduction rate of benzyl bromide by SmI$_2$ was then monitored in the presence of increasing quantities of diglycol 186, methyldiglycol 187, and dimethyldiglycol 188 to determine the affinity of each ligand for Sm(II) and the impact they have on reactivity (Scheme 42). 186 demonstrated first-order kinetics at concentrations up to 6 mM (3 eq) whilst at higher concentrations the reaction approached inverse-first order. This suggests that one equivalent of 186 is involved in the reduction of benzyl bromide at lower additive concentrations, whilst higher concentrations impede reduction. A similar relationship was observed with 187 but to a lesser extent, with first-order kinetics being demonstrated at concentrations of up to 60 mM (30 eq), above which inhibition was observed. Addition of higher concentrations of 188 showed no appreciable impact on the rate of reduction of benzyl bromide. The affinity of these additives for SmI$_2$ was found to be of the order diglycol $>$ methyldiglycol $>$ dimethyldiglycol.
The crystal structure of various Sm(II)-glyme complexes was also studied to help explain reactivity trends. [Sm(dg)₃]I₂ 189 crystals displayed a 9-coordinate Sm(II) complexed to each oxygen of the three diglycol ligands, with iodide ligands being displaced to the outer coordination sphere of the metal centre (Scheme 43).

Additionally, the UV/vis spectrum of these crystals in THF was comparable to that of a solution of SmI₂-THF containing three equivalents of diglycol, therefore reflecting the solution state structure of this system. Crystallographic studies also showed that substituting a hydroxyl hydrogen atom with a methyl group causes a lengthening of the corresponding Sm-O bond, an effect which is further extenuated when both hydroxyl hydrogen atoms are replaced with methyl groups. Furthermore, the diminished affinity of the ligand results in only two dimethylglycol ligands binding to Sm(II) and hence the two iodides are still bound to the inner coordination sphere of the metal. Displacement of iodide ligands from SmI₂ was found to be crucial for facilitating reduction hence no benefit on reduction rate was observed when using dimethylglycol as an additive.

Conductance experiments carried out by Flowers indicated that ethylene glycol 185 has an intermediate affinity for Sm(II), between that of water and diglycol 186. Although high concentrations of water increase the reducing power of SmI₂ significantly, the SmI₂-H₂O system readily oxidises and it was hypothesised that use of ethylene glycol as an additive would generate a more robust reductant. Due to its bidentate nature, lower quantities of ethylene glycol compared to water would be required to displace iodide ligands and enhance reactivity without saturating the coordination sphere. The reduction rate of benzyl bromide with SmI₂ was monitored over increasing concentrations of additive. Water and ethylene glycol additives were shown to significantly increase the reduction rate but also displayed saturation kinetics, albeit at lower concentrations of ethylene glycol. The affinity of each additive for SmI₂ determines the quantity required to displace bulk solvent and iodide ligands from the coordination sphere of Sm. The concentration of additives

Scheme 43
therefore needs to be tuned to sufficiently activate Sm whilst leaving open coordination sites for substrates to bind.

A comparative study of the SmI$_2$-mediated reduction of 5-decanolide 190 using either ethylene glycol or H$_2$O was conducted to determine whether ethylene glycol was a suitable substitute for water (Table 7).

<table>
<thead>
<tr>
<th>Additive</th>
<th>Equivalents</th>
<th>Time (h)</th>
<th>Yield 191 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H$_2$O</td>
<td>150</td>
<td>7</td>
<td>83</td>
</tr>
<tr>
<td>Ethylene glycol</td>
<td>4</td>
<td>12</td>
<td>80</td>
</tr>
</tbody>
</table>

Reduction to diol 191 was successfully achieved using ethylene glycol as an additive, requiring lower concentrations of ethylene glycol than with water. Although higher concentrations of ethylene glycol enhanced the rate of reduction, transesterification became a competing reaction and the major product.

Ketone-alkene cyclisations were also studied to determine if this methodology could be extended to more complex carbon-carbon bond-forming reactions that usually require HMPA as an additive (Table 8).
Comparable yields of the cyclised product 193 could be obtained using either ethylene glycol or water though required the use of over 6-times the quantity of water in comparison to ethylene glycol. Diastereoselectivity was modest in both cases with neither additive able to achieve selectivity comparable to that obtained when using the traditional HMPA additive. Although good yields were obtained using lower concentrations of ethylene glycol and water, higher quantities of the reduced product 194 were isolated. Lewis basic additives such as ethylene diamine and trans-$N,N'$-dimethyl-1,2-cyclohexyldiamine have also shown potential as alternative SmI$_2$ additives and were employed in the ketone-alkene cyclisation. Quantitative yields of 193 were obtained for both (determined by $^1$H NMR), with trans-$N,N'$-dimethyl-1,2-cyclohexyldiamine providing enhanced diastereoselectivity compared to water and ethylene glycol. The increased steric bulk of trans-$N,N'$-dimethyl-1,2-cyclohexyldiamine was thought to be partially accountable for the increased diastereoselectivity.
This study demonstrates a variety of novel additives that can be used in SmI₂-mediated transformations, including those thought previously to be only accessible using SmI₂-H₂O. The enhanced rate of reaction was attributed to the displacement of iodide ligands from the inner coordination sphere of Sm(II) at a concentration that does not saturate the metal centre and therefore inhibit substrate reduction.

1.7 SmI₂ in sequential radical processes and cyclisation cascades

The unique ability of SmI₂ in performing both radical and anionic processes in combination with its excellent chemoselectivity has led to the reagent’s application in multiple bond forming processes involving progressive transformations and cyclisation cascades, with numerous applications in complex natural product synthesis. One of the first examples utilizing a SmI₂-mediated sequential process was reported by Curran, employing SmI₂-HMPA for the key step in the synthesis of (±)-hypnophilin 197 and the formal total synthesis of (±)-coriolin 198 (Scheme 44).

![Scheme 44](image)

Single electron reduction of aldehyde 195 initiates a 5-exo-trig cyclisation, which generates a tertiary carbon-centred radical that undergoes successive 5-exo-dig cyclisation. The transformation generates 196 with full diastereoccontrol of the three new contiguous stereocentres.79

In 1998, Kilburn used a radical-radical sequence to create the carbon skeleton of paeonilactone B 203 (Scheme 45).80,81 A SmI₂-mediated cascade involving 5-exo-trig mediated cyclopropyl fragmentation of 200 followed by 5-exo-dig cyclisation afforded the cis-fused bicycle 202 in good yield and diastereoselectivity.
Further elaboration of these studies by Kilburn found the fragmentation could be used to afford densely functionalised tricycles 205 (Scheme 46). Initial 6-exo-trig cyclisation facilitates cyclopropyl ring opening and subsequent 5-exo-dig cyclisation. Employing an alkynyl trimethylsilane present in 204 provided the steric hindrance necessary to inhibit competitive 8-endo-trig cyclisation. Several examples of reductive fragmentation-cyclisation cascades have been described in the synthesis of natural products including (−)-(α)-kainic acid83 and (+)-crotogoudin.84

Scheme 46

In 2004, Kilburn demonstrated a highly effective SmI₂-MeOH initiated sequence using α-allyloxy enone 206 to generate a highly functionalised tetracycle.85 Initial enone dimerisation gave intermediate 207 poised for intramolecular aldol cyclisation. Reduction of the resulting ketone 208 facilitated ketyl-radical 5-exo-trig cyclisation to produce complex tetracycle 209 bearing seven contiguous stereocenters in 67% yield and as a single diastereoisomer (Scheme 47).
In 2007, Kobayashi utilized a Sm(II)-mediated ketyl radical cascade cyclisation to generate spiro[4.5]decane scaffolds (Scheme 48). A ketyl-radical initiated 6-exo-trig event produced a stabilized radical anion that could subsequently undergo 5-exo-dig cyclisation to afford spiro-fused bicycles 211.

A dramatic additive effect was observed for the tandem cyclisation: utilising either SmI$_2$-HMPA or SmI$_2$-Sm facilitated either syn or anti cyclisation respectively. Electrostatic repulsion resulting from the use of SmI$_2$-HMPA afforded anti cyclisation products whilst chelation controlled syn cyclisation was facilitated by SmI$_2$-Sm.

In 2009, Procter reported a dialdehyde cascade which utilized an additive controlled SmI$_2$-mediated ‘radical then aldol’ transformation (Scheme 49). Treatment of dialdehydes 212 with SmI$_2$-t-BuOH permitted ketyl radical-alkene 5-exo-trig cyclisation, leaving the pendant aldehyde untouched. This aldehyde could then undergo chelation-controlled aldol cyclisation with the ensuing Sm(III) enolate 213 to generate spirocyclic lactones 214. A series of spirocyclic lactones were isolated in good yield, comprising four contiguous stereocentres with complete diastereocontrol.
It was also shown that successive treatment of spirocyclic lactones with SmI$_2$-H$_2$O could effect lactone reduction to generate tetraol 215 in a one-pot sequence. Procter utilised this ‘radical then aldol’ cyclisation cascade to construct the highly oxygenated carbocyclic skeleton of (+)-pleuromutilin 218 (Scheme 50).\textsuperscript{88,89}

Scheme 50

SmI$_2$-t-BuOH effected 5-exo-trig/aldol cascade cyclisation of dialdehyde 216 to afford 217, the 5,6,8-tricyclic core of (+)-pleuromutilin 218, with full diastereocontrol of the four contiguous stereocentres and in 88\% yield. Furthermore, this transformation was successfully demonstrated on a 30.0 mmol scale. Single electron reduction of the sterically more accessible aldehyde generates a ketyl radical which undergoes ester chelation-controlled 5-exo-trig cyclisation. Subsequent single electron reduction then facilitates diastereoselective aldol cyclisation to afford the tricyclic skeleton en route to the first enantiospecific total synthesis of (+)-pleuromutilin 218.

In 2011, Reisman utilised a similar Sm(II)-mediated reductive cyclisation to gain access to the core of (−)-maoeystal Z 221 (Scheme 51).\textsuperscript{90} This synthetic approach permitted the formation of two rings and four contiguous stereogenic centers in a single step.
The reaction proceeds through an unusual 6-endo-trig cyclisation and subsequent aldol cyclisation to obtain \( \text{220} \) in moderate yield and with full diastereocontrol of the four contiguous stereocentres. LiBr was required as an additive in combination with \( \text{SmI}_2-t\text{-BuOH} \), presumably to effect \textit{in situ} formation of \( \text{SmBr}_2 \), which has a greater reduction potential than \( \text{SmI}_2 \).\(^5\) This multi-component reducing system was essential for the desired reactivity and allowed access to an advanced stage intermediate in the synthesis of \((\text{-})\text{-maecrystal Z} \).

\textbf{Scheme 51}

\( \text{SmI}_2\text{-LiBr} \)
2. Asymmetric desymmetrisation of Meldrum’s acids

2.1 Previous work: Reduction of Meldrum’s acids using SmI$_2$-H$_2$O

The success of the selective reduction of lactones using SmI$_2$-H$_2$O led to further speculation as to the reducing capacity of the system and the enhanced reactivity achieved by using water as an additive.\(^8\) It was proposed that Meldrum’s acid derivatives could also be reduced and that only mono-reduction would occur to give the β-hydroxy acid. Applying the SmI$_2$-H$_2$O reducing system to various substituted cyclic 1,3-diesters pleasingly effected reduction to generate β-hydroxy acids in good to excellent yields. Furthermore, only monoreduction products were isolated with no diol produced from potential over-reduction (Scheme 52).\(^9\) This is the first example of the monoreduction of Meldrum’s acids.

\[ \text{Scheme 52} \]

Competition experiments demonstrated that the reducing system was selective for cyclic diesters 224 over both acyclic diesters 225 and simple esters (Scheme 53).
The discrimination between cyclic and acyclic diesters can be ascribed to the presence or absence of anomeric stabilisation of radical anion intermediates (Scheme 54). This stabilisation present in cyclic diesters appears to promote the first electron transfer to the carbonyl by reducing the relative energy barrier from 114.3 kJ mol\(^{-1}\) for acyclic diesters to 47.9 kJ mol\(^{-1}\) for Meldrum’s acids.

Deuteration experiments were carried out in early mechanistic investigations of the monoreduction of cyclic diesters. The dialkylated Meldrum’s acid derivative 224 was reduced using SmI\(_2\)-D\(_2\)O yielding the deuterated β-hydroxy acid product 232 (Scheme 55), indicating the presence of an anionic intermediate that is protonated by water.

Following these observations, the mechanism of the monoreduction was hypothesised (Scheme 56).\(^{91}\) After the initial electron transfer to the activated ester 233, a pseudoaxial radical-anion 234 is generated that is anomerically stabilised by the \textit{anti}-periplanar oxygen.
lone pairs. This intermediate is subsequently protonated by a H₂O molecule ligated to the metal centre. A further reduction-protonation sequence then gives rise to hemi-acetal 237 that is in equilibrium with the activated aldehyde 238. Electron transfer to the aldehyde generates a second ketyl-radical anion 239. A final electron transfer yields an organosamarium which is subsequently protonated and final collapse of the acetal moiety affords the β-hydroxy acid product 241.

Scheme 56

The chemoselectivity achieved was proposed to arise from the more favourable initial electron transfer to the Meldrum’s acid in comparison to acyclic esters.⁹⁰⁻⁹¹ Anomeric stabilisation occurs to a much lesser extent in acyclic esters and diesters and hence this initial transfer would be less facile. Electronic stabilisation of the pseudoaxial radical produced promotes the initial reduction of cyclic diesters. Reduction of the resultant β-hydroxy acid is not thought possible as 241 cannot achieve the anomeric stabilisation thought necessary to promote reduction by SmI₂-H₂O. Additionally, literature reports by Kamochi and Kudo indicated that reduction of unactivated carboxylic acids would not be feasible under SmI₂-H₂O conditions.³¹⁻³²

The synthesis of β-hydroxy acids from Meldrum’s acid derivatives was previously described by Pollo et al. and required a multi-step approach (Scheme 57).⁹³
The use of SmI$_2$-H$_2$O for the monoreduction of cyclic 1,3-diesters now provides an effective way of synthesising β-hydroxy acids in a single step from cyclic diesters (Scheme 52).

### 2.2 Enantioselective desymmetrisation of Meldrum’s acids

SmI$_2$-H$_2$O mediated monoreduction of Meldrum’s acid derivatives generates β-hydroxy acids as racemates but enantioenriched products would be highly desirable. It was hypothesized that the use of a chiral additive could induce enantioselective desymmetrisation thereby providing enantiomerically enriched β-hydroxy acids. Currently there are no single-electron reductive methods for the enantioselective desymmetrisation of malonate derivatives. An enantiopure ligand is proposed to coordinate to Sm(II), simultaneously enhancing the reduction potential of the metal centre and providing an asymmetric environment for carbonyl reduction to deliver enantioenriched products (Scheme 58).

Recent studies by Flowers have shown the successful use of bidentate ligands in SmI$_2$-mediated reductions and hence we chose to use these in preliminary studies to determine an efficient ligand scaffold for reduction (see section 1.6 Novel SmI$_2$ additives). Additives used in combination with SmI$_2$ were proposed to coordinate to Sm(II) through displacement of bulk solvent and both iodide ligands. Although water can
be used at high concentrations to increase the reactivity of SmI₂, multidentate ligands such as ethylene glycol were shown to exhibit inhibitory activity at high concentrations as they saturate the coordination sphere of Sm(II) thereby precluding substrate binding and preventing reduction. Reduction is therefore sensitive to the additive used and the concentration employed. Diamines including ethylene diamine and trans-$N,N'$-dimethyl-1,2-cyclohexyldiamine demonstrated similar reactivity to water in ketone-alkene cyclisations. Combined, these findings suggest an initial screen of simple diols, diamines and amino alcohols to determine the optimal ligand scaffold for the SmI₂-mediated monoreduction of cyclic 1,3-diesters would be appropriate. Once a suitable ligand framework had been identified, chiral additives encompassing this basic motif would be employed in an attempt to achieve enantioselective desymmetrisation (Scheme 59).

**Scheme 59**

Chiral non-racemic ligands are proposed to coordinate to Sm(II) in a highly organised manner, presumably without saturating the metal coordination sphere thereby permitting substrate binding. Interactions between substituents on the ligand and the quaternary centre of the cyclic diester would then determine which prochiral carbonyl is reduced (Scheme 59). Investigation of the literature suggests several easily accessible ligand scaffolds that could be suitable for the desired transformation (Scheme 60).

**Scheme 60**

$R = \text{alkyl, aryl}$

$X = Y = \text{OH, NH}_2$ or $X = \text{OH}$; $Y = \text{NH}_2$
Reports by Shibasaki have shown ligand scaffold 247 to be a good ligand for Sm-mediated transformations. Further elaborated ligand frameworks 248-250 have also proven useful for the asymmetric protonation of Sm(III)-enolates in the work of Nakamura and Takeuchi. More specifically, unpublished results within the Procter group have shown enantiopure ligand frameworks 252-254 to be good chiral additives for asymmetric transformations using Sm(II) (Scheme 61). Evans has also successfully demonstrated the use of Sm(III)-251 complexes in the asymmetric Meerwein-Ponndorf-Verley reduction or aryl methyl ketones.

![Scheme 61](image)

Furthermore, it has been shown that multidentate achiral ethers are excellent ligands for Sm(II) hence ligand scaffolds 247-251 are expected to be particularly promising for the enantioselective desymmetrisation of Meldrum’s acid derivatives.

### 2.3 Results and discussion

Initially two substrates were envisaged for methodology development: commercially available phenyl Meldrum’s acid 259 and 5-isobutyl substituted Meldrum’s acid 258, which could be synthesised directly from Meldrum’s acid. Knoevenagel condensation was accomplished using facile conditions described by Bigi, which involved heating Meldrum’s acid 256 with isobutyraldehyde in H₂O. Conjugate reduction with NaBH₄ then afforded 258 in overall good yield (Scheme 62).

![Scheme 62](image)
Meldrum’s acid substrates 258 and 259 were then reduced using the SmI\(_2\)-H\(_2\)O system to afford the corresponding racemic \(\beta\)-hydroxy acids 261a and 261b, which could subsequently be resolved using analytical methods (Scheme 63).

![Scheme 63](image-url)

Chiral HPLC and GC were used to separate the enantiomers of each \(\beta\)-hydroxy acid product to allow the measurement of enantiomeric excess from successful SmI\(_2\)-mediated reductions using chiral ligands.

An initial ligand screen was performed using ethylene glycol, ethylene diamine and ethanolamine as simple ligand frameworks that should coodinate to the metal centre and hence facilitate reduction. Flowers previously reported the use of these ligands in equimolar quantities of SmI\(_2\):ligand to successfully effect reduction of 6-membered lactones thus reactions were carried out using 1 and 4 equivalents of additive (with respect to SmI\(_2\)) in these studies (Scheme 64).\(^{29}\)

![Scheme 64](image-url)

Ethylene diamine appeared to be too reactive as it caused decomposition of both Meldrum’s acid derivatives, presumably through nucleophilic addition and successive collapse of the ketal moiety. This detrimental activity was also observed with ethanolamine. Ethylene glycol showed promising results when used as an additive, affording 50% of the desired \(\beta\)-hydroxy acid product 261a from the reduction of 260a.
Reduction of 260b was also successful yielding 15% of 261b. Yield losses were attributed to transesterification in both cases, the products of which could be observed by crude $^1$H NMR.

With these promising results in hand, chiral diols were then employed in an attempt to achieve enantioselective reduction. (2R,3R)-Butanediol 265 and (R,R)-hydrobenzoin 266 were initially selected as economical, commercially available diols for use in the SmI$_2$-mediated reduction. Reduction of 260a did not occur using either chiral diol, recovering starting material and, when butanediol 265 was employed, transesterification products. Hydrobenzoin 266 did not appear to react with the cyclic 1,3-diester in this manner: nucleophilic addition being seemingly suppressed by steric of the 1,2-diol framework. Limited reduction of 260b was observed, obtaining less than 20% yield of the 261b in both instances and recovering most of the starting material (Scheme 65).

Interestingly, products of transesterification were not isolated in these cases, presumably due to steric hindrance present in the hydrobenzoin scaffold.

![Scheme 65](image)

Chiral GC analysis showed the β-hydroxy acid product from both reactions to be racemic with no enantiomeric excess detected. The α-proton of this product is innately acidic due to its benzylic nature and presence of the neighbouring α-acid group so it was thought that reduction could be occuring enantioselectively but scrambling of the stereocentre through formation of an intermediate prochiral enol could result in a racemic product. Alkylation of 260b with MeI would therefore block this position thus preventing enol formation and hence racemization. Attractively, asymmetric reduction of this substrate would deliver
products containing challenging quaternary stereocentres. Alkylation of α-phenyl Meldrum’s acid with MeI proceeded in good yield to afford the dialkylated Meldrum’s acid derivative 267 (Scheme 66). This substrate was then subjected to standard SmI$_2$-H$_2$O conditions to obtain the β-hydroxy acid racemate 268 in 83% yield. Furthermore, esterification of 269 with TMSCHN$_2$/MeOH was required to achieve baseline separation of enantiomers by chiral HPLC.

![Scheme 66](image)

Employing equimolar quantities of SmI$_2$ and ethylene glycol successfully reduced 267 to the corresponding β-hydroxy acid 268 in 45% yield (Scheme 67). The depleted yield observed when using equimolar quantities of ethylene glycol was the result of competing transesterification (cf. SmI$_2$-H$_2$O; 83% yield). Transesterification accounted for the sole product when a higher concentration of ethylene glycol (28 eq) was used.

![Scheme 67](image)

Commercially available chiral non-racemic diols were therefore employed in an attempt to produce enantioenriched β-hydroxy acid products (Scheme 68).
Unfortunately neither \((2R,3R)\)-butanediol 265 or \((R,R)\)-hydrobenzoin 266 effected reduction and only starting material was recovered, which is reminiscent of the low reactivity seen previously (Scheme 65). The more sterically demanding disubstituted Meldrum’s acid derivative may not be able to bind the already sterically encumbered Sm(II)-dial complex efficiently to allow for reduction. In the cases of both mono- and disubstituted Meldrum’s acids used, it appeared that the SmI₂-dial system was not sufficiently reactive to facilitate efficient reduction. Binding of the 1,2-diols to Sm(II) may not enhance the reduction potential of samarium sufficiently to promote the monoreduction of Meldrum’s acid. It was therefore hypothesised that a more activated Sm(II)-species was required to effect reduction.

Recently Procter described a multicomponent system that effected the novel reduction of unactivated acyclic esters 166 selectively to the corresponding alcohols 167; a transformation previously thought inaccessible to SmI₂. Addition of Lewis basic Et₃N to SmI₂-H₂O produces a more powerful reductant capable of reducing aliphatic esters (Scheme 69).

Scheme 68

Scheme 69
A system involving the use of amine bases was therefore envisaged for the monoreduction of cyclic 1,3-diesters. Competition experiments have shown that reduction of aliphatic esters and carboxylic acids proceed at a similar rate. This system therefore has the potential to further reduce β-hydroxy acid products generated from the monoreduction of Meldrum’s acid derivatives at a comparable rate to that of esters hence the reactivity of the Sm(II) reagent may require fine-tuning to prevent over-reduction. If this method proves successful though, either non-racemic amines or alcohols could be employed to obtain enantioenriched β-hydroxy acid products.

α-Phenyl-methyl Meldrum’s acid was chosen as the model substrate as the α-position is non-enolizable and the two different sized α-substituents would allow differentiation in the enantiodetermining step and resultantly grant access to a product containing a challenging quaternary stereogenic centre. Pleasingly, addition of SmI₂ to 267 followed by Et₃N and H₂O gave the desired β-hydroxy acid product 268 in 52% yield (Scheme 70).

![Scheme 70](image)

Although the reaction did not go to completion, a small quantity of diol 270 was isolated, resulting from the reduction of 268. This result suggests that reduction of the carboxylic acid could be faster than that of the cyclic diester. The reducing ability of the system could be lowered by decreasing the concentration of Et₃N thereby preventing over-reduction. A slight excess of Sm(II) was required to ensure complete conversion (Scheme 71).

![Scheme 71](image)
Additionally it was shown that the use of alternative proton donors MeOH and t-BuOH alongside SmI₂-Et₃N did not enable reduction, instead leading to the recovery of starting material and, in the case of MeOH, products of transesterification.

With this result in hand, a ligand screen was carried out using SmI₂-H₂O and a variety of commercially available chiral non-racemic amines (Scheme 72).

![Scheme 72](image)

Reduction was achieved when using SmI₂-H₂O in combination with the sparteine surrogate 271, isolating the β-hydroxy acid in 31% yield. The enantiomeric ratio was determined from the corresponding methyl ester and showed that the product was in fact racemic. Employing the cinchona alkaloids 272 and 27 did not result in reduction of the Meldrum’s acid group but in fact reduction of the quinoline ring was observed in both cases. Investigation of the literature found that Kamochi has demonstrated the SmI₂-H₂O-mediated reduction of heterocycles – pyridine derivatives were reduced completely to the corresponding saturated piperidines. The nucleophilic nature of primary amines 274, 277 and 278 caused them to react with the starting material by
addition into the carbonyl, resulting in degradation rather than reduction. The TMS-protected prolinol additive 282 was not stable to the SmI$_2$-H$_2$O conditions – loss of the silyl group was observed with no indication of Meldrum’s acid reduction.

Pyrrolidine catalysts 279 and 280 were successful in generating β-hydroxy acid product 268 in 33% and 43% yields respectively, though the corresponding methyl esters were racemic. Experiments using the pyrrolidine-based ligands 279 and 280 were repeated at −78 °C in an attempt to achieve enantioenrichment (Scheme 73).

![Scheme 73](image)

Although the β-hydroxy acid was generated with an improved yield in both cases, the methyl esters were racemic.

Recent studies by Procter revealed new mechanistic insights in the SmI$_2$-Et$_3$N-H$_2$O reduction of unactivated esters. Kinetic studies strongly indicated that the amine component assists deprotonation of the proton donor and that whilst it functions to provide a more powerful Sm(II) reductant, it may not be directly involved in the electron transfer and protonation steps (Scheme 74). By analogy to the asymmetric system, this would mean that it may not be involved in the enantiodetermining step and hence enantioinduction cannot be achieved using chiral non-racemic amines.
Consequently, it was hypothesised that the proton sources would be more likely to have an effect on the enantiodetermining step. The component acting as the chiral source was therefore changed from the amine to the proton donor. Commercially available (R,R)-hydrobenzoin was employed as a chiral proton source in combination with Et₃N (Scheme 75). The stoichiometry used was based on previous results using ethylene glycol, whereby equimolar quantities promoted monoreduction of Meldrum’s acid derivatives without saturating the coordination sphere of Sm(II).

At room temperature, (R,R)-hydrobenzoin partially reduced 267 to the corresponding β-hydroxy acid and so the enantiomeric ratio was determined by conversion to the methyl ester. Chiral HPLC analysis measured 5% ee and so the reaction was repeated at −78 °C in an effort to enhance this further (Scheme 76).
Carrying out the reaction at $-78 \, ^\circ \text{C}$ led to the isolation of the monoreduction product in comparable yield and, after converting to the methyl ester, was shown to be non-racemic, with 31% ee. This could be improved to 40% ee by recrystallising the diol from $i$-PrOH prior to the reaction. Extensive screening experiments showed the stoichiometry of each reaction component could be decreased marginally to 6:6:6 equivalents of SmI$_2$-266-Et$_3$N to afford 269 in 41% ee (Scheme 77).

Scheme 77

Importantly no over-reduction was seen during screening studies and transesterification was not observed either. In a control experiment carried out at room temperature and in the absence of SmI$_2$, complete recovery of starting material was achieved. This indicates that transesterification of 267 by hydrobenzoin is not facile and that SmI$_2$ is necessary for reactivity. To examine the possibility of Lewis acid mediated transesterification, 267 was treated with SmI$_3$-THF, which again gave complete recovery of 267.

Encouraged by these promising results, the improved set of conditions could be used to further study the impact of the amine component (Table 9).
Comparing different tertiary amines (entries 1-3) showed Et₃N to be optimal, obtaining highest yield and enantioselectivity in this case. Secondary amines pyrrolidine and piperidine (entries 5-6) gave similar yields to the model system though enantioselectivity was diminished. Interestingly, use of morpholine (entry 4) gave the highest enantioselectivity out of the secondary amines investigated. This may be due to secondary hydrogen-bonding interactions occurring with the ether oxygen making a more selective Sm(II) complex. From this set of results it was concluded that Et₃N was optimal, balancing basicity and steric properties of the amine to achieve the highest yield and selectivity. This is consistent with the optimized conditions required for the reduction of unactivated esters.⁷²

Alternative chiral proton sources were explored with a view to improving selectivity and conversion. A variety of commercially available 1,2-diols and multi-dentate alcohols were employed but with limited success (Scheme 78).
It was thought that increasing the size of the 1,2-diol moiety from phenyl to naphthyl would provide more steric influence and hence increase selectivity. Unfortunately, products of reduction were not observed using 285 and only starting material was recovered. In this case, the steric bulk may be preventing coordination of the substrate to Sm(II).

Previously employed (2R,3R)-butanediol 265 and another aliphatic ligand scaffold (1R,2R)-1,2-dicyclohexyl-1,2-ethanediol 286 were also utilized in the reaction though these additives did not effect reduction either. This is presumably due to the ligands having a lower affinity for the metal centre and hence the reduction potential of Sm(II) would be insufficient to promote reduction. Exposure of (1R,2R,3S,5R)-(−)-pinanediol 287 to the SmI$_2$ reduction conditions resulted in degradation of the additive and so reduction of the Meldrum’s acid derivative was not observed. A similar unproductive process was also observed when TADDOL 288 was used. No reduction was observed with (S)-BINOL 289, potentially because the bite angle of the ligand is not sufficient to accommodate Sm(II). Multidentate ligands 252 and 254 were previously employed by Nakamura for the enantioselective protonation of samarium enolates$^{78}$ and hence were thought to be suitable for the enantioselective monoreduction of 267. Unfortunately no product was isolated from reactions with either ligand. Commercially available diol 290 was employed, containing...
four coordinating oxygen atoms and a flexible bite angle to accommodate the metal centre (Scheme 79).

Indeed 290 successfully reduced the cyclic 1,3-diester in comparable yield to the model system though lower selectivity was observed obtaining only 13% ee. This is likely due to the scaffold providing insufficient steric bias in the diastereomeric transition state. It was thought that the reduction potential was insufficient to reduce 267 using these additives or that the multidentate ligands provide too much steric hindrance around the metal centre thus preventing efficient complexation of Sm(II) with Et₃N and/or the substrate. This could be remedied by combining the amine and alcohol into one additive, providing a ligand that could bind samarium to produce a more thermodynamically stable complex, capable of reducing Meldrum’s acid derivatives. Several amino alcohol ligands were envisaged that have been successfully used in SmI₂-mediated processes (Scheme 80).

These amino alcohols were used as the sole additive containing both the alcohol and amine moieties thought necessary for reduction to occur. Amino alcohols 253 and 291 were previously used by Nakamura⁷⁸ and Evans⁹⁵ respectively in samarium-based systems to
achieve asymmetric transformations. Regrettably, neither ligand in combination with SmI$_2$ was successful in reducing 267 and only starting material was recovered.

Cinchona alkaloids, such as cinchonidine 272, have been used extensively as bifunctional catalysts for asymmetric synthesis whereby the Lewis basic bridgehead nitrogen and neighbouring hydroxyl group can act as metal binding sites. Theoretically samarium could coordinate to one or both sites thereby providing an asymmetric environment for reduction to take place providing a proton donor that is in close proximity to the developing ketyl-radical anion. Unfortunately no β-hydroxy acid product was detected when used with SmI$_2$ and only starting material was recovered. It was thought that smaller ligands of comparable size to hydrobenzoin might be more effective in promoting efficient reduction. The proline-derived pyrrolidine ligands contain a 1,2-amino alcohol moiety that may bind to Sm(II) as desired. Together with ephedrine 296 and N-methylephedrine 295, secondary and tertiary pyrrolidines 292-294 were employed in order to compare differences in reactivity (Scheme 81).

Scheme 81

The use of secondary amines 293 and 294 with SmI$_2$ successfully reduced the cyclic diester in comparable yield to the model system, whilst tertiary amine 292 did not result in reduction, recovering only starting material. Enantiomeric ratios could now be determined directly from β-hydroxy acid products due to the availability of new analytical techniques.
Unfortunately the reduction products isolated were racemic. Analogous results were obtained using ephedrine 296 and \(N\)-methylephedrine 295: the secondary amine 296 reduced the cyclic diester also giving a racemic product whilst the tertiary amine 295 yielded no product. Combined these results show that the class of the amine can significantly influence reactivity. The bidentate nature of the hydrobenzoin proton donor must also play a considerable role in inducing enantioselective reduction.

Limited success in using alternative 1,2-diol frameworks and various amino alcohols required the re-evaluation of the original hydrobenzoin scaffold. It was thought that the diastereomeric transition state could be manipulated by varying the substitution on the aryl groups of hydrobenzoin by affecting either steric or electronic changes (Scheme 82).

![Scheme 82](image)

A two-step approach could be used for direct access to differentially substituted hydrobenzoin compounds. Stilbenes were synthesised by cross-metathesis of styrenes using Grubbs II generation catalyst, and by Zn-TiCl$_4$-mediated McMurry coupling of the appropriate benzaldehyde. Stilbene-derivatives could then be subject to Sharpless asymmetric dihydroxylation conditions to generate enantiomerically pure diols. \(p\)-Methoxy and \(p\)-trifluoromethyl substituted diols 299 and 301 were first synthesised to probe the effects of electronics on enantioselectivity and yield (Scheme 83).
It was hypothesised that altering the electronics of the ligand would affect its binding to Sm(II) and hence influence enantioselectivity and yield. Exposing the model substrate to the same SmI$_2$-Et$_3$N conditions but using the newly synthesised 1,2-diols demonstrated an unexpected result (Scheme 84).

Both the electron rich and electron poor aryl substituted diols yielded β-hydroxy acids with lower enantioselectivity than the standard (R,R)-hydrobenzoin additive and in lower yield. Varying the substitution pattern on the aryl rings was also explored, synthesising...
electronically differentiated 3,5- and 2-substituted aryl containing hydrobenzoin scaffolds (Scheme 85).

Scheme 85

2-Substituted aryl alkenes were generated by Zn-TiCl₄-mediated McMurry coupling conditions of benzaldehydes 302 whilst 3,5-substituted stilbenes were produced by a protocol described by Barrero using Nugent’s reagent: an air stable solid used as a more practical alternative to TiCl₄. The aforementioned dihydroxylation procedure was then used to synthesise a series of differentially substituted hydrobenzoin ligands. Diols 303a-c and 305a-b were all isolated in good yield and high purity (>99% ee by chiral HPLC).

With a variety of substituted chiral diols available, improvements to the Sm(II)-mediated asymmetric reduction could now be explored. Employing the optimal SmI₂-Et₃N-diol system at −78 °C successfully effected reduction of Meldrum’s acid derivative 267 in the majority of cases (Table 10).
Table 10

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl substitution</th>
<th>ee (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>35</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>Br</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Me</td>
<td>13</td>
</tr>
<tr>
<td>6</td>
<td>OMe</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup>Enantiomeric excess measured from crude reaction mixture by chiral HPLC.

The newly synthesised ligands used in conjunction with Et<sub>3</sub>N and SmI<sub>2</sub> were all able to generate β-hydroxy acid product 267, albeit with lower enantioselectivity than the model system. In the case of entry 5, no reduction products were isolated, recovering only starting material. This could be due to the Lewis base bridging the halogen and proton through both halogen bonding and hydrogen bonding respectively, which could inhibit complexation of the diol to Sm(II) and therefore prevent reduction.<sup>100,101</sup> Substitution on the aryl rings of the ligand was detrimental to the enantioselectivity in all other cases. This is most likely due to steric repulsion in the Sm(II)-diol complex inhibiting well-organized coordination of the substrate to the metal centre.

It was next decided to explore the substrate scope of the asymmetric reduction. Several Meldrum’s acid derivatives were envisaged containing α-substituents whose size could lead to greater differentiation in the proposed diastereomeric transition state model. This could be accomplished by exchanging the phenyl moiety with larger aryl groups. Well established methodology developed by Hartwig could be used to prepare malonate derivatives (Scheme 86).<sup>102</sup>
Pd(OAc)$_2$ catalysed α-arylation of diethylmalonate 306 with 307 successfully yielded 308, which could be alkylated with MeI as previously described. Hydrolysis and ketalisation then provided the disubstituted Meldrum’s acid substrate 309 in moderate yield. Gem-substitution was thought to aid ketalisation under these conditions due to the operation of the Thorpe-Ingold effect though disubstitution also brought about other unforeseen problems. Decarboxylation of the diacid was a contributing factor to yield losses in both steps, degrading starting material during the process and therefore producing lower quantities of the desired cyclic diester. Fortunately, a sufficient quantity of the disubstituted Meldrum’s acid derivative 309 could be accessed in order to attempt monoreduction. Exposing 309 to SmI$_2$-H$_2$O conditions gave β-hydroxy acid 310 in good yield (Scheme 87). The racemate could subsequently be resolved using chiral HPLC.

With a provisional route to reduction substrates in hand, additional α-arylated malonates could now be constructed. 1-naphthyl and 2-naphthyl substituted malonates were next synthesised (Scheme 88).
α-Arylation successfully generated 312a and 312b in good yield, however the ensuing steps were not without difficulties. Unfortunately, hydrolysis of the disubstituted cyclic diesters also resulted in significant quantities of decarboxylation products, presumably promoted by the formation of a stabilised tertiary-benzyl carbocation. Furthermore, acid-catalysed ketalisation yielded none of the desired product, with decarboxylation being a major issue under the harsh reaction conditions. Attempts to perform the hydrolysis-ketalisation sequence on the monosubstituted α-arylated malonates were also unsuccessful again due to competing decarboxylation.

Conversely, aliphatic substituted Meldrum’s acids could be easily accessed by the aforementioned Knoevenagel condensation-conjugate reduction sequence (Scheme 89). Subsequent alkylation of 265 gave an additional disubstituted substrate 324 for monoreduction. Exposure of 324 to the SmI2-H2O conditions yielded 325 in excellent yield allowing the racemate to be resolved by chiral HPLC.

With both aromatic and aliphatic substrates in hand, Sm(II)-mediated asymmetric reduction could next be explored. Use of the optimal SmI2-Et3N-hydrobenzoin system at −78 °C successfully effected reduction of both substrates (Scheme 90).
Substrate 309 generated β-hydroxy acid 310 in low yield and with low selectivity, obtaining the product in only 15% ee. Conversely, the aliphatic substrate 314 underwent reduction in good yield, producing 73% of β-hydroxy acid 315. Unfortunately, enantioenrichment was again minimal, measuring only 14% ee of the product. In both instances, competitive binding of the substrate and ligand to Sm(II) could have led to a decrease in selectivity. Furthermore, the bulky biphenyl moiety present in 309 could be inhibiting coordination of the substrate to the metal centre, thereby preventing reduction and causing the low yield observed. In the case of 315, the depleted enantioenrichment appears to be the result of an efficient non-asymmetric reduction process, which could be caused by a breakdown of the in situ generated chiral metal complex during monoreduction. Another explanation could be that there is insufficient distinction between the two α-substituents of 315, resulting in poor differentiation between them in the transition state.

It was suspected that upon protonation of the radical anion 317, hydrobenzoin became covalently bound to the metal centre as in 319 thereby depleting the hydrobenzoin supply in the reaction mixture and thus preventing the formation of the chiral complex for the next reduction process to take place (Scheme 91).
Use of a more acidic or bulky achiral proton source could regenerate this metal complex by re-protonating the ligand. This would require an achiral proton source that would not coordinate to the metal centre or a standard racemic reduction would compete. Fluorinated alcohols have been used extensively in combination with SmI₂ for this purpose (Table 11).

**Table 11**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Achiral alcohol</th>
<th>Yield 268 (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Absent (control)</td>
<td>27</td>
<td>41</td>
</tr>
<tr>
<td>2</td>
<td>2,2,2-Trifluoroethanol</td>
<td>44</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>1,1,1,3,3,3-Hexafluoro-2-propanol</td>
<td>37</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>Perfluoro-(\tau)-butanol</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Trityl alcohol</td>
<td>50</td>
<td>28</td>
</tr>
</tbody>
</table>

A decreasing trend in both yield and enantioselectivity was observed with increased fluorination from TFE to PFTB (entry 1-4). This could suggest that the Sm(II) complex previously generated *in situ* is being destroyed by the fluorinated alcohols. The reducing system created when using fluorinated alcohols produces a Sm(II) species that is both unable to effect monoreduction or enantioselective desymmetrisation. Conversely, employing bulky, achiral trityl alcohol (entry 5) results in an increased yield though the
enantiomeric excess was marginally eroded, presumably due to the background reduction from SmI₂-Et₃N-trityl alcohol reducing system.

A time course analysis was also carried out to determine the variation of enantiomeric excess with time. Aliquots of the reaction mixture were quenched at regular intervals after the addition of 267 to the SmI₂-Et₃N-hydrobenzoin mixture. The enantiomeric excess of 268 was measured as 0% at t = 30 s and was shown to gradually increase to 40% at t = 2 h, after which the reaction did not progress further. This could indicate an autocatalytic process, whereby the reduction product 268 is chiral and hence acts as a chiral catalyst for subsequent monoreduction processes.¹⁰³

Following these results it was decided that more mechanistic insight was required to develop the enantioselective reduction further. Investigations into both the solid- and solution-state crystal structures of the Sm(II) complexes generated during this process would also be highly desirable.

### 2.4 Mechanistic studies

Following on from the SmI₂-H₂O-mediated reduction of cyclic 1,3-diesters, a study was conducted on the mechanistic basis for this transformation.¹⁰⁴ Originally it was proposed that the reduction proceeds through a rate determining electron transfer to the carbonyl, which would generate an anomerically stabilised ketyl radical. Subsequent single electron reduction would then produce an anion (Scheme 56).¹⁰¹,¹⁰² Deuteration experiments were therefore performed on selected α-mono and α,α-disubstituted substrates using SmI₂-D₂O to confirm the presence of anionic intermediates in the reduction process (Table 12).

#### Table 12

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹, R²</th>
<th>conv. (%)</th>
<th>yield (%)</th>
<th>D² (%)</th>
<th>α-D¹ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me, Ph</td>
<td>&gt;98</td>
<td>84</td>
<td>&gt;98</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>H, Ph</td>
<td>&gt;98</td>
<td>82</td>
<td>&gt;98</td>
<td>&gt;98</td>
</tr>
<tr>
<td>3</td>
<td>H, t-Bu</td>
<td>&gt;98</td>
<td>97</td>
<td>&gt;98</td>
<td>&gt;98</td>
</tr>
</tbody>
</table>
β-Hydroxy acid products 320 were isolated with complete $D^2$ incorporation, suggesting that anions are protonated in a series of electron transfer steps. Control experiments in which α-phenyl and benzyl-substituted Meldrum’s acids were treated with THF–D$_2$O resulted in complete recovery of the starting material with $>98\%$ $D^1$ incorporation at the α-position. Exposing 2-methyl-3-phenylpropanoic acid 322 (a derivative of the β-hydroxy acid product) to the same control conditions resulted in complete recovery of the starting material with $<2\%$ $D^1$ incorporation at the α-position (Scheme 92).

![Scheme 92](image)

Combined, these results indicate that $D^1$-exchange in α-monomosubstituted cyclic diesters is faster than monoreduction of Meldrum’s acids to β-hydroxy acids. Furthermore, a secondary kinetic isotope effect of 1.5 (from intramolecular competition experiments) indicates that proton transfer to carbon is not involved in the rate determining step of the reaction.$^{104}$

To further elucidate the nature of the electron transfer steps, substrates containing validated cyclopropyl clocks were exposed to various SmI$_2$ reduction conditions (Table 13).$^{105}$ Rapid cyclopropyl ring opening was observed upon exposure to SmI$_2$–H$_2$O (2:200 eq; entry 1) with no detection of the cyclopropyl carbinol 326. Furthermore, use of excess SmI$_2$–H$_2$O (10:1000 eq; entry 2) effected complete reduction to the β-hydroxy acid 325. Use of an intermediate quantity of SmI$_2$–H$_2$O (8:200 eq; entry 3) gave an approximately 1:1 ratio of the diester 324 and β-hydroxy acid 325. These results strongly indicate that reduction of Meldrum’s acids with SmI$_2$–H$_2$O occurs via fast, reversible electron transfer. Use of SmI$_2$–MeOH and SmI$_2$–THF gave products of alcoholysis and degradation products.
respectively thus providing evidence for the role of H$_2$O in activating Sm(II) toward electron transfer.

Table 13

<table>
<thead>
<tr>
<th>Entry</th>
<th>SmI$_2$ (equiv)</th>
<th>ROH</th>
<th>ROH (equiv)</th>
<th>time</th>
<th>conv. (%)</th>
<th>324:325 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>H$_2$O</td>
<td>200</td>
<td>&lt; 1 min</td>
<td>87</td>
<td>&gt;98:2$^b$</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>H$_2$O</td>
<td>1000</td>
<td>2 h</td>
<td>&gt;95</td>
<td>&lt;5:95$^a$</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>H$_2$O</td>
<td>200</td>
<td>0.25 h</td>
<td>&gt;95</td>
<td>42:58$^b$</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>MeOH</td>
<td>200</td>
<td>1 h</td>
<td>&gt;95</td>
<td>&gt;98:2$^{b,c}$</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>3 h</td>
<td>50</td>
<td>&gt;98:2$^b$</td>
</tr>
</tbody>
</table>

$^a$Guazzelli et al., J. Am. Chem. Soc. 2009, 131, 7214. $^b$Work undertaken by Dr M. Sztostak. $^c$Fragmentation product consists of 5-ethyl-2,2-dimethyl-1,3-dioxane-4,6-dione and its methanolysis product (15:85 ratio).

To examine the effect of steric and electronic stabilisation in the reduction, a series of intermolecular competition experiments were performed. Substrates were synthesised by Knoevenagel condensation followed by reduction and alkylation (Scheme 93).
Substrates \textbf{329-331} could then be exposed to the optimized SmI$_2$-H$_2$O conditions. Complete selectivity was observed for the reduction of $\alpha,\alpha$-disubstituted esters over $\alpha$-monosubstituted esters (Table 14; entries 4 and 5). The electronic nature of the $\alpha$-substituent also affected the selectivity (entries 1-3), which is consistent with electronic stabilisation of ketyl-type radicals generated \textit{in situ}. An unusual steric acceleration was also observed, that contrasts to previous findings whereby coordination of polar groups to Sm(II) in the reduction of lactones and acyclic esters results in steric inhibition.$^{59,97}$ This steric acceleration could arise from the radical anion intermediate existing in a half-chair conformation, causing it to experience torsional strain and hence rate enhancement in its further reduction.

\textbf{Table 14}

<table>
<thead>
<tr>
<th>Entry</th>
<th>$R^1, R^2$</th>
<th>$R^3, R^4$</th>
<th>$k_A/k_B$\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph, H</td>
<td>Bn, H</td>
<td>1.66:1</td>
</tr>
<tr>
<td>2</td>
<td>Bn, H</td>
<td>\textit{i}-Bu, H</td>
<td>2.46:1</td>
</tr>
<tr>
<td>3</td>
<td>Ph, H</td>
<td>\textit{i}-Bu, H</td>
<td>5.21:1</td>
</tr>
<tr>
<td>4</td>
<td>Ph, Me</td>
<td>Ph, H</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>5</td>
<td>\textit{i}-Bu, Me</td>
<td>\textit{i}-Bu, H</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>6</td>
<td>Ph, Me</td>
<td>\textit{i}-Bu, Me</td>
<td>3.74:1</td>
</tr>
<tr>
<td>7</td>
<td>\textit{=CH\textit{i}-Pr}</td>
<td>\textit{i}-Bu, Me</td>
<td>&gt;20:1\textsuperscript{b}</td>
</tr>
<tr>
<td>8</td>
<td>\textit{=CH\textit{i}-Pr}</td>
<td>Ph, Me</td>
<td>&gt;20:1\textsuperscript{b}</td>
</tr>
<tr>
<td>9</td>
<td>-(CH$_2$)$_2$-</td>
<td>\textit{i}-Bu, Me</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>10</td>
<td>-(CH$_2$)$_2$-</td>
<td>Ph, Me</td>
<td>5.13:1</td>
</tr>
<tr>
<td>11</td>
<td>\textit{=CH\textit{i}-Pr}</td>
<td>-(CH$_2$)$_2$-</td>
<td>&gt;20:1\textsuperscript{b}</td>
</tr>
<tr>
<td>12</td>
<td>\textit{=CH\textit{i}-Pr}</td>
<td>\textit{=CHPh}</td>
<td>1.37:1\textsuperscript{b}</td>
</tr>
</tbody>
</table>

Work undertaken by Dr M. Szostak. \textsuperscript{a}Determined by $^1$H NMR. \textsuperscript{b}Conditions: SmI$_2$ (1.0 eq), H$_2$O (200 eq).
Chemoselective reduction of α,β-unsaturated Meldrum’s acids over both the corresponding fully saturated substrates (entries 7 and 8) and also the cyclopropyl containing substrate (entry 11) was observed. Reduction of the cyclopropyl containing substrate was also faster than that of α,α-disubstituted Meldrum’s acids (entries 9 and 10), which is consistent with electronic activation. Overall these results provide the following order of reactivity of Meldrum’s acids with SmI$_2$-H$_2$O: α,β-unsaturated >> cyclopropyl > α,α-disubstituted >> α-monosubstituted. Furthermore, these findings also conclusively reveal high levels of chemoselectivity in the reduction of Meldrum’s acids with SmI$_2$–H$_2$O.

Further exploration of the reaction of alkylidene Meldrum’s acid with SmI$_2$-H$_2$O showed complete selectivity for conjugate reduction (1,4/1,2-selectivity >95:5 by $^1$H NMR) to give saturated Meldrum’s acid derivatives 329, with no detection of β-hydroxy acid products 332 (Scheme 94).

Scheme 94

A series of rate studies were carried out by Dr M. Szostak to determine the role of water as an additive in the Sm(II)-mediated reductions of cyclic 1,3-diesters. Isobutyl-substituted Meldrum’s acid was exposed to SmI$_2$ with increasing concentrations of water, quenching at low conversions and a non-linear dependence on water concentration was observed. At low concentrations and in the absence of water no reaction was observed, whilst increasing concentrations of water facilitated a linear increase in the rate. Although exceeding 400 equivalents of water caused a significant decrease in the rate, consistent with substrate dissociation from the inner coordination sphere of Sm(II).

Accordingly, the role of SmI$_2$ in the monoreduction of isobutyl-substituted Meldrum’s acid was also investigated. Experiments were conducted by varying the equivalents of SmI$_2$ using a set water concentration then quenching the reaction upon decolourisation i.e. when the Sm(II) complex was no longer active. The reduction was found to be linear in SmI$_2$, requiring more than 6 equivalents of the reductant to facilitate complete conversion. These
results are in agreement with a 6-electron process encompassing the monoreduction of Meldrum’s acid and reduction of the by-product acetone. Furthermore, these findings are consistent with previous mechanistic investigations on the reduction of carbonyl groups with SmI$_2$.\textsuperscript{14,29,56}

Reduction of the model $\alpha,\alpha$-disubstituted Meldrum’s acid substrate 267 using various Sm(II) additives suggested that other SmI$_2$-additive reduction systems could be used to effect selective monoreduction (Table 15). Of particular significance, no over-reduction to the 1,3-diol was observed under the optimized reaction conditions.

**Table 15**

<table>
<thead>
<tr>
<th>Entry</th>
<th>ROH (+ Lewis base)</th>
<th>ROH (+ Lewis base) (eq)</th>
<th>Time</th>
<th>Yield (%)</th>
<th>Selectivity 268:270</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeOH</td>
<td>4/1 v/v</td>
<td>2 h</td>
<td>&lt;5</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Ethylene diamine</td>
<td>36</td>
<td>2 h</td>
<td>&lt;5</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>trans-N,N$'$.dimethyl-1,2-cyclohexyldiamine</td>
<td>36</td>
<td>2 h</td>
<td>&lt;5</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Ethylene glycol</td>
<td>36</td>
<td>2 h</td>
<td>84</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>5</td>
<td>$n$-BuNH$_2$/H$_2$O</td>
<td>12/18</td>
<td>5 min</td>
<td>&lt;5</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>pyrrolidine/H$_2$O</td>
<td>12/18</td>
<td>5 min</td>
<td>&lt;5</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>Et$_3$N/H$_2$O</td>
<td>12/18</td>
<td>5 min</td>
<td>92</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>8</td>
<td>Et$_3$N/ethylene glycol</td>
<td>12/18</td>
<td>5 min</td>
<td>84</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>9</td>
<td>Et$_3$N/MeOH</td>
<td>12/18</td>
<td>2 h</td>
<td>&lt;5</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>TMEDA/H$_2$O</td>
<td>12/18</td>
<td>5 min</td>
<td>46</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>11</td>
<td>$N$-Me-morpholine/H$_2$O</td>
<td>12/18</td>
<td>5 min</td>
<td>80</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>12</td>
<td>DIPEA/H$_2$O</td>
<td>12/18</td>
<td>5 min</td>
<td>48</td>
<td>&gt;95:5</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Conditions: Meldrum’s acid (1 eq.), SmI$_2$ (4–6 eq., THF), 23 °C. \textsuperscript{b}Determined by $^1$H NMR. In all entries, yield based on reacted starting material.
Interestingly, the reactivity trend differed from the ligand effects previously observed for the reduction of other carbonyl groups using Sm(II).\textsuperscript{72,73} This can be attributed to substrates having a lower kinetic reactivity under the specified reaction conditions (entries 1-3). Furthermore, instability of \textit{267} towards the reaction conditions (entries 5 and 6) resulted in degradation of the substrate. Varying reactivity trends were also the result of differential coordination of sterically-encumbered reductants to the Meldrum’s acid carbonyl groups (entries 7-12). Combined, these results demonstrate that Sm(II) reagents based on chelating ligands and multicomponent Sm(II) systems are new chemoselective reductants suitable for the reduction of Meldrum’s acids.

In accordance with these kinetic and reactivity studies, a better defined mechanism can be proposed to involve (Scheme 95):

1. Fast and reversible initial electron transfer
2. Non-linear rate dependence on water concentration
3. Rate determining second electron transfer that is inhibited by high water concentrations

Scheme 95
3. SmI₂-H₂O Cyclisation Cascades of Meldrum’s acids

3.1 Previous work: SmI₂-H₂O cyclisations of Meldrum’s acids

Unusual radical anion intermediates generated by reduction of cyclic 1,3-diesters have been exploited in couplings with alkene acceptors.\(^{90-91}\) Substrates 340 effectively undergo intramolecular 5-\textit{exo}-trig cyclisations, initially generating cyclopentanols 341 containing three new chiral centres. Crude cyclopentanols were then subjected to an esterification/oxidation sequence to simplify the diastereomeric mixture and hence determine the stereochemical outcome of the cyclisation. Cyclopentanones 342 were isolated in good yield and with modest diastereoselectivity of up to 5:1 d.r (Scheme 96).

\[
\begin{array}{c}
\text{O} \\
\text{SmI₂-H₂O (8:1200 eq)} \\
\text{THF, rt} \\
\text{O} \\
\end{array}
\xrightarrow{\text{R³ = R² = H}}
\begin{array}{c}
\text{R²} \\
\text{HO} \\
\text{HOOC} \\
\end{array}
\xrightarrow{\text{R²} = \text{Ph}}
\begin{array}{c}
\text{HO} \\
\text{HOOC} \\
\end{array}
\xrightarrow{\text{R²} = \text{Ph}}
\begin{array}{c}
\text{O} \\
\text{MeO₂C} \\
\text{MeO₂C} \\
\end{array}
\]

**Scheme 96**

In an attempt to improve the diastereoselectivity of the cyclisation, it was hypothesised that changing the ketal moiety may influence diastereocontrol in the cyclisation event. Altering the ketal unit proved successful, enhancing the diastereomeric ratio from 3:1 for the acetone derived ketal to 7:1 for the acetophenone derived ketal (Table 16).

| **Table 16** |
|------------------|------------------|------------------|------------------|
| **R¹** | **R²** | **Yield 345 (%)** | **dr** |
| Me | Me | 93 | 3:1 |
| Et | Et | 75 | 2:1 |
| Ph | Me | 79 | 7:1 |
| -(CH₂)₅- | | 77 | 5:1 |
The selectivity observed suggests a discrete mechanism involving radical intermediates. Cyclisation could proceed through an anionic pathway, but the high concentration of H₂O coordinating to the metal centre would be expected to rapidly quench anionic intermediates intramolecularly and prevent cyclisation from occurring hence an anionic process can be discounted. The radical pathway is thought to proceed by initial electron transfer to the carbonyl, which would generate two pseudoaxial radical anion intermediates 346 and 347 (Scheme 97). In the case of dimethyl ketal (R = Me), it is proposed that the two primary intermediates are comparable in energy and hence both are accessible.⁵³,¹⁰⁶ Although both are viable, cyclisation can only occur in the case of axial radical 346a.¹⁰⁷ 346a can cyclise directly through an electronically favoured anti transition structure to produce the major diastereomer, whilst 347a cannot cyclise in this conformation. Ring interconversion between 346a and 347a would be expected to have a higher energy barrier than radical interconversion hence radical interconversion of 347a must first occur to generate an equatorial radical 348a that can subsequently cyclise to yield the minor diastereomer (Scheme 97).¹⁰⁸

![Scheme 97](image-url)
The acetophenone ketal (R = Ph) is therefore thought to improve diastereoselectivity of the cyclisation by exerting greater conformational constraint over the substrate and hence the intermediate radical anions. As a result, the phenyl group of the ketal preferentially exists in a pseudoequatorial orientation thus providing a bias toward formation of axial radical 346b, which subsequently cyclises directly to give the major diastereomer. The relative stereochemical control is therefore thought to result from the destabilisation of the alternative chair conformation 347b, which places the acetonide phenyl group in an unfavourable pseudoaxial position.

An unusual temperature dependence was also reported, with diastereoselectivity shown to increase with temperature (Table 17). An explanation for this observation has so far proved elusive though could be due to being able to access a higher energy conformation favouring cyclisation of the major isomer.

Table 17

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>Yield 345 (%)</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>81</td>
<td>3:1</td>
</tr>
<tr>
<td>rt</td>
<td>79</td>
<td>7:1</td>
</tr>
<tr>
<td>50</td>
<td>89</td>
<td>12:1</td>
</tr>
</tbody>
</table>
This approach granted rapid access to complex carbocyclic compounds from simple, symmetrical starting materials in a single step using an operationally simple method.

### 3.2 Cyclisation cascades

Successful use of the SmI$_2$-H$_2$O reducing system within the Procter group has established valuable transformations previously thought impossible. This methodology has been employed in the selective reduction of both lactones and cyclic 1,3-diesters; substrates previously thought to lie outside the reducing range of SmI$_2$. Furthermore, exploitation of unique radical anion intermediates generated within these transformations has provided rapid access to highly decorated and complex carbocycles. Building on from the successful cyclisation of α,α-disubstituted Meldrum’s acid scaffolds, it was decided to further explore the scope of the cyclisation cascades by preparing substrates bearing two differentially substituted side chains. Furthermore, use of different tether lengths would grant rapid access to various sized bicycles. Synthesis of these non-symmetrical substrates proved more challenging than expected.

#### 3.2.1 Substrate synthesis

Synthesis of non-symmetrical Meldrum’s acid substrates for SmI$_2$-H$_2$O-mediated cascade cyclisations proved challenging. Due to the innate high reactivity of monoalkylated Meldrum’s acid derivatives, direct monoalkylation is not feasible and so other methods were sought to synthesise substrates. Knoevenagel condensation is frequently used in the synthesis of α-substituted Meldrum’s acid derivatives and was thought to be a suitable alternative. Unfortunately, the high propensity of alkylidene diesters to be intercepted by nucleophiles means that bis-adducts of Meldrum’s acid 374 are readily formed when R is small and that this method was therefore not suitable (Scheme 99).
Such reactivity has been exploited by capturing and hence protecting intermediate alkylidenes with an alternative nucleophile such as thiols; subsequent elimination then affords the $\alpha,\beta$-unsaturated diester. Previous attempts to access the desired alkylidene Meldrum’s acid by this method were unsuccessful though and so another route to access these substrates was required.

A sequence described by Danishefsky was subsequently realised, whereby alkylation of diethyl malonate with sequential hydrolysis and ketalisation could afford substituted Meldrum’s acid derivatives (Scheme 100).

A late-stage ketal formation was therefore envisaged, which utilized established and high yielding malonate monoalkylation to generate disubstituted precursors of the Meldrum’s acid derivative targets. Ester hydrolysis followed by ketalisation would then afford the desired cascade substrates. Accordingly, homoallylic bromides were first synthesised using a procedure reported by Wong (Scheme 101).109
Homoallylic bromides were produced by Grignard addition of cyclopropylmagnesium bromide to benzaldehyde, subsequently quenching with acetyl bromide. Heating in the presence of Lewis acid resulted in ring-opening to generate the desired homoallylic bromides in moderate yield. With several readily available bromides to hand, monoalkylation of diethyl malonate could next be addressed. Sequential alkylation of diethylmalonate with differentially substituted homoallylic bromides provided disubstituted malonates in good yield (Scheme 102).

It was hypothesised that the gem-substitution would also assist ketalisation under these conditions by invoking the Thorpe-Ingold effect. Hydrolysis of the dialkylated malonates 360 afforded the malonic acids 361 quantitatively (Scheme 104). Unfortunately, subjecting...
362 to the literature ketalisation conditions yielded none of the desired substituted Meldrum’s acids 363 and poor recovery of the starting material.

Incomplete recovery of the malonic acids was thought to be the result of degradation processes brought about by the harsh conditions required for ketalisation. Protonation of the styryl-type double bond would generate stable benzylic carbocations, incidentally scavenging the acid catalyst and impeding ketal formation. Furthermore, acid-catalysed decarboxylation may also have been a factor in the poor recovery of starting materials.

An alternative route was therefore designed involving late-stage cross-metathesis of the terminal alkene 356 with various styrenes. Alkylation of the monosubstituted Meldrum’s acid would then afford differentially disubstituted Meldrum’s acid derivatives. The first step toward these substrates used the previously successful monoalkylation of diethylmalonate 306, thus providing the terminal olefin functionality ultimately required for cross-metathesis (Scheme 105). Hydrolysis and subsequent ketalisation afforded the desired 5-substituted Meldrum’s acid 356 in good yield. Cross-metathesis of the terminal alkene with styrene using Hoveyda-Grubbs II generation catalyst generated 364 in adequate yield.

Addition of a second differentially substituted alkyne tether by alkylation of 364 was next investigated. Alkynyl bromides were accessed by Sonogashira coupling of alkynols 365 followed by an Appel reaction (Scheme 106).
This route utilized high-yielding, well established processes to gain access to alkynyl bromide tethers \(367a-c\) of varying length. With a selection of alkynyl bromides in hand, the final alkylation step in the synthesis of non-symmetrical disubstituted Meldrum’s acid derivatives could be explored. Alkylation was carried out using \(\text{K}_2\text{CO}_3\) and alkynyl bromide \(367c\) to provide the cascade cyclisation substrate \(368\) (Scheme 107)

Scheme 107

The final substrates that were required could not be accessed by this route due to the instability of the required homoallylic alkynyl bromide over the extended reaction period (2 days) required for the alkylation. A simple change in reaction sequence was therefore required to grant access to this final substrates. Monoalkylation of diethylmalonate with the appropriate alkynyl bromide followed by successive hydrolysis and ketalisation gave the 5-substituted cyclic diesters \(369a-c\) in good yield over two steps. \(369a-c\) were then alkylated as previously described, installing the alkene tether last to provide the cyclisation cascade substrates \(370a-c\) (Scheme 108).
3.2.2 Cyclisation cascades

The substrates were then subjected to the optimized SmI$_2$-H$_2$O conditions: a 2 h addition of SmI$_2$ to a THF-H$_2$O solution of the cyclic diesters. Pleasingly, cascade cyclisation was effected in good overall yield and full diastereocontrol in most cases to afford highly decorated 5,5-carbocycles 373a-g (Scheme 109).$^{110}$

![Diagram of cyclisation cascades](image)

373a 52%$^{a,c}$

373b 64%$^a$

373c 54%$^a$

373d

R = Ph; 52%$^b$
R = H; 43%$^b$

373e

R = Ph; 63%$^b$
R = H; 46%$^b$

373f

50%$^b$

373g

44%$^{b,d}$

$^a$Work undertaken by S. E. Lyons. $^b$Work undertaken by B. Sautier. $^c$2:1 E:Z ratio. $^d$Mixture of isomers.

Scheme 109

The first examples of SmI$_2$-H$_2$O-mediated 5-exo-trig/5-exo-dig were established using this methodology to afford complex bicycles containing an exocyclic olefin. Complete sequence integrity was observed for alkene-alkyne cyclisations, with the cascade initiated by cyclisation onto the alkene. Furthermore, substrate 369a containing an unactivated terminal alkyne underwent efficient cyclisation to generate 373b as a single diastereomer in good yield, generating a terminal alkene that could potentially be used as a synthetic
handle for further manipulation. 5-exo-trig/5-exo-trig cascade cyclisations were also accomplished using SmI$_2$-H$_2$O, yielding densely functionalised 5,5-bicycles. Additionally, 5,6-bicycles could also be accessed in this manner (Scheme 110).

![Scheme 110](image)

*Work undertaken by S. E. Lyons. ‡Work undertaken by B. Sautier. $10:1$ E/Z ratio.

Scheme 110

5,6-carbocycles were successfully synthesised by sequential 5-exo-trig/6-exo-dig and 5-exo-trig/6-exo-trig cascade cyclisation. The exocyclic olefin was isolated as mixtures of E/Z isomers, with greater selectivity observed in the case of 5,6-carbocycles. It is hypothesised that preferential formation of the $E$ isomer is established through selective formation of the most stable vinyl radical post-cyclisation. This is supported by the higher selectivity observed in the formation of 5,6-carbocycles, whereby steric clash between the Z-alkene and the bridgehead hydroxyl moiety in 375 is far greater than when forming 5,5-carbocycles as in 376 (Scheme 111).

![Scheme 111](image)

Scheme 111

The stereochemistry of the bicyclic scaffolds was confirmed by X-ray crystallographic analysis of 372d by B. Sautier (Scheme 112).
Furthermore, efforts to generate 5,7-bicycles proved ineffective, with treatment of 367 under the standard conditions effecting monocyclisation only, leaving the pendant alkyne untouched (Scheme 113). It is thought that the 7-exo-dig cyclisation is too slow to compete with further reduction of the intermediate ketyl-radical anion.

Successive exo-trig/exo-trig cyclisations were also demonstrated, generating carbocycles in moderate to good yields and as single diastereomers in the majority of cases. Sequence integrity was also maintained, with the first cyclisation proceeding onto the most activated alkene. Combined, these results indicate several interesting mechanistic aspects of cyclisation. The high stereocontrol suggests the initial selective formation of an axial radical 378, from which cyclisation occurs through an anti-transition state (Scheme 114). Collapse of the ketal moiety reveals cyclopentanone intermediate 380 that can be reduced by a second electron transfer, thus generating ketyl-radical 381. Cyclisation of this equatorial radical then proceeds under the influence of chelation control from the Sm(III)-carboxylate, allowing cyclisation to occur through an anti-transition state and thus deliver the carbocyclic product 383. Furthermore, use of SmI$_2$-D$_2$O resulted in deuterium incorporation at the benzylic and vinylic positions suggesting that each cyclisation event is completed by protonation of an organosamarium intermediate.
This method further expands the scope of SmI₂ chemistry, granting rapid access to highly decorated asymmetric bicyclic compounds from simple, easily accessible starting materials in a single step using an operationally simple method.
4. Cyclisation cascades of lactones

4.1 Previous work: Lactone cyclisation cascades

It was previously shown within the Procter group that single-electron reduction of substituted δ-valerolactones 384 could produce unique ketyl-radical anions that can be utilized in novel cyclisation events.\textsuperscript{54,55} Trapping of ketyl-radicals with suitably placed alkene tethers allowed rapid access to highly decorated cyclopentanones 385 and cycloheptanone 388 motifs (Scheme 115).

\textbf{Scheme 115}

Following the success of these SmI\textsubscript{2}-H\textsubscript{2}O mediated cyclisations, it was proposed that ketones generated post-cyclisation could be utilized in a second ketyl-olefin cyclisation. Lactone substrates containing alkene tethers at both the 2- and 5-positions would allow access to cyclisation cascades, with the potential to generate complex bicyclic azulene scaffolds in a single step. Calculations indicated that \textit{cis}-configured lactones should undergo cascade cyclisation with high-sequence integrity.\textsuperscript{55} Radical-anions were proposed to first undergo 5-\textit{exo}-trig cyclisation with the alkene tether at the 5-position as the activation energy for this process was calculated to be significantly lower than that for the corresponding process involving the alkene tether at the 2-position (\textit{cf}. 6.3 kJ mol\textsuperscript{-1} vs. 28.1 kJ mol\textsuperscript{-1}) (Scheme 116).
In order to confirm the predicted effect of the relative configuration in the lactone on the sequence integrity of the cyclisation cascade, cis-389 and trans-389 were treated with SmI$_2$-H$_2$O (Scheme 117).

**Scheme 117**

*Cis*-389 lactone successfully underwent cascade cyclisation with high-sequence integrity as anticipated to afford diol *trans*-390 in 71% yield and 3:1 dr. Conversely, cyclisation of *trans*-389 misfired resulting in only monocyclisation proceeding with ketyl-olefin coupling with the terminal alkene at the 2-position to produce cyclopentanol 391 in 75% yield and as a mixture of diastereomers.

With the *cis*-configured lactones confirmed as the optimal substrates for cascade cyclisation, an evaluation of substrate scope was performed. Exposure of *cis*-substituted lactones to SmI$_2$-H$_2$O successfully effected cascade cyclisation to generate complex 5,7-carbocycles in good to excellent yield and with modest diastereoselectivity (Scheme 118). The stereochemistry of the major diastereomeric product was confirmed by X-ray crystallography.
In efforts to gain higher diastereoselectivity and higher complexity in cyclisation cascades, it was thought that allenyllactones could provide an additional substituent and an additional stereocentre on the cycloheptane ring that may influence selectivity. Pleasingly, treatment of lactones 395 with SmI$_2$-H$_2$O successfully effected sequential cyclisation producing highly decorated azulene motifs in excellent yield and high diastereoselectivity (Scheme 119). In contrast to alkene-alkene cyclisations, both cis-395 and trans-395 allenyllactone diastereomers underwent efficient cyclisation cascade to give trans-396 and cis-396. Thus, both cis- and trans-fused bicyclic products could be accessed simply by using allenyllactones with the correct relative configuration.

Scheme 119
It was hoped that the positive results gained from using allenyl-acceptors for the first cyclisation event would transfer to the cascade cyclisation of other differentially substituted lactones with the prospect of generating novel ring-sized bicycles. By extending the tether length at the 2-position, it was anticipated that sequential cyclisation could rapidly provide access to densely functionalised 6,7-bicycles 400; a motif found in a number of biologically important and synthetically challenging natural products such as phorbol 401a and prostratin 401b (Scheme 120).\textsuperscript{112–115}

Scheme 120

This would require a demanding Sml\(_2\)-mediated 6-\textit{exo}-trig cyclisation as the second cyclisation event, of which there are relatively few examples. In 1993, Gillmann successfully demonstrated an intramolecular 6-\textit{exo}-trig cyclisation involving an aldehyde and a pendant allenyl group (Scheme 121). The cyclohexanol product 403 was generated in high yield and modest diastereoselectivity.\textsuperscript{116}
Ketone-alkene cyclisations remain a challenging transformation though and have previously required the use of toxic HMPA as an additive (Scheme 122).\textsuperscript{117,118} Employing the more environmentally benign SmI\textsubscript{2}-H\textsubscript{2}O system would therefore be more highly desirable.

\begin{center}
\begin{tikzpicture}
  \node [draw] (A) at (0,0) {404};
  \node [draw] (B) at (1,0) {SmI\textsubscript{2}-i-BuOH};
  \node [draw] (C) at (2,0) {THF-HMPA, rt};
  \node [draw] (D) at (3,0) {405};
  \node [draw] (E) at (4,0) {93\% yield};
  \node [draw] (F) at (5,0) {9.2:1 dr};

  \draw [->] (A) -- (B);
  \draw [->] (B) -- (C);
  \draw [->] (C) -- (D);
\end{tikzpicture}
\end{center}

Scheme 122

4.2 Results and discussion

4.2.1 Allene-alkyne 5-exo-trig/6-exo-dig cyclisation cascades

Work undertaken within the group had successfully demonstrated sequential 5-exo-trig/6-exo-trig cyclisation cascade of \textit{trans}-406 to yield \textit{cis}-407 albeit in low yield. This was due to competing reduction of the radical anion required for cyclisation of the second tether (Scheme 123).

\begin{center}
\begin{tikzpicture}
  \node [draw] (A) at (0,0) {trans-406};
  \node [draw] (B) at (1,0) {SmI\textsubscript{2}-H\textsubscript{2}O (8:4000 eq)};
  \node [draw] (C) at (2,0) {THF, rt};
  \node [draw] (D) at (3,0) {cis-407};
  \node [draw] (E) at (4,0) {37\%};
  \node [draw] (F) at (5,0) {17\%};

  \draw [->] (A) -- (B);
  \draw [->] (B) -- (C);
  \draw [->] (C) -- (D);
\end{tikzpicture}
\end{center}

Scheme 123

Allene-alkyne cyclisations had not been explored and it was hypothesised that an alkyne acceptor could perform better in the second coupling event. The first successful example of 5/6 cascade cyclisation was reported by the group and involved a sequential 5-exo-trig/6-exo-dig of Meldrum’s acid scaffolds (Scheme 124).\textsuperscript{110}
It was therefore thought that 5-ordo-trig/6-ordo-dig cyclisations of allene-alkynyl lactones could be accomplished. To gain access to the desired cyclisation substrates, a demanding Barbier-promoted lactonisation between keto-esters 399 and propargyl bromides 409 was required (Scheme 125). Keto-esters 410 could be readily accessed by alkylation of the corresponding protected acetal-ester 411 with the appropriate alkyne tether 412.

The alkyne tether was synthesised by Sonogashira coupling of the terminal alkyne 4-pentyn-1-ol 413 and iodobenzene followed by Appel reaction to afford the desired iodide 415 for alkylation (Scheme 126).

A simple three-step process was then employed to gain access to keto-esters for the Barbier-induced lactonisation. Acetal protection was performed under Dean-Stark conditions using ethylene glycol and benzene to afford 417. Alkylation of 417 using LDA
and iodide 415 afforded the substituted acetal-ester, which was subsequently deprotected using \( p \)-TsOH in acetone to yield the desired ketone 418 in 66% yield (2 steps).

\[
\begin{align*}
\text{416} & \quad \text{HO} \quad \text{OH} \\
& \quad \text{p-TsOH.H2O} \\
& \quad \text{C6H5, \Delta} \\
& \quad 93\% \\
\text{417} & \quad \text{O} \quad \text{O} \\
& \quad \text{CO2Et} \\
& \quad \text{i) LDA, THF, \text{\textdegree}78 \text{\textdegree} \\
& \quad \text{ii) HMPT, 415} \\
& \quad \text{iii) \text{p-TsOH.H2O}} \\
& \quad 66\% \text{ (2 steps)} \\
\text{418} & \quad \text{CO2Et} \\
& \quad 3 \quad \text{\textdegree} \text{Prop} \\
\end{align*}
\]

**Scheme 127**

Propargyl bromides were next synthesised in preparation for the Barbier-mediated lactonisation. These were readily accessed by Appel reaction of the commercially available alcohol or by silylation of the terminal propargyl bromide (Scheme 128).

\[
\begin{align*}
\text{R} & \quad \text{\textdegree} \text{OH} \\
\text{419} & \quad \text{\textdegree} \text{Br} \\
& \quad \text{CBBr3, PPh3} \\
& \quad \text{CH2Cl2, 0 \textdegree C} \\
& \quad \text{a R = Ph; 75\%} \\
& \quad \text{b R = 4-MeOC6H4; 79\%} \\
\text{420} & \quad \text{R} \\
\end{align*}
\]

**Scheme 128**

Propargyl alcohols were reacted with CBr₄ and PPh₃ to generate propargyl bromides 420a-b in good yield. Synthesis of the dimethylphenyl silyl substituted propargyl bromide was facilitated by deprotonation of 421 with LDA and subsequent quenching of the anion with chloro(dimethyl)phenylsilane to produce 420c in excellent yield.

With a selection of propargyl bromides in hand, the final Barbier step could be attempted. Conditions previously described within the group required a SmI₂-mediated Barbier-type lactonisation to gain access to lactone substrates (Scheme 129).
Substituted keto-ester 418 was exposed to SmI₂-NiI₂ and the propargyl bromides 420a-c to produce the target lactone substrates 422a-c in modest yield as a 1:1 separable mixture of diastereomers. The main by-products from the reaction were alcohol 423, which is the result of incomplete lactonisation, and propargyl lactones 424 (Scheme 130).

Previous studies from the cascade cyclisation of allenylation-alkene lactones had shown that the trans-diastereomer was able to undergo the desired transformation under SmI₂-H₂O conditions. It was therefore decided to explore the cascade cyclisations of the trans-422a-c lactones (Scheme 131).
The substrates were subjected to the optimized SmI$_2$-H$_2$O conditions: a 30 minutes addition of SmI$_2$ to a THF-H$_2$O solution of the lactones. Unfortunately, cascade cyclisation products were not detected and only products of monocyclisation from the initial 5-exo-trig cyclisation were observed. Sm(II)-mediated reduction of \textit{trans-422a} containing a bulky silicon group on the internal double of the allene produced the hemi-ketal \textit{425a} in good yield. This suggests that in this particular case, the product of the first cyclisation exists preferentially as the hemi-ketal \textit{in situ} rather than the open ketone form. Single electron reduction of the ketone is therefore less feasible and so the challenging 6-exo-dig cyclisation cannot take place. In contrast, treatment of \textit{trans-422b} and \textit{trans-422c} with SmI$_2$-H$_2$O gave diols \textit{425b} and \textit{425c} respectively, resulting from the reduction of the intermediate ketone produced from monocyclisation. Furthermore, hemi-ketal products were not observed in either case suggesting that the open ketone preferentially exists \textit{in situ} and is therefore available for subsequent reduction and cyclisation. The absence of cascade products indicates that reduction of the radical-anion derived from the ketone carbonyl is more facile than 6-exo-dig cyclisation. This challenging cyclisation may not be attainable due to the required Bürgi-Dunitz approach angle being inaccessible in these cases. The low isolated yield of these products could indicate their instability toward prolonged exposure to Lewis acidic Sm(II)/Sm(III), causing dehydration and complex mixtures of products. Furthermore, attempts to perform SmI$_2$-H$_2$O-mediated cyclisation on the \textit{cis-435c} afforded only a complex mixture of products with no cascade products detected (Scheme 132).
4.2.2 Alkene-alkene 5-exo-trig/6-exo-trig cyclisation cascades

Published findings from within the group successfully demonstrated the domino 5-exo-trig/5-exo-trig cyclisation of alkene-alkene lactones to produce densely substituted 5,7-azulene motifs (Scheme 133). 55

It was therefore thought that the substrate scope could be expanded to 5-exo-trig/6-exo-trig cyclisation cascades in the construction of 6,7-carbocycles, a transformation yet to be demonstrated with SmI$_2$-H$_2$O. Synthesis of the desired lactone substrate initially required a straightforward three-step sequence (Scheme 134).

Barbier-mediated lactonisation was carried out by exposing commercially available ethyl 4-acetylbutyrate 416 and allyl bromide to the aforementioned SmI$_2$-NiI$_2$ conditions. Cross-metathesis of the terminal alkene 427 with styrene and Grubbs II generation catalyst afforded 428 in moderate yield. Dimerization of the starting terminal alkene during the course of the reaction resulted in a lower than expected yield. The second alkene tether was next synthesised using a similar sequence to that described previously (Scheme 135).
After Sonogashira coupling, 414 could be reduced using LiAlH₄ to give exclusively the (E)-alkene 429 in 84% yield. Appel reaction then afforded the iodide 430 required for subsequent alkylation.

At this stage, lactone 428 had previously been acylated with Mander’s reagent to facilitate alkylation with 430, requiring an additional decarboxylation step to afford cyclisation substrates 431. An attempt was therefore made to synthesise the desired target compounds by direct alkylation of 428. Pleasingly, deprotonation with LDA and subsequent HMPA-mediated alkylation with iodide 430 afforded the desired substrate 431 in 49% yield as a 1:1 separable mixture of diastereomers (Scheme 136).

Initial attempts were made at cyclising trans-431 using SmI₂-H₂O. Unfortunately only the monocyclisation product was obtained with no cascade product detected (Scheme 137).

Furthermore, attempted cyclisation of cis-431 gave a complex mixture of products.
This particular class of substituted lactone has proved unsuccessful in SmI$_2$-H$_2$O-mediated cascade cyclisations. This could be due to the rate of ketyl-alkene coupling in the second stage being slower than the competing reduction of the ketyl radical. Furthermore, the intermediate generated after initial 5-exo-trig cyclisation may not be able to achieve the correct geometry for successive 6-exo-trig cyclisation.

### 4.2.3 Allene-alkene 5-exo-trig/6-exo-trig cyclisation cascades

The limited success of alternative cascade substrates required the re-evaluation of allene-alkene lactones. Limited success in optimizing the reaction conditions meant that substrate scope could now be investigated. The current route to such substrates required first synthesising alkene tethers by a three-step process of Sonogashira coupling, LiAlH$_4$ mediated alkyne reduction and finally Appel reaction. This provided the iodide necessary for alkylation and consequently the keto-ester required for the Barbier-step (Scheme 138).

![Scheme 138](image)

An improved route was envisaged to provide a shorter, more convergent synthesis to lactone substrates. This method utilized a late-stage cross-metathesis of the terminal alkene with a variety of styrenes, granting rapid access to a library of substituted keto-ester substrates and subsequently lactone substrates (Scheme 139).
Alkylation of acetal 417 with 5-bromo-1-pentene in HMPA-THF afforded 434 in 45% yield. Subsequent deprotection using $p$-TsOH yielded the keto-ester 435 in quantitative yield, providing the terminal alkene necessary for cross-metathesis. Cross-metathesis of 435 and the appropriate styrenes using Grubbs II generation catalyst generated keto-esters 436a-c in moderate yield (Scheme 140).

Employing 1-vinyl-naphthalene yielded a 1:1 mixture of $E/Z$ isomers of 436c which were inseparable by column chromatography. Unfortunately, attempted coupling of 1,1-diphenylethylene with 435 generated none of the desired keto-ester, effecting dimerization of 435 only. An alternative route was therefore required to access these substrates. To access these substrates, the corresponding iodide tethers were synthesised for alkylation.
As the isomerically pure 1-naphthyl substituted keto-ester could not be accessed by cross-metathesis, the alkene tether was synthesised in an alternative way. This could be achieved by Johnson-Claisen rearrangement of the readily accessible allyl alcohol 38. Due to the concerted and cyclic nature of this [3,3]-sigmatropic rearrangement, the reaction should be highly stereoselective, generating the (E)-alkene as the sole double-bond isomer (Scheme 141). Addition of vinylmagnesium bromide to 1-naphthaldehyde afforded the corresponding allyl alcohol in 82% yield. Alcohol 438 could then be heated at reflux in triethyl orthoacetate and toluene in the presence of catalytic acetic acid to afford the Johnson-Claisen rearrangement product 439. DIBAL-H reduction followed by Appel reaction generated the iodide 440 necessary for subsequent alkylation.

![Scheme 141](image)

Synthesis of the 1,1-diphenylethylene containing substrate commenced with a straightforward two-step process for the preparation of the required iodide (Scheme 142). Treatment of commercially available ethyl 5-bromopentanoate 441 with two equivalents of phenylmagnesium bromide produced the corresponding tertiary alcohol, dehydration of which using catalytic p-toluenesulfonic acid gave the olefin 442 in excellent overall yield. Subsequent Finklestein displacement then afforded iodide 443 in 72% yield.

![Scheme 142](image)

A novel furyl containing tether was also envisaged, which could be readily made from Meldrum’s acid 263. Furthermore, this would provide the first example of a SmI$_2$-H$_2$O mediated cascade cyclisation involving a substrate bearing a heterocyclic group (Scheme 143).
Knoevenagel condensation and successive conjugate reduction afforded 444 in good overall yield. Microwave-assisted decarboxylation followed by DIBAL-H reduction of the resultant ester then afforded the corresponding alcohol. Treatment of the alcohol under Appel reaction conditions then generated the iodide 445.

With several novel iodide tethers in hand, the preparation of α-substituted keto-esters for the key Barbier-lactonisation step could be carried out. Synthesis of the substituted keto-esters commenced with alkylation of acetal 416 as previously described (Scheme 144).

Scheme 144

The previously described alkylation-deprotection sequence was then employed, proceeding without complication to afford 446a-c in moderate to good overall yield. Furthermore, a disubstituted keto-ester 450 was synthesised by alkylation of 448 with 430, which was subsequently deprotected (Scheme 145). This provided a range of keto-esters for the final Barbier-mediated lactonisation.
Treatment of keto-esters 436a-b and 447a-c under the standard SmI$_2$-NiI$_2$ Barbier conditions with propargyl bromide 420a gave the desired lactone substrates in moderate yield as 1:1 separable mixture of diastereomers (Scheme 146).

The reaction suffered from both unselective addition of the intermediate organometallic species to the ketone and incomplete lactonisation. Furthermore, attempted Barbier-mediated lactonisation of doubly alkylated keto-ester 450 yielded alcohol 452.
only, with lactonisation presumably being inhibited by steric hindrance from the second tether (Scheme 147).

Scheme 147

Unfortunately, suitable conditions could not be found to successfully cyclise the alcohol 452 onto the very sterically encumbered ester and only starting material was recovered.

Substrates 451a-e were then subjected to the optimized SmI₂-H₂O conditions: a 30 min addition of SmI₂ to a THF-H₂O solution of the lactones. Pleasingly, cascade cyclisation was effected with complete diastereoccontrol to afford highly decorated 6,7-carbocycles 453a-d (Scheme 148).¹¹⁹

Carbo[5.4.0]bicyclic products were generated as single diastereoisomers in moderate overall yield for the 6-electron transformation. The first example of a SmI₂-mediated cascade cyclisation of a lactone containing a reducible furyl ring (453b) was also successfully demonstrated with no over-reduction observed. Furthermore, trifluoromethyl
and bromo substituents were also tolerated under the mild SmI$_2$-H$_2$O conditions. Incomplete 6-\textit{exo}-trig cyclisation of the intermediate ketone resulted in moderate yields.

Surprisingly, treatment of lactone 451c under the optimised cyclisation conditions resulted in only monocyclisation, isolating ketone 454 with no evidence of cascade cyclisation (Scheme 149).

![Scheme 149](image)

**Scheme 149**

A similar result was obtained in the attempted cyclisation of 464, isolating complex mixtures of reduction products with no observation of 453d. Presumably, the bulky biphenyl moiety further hinders the already challenging 6-\textit{exo}-trig cyclisation event (Scheme 150).

![Scheme 150](image)

**Scheme 150**

The stereochemistry of the bicyclic scaffolds was successfully confirmed by X-ray crystallographic analysis of 451a (Scheme 151).

![Scheme 151](image)
A mechanism accounting for the stereochemical outcome of the reaction has been proposed (Scheme 152). Single electron reduction of lactone 455 generates axial radical anion 456, which undergoes 5-exo-trig cyclisation onto the allene. Subsequent conjugate reduction and protonation of enone 457 then affords ketal 458. Ketal 458 exists in equilibrium with ketone 459, which undergoes reduction to give radical anion 460. Selective 6-exo-trig cyclisation with successive reduction and protonation yields 462 as a single diastereomer.

Scheme 152

In summary, 5-exo-trig/6-exo-trig cascade cyclisation of allenyllactones bearing a tethered alkene has been successfully demonstrated, creating carbo[5.4.0]bicyclic motifs with complete diastereocontrol in moderate overall yield. This process generates 5,6-bicyclic scaffolds bearing four new stereocentres and as a single diastereomer from readily available starting materials.
5. Summary and future work

5.1 Enantioselective Meldrum’s acid reductions

5.1.1 Summary

A non-racemic monoreduction of Meldrum’s acid derivatives has been developed using the commercially available \((R,R)\)-hydrobenzoin 266 as both the proton donor and as the source of chirality (Scheme 153).

\[
\begin{align*}
\text{O} & \text{Ph} \quad \text{Sml}_2-266-\text{Et}_3\text{N} \\
\text{O} & \text{Me} \quad \text{THF}, -78 \ ^\circ\text{C} \\
\text{267} & \text{268} \
\end{align*}
\]

Scheme 153

Additionally, it has been shown that use of the bulky, achiral proton source trityl alcohol 463 facilitates increased conversion whilst maintaining modest selectivity (Scheme 154).

\[
\begin{align*}
\text{O} & \text{Ph} \quad \text{Sml}_2-266-\text{Et}_3\text{N-TrOH} \\
\text{O} & \text{Me} \quad \text{THF}, -78 \ ^\circ\text{C} \\
\text{267} & \text{268} \quad \text{TrOH} \
\end{align*}
\]

Scheme 154

5.1.2 Future work

Few asymmetric ligand-controlled processes involving \(\text{Sml}_2\) have been reported. Despite this, significant progress has been made towards the first enantioselective single electron reduction of Meldrum’s acid derivatives. Further mechanistic understanding could allow the advancement of the reaction in the hope of generating enantiopure \(\beta\)-hydroxy acids in a high yielding process. Flowers has demonstrated the successful crystallographic analysis of various \(\text{Sm(II)}\)-glycol complexes and so obtaining crystals from the \(\text{Sml}_2-\text{Et}_3\text{N-HB}^+\)
mixture may provide a greater understanding of the complexes made *in situ* during the reduction process.

Furthermore, could this SmI₂-mediated asymmetric reduction be applied to the Meldrum’s acid cyclisation cascades? This would utilize readily accessible, symmetrical substrates to obtain complex, enantioenriched molecular architecture in a single step (Scheme 155).

![Scheme 155](image)

Unpublished work from an industrial team has also demonstrated the first diastereoselective monoreduction of Meldrum’s acid derivatives. A distal stereogenic centre in 464 provides the necessary influence to generate β-hydroxy acids 465 with modest diastereocontrol (Scheme 156). This provides another avenue for further development.

![Scheme 156](image)

The influential role of the ketal moiety on the diastereomeric outcome of Meldrum’s acid cyclisation events has been demonstrated previously (see Section 3.1; Table 16). In this case, diastereocontrol was improved by using an acetophenone derived ketal rather than an acetone derived ketal. Variation of the ketal unit could be an effective strategy to gain improved access to enantioenriched β-hydroxy acids using SmI₂-H₂O.

![Scheme 157](image)
5.2 Meldrum’s acid cyclisation cascades

Unique radical-anions generated from the SmI₂-mediated reduction of substituted Meldrum’s acids have been successfully utilised in sequential carbon-carbon bond forming processes. SmI₂-H₂O has been shown to perform cascade cyclisation of simple, achiral starting materials, creating complex molecular scaffolds containing up to four contiguous stereocentres with high diastereoencontrol. Densely functionalised 5,5-bicycles were accessed by initial 5-*exo*-trig cyclisation to generate cyclopentanones, which could be further reduced and the ensuing ketyl-radical exploited in a second cyclisation with both alkene and alkyne acceptors (Scheme 158).

![Scheme 158](image)

Tether extension also granted access to 5,6-bicyclic compounds that were isolated as single diastereomers in most cases (Scheme 159). Successful use of an unactivated, terminal alkyne acceptor allowed access to a complex architecture bearing a terminal alkene that can be exploited as a synthetic handle for further functionalization.

![Scheme 159](image)
5.3 Lactone cascade cyclisations

A challenging 5-exo/6-exo lactone cyclisation cascade has been demonstrated that uses the SmI₂-H₂O reagent system to generate carbo[5.4.0]bicyclic scaffolds with complete diastereoccontrol (Scheme 160). Highly decorated 6,7-bicycles were generated by initial 5-exo-trig cyclisation to generate cycloheptanones, further reduction of which granted access to a second ketyl-radical cyclisation event onto alkene tethers. This one-pot method creates two new carbocyclic rings containing four new stereocentres in moderate overall yield for the 6-electron process.

Scheme 160

Future exploitation of the cascade in natural product target synthesis will be investigated within the group.
6. Experimental

6.1 General information

All experiments were performed under an atmosphere of N\textsubscript{2}, using anhydrous solvents, unless stated otherwise. THF was distilled from sodium/benzophenone, stored under N\textsubscript{2} and, when used in conjunction with SmI\textsubscript{2}, deoxygenated by bubbling with N\textsubscript{2} for 15 minutes. CH\textsubscript{2}Cl\textsubscript{2}, Et\textsubscript{3}N, DIPA and toluene were distilled from CaH\textsubscript{2} and stored under N\textsubscript{2}. All other anhydrous solvents were purchased from Sigma-Aldrich, Acros Organics and Alfa Aesar and used without further purification. Water was distilled before being deoxygenated by bubbling with N\textsubscript{2} for 4 h. K\textsubscript{2}CO\textsubscript{3} was oven dried at 120 °C overnight prior to use.

\textsuperscript{1}H NMR and \textsuperscript{13}C NMR spectra were recorded on Bruker Avance 300 (300 MHz, 75 MHz for \textsuperscript{13}C-NMR), Bruker Ultraschield 400 (400 MHz, 100 MHz for \textsuperscript{13}C-NMR) or Bruker Avance 500 (500 MHz, 125 MHZ for \textsuperscript{13}C-NMR) spectrometers. \textsuperscript{1}H NMR chemical shifts and \textsuperscript{13}C NMR chemical shifts values were reported in ppm relative to residual chloroform (\textsuperscript{1}H NMR = 7.27 or \textsuperscript{13}C NMR = 77.0) and acetone (\textsuperscript{1}H NMR = 2.05 or \textsuperscript{13}C NMR = 29.8) as internal standards. All coupling constants (J) are reported in Hertz (Hz). Abbreviations are: s, singlet; d, doublet; t, triplet; q, quartet; br s, broad singlet; m, multiplet.

Infrared spectra were recorded on a Bruker Alpha FTIR spectrometer and were recorded as evaporated films or neat using FT/IR spectrometers. Mass spectra were obtained using Micromass Platform II (ESI), Agilent 5975C Triple Axis GCMS (GC-MS, EI/CI) and Waters QTOF (HRMS).

Column chromatography was carried out using 30-70 µ, 60 Å silica gel. Routine TLC analysis was carried out on aluminium sheets coated with silica gel 60 Å F254, 0.2 mm thickness. Plates were viewed using a 254 nm ultraviolet lamp and dipped in aqueous potassium permanganate or \textit{p}-anisaldehyde.
6.2 Preparation of Samarium diodide (SmI$_2$)$^{120}$

An oven-dried 100 mL round-bottomed flask equipped with a Teflon-coated magnetic stir bar and a septum was flushed with N$_2$ for 20 min. Samarium metal (1.20 g, 8.00 mmol, 1.4 eq) and freshly washed 1,2-diiodoethane (see below) (1.60 g, 5.70 mmol, 1.0 eq) were weighed out and added to the reaction flask. The flask was sealed with a septum and flushed with N$_2$ for 20 min. THF (55 mL) was added and the flask was covered in aluminium foil and stirred at room temperature for 12 h under a positive pressure of N$_2$. The stirring was then turned off, and the solution of SmI$_2$ was allowed to settle for 1 hour and titrated according to ref 119.

6.3 Purification of Commercial 1,2-Diiodoethane

1,2-Diiodoethane (20 g) was dissolved in Et$_2$O (~400 mL), and the organic layer was washed with aqueous saturated Na$_2$S$_2$O$_3$ solution (2 × 100 mL) and H$_2$O (1 × 100 mL), dried (Na$_2$SO$_4$), and concentrated in vacuo to give a white solid. The flask containing 1,2-diiodoethane was wrapped in aluminium foil and placed under high-vacuum for 30 min.
6.4 Experimental for Chapter 2

6.4.1 General procedure A: Knoevenagel condensation

2,2-Dimethyl-5-(2-methylpropylidene)-1,3-dioxane-4,6-dione (257)\textsuperscript{121}

To a solution of Meldrum’s acid (500 mg, 3.47 mmol, 1.1 eq) in water (10 mL) was added isobutyraldehyde (0.29 mL, 3.15 mmol, 1.0 eq) and the reaction mixture was heated for 3 h at 75 °C. After cooling to room temperature, filtration gave 2,2-dimethyl-5-(2-methylpropylidene)-1,3-dioxane-4,6-dione 257 (522 mg, 2.6 mmol, 84%) as a white solid; mp 73-75 °C.

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) ppm 1.16 (6 H, d, \(J = 6.6 \) Hz, 2 \(\times \) CH\textsubscript{3}), 1.75 (6 H, s, 2 \(\times \) C(O)CH\textsubscript{3}), 3.72 - 3.86 (1 H, m, C\textsubscript{6}H\textsubscript{1}(CH\textsubscript{3})), 7.70 (1 H, d, \(J = 10.6 \) Hz, C=CH).

\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) \(\delta\) ppm 21.3 (2 \(\times \) CH\textsubscript{3}), 27.6 (2 \(\times \) C(O)CH\textsubscript{3}), 29.5 (CH\textsubscript{3}), 104.8 (OCO), 116.2 (C=CH), 159.6 (C=O), 162.1 (C=O), 173.6 (C=CH).

5-Benzylidene-2,2-dimethyl-1,3-dioxane-4,6-dione (328b)\textsuperscript{121}

To pyrrolidine (0.08 mL, 1.00 mmol, 0.1 eq) in C\textsubscript{6}H\textsubscript{6} (2.0 mL) was added dropwise AcOH (0.06 mL, 1.00 mmol, 0.1 eq). The resulting solution was added to a stirred suspension of Meldrum’s acid (1.58 g, 11.0 mmol, 1.1 eq) and benzaldehyde (1.0 mL, 10.0 mmol, 1.0 eq) in C\textsubscript{6}H\textsubscript{6} (40 mL). After stirring for 3 h at room temperature, the reaction mixture was filtered and the solid washed with MeOH to give 5-benzylidene-2,2-dimethyl-1,3-dioxane-4,6-dione 328b (577 mg, 2.49 mmol, 23%) as a white solid; mp 69-71 °C.

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) ppm 1.82 (6 H, s, C(O)CH\textsubscript{3}), 7.46 - 7.53 (2 H, m, 2 \(\times \) ArCH), 7.54 - 7.60 (1 H, m, ArCH), 8.04 - 8.09 (2 H, m, 2 \(\times \) ArCH), 8.44 (1 H, s, C=CH).
$^{13}$C NMR (101 MHz, CDCl$_3$) δ ppm 27.6 (2 × C(O)CH$_3$), 104.6 (OCO), 114.8 (C=CH), 128.7 (ArCH), 131.7 (ArC), 133.6 (2 × ArCH), 133.7 (2 × ArCH), 158.1 (C=CH), 159.7 (C=O), 163.3 (C=O).

6.4.2 General procedure B: Conjugate reduction

5-Isobutyl-2,2-dimethyl-1,3-dioxane-4,6-dione (258)$^{122}$

To 5-isobutyl-2,2-dimethyl-1,3-dioxane-4,6-dione 257 (240 mg, 1.21 mmol, 1.0 eq) in ethanol (8.0 mL) at 0 °C was added NaBH$_4$ (71.6 mg, 1.81 mmol, 1.5 eq) portion wise. The reaction mixture was allowed to warm up to room temperature and stirred for 1 h. The reaction was then quenched with 1 M aqueous HCl at 0 °C. Filtration and washing with n-hexane afforded 5-isobutyl-2,2-dimethyl-1,3-dioxane-4,6-dione 258 (181 mg, 0.90 mmol, 75%) as a white solid; mp 119-121 °C.

$^1$H NMR (400 MHz, CDCl$_3$) δ ppm 0.96 (6 H, d, J = 6.3 Hz, CH(CH$_3$)$_2$), 1.77 (3 H, s, C(O)CH$_3$), 1.81 (3 H, s, C(O)CH$_3$), 1.96 - 2.10 (3 H, m, CH$_2$ + CH(CH$_3$)$_2$), 3.45 (1 H, t, J = 5.6 Hz, CH).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ ppm 22.1 (CH(CH$_3$)$_2$), 25.9 (C(O)CH$_3$), 26.8 (C(O)CH$_3$), 28.6 (CH(CH$_3$)$_2$), 35.3 (CH$_2$), 44.2 (CHCH$_2$), 104.9 (OCO), 166.0 (2 × C=O).

5-Benzyl-2,2-dimethyl-1,3-dioxane-4,6-dione (329b)$^{122}$

As for general procedure B, 5-benzylidene-2,2-dimethyl-1,3-dioxane-4,6-dione 328b (200 mg, 0.86 mmol, 1.0 eq) and NaBH$_4$ (50.0 mg, 1.29 mmol, 1.5 eq) in ethanol (5.0 mL) after filtration gave 5-benzyl-2,2-dimethyl-1,3-dioxane-4,6-dione 329b (190 mg, 0.81 mmol, 94%) as a white solid; mp 78-83 °C.
1H NMR (500 MHz, CDCl₃) δ ppm 1.50 (3 H, s, C(O)CH₃), 1.74 (3 H, s, C(O)CH₃), 3.51 (2 H, d, J = 5.0 Hz, CH₂), 3.77 (1 H, t, J = 5.0 Hz, CH), 7.23 - 7.26 (1 H, m, ArCH), 7.28 - 7.35 (4 H, m, 4 × ArCH).

13C NMR (101 MHz, CDCl₃) δ ppm 27.2 (C(O)CH₃), 28.4 (C(O)CH₃), 32.1 (CH₂), 48.2 (CH), 105.2 (OCO), 127.2 (ArCH), 128.7 (2 × ArCH), 129.7 (2 × ArCH), 137.2 (ArC), 165.3 (2 × C=O).

6.4.3 General procedure C: Alkylation of Meldrum’s acid

2,2,5-Trimethyl-5-phenyl-1,3-dioxane-4,6-dione (267)

To 2,2-dimethyl-5-phenyl-1,3-dioxane-4,6-dione 260b (3.0 g, 13.4 mmol, 1.0 eq) in DMF (35 mL) was added K₂CO₃ (3.7 g, 26.8 mmol, 2.0 eq) and the resulting suspension stirred for 30 mins before the addition of MeI (4.2 mL, 67.0 mmol, 5.0 eq). After stirring for 24 h, saturated aqueous NaHCO₃ (15 mL) was added and the aqueous phase extracted with ethyl acetate (3 × 30 mL). The combined organic phase was then washed with H₂O (2 × 30 mL), dried (MgSO₄) and concentrated in vacuo. Purification by flash column chromatography on silica gel, eluting with 10% ethyl acetate in petroleum ether (40-60 °C) gave 2,2,5-trimethyl-5-phenyl-1,3-dioxane-4,6-dione 267 (2.1 g, 9.0 mmol, 67%) as a white solid; mp 148-151 °C.

1H NMR (400 MHz, CDCl₃) δ ppm 1.26 (3 H, s, CH₃), 1.73 (3 H, s, C(O)CH₃), 1.87 (3 H, s, C(O)CH₃), 7.32 - 7.44 (5 H, m, 5 × ArCH).

13C NMR (100 MHz, CDCl₃) δ ppm 26.3 (C(O)CH₃), 27.2 (C(O)CH₃), 29.4 (CH₃), 55.4 (Cₙ), 105.5 (OCO), 125.6 (2 × ArCH), 128.8 (ArCH), 129.7 (2 × ArCH), 137.0 (ArC), 167.4 (2 × C=O).
5-Isobutyl-2,2,5-trimethyl-1,3-dioxane-4,6-dione (314)

As for general procedure C, 5-isobutyl-2,2-dimethyl-1,3-dioxane-4,6-dione 258 (200 mg, 1.00 mmol, 1.0 eq), K$_2$CO$_3$ (2.76 g, 2.00 mmol, 2.0 eq), MeI (0.31 mL, 5.00 mmol, 5.0 eq) in DMF (4.0 mL) were stirred at room temperature for 2 days. After work-up, purification by flash column chromatography on silica gel, eluting with 10% ethyl acetate in petroleum ether (40-60 °C) gave 5-isobutyl-2,2,5-trimethyl-1,3-dioxane-4,6-dione 314 (207 mg, 0.97 mmol, 97%) as a white solid; mp 56-57 °C.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ ppm 0.90 (6 H, d, $J = 6.8$ Hz, CH(CH$_3$)$_2$), 1.60 - 1.70 (4 H, m, CH$_3$ + CH(CH$_3$)$_2$), 1.75 (3 H, s, C(O)CH$_3$), 1.78 (3 H, s, C(O)CH$_3$), 2.03 (2 H, d, $J = 6.6$ Hz, CH$_2$).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ ppm 22.9 (CH(CH$_3$)$_2$), 25.6 (CHCH$_3$), 25.8 (CH$_3$), 28.3 (C(O)CH$_3$), 30.0 (C(O)CH$_3$), 48.1 (C$_{eq}$), 49.9 (CH$_2$), 104.9 (OCO), 170.5 (2 $\times$ C=O).

5-Benzyl-2,2,5-trimethyl-1,3-dioxane-4,6-dione (342b)

As for general procedure C, 5-benzyl-2,2-dimethyl-1,3-dioxane-4,6-dione 329b (340 mg, 1.45 mmol, 1.0 eq), K$_2$CO$_3$ (401 mg, 2.90 mmol, 2.0 eq), MeI (0.45 mL, 7.26 mmol, 5.0 eq) in DMF (4.0 mL) were stirred for 2 days. After work-up, purification by recrystallisation from n-hexane gave 5-benzyl-2,2,5-trimethyl-1,3-dioxane-4,6-dione 342b (207 mg, 0.83 mmol, 56%) as a white solid; mp 115-117 °C.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 0.90 (3 H, s, CH$_3$), 1.61 (3 H, s, C(O)CH$_3$), 1.77 (3 H, s, C(O)CH$_3$), 3.34 (2 H, s, CH$_2$), 7.16 - 7.21 (2 H, m, 2 $\times$ ArCH), 7.22 - 7.31 (3 H, m, 3 $\times$ ArCH).
13C NMR (101 MHz, CDCl3) δ ppm 25.9 (CH₃), 28.3 (C(O)CH₃), 29.4 (C(O)CH₃), 44.8 (CH₂), 52.2 (C₈), 105.3 (OCO), 127.8 (ArCH), 128.8 (2 × ArCH), 130.1 (2 × ArCH), 135.4 (ArC), 169.8 (2 × C=O).

Anal. calcd for C₁₄H₁₆O₄: C (67.73 %), H (6.50 %). Found C (67.82 %), H (6.55 %).

6.4.4 General procedure D: Malonate arylation

Diethyl 2-([1,1'-biphenyl]-4-yl)malonate (308)125

To a stirred solution of Pd(OAc)₂ (64.0 mg, 0.28 mmol, 2 mol%), NaOtBu (1.42 g, 14.8 mmol, 1.04 eq), P(tBu)₃ (1.0 M in toluene, 0.28 mL, 0.28 mmol, 2 mol%) and 4-bromo-1,1'-biphenyl (3.34 g, 14.2 mmol, 1.0 eq) in 1,4-dioxane (30 mL) was added diethyl malonate (2.50 g, 15.6 mmol, 1.1 eq) and the resulting solution heated to 70 °C under N₂ overnight. The reaction mixture was cooled to room temperature, filtered through celite® and the filtrate concentrated in vacuo. Purification by flash column chromatography on silica gel, eluting with 0–5% ethyl acetate in petroleum ether (40-60 °C) afforded diethyl 2-([1,1'-biphenyl]-4-yl)malonate 308 (2.40 g, 8.44 mmol, 60%) as a white solid; mp 203-208 °C.

1H NMR (400 MHz, CDCl₃) δ ppm 1.26 - 1.34 (6 H, m, 2 × OCH₂CH₃), 4.20 - 4.30 (4 H, m, 2 × OCH₂CH₃), 4.67 (1 H, s, CH), 7.32 - 7.40 (1 H, m, ArCH), 7.42 - 7.52 (4 H, m, 4 × ArCH), 7.56 - 7.63 (4 H, m, 4 × ArCH).

13C NMR (101 MHz, CDCl₃) δ ppm 14.0 (2 × OCH₂CH₃), 57.3 (CH), 61.9 (2 × OCH₂CH₃), 127.1 (ArCH), 127.3 (2 × ArCH), 127.4 (2 × ArCH), 128.8 (2 × ArCH), 129.7 (2 × ArCH), 131.8 (ArC), 141.1 (ArC), 140.6 (ArC), 168.2 (2 × CO₂Et).
Diethyl 2-(naphthalen-1-yl)malonate (312a)\(^{125}\)

![Diethyl 2-(naphthalen-1-yl)malonate (312a)](image)

As for general procedure D, Pd(OAc)\(_2\) (64.0 mg, 0.28 mmol, 2 mol%), NaO\textsuperscript{t}Bu (1.42 g, 14.8 mmol, 1.04 eq), P(\textsuperscript{t}Bu)\(_3\) (1.0 M in toluene, 0.28 mL, 0.28 mmol, 2 mol%), 1-bromonaphthalene (2.00 mL, 14.2 mmol, 1.0 eq) and diethyl malonate (2.50 g, 15.6 mmol, 1.1 eq) in 1,4-dioxane (30 mL) were heated at 70 °C overnight. After work-up, purification by flash column chromatography on silica gel, eluting with 0–5% ethyl acetate in petroleum ether (40-60 °C) followed by recrystallisation from n-hexane afforded diethyl 2-(naphthalen-1-yl)malonate 312a (2.66 g, 9.29 mmol, 65%) as a white solid; mp 59-61 °C.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 1.27 (6 H, t, \(J = 7.1\) Hz, 2 × OCH\(_2\)CH\(_3\)), 4.26 (4 H, q, \(J = 7.1\) Hz, 2 × OCH\(_2\)CH\(_3\)), 5.43 (1 H, s, CH), 7.47 - 7.60 (4 H, m, 4 × ArCH), 7.83 - 7.92 (2 H, m, 2 × ArCH), 7.97 (1 H, d, \(J = 8.6\) Hz, ArCH).

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) ppm 14.0 (2 × OCH\(_2\)CH\(_3\)), 54.4 (CH), 61.9 (2 × OCH\(_2\)CH\(_3\)), 122.8 (ArCH), 125.4 (ArCH), 125.8 (ArCH), 126.7 (ArCH), 127.0 (ArCH), 128.9 (ArCH), 129.0 (ArCH), 129.3 (ArC), 131.6 (ArC), 133.8 (ArC), 168.5 (2 × CO\(_2\)Et).

Diethyl 2-(naphthalen-2-yl)malonate (312b)\(^{125}\)

![Diethyl 2-(naphthalen-2-yl)malonate (312b)](image)

As for general procedure D, Pd(OAc)\(_2\) (127 mg, 0.57 mmol, 2 mol%), NaO\textsuperscript{t}Bu (2.73 g, 28.4 mmol, 1.04 eq), P(\textsuperscript{t}Bu)\(_3\) (1.0 M in toluene, 0.57 mL, 0.57 mmol, 2 mol%), 2-bromonaphthalene (5.89 g, 28.4 mmol, 1.0 eq) and diethyl malonate (5.00 g, 31.2 mmol, 1.1 eq) in 1,4-dioxane (60 mL) were heated at 70 °C overnight. After work-up, purification by flash column chromatography on silica gel, eluting with 0–5% ethyl acetate in petroleum ether (40-60 °C) followed by recrystallisation from n-hexane afforded diethyl 2-(naphthalen-2-yl)malonate 312b (7.48 g, 26.1 mmol, 84%) as a white solid; mp 98-100 °C.
\[ ^1H \text{ NMR} (400 \text{ MHz}, \text{CDCl}_3) \delta \text{ ppm} \ 1.28 \ (6 \ H, \ t, \ J = 7.1 \text{ Hz}, \ 2 \times \text{OCH}_2\text{CH}_3), \ 4.21 - 4.29 \ (4 \ H, \ m, \ 2 \times \text{OCH}_2\text{CH}_3), \ 4.79 \ (1 \ H, \ s, \text{CH}), \ 7.47 - 7.53 \ (2 \ H, \ m, \ 2 \times \text{ArCH}), \ 7.56 \ (1 \ H, \ dd, \ J = 8.7, \ 1.6 \text{ Hz}, \text{ArCH}), \ 7.81 - 7.89 \ (4 \ H, \ m, \ 4 \times \text{ArCH}). \]

\[ ^13C \text{ NMR} (101 \text{ MHz}, \text{CDCl}_3) \delta \text{ ppm} \ 14.0 \ (2 \times \text{OCH}_2\text{CH}_3), \ 58.1 \ (\text{CH}), \ 61.9 \ (2 \times \text{OCH}_2\text{CH}_3), \ 125.9 \ (\text{ArCH}), \ 126.2 \ (\text{ArCH}), \ 126.3 \ (\text{ArCH}), \ 126.7 \ (\text{ArCH}), \ 127.6 \ (\text{ArCH}), \ 128.0 \ (\text{ArCH}), \ 128.3 \ (\text{ArCH}), \ 128.6 \ (\text{ArC}), \ 133.0 \ (\text{ArC}), \ 133.2 \ (\text{ArC}), \ 168.2 \ (2 \times \text{CO}_2\text{Et}). \]

_5-[(1,1'-Biphenyl)-4-yl]-2,2,5-trimethyl-1,3-dioxane-4,6-dione (309)_

![Chemical Structure](image)

To a stirred solution of diethyl 2-[(1,1'-biphenyl)-4-yl]malonate **308** (2.00 g, 6.40 mmol, 1.0 eq) in EtOH (10 mL) was added NaOEt (21 % in EtOH, 4 mL, 12.8 mmol, 2.0 eq). After 30 min stirring, MeI (0.92 mL, 14.7 mmol, 2.3 eq) was added dropwise and the reaction mixture was heated at reflux overnight. After cooling to room temperature, the reaction mixture was quenched with 1.0 M aqueous HCl (30 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine (30 mL), dried (MgSO\(_4\)) and concentrated \textit{in vacuo} to afford diethyl 2-[(1,1'-biphenyl)-4-yl]-2-methylmalonate (2.10 g, 6.40 mmol, 100%) as a brown oil.

To the crude product (1.4 g, 4.29 mmol, 1.0 eq) in EtOH (25 mL) was added aqueous NaOH (3.25 M in H\(_2\)O, 15 mL, 42.9 mmol, 10 eq) and the reaction was stirred at room temperature overnight. The reaction mixture was quenched with 1 M HCl (25 mL) and extracted with ethyl acetate (3 × 25 mL). The combined organic extracts were washed with brine (25 mL), dried (MgSO\(_4\)) and concentrated \textit{in vacuo}. To a stirred solution of the residue (290 mg, 1.07 mmol, 1.0 eq) in Ac\(_2\)O (1.5 mL) was added conc. H\(_2\)SO\(_4\) (2 drops). The reaction mixture was stirred at room temperature overnight. To this slurry was added acetone (0.4 mL) dropwise over 40 min. The reaction mixture was stirred at room temperature for 3 h then quenched with water (5 mL). The aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried (MgSO\(_4\)) and concentrated \textit{in vacuo}. Purification by flash column
chromatography, eluting with 0–10% ethyl acetate in hexane gave 5-[[1,1'-biphenyl]-4-yl]-2,2,5-trimethyl-1,3-dioxane-4,6-dione 309 (135 mg, 41%) as a white solid; mp 100-104 °C.

$\nu_{\text{max}}$(neat)/cm$^{-1}$ 2917, 1769 (C=O), 1729 (C=O), 1700 (C=O), 1485.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 1.35 (3 H, s, CH$_3$), 1.76 (3 H, s, C(O)CH$_3$), 1.92 (3 H, s, C(O)CH$_3$), 7.43 – 7.47 (2 H, m, 2 × ArCH), 7.47 – 7.52 (3 H, m, 3 × ArCH), 7.56 – 7.61 (2 H, m, 2 × ArCH), 7.62 – 7.67 (2 H, m, 2 × ArCH).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ ppm 26.4 (C(O)CH$_3$), 27.4 (C(O)CH$_3$), 29.4 (CH$_3$), 48.8 (C$_6$), 105.6 (OCO), 126.2 (2 × ArCH), 127.0 (ArCH), 128.0 (2 × ArCH), 128.2 (2 × ArCH), 128.9 (2 × ArCH), 139.6 (ArC), 141.7 (ArC), 167.5 (2 × C=O).

The mass spectrum was not informative.

6.4.5 General procedure E: SmI$_2$ mediated reductions

3-Hydroxy-2-methyl-2-phenylproanoic acid (268)$^{126}$

To a stirred solution of SmI$_2$ (0.1 M in THF, 7.5 mL, 0.75 mmol, 7.0 eq) was added distilled water (1.92 mL, 107 mmol, 1000 eq) causing a colour change from deep blue/black to deep red/purple. A solution of 2,2,5-trimethyl-5-phenyl-1,3-dioxane-4,6-dione 267 (25 mg, 0.11 mmol, 1.0 eq) in THF (3.0 mL) was added and the solution stirred until complete decolourisation had occurred. The reaction was quenched by exposing to air, subsequently adding aqueous saturated NaCl (25 mL) and tartaric acid (10 mg). The aqueous layer was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers dried (Na$_2$SO$_4$) and concentrated in vacuo. Purification by flash column chromatography on silica gel, eluting with 30% ethyl acetate in petroleum ether (40-60 °C) and 0.1% acetic acid gave 3-hydroxy-2-methyl-2-phenylproanoic acid 268 (16 mg, 89.0 μmol, 83%) as a white solid.
\textsuperscript{1}H NMR (300 MHz, CDCl$_3$) $\delta$ ppm 1.69 (3 H, s, CH$_3$), 3.67 (1 H, d, $J = 11.4$ Hz, CH$_2$OH), 4.11 (1 H, d, $J = 11.4$ Hz, CH$_2$OH), 7.28 - 7.41 (5 H, m, ArCH).

\textsuperscript{13}C NMR (400 MHz, CDCl$_3$) $\delta$ ppm 20.1 (CH$_3$), 52.4 (C$_q$), 69.1 (CH$_2$), 126.3 (2 $\times$ ArCH), 127.7 (ArCH), 128.8 (2 $\times$ ArCH), 139.6 (ArC), 181.1 (COOH).

\textbf{3-Hydroxy-2-phenylpropanoic acid (261b)}$^{91}$

As for general procedure E, reaction of 2,2-dimethyl-5-phenyl-1,3-dioxane-4,6-dione 260b (30 mg, 0.14 mmol, 1.0 eq) in THF (3.0 mL) with SmI$_2$ (0.1 M in THF, 9.54 mL, 0.95 mmol, 7.0 eq) and distilled water (2.45 mL, 136 mmol, 1000 eq). After work-up, purification by column chromatography on silica gel, eluting with 20% ethyl acetate in petroleum ether (40-60 °C) and 0.1% acetic acid gave 3-hydroxy-2-phenylpropanoic acid 261b (16.3 mg, 98.2 μmol, 72%) as a white solid.

\textsuperscript{1}H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 3.76 - 3.83 (2 H, m, CH$_2$), 4.09 - 4.21 (1 H, m, CH), 7.21 - 7.30 (5 H, m, Ar CH).

\textsuperscript{13}C NMR (100 MHz, CD$_3$OD) $\delta$ ppm 55.9 (CH), 65.1 (CH$_2$), 128.5 (ArCH), 129.2 (2 $\times$ ArCH), 129.7 (2 $\times$ ArCH), 137.9 (ArC), 176.1 (COOH).

\textbf{2-(Hydroxymethyl)-4-methylpentanoic acid (261a)}$^{127}$

As for general procedure E, reaction of 5-isobutyl-2,2-dimethyl-1,3-dioxane-4,6-dione 260a (30 mg, 0.15 mmol, 1.0 eq) in THF (3.0 mL) with SmI$_2$ (0.1 M in THF, 10.5 mL, 1.05 mmol, 7.0 eq) and distilled water (2.72 mL, 150 mmol, 1000 eq). After work-up, purification by column chromatography on silica gel, eluting with 20% ethyl acetate in petroleum ether (40-60 °C) and 0.1% acetic acid gave 2-(hydroxymethyl)-4-methylpentanoic acid 261a (21.9 mg, 0.150 mmol, 87%) as a colourless oil.
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 0.94 (6 H, d, $J = 6.2$ Hz, CH(CH$_3$)$_2$), 1.37 (1 H, m, CH(CH$_3$)$_2$), 1.58 - 1.72 (2 H, m, CH$_2$), 2.68 - 2.75 (1 H, m, CHCH$_2$OH), 3.77-3.79 (2 H, m, CH$_2$OH).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 22.3 (CHCH$_3$), 22.5 (CHCH$_3$), 25.8 (CH(CH$_3$)$_2$), 37.2 (CH$_2$), 45.7 (CH), 63.4 (CH$_2$OH), 180.8 (COOH).

**2-(Hydroxymethyl)-2,4-dimethylpentanoic acid (315)$^{104}$**

![Chemical Structure](image)

As for general procedure E, reaction of 5-isobutyl-2,2,5-trimethyl-1,3-dioxane-4,6-dione 314 (25 mg, 0.12 mmol, 1.0 eq) in THF (3.0 mL) with SmI$_2$ (0.09 M in THF, 9.10 mL, 0.82 mmol, 7.0 eq) and distilled water (2.10 mL, 117 mmol, 1000 eq). After work-up, purification by column chromatography on silica gel, eluting with 20% ethyl acetate in petroleum ether (40-60 °C) and 0.1% acetic acid gave 2-(hydroxymethyl)-2,4-dimethylpentanoic acid 315 (17.6 mg, 0.11 mmol, 94%) as a colourless oil.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ ppm 0.91 (6 H, t, $J = 7.2$ Hz, CH(CH$_3$)$_2$), 1.24 (3 H, s, CH$_3$), 1.42 - 1.66 (2 H, m, CH$_2$), 1.75 (1 H, dt, $J = 13.0, 6.5$ Hz, CH), 3.48 (1 H, d, $J = 11.0$ Hz, 1 H from CH$_2$OH), 3.81 (1 H, d, $J = 11.0$ Hz, 1 H from CH$_2$OH).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ ppm 19.9 (C$q$(CH$_3$)), 23.7 (CH$_3$), 24.1 (CH$_3$), 24.5 (CH), 44.7 (CH$_2$), 47.4 (C$q$), 68.8 (CH$_2$OH), 183.0 (COOH).
2-Benzyl-3-hydroxyproanoic acid (332b)\textsuperscript{128}

![Structure of 2-Benzyl-3-hydroxyproanoic acid]

As for general procedure E, reaction of 5-benzyl-2,2-dimethyl-1,3-dioxane-4,6-dione \textbf{329b} (23 mg, 0.10 mmol, 1.0 eq) in THF (1.5 mL) with SmI\textsubscript{2} (0.1 M in THF, 7.00 mL, 0.70 mmol, 7.0 eq) and distilled water (1.80 mL, 100 mmol, 1000 eq). After work-up, purification by column chromatography on silica gel, eluting with 20% ethyl acetate in petroleum ether (40-60 °C) and 0.1% acetic acid gave 2-benzyl-3-hydroxy-2-methylpropanoic acid \textbf{332b} (15.4 mg, 84.5 μmol, 84%) as a colourless oil.

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ ppm 2.84 - 2.94 (1 H, m, CH, 1 H from CH\textsubscript{2}Ph), 3.04 - 3.14 (1 H, m, 1 H from CH\textsubscript{2}Ph), 3.70 - 3.84 (2 H, m, CH\textsubscript{2}OH), 7.21 - 7.35 (5 H, s, 5 × ArCH).

\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) δ ppm 34.0 (CH\textsubscript{2}Ph), 48.7 (CH), 61.9 (CH\textsubscript{2}OH), 126.7 (ArCH), 128.6 (2 × ArCH), 129.0 (2 × ArCH), 138.2 (ArC), 179.3 (COOH).

2-Benzyl-3-hydroxy-2-methylpropanoic acid\textsuperscript{129}

![Structure of 2-Benzyl-3-hydroxy-2-methylpropanoic acid]

As for general procedure E, reaction of 5-benzyl-2,2,5-trimethyl-1,3-dioxane-4,6-dione \textbf{342b} (25 mg, 0.10 mmol, 1.0 eq) in THF (1.5 mL) with SmI\textsubscript{2} (0.1 M in THF, 7.00 mL, 0.70 mmol, 7.0 eq) and distilled water (1.80 mL, 100 mmol, 1000 eq). After work-up, purification by column chromatography on silica gel, eluting with 20% ethyl acetate in petroleum ether (40-60 °C) and 0.1% acetic acid gave 2-benzyl-3-hydroxy-2-methylpropanoic acid (12.9 mg, 66.5 μmol, 66%) as a yellow oil.

\textsuperscript{1}H NMR (400 MHz, Acetone-d\textsubscript{6}) δ ppm 1.10 (3 H, s, CH\textsubscript{3}), 2.86 (1 H, d, J = 13.1 Hz, 1 from C\textsubscript{4}CH\textsubscript{2}), 2.96 (1 H, d, J = 13.1 Hz, 1 from C\textsubscript{4}CH\textsubscript{2}), 3.56 (1 H, d, J = 10.6 Hz, 1 from CH\textsubscript{2}OH), 3.63 (1 H, d, J = 10.6 Hz, 1 from CH\textsubscript{2}OH), 7.16 - 7.29 (5 H, m, 5 × ArCH).
\[
\text{\textsuperscript{13}C NMR (101 MHz, Acetone-\textit{d}^6) } \delta \text{ ppm } 19.7 \text{ (CH}_3\text{)}, 41.4 \text{ (C}_q\text{CH}_2\text{)}, 49.6 \text{ (C}_q\text{)}, 67.6 \text{ (CH}_2\text{OH)}\), 127.2 \text{ (ArCH)}, 128.8 \text{ (2 × ArCH)}, 131.3 \text{ (2 × ArCH)}, 138.7 \text{ (ArC)}, 177.4 \text{ (COOH).}
\]

2-([1,1'-Biphenyl]-4-yl)-3-hydroxy-2-methylproanoic acid (310)

As for general procedure E, reaction of 5-([1,1'-biphenyl]-4-yl)-2,2,5-trimethyl-1,3-dioxane-4,6-dione \textbf{309} (30 mg, 0.097 mmol, 1.0 eq) in THF (1.5 mL) with SmI\textsubscript{2} (0.1 M in THF, 6.80 mL, 0.68 mmol, 7.0 eq) and distilled water (1.74 mL, 96.7 mmol, 1000 eq). After work-up, purification by column chromatography on silica gel, eluting with 20% ethyl acetate in petroleum ether (40-60 °C) and 0.1% acetic acid gave 2-([1,1'-biphenyl]-4-yl)-3-hydroxy-2-methylproanoic acid \textbf{310} (15.4 mg, 60.1 μmol, 63%) as a yellow oil.

\[
\text{\textsuperscript{1}H NMR (400 MHz, CDCl}_3\text{)} \delta \text{ ppm } 1.75 \text{ (3 H, s, C}_3\text{H}_3\text{)}, 3.75 \text{ (1 H, d, } J = 11.5 \text{ Hz, 1 H from CH}_2\text{OH)}, 4.16 \text{ (1 H, d, } J = 11.5 \text{ Hz, 1 H from CH}_2\text{OH)}, 7.33 - 7.39 \text{ (1 H, m, ArCH)}, 7.42 - 7.49 \text{ (4 H, m, 4 × ArCH)}, 7.55 - 7.66 \text{ (4 H, m, 4 × ArCH).}
\]

\[
\text{\textsuperscript{13}C NMR (101 MHz, CDCl}_3\text{)} \delta \text{ ppm } 20.2 \text{ (CH}_3\text{)}, 52.1 \text{ (C}_q\text{)}, 69.1 \text{ (CH}_2\text{)}, 126.7 \text{ (ArC)}, 126.9 \text{ (ArC)}, 127.1 \text{ (2 × ArCH)}, 127.5 \text{ (2 × ArCH)}, 127.9 \text{ (2 × ArCH)}, 128.1 \text{ (2 × ArCH)}, 128.8 \text{ (ArCH)}, 138.5 \text{ (ArC)}, 179.8 \text{ (COOH).}
\]

2-Methyl-2-phenylpropane-1,3-diol (270)\textsuperscript{130}

To a flask containing 2,2,5-trimethyl-5-phenyl-1,3-dioxane-4,6-dione \textbf{267} (25 mg, 0.107 mmol, 1.0 eq) in THF (2.0 mL) was added SmI\textsubscript{2} (0.1 M in THF, 6.40 mL, 0.64 mmol, 6.0 eq), Et\textsubscript{3}N (0.27 mL, 1.92 mmol, 18 eq) and distilled water (35 μL, 1.92 mmol, 18 eq), and the resulting solution stirred until complete decolourisation had occurred. The reaction was quenched by exposing to air, subsequently adding aqueous saturated NaCl (25 mL) and
tartaric acid (10 mg). The aqueous layer was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography on silica gel, eluting with 20% ethyl acetate in petroleum ether (40-60 °C) and 0.1% acetic acid gave 3-hydroxy-2-methyl-2-phenylpropanoic acid 268 (9.9 mg, 55.0 μmol, 52%) and 2-methyl-2-phenylpropane-1,3-diol 270 (1.9 mg, 11.4 μmol, 11%) as a colourless oil.

\[ ^1H \text{ NMR (400 MHz, CDCl}_3\delta \text{ ppm 1.32 (3 H, s, CH}_3\text{), 1.94 (2 H, s, 2 × OH), 3.87 (2 H, d, J = 11.0 Hz, CH}_2\text{), 4.00 (2 H, d, J = 11.0 Hz, CH}_2\text{), 7.25 - 7.30 (1 H, m, ArCH), 7.36 - 7.42 (2 H, m, 2 × ArCH), 7.42 - 7.47 (2 H, m, 2 × ArCH).} \]

\[ ^{13}C \text{ NMR (101 MHz, CDCl}_3\delta \text{ ppm 20.8 (CH}_3\text{) 44.6 (C}_q\text{) 70.2 (2 × CH}_2\text{) 126.7 (ArCH) 126.8 (2 × ArCH) 128.7 (2 × ArCH) 142.8 (ArC).} \]

### 6.4.6 General procedure F: Asymmetric desymmetrisation

**3-Hydroxy-2-methyl-2-phenylpropanoic acid (268)**

To a stirred solution of SmI₂ (0.1 M in THF, 7.70 mL, 0.77 mmol, 6.0 eq) at −78 °C was added Et₃N (0.11 mL, 0.77 mmol, 6.0 eq) at −78 °C, a solution of (R,R)-hydrobenzoin (165 mg, 0.77 mmol, 6.0 eq) in THF (2 mL) at −78 °C, and a solution of 2,2,5-trimethyl-5-phenyl-1,3-dioxane-4,6-dione 267 (30 mg, 0.13 mmol, 1.0 eq) in THF (2 mL) at −78 °C and the resulting solution stirred −78 °C for 2 h. The reaction was quenched by exposing to air and warming to room temperature, subsequently adding aqueous saturated NaCl (25 mL) and tartaric acid (10 mg). The aqueous layer was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography on silica gel, eluting with 0-30% ethyl acetate in CHCl₃ afforded 3-hydroxy-2-methyl-2-phenylpropanoic acid 268 (8.1 mg, 0.45 mmol, 35%) as a white solid.

Spectral data was identical to that described previously.
Enantiomeric excess was measured as 41% using chiral HPLC (ChiralPak IA column, 90:10 \textit{n}-hexane–EtOH 0.2% TFA, 15 °C, flow rate 1 mL/min, UV detection at 210 nm).

\textbf{2-([1,1'-Biphenyl]-4-yl)-3-hydroxy-2-methylpropanoic acid (310)}

![Structure of 2-([1,1'-Biphenyl]-4-yl)-3-hydroxy-2-methylpropanoic acid (310)](image)

As for general procedure F, reaction of 5-([1,1'-biphenyl]-4-yl)-2,2,5-trimethyl-1,3-dioxane-4,6-dione \textbf{309} (30 mg, 0.097 mmol, 1.0 eq), SmI$_2$ (0.1 M in THF, 5.68 mL, 0.58 mmol, 6.0 eq), Et$_3$N (0.081 mL, 0.58 mmol, 6.0 eq) and (\textit{R},\textit{R})-hydrobenzoin (124 mg, 0.58 mmol, 6.0 eq). After work-up, purification by flash column chromatography, eluting with 0–30% ethyl acetate in CHCl$_3$ afforded 2-([1,1'-biphenyl]-4-yl)-3-hydroxy-2-methylpropanoic acid \textbf{310} (4.1 mg, 0.016 mmol, 17%) as a yellow oil.

Spectral data was identical to that described previously.

Enantiomeric excess was measured as 15% using chiral HPLC (ChiralPak IA column, 90:10 \textit{n}-hexane–EtOH 0.2% TFA, 15 °C, flow rate 1 mL/min, UV detection at 210 nm).

\textbf{2-(Hydroxymethyl)-2,4-dimethylpentanoic acid (315)}

![Structure of 2-(Hydroxymethyl)-2,4-dimethylpentanoic acid (315)](image)

As for general procedure F, reaction of 5-isobutyl-2,2,5-trimethyl-1,3-dioxane-4,6-dione \textbf{314} (27 mg, 12.8 μmol, 1.0 eq), SmI$_2$ (0.1 M in THF, 7.70 mL, 0.77 mmol, 6.0 eq), Et$_3$N (0.11 mL, 0.77 mmol, 6.0 eq) and (\textit{R},\textit{R})-hydrobenzoin (165 mg, 0.77 mmol, 6.0 eq). After work-up, purification by flash column chromatography, eluting with 0–30% ethyl acetate in CHCl$_3$ afforded 2-(hydroxymethyl)-2,4-dimethylpentanoic acid \textbf{315} (15 mg, 0.093 mmol, 73%) as a yellow oil.

Spectral data was identical to that described previously.
Enantiomeric excess of benzyl ester (J. Am. Chem. Soc. 2010, 132, 10920) was measured as 14% using chiral HPLC (ChiralPak IA column, 98:2 n-hexane–i-PrOH 0.2% TFA, 20 °C, flow rate 1 mL/min, UV detection at 210 nm).

### 6.4.7 Preparation of chiral/nonracemic ligands

(1S,1'S)-2,2'-(Benzylazanediyl)bis(1-phenylethanol) (291)

(R)-(+) Styrene oxide (420 mg, 3.48 mmol, 6.0 eq) and benzylamine (62 μL, 0.58 mmol, 1.0 eq) were stirred for 12 h at 120 °C. After cooling to room temperature, the reaction mixture was purified by flash column chromatography on silica gel, eluting with 20% ethyl acetate in petroleum ether (40-60 °C) to afford (1S,1'S)-2,2'-(benzylazanediyl)bis(1-phenylethanol) 291 (120 mg, 0.35 mmol, 68%) as a clear, colourless oil.

$^1$H NMR (300 MHz, CDCl$_3$) δ ppm 2.62 - 2.83 (4 H, m, 2 × CH$_2$Ph), 3.65 (1 H, d, $J = 13.6$ Hz, 1 H from ArCH$_2$), 3.93 (1 H, d, $J = 13.6$ Hz, 1 H from ArCH$_2$), 4.71 (2 H, dd, $J = 9.1$, 3.9 Hz, 2 × CH$_2$CH$_2$), 7.10 - 7.34 (15 H, m, ArCH).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ ppm 59.7 (2 × CH$_2$), 62.5 (2 × CH$_2$CH$_2$), 70.7 (2 × CH), 125.9 (4 × ArCH), 127.4 (ArCH), 127.5 (2 × ArCH), 128.3 (4 × ArCH), 128.5 (2 × ArCH), 129.1 (2 × ArCH), 138.0 (ArC), 142.1 (2 × ArC).

### 6.4.8 General procedure G: Cross-metathesis

(E)-1,2-bis(4-Methoxyphenyl)ethane

To a stirred solution of 4-methoxystyrene (1.50 mL, 11.2 mmol, 1.0 eq) in CH$_2$Cl$_2$ (30 mL) was added Grubbs 2nd generation catalyst (190 mg, 0.24 mmol, 2 mol%) and the resulting solution heated at reflux for 24 h then concentrated in vacuo. Purification by flash column
chromatography on silica gel, eluting with 20% ethyl acetate in petroleum ether (40-60 °C) afforded (E)-1,2-\textit{bis}(4-methoxyphenyl)ethene (1.10 g, 4.58 mmol, 82%) as a white solid.

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) ppm 3.84 (6 H, s, 2 × OCH\textsubscript{3}), 6.87 - 6.93 (4 H, m, 2 × ArCH), 6.94 (2 H, s, CH=CH), 7.41 - 7.47 (4 H, m, 2 × ArCH).

\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) \(\delta\) ppm 55.3 (2 × OCH\textsubscript{3}), 114.1 (4 × ArCH), 126.1 (2 × CH=CH), 127.4 (4 × ArCH), 130.4 (2 × ArC), 159.0 (2 × ArC).

6.4.9 General procedure H: McMurry coupling I

\textit{(E)-1,2-\textit{bis}(4-(Trifluoromethyl)phenyl)ethene\textsuperscript{133}}

\begin{center}
\includegraphics[width=0.5\textwidth]{mcmurry_coupling}
\end{center}

To a suspension of Zn dust (4.5 g, 68.9 mmol, 3.0 eq) in THF (120 mL) was added dropwise TiCl\textsubscript{4} (1.0 M in CH\textsubscript{2}Cl\textsubscript{2}, 34.0 mL, 34.4 mmol, 1.5 eq) and the reaction mixture heated at reflux for 1 hour. 4-(Trifluoromethyl)benzaldehyde (4.00 g, 23.0 mmol, 1.0 eq) was added and the reaction mixture heated at reflux for a further 4 h then cooled to room temperature. The reaction mixture was quenched with ice-cold 1.0 N aqueous HCl then the solution filtered through celite\textsuperscript{\textregistered} and extracted with CH\textsubscript{2}Cl\textsubscript{2} (2 × 50 mL), dried (MgSO\textsubscript{4}) and concentrated \textit{in vacuo}. Purification by flash column chromatography on silica gel, eluting with 1-5% ethyl acetate in hexane followed by recrystallisation from MeOH afforded (E)-1,2-\textit{bis}(4-(trifluoromethyl)phenyl)ethene (2.20 g, 6.96 mmol, 61%) as a white solid.

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) ppm 7.22 (2 H, s, CH=CH), 7.64 (8 H, s, 8 × ArCH).

\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) \(\delta\) ppm 125.8 (q, \(J = 265.1\) Hz, 2 × CF\textsubscript{3}), 126.9 (8 × ArCH), 129.7 (2 × CH=CH), 130.0 (2 × ArCCF\textsubscript{3}), 140.0 (2 × ArC).
(E)-1,2-bis(2-Bromophenyl)ethene

As for general procedure H, Zn dust (1.40 g, 22.0 mmol, 3.0 eq), TiCl₄ (1.2 mL, 11.0 mmol, 1.5 eq) and 2-bromobenzaldehyde (0.86 mL, 7.33 mmol, 1.0 eq) in THF (30 mL) were heated at reflux overnight. After work-up, purification by column chromatography on silica gel, eluting with 100% petroleum ether (40-60 °C) afforded (E)-1,2-bis(2-bromophenyl)ethene (1.10 g, 3.27 mmol, 90%) as a white solid.

1H NMR (400 MHz, CDCl₃) δ ppm 7.16 (2 H, td, J = 7.7, 1.7 Hz, 2 × ArCH), 7.35 (2 H, td, J = 7.7, 1.3 Hz, 2 × ArCH), 7.41 (2 H, s, CH=CH), 7.61 (2 H, dd, J = 8.0, 1.3 Hz, 2 × ArCH), 7.74 (2 H, dd, J = 8.0, 1.7 Hz, 2 × ArCH).

13C NMR (101 MHz, CDCl₃) δ ppm 124.2 (2 × ArC), 127.1 (2 × ArCH), 127.7 (2 × ArCH), 129.2 (2 × ArCH), 130.1 (CH=CH), 133.1 (2 × ArCH), 136.8 (2 × ArC).

(E)-1,2-Di-o-tolythene

As for general procedure H, Zn dust (1.40 g, 22.0 mmol, 3.0 eq), TiCl₄ (1.20 mL, 11.0 mmol, 1.5 eq) and o-tolualdehyde (0.85 mL, 7.33 mmol, 1.0 eq) in THF (30 mL) were heated at reflux overnight. After work-up, purification by column chromatography on silica gel, eluting with 100% petroleum ether (40-60 °C) afforded 1,2-di-o-tolythene as a 17:1 mixture of E/Z alkenes. The mixture was heated at reflux for 12 h in o-toluene with a catalytic quantity of I₂, then concentrated in vacuo and filtered through a plug of silica. The organic phase was concentrated in vacuo to afford (E)-1,2-di-o-tolythene (700 mg, 3.36 mmol, 93%) as a white solid.

1H NMR (400 MHz, CDCl₃) δ ppm 2.45 (6 H, s, 2 × CH₃), 7.18 - 7.31 (8 H, m, 6 × ArCH + CH=CH), 7.62 (2 H, d, J = 7.1 Hz, 2 × ArCH).
\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) ppm 19.9 (CH\(_3\)), 125.5 (ArCH), 126.2 (ArCH), 127.5 (ArCH), 128.0 (ArCH), 130.4 (CH=CH), 135.8 (ArC), 136.8 (ArC).

*(E)-1,2-bis(2-Methoxyphenyl)ethene*\(^\text{136}\)

As for general procedure H, Zn dust (2.20 g, 33.0 mmol, 3.0 eq), TiCl\(_4\) (1.8 mL, 16.5 mmol, 1.5 eq) and 2-methoxybenzaldehyde (1.50 g, 11.0 mmol, 1.0 eq) in THF (35 mL) were heated at reflux overnight. After work-up, purification by column chromatography on silica gel, eluting with 1-5% ethyl acetate in hexane followed by recrystallisation from hexane gave *(E)-1,2-bis(2-methoxyphenyl)ethene* (890 mg, 3.7 mmol, 67%) as a white solid.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 3.89 (6 H, s, 2 × CH\(_3\)), 6.90 (2 H, dd, \(J = 8.2, 0.9\) Hz, 2 × ArCH), 6.98 (2 H, td, \(J = 7.4, 1.0\) Hz, 2 × ArCH), 7.21 - 7.26 (2 H, m, 2 × ArCH), 7.48 (2 H, s, CH=CH), 7.66 (2 H, dd, \(J = 7.7, 1.6\) Hz, 2 × ArCH).

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) ppm 55.5 (2 × CH\(_3\)), 110.9 (2 × ArCH), 120.7 (2 × ArCH), 123.6 (CH=CH), 126.4 (2 × ArCH), 127.1 (2 × ArC), 128.4 (2 × ArCH), 156.8 (2 × ArC).

### 6.4.10 General procedure I: McMurry coupling II

*(E)-1,2-bis(3,5-Dimethylphenyl)ethene*\(^\text{132}\)

To a suspension of Zn dust (1.10 g, 16.9 mmol, 2.4 eq) in THF (30 mL) was added Cp\(_2\)TiCl\(_2\) (2.10 g, 8.45 mmol, 1.2 eq) and the reaction mixture heated at reflux for 10 min. 3,5-dimethylbenzaldehyde (1.00 mL, 7.04 mmol, 1.0 eq) was added and the reaction
mixture heated at reflux for a further 2 h and then cooled to room temperature. The reaction mixture was quenched with ice-cold 1.0 N aqueous HCl and extracted with Et₂O (2 × 50 mL), then the combined organic layers were dried (MgSO₄) and concentrated in vacuo. Purification by flash column chromatography on silica gel, eluting with 100% petroleum ether (40-60 °C) followed by recrystallisation from MeOH afforded (E)-1,2-

\[ \text{bis}(3,5\text{-dimethylphenyl})\text{ethene} \] (600 mg, 2.5 mmol, 68%) as a white solid.

\[ ^1\text{H NMR} \ (400 \text{ MHz, CDCl}_3) \text{ δ ppm} \]

- 2.35 (12 H, s, 4 × CH₃), 6.91 (2 H, s, CH=CH), 7.04 (2 H, s, 2 × ArCH), 7.14 (4 H, s, 4 × ArCH).

\[ ^{13}\text{C NMR} \ (101 \text{ MHz, CDCl}_3) \text{ δ ppm} \]

- 21.3 (4 × CH₃), 124.3 (4 × ArCH), 128.5 (2 × ArCH), 129.2 (CH=CH), 137.4 (2 × ArC), 138.1 (4 × ArC).

\[(E)-1,2\text{-bis}(3,5\text{-Difluorophenyl})\text{ethene}^{134} \]

As for general procedure I, Zn dust (1.10 g, 16.9 mmol, 2.4 eq), Cp₂TiCl₂ (2.10 g, 8.45 mmol, 1.2 eq), 3,5-difluorobenzaldehyde (0.80 mL, 7.04 mmol, 1.0 eq) in THF (30 mL) were heated at reflux overnight. After work-up, purification by column chromatography on silica gel, eluting with 100% petroleum ether (40-60 °C) followed by recrystallisation from petroleum ether (40-60 °C) afforded (E)-1,2-

\[ \text{bis}(3,5\text{-difluorophenyl})\text{ethene} \] (507 mg, 2.0 mmol, 57%) as a white solid.

\[ ^1\text{H NMR} \ (400 \text{ MHz, CDCl}_3) \text{ δ ppm} \]

- 7.02 (2 H, t, J = 8.7, 2.3 Hz, 2 × ArCH), 7.24 - 7.32 (4 H, m, 4 × ArCH), 7.53 (2 H, s, CH=CH).
6.4.11 General procedure J: Sharpless asymmetric dihydroxylation

\[ (1R,2R)-1,2-bis(4-Methoxyphenyl)ethane-1,2-diol (299) \]

\[
\begin{align*}
\text{MeO} & \quad \text{OMe} \\
\text{OH} & \quad \text{OH}
\end{align*}
\]

AD-mix-\( \alpha \) (1.7 g) was dissolved in H\(_2\)O (10 mL) and \( t \)-BuOH (10 mL) and the resulting orange solution cooled to 0 °C. (\( E \))-1,2-\( \text{bis}(4\text{-methoxyphenyl}) \)ethene (500 mg, 2.10 mmol, 1.0 eq) was added followed by methanesulfonamide (200 mg, 2.10 mmol, 1.0 eq) and the resulting solution was allowed to warm to room temperature and stirred for 12 h. \( \text{Na}_2\text{SO}_3 \) (6.2 g) was added and the resulting solution stirred for 1 hour after which 1.0 N aqueous KOH (15 mL) was added. The aqueous layer was extracted with ethyl acetate (2 \( \times \) 10 mL) and the combined organic extracts washed with brine (10 mL), dried (\( \text{MgSO}_4 \)) and concentrated \textit{in vacuo}. Purification by flash column chromatography on silica gel, eluting with 5-20% ethyl acetate in petroleum ether (40-60 °C) followed by recrystallisation from CH\(_2\)Cl\(_2\)/MeOH afforded \( (1R,2R)-1,2-bis(4\text{-methoxyphenyl}) \)ethane-1,2-diol \( 299 \) (428 mg, 1.56 mmol, 76%) as a white solid; mp 124-127 °C.

\[
[\alpha]_D = +112.27 \quad (c = 1.50; \text{CH}_2\text{Cl}_2); \quad \text{literature value for} \ (R,R) \text{-isomer} \ [\alpha]_D = +132.4 \quad (c = 1.50; \text{CH}_2\text{Cl}_2).
\]

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) ppm 3.78 (6 H, s, 2 \( \times \) OCH\(_3\)), 4.65 (2 H, s, CH(OH)), 6.74 - 6.80 (4 H, m, 4 \( \times \) ArCH), 7.02 - 7.08 (4 H, m, 4 \( \times \) ArCH).

\(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \( \delta \) ppm 55.2 (2 \( \times \) OCH\(_3\)), 78.8 (2 \( \times \)CH(OH)), 113.5 (4 \( \times \) ArCH), 128.1 (4 \( \times \) ArCH), 132.0 (2 \( \times \) ArC), 159.2 (2 \( \times \) ArC).

\[ (1R,2R)-1,2-bis(4-(\text{Trifluoromethyl})\text{phenyl})ethane-1,2-diol (301) \]

\[
\begin{align*}
\text{CF}_3 & \quad \text{CF}_3 \\
\text{OH} & \quad \text{OH}
\end{align*}
\]

As for general procedure J, AD-mix-\( \alpha \) (2.7 g), \( (E) \)-1,2-\( \text{bis}(4\text{-}(\text{trifluoromethyl})\text{phenyl}) \)ethene (1.00 g, 3.15 mmol, 1.0 eq), methanesulfonamide (300 mg,
3.15 mmol, 1.0 eq) in H$_2$O (15 mL) and t-BuOH (15 mL) were stirred at room temperature overnight. After work-up, purification by column chromatography on silica gel, eluting with 5-20% ethyl acetate in petroleum ether (40-60 °C) followed by recrystallisation from CCl$_4$ afforded (1S,2S)-1,2-bis(4-(trifluoromethyl)phenyl)ethane-1,2-diol 301 (1.10 g, 3.14 mmol, 97%) as a white solid; mp 138-140 °C.

$[\alpha]_D = +71.1$ (c = 0.95; CHCl$_3$); literature value for (R,R)-isomer $[\alpha]_D = +76.7$ (c = 0.95; CHCl$_3$).

$^1$H NMR (400 MHz, CDCl$_3$) δ ppm 2.99 (2 H, br s, 2 × OH), 4.76 (2 H, s, 2 × C$_H$(OH)), 7.24 (4 H, d, $J = 8.1$ Hz, 4 × ArCH), 7.52 (4 H, d, $J = 8.1$ Hz, 4 × ArCH).

Anal. calcd for C$_{16}$H$_{12}$F$_6$O$_2$: C (54.87 %), H (3.45 %), found C (54.86 %), H (3.05 %).

(1R,2R)-1,2-bis(2-Bromophenyl)ethane-1,2-diol (303a)

As for general procedure J, AD-mix-α (2.7 g), (E)-1,2-bis(2-bromophenyl)ethene (1.10 g, 3.23 mmol, 1.0 eq), methanesulfonylamine (310 mg, 3.23 mmol, 1.0 eq) in H$_2$O (16 mL) and t-BuOH (16 mL) were stirred at room temperature overnight. After work-up, purification by column chromatography on silica gel, eluting with 5-20% ethyl acetate in petroleum ether (40-60 °C) followed by recrystallisation from hexane/CH$_2$Cl$_2$ afforded (1S,2S)-1,2-bis(2-bromophenyl)ethane-1,2-diol 303a (920 mg, 2.49 mmol, 76%) as a white solid; mp 112-116 °C.

$[\alpha]_D = +37.0$ (c = 1.0; EtOH); literature value for (R,R)-isomer $[\alpha]_D = +37.0$ (c =1.0; EtOH).

$^1$H NMR (400 MHz, CDCl$_3$) δ ppm 2.50 - 3.03 (2 H, br s, 2 × OH), 5.33 (2 H, s, 2 × CH(OH)), 7.15 (2 H, td, $J = 7.6$, 1.6 Hz, 2 × ArCH), 7.35 (2 H, td, $J = 7.6$, 1.2 Hz, 2 × ArCH), 7.46 (2 H, dd, $J = 7.9$, 1.2 Hz, 2 × ArCH), 7.70 (2 H, dd, $J = 7.9$, 1.6 Hz, 2 × ArCH).
\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) ppm 75.2 (2 × CH(OH)), 122.9 (2 × ArC), 127.5 (2 × ArCH), 129.6 (2 × ArCH), 129.7 (2 × ArCH), 132.8 (2 × ArCH), 138.7 (2 × ArC).

Anal. calcd for C\(_{14}\)H\(_{12}\)Br\(_2\)O\(_2\): C (45.20 %), H (3.25 %), found C (45.22 %), H (3.61 %).

\((1R,2R)-1,2\text{-Di-o-tolylethane-1,2-diol} (303b)^{135}\)

As for general procedure J, AD-mix-\(\alpha\) (2.8 g), (E)-1,2-di-o-tolylethene (700 mg, 3.36 mmol, 1.0 eq), methanesulfonyl chloride (320 mg, 3.36 mmol, 1.0 eq) in H\(_2\)O (17 mL) and \(t\)-BuOH (17 mL) were stirred at room temperature overnight. After work-up, purification by column chromatography on silica gel, eluting with 5-20% ethyl acetate in petroleum ether (40-60 °C) followed by recrystallisation from CCl\(_4\) afforded (1S,2S)-1,2-di-o-tolylethane-1,2-diol 303b (488 mg, 2.0 mmol, 60%) as a white solid; mp 120-122 °C.

\([\alpha]_D^\circ = +65.5\) (c = 0.83; EtOH); literature value for (\(R,R\))-isomer \([\alpha]_D^\circ = +60.6\) (c = 0.83, EtOH).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 1.67 (6 H, s, 2 × CH\(_3\)), 4.98 (2 H, s, 2 × CH(OH)), 6.93 (2 H, d, \(J = 7.5\) Hz, 2 × ArCH), 7.13 (2 H, td, \(J = 7.5, 1.5\) Hz, 2 × ArCH), 7.22 (2 H, t, \(J = 7.7\) Hz, 2 × ArCH), 7.63 (2 H, dd, \(J = 7.7, 1.1\) Hz, 2 × ArCH).

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) ppm 18.7 (2 × CH\(_3\)), 74.6 (2 × CH(OH)), 125.9 (2 × ArCH), 127.1 (2 × ArCH), 127.7 (2 × ArCH), 130.2 (2 × ArCH), 135.9 (2 × ArC), 137.9 (2 × ArC).

Anal. calcd for C\(_{16}\)H\(_{16}\)O\(_2\): C (79.31%), H (7.49%), found C (78.95%), H (7.52%).
(1R,2R)-1,2-bis(2-Methoxyphenyl)ethane-1,2-diol (303c)

As for general procedure J, AD-mix-α (2.8 g), gave (E)-1,2-bis(2-methoxyphenyl)ethene (890 mg, 3.70 mmol, 1.0 eq), methanesulfonamide (352 mg, 3.70 mmol, 1.0 eq) in H₂O (19 mL) and t-BuOH (19 mL) were stirred at room temperature overnight. After work-up, purification by column chromatography on silica gel, eluting with 5-20% ethyl acetate in petroleum ether (40-60 °C) followed by recrystallisation from CCl₄ afforded (1S,2S)-1,2-bis(2-methoxyphenyl)ethane-1,2-diol 303c (752 mg, 2.7 mmol, 73%) as a white solid; mp 79-83 °C.

[α]D = +67.5 (c = 2.78; CHCl₃); literature value for (R,R)-isomer [α]D = +70.31 (c = 2.78; CHCl₃).

¹H NMR (500 MHz, CDCl₃) δ ppm 3.66 (6 H, s, 2 × CH₃), 5.04 (2 H, s, 2 × CH(OH)), 6.76 (2 H, d, J = 8.2 Hz, 2 × ArCH), 6.85 (2 H, td, J = 7.4, 0.9 Hz, 2 × ArCH), 7.15 - 7.21 (4 H, m, 4 × ArCH).

¹³C NMR (126 MHz, CDCl₃) δ ppm 55.2 (2 × CH₃), 74.5 (2 × CH(OH)), 110.2 (2 × ArCH), 120.4 (2 × ArCH), 128.2 (2 × ArCH), 128.4 (2 × ArCH), 128.5 (2 × ArC), 156.9 (2 × ArC).

Anal. calcd for C₁₆H₁₈O₄: C (70.06 %), H (6.61 %), found C (70.06 %), H (6.53 %).

(1R,2R)-1,2-bis(3,5-Difluorophenyl)ethane-1,2-diol (305a)

As for general procedure J, AD-mix-α (2.8 g), (E)-1,2-bis(3,5-difluorophenyl)ethene (700 mg, 3.3 mmol, 1.0 eq), methanesulfonamide (320 mg, 3.3 mmol, 1.0 eq) in H₂O (17 mL) and t-BuOH (17 mL) were stirred at room temperature overnight. After work-up,
purification by column chromatography on silica gel, eluting with 5-20% ethyl acetate in petroleum ether (40-60 °C) followed by recrystallisation from CCl₄ afforded (1R,2R)-1,2-bis(3,5-difluorophenyl)ethane-1,2-diol 305a (488 mg, 2.0 mmol, 60%) as a white solid; mp 112-114 °C. 

\([\alpha]_D = +62.4 \quad (c = 1.0; \text{CH}_2\text{Cl}_2); \text{literature value for } (R,R)-\text{isomer } [\alpha]_D = +64.5 \quad (c = 1.0; \text{CH}_2\text{Cl}_2).\]

\(^1\)H NMR (400 MHz, CDCl₃) δ ppm 2.92 (2 H, br s, 2 × OH), 4.64 (2 H, s, 2 × CH(OH)), 6.65 - 6.77 (6 H, m, 6 × ArCH).

\(^{13}\)C NMR (101 MHz, CDCl₃) δ ppm 77.8 (2 × CH(OH)), 103.7 (t, J = 25.8 Hz, 2 × ArCH), 109.5 - 110.0 (m, 4 × ArCH), 143.1 - 143.4 (m, 2 × ArC), 162.9 (dd, J = 249.2, 12.5 Hz, 4 × ArC).

(1R,2R)-1,2-bis(3,5-Dimethylphenyl)ethane-1,2-diol (305b)

As for general procedure J, AD-mix-α (2.8 g), (E)-1,2-bis(3,5-dimethylphenyl)ethene (700 mg, 3.3 mmol, 1.0 eq), methanesulfonamide (320 mg, 3.3 mmol, 1.0 eq) in H₂O (17 mL) and t-BuOH (17 mL) were stirred at room temperature overnight. After work-up, purification by column chromatography on silica gel, eluting with 5-20% ethyl acetate in petroleum ether (40-60 °C) followed by recrystallisation from CCl₄ afforded (1R,2R)-1,2-bis(3,5-dimethylphenyl)ethane-1,2-diol 305b (488 mg, 2.0 mmol, 60%) as a white solid; mp 111-117 °C. 

\([\alpha]_D = +66.3 \quad (c = 2.97; \text{CHCl}_3); \text{literature value for } (R,R)-\text{isomer } [\alpha]_D = +66.36 \quad (c = 2.97; \text{CHCl}_3).\]

\(^1\)H NMR (400 MHz, CDCl₃) δ ppm 2.28 (12 H, s, 4 × CH₃), 4.70 (2 H, s, 2 × CH(OH)), 6.85 (4 H, s, 4 × ArCH), 6.90 (2 H, s, 2 × ArCH).
\[ ^{13}C \text{ NMR (101 MHz, CDCl}_3) \delta \text{ ppm 21.3 (4 x CH}_3\text{), 78.4 (2 x CH(OH)), 124.4 (4 x ArCH), 129.4 (2 x ArCH), 137.7 (4 x ArC), 140.1 (2 x ArC).} \]

6.4.12 Deuteration experiments

3-Hydroxy-2-methyl-2-phenylpropanoic-3,3-d\(_2\) acid

As for general procedure E, reaction of 2,2,5-trimethyl-5-phenyl-1,3-dioxane-4,6-dione (23.5 mg, 0.10 mmol, 1.0 eq) in THF (1.5 mL) with SmI\(_2\) (0.1 M in THF, 8.00 mL, 0.80 mmol, 8.0 eq) and D\(_2\)O (2.00 mL, 100 mmol, 1000 eq). After work-up, purification by column chromatography on silica gel, eluting with 20% ethyl acetate in petroleum ether (40-60 °C) and 0.1% acetic acid gave 3-hydroxy-2-methyl-2-phenylpropanoic-3,3-d\(_2\) acid (15.4 mg, 84.5 μmol, 84%) as a white solid.

\[ ^1H \text{ NMR (400 MHz, Acetone-d}_6) \delta \text{ ppm 1.59 (3 H, s, CH}_3\text{), 7.21 - 7.27 (1 H, m, ArCH), 7.29 - 7.36 (2 H, m, 2 x ArCH), 7.38 - 7.43 (2 H, m, 2 x ArCH).} \]

\[ ^{13}C \text{ NMR (101 MHz, Acetone-d}_6) \delta \text{ ppm 21.2 (CH}_3\text{), 53.0 (C}_q\text{), 127.3 (2 x ArCH), 127.6 (ArCH), 129.2 (2 x ArCH), 143.1 (ArC), 176.8 (COOH).} \]

3-Hydroxy-2-phenylpropanoic-2,3,3-d\(_3\) acid

As for general procedure E, reaction of 2,2-dimethyl-5-phenyl-1,3-dioxane-4,6-dione (22.0 mg, 0.10 mmol, 1.0 eq) in THF (1.5 mL) with SmI\(_2\) (0.1 M in THF, 8.00 mL, 0.80 mmol, 8.0 eq) and D\(_2\)O (2.00 mL, 100 mmol, 1000 eq). After work-up, purification by column chromatography on silica gel, eluting with 20% ethyl acetate in petroleum ether (40-60 °C) and 0.1% acetic acid gave 3-hydroxy-2-phenylpropanoic-2,3,3-d\(_3\) acid (12.9 mg, 76.7 μmol, 77%) as a colourless oil.
$^1$H NMR (400 MHz, Acetone-$d^6$) δ ppm 7.23 - 7.29 (1 H, m, ArCH), 7.30 - 7.40 (4 H, m, 4 × ArCH).

$^{13}$C NMR (100 MHz, CD$_3$OD) δ ppm 55.9 (CD), 65.1 (CD$_2$), 128.5 (ArCH), 129.2 (2 × ArCH), 129.7 (2 × ArCH), 137.9 (ArC), 176.1 (COOH).

2-(Hydroxymethyl-$d_2$)-4-methylpentanoic-2-$d$ acid

As for general procedure E, reaction of 5-isobutyl-2,2-dimethyl-1,3-dioxane-4,6-dione (20.0 mg, 0.10 mmol, 1.0 eq) in THF (1.5 mL) with SmI$_2$ (0.1 M in THF, 8.00 mL, 0.80 mmol, 8.0 eq) and D$_2$O (2.00 mL, 100 mmol, 1000 eq). After work-up, purification by column chromatography on silica gel, eluting with 20% ethyl acetate in petroleum ether (40-60 °C) and 0.1% acetic acid gave 2-(hydroxymethyl-$d_2$)-4-methylpentanoic-2-$d$ acid (12.8 mg, 86.4 μmol, 87%) as a colourless oil.

$^1$H NMR (400 MHz, Acetone-$d^6$) δ ppm 0.90 (6 H, t, $J = 6.3$ Hz, CH(CH$_3$)$_2$), 1.30 (1 H, dd, $J = 13.6$, 8.3 Hz, CH(CH$_3$)$_2$), 1.44 - 1.53 (1 H, m, CHCD$_2$OH), 1.63 (1 H, dq, $J = 8.2$, 6.4 Hz, CH$_2$).

$^{13}$C NMR (101 MHz, Acetone-$d^6$) δ ppm 22.5 (CHCH$_3$), 23.4 (CHCH$_3$), 26.9 (CH(CH$_3$)$_2$), 38.5 (CH$_2$), 180.8 (COOH).
6.5 Experimental for Chapter 3

6.5.1 General procedure K: Synthesis of homoallyl bromides

\((E)-(4\text{-Bromobut-1-en-1-yl})\text{benzene (358a)}\)^{109}

To a 3-neck oven dried flask fitted with a reflux condenser was added Mg turnings (0.18 g, 7.51 mmol, 1.0 eq) in THF (8 mL). To this stirred suspension was added cyclopropyl bromide (0.7 mL, 8.26 mmol, 1.1 eq) dropwise whilst warming to 30 °C. Upon refluxing, heating was stopped and the remaining cyclopropyl bromide was added. The reaction was then heated at 65 °C for 1 h and subsequently allowed to cool to room temperature before cooling to 0 °C. Benzaldehyde (1.27 mL, 8.26 mmol, 1.0 eq) was then added dropwise and the solution stirred for 15 min with subsequent addition of acetyl bromide (0.61 mL, 8.26 mmol, 1.1 eq). The reaction was heated to 65 °C for 1 h and then allowed to cool to room temperature. The reaction mixture was quenched by the addition of NH₄Cl and the aqueous layer was extracted with EtOAc (2 × 25 mL). The combined organic layers were dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography on silica gel eluting with petroleum ether (40-60 °C) gave \((E)-(4\text{-bromobut-1-en-1-yl})\text{benzene 358a}\) (0.49 mg, 2.34 mmol, 31%) as a yellow oil.

^1\text{H} NMR (400 MHz, CDCl₃) δ ppm 2.81 (2 H, qd, \(J = 7.0, 1.4\) Hz, \(\text{CH}_2\)), 3.51 (2 H, t, \(J = 7.0\) Hz, \(\text{CH}_2\text{Br}\)), 6.22 (1 H, dt, \(J = 15.8, 7.0\) Hz, \(\text{CH}=\text{CHAr}\)), 6.52 (1 H, d, \(J = 15.8\) Hz, \(\text{CH}=\text{CHAr}\)), 7.23 - 7.28 (1 H, m, ArCH), 7.31 - 7.37 (2 H, m, 2 × ArCH), 7.38 - 7.42 (2 H, m, 2 × ArCH).

^13\text{C} NMR (75 MHz, CDCl₃) δ ppm 32.2 (CH₂), 36.3 (CH₂Br), 126.2 (2 × ArCH), 126.6 (CH=CHAr), 127.4 (CH=CHAr), 128.6 (2 × ArCH), 132.7 (ArCH), 137.0 (ArC).
(E)-1-Bromo-4-(4-bromobut-1-en-1-yl)benzene (358b)

As for general procedure K, cyclopropylmagnesium bromide was prepared by the addition of cyclopropyl bromide (1.32 mL, 16.5 mmol, 1.1 eq) to a suspension of Mg turnings (0.37 g, 15.0 mmol, 1.0 eq) in THF (15 mL) and to this was added 4-bromobenzaldehyde (3.06 g, 16.5 mmol, 1.1 eq) followed by acetyl bromide (1.22 mL, 16.5 mmol, 1.1 eq). After workup, purification by flash column chromatography on silica gel eluting with 100% petroleum ether (40 – 60 °C) gave (E)-1-bromo-4-(4-bromobut-1-en-1-yl)benzene 358b (986 mg, 3.42 mmol, 18%) as a yellow oil.

\[ \text{1H NMR (300 MHz, CDCl}_3\text{) } \delta \text{ ppm 2.78 (2 H, qd, } J = 7.0, 1.2 \text{ Hz, } \text{CH}_2\text{), 3.48 (2 H, t, } J = 7.0 \text{ Hz, } \text{CH}_2\text{Br), 6.19 (1 H, dt, } J = 15.8, 7.0 \text{ Hz, } \text{CH}=\text{CHAr), 6.36 - 6.50 (1 H, m, } \text{CH}=\text{CHAr), 7.17 - 7.29 (2 H, m, 2 } \times \text{ ArCH), 7.36 - 7.49 (2 H, m, 2 } \times \text{ ArCH).} \]

\[ \text{13C NMR (101 MHz, CDCl}_3\text{) } \delta \text{ ppm 32.1 (CH}_2\text{), 36.2 (CH}_2\text{Br), 121.2 (ArC), 127.6 (CH}=\text{CHAr), 127.7 (2 } \times \text{ ArCH), 131.6 (CH}=\text{CHAr), 131.7 (2 } \times \text{ ArCH), 136.0 (ArC).} \]

(E)-1-(4-Bromobut-1-en-1-yl)-3,5-dimethoxybenzene (358c)

As for general procedure K, cyclopropylmagnesium bromide was prepared by the addition of cyclopropyl bromide (2.00 mL, 24.8 mmol, 1.1 eq) to a suspension of Mg turnings (0.55 g, 22.5 mmol, 1.0 eq) in THF (15 mL) and to this was added 3,5-dimethoxybenzaldehyde (4.12 g, 24.8 mmol, 1.1 eq) followed by acetyl bromide (1.83 mL, 24.8 mmol, 1.1 eq). After workup, purification by flash column chromatography on silica gel eluting with 100% petroleum ether (40 – 60 °C) gave (E)-1-(4-bromobut-1-en-1-yl)-3,5-dimethoxybenzene 358c (2.77 g, 10.2 mmol, 45%) as a yellow oil.

\[ \text{1H NMR (400 MHz, CDCl}_3\text{) } \delta \text{ ppm 2.68 (2 H, qd, } J = 7.0, 1.3 \text{ Hz, } \text{CH}_2\text{), 3.39 (2 H, t, } J = 7.0 \text{ Hz, } \text{CH}_2\text{Br), 3.74 (6 H, m, 2 } \times \text{ OCH}_3\text{), 5.99 (1 H, dt, } J = 15.9, 7.0 \text{ Hz, } \text{CH}=\text{CHAr),} \]
6.33 - 6.42 (2 H, m, 2 × ArCH), 6.63 (1 H, d, J = 15.9 Hz, CH=CHAr), 7.26 (1 H, d, J = 8.3 Hz, ArCH).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ ppm 32.7(CH$_2$), 36.8 (CH$_2$Br), 55.4 (2 × OCH$_3$), 98.5 (ArCH), 104.7 (ArCH), 119.1 (ArC), 125.0 (CH=CHAr), 127.0 (CH=CHAr), 127.3 (ArCH), 157.5 (ArC), 160.2 (ArC).

6.5.2 General procedure L: Sonagashira coupling

4-Phenylbut-3-yn-1-ol (366a)$^{141}$

To a solution of but-3-yn-1-ol (1.00 mL, 13.2 mmol, 1.0 eq) in THF (30 mL) was added iodobenzene (2.95 mL, 26.4 mmol, 2.0 eq) diisopropylamine (11 mL) and Pd(PPh$_3$)$_4$ (305 mg, 0.26 mmol, 2 mol%). The reaction was stirred for 20 mins, before adding CuI (25.6 mg, 0.13 mmol, 1 mol%) and heating at reflux overnight. After cooling to room temperature, the reaction mixture was filtered through celite® and concentrated in vacuo. Purification by column chromatography on silica gel, eluting with 0-20% ethyl acetate in petroleum ether (40-60 °C) gave 4-phenylbut-3-yn-1-ol 366a (1.83 g, 12.5 mmol, 95%) as a colourless oil.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 2.71 (2 H, t, J = 6.3 Hz, CH$_2$C≡C), 3.82 (2 H, t, J = 6.3 Hz, CH$_2$OH), 7.28 - 7.34 (3 H, m, 3 × ArCH), 7.39-7.46 (2 H, m, 2 × ArCH).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 23.8 (CH$_2$C≡C), 61.2 (CH$_2$OH), 82.5 (C≡CAr), 86.4 (C≡CAr), 123.3 (ArC), 128.0 (ArCH), 128.3 (2 × ArCH), 131.7 (2 × ArCH).
5-Phenylpent-4-yn-1-ol (366b)

As for general procedure L, pent-4-yn-1-ol (1.00 mL, 10.6 mmol, 1.0 eq) with iodobenzene (2.37 mL, 21.2 mmol, 2.0 eq), Pd(PPh3)4 (250 mg, 0.21 mmol, 2 mol%) and CuI (20.0 mg, 0.11 mmol, 1 mol%) in diisopropylamine (10 mL) and THF (25 mL) were heated at reflux overnight. After work-up, purification by flash column chromatography on silica gel eluting with 0-20% ethyl acetate in petroleum ether (40-60 °C) gave 5-phenylpent-4-yn-1-ol 366b (1.47 g, 9.14 mmol, 86%) as colourless oil.

1H NMR (400 MHz, CDCl3) δ ppm 1.82 - 1.91 (2 H, m, CH2CH2C≡C), 2.54 (2 H, t, J = 6.9 Hz, CH2C≡C), 3.81 (2 H, t, J = 6.2 Hz, CH2OH), 7.26 - 7.30 (3 H, m, 3 × ArCH), 7.37 - 7.42 (2 H, m, 2 × ArCH).

13C NMR (100 MHz, CDCl3) δ ppm 15.9 (CH2C≡C), 31.3 (CH2CH2C≡C), 61.7 (CH2OH), 81.1 (C≡CAr), 89.3 (C≡CAr), 123.6 (ArC), 127.6 (ArCH), 128.2 (2 × ArCH), 131.5 (2 × ArCH).

6-Phenylhex-5-yn-1-ol (366c)

As for general procedure L, hex-5-yn-1-ol (1.00 mL, 9.07 mmol, 1.0 eq) with iodobenzene (2.02 mL, 18.1 mmol, 2.0 eq), Pd(PPh3)4 (210 mg, 0.18 mmol, 2 mol%) and CuI (17 mg, 90.0 μmol, 1 mol%) in diisopropylamine (8.0 mL) and THF (20 mL) were heated at reflux overnight. After work-up, purification by flash column chromatography on silica gel eluting with 0-20% ethyl acetate in petroleum ether (40-60 °C) gave 6-phenylhex-5-yn-1-ol 366c (1.2 g, 6.89 mmol, 76%) as a colourless oil.

1H NMR (400 MHz, CDCl3) δ ppm 1.66 - 1.81 (4 H, m, 2 × CH2), 1.83 (1 H, br s, OH), 2.47 (2 H, t, J = 6.7 Hz, CH2C≡C), 3.82 (2 H, t, J = 6.3 Hz, CH2OH), 7.26 - 7.36 (3 H, m, 3 × ArCH), 7.38 - 7.45 (2 H, m, 2 × ArCH).
$^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm 19.2 (CH$_2$C≡C), 25.0 (CH$_2$CH$_2$C≡C), 31.9 (CH$_2$CH$_2$CH$_2$C≡C), 62.4 (CH$_2$OH), 81.0 (C≡CAr), 89.9 (C≡CAr), 123.9 (ArC), 127.6 (ArCH), 128.2 (2 × ArCH), 131.5 (2 × ArCH).

6.5.3 General procedure M: Appel reaction

(4-Bromobut-1-yn-1-yl)benzene (367a)$^{144}$

\[
\text{\includegraphics[width=0.2\textwidth]{bromobutynylbenzene.png}}
\]

To a stirred solution of 4-phenylbut-3-yn-1-ol 366a (400 mg, 2.74 mmol, 1.0 eq) in Et$_2$O (6.0 mL) at –78 °C was added CBr$_4$ (1.36 g, 4.11 mmol, 1.5 eq) followed by aliquot addition of PPh$_3$ (1.17 g, 4.45 mmol, 1.6 eq), stirring until the reaction was complete by TLC. The reaction mixture was filtered and the solvent removed in vacuo. Purification by column chromatography on silica gel, eluting with 0-10% ethyl acetate in petroleum ether (40-60 °C) gave (4-bromobut-1-yn-1-yl)benzene 367a (433 mg, 2.07 mmol, 76%) as a yellow oil.

$^1$H NMR (400 MHz, CDCl$_3$) δ ppm 3.00 (2 H, t, $J = 7.3$ Hz, CH$_2$C≡C), 3.54 (2 H, t, $J = 7.3$ Hz, CH$_2$Br), 7.29 - 7.38 (4 H, m, 4 × ArCH), 7.41 - 7.47 (1 H, m, ArCH).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ ppm 23.8 (CH$_2$C≡C), 29.5 (CH$_2$Br), 82.4 (C≡CAr), 86.5 (C≡CAr), 123.0 (ArC), 128.1 (ArCH), 128.2 (2 × ArCH), 131.6 (2 × ArCH).

(5-Bromopent-1-yn-1-yl)benzene (367b)$^{145}$

\[
\text{\includegraphics[width=0.2\textwidth]{bromopentynylbenzene.png}}
\]

As for general procedure M, 5-phenylpent-4-yn-1-ol 366b (500 mg, 3.12 mmol, 1.0 eq) with CBr$_4$ (1.24 g, 3.75 mmol, 1.2 eq) and PPh$_3$ (1.06 g, 4.06 mmol, 1.3 eq) in Et$_2$O (6.0 mL) were stirred at room temperature for 2 h. After work-up, purification by column chromatography on silica gel eluting with 0-10% ethyl acetate in petroleum ether (40-60 °C) gave (5-bromopent-1-yn-1-yl)benzene 367b (546 mg, 2.45 mmol, 78%) as a yellow oil.
$^1$H NMR (400 MHz, CDCl$_3$) δ ppm 2.15 (2 H, quint, $J = 6.6$ Hz, CH$_2$CH$_2$C≡C), 2.62 (2 H, t, $J = 6.6$ Hz, CH$_2$C≡C), 3.60 (2 H, t, $J = 6.6$ Hz, CH$_2$Br), 7.28 - 7.32 (3 H, m, 3 × ArCH), 7.38 - 7.43 (2 H, m, 2 × ArCH).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm 18.1 (C≡C), 31.5 (CH$_2$CH$_2$C≡C), 32.5 (CH$_2$Br), 81.6 (C≡C), 87.9 (C≡C), 123.5 (ArC), 127.8 (ArCH), 128.2 (2 × ArCH), 131.6 (2 × ArCH).

(6-Bromohex-1-yn-1-yl)benzene (367c)$^{145}$

As for general procedure M, 6-phenylhex-5-yn-1-ol 366c (600 mg, 3.44 mmol, 1.0 eq) with CBr$_4$ (1.37 g, 4.13 mmol, 1.2 eq) and PPh$_3$ (1.17 g, 4.48 mmol, 1.3 eq) in Et$_2$O (9.0 mL) were stirred at room temperature for 2 h. After work-up, purification by column chromatography on silica gel eluting with 0-10% ethyl acetate in petroleum ether (40-60 °C) gave (6-bromohex-1-yn-1-yl)benzene 367c (615 mg, 2.59 mmol, 76%) as a yellow oil.

$^1$H NMR (400 MHz, CDCl$_3$) δ ppm 1.79 (2 H, quint, $J = 7.0$ Hz, CH$_2$CH$_2$C≡C), 2.08 (2 H, quint, $J = 7.0$ Hz, CH$_2$CH$_2$CH$_2$C≡C), 2.49 (2 H, t, $J = 7.0$ Hz, CH$_2$C≡C), 3.50 (2 H, t, $J = 7.0$ Hz, CH$_2$Br), 7.20 - 7.60 (5 H, m, 5 × ArCH).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ ppm 18.6 (CH$_2$C≡C), 27.1 (CH$_2$CH$_2$C≡C), 31.8 (CH$_2$CH$_2$CH$_2$C≡C), 33.2 (CH$_2$Br), 81.3 (C≡C), 89.2 (C≡C), 123.8 (ArC), 127.6 (ArCH), 128.2 (2 × ArCH), 131.5 (2 × ArCH).
6.5.4 General procedure N: Alkylations of diethyl malonate

\((E)\)-Diethyl 2-(4-phenylbut-3-en-1-yl)malonate (359a)\(^{146}\)

To a stirred suspension of sodium hydride (60% in oil, 290 mg, 7.32 mmol, 1.0 eq) in THF (20 mL) at 0 °C was added dropwise diethyl malonate (1.11 mL, 7.32 mmol, 1.0 eq) and the solution stirred at room temperature for 30 min. (E)-(4-bromobut-1-en-1-yl)benzene 358a (1.70 g, 8.50 mmol, 1.1 eq) was added dropwise and the solution heated at reflux for 16 h. The reaction was quenched with H\(_2\)O (10 mL) and the aqueous phase extracted with ethyl acetate (3 x 20 mL). The combined organic phases were dried (Na\(_2\)SO\(_4\)) and concentrated in vacuo. Purification by column chromatography on silica gel, eluting with 0-5% ethyl acetate in petroleum ether (40-60 °C) gave (E)-diethyl 2-(4-phenylbut-3-en-1-yl)malonate 359a (1.46 g, 1.60 mmol, 62%) as a colourless oil.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 1.27 (6 H, t, \(J = 7.2\) Hz, 2 x OCH\(_2\)CH\(_3\)), 2.10 (2 H, q, \(J = 7.4\) Hz, CHCH\(_2\)), 2.24 - 2.32 (2 H, m, CH\(_2\)CH=CH), 3.41 (1 H, t, \(J = 7.4\) Hz, CHCH\(_2\)), 4.20 (4 H, q, \(J = 7.2\) Hz, 2 x OCH\(_2\)CH\(_3\)), 6.17 (1 H, dt, \(J = 15.8, 7.0\) Hz, CH=CHAr), 6.41 (1 H, d, \(J = 15.8\) Hz, CH=CHAr), 7.18 - 7.24 (1 H, m, ArCH), 7.28 - 7.37 (4 H, m, 4 x ArCH).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) ppm 14.1 (2 x OCH\(_2\)CH\(_3\)), 28.3 (CHCH\(_2\)), 30.6 (CH\(_2\)CH=CH), 51.2 (CHCH\(_2\)), 61.4 (2 x OCH\(_2\)CH\(_3\)), 126.0 (2 x ArCH), 127.1 (ArCH), 128.5 (2 x ArCH), 128.6 (CH=CHAr), 131.3 (CH=CHAr), 137.3 (ArC), 169.4 (2 x CO\(_2\)Et).
(E)-Diethyl 2-(4-(4-methoxyphenyl)but-3-en-1-yl)malonate (359b)

As for general procedure N, reaction of sodium hydride (60% in oil, 370 mg, 9.37 mmol, 1.0 eq) and diethyl malonate (1.50 g, 9.37 mmol, 1.0 eq) in THF (15 mL) with sodium iodide (0.55 mg, 3.68 mmol, 0.5 eq) and (E)-1-(4-bromobut-1-en-1-yl)-4-methoxybenzene 358b (2.48 g, 10.3 mmol, 1.1 eq) overnight at reflux. After work-up, purification by column chromatography on silica gel, eluting with 5% ethyl acetate in petroleum ether (40-60 °C) gave (E)-diethyl 2-(4-(4-methoxyphenyl)but-3-en-1-yl)malonate 359b (2.49 g, 7.78 mmol, 83%) as a colourless oil.

$\nu_{\text{max}}$ (neat)/cm$^{-1}$ 2980, 1730 (C=O), 1610, 1510.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 1.27 (3 H, t, $J = 7.2$ Hz, $2 \times$ OCH$_2$CH$_3$), 2.08 (2 H, q, $J = 7.3$ Hz, CHCH$_2$), 2.25 (2 H, q, $J = 7.3$ Hz, CH$_2$CH$_2$), 3.40 (1 H, t, $J = 7.3$ Hz, CHCH$_2$), 3.81 (3 H, s, OCH$_3$), 4.20 (2 H, q, $J = 7.4$ Hz, $2 \times$ OCH$_2$CH$_3$), 6.02 (1 H, dt, $J = 15.9, 7.3$ Hz, $CH=CH$Ar), 6.35 (1 H, d, $J = 15.9$ Hz, CH=CHAr), 6.84 (2 H, d, $J = 8.7$ Hz, $2 \times$ ArCH), 7.27 (2 H, d, $J = 8.7$ Hz, $2 \times$ ArCH).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 14.1 (2 $\times$ OCH$_2$CH$_3$), 28.4 (CHCH$_2$), 30.6 (CH$_2$CH$_2$), 51.3 (CH), 55.3 (OCH$_3$), 61.4 (OCH$_2$CH$_3$), 113.9 (2 $\times$ ArCH), 126.4 (CH=CHAr), 127.1 (2 $\times$ ArCH), 130.2 (CH=CHAr), 130.7 (ArC), 158.9 (ArCOCH$_3$), 169.5 (CO$_2$Et).

$m/z$ (ES+) 343 [M+Na]; HRMS calcd for C$_{18}$H$_{20}$O$_5$Na: 343.1516; found: 343.1509.
(E)-Diethyl 2-(but-3-en-1-yl)-2-(4-(4-methoxyphenyl)but-3-en-1-yl)malonate (360b)

As for general procedure N, reaction of sodium hydride (60% in oil, 125 mg, 3.12 mmol, 1.0 eq) and 2-(4-(4-methoxyphenyl)but-3-en-1-yl)malonate 359b (1.0 g, 3.12 mmol, 1.0 eq) in THF (15 mL) with sodium iodide (468 mg, 3.12 mmol, 1.0 eq) and 4-bromobut-1-ene (464 mg, 3.43 mmol, 1.1 eq) overnight at reflux. After work-up, purification by column chromatography on silica gel, eluting with 5% ethyl acetate in petroleum ether (40-60 °C) gave (E)-diethyl 2-(but-3-en-1-yl)-2-(4-(4-methoxyphenyl)but-3-en-1-yl)malonate 360b (0.77 g, 2.07 mmol, 66%) as a colourless oil.

$\nu_{\text{max}}$(neat)/cm$^{-1}$ 2981, 2838, 1728 (C=O), 1607.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 1.26 (3H, t, $J = 6.9$ Hz, OCH$_2$CH$_3$), 1.94 - 2.15 (8 H, m, 4 × CH$_2$), 3.81, (3 H, s, OCH$_3$), 4.20 (4 H, q, $J = 6.9$ Hz, OCH$_2$CH$_3$), 4.95 - 5.08 (2 H, m, CH=CH$_2$), 5.76 - 5.86 (1 H, m, CH=CH$_2$), 6.00 - 6.08 (1 H, m, CH=CHAr), 6.26 (1 H, d, $J = 15.8$ Hz, CH=CHAr), 6.76 (2 H, d, $J = 8.5$ Hz, 2 × ArCH), 7.19 (2 H, d, $J = 8.5$ Hz, 2 × ArCH).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 14.1 (2 × OCH$_2$CH$_3$), 27.6 (C$_q$CH$_2$), 28.4 (C$_q$CH$_2$), 31.6 (CH=CH$_2$), 32.1 (CH=CH$_2$), 55.3 (OCH$_3$), 57.0 (C$_q$), 61.2 (2 × OCH$_2$CH$_3$), 113.9 (2 × ArCH), 115.1 (CH=CH$_2$), 127.0 (2 × ArCH), 127.2 (CH=CHAr), 129.8 (CH=CH$_2$), 130.3 (ArC), 137.6 (CH=CHAr), 158.8 (ArCOCH$_3$), 171.5 (2 × CO$_2$Et).
Diethyl 2-((E)-4-(4-methoxyphenyl)but-3-en-1-yl)-2-((E)-4-phenylbut-3-en-1-yl) malonate (360a)

As for general procedure N, reaction of sodium hydride (60% in oil, 245 mg, 6.12 mmol, 1.0 eq) and (E)-diethyl 2-(4-phenylbut-3-en-1-yl)malonate 359a (1.77 g, 6.12 mmol, 1.0 eq) in THF (15 mL) with sodium iodide (917 mg, 6.12 mmol, 1.0 eq) and (E)-1-(4-bromobut-1-en-1-yl)-4-methoxybenzene (1.62 g, 6.73 mmol, 1.1 eq) overnight at reflux. After work-up, purification by column chromatography on silica gel, eluting with 5% ethyl acetate in petroleum ether (40-60 °C) gave diethyl 2-((E)-4-(4-methoxyphenyl)but-3-en-1-yl)-2-((E)-4-phenylbut-3-en-1-yl)malonate 360a (1.26 g, 2.80 mmol, 46%) as a colourless oil.

ν_max (neat)/cm⁻¹ 2978, 1725 (C=O), 1606, 1510.

¹H NMR (500MHz, CDCl₃) δ ppm 1.18 (6 H, t, J = 7.2 Hz, OCH₂CH₃), 2.05 (8 H, m, 4 × CH₂), 3.73 (3 H, s, OCH₃), 4.12 (4 H, d, J = 7.2 Hz, 2 × OCH₂CH₃), 5.93 - 6.00 (1 H, m, CH=CHAr), 6.07 - 6.15 (1 H, m, CH=CHAr), 6.23 - 6.36 (2 H, m, 2 × CH=CHAr), 6.76 (2 H, d, J = 8.8 Hz, 2 × ArCH), 7.10 - 7.15 (1 H, m, ArCH), 7.15 - 7.27 (6 H, m, 6 × ArCH).

¹³C NMR (75 MHz, CDCl₃) δ ppm 14.2 (2 × OCH₂CH₃), 27.7 (2 × CH₂CH₂), 32.2 (2 × CH₂CH₂), 55.3 (OCH₃), 57.1 (C₉), 61.3 (2 × OCH₂CH₂), 114.0 (2 × ArCH), 125.6 (2 × ArCH), 127.1 (2 × ArCH), 127.2 (CH=CHAr + ArCH), 128.5 (2 × ArCH), 129.4 (CH=CHAr), 130.4 (CH=CHAr), 130.5 (CH=CHAr), 137.5 (2 × ArC), 158.8 (ArOCH₃), 171.5 (CO₂Et).

m/z (ES⁺) 451 [M+H]; HRMS calcd for C₂₈H₃₄O₅Na: 473.2299; found: 473.22992.
Diethyl 2-(but-3-en-1-yl)malonate (355)

As for general procedure N, reaction of sodium hydride (60% in oil, 1.4 g, 35.0 mmol, 1.0 eq) and diethyl malonate (5.65 g, 5.31 mL, 35.0 mmol, 1.0 eq) in THF (50 mL) with sodium iodide (2.62 g, 17.5 mmol, 0.5 eq) and 4-bromobut-1-ene (5.20 g, 3.91 mL, 38.5 mmol, 1.1 eq) overnight at reflux. After work-up, purification by column chromatography on silica gel, eluting with 5% ethyl acetate in petroleum ether (40-60 °C) gave diethyl 2-(but-3-en-1-yl)malonate 355 (5.06 g, 23.6 mmol, 67%) as a colourless oil.

$^1$H NMR (400 MHz, CDCl$_3$) δ ppm 1.26 (6 H, t, $J = 7.1$ Hz, 2 × OCH$_2$CH$_3$), 1.94 - 2.05 (2 H, m, CHCH$_2$), 2.05 - 2.14 (2 H, m, CH$_2$CH=CH$_2$), 3.34 (1 H, t, $J = 7.3$ Hz, CHCH$_2$), 4.19 (4 H, q, $J = 7.1$ Hz, 2 × OCH$_2$CH$_3$), 4.97 - 5.08 (2 H, m, CH=CH$_2$), 5.69 - 5.84 (1 H, m, CH=CH$_2$).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm 14.0 (2 × OCH$_2$CH$_3$), 27.8 (CHCH$_2$), 31.2 (CH$_2$C=CH), 51.1 (CHCH$_2$), 61.3 (2 × OCH$_2$CH$_3$), 115.9 (CH=CH$_2$), 136.8 (CH=CH$_2$), 169.4 (2 × CO$_2$Et).

Diethyl 2-(but-3-yn-1-yl)malonate

As for general procedure N, reaction of sodium hydride (60% in oil, 0.50 g, 12.5 mmol, 1.0 eq) and diethyl malonate (1.90 mL, 12.5 mmol, 1.0 eq) in THF (10 mL) with sodium iodide (0.94 g, 6.27 mmol, 0.5 eq) and 4-bromobut-1-yn-1-ene (1.29 mL, 13.8 mmol, 1.1 eq) overnight at reflux. After work-up, purification by column chromatography on silica gel, eluting with 5% ethyl acetate in petroleum ether (40-60 °C) gave diethyl 2-(but-3-yn-1-yl)malonate (1.73 g, 8.15 mmol, 65%) as a colourless oil.
\[ ^1H \text{ NMR (400 MHz, CDCl}_3) \delta \text{ ppm} 1.28 (6 \text{ H, t, } J = 7.1 \text{ Hz}, 2 \times \text{OCH}_2\text{CH}_3), 2.01 (1 \text{ H, t, } J = 2.6 \text{ Hz}, \text{CH}_2\text{C≡CH}), 2.13 (2 \text{ H, q, } J = 7.4 \text{ Hz}, \text{CHCH}_2), 2.28 - 2.34 (2 \text{ H, m, CH}_2\text{C≡CH}), 3.58 (1 \text{ H, t, } J = 7.4 \text{ Hz}, \text{CHCH}_2), 4.22 (4 \text{ H, q, } J = 7.1 \text{ Hz}, 2 \times \text{OCH}_2\text{CH}_3). \]

\[ ^{13}C \text{ NMR (100 MHz, CDCl}_3) \delta \text{ ppm} 14.0 (2 \times \text{OCH}_2\text{CH}_3), 16.4 (\text{CH}_2\text{C≡CH}), 27.3 (\text{CHCH}_2), 50.5 (\text{CHCH}_2), 61.5 (2 \times \text{OCH}_2\text{CH}_3), 69.6 (\text{CH}_2\text{C≡CH}), 82.4 (\text{CH}_2\text{C≡CH}), 169.0 (2 \times \text{CO}_2\text{Et}). \]

**Diethyl 2-(4-phenylbut-3-yn-1-yl)malonate**

![Diethyl 2-(4-phenylbut-3-yn-1-yl)malonate](image)

As for general procedure N, reaction of sodium hydride (60% in oil, 0.30 g, 7.39 mmol, 1.0 eq) and diethyl malonate (1.12 mL, 7.39 mmol, 1.0 eq) in THF (20 mL) with sodium iodide (0.55 mg, 3.68 mmol, 0.5 eq) and (4-bromobut-1-yn-1-yl)benzene (1.70 g, 8.13 mmol, 1.1 eq) overnight at reflux. After work-up, purification by column chromatography on silica gel, eluting with 5% ethyl acetate in petroleum ether (40-60 °C) gave diethyl 2-(4-phenylbut-3-yn-1-yl)malonate (1.10 g, 3.47 mmol, 52%) as a colourless oil.

\[ ^1H \text{ NMR (400 MHz, CDCl}_3) \delta \text{ ppm} 1.20 (6 \text{ H, t, } J = 7.1 \text{ Hz}, 2 \times \text{OCH}_2\text{CH}_3), 2.13 (2 \text{ H, q, } J = 7.2 \text{ Hz}, \text{CHCH}_2), 2.45 (2 \text{ H, t, } J = 6.9 \text{ Hz}, \text{CH}_2\text{C≡C}), 3.55 (1 \text{ H, t, } J = 7.2 \text{ Hz}, \text{CHCH}_2), 4.14 (4 \text{ H, q, } J = 7.2 \text{ Hz}, 2 \times \text{OCH}_2\text{CH}_3), 7.18 - 7.23 (3 \text{ H, m, 3 × ArCH}), 7.30 - 7.35 (2 \text{ H, m, 2 × ArCH}). \]

\[ ^{13}C \text{ NMR (100 MHz, CDCl}_3) \delta \text{ ppm} 14.0 (2 \times \text{OCH}_2\text{CH}_3), 17.4 (\text{CH}_2\text{C≡C}), 27.6 (\text{CHCH}_2), 50.8 (\text{CHCH}_2), 61.5 (2 \times \text{OCH}_2\text{CH}_3), 81.8 (\text{C≡CAr}), 87.9 (\text{C≡CAr}), 123.5 (\text{ArC}), 127.8 (\text{ArCH}), 128.2 (2 \times \text{ArCH}), 131.6 (2 \times \text{ArCH}), 169.1 (2 \times \text{CO}_2\text{Et}). \]
Diethyl 2-(5-phenylpent-4-yn-1-yl)malonate

As for general procedure N, reaction of sodium hydride (60% in oil, 0.31 g, 7.83 mmol, 1.0 eq) and diethyl malonate (1.20 mL, 7.90 mmol, 1.0 eq) in THF (11 mL) with sodium iodide (0.58 mg, 3.88 mmol, 0.5 eq) and (5-bromopent-1-yn-1-yl)benzene (2.41 g, 8.53 mmol, 1.1 eq) overnight at reflux. After work-up, purification by column chromatography on silica gel, eluting with 5% ethyl acetate in petroleum ether (40-60 °C) gave diethyl 2-(5-phenylpent-4-yn-1-yl)malonate (2.11 g, 7.00 mmol, 89%) as a colourless oil.

$v_{\text{max}}$ (neat)/cm$^{-1}$ 2981, 1728 (C=O), 1599.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 1.27 (6 H, t, $J = 7.2$ Hz, 2 × OCH$_2$CH$_3$), 1.61 - 1.71 (2 H, m, CHCH$_2$CH$_3$), 2.04 - 2.12 (2 H, m, CHCH$_2$), 2.46 (2 H, t, $J = 7.1$ Hz, CH$_2$C≡C), 3.40 (1 H, t, $J = 7.6$ Hz, CH), 4.21 (4 H, q, $J = 7.2$ Hz, 2 × OCH$_2$CH$_3$), 7.24 - 7.30 (3 H, m, 3 × ArCH), 7.36 - 7.42 (2 H, m, 2 × ArCH).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 14.0 (2 × OCH$_2$CH$_3$), 19.0 (CH$_2$C≡C), 26.3 (CHCH$_2$), 27.9 (CHCH$_2$CH$_2$), 51.5 (CH), 61.3 (2 × OCH$_2$CH$_3$), 81.1 (C≡CAr), 89.0 (C≡CAr), 123.7 (ArC), 127.5 (ArCH), 128.1 (2 × ArCH), 131.5 (2 × ArCH), 169.3 (2 × CO$_2$Et).

$m/z$ (ES+) 325 [M+Na]; HRMS calcd for C$_{18}$H$_{22}$O$_4$Na: 325.1411; found: 325.1406.

6.5.5 Cross-metathesis

(E)-2,2-Dimethyl-5-(4-phenylbut-3-en-1-yl)-1,3-dioxane-4,6-dione (364)

As for general procedure G, 5-(but-3-enyl)-2,2-dimethyl-1,3-dioxane-4,6-dione 356 (1.0 g, 5.0 mmol, 1.0 eq), Hoveyda–Grubbs II (31.6 mg, 75.7 μmol, 1.5 mol%) and trans-stilbene
(1.8 g, 10.1 mmol, 2.0 eq) in CH$_2$Cl$_2$ (10 mL) were heated at reflux overnight. After work-up, purification by column chromatography on silica gel eluting with 20-80% CH$_2$Cl$_2$ in petroleum ether (40-60 °C) gave (E)-2,2-dimethyl-5-(4-phenylbut-3-enyl)-1,3-dioxane-4,6-dione 364 (790 mg, 2.88 mmol, 57%) as a white solid; mp 86-88 °C.

\[ \nu_{\text{max}} \text{(neat)/cm}^{-1} \] 3081, 2889, 1782 (C=O), 1735 (C=O), 1495.

$^1$H NMR (400 MHz, CDCl$_3$) δ ppm 1.70 (3 H, s, C(O)CH$_3$), 1.76 (3 H, s, C(O)CH$_3$), 2.34 (2 H, dt, $J = 7.8$, 5.4 Hz, CHCH$_2$), 2.48 (2 H, q, $J = 7.3$ Hz, CH$_2$CH=CH), 3.56 (1 H, t, $J = 5.4$ Hz, CH), 6.17 (1 H, dt, $J = 15.7$, 7.3 Hz, CH=CHAr), 6.45 (1 H, d, $J = 15.7$ Hz, CH=CHAr), 7.19 - 7.25 (1 H, m, ArCH), 7.28 - 7.38 (4 H, m, 4 × ArCH).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm 25.9 (CH$_2$CH$_2$), 26.8 (C(O)CH$_3$), 28.3 (C(O)CH$_3$), 29.8 (CH$_2$CH=CH), 44.8 (CH), 104.9 (OCO), 126.1 (2 × ArCH), 127.3 (ArCH), 128.3 (CH=CHAr), 128.4 (2 × ArCH), 132.1 (CH=CHAr), 137.1 (ArC), 165.6 (2 × C=O).

$m/z$ (ES$^-$) 273 [M-H]; HRMS calcd for C$_{16}$H$_{17}$O$_4$: 273.1132; found: 273.1139.

6.5.6 General procedure O: Hydrolysis and ketalizations

5-(But-3-yn-1-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (369a)

To a stirred solution of diethyl 2-(but-3-yn-1-yl)malonate (1.10 g, 5.18 mmol, 1.0 eq) in MeOH (25 mL) and H$_2$O (6.0 mL) was added NaOH (1.04 g, 25.9 mmol, 5.0 eq) and the solution stirred at 85 °C for 12 h. The reaction was quenched with conc. aqueous HCl (36%, 24 mL), the volume reduced to ~50 mL in vacuo, and the aqueous phase extracted with ethyl acetate (3 × 50 mL). The combined organic phases were dried (MgSO$_4$) and concentrated in vacuo. To the residue was added isopropenyl acetate (0.86 mL, 7.77 mmol, 1.5 eq) and the suspension stirred for 10 min. Conc. H$_2$SO$_4$ (3 drops) was added subsequently over 30 min and the reaction stirred at room temperature during 3 h. Purification by column chromatography on silica gel, eluting with 30% ethyl acetate in
petroleum ether (40-60 °C) gave 5-(but-3-yn-1-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione \(369a\) (454 mg, 2.31 mmol, 45%) as a white oil.

\[ v_{\text{max}} \text{ (neat)/cm}^{-1} 3304, 2885, 1785 \text{ (C=O)}, 1738 \text{ (C=O)}, 1450. \]

\[ 1^H \text{ NMR (400 MHz, CDCl}_3\text{)} \delta \text{ ppm 1.78 (3 H, s, C(O)CH}_3\text{)}, 1.85 (3 H, s, C(O)CH}_3\text{)}, 2.05 (1 H, t, J = 2.6 Hz, CH}_2\text{C≡CH)}, 2.31 (2 H, q, J = 6.7 Hz, CH}_2\text{C≡CH)}, 2.60 (2 H, td, J = 6.9, 2.5 Hz, CHCH}_2\text{)}, 3.82 (1 H, t, J = 5.8 Hz, CHCH}_2\text{)}. \]

\[ 13^C \text{ NMR (100 MHz, CDCl}_3\text{)} \delta \text{ ppm 16.2 (CHCH}_2\text{C}\text{H}_2\text{)}, 24.5 (CH}_2\text{C≡C)}, 26.4 (C(O)CH}_3\text{)}, 28.5 (C(O)CH}_3\text{)}, 44.4 (CHCH}_2\text{)}, 70.7 (C≡CH), 82.2 (C≡CH), 105.1 (OCO), 165.2 (2 \times \text{C=O}) \]

\[ m/z \text{ (ES–)} 195 [\text{M-H}]; \text{HRMS calcd for C}_{10}\text{H}_{11}\text{O}_4: 195.0662; \text{found: 195.0664.} \]

5-(But-3-en-1-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione \(356\)^110

As for general procedure O, reaction of diethyl 2-(but-3-en-1-yl)malonate (6.43 g, 30.0 mmol, 1 eq) in MeOH (100 mL) and H\(_2\)O (33 mL) with NaOH (6.0 g, 150 mmol, 5.1 eq), and treatment of the residue with isopropenyl acetate (2.84 mL, 2.58 g, 25.8 mmol, 1.1 eq) and conc. H\(_2\)SO\(_4\) (2 drops) over 1 h. After work-up, purification by column chromatography on silica gel, eluting with 30% ethyl acetate in petroleum ether (40-60 °C) gave 5-(but-3-en-1-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione \(356\) (2.695 g, 13.5 mol, 58%) as a white solid; mp 65-67 °C.

\[ 1^H \text{ (400 MHz, CDCl}_3\text{)} \delta \text{ ppm 1.53 - 1.62 (2 H, m, CHCH}_2\text{CH}_2\text{)}, 1.77 (3 H, s, C(O)CH}_3\text{)}, 1.80 (3 H, s, C(O)CH}_3\text{)}, 2.09 - 2.17 (4 H, m, CHCH}_2\text{H}_2\text{+CH}_2\text{CH=CH}_2\text{)}, 3.53 (1 H, t, J = 5.0 Hz, CHCH}_2\text{)}, 4.96 - 5.09 (2 H, m, CH=CH}_2\text{)}, 5.81 (1 H, ddt, J = 17.0, 10.3, 6.7 Hz, CH=CH}_2\text{)}. \]

\[ 13^C \text{ NMR (100 MHz, CDCl}_3\text{)} \delta \text{ ppm 25.6 (CHCH}_2\text{CH}_2\text{)}, 26.0 (CHCH}_2\text{)}, 26.9 (C(O)CH}_3\text{)}, 28.4 (C(O)CH}_3\text{)}, 33.5 (CH}_2\text{CH=CH}_2\text{)}, 46.0 (CHCH}_2\text{)}, 104.8 (OCO), 115.2 (CH=CH}_2\text{)}, 137.7 (CH=CH}_2\text{)}, 165.5 (2 \times \text{C=O}). \]
2,2-Dimethyl-5-(4-phenylbut-3-ynyl)-1,3-dioxane-4,6-dione (369b)

As for general procedure O, reaction of diethyl 2-(4-phenylbut-3-ynyl)malonate (0.72 g, 1.97 mmol, 1.0 eq) in MeOH (8.5 mL) and H₂O (2.8 mL) with NaOH (0.40 g, 10.1 mmol, 5.1 eq), and treatment of the residue with isopropenyl acetate (0.25 mL, 2.27 mmol, 1.1 eq) and conc. H₂SO₄ (2 drops) over 1 h. After work-up, purification by column chromatography on silica gel, eluting with 30% ethyl acetate in petroleum ether (40-60 °C) gave 2,2-dimethyl-5-(4-phenylbut-3-ynyl)-1,3-dioxane-4,6-dione 369b (319 mg, 1.17 mmol, 60%) as a white solid; mp 85-87 °C.

ν_max (neat)/cm⁻¹ 3046, 2884, 1772 (C=O), 1728 (C=O), 1597.

¹H NMR (400 MHz, CDCl₃) δ ppm 1.74 (3 H, s, C(O)CH₃), 1.83 (3 H, s, C(O)H₃), 2.42 (2 H, td, J = 6.9, 5.5 Hz, CHCH₂), 2.81 (2 H, t, J = 6.9 Hz, CH₂C≡C), 3.85 (1 H, t, J = 5.5 Hz, C≡CCH₂), 7.28 - 7.32 (3 H, m, 3 × ArCH), 7.36 - 7.42 (2 H, m, 2 × ArCH).

¹³C NMR (100 MHz, CDCl₃) δ ppm 17.0 (CH₂C≡C), 24.8 (CHCH₂), 26.5 (C(O)CH₃), 28.4 (C(O)CH₃), 44.5 (CHCH₂), 77.2 (C≡CAr), 87.4 (C≡CAr), 105.1 (OCO), 123.1 (ArC), 128.0 (ArCH), 128.3 (2 × ArCH), 131.6 (2 × ArCH), 165.3 (2 × C=O).

m/z (ES⁻) 271 [M-H]; HRMS calcd for C₁₆H₁₅O₄: 271.0975; found: 271.0969.

2,2-Dimethyl-5-(5-phenylpent-4-ynyl)-1,3-dioxane-4,6-dione (369c)

As for general procedure O, reaction of diethyl 2-(5-phenylpent-4-ynyl)malonate (2.00 g, 6.61 mmol, 1.0 eq) in MeOH (30 mL) and H₂O (10 mL) with NaOH (1.35 g, 33.8 mmol, 5.1 eq), and treatment of the residue with isopropenyl acetate (0.80 mL, 7.27 mmol, 1.1 eq) and conc. H₂SO₄ (4 drops) over 2 h. After work-up, purification by column
chromatography on silica gel, eluting with 30% ethyl acetate in petroleum ether (40-60 °C) gave 2,2-dimethyl-5-(5-phenylpent-4-yn-1-yl)-1,3-dioxane-4,6-dione 369c (998 mg, 3.49 mmol, 53%) as a yellow oil.

\( \nu_{\text{max}} \text{(neat)/cm}^{-1} 3056, 2873, 1783 \text{ (C=O)}, 1742 \text{ (C=O)}, 1490. \)

\(^1\text{H NMR (400 MHz, CDCl}_3\text{)} \delta \text{ ppm 1.75 (3 H, s, C(O)CH}_3\text{)}, 1.76 (3 H, s, C(O)CH}_3\text{)}, 1.81 - 1.86 (2 H, m, \text{CH}_2\text{CH}_2\text{C≡C}), 2.26 - 2.32 (2 H, m, CHCH}_2\text{)}, 2.50 (2 H, t, } J = 6.9 \text{ Hz, CH}_2\text{C≡C}), 3.69 (1 H, t, } J = 5.2 \text{ Hz, CHCH}_2\text{)}, 7.25 - 7.29 (2 H, m, 2 × \text{ArCH}), 7.37 - 7.42 (3 H, m, 3 × \text{ArCH}).

\(^{13}\text{C NMR (100 MHz, CDCl}_3\text{)} \delta \text{ ppm 19.3 (CH}_2\text{C≡C), 25.5 (CH}_2\text{CH}_2\text{CH}_2\text{)}, 25.7 (\text{CHCH}_2\text{)}, 26.6 (\text{C(O)CH}_3\text{)}, 28.4 (\text{C(O)CH}_3\text{)}, 45.8 (\text{CH}), 81.4 (\text{C≡CAr}), 89.0 (\text{C≡CAr}), 104.9 (\text{OCO}), 123.6 (\text{ArC}), 127.6 (\text{ArCH}), 128.2 (2 × \text{ArCH}), 131.5 (2 × \text{ArCH}), 165.4 (2 × \text{C=O}).

The mass spectrum was not informative.

6.5.7 Alkylations of Meldrum’s acid

\((E)-2,2\text{-Dimethyl-5-(4-phenylbut-3-en-1-yl)-5-(6-phenylhex-5-yn-1-yl)-1,3-dioxane-4,6-dione (368)}\)

As for general procedure F, reaction of \((E)-2,2\text{-dimethyl-5-(4-phenylbut-3-en-1-yl)-1,3-dioxane-4,6-dione 363 (270 mg, 0.98 mmol, 1 eq) in DMF (2.5 mL) with K}_2\text{CO}_3\text{ (272 mg, 1.97 mmol, 2.0 eq) and (6-bromohex-1-yn-1-yl)benzene 366c (280 mg, 1.18 mmol, 1.2 eq)}\text{ after column chromatography on silica gel eluting with 5% ethyl acetate in petroleum ether (40-60 °C) gave (E)-2,2\text{-dimethyl-5-(4-phenylbut-3-en-1-yl)-5-(6-phenylhex-5-yn-1-yl)-1,3-dioxane-4,6-dione 368 (100 mg, 0.23 mmol, 27%) as an amorphous solid.} \)

\( \nu_{\text{max}} \text{(neat)/cm}^{-1} 3026, 2861, 1773 \text{ (C=O)}, 1737 \text{ (C=O), 1490.} \)
\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) ppm 1.37 - 1.60 (6 H, m, 3 \(\times\) CH\(_2\)), 1.65 (3 H, s, C(O)CH\(_3\)), 1.66 (3 H, s, C(O)CH\(_3\)), 1.95 - 2.06 (2 H, m, CH\(_2\)), 2.14 (4 H, s, 2 \(\times\) CH\(_2\)), 5.95 - 6.08 (1 H, m, CH=CHAr), 6.33 (1 H, d, \(J = 15.8\) Hz, CH=CHAr), 7.10 - 7.26 (8 H, m, 8 \(\times\) ArCH), 7.30 (2 H, m, 2 \(\times\) ArCH).

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) ppm 19.1 (C\(\text{H}_2\)C≡C), 24.9 (CH\(_2\)CH\(_2\)C≡C), 28.3 (CH\(_2\)), 29.1 (CH\(_2\)CH=CH), 29.7 (C(O)CH\(_3\)), 29.8 (C(O)CH\(_3\)), 38.6 (CH\(_2\)), 38.8 (CH\(_2\)), 54.3 (C\(_q\)(CH\(_2\))\(_2\)), 81.3 (C=CAr), 89.1 (C=CAr), 105.7 (OCO), 123.8 (ArC), 126.1 (ArCH), 127.3 (ArCH), 127.6 (2 \(\times\) ArCH), 127.7 (CH=CHAr), 128.2 (2 \(\times\) ArCH), 128.6 (2 \(\times\) ArCH), 131.6 (2 \(\times\) ArCH), 131.7 (CH=CHAr), 137.1 (ArC), 169.1 (C=O).

The mass spectrum was not informative.

\((E)-5\)-(But-3-yn-1-yl)-2,2-dimethyl-5-(4-phenylbut-3-en-1-yl)-1,3-dioxane-4,6-dione (370a)

As for general procedure C, 5-(but-3-yn-1-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione 369a (445 mg, 2.27 mmol, 1.0 eq), K\(_2\)CO\(_3\) (627 mg, 4.54 mmol, 2.0 eq) and (E)-(4- bromobut-1-en-1-yl)benzene (575 mg, 2.72 mmol, 1.2 eq) in DMF (5.0 mL) were stirred at room temperature for 4 days. After work-up, purification by flash column chromatography on silica gel, eluting with 5% ethyl acetate in petroleum ether (40-60 °C) gave (E)-5-(but-3-yn-1-yl)-2,2-dimethyl-5-(4-phenylbut-3-en-1-yl)-1,3-dioxane-4,6-dione 370a (241 mg, 0.74 mmol, 33%) as a yellow solid; mp 62-64 °C.

\(\nu\)\(_{\text{max}}\) (neat)/cm\(^{-1}\) 3289, 3000, 2941, 1773 (C=O), 1736 (C=O).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 1.75 (3 H, s, C(O)CH\(_3\)), 1.79 (3 H, s, C(O)CH\(_3\)), 2.04 (1 H, s, C=CH), 2.15 - 2.29 (4 H, m, CH\(_2\)CH\(_2\)CH=CH + CH\(_2\)CH=CH), 2.31 - 2.33 (4 H, m, CH\(_2\)CH\(_2\)C=CH + CH\(_2\)C=CH), 6.09 (1 H, dt, \(J = 15.9, 6.4\) Hz, CH=CHAr), 6.42 (1 H, d, \(J = 15.9\) Hz, CH=CHAr), 7.18 - 7.26 (1 H, m, ArCH), 7.28 - 7.35 (4 H, m, 4 \(\times\) ArCH).
$^{13}$C NMR (101 MHz, CDCl$_3$) δ ppm 15.0 (CH$_2$C≡CH), 28.9 (CH$_2$CH=CH), 29.6 (C(O)CH$_3$), 29.8 (C(O)CH$_3$), 36.7 (CH$_2$CH$_2$C≡C), 38.9 (CH$_2$CH$_2$CH=CH), 53.1 (C$_{q}$), 70.6 (C≡CH), 81.6 (CH$_2$C≡C), 106.0 (OCO), 126.1 (2 × ArCH), 127.4 (CH=CHAr + ArCH), 128.6 (2 × ArCH), 131.8 (CH=CHAr), 137.0 (ArC), 168.5 (2 × C=O).

The mass spectrum was not informative.

$^{(E)}$-2,2-Dimethyl-5-(4-phenylbut-3-en-1-yl)-5-(4-phenylbut-3-yn-1-yl)-1,3-dioxane-4,6-dione (381b)

As for general procedure C, 2,2-dimethyl-5-(4-phenylbut-3-yn-1-yl)-1,3-dioxane-4,6-dione 370b (390 mg, 1.43 mmol, 1.0 eq), K$_2$CO$_3$ (396 mg, 2.86 mmol, 2.0 eq) and $^{(E)}$-(4-bromobut-1-en-1-yl)benzene (465 mg, 2.20 mmol, 1.2 eq) in DMF (4.0 mL) were stirred at room temperature for 4 days. After work-up, purification by flash column chromatography on silica gel, eluting with 5% ethyl acetate in petroleum ether (40-60 °C) gave $^{(E)}$-2,2-dimethyl-5-(4-phenylbut-3-en-1-yl)-5-(4-phenylbut-3-yn-1-yl)-1,3-dioxane-4,6-dione 370b (221 mg, 0.53 mmol, 30%) as a colourless oil.

ν$_{max}$ (neat)/cm$^{-1}$ 2940, 2846, 1772 (C=O), 1736 (C=O), 1491.

$^{1}$H NMR (400 MHz, CDCl$_3$) δ ppm 1.65 (3 H, s, C(O)CH$_3$), 1.66 (3 H, s, C(O)CH$_3$), 2.09 - 2.22 (4 H, m, CH$_2$CH$_2$CH=CH + CH$_2$CH=CH), 2.27 - 2.37 (2 H, m, CH$_2$CH$_2$C≡C), 2.42 - 2.50 (2 H, m, CH$_2$C≡C), 6.00 (1 H, dt, J = 15.9, 6.4 Hz, CH=CHAr), 6.33 (1 H, d, J = 15.9 Hz, CH=CHar), 7.09 - 7.25 (8 H, m, 8 × ArCH), 7.28 - 7.35 (2 H, m, 2 × ArCH).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm 16.0 (CH$_2$C≡C), 28.9 (CH$_2$CH=CH), 29.6 (C(O)CH$_3$), 29.7 (C(O)CH$_3$), 36.9 (CH$_2$CH$_2$C≡C), 39.4 (CH$_2$CH$_2$C≡C), 53.2 (C$_{q}$), 82.9 (C≡CAr), 87.2 (C≡CAr), 106.0 (OCO), 123.2 (ArC), 126.1 (2 × ArCH), 127.4 (CH=CHAr), 127.5
(ArCH), 128.0 (ArCH), 128.3 (2 × ArCH), 128.6 (2 × ArCH), 131.5 (2 × ArCH), 131.8 (CH=CHAr), 137.0 (ArC), 168.5 (2 × C=O).

The mass spectrum was not informative.

(E)-2,2-Dimethyl-5-(4-phenylbut-3-en-1-yl)-5-(5-phenylpent-4-yn-1-yl)-1,3-dioxane-4,6-dione (370c)

As for general procedure C, 2,2-dimethyl-5-(5-phenylpent-4-yn-1-yl)-1,3-dioxane-4,6-dione 369c (500 mg, 1.82 mmol, 1.0 eq), K₂CO₃ (503 mg, 3.65 mmol, 2.0 eq) and (E)-(4-bromobut-1-en-1-yl)benzene (524 mg, 2.19 mmol, 1.2 eq) in DMF (4.6 mL) were stirred at room temperature for 3 days. After work-up, purification by flash column chromatography on silica gel, eluting with 5% ethyl acetate in petroleum ether (40-60 °C) gave (E)-2,2-dimethyl-5-(4-phenylbut-3-en-1-yl)-5-(5-phenylpent-4-yn-1-yl)-1,3-dioxane-4,6-dione 370c (314 mg, 0.75 mmol, 41%) as a pale yellow solid; mp 83-85 °C.

νmax (neat)/cm⁻¹ 2933, 2860, 1773 (C=O), 1738 (C=O).

¹H NMR (400 MHz, CDCl₃) δ ppm 1.62 - 1.73 (2 H, m, CH₂CH₂C≡C), 1.75 (3 H, s, C(O)CH₃), 1.78 (3 H, s, C(O)CH₃), 2.17 - 2.29 (6 H, m, 2 × CCH₂, CH₂CH=CH), 2.46 (2 H, t, J = 6.9 Hz, CH₂C≡C), 6.03 - 6.21 (1 H, m, CH=CHAr), 6.43 (1 H, d, J = 15.8 Hz, CH=CHAr), 7.16 - 7.46 (10 H, m, 10 × ArCH).

¹³C NMR (100 MHz, CDCl₃) δ ppm 19.4 (CH₂C≡C), 24.7 (CH₂CH₂C≡C), 29.1 (CH₂CH=CH), 29.7 (C(O)CH₃), 29.8 (C(O)CH₃), 38.3 (CH₂CH₂CH₂C≡C + CH₃CH₂CH=CH), 54.0 (Cq), 81.7 (C≡CAr), 88.2 (C≡CAr), 105.7 (OCO), 123.6 (ArC), 126.1 (2 × ArCH), 127.3 (ArCH), 127.7 (ArCH), 127.8 (CH=CHAr), 128.2 (2 × ArCH), 128.6 (2 × ArCH), 131.6 (2 × ArCH), 131.7 (CH=CHAr), 137.1 (ArC), 169.0 (2 × C=O).

The mass spectrum was not informative.
6.5.8 General procedure P: SmI$_2$-H$_2$O mediated cyclisation cascades

*rac-(1S,3aR,6aS,E)-1-Benzyl-6-benzylidene-6a-hydroxyoctahydropentalene-3a-carboxylic acid (373a)*

![Chemical Structure](image)

To a stirred solution of (E)-2,2-dimethyl-5-(4-phenylbut-3-en-1-yl)-5-(4-phenylbut-3-yn-1-yl)-1,3-dioxane-4,6-dione 370b (30.0 mg, 75.0 μmol, 1.0 eq) in THF (2.00 mL) and H$_2$O (1.6 mL, 1200 eq) at room temperature was added SmI$_2$ (0.1 M in THF, 5.9 mL, 0.59 mmol, 8.0 eq) dropwise using a syringe pump over 2 h. After decolourisation of the reaction mixture, the reaction was exposed to air, subsequently adding H$_2$O (10 mL) and tartaric acid (25 mg). The aqueous phase was extracted with ethyl acetate (3 × 20 mL) and the combined organic phases dried (Na$_2$SO$_4$) and concentrated *in vacuo*. Purification by column chromatography on silica gel, eluting with 10-20% ethyl acetate in hexane with 1% acetic acid gave *rac-(1S,3aR,6aS,E)-1-benzyl-6-benzylidene-6a-hydroxyoctahydropentalene-3a-carboxylic acid* 373a (12.0 mg, 34.0 μmol, 46%) as a colourless oil and as a 2:1 mixture of double-bond isomers.

$\nu_{\text{max}}$(neat)/cm$^{-1}$ 3484 (br. OH), 3275, 2867, 1740 (C=O), 1692 (C=O), 1600.

For the major double-bond isomer:

$^1$H NMR (400 MHz, CDCl$_3$) δ ppm 1.66 - 1.77 (1 H, m, 1 H from CH$_2$CH$_2$CH), 1.78 - 1.88 (3 H, m, CH$_2$CH$_2$CH, + 1 H from CH$_2$CH$_2$C=C), 2.07 - 2.17 (1 H, m, CH), 2.33 - 2.50 (2 H, m, 1 H from CH$_2$CH$_2$CH, 1 H from CH$_2$CH$_2$C=C), 2.54 - 2.64 (1 H, m, 1 H from CH$_2$Ar), 2.72 - 2.84 (1 H, m, 1 H from CH$_2$C=C), 2.86 - 2.97 (1 H, m, 1 H from CH$_2$C=C), 2.97 - 3.05 (1 H, m, 1 H from CH$_2$Ar), 6.57 (1 H, s, C=CH), 7.11 - 7.20 (3 H, m, 3 × ArCH), 7.21 - 7.32 (3 H, m, 3 × ArCH), 7.32 - 7.40 (4 H, m, 4 × ArCH).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm 27.9 (CH$_2$C=CH), 30.6 (CH$_2$CH$_2$CH), 32.8 (CH$_2$CH$_2$CH), 33.8 (CH$_2$Ar), 34.7 (CH$_2$CH$_2$C=CH), 51.3 (CH$_2$CH$_2$CH), 62.4 (C$_q$), 92.4 (C$_q$), 121.9 (C=CH), 125.7 (ArCH), 126.6 (ArCH), 128.3 (2 × ArCH), 128.4 (2 × ArCH),
128.7 (2 × ArCH), 128.9 (2 × ArCH), 137.5 (ArC), 141.7 (ArC), 146.9 (C=CH), 181.1 (COOH).

\( m/z \) (ES+) 371 [M+Na]; HRMS calcd for C\(_{23}\)H\(_{24}\)O\(_3\)Na: 371.1618; found: 371.1612.

**rac-(1S,3aR,6aS)-1-Benzyl-6a-hydroxy-6-methyleneoctahydrotentalene-3a-carboxylic acid (373b)**

![Structure of rac-(1S,3aR,6aS)-1-Benzyl-6a-hydroxy-6-methyleneoctahydrotentalene-3a-carboxylic acid]

As for general procedure P, 5-(but-3-yn-1-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione 370a (30.0 mg, 92.0 μmol, 1.0 eq) in THF (2.00 mL) and H\(_2\)O (2.00 mL, 1200 eq) with SmI\(_2\) (0.1 M in THF, 7.4 mL, 0.74 mmol, 8.0 eq) were stirred at room temperature until complete decolourisation had occurred. After work-up, purification by column chromatography on silica gel, eluting with 30% ethyl acetate in hexane with 1% acetic acid gave **rac-(1S,3aR,6aS)-1-benzyl-6a-hydroxy-6-methyleneoctahydrotentalene-3a-carboxylic acid 373b** (16.0 mg, 59.0 μmol, 64%) as a colourless oil.

\( \nu_{\text{max}} \) (neat)/cm\(^{-1}\) 3083 (br. OH), 3061, 1693 (C=O), 1603.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) ppm 1.56 (1 H, dt, \( J = 13.4, 8.7 \) Hz, 1 H from CH\(_2\)CH\(_2\)CH), 1.65 - 1.73 (1 H, m, 1 H from CH\(_2\)CH\(_2\)C=CH), 1.73 - 1.81 (2 H, m, CH\(_2\)CH), 1.92 - 2.02 (1 H, m, CH\(_2\)CH), 2.32 (1 H, ddd, \( J = 13.4, 8.7, 7.2 \) Hz, 1 H from CH\(_2\)CH\(_2\)C=CH), 2.45 - 2.51 (1 H, m, 1 H from CH\(_2\)CH=CH), 2.52 - 2.60 (3 H, m, 1 H from CH\(_2\)Ar + CH\(_2\)C=CH), 2.94 (1 H, dd, \( J = 13.6, 3.3 \) Hz, 1 H from CH\(_2\)Ar), 5.00 - 5.02 (1 H, m, 1 H from C=CH\(_2\)), 5.13 - 5.15 (1 H, m, 1 H from C=CH\(_2\)), 7.14 - 7.21 (3 H, m, 3 × ArCH), 7.24 - 7.30 (2 H, m, 2 × ArCH).

\(^13\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) ppm 29.3 (CH\(_2\)C=CH), 30.9 (CH\(_2\)CH\(_2\)CH), 33.7 (CH\(_2\)CH\(_2\)CH), 33.9 (CH\(_2\)Ar), 34.3 (CH\(_2\)CH\(_2\)C=CH), 51.5 (CH\(_2\)CH\(_2\)CH), 63.4 (C\(_q\)), 91.1 (C\(_q\)), 106.1 (C=CH), 125.7 (ArCH), 128.2 (2 × ArCH), 128.9 (2 × ArCH), 141.8 (ArC), 154.9 (C=CH\(_2\)), 181.4 (COOH).

\( m/z \) (ES-) 271 [M-H]; HRMS calcd for C\(_{17}\)H\(_{19}\)O\(_3\)Na: 271.1339; found: 271.1339.
As for general procedure P, reaction of \((E)\)-2,2-dimethyl-5-(4-phenylbut-3-en-1-yl)-5-(5-phenylpent-4-yn-1-yl)-1,3-dioxane-4,6-dione 370c (30 mg, 72.0 μmol, 1.0 eq) in THF (2.0 mL) and H₂O (1.6 mL, 1200 eq) with SmI₂ (0.1 M in THF, 5.77 mL, 0.58 mmol, 8.0 eq) were stirred at room temperature until complete decolourisation had occurred. After work-up, purification by column chromatography on silica gel, eluting with 30% ethyl acetate in hexane and 1% acetic acid gave rac-(1S,3aS,7aS,E)-1-benzyl-7-benzylidene-7a-hydroxyoctahydro-1H-indene-3a-carboxylic acid 374a (14 mg, 39.0 μmol, 54%) as a colourless oil and as a 10:1 mixture of double-bond isomers.

\[ \nu_{\text{max}} \text{(neat)/cm}^{-1} = 3438 \text{ (br. OH), 3273, 2871, 1690 (C=O), 1493.} \]

For the major double-bond isomer:

\[ ^1\text{H NMR (400 MHz, CDCl}_3) \delta \text{ ppm} \]

1.30 - 1.46 (1 H, m, 1 H from \( \text{CH}_2\text{CH}_2\text{C} = \text{C} \)), 1.57 - 1.87 (4 H, m, 1 H from \( \text{CH}_2\text{CH}_2\text{CH} + 1 \text{ H from CH}_2\text{CH}_2\text{CH} + 1 \text{ H from CH}_2\text{CH}_2\text{CH}_2\text{C} = \text{C} + 1 \text{ H from CH}_2\text{CH}_2\text{C} = \text{C} \)), 1.93 (1 H, td, 1 H from \( \text{CH}_2\text{C} = \text{C} \)), 2.06 (1 H, t, \( J = 13.0 \text{ Hz} \), 1 H from \( \text{CH}_2\text{CH} = \text{CH} \)), 2.21 (1 H, d, \( J = 13.9 \text{ Hz} \), 1 H from \( \text{CH}_2\text{CH}_2\text{CH}_2\text{C} = \text{C} \)), 2.39 (1 H, td, \( J = 12.3, 5.4 \text{ Hz} \), 1 H from \( \text{CH}_2\text{CH}_2\text{CH} \)), 2.51 - 2.66 (2 H, m, CH, 1 H from \( \text{CH}_2\text{Ar} \)), 2.85 (1 H, dd, \( J = 12.9, 2.3 \text{ Hz} \), 1 H from \( \text{CH}_2\text{Ar} \)), 2.97 (1 H, d, \( J = 14.9 \text{ Hz} \), 1 H from \( \text{CH}_2\text{C} = \text{C} \)), 6.91 (1 H, s, \( \text{C} = \text{CH} \)), 7.13 - 7.37 (10 H, m, \( \text{ArCH} \)).

\[ ^{13}\text{C NMR (100 MHz, CDCl}_3) \delta \text{ ppm} \]

24.1 (\( \text{CH}_2\text{CH}_2\text{C} = \text{C} \)), 26.7 (\( \text{CH}_2\text{C} = \text{C} \)), 27.3 (\( \text{CH}_2\text{CH}_2\text{CH} \)), 34.2 (\( \text{CH}_2\text{CH}_2\text{CH}_2\text{C} = \text{C} + \text{CH}_2\text{CH}_2\text{CH} \)), 34.5 (\( \text{CH}_2\text{Ar} \)), 46.7 (\( \text{CH} \)), 59.5 (\( \text{C}_q \)), 84.1 (\( \text{C}_q \)), 124.6 (\( \text{C} = \text{CH} \)), 125.6 (\( \text{ArCH} \)), 126.2 (\( \text{ArCH} \)), 128.0 (2 × \( \text{ArCH} \)), 128.3 (2 × \( \text{ArCH} \)), 128.8 (2 × \( \text{ArCH} \)), 129.2 (2 × \( \text{ArCH} \)), 138.1 (\( \text{ArC} \)), 141.2 (\( \text{ArC} \)), 142.0 (\( \text{C} = \text{CH} \)), 182.1 (\( \text{COOH} \)).

\[ m/z \text{(ES+)} = 385 \text{ [M+Na]} \text{; HRMS calcd for C}_{24}\text{H}_{26}\text{O}_3\text{Na: 385.1775; found: 385.1775.} \]
6.6 Experimental for Chapter 4

Ethyl 4-(2-methyl-1,3-dioxolan-2-yl)butanoate (417)

To a stirred solution of ethyl 5-oxohexanoate (3.20 mL, 19.5 mmol, 1.0 eq) and ethylene glycol (3.34 mL, 58.6 mmol, 1.5 eq) in benzene (20 mL) was added p-toluenesulfonic acid monohydrate (76.0 mg, 0.390 mmol, 2 mol%) and the mixture was heated at reflux for 3 h under Dean-Stark conditions. The solvent was removed in vacuo and purification by flash column chromatography eluting with 0-10% ethyl acetate in petroleum ether (40-60 °C) gave ethyl 4-(2-methyl-1,3-dioxolan-2-yl)butanoate 417 (3.34 g, 16.5 mmol, 85%) as a pale yellow oil.

\[ \text{CH}_2\text{CH}_{(3)} \]

\( ^1H \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) ppm 1.26 (3 H, t, \( J = 7.1 \) Hz, OCH\(_2\)C\(_3\)), 1.61 - 1.79 (4 H, m, 2 \( \times \) CH\(_2\)), 2.33 (2 H, t, \( J = 7.1 \) Hz, C\(_2\)H\(_3\)), 3.89 - 3.99 (4 H, m, 2 \( \times \) C(OCH\(_2\))\(_2\)), 4.13 (2 H, q, \( J = 7.1 \) Hz, OC\(_3\)H\(_2\)CH\(_3\)).

\( ^13C \) NMR (101 MHz, CDCl\(_3\)) \( \delta \) ppm 14.2 (OCH\(_2\)CH\(_3\)), 19.6 (CH\(_3\)), 23.8 (CH\(_2\)), 34.3 (CH\(_2\)), 38.3 (CH\(_2\)), 60.2 (OCH\(_2\)CH\(_3\)), 64.6 (2 \( \times \) OCH\(_2\)), 109.8 (C(OCH\(_2\))\(_2\)), 173.5 (CO\(_2\)Et).

\((E)-5-(3-(Furan-2-yl)allylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione\)

As for general procedure A, Meldrum’s acid (3.00 g, 20.1 mmol, 1.0 eq), (E)-3-(furan-2-yl) acrylaldehyde (2.80 g, 22.9 mmol, 1.1 eq) in H\(_2\)O (40 mL) after filtration gave (E)-5-(3-(furan-2-yl)allylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (4.80 g, 20.0 mmol, 94%) as a yellow solid.

\( ^1H \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) ppm 1.76 (6 H, s, 2 \( \times \) CH\(_3\)), 6.58 (1 H, dd, \( J = 3.5, 1.8 \) Hz, ArCH), 6.87 (1 H, d, \( J = 3.6 \) Hz, ArCH), 7.16 (1 H, d, \( J = 14.0 \) Hz, CH=CHAr), 7.64 (1 H, d, \( J = 1.6 \) Hz, ArCH), 8.07 - 8.20 (2 H, m, C=CH + CH=CHAr).
\( ^{13}\text{C} \) NMR (101 MHz, CDCl\(_3\)) \( \delta \) ppm 27.5 (2 \( \times \) CH\(_3\)), 110.6 (OCO), 112.8 (C=CH), 113.4 (ArCH), 118.2 (ArCH), 122.6 (CH=CHAr), 138.6 (CH=CHAr), 146.9 (ArCH), 151.8 (ArC), 157.0 (C=CH), 160.6 (C=O), 162.9 (C=O).

\((E)-5-(3-(\text{Furan}-2-\text{yl})\text{allyl})-2,2\text{-dimethyl-1,3-dioxane-4,6-dione (444)}\)\(^{148}\)

To \((E)-5-(3-(\text{furan-2-yl})\text{allylidene})-2,2\text{-dimethyl-1,3-dioxane-4,6-dione (4.80 g, 20.0 mmol, 1.0 eq})\) in glacial acetic acid (16 mL) and CH\(_2\)Cl\(_2\) (120 mL) was added NaBH\(_4\) (2.20 g, 58.0 mmol, 2.9 eq) portion wise at 0°C. The reaction mixture was allowed to warm to room temperature and stirred for 1 h before quenching with H\(_2\)O. The aqueous layer was then extracted with ethyl acetate (3 \( \times \) 20 mL), dried (MgSO\(_4\)) and concentrated \textit{in vacuo}. Addition of \(n\)-heptane to the resulting crude residue resulted in crystallisation. Filtration and washing with \(n\)-heptane afforded \((E)-5-(3-(\text{furan-2-yl})\text{allyl})-2,2\text{-dimethyl-1,3-dioxane-4,6-dione 444 (3.60 g, 14.4 mmol, 76\%) as a white solid.}\)

\(^1\text{H} \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) ppm 1.76 (3 H, s, CH\(_3\)), 1.80 (3 H, s, CH\(_3\)), 3.01 (2 H, dd, \( J = 6.6, 5.3 \) Hz, CH\(_2\)), 3.65 (1 H, t, \( J = 5.3 \) Hz, CH), 6.11 - 6.24 (2 H, m, CH\(_2\)CH=CH + ArCH)), 6.32 - 6.47 (2 H, m, CH\(_2\)CH=CH + 1 H from ArCH), 7.32 (1 H, s, ArCH).

\(^{13}\text{C} \) NMR (126 MHz, CDCl\(_3\)) \( \delta \) ppm 27.0 (CH\(_3\)), 28.4 (CH\(_3\)), 29.4 (CH\(_2\)), 46.6 (CH), 105.1 (OCO), 107.8 (ArCH), 111.2 (ArCH), 122.6 (CH\(_2\)CH=CH), 123.1 (CH\(_2\)CH=CH), 141.9 (ArCH), 152.3 (ArC), 164.9 (2 \( \times \) C=O).

\((E)-5-(\text{Furan-2-yl})\text{pent-4-eno-1-ol}\)\(^{148}\)

(E)-5-(3-(Furan-2-yl)allyl)-2,2-dimethyl-1,3-dioxane-4,6-dione 444 (3.50 g, 14.0 mmol, 1.0 eq) in EtOH (24 mL) was heated to 170 °C in a microwave for 1.5 h. The resulting solution was concentrated \textit{in vacuo} to give the crude ester, which was dissolved in CH\(_2\)Cl\(_2\) (55 mL). To this solution was added a solution of DIBAL-H (1.0 M in hexanes, 39.0 mL,
38.6 mmol, 2.7 eq) at 0 °C. The reaction mixture was then stirred for 1 h at room temperature, after which time the reaction mixture was diluted with Et₂O and cooled to 0 °C. The reaction mixture was then quenched by the sequential dropwise addition of water (1.5 mL), 15% aqueous NaOH (1.5 mL) and water (3.9 mL), then the resulting solution was allowed to warm up to room temperature. The solution was then dried (MgSO₄) and stirred for 15 min before filtering and concentrating in vacuo. Purification by flash column chromatography eluting with 0-20% ethyl acetate in petroleum ether (40-60 °C) gave (E)-5-(furan-2-yl)pent-4-en-1-ol (1.75 g, 11.5 mmol, 83%) as a yellow oil.

¹H NMR (400 MHz, CDCl₃) δ ppm 1.74 (2 H, quin, J = 6.8 Hz, CH₂CH₂CH=CH), 2.28 (2 H, q, J = 6.8 Hz, CH₂CH₂CH=CH), 3.70 (2 H, t, J = 6.1 Hz, CH₂OH), 6.05 - 6.42 (4 H, m, CH₂CH=CH + CH₂CH=CH + 2 × ArCH), 7.30 (1 H, s, ArCH);

¹³C NMR (101 MHz, CDCl₃) δ ppm 29.0 (CH₂CH₂CH=CH), 32.1 (CH₂CH₂CH=CH), 62.3 (CH₂OH), 106.2 (ArCH), 111.1 (ArCH), 119.1 (CH₂CH=CH), 129.0 (CH₂CH=CH), 141.3 (ArCH), 153.1 (ArC).

(E)-2-(5-Iodopent-1-en-1-yl)furan (445)¹⁴⁹

As for general procedure L, (E)-5-(furan-2-yl)pent-4-en-1-ol (1.70 g, 11.5 mmol, 1.0 eq), PPh₃ (3.90 g, 14.9 mmol, 1.3 eq), imidazole (0.94 g, 13.8 mmol, 1.2 eq), I₂ (3.50 g, 13.8 mmol, 1.2 eq) in CH₂Cl₂ (40 mL) were stirred at room temperature for 1.5 h. After work-up, purification by column chromatography on silica gel eluting with 100% petroleum ether (40-60 °C) gave (E)-2-(5-iodopent-1-en-1-yl)furan 445 (2.10 g, 8.00 mmol, 70%) as a yellow oil.

¹H NMR (400 MHz, CDCl₃) δ ppm 1.98 (2 H, quin, J = 6.8 Hz, CH₂CH₂CH=CH), 2.30 (2 H, q, J = 6.3 Hz, CH₂CH=CH), 3.22 (2 H, t, J = 6.7 Hz, ICH₂), 6.01 - 6.31 (3 H, m, 2 × ArCH + CH=CHAr), 6.34 (1 H, d, J = 15.9 Hz, CH=CHAr), 7.31 (1 H, s, ArCH).

¹³C NMR (101 MHz, CDCl₃) δ ppm 6.2 (ICH₂), 32.7 (CH₂CH₂CH=CH), 33.3 (CH₂CH=CH), 106.6 (ArCH), 111.1 (ArCH), 119.9 (CH₂CH=CH), 127.2 (CH₂CH=CH), 141.5 (ArCH), 152.9 (ArC).
1-(Naphthalen-1-yl)prop-2-en-1-ol (438)

To a solution of 1-naphthylaldehyde (3.10 g, 20.0 mmol, 1.0 eq) in THF (18 mL) was added vinylmagnesium bromide solution (1.0 M in THF, 22.0 mL, 22.0 mmol, 1.1 eq) at 0 °C. The resulting mixture was allowed to warm to room temperature and stirred for 30 min before adding aqueous saturated NH₄Cl (30 mL). The aqueous layer was extracted with ethyl acetate (2 × 20 mL) and the combined organic layers dried (MgSO₄) and concentrated in vacuo. Purification by flash column chromatography eluting with 0–20% ethyl acetate in petroleum ether (40–60 °C) gave 1-(naphthalen-1-yl)prop-2-en-1-ol 438 (3.00 g, 16.3 mmol, 82%) as a yellow oil.

¹H NMR (400 MHz, CDCl₃) δ ppm 2.06 (1 H, d, J = 4.1 Hz, OH), 5.30 (1 H, dt, J = 10.4, 1.4 Hz, 1 H from CH=CH₂), 5.47 (1 H, dt, J = 17.2, 1.4 Hz, 1 H from CH=CH₂), 5.97 (1 H, br. s., OH), 6.27 (1 H, ddd, J = 17.2, 10.4, 5.4 Hz, CH=CH₂), 7.46 – 7.57 (3 H, m, 3 × ArCH), 7.64 (1 H, d, J = 7.0 Hz, ArCH), 7.82 (1 H, d, J = 8.2 Hz, ArCH), 7.86 – 7.91 (1 H, m, ArCH), 8.21 (1 H, d, J = 8.2 Hz, ArCH).

¹³C NMR (101 MHz, CDCl₃) δ ppm 72.3 (CH), 115.7 (CH=CH₂), 123.7 (ArCH), 123.9 (ArCH), 125.4 (ArCH), 125.7 (ArCH), 126.1 (ArCH), 128.5 (ArCH), 128.8 (ArCH), 130.7 (ArC), 134.0 (ArC), 138.1 (ArC), 139.6 (CH=CH₂).

(E)-5-(Naphthalen-1-yl)pent-4-en-1-ol

A solution of 1-(naphthalen-1-yl)prop-2-en-1-ol 438 (3.00 g, 16.3 mmol, 1.0 eq), propanoic acid (0.093 mL, 0.16 mmol, 10 mol%) and trimethyl orthoacetate (10.2 mL, 81.4 mmol, 5.0 eq) in toluene (120 mL) was heated to 135 °C for 12 h. The resulting solution was concentrated in vacuo to give the crude ester and dissolved in CH₂Cl₂ (60 mL). To this solution was added a solution of DIBAL-H (1.0 M in hexanes, 72.3 mL, 72.3
mmol, 5.0 eq) at 0 °C, and the reaction mixture stirred for 1 h at room temperature. The reaction mixture was then stirred for 1 h at room temperature, after which time the reaction mixture was diluted with Et$_2$O and cooled to 0 °C. The reaction mixture was then quenched by the sequential dropwise addition of water (1.5 mL), 15% aqueous NaOH (1.5 mL) and water (3.9 mL), then the resulting solution was allowed to warm to room temperature. The solution was then dried (MgSO$_4$) and stirred for 15 min before filtration and concentration in vacuo. Purification by flash column chromatography eluting with 0-20% ethyl acetate in petroleum ether (40-60 °C) gave (E)-5-(naphthalen-1-yl)pent-4-en-1-ol (1.40 g, 6.60 mmol, 38%) as a yellow oil.

$\nu_{\text{max}}$ (neat)/cm$^{-1}$ $3330$ (br. OH), 2934, 1590, 1508, 1435.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm $1.69$ (1 H, br. S, OH), $1.85$ (2 H, quin, $J = 6.9$ Hz, CH$_2$CH$_2$OH), $2.34$ - $2.55$ (2 H, m, ArCH=CHCH$_2$), $3.78$ (2 H, t, $J = 6.5$ Hz, CH$_2$OH), $6.27$ (1 H, dt, $J = 15.4$, 7.0 Hz, ArCH=CH), $7.19$ (1 H, d, $J = 15.4$ Hz, ArCH=CH), $7.40$ - $7.61$ (4 H, m, $4 \times$ ArCH), $7.78$ (1 H, d, $J = 8.1$ Hz, ArCH), $7.82$ - $7.90$ (1 H, m, ArCH), $8.15$ (1 H, s, ArCH).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ ppm $29.7$ (ArCH=CHCH$_2$), $32.3$ (CH$_2$CH$_2$OH), $62.4$ (CH$_2$OH), $123.5$ (ArCH), $123.8$ (ArCH), $125.6$ (2 × ArCH), $125.8$ (ArCH), $127.3$ (ArCH=CH), $127.5$ (ArCH), $128.4$ (ArCH), $131.1$ (ArC), $133.3$ (ArCH=CH), $133.6$ (ArC), $135.4$ (ArC).

$m/z$ (ES+) 195.3 [M–H$_2$O]; HRMS calcd for C$_{15}$H$_{15}$: 195.1168; found: 195.1170.

(E)-1-(5-Iodopent-1-en-1-yl)naphthalene (440)

As for general procedure L, (E)-5-(naphthalen-1-yl)pent-4-en-1-ol (1.40 g, 6.59 mmol, 1.0 eq), PPh$_3$ (2.24 g, 8.57 mmol, 1.3 eq), imidazole (0.54 g, 7.91 mmol, 1.2 eq), I$_2$ (2.01 g, 7.91 mmol, 1.2 eq) in CH$_2$Cl$_2$ (25 mL) were stirred at room temperature for 2 h. After work-up, purification by column chromatography on silica gel eluting with 100%
petroleum ether (40-60 °C) gave (E)-1-(5-iodopent-1-en-1-yl)naphthalene 440 (1.82 g, 5.65 mmol, 86%) as a yellow oil.

\( \nu_{\text{max}} \) (neat)/cm\(^{-1}\) 2925, 2844, 1590, 1508, 1427, 1394.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) ppm 2.03 - 2.13 (2 H, m, \( CH_2CHCH=CH \)), 2.48 (2 H, qd, \( J = 7.1, 1.4 \) Hz, \( CH_2CH=CH \)), 3.31 (2 H, t, \( J = 6.8 \) Hz, ICH\(_2\)), 6.17 (1 H, dt, \( J = 15.6, 7.1 \) Hz, CH=CHAr), 7.22 (1 H, d, \( J = 15.6 \) Hz, CH=CHAr), 7.41 - 7.58 (4 H, m, 4 \( \times \) ArCH), 7.77 (1 H, d, \( J = 8.2 \) Hz, ArCH), 7.83 - 7.88 (1 H, m, ArCH), 8.10 - 8.16 (1 H, m, ArCH).

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) ppm 6.4 (ICH\(_2\)), 32.7 (CH\(_2\)CH=CH), 33.9 (CH\(_2\)CH\(_2\)CH=CH), 123.6 (ArCH), 123.9 (ArCH), 125.6 (ArCH), 125.7 (ArCH), 125.9 (ArCH), 127.5 (ArCH), 128.5 (ArCH), 128.7 (CH=CHAr), 131.1 (ArC), 131.6 (CH=CHAr), 133.6 (ArC), 135.3 (ArC).

The mass spectrum was not informative.

5-Bromo-1,1-diphenylpentan-1-ol\(^{151}\)

To a solution of ethyl 5-bromovalerate (2.00 g, 9.57 mmol, 1.0 eq) in THF (10 mL) was added phenylmagnesium bromide solution (1.0 M in THF, 28.7 mL, 28.7 mmol, 3.0 eq) at 0 °C. The resulting solution was stirred for 12 h at room temperature then quenched with saturated aqueous NH\(_4\)Cl (10 mL), extracted with ethyl acetate (2 \( \times \) 20 mL) and concentrated in vacuo. Purification by flash column chromatography eluting with 100% petroleum ether (40-60 °C) gave 5-bromo-1,1-diphenylpentan-1-ol (2.80 g, 8.77 mmol, 93%) as a colourless oil.

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) ppm 1.41 - 1.51 (2 H, m, CH\(_2\)), 1.91 (2 H, quin, \( J = 7.3 \) Hz, CH\(_2\)), 2.16 (1 H, s, OH), 2.28 - 2.36 (2 H, m, CH\(_2\)), 3.38 (2 H, t, \( J = 6.9 \) Hz, CH\(_2\)Br), 7.22 - 7.28 (2 H, m, 2 \( \times \) ArCH), 7.31 - 7.37 (4 H, m, 4 \( \times \) ArCH), 7.41 - 7.45 (4 H, m, 4 \( \times \) ArCH).
$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ ppm 22.6 (CH$_2$CH$_2$C$_q$), 33.1 (CH$_2$), 33.4 (CH$_2$), 41.0 (CH$_2$C$_q$), 78.1 (C$_q$), 125.9 (4 $\times$ ArCH), 126.9 (2 $\times$ ArCH), 128.2 (4 $\times$ ArCH), 146.8 (2 $\times$ ArC).

(5-Bromopent-1-ene-1,1-diyl)dibenzene (442)$^{151}$

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

A solution of 5-bromo-1,1-diphenylpentan-1-ol (2.68 g, 8.39 mmol, 1.0 eq) and $p$-toluenesulfonic acid monohydrate (79.8 mg, 0.420 mmol, 5 mol%) in toluene (35 mL) was heated to 70 °C for 2 h. The resulting solution was concentrated in vacuo. Purification by flash column chromatography eluting with 100% petroleum ether (40-60 °C) gave (5-bromopent-1-ene-1,1-diyl)dibenzene 442 (2.40 g, 8.00 mmol, 95%) as a yellow oil.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ ppm 2.01 (2 H, quin, $J = 7.0$ Hz, CH$_2$CHBr), 2.28 (2 H, q, $J = 7.5$ Hz, C=CHCH$_2$), 3.40 (2 H, t, $J = 7.0$ Hz, CHBr), 6.06 (1 H, t, $J = 7.5$ Hz, CH), 7.16 - 7.42 (10 H, m, 10 $\times$ ArCH).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ ppm 28.4 (C=CHCH$_2$), 33.0 (2 $\times$ CH$_2$), 127.1 (2 $\times$ ArCH), 127.2 (ArCH + C=CH), 127.5 (ArCH), 128.1 (2 $\times$ ArCH), 128.2 (2 $\times$ ArCH), 129.8 (2 $\times$ ArCH), 139.8 (ArC), 142.4 (C=CH), 143.0 (ArC).

(5-Iodopent-1-ene-1,1-diyl)dibenzene (443)$^{152}$

\[ \text{I} \quad \begin{array}{c} \text{C} \\ \text{H} \end{array} \quad \begin{array}{c} \text{C} \\ \text{H} \end{array} \]

A suspension of (5-bromopent-1-ene-1,1-diyl)dibenzene 442 (2.5 g, 8.33 mmol, 1.0 eq) and NaI (2.5 g, 16.7 mmol, 2.0 eq) in acetone (15 mL) was heated at reflux overnight. The resulting solution was concentrated in vacuo. Purification by flash column chromatography
eluting with 100% petroleum ether (40-60 °C) gave (5-iodopent-1-ene-1,1-diyl)dibenzene 443 (2.10 g, 6.03 mmol, 72%) as an orange oil.

$^{1}$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 2.03 (2 H, quin, $J = 7.2$ Hz, $CH_2CH_2CH=$C), 2.27 (2 H, q, $J = 7.4$ Hz, $CH_2CH=$C), 3.21 (2 H, t, $J = 7.1$ Hz, ICH$_2$), 6.08 (1 H, t, $J = 7.5$ Hz, C=CH), 7.17 - 7.46 (10 H, m, 10 $\times$ ArCH).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ ppm 5.9 (ICH$_2$), 30.7 ($CH_2CH=CH$), 33.9 ($CH_2CH_2CH=CH$), 127.1 (2 $\times$ ArCH), 127.2 (ArCH + C=CH), 127.3 (ArCH), 128.1 (2 $\times$ ArCH), 128.3 (2 $\times$ ArCH), 129.8 (2 $\times$ ArCH), 139.9 (ArC), 142.4 (CH=C), 143.1 (ArC).
6.6.1 General procedure Q: Alkylation

**Ethyl 2-(3-oxobutyl)-7-phenylhept-6-ynoate (418)**

![Structure of Ethyl 2-(3-oxobutyl)-7-phenylhept-6-ynoate](image)

To a solution of LDA (2.0 M in hexanes, 3.50 mL, 5.50 mmol, 1.1 eq) at −78 °C was added ethyl 4-(2-methyl-1,3-dioxolan-2-yl)butanoate 417 (1.00 g, 4.94 mmol, 1.0 eq) in THF (2.0 mL) using a syringe pump over 30 min and the resulting solution stirred for 45 min. To this was added (5-bromopent-1-yn-1-yl)benzene 415 (1.32 g, 5.93 mmol, 1.2 eq) in HMPA (1.0 mL) and the resulting solution warmed to room temperature overnight. The reaction was quenched with aqueous saturated NH₄Cl (10 mL), the aqueous layer extracted with ethyl acetate (3 × 10 mL) and the combined organic layers washed with brine (10 mL), dried (Na₂SO₄) and concentrated in vacuo. The resulting crude oil was then dissolved in acetone (50 mL). To this solution was added p-toluenesulfonic acid monohydrate (1.89 g, 9.89 mmol, 2.0 eq) and the reaction was stirred for 1.5 h. The reaction was quenched with aqueous saturated NaHCO₃ (20 mL), the aqueous layer was extracted with CH₂Cl₂ (3 × 30 mL) and the combined organic layers dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography on silica gel eluting with 0-30% CH₂Cl₂ in petroleum ether (40-60 °C) gave ethyl 2-(3-oxobutyl)-7-phenylhept-6-ynoate 418 (0.98 g, 3.26 mmol, 66%) as a colourless oil.

ν̴max (neat)/cm⁻¹ 2937, 1716 (C=O), 1598, 1490.

¹H NMR (500 MHz, CDCl₃) δ ppm 1.27 (3 H, t, J = 7.1 Hz, OCH₂CH₃), 1.57 - 1.70 (3 H, m, CH₂ + 1 from CHCH₂), 1.76 - 1.82 (1 H, m, 1 from CHCH₂), 1.85 (2 H, q, J = 7.8 Hz, CH₂CH₂C(O)), 2.13 (3 H, s, CH₃), 2.37 - 2.49 (6 H, m, CHCO₂Et + CH₂C(O) + CH₂), 4.16 (2 H, q, J = 7.1 Hz, OCH₂CH₃), 7.26 - 7.31 (3 H, m, 3 × ArCH), 7.37 - 7.41 (2 H, m, 2 × ArCH).

¹³C NMR (126 MHz, CDCl₃) δ ppm 14.3 (OCH₂CH₃), 19.2 (CH₂), 25.8 (CH₂CH₂C(O)), 26.3 (CH₂), 30.0 (CH₃), 31.4 (CHCH₂), 41.0 (CH₂C(O)), 44.3 (CHCO₂Et), 60.3
(OCH₂CH₃), 81.0 (C=CAr), 89.4 (C=CAr), 123.8 (ArC), 127.6 (ArCH), 128.2 (2 × ArCH), 131.5 (2 × ArCH), 175.5 (CO₂Et), 207.9 (C=O).

m/z (ES+) 301.3 [M+H]; HRMS calcd for C₁₉H₂₄O₃Na: 323.1623; found: 323.1613.

(3R,6S)-6-Cinnamyl-6-methyl-3-((E)-5-phenylpent-4-en-1-yl)tetrahydro-2H-pyran-2-one (trans-431)

As for general procedure Q, LDA was prepared using n-BuLi (1.6 M in hexane, 0.76 mL, 1.20 mmol, 1.1 eq.), diisopropylamine (0.16 mL, 1.20 mmol, 1.1 eq) and THF (0.3 mL). 6-Cinnamyl-6-methyltetrahydro-2H-pyran-2-one 428 (250 mg, 1.08 mmol, 1.0 eq) in THF (0.6 mL) was added followed by (E)-(5-iodopent-1-en-1-yl)benzene 430 (887 mg, 3.25 mmol, 3.0 eq) in HMPA (0.5 mL). After work-up, purification by column chromatography on silica gel eluting with 0-10% ethyl acetate in petroleum ether (40-60 °C) gave (3R,6S)-6-cinnamyl-6-methyl-3-((E)-5-phenylpent-4-en-1-yl)tetrahydro-2H-pyran-2-one trans-431 (197 mg, 0.53 mmol 49%) as a yellow oil.

ν max (neat)/cm⁻¹ 2975, 2944, 1721 (C=O), 1494.

¹H NMR (400 MHz, CDCl₃) δ ppm 1.41 - 1.45 (3 H, s, CH₃), 1.54 - 1.79 (5 H, m, 1 H from CH₂ + CH₂ + CHCH₂), 1.85 - 2.04 (3 H, m, 1 H from CH₂ + CHCH₂), 2.24 (2 H, q, J = 7.1 Hz, CH₂), 2.40 - 2.48 (1 H, m, CH), 2.50 - 2.62 (2 H, m, CqCH₂CH=CHAr), 6.13 - 6.25 (2 H, m, 2 × ArCH=CH), 6.36 - 6.50 (2 H, m, 2 × ArCH=CH), 7.17 - 7.26 (2 H, m, 2 × ArCH), 7.27 - 7.39 (8 H, m, 8 × ArCH).

¹³C NMR (101 MHz, CDCl₃) δ ppm 22.3 (CH₂), 26.7 (CH₂), 27.5 (CH₃), 31.0 (CH₂), 31.4 (CH₂), 32.9 (CH₂), 39.5 (CH), 44.6 (CqCH₂CH=CHAr), 83.8 (Cq), 123.9 (CH=CHAr), 125.9 (2 × ArCH), 126.2 (2 × ArCH), 126.9 (ArCH), 127.5 (ArCH), 128.5 (2 × ArCH), 128.6 (2 × ArCH), 130.2 (CH=CHAr + CH=CHAr), 134.2 (CH=CHAr), 137.0 (ArC), 137.7 (ArC), 174.2 (C=O).

m/z (ES+) 375.4 [M+H]; HRMS calcd for C₂₆H₃₀O₂Na: 397.2144; found: 397.2128.
**Ethyl 2-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)hept-6-enoate (434)**

![Chemical Structure](image)

As for general procedure Q, LDA was prepared using *n*-BuLi (1.6 M in hexane, 4.50 mL, 7.10 mmol, 1.1 eq), diisopropylamine (0.92 mL, 7.10 mmol, 1.1 eq) and THF (1.6 mL). Ethyl 4-(2-methyl-1,3-dioxolan-2-yl)butanoate 417 (1.30 g, 6.40 mmol, 1.0 eq) in THF (2.0 mL) was added followed by 5-bromo-1-pentene (1.15 g, 7.70 mmol, 1.2 eq) in HMPA (1.3 mL). After work-up, purification by column chromatography on silica gel eluting with 0-10% ethyl acetate in petroleum ether (40-60 °C) gave ethyl 2-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)hept-6-enoate 434 (1.20 g, 4.44 mmol, 69%) as a colourless oil.

$\nu_{\text{max}}/\text{cm}^{-1}$ 3078, 2862, 1718 (C=O), 1641, 1446.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 1.22 (3 H, t, $J = 7.4$ Hz, OCH$_2$CH$_3$), 1.26 (3 H, s, CH$_3$), 1.31 - 1.38 (2 H, m, CH$_2$), 1.39 - 1.71 (6 H, m, 3 $\times$ CH$_2$), 1.97–2.05 (2 H, m, C=CHCH$_2$), 2.24 – 2.33 (1 H, m, CHCO$_2$Et), 3.83 - 3.93 (4 H, m, 2 $\times$ C(OCH$_2$)$_2$), 4.10 (2 H, qd, $J = 7.4$, 1.3 Hz, OCH$_2$CH$_3$), 4.87 - 5.10 (2 H, m, CH=CH$_2$), 5.67 - 5.79 (1 H, m, CH=CH$_2$).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 14.2 (OCH$_2$CH$_3$), 23.6 (CH$_3$), 26.5 (CH$_3$CHCO$_2$Et), 26.6 (CH$_2$), 31.7 (CH$_2$), 33.5 (CH$_2$), 36.5 (CH$_2$), 45.3 (CH), 60.0 (OCH$_2$CH$_3$), 64.5 (2 $\times$ OCH$_2$), 109.6 (C(OCH$_2$)$_2$), 114.6 (CH=CH$_2$), 138.3 (CH=CH$_2$), 175.9 (CO$_2$Et).

$m/z$ (ESI+) 294 [M+Na]; HRMS calcd for C$_{15}$H$_{27}$O$_4$: 271.1904; found: 271.1899.
Ethyl (E)-2-(2-(methyl-1,3-dioxolan-2-yl)ethyl)-7-(naphthalen-1-yl)hept-6-enoate (446a)

As for general procedure Q, to a solution of LDA (2.0 M in hexanes, 3.10 mL, 6.10 mmol, 1.3 eq) was added ethyl 4-(2-methyl-1,3-dioxolan-2-yl)butanoate 430 (0.95 g, 4.70 mmol, 1.0 eq) in THF (3.0 mL) followed by (E)-1-(5-iodopent-1-en-1-yl)naphthalene 440 (1.82 g, 5.65 mmol, 1.2 eq) in HMPA (1.0 mL). After work-up, purification by column chromatography on silica gel eluting with 0-10% ethyl acetate in petroleum ether (40-60 °C) gave ethyl (E)-2-(2-(methyl-1,3-dioxolan-2-yl)ethyl)-7-(naphthalen-1-yl)hept-6-enoate 446a (950 mg, 2.46 mmol, 51%) as a yellow oil.

ν max (neat)/cm⁻¹: 2936, 1727 (C=O), 1591, 1456.

¹H NMR (400 MHz, CDCl₃) δ ppm: 1.26 (3 H, t, J = 7.1 Hz, OCH₂CH₃), 1.31 (3 H, s, CH₃), 1.49 - 1.79 (8 H, m, CH₂, 4 × CH₂), 2.28 - 2.43 (3 H, m, CHCO₂Et + CH₂CH=CH), 3.86 - 3.97 (4 H, m, C(OCH₂)₂), 4.16 (2 H, qd, J = 7.1, 1.0 Hz, OCH₂CH₃), 6.20 (1 H, dt, J = 15.6, 7.0 Hz, CH=CHAr), 7.11 (1 H, d, J = 15.6 Hz, CH=CHAr), 7.39 - 7.56 (4 H, m, 4 × ArCH), 7.73 (1 H, d, J = 8.1 Hz, ArCH), 7.79 - 7.86 (1 H, m, ArCH), 8.11 (1 H, d, J = 7.9 Hz, ArCH).

¹³C NMR (101 MHz, CDCl₃) δ ppm: 14.4 (OCH₂CH₃), 23.8 (CH₃), 26.8 (CH₂CHCO₂Et), 27.1 (CH₂), 32.0 (CH₂), 33.3 (CH₂CH=CH), 36.7 (CH₂), 45.5 (CHCO₂Et), 60.2 (OCH₂CH₃), 64.6 (2 × OCH₂), 109.8 (C(OCH₂)₂), 123.6 (ArCH), 123.9 (ArCH), 125.6 (ArCH), 125.7 (ArCH), 125.8 (ArCH), 127.3 (ArCH), 127.4 (CH=CHAr), 128.5 (ArCH), 131.1 (ArC), 133.6 (ArC), 133.7 (CH=CHAr), 135.6 (ArC), 176.1 (CO₂Et).

m/z (ES⁺) 397 [M+H]; HRMS calcd for C₂₅H₃₃O₄: 397.2373; found: 397.2368.
As for general procedure Q, LDA was prepared using n-BuLi (1.4 M in hexane, 4.90 mL, 6.92 mmol, 1.4 eq), diisopropylamine (0.97 mL, 6.92 mmol, 1.4 eq) and THF (1.3 mL). Ethyl 4-(2-methyl-1,3-dioxolan-2-yl)butanoate 417 (1.00 g, 4.94 mmol, 1.0 eq) in THF (2.0 mL) was added followed by (5-iodopent-1-ene-1,1-diyl) dibenzene 456 (2.23 g, 6.92 mmol, 1.4 eq) in HMPA (1.0 mL). After work-up, purification by column chromatography on silica gel eluting with 0-10% ethyl acetate in petroleum ether (40-60 °C) gave ethyl 2-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)-7,7-diphenylhept-6-enoate 446b (1.40 g, 3.24 mmol, 65%) as a yellow oil.

$\nu_{\text{max}}$ (neat)/cm$^{-1}$ 2938, 1728 (C=O), 1585, 1445.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 1.25 (3 H, t, $J = 7.2$ Hz, OCH$_2$CH$_3$), 1.30 (3 H, s, CH$_3$), 1.38 - 1.51 (3 H, m, ArC=CHCH$_2$CH$_2$ + 1 H from CH$_2$), 1.51 - 1.73 (5 H, m, 2 $\times$ CH$_2$ + 1 H from CH$_2$), 2.12 (2 H, q, $J = 6.9$ Hz, ArC=CHCH$_2$), 2.24 - 2.33 (1 H, m, CHCO$_2$Et), 3.86 - 3.98 (4 H, m, C(OCH$_2$)$_2$), 4.13 (2 H, q, $J = 7.1$ Hz, OCH$_2$CH$_3$), 6.05 (1 H, t, $J = 7.5$ Hz, C=CH), 7.13 - 7.40 (10 H, m, 10 $\times$ ArCH).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ ppm 14.3 (OCH$_2$CH$_3$), 23.7 (CH$_3$), 26.7 (CH$_2$), 27.6 (CH$_2$CH$_2$CH=CH), 29.6 (ArCH=CHCH$_2$), 32.0 (CH$_2$), 36.6 (CH$_2$C(OCH$_2$)$_2$), 45.4 (CHCO$_2$Et), 60.1 (OCH$_2$CH$_3$), 64.6 (2 $\times$ OCH$_2$), 109.7 (C(OCH$_2$)$_2$), 126.8 (2 $\times$ ArCH), 127.2 (2 $\times$ ArCH), 128.0 (2 $\times$ ArCH), 128.1 (2 $\times$ ArCH), 129.4 (C=CH), 129.9 (2 $\times$ ArCH), 140.2 (ArC), 141.9 (C=CH), 142.7 (ArC), 176.0 (CO$_2$Et).

$m/z$ (ES+) 423 [M+H]; HRMS calcd for C$_{27}$H$_{34}$O$_4$: 423.2530; found: 423.2524.
Ethyl (E)-7-(furan-2-yl)-2-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)hept-6-enoate (446c)

As for general procedure Q, to a solution of LDA (2.0 M in hexanes, 3.30 mL, 6.43 mmol, 1.3 eq) was added ethyl 4-(2-methyl-1,3-dioxolan-2-yl)butanoate 417 (1.00 g, 4.94 mmol, 1.0 eq) in THF (2.0 mL) followed by (E)-2-(5-iodopent-1-en-1-yl)furan 445 (1.90 g, 7.25 mmol, 1.4 eq) in HMPA (1.2 mL). After work-up, purification by column chromatography on silica gel eluting with 0-10% ethyl acetate in petroleum ether (40-60 °C) gave ethyl (E)-7-(furan-2-yl)-2-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)hept-6-enoate 446c (820 mg, 2.45 mmol, 51%) as a yellow oil.

$\nu_{\text{max}}$ (neat)/cm$^{-1}$ 2937, 1728 (C=O), 1456, 1378.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 1.26 (3 H, t, $J = 7.1$ Hz, OCH$_2$CH$_3$) 1.31 (3 H, s, CH$_3$) 1.41 - 1.77 (8 H, m, 4 $\times$ CH$_2$) 2.18 (2 H, q, $J = 6.7$ Hz, CH$_2$CH=CH) 2.30 - 2.38 (1 H, m, CHCO$_2$Et) 3.87 - 3.97 (4 H, m, C(OCH$_2$)$_2$) 4.10 - 4.18 (2 H, m, OCH$_2$CH$_3$) 6.07 - 6.23 (3 H, m, ArCH + 2 $\times$ CH=CH) 6.33 (1 H, dd, $J = 3.2$, 2.0 Hz, ArCH) 7.30 (1 H, s, ArCH).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ ppm 14.3 (OCH$_2$CH$_3$), 23.7 (CH$_3$), 26.7 (CH$_2$CHCO$_2$Et), 26.9 (CH$_2$), 31.9 (CH$_2$), 32.6 (CH$_2$CH=CH), 36.6 (CH$_2$), 45.5 (CHCO$_2$Et), 60.2 (OCH$_2$CH$_3$), 64.6 (2 $\times$ OCH$_2$), 106.0 (ArCH), 109.7 (C(OCH$_2$)$_2$), 111.0 (ArCH), 118.9 (CH=CHAr), 129.4 (CH=CHAr), 141.2 (ArCH), 153.2 (ArC), 176.0 (CO$_2$Et).

$m/z$ (ES+) 337 [M+H]; HRMS calcd for C$_{19}$H$_{29}$O$_5$: 337.2010; found: 337.2013.
**Ethyl (E)-2-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)-7-phenyl-2-((E)-5-phenylpent-4-en-1-yl)hept-6-enoate (449)**

[Chemical structure image]

As for general procedure Q, LDA was prepared using \( n\)-BuLi (1.4 M in hexane, 4.90 mL, 6.92 mmol, 1.4 eq), diisopropylamine (0.97 mL, 6.92 mmol, 1.4 eq) and THF (1.3 mL). Ethyl (E)-2-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)-7-phenylhept-6-enoate 448 (1.00 g, 4.94 mmol, 1.0 eq) in THF (2.0 mL) was added followed by (E)-(5-iodopent-1-en-1-yl)benzene 430 (2.23 g, 6.92 mmol, 1.4 eq) in HMPA (1.0 mL). After work-up, purification by column chromatography on silica gel eluting with 0-10% ethyl acetate in petroleum ether (40-60 °C) gave ethyl (E)-2-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)-7-phenyl-2-((E)-5-phenylpent-4-en-1-yl)hept-6-enoate 449 (1.40 g, 3.24 mmol, 65%) as a yellow oil.

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) ppm 1.25 (3 H, t, \( J = 7.0 \) Hz, OCH\(_2\)CH\(_3\)), 1.30 - 1.42 (7 H, m, CH\(_3\) + 2 \( \times \) CH\(_2\)CH\(_2\)CH=CH), 1.48 - 1.54 (2 H, m, CH\(_2\)C\(_q\)), 1.57 - 1.64 (4 H, m, 2 \( \times \) CH\(_2\)CH\(_2\)CH=CH), 1.66 - 1.72 (2 H, m, CH\(_2\)), 2.20 (4 H, q, \( J = 7.0 \) Hz, 2 \( \times \) CH\(_2\)CH=CH), 3.87 - 3.97 (4 H, m, C(OCH\(_2\)OH), 4.15 (2 H, q, \( J = 7.0 \) Hz, OCH\(_2\)CH\(_3\)), 6.20 (2 H, dt, \( J = 15.8, 6.9 \) Hz, CH=CHAr), 6.39 (2 H, d, \( J = 15.8 \) Hz, CH=CHAr), 7.17 - 7.23 (2 H, m, 2 \( \times \) ArCH), 7.26 - 7.38 (8 H, m, 8 \( \times \) ArCH).

\(^13\)C NMR (126 MHz, CDCl\(_3\)) \( \delta \) ppm 14.3 (OCH\(_2\)CH\(_3\)), 23.7 (CH\(_3\) + 2 \( \times \) CH\(_2\)CH\(_2\)CH=CH), 28.4 (CH\(_2\)C\(_q\)), 33.3 (2 \( \times \) CH\(_2\)CH=CH + CH\(_2\)), 34.0 (2 \( \times \) CH\(_2\)CH\(_2\)CH\(_2\)CH=CH), 48.3 (C\(_q\)), 60.2 (OCH\(_2\)CH\(_3\)), 64.6 (2 \( \times \) OCH\(_2\)), 109.9 (C(OCH\(_2\)OH), 125.9 (4 \( \times \) ArCH), 126.8 (2 \( \times \) ArCH), 128.4 (4 \( \times \) ArCH), 130.1 (2 \( \times \) CH=CHAr), 130.4 (2 \( \times \) CH=CHAr), 137.6 (2 \( \times \) ArC), 176.8 (CO\(_2\)Et).

\( m/z \) (ES+) 513.5 [M+H]; HRMS calcd for C\(_{32}\)H\(_{42}\)O\(_4\)Na: 513.2975; found: 513.2961.
(3-Bromoprop-1-yn-1-yl)benzene (420a)\textsuperscript{153}

\[
\begin{array}{c}
\text{Br} \\
\text{\textbullet} \\
\text{\textbullet} \\
\end{array}
\]

As for general procedure M, 3-phenylprop-2-yn-1-ol (900 mg, 6.80 mmol, 1.0 eq) with CBr\textsubscript{4} (2.70 g, 8.20 mmol, 1.2 eq) and PPh\textsubscript{3} (2.30 g, 8.90 mmol, 1.3 eq) in CH\textsubscript{2}Cl\textsubscript{2} (20 mL) were stirred at room temperature for 2 h. After work-up, purification by column chromatography on silica gel eluting with 100\% petroleum ether (40-60 °C) gave (3-bromoprop-1-yn-1-yl)benzene \textbf{420a} (1.0 g, 5.1 mmol, 75\%) as a yellow oil.

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ ppm 4.15 - 4.22 (2 H, m, CH\textsubscript{2}Br), 7.30 - 7.38 (3 H, m, 3 × ArCH), 7.42 - 7.49 (2 H, m, 2 × ArCH).

\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) δ ppm 15.3 (CH\textsubscript{2}Br), 84.2 (C≡CAr), 86.7 (C≡CAr), 122.1 (ArC), 128.3 (2 × ArCH), 128.9 (ArCH), 131.9 (2 × ArCH).

1-(3-Bromoprop-1-yn-1-yl)-4-methoxybenzene (420b)\textsuperscript{153}

\[
\begin{array}{c}
\text{Br} \\
\text{\textbullet} \\
\text{\textbullet} \text{OCH}_3
\end{array}
\]

As for general procedure M, 3-(4-methoxyphenyl)prop-2-yn-1-ol (730 mg, 4.50 mmol, 1.0 eq) with CBr\textsubscript{4} (1.79 g, 5.40 mmol, 1.2 eq) and PPh\textsubscript{3} (1.53 g, 5.85 mmol, 1.3 eq) in CH\textsubscript{2}Cl\textsubscript{2} (20 mL) were stirred at room temperature for 2 h. After work-up, purification by column chromatography on silica gel eluting with 100\% petroleum ether (40-60 °C) gave 1-(3-bromoprop-1-yn-1-yl)-4-methoxybenzene \textbf{420b} (830 mg, 3.69 mmol, 82\%) as an amorphous solid.

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ ppm 3.82 (3 H, s, OCH\textsubscript{3}), 4.18 (2 H, s, CH\textsubscript{2}Br), 6.85 (2 H, d, J = 9.0 Hz, 2 × ArCH), 7.39 (2 H, d, J = 9.0 Hz, 2 × ArCH).

\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) δ ppm 15.9 (CH\textsubscript{2}Br), 55.3 (OCH\textsubscript{3}), 82.9 (C≡CAr), 86.9 (C≡CAr), 113.9 (2 × ArCH), 114.1 (ArC), 133.4 (2 × ArCH), 160.0 (ArC).
As for general procedure B, LDA was prepared using n-BuLi (1.54 M in hexane, 11.4 mL, 17.6 mmol, 1.1 eq), diisopropylamine (2.40 mL, 17.6 mmol, 1.1 eq) and Et₂O (27 mL). Propargylic bromide (80% in toluene, 1.80 mL, 16.0 mmol, 1.0 eq) was added followed by chlorodimethyl(phenyl)silane (2.72 g, 16.0 mmol, 1.0 eq). After work-up, purification by column chromatography on silica gel eluting with 1:80 Et₂O in pentane, gave (3-bromoprop-1-ynyl)dimethyl(phenyl)silane 420c (3.70 g, 0.15 mmol, 91%) as an orange oil.

\[^1H\text{NMR} (500 \text{MHz, CDCl}_3) \delta \text{ ppm} 0.31 (6 \text{ H, s, Si(CH}_3)_2\text{Ph}), 3.82 (2 \text{ H, s, C}_2\text{HBr}), 7.22 - 7.27 (3 \text{ H, m, ArCH}), 7.48 - 7.50 (2 \text{ H, m, ArCH}).\]

\[^{13}\text{C NMR} (100 \text{MHz, CDCl}_3) \delta \text{ ppm} -1.3 (\text{Si(CH}_3)_2\text{Ph}), -1.1 (\text{Si(CH}_3)_2\text{Ph}), 14.5 (\text{CH}_2\text{Br}), 90.3 (C≡\text{CCH}_2\text{Br}), 101.6 (C≡\text{CSi(CH}_3)_2\text{Ph}), 127.9 (\text{ArCH}), 133.6 (\text{ArCH}), 133.8 (\text{ArCH}), 136.2 (\text{ArC}).\]

6.6.2 General procedure R: Acetal deprotection

Ethyl 2-(3-oxobutyl)hept-6-enoate (435)

Ethyl 2-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)hept-6-enoate 434 (1.60 g, 5.92 mmol, 1.0 eq), p-toluenesulfonic acid monohydrate (2.25 g, 11.8 mmol, 2.0 eq) and acetone (90 mL) were stirred at room temperature for 2 h. The reaction was quenched with aqueous saturated NaHCO₃ (20 mL), the aqueous layer was extracted with CH₂Cl₂ (3 × 30 mL) and the combined organic layers dried (Na₂SO₄) and concentrated \textit{in vacuo}. Purification by flash column chromatography on silica gel, eluting with 10% ethyl acetate in petroleum ether (40-60 °C) gave ethyl 2-(3-oxobutyl)hept-6-enoate 435 (1.30 g, 5.74 mmol, 96%) as a colourless oil.
\[
\nu_{\text{max}} \text{(neat)/cm}^{-1} 2936, 1717 (\text{C=O}), 1640, 1445.
\]

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 1.26 (3 H, t, \(J = 7.0\) Hz, OCH\(_2\)CH\(_3\)), 1.33 - 1.52 (3 H, m, 1 H from CH\(_2\) + CH\(_2\)), 1.58 - 1.69 (1 H, m, 1 H from CH\(_2\)), 1.81 (2 H, q, \(J = 7.5\) Hz, CH\(_2\)), 2.05 (2 H, q, \(J = 6.8\) Hz, CH\(_2\)CH=CH), 2.13 (3 H, s, CH\(_3\)), 2.29 - 2.38 (1 H, m, CHCO\(_2\)Et), 2.44 (2 H, td, \(J = 7.6, 3.0\) Hz, CH\(_2\)C(O)), 4.14 (2 H, q, \(J = 7.0\) Hz, OCH\(_2\)CH\(_3\)), 4.92 - 5.04 (2 H, m, CH=CH\(_2\)), 5.71 - 5.84 (1 H, m, CH=CH\(_2\)).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) ppm 14.3 (OCH\(_2\)CH\(_3\)), 25.9 (CH\(_2\)), 26.5 (CH\(_2\)), 29.9 (CH\(_3\)), 31.8 (CH\(_2\)), 33.5 (CH\(_2\)C(O)), 41.1 (CH\(_2\)) 44.6 (CHCO\(_2\)Et), 60.3 (OCH\(_2\)CH\(_3\)), 114.7 (CH=CH\(_2\)), 138.3 (CH=CH\(_2\)), 175.7 (CO\(_2\)Et), 208.0 (C=O).

\(m/z\) (ES+) 227.2 [M+H]; HRMS calcd for C\(_{13}\)H\(_{22}\)O\(_3\)Na: 249.1467; found: 249.1470.

**Ethyl (\(E\))-(naphthalen-1-yl)-2-(3-oxobutyl)hept-6-enoate (447a)**

![Ethyl (E)-7-(naphthalen-1-yl)-2-(3-oxobutyl)hept-6-enoate (447a)](image)

As for general procedure R, ethyl (\(E\))-2-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)-7-(naphthalen-1-yl)hept-6-enoate 446a (950 mg, 2.46 mmol, 1.0 eq) and \(p\)-toluenesulfonic acid monohydrate (934 mg, 4.91 mmol, 2.0 eq) were stirred in acetone (35 mL) for 2 h. After work-up, purification by column chromatography on silica gel eluting with 0-10% ethyl acetate in petroleum ether (40-60 °C) gave ethyl (\(E\))-7-(naphthalen-1-yl)-2-(3-oxobutyl)hept-6-enoate 447a (763 mg, 2.17 mmol, 87%) as a colourless oil.

\(\nu_{\text{max}}\) (neat)/cm\(^{-1}\) 2936, 1717 (C=O), 1590.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 1.28 (3 H, t, \(J = 7.1\) Hz, OCH\(_2\)CH\(_3\)), 1.51 - 1.62 (3 H, m, CH\(_2\) + 1 H from CH\(_2\)CH\(_2\)), 1.70 - 1.80 (1 H, m, 1 H from CH\(_2\)CH\(_2\)), 1.86 (2 H, q, \(J = 7.3\) Hz, CH\(_2\)), 2.14 (3 H, s, CH\(_3\)), 2.29 - 2.50 (5 H, m, 2 × CH\(_2\) + CHCO\(_2\)Et), 4.17 (2 H, q, \(J = 7.1\) Hz, OCH\(_2\)CH\(_3\)), 6.14 - 6.28 (1 H, m, CH=CHAr), 7.12 (1 H, d, \(J = 15.4\) Hz, CH=CHAr), 7.40 - 7.58 (4 H, m, 4 × ArCH), 7.75 (1 H, d, \(J = 8.1\) Hz, ArCH) 7.84 (1 H, d, \(J = 7.8\) Hz, ArCH) 8.12 (1 H, d, \(J = 7.8\) Hz, ArCH).
$^{13}$C NMR (101 MHz, CDCl$_3$) δ ppm 14.3 (OCH$_2$CH$_3$), 26.0 (CH$_2$CHCO$_2$Et), 27.0 (CH$_2$), 30.0 (CH$_3$), 31.9 (CH$_2$), 33.2 (CH$_2$CH=CH), 41.1 (CH$_2$C(O)), 44.7 (CHCO$_2$Et), 60.3 (OCH$_2$CH$_3$), 123.5 (ArCH), 123.9 (ArCH), 125.7 (2 × ArCH), 125.8 (ArCH), 127.3 (ArCH), 127.5 (CH=CHAr), 128.4 (ArCH), 131.1 (ArC), 133.5 (CH=CHAr), 133.6 (ArC), 135.5 (ArC), 175.7 (CO$_2$Et), 207.9 (C=O).

$m/z$ (ES+) 353 [M+H]; HRMS calcd for $C_{23}H_{28}O_3$Na: 375.1931; found: 375.1927.

**Ethyl 2-(3-oxobutyl)-7,7-diphenylhept-6-enoate (447b)**

As for general procedure R, ethyl 2-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)-7,7-diphenylhept-6-enoate 446b (1.37 g, 3.24 mmol, 1.0 eq) and p-toluenesulfonic acid monohydrate (1.23 g, 6.49 mmol, 2.0 eq) were stirred in acetone (40 mL) for 2 h. After work-up, purification by column chromatography on silica gel eluting with 0-10% ethyl acetate in petroleum ether (40-60 °C) gave ethyl 2-(3-oxobutyl)-7,7-diphenylhept-6-enoate 447b (446 mg, 1.18 mmol, 38%) as a colourless oil.

$\nu_{\text{max}}$ (neat)/cm$^{-1}$ 2937, 1717 (C=O), 1598, 1495.

$^1$H NMR (400 MHz, CDCl$_3$) δ ppm 1.26 (3 H, t, $J = 7.2$ Hz, OCH$_2$CH$_3$), 1.39 - 1.50 (3 H, m, CH$_2$ + 1 H from CHCH$_2$), 1.58 - 1.68 (1 H, m, 1 H from CHCH$_2$), 1.79 (2 H, q, $J = 7.5$ Hz, CH$_2$), 2.08 - 2.17 (5 H, m, CH$_3$ + CH$_2$CH=CH), 2.25 - 2.33 (1 H, m, CHCO$_2$Et), 2.37 - 2.45 (2 H, m, CH$_2$C(O)), 4.12 (2 H, q, $J = 7.1$ Hz, OCH$_2$CH$_3$), 6.04 (1 H, t, $J = 7.5$ Hz, CH=CH), 7.14 - 7.41 (10 H, m, 10 × ArCH).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ ppm 14.3 (OCH$_2$CH$_3$), 25.9 (CH$_2$CHCO$_2$Et), 27.5 (CH$_2$), 29.5 (CH$_3$), 30.0 (CH$_2$), 32.0 (CH$_2$CH=C), 41.1 (CH$_2$C(O)), 44.7 (CHCO$_2$Et), 60.2 (OCH$_2$CH$_3$), 126.9 (2 × ArCH), 127.2 (2 × ArCH), 128.1 (2 × ArCH), 128.2 (2 × ArCH), 129.3 (2 × ArCH), 129.9 (CH=C), 140.1 (ArC), 142.0 (CH=C), 142.7 (ArC), 175.6 (CO$_2$Et), 207.9 (C=O).
Ethyl (E)-7-(furan-2-yl)-2-(3-oxobutyl)hept-6-enoate (447c)

As for general procedure R, ethyl (E)-7-(furan-2-yl)-2-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)hept-6-enoate 446c (820 mg, 2.45 mmol, 1.0 eq) and p-toluenesulfonic acid monohydrate (932 mg, 4.90 mmol, 2.0 eq) were stirred in acetone (35 mL) for 2 h. After work-up, purification by column chromatography on silica gel eluting with 0-10% ethyl acetate in petroleum ether (40-60 °C) gave ethyl (E)-7-(furan-2-yl)-2-(3-oxobutyl)hept-6-enoate 447c (503 mg, 1.72 mmol, 71%) as a colourless oil.

$\nu_{\text{max}}$ (neat)/cm$^{-1}$: 2936, 1716 (C=O), 1447.

$^{1}$H NMR (400 MHz, CDCl$_3$) δ ppm: 1.27 (3 H, t, $J = 7.2$ Hz, OCH$_2$CH$_3$), 1.41 - 1.55 (3 H, m, CH$_2$ + 1 H from CHCH$_2$), 1.67 (1 H, ddd, $J = 8.6$, 6.3, 2.6 Hz, 1 H from CHCH$_2$), 1.82 (2 H, q, $J = 7.5$ Hz, CH$_2$CH$_2$C(O)), 2.11 - 2.22 (5 H, m, CH$_3$ + ArCH=CHCH$_2$), 2.35 (1 H, td, $J = 7.7$, 4.3 Hz, CHCO$_2$Et), 2.44 (2 H, td, $J = 7.5$, 2.6 Hz, CH$_2$C(O)), 4.15 (2 H, q, $J = 7.2$ Hz, OCH$_2$CH$_3$), 6.08 - 6.16 (2 H, m, ArCH + CH=CHAr), 6.17 - 6.23 (1 H, m, CH=CHAr), 6.34 (1 H, dd, $J = 3.3$, 1.8 Hz, ArCH), 7.31 (1 H, d, $J = 1.6$ Hz, ArCH).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ ppm: 14.3 (OCH$_2$CH$_3$), 25.9 (CH$_2$CH$_2$C(O)), 26.8 (CH$_2$), 30.0 (CH$_3$), 31.8 (CHCH$_2$), 32.5 (ArCH=CHCH$_2$), 41.1 (CH$_2$C(O)), 44.6 (CHCO$_2$Et), 60.3 (OCH$_2$CH$_3$), 106.1 (ArCH), 111.1 (ArCH), 118.9 (ArCH=CH), 129.2 (ArCH=CH), 141.3 (ArCH), 153.1 (ArC), 175.7 (CO$_2$Et), 208.0 (C=O).

$m/z$ (ES+) 293 [M+H]; HRMS calcd for C$_{17}$H$_{24}$O$_4$Na: 315.1567; found: 315.1567.
Ethyl (E)-2-(3-oxobutyl)-7-phenyl-2-((E)-5-phenylpent-4-en-1-yl)hept-6-enate (450)

As for general procedure R, ethyl (E)-2-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)-7-phenyl-2-((E)-5-phenylpent-4-en-1-yl)hept-6-enate 449 (1.65 g, 3.36 mmol, 1.0 eq) and p-toluenesulfonic acid monohydrate (1.28 g, 6.73 mmol, 2.0 eq) were stirred in acetone (50 mL) for 2 h. After work-up, purification by column chromatography on silica gel eluting with 0-10% ethyl acetate in petroleum ether (40-60 °C) gave ethyl (E)-2-(3-oxobutyl)-7-phenyl-2-((E)-5-phenylpent-4-en-1-yl)hept-6-enate 450 (1.10 g, 2.46 mmol, 73%) as a colourless oil.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ ppm 1.25 (3 H, t, $J = 7.0$ Hz, OCH$_2$CH$_3$), 1.32 - 1.41 (4 H, m, 2 $\times$ CH$_2$CH$_2$CH=CH), 1.58 - 1.67 (4 H, m, 2 $\times$ CH$_2$CH$_2$CH$_2$CH=CH), 1.83 - 1.89 (2 H, m, CH$_2$CH$_2$C(O)), 2.11 (3 H, s, CH$_3$), 2.20 (4 H, q, $J = 6.8$ Hz, 2 $\times$ CH$_2$CH=CH), 2.30 - 2.36 (2 H, m, CH$_2$C(O)), 4.14 (2 H, q, $J = 7.0$ Hz, OCH$_2$CH$_3$), 6.18 (2 H, dt, $J = 15.8$, 6.9 Hz, CH=CHAr), 6.39 (2 H, d, $J = 15.8$ Hz, CH=CHAr), 7.17 - 7.22 (2 H, m, 2 $\times$ ArCH), 7.28 - 7.37 (8 H, m, 8 $\times$ ArCH).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ ppm 14.3 (OCH$_2$CH$_3$), 23.7 (2 $\times$ CH$_2$CH$_2$CH=CH), 28.3 (CH$_2$CH$_2$C(O)), 29.9 (CH$_3$), 33.3 (2 $\times$ CH$_2$CH=CH), 33.9 (2 $\times$ CH$_2$CH$_2$CH$_2$CH=CH), 38.7 (CH$_2$C(O)), 48.1 (CO$_2$Et), 60.4 (OCH$_2$CH$_3$), 125.9 (4 $\times$ ArCH), 126.9 (2 $\times$ ArCH), 128.5 (4 $\times$ ArCH), 130.2 (2 $\times$ CH=CHAr), 130.4 (2 $\times$ CH=CHAr), 137.7 (2 $\times$ ArC), 176.5 (CO$_2$Et), 207.4 (C=O).

$m/z$ (ES+) 469.6 [M+Na]; HRMS calcd for C$_{30}$H$_{38}$O$_3$Na: 469.2719; found: 469.2718.
6.6.3 Cross-metathesis

**Ethyl (E)-2-(3-oxobutyl)-7-(p-tolyl)hept-6-enoate (436b)**

As for general procedure G, ethyl 2-(3-oxobutyl)hept-6-enoate 435 (150 mg, 0.66 mmol, 1.0 eq), Grubbs 2nd generation catalyst (6.00 mg, 6.60 µmol, 1 mol%) and 4-methylstylene (234 mg, 2.00 mmol, 3.0 eq) in CH₂Cl₂ (4.0 mL) were stirred at reflux overnight. After work-up, purification by column chromatography on silica gel eluting with 20-80% CH₂Cl₂ in petroleum ether (40-60 °C) gave ethyl (E)-2-(3-oxobutyl)-7-(p-tolyl)hept-6-enoate 436b (114 mg, 0.29 mmol, 49%) as a yellow oil.

ν_max (neat)/cm⁻¹ 2932, 2859, 1717 (C=O), 1512.

¹H NMR (500 MHz, CDCl₃) δ ppm 1.27 (3 H, t, J = 7.1 Hz, OCH₂CH₃), 1.42 - 1.58 (3 H, m, CH₂ + 1 H from CHCH₂), 1.64 - 1.73 (1 H, m, 1 H from CHCH₂), 1.83 (2 H, q, J = 7.5 Hz, CH₂CH₂C(O)), 2.13 (3 H, s, CH₃), 2.17 - 2.24 (2 H, m, CH₂CH=CH), 2.33 (3 H, s, ArCH₃), 2.34 - 2.47 (3 H, m, CH₂C(O) + CHCO₂Et), 4.15 (2 H, q, J = 7.1 Hz, OCH₂CH₃), 6.13 (1 H, dt, J = 15.8, 6.9 Hz, CH=CHAr), 6.35 (1 H, d, J = 15.8 Hz, CH=CHAr), 7.10 (2 H, d, J = 7.9 Hz, 2 × ArCH), 7.23 (2 H, d, J = 7.9 Hz, 2 × ArCH).

¹³C NMR (126 MHz, CDCl₃) δ ppm 14.3 (OCH₂CH₃), 21.1 (ArCH₃), 25.9 (CH₂), 27.0 (CH₂), 30.0 (CH₃), 31.9 (CHCH₂), 32.8 (CH₂CH=CH), 41.1 (CH₂C(O)), 44.6 (CHCO₂Et), 60.3 (OCH₂CH₃), 125.8 (2 × ArCH), 129.2 (CH=CHAr + 2 × ArCH), 130.1 (CH=CHAr), 134.9 (ArC), 136.6 (ArC), 175.7 (CO₂Et), 208.0 (C=O).

m/z (ES+) 317.5 [M+H], 339.5 [M+Na] ; HRMS calcd for C₂₀H₂₈O₃Na: 339.1936; found: 339.1931.
Ethyl \((E)-7-(4\text{-bromophenyl})-2\text{-}(3\text{-oxobutyl})\text{-hept}-6\text{-enoate (436a)}\)

As for general procedure G, ethyl 2-(3-oxobutyl)hept-6-enoate \(435\) (200 mg, 0.88 mmol, 1.0 eq), Grubbs 2\text{nd} generation catalyst (5.50 mg, 8.80 \(\mu\)mol, 1 mol\%) and 4-bromostyrene (485 g, 2.65 mmol, 3.0 eq) in \(\text{CH}_2\text{Cl}_2\) (5.0 mL) were stirred at reflux overnight. After work-up, purification by column chromatography on silica gel eluting with 0-10% ethyl acetate in petroleum ether (40-60 °C) gave ethyl \((E)-7-(4\text{-bromophenyl})-2\text{-}(3\text{-oxobutyl})\text{-hept}-6\text{-enoate (436a)}\) (152 mg, 0.40 mmol, 45\%) as a yellow oil.

\(\nu_{\text{max}}\) (neat)/cm\(^{-1}\) 2935, 1716 (C=O), 1587, 1487.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 1.27 (3 H, t, \(J = 7.1\) Hz, OCH\(_2\)CH\(_3\)), 1.41 - 1.56 (3 H, m, CH\(_2\)CH\(_2\)CH=CH + 1 H from CHCH\(_2\)), 1.61 - 1.74 (1 H, m, 1 H from CHCH\(_2\)), 1.78 - 1.86 (2 H, m, CH\(_2\)CH\(_2\)C(O)), 2.13 (3 H, s, CH\(_3\)), 2.17 - 2.24 (2 H, m, CH\(_2\)CH=CH), 2.32 - 2.40 (1 H, m, CHCO\(_2\)Et), 2.41 - 2.49 (2 H, m, CH\(_2\)C(O)), 4.15 (2 H, q, \(J = 7.1\) Hz, OCH\(_2\)CH\(_3\)), 6.12 - 6.22 (1 H, m, CH=CHAr), 6.27 - 6.36 (1 H, m, CH=CHAr), 7.20 (2 H, d, \(J = 8.6\) Hz, 2 \(\times\) ArCH), 7.41 (2 H, d, \(J = 8.6\) Hz, 2 \(\times\) ArCH).

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) ppm 14.3 (OCH\(_2\)CH\(_3\)), 25.9 (CH\(_2\)CH\(_2\)C(O)), 26.8 (CH\(_2\)CH\(_2\)CH=CH), 30.0 (CH\(_3\)), 31.9 (CHCH\(_2\)), 32.8 (CH\(_2\)CH=CH), 41.1 (CH\(_2\)C(O)), 44.6 (CHCO\(_2\)Et), 60.3 (OCH\(_2\)CH\(_3\)), 120.5 (ArC), 127.5 (2 \(\times\) ArCH), 129.1 (CH=CHAr), 131.1 (CH=CHAr), 131.5 (2 \(\times\) ArCH), 136.6 (ArC), 175.6 (CO\(_2\)Et), 207.9 (C=O).

\(m/z\) (ES+) 381.0 [M+H]; HRMS calcd for C\(_{19}\)H\(_{25}\)O\(_3\)BrNa: 403.0885; found: 403.0898.
6-Cinnamyl-6-methyltetrahydro-2H-pyran-2-one (428)

As for general procedure G, 6-allyl-6-methyltetrahydro-2H-pyran-2-one 427 (500 mg, 3.57 mmol, 1.0 eq), Hoveyda–Grubbs 2nd generation catalyst (52.0 mg, 82.0 μmol, 2.3 mol%) and trans-stilbene (1.93 g, 10.7 mmol, 3.0 eq) in CH2Cl2 (10 mL) were stirred at reflux overnight. After work-up and purification by column chromatography on silica gel eluting with 0-10% ethyl acetate in petroleum ether (40-60 °C) gave 6-cinnamyl-6-methyltetrahydro-2H-pyran-2-one 428 (300 mg, 0.80 mmol, 40%) as a yellow oil.

^1^H NMR (400 MHz, CDCl3) δ ppm 1.34 (3 H, s, CH3), 1.59 - 1.67 (2 H, m, CH2), 1.73 - 1.87 (2 H, m, CH2CH2C(O)), 2.33 - 2.47 (2 H, m, CH2C(O)), 2.50 (2 H, dd, J = 7.5, 1.1 Hz, CH2CH=CHAr), 6.12 (1 H, dt, J = 15.7, 7.5 Hz, ArCH=CH), 6.39 (1 H, d, J = 15.7 Hz, ArCH=CH), 7.12 - 7.31 (5 H, m, 5 × ArCH).

^1^3^C NMR (101 MHz, CDCl3) δ ppm 16.5 (CH2), 26.4 (CH3), 29.3 (CH2C(O)), 31.6 (CH2), 45.4 (CH2CH=CH2), 84.0 (Cq), 123.8 (CH=CHAr), 126.1 (2 × ArCH), 127.4 (ArCH), 128.5 (2 × ArCH), 134.2 (CH=CHAr), 136.9 (ArC), 171.2 (C=O).

6.6.4 General procedure S: Barbier-type lacoisation

rac-(3R,6S)-6-Methyl-6-(1-phenyl-2i,5'-propa-1,2-dien-1-yl)-3-(5-phenylpent-4-yn-1-yl)tetrahydro-2H-pyran-2-one (trans-422a) and rac-(3S,6S)-6-Methyl-6-(1-phenyl-2i,5'-propa-1,2-dien-1-yl)-3-(5-phenylpent-4-yn-1-yl)tetrahydro-2H-pyran-2-one (cis-422a)

To a flask containing NiI2 (15.6 mg, 0.05 mmol, 8 mol%) was added SmI2 (29.0 mL, 2.90 mmol, 3.5 eq) and the resulting mixture cooled to 0 °C. Ethyl 2-(3-oxobutyl)-7-phenylhept-6-ynoate 418 (250 mg, 0.83 mmol, 1.0 eq) was then added followed
immediately by dropwise addition of (3-bromoprop-1-yn-1-yl)benzene 420a (179 mg, 0.91 mmol, 1.1 eq) in THF (8 mL) over 30 min. Once the addition was complete, the reaction mixture was warmed to room temperature and exposed to air until decolourisation occurred. The reaction was quenched with aqueous saturated Rochelle’s solution (10 mL) and extracted with Et₂O (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography eluting with 0-10% ethyl acetate in petroleum ether (40-60 °C) gave a 1:1 mixture of diastereomers rac-(3R,6S)-6-methyl-6-(1-phenyl-2λ⁵-propa-1,2-dien-1-yl)-3-(5-phenylpent-4-yn-1-yl)tetrahydro-2H-pyrano-2-one trans-422a and rac-(3S,6S)-6-methyl-6-(1-phenyl-2λ⁵-propa-1,2-dien-1-yl)-3-(5-phenylpent-4-yn-1-yl)tetrahydro-2H-pyrano-2-one cis-422a (131.6 mg, 0.36 mmol, 43%) as a yellow oil. The diastereomers could be separated by column chromatography.

trans-diastereomer:

νₘₐₓ (neat)/cm⁻¹ 2937, 1729 (C=O), 1490.

¹H NMR (400 MHz, CDCl₃) δ ppm 1.62 (3 H, s, CH₃), 1.65 - 1.75 (4 H, m, 2 × CH₂), 1.82 - 1.92 (1 H, m, 1 H from CH₂), 1.98 - 2.09 (1 H, m, 1 H from CH₂), 2.14 (1 H, d, J = 7.3 Hz, 1 H from CH₂), 2.24 (1 H, d, J = 6.3 Hz, 1 H from CH₂), 2.40 - 2.53 (3 H, m, CH + CH₂C≡C), 5.11 (2 H, s, C=CH₂), 7.23 - 7.49 (10 H, m, 10 × ArCH).

¹³C NMR (101 MHz, CDCl₃) δ ppm 19.4 (CH₂C≡C), 22.8 (CH₂), 26.1 (CH₂), 28.2 (CH₃), 30.8 (CH₂), 31.8 (CH₄CH₂), 38.4 (CH), 78.7 (C=CH₂), 81.0 (C≡CAr), 83.1 (C₆), 89.5 (C≡CAr), 110.2 (ArC=C=CH₂), 123.8 (ArC), 127.5 (ArCH), 127.6 (ArCH), 128.2 (2 × ArCH), 128.4 (2 × ArCH), 129.0 (2 × ArCH), 131.5 (2 × ArCH), 134.1 (ArC), 173.8 (C=O), 206.9 (C=CH₂).

m/z (ES⁺) 388.3 [M+Na]; HRMS calcd for C₂₆H₂₆O₂Na: 393.1831; found: 393.1818.

cis-diastereomer:

νₘₐₓ (neat)/cm⁻¹ 2935, 1729 (C=O), 1490, 1444.
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 1.61 (3 H, s, CH$_3$), 1.63 - 1.91 (5 H, m, 1 H from CH$_2$ + 2 $\times$ CH$_2$), 1.92 - 2.10 (2 H, m, CH$_2$), 2.21 - 2.28 (1 H, m, 1 H from CH$_2$), 2.41 - 2.52 (3 H, m, CH + CH$_2$C=C), 4.99 - 5.14 (2 H, m, C=CH$_2$), 7.25 - 7.42 (10 H, m, 10 $\times$ ArCH).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ ppm 19.4 (C$_{q}$CH$_2$C≡C), 23.0 (CH$_2$), 26.0 (CH$_2$), 28.6 (CH$_3$), 31.2 (CH$_2$), 32.4 (C$_{q}$CH$_2$), 39.6 (CH), 78.7 (C=CH$_2$), 80.9 (C=CAr), 83.4 (C$_{q}$), 89.8 (C=CAr), 110.7 (ArC=C=CH$_2$), 123.8 (ArC), 127.6 (2 $\times$ ArCH), 128.2 (2 $\times$ ArCH), 128.4 (2 $\times$ ArCH), 129.1 (2 $\times$ ArCH), 131.5 (2 $\times$ ArCH), 134.7 (ArC), 173.4 (C=O), 206.8 (C=CH$_2$).

$m/z$ (ES+) 388.3 [M+Na]; HRMS calcd for C$_{26}$H$_{26}$O$_2$Na: 393.1831; found: 393.1826.

**rac-(3R,6S)-6-(1-(4-Methoxyphenyl)-2,5-propa-1,2-dien-1-yl)-6-methyl-3-(5-phenylpent-4-yn-1-yl)tetrahydro-2H-pyran-2-one (trans-422b)**

![Structure of rac-(3R,6S)-6-(1-(4-Methoxyphenyl)-2,5-propa-1,2-dien-1-yl)-6-methyl-3-(5-phenylpent-4-yn-1-yl)tetrahydro-2H-pyran-2-one (trans-422b)](image)

As for general procedure S, reaction of NiI$_2$ (15.6 mg, 0.05 mmol, 8 mol%), SmI$_2$ (25.0 mL, 2.50 mmol, 3.0 eq), ethyl 2-(3-oxobutyl)-7-phenylhept-6-ynoate 418 (250 mg, 0.83 mmol, 1.0 eq) and 1-(3-bromoprop-1-yn-1-yl)-4-methoxybenzene 420b (206 mg, 0.91 mmol, 1.1 eq) in THF (8 mL). After work-up, purification by column chromatography on silica gel eluting with 0-10% ethyl acetate in petroleum ether (40-60 °C) gave rac-(3R,6S)-6-(1-(4-methoxyphenyl)-2,5-propa-1,2-dien-1-yl)-6-methyl-3-(5-phenylpent-4-yn-1-yl)tetrahydro-2H-pyran-2-one **trans-422b** (combined yield for cis and trans isomers: 42%; for trans: 69.3 mg, 0.17 mmol, 21%) as a yellow oil.

**trans-diastereomer:**

$\nu_{\text{max}}$ (neat)/cm$^{-1}$ 2935, 1729 (C=O), 1606, 1509.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ ppm 1.61 (3 H, s, CH$_3$), 1.63 - 1.74 (4 H, m, 2 $\times$ CH$_2$), 1.86 (1 H, dt, $J$ = 14.0, 6.9 Hz, 1 H from C$_{q}$CH$_2$), 1.99 - 2.08 (1 H, m, 1 H from CH$_2$), 2.14 (1
H, dd, \( J = 14.2, \ 6.9 \) Hz, 1 H from CH\(_2\)), 2.24 (1 H, dd, \( J = 14.2, \ 7.3 \) Hz, 1 H from C\(_4\)CH\(_2\)),

\[ \text{2.40} - 2.51 \ (3 \ H, \ m, \ CH + CH\(_2\)C=C), \ 3.80 \ (3 \ H, \ s, \ OCH), \ 5.08 \ (2 \ H, \ s, \ C=CH\(_2\)), \ 6.84 - 6.89 \ (2 \ H, \ m, \ 2 \times \text{ArCH}), \ 7.26 - 7.30 \ (3 \ H, \ m, \ 3 \times \text{ArCH}), \ 7.34 - 7.41 \ (4 \ H, \ m, \ 4 \times \text{ArCH}). \]

\(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \( \delta \) ppm 19.4 (CH\(_2\)C≡C), 22.8 (CH\(_2\)), 26.1 (CH\(_2\)), 28.2 (CH\(_3\)),

30.8 (CH\(_2\)), 31.9 (C\(_4\)CH\(_2\)), 38.3 (CH), 55.2 (OCH\(_3\)), 78.5 (C=CH\(_2\)), 81.0 (C=CAr), 83.1 (C\(_q\)), 89.6 (C=CAr), 109.8 (ArC=CH\(_2\)), 113.8 (2 \times \text{ArCH}), 123.8 (ArC), 126.0 (ArC),

127.6 (ArCH), 128.2 (2 \times \text{ArCH}), 130.1 (2 \times \text{ArCH}), 131.5 (2 \times \text{ArCH}), 159.0 (ArCOCH\(_3\)), 173.9 (C=O), 207.3 (C=CH\(_2\)).

\( m/z \) (ES+) 401.3 [M+H]; HRMS calcd for C\(_{27}\)H\(_{28}\)O\(_3\)Na: 423.1932; found: 423.1936.

\( \text{rac-}(3R,6S)-6-(1-(\text{dimethyl(phenyl)silyl})-2\lambda^5\text{-propa-1,2-dien-1-yl})-6\text{-methyl-3-(5-phenylpent-4-yn-1-yl)tetrahydro-2H-pyran-2-one (trans-422c)} \)

As for general procedure S, reaction of NiI\(_2\) (15.6 mg, 0.05 mmol, 8 mol%), SmI\(_2\) (25.0 mL, 2.50 mmol, 3.0 eq), ethyl 2-(3-oxobutyl)-7-phenylhept-6-ynoate 418 (250 mg, 0.83 mmol, 1.0 eq) and (3-bromoprop-1-yn-1-yl)dimethyl(phenyl)silane 420c (232 mg, 0.91 mmol, 1.1 eq) in THF (9 mL). After work-up, purification by column chromatography on silica gel eluting with 0-10% ethyl acetate in petroleum ether (40-60 °C) gave \( \text{rac-}(3R,6S)-6-(1-(\text{dimethyl(phenyl)silyl})-2\lambda^5\text{-propa-1,2-dien-1-yl})-6\text{-methyl-3-(5-phenylpent-4-yn-1-yl)tetrahydro-2H-pyran-2-one (trans-422c)} \) (combined yield for cis and trans isomers: 41%; for trans: 72.4 mg, 0.17 mmol, 20%) as a viscous orange oil.

\( \text{trans-diastereomer:} \)

\( \nu_{\text{max}} \) (neat)/cm\(^{-1}\) 2954, 1927, 1731 (C=O), 1489.

\(^{1}\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) ppm 0.35 - 0.38 (3 H, s, SiCH\(_3\)), 0.45 - 0.49 (3 H, m, SiCH\(_3\)),

1.33 (3 H, s, CH\(_3\)), 1.35 - 1.49 (4 H, m, 2 \times \text{CH}_2), 1.58 - 1.64 (1 H, m, 1 H from CH\(_2\)),

1.70 - 1.83 (4 H, m, 2 \times \text{CH}_2), 1.89 (1 H, ddd, \( J = 13.7, \ 7.9, \ 5.5 \) Hz, 1 H from CH\(_2\)), 196
2.27 (2 H, td, \( J = 7.0, 2.4 \text{ Hz}, \text{CH} \)), 4.53 (2 H, s, C=CH\text{2}), 7.18 - 7.33 (8 H, m, 8 \times \text{ArCH}), 7.47 - 7.51 (2 H, m, 2 \times \text{ArCH}).

\(^{13}\text{C NMR} (126 \text{ MHz, CDCl}_3) \delta \text{ ppm} -1.9 (\text{SiCH}_3), -1.5 (\text{SiCH}_3), 19.4 (\text{CH}_2), 22.8 (\text{CH}_2), 26.1 (\text{CH}_2), 29.6 (\text{CH}_3), 30.7 (\text{CH}_2), 33.3 (\text{CH}_2), 38.3 (\text{CH}), 72.3 (\text{C}=\text{CH}_2), 80.9 (\text{C}=\text{CAr}), 84.8 (\text{C}=\text{Ar}), 89.7 (\text{C}=\text{Ar}), 102.7 ((\text{PhMe}_2\text{Si})\text{C}=\text{CH}_2), 123.9 (\text{ArC}), 127.5 (\text{ArCH}), 127.8 (2 \times \text{ArCH}), 128.2 (2 \times \text{ArCH}), 129.2 (\text{ArCH}), 131.5 (2 \times \text{ArCH}), 134.1 (2 \times \text{ArCH}), 137.8 (\text{ArC}), 173.6 (\text{C}=\text{O}), 207.9 (\text{C}=\text{CH}_2).

\(m/z\) (ES+) 429.0 [M+H]; HRMS calcd for C\(_{28}\)H\(_{32}\)O\(_2\)SiNa: 451.2069; found: 451.2048.

6-Allyl-6-methyltetrahydro-2\(H\)-pyran-2-one (427)

As for general procedure S, reaction of NiI\(_2\) (48 mg, 0.15 mmol, 8 mol%), SmI\(_2\) (76.0 mL, 7.59 mmol, 4.0 eq), methyl 5-oxohexanoate (300 mg, 1.90 mmol, 1.0 eq), allyl bromide (252 mg, 2.09 mmol, 1.1 eq) in THF (19 mL). After work-up, purification by column chromatography on silica gel eluting with 0-10\% ethyl acetate in petroleum ether (40-60 °C) gave the title compound 6-allyl-6-methyltetrahydro-2\(H\)-pyran-2-one 427 (245 mg, 1.59 mmol, 84\%) as a yellow oil.

\(^1\text{H NMR} (400 \text{ MHz, CDCl}_3) \delta \text{ ppm} 1.37 (3 \text{ H, s, CH}_3), 1.63 - 1.71 (1 \text{ H, m, 1 H from CH}_2), 1.77 - 1.93 (3 \text{ H, m, 1 H from CH}_2 + CH\text{2CH}_2\text{C(O)}), 2.40 - 2.58 (4 \text{ H, m, CH\text{2CH}=CH}_2 + CH\text{2C(O)}), 5.10 - 5.19 (2 \text{ H, m, CH=CH}_2), 5.80 (1 \text{ H, ddt, } J = 14.5, 10.2, 7.3 \text{ Hz, CH}=\text{CH}_2).

\(^{13}\text{C NMR} (101 \text{ MHz, CDCl}_3) \delta \text{ ppm} 16.5 (\text{CH}_2), 26.3 (\text{CH}_3), 29.3 (\text{CH\text{2C(O)}}), 31.4 (\text{CH}_2), 46.1 (\text{CH\text{2CH}=CH}_2), 83.6 (\text{C}=\text{O}), 119.4 (\text{CH=CH}_2), 132.3 (\text{CH=CH}_2), 171.2 (\text{C}=\text{O}).
rac-(3R,6S)-6-Methyl-6-(1-phenyl-2λ5-propa-1,2-dien-1-yl)-3-((E)-5-(p-tolyl)pent-4-en-1-yl)tetrahydro-2H-pyran-2-one (trans-451a)

As for general procedure S, reaction of NiI\(_2\) (17 mg, 0.06 mmol, 8 mol%), SmI\(_2\) (28.0 mL, 2.80 mmol, 3.0 eq), ethyl (E)-2-(3-oxobutyl)-7-(p-tolyl)hept-6-enoate 436b (250 mg, 0.79 mmol, 1.0 eq), (3-bromoprop-1-y1n-1-y1)benzene 420a (170 mg, 0.87 mmol, 1.1 eq) in THF (8 mL). After work-up, purification by column chromatography on silica gel eluting with 0-10% ethyl acetate in petroleum ether (40-60 °C) gave rac-(3R,6S)-6-methyl-6-(1-phenyl-2λ5-propa-1,2-dien-1-yl)-3-((E)-5-(p-tolyl)pent-4-en-1-yl)tetrahydro-2H-pyran-2-one trans-451a (combined yield for cis and trans isomers: 54%; for trans: 81.7 mg, 0.21 mmol, 27%) as a colourless oil.

trans-diastereomer:

_ν_{max} (neat)/cm\(^{-1}\) 2934, 1946, 1728 (C=O), 1598.

\(^1\)H NMR (500 MHz, CDCl\(_3\)) δ ppm 1.49 - 1.71 (4 H, m, 2 × CH\(_2\)), 1.62 (3 H, s, CH\(_3\)), 1.86 (1 H, dt, _J_ = 14.0, 6.7 Hz, 1 H from ArCH=CHCH\(_2\)), 1.92 - 1.99 (1 H, m, 1 H from CHCH\(_2\)), 2.11 (1 H, dq, _J_ = 13.8, 6.9 Hz, 1 H from CHCH\(_2\)), 2.19 - 2.27 (3 H, m, CH\(_2\) + 1 H from ArCH=CHCH\(_2\)), 2.33 (3 H, s, ArCH\(_3\)), 2.41 - 2.48 (1 H, m, CH), 5.12 (2 H, s, C=CH\(_2\)), 6.16 (1 H, dt, _J_ = 15.8, 6.9 Hz, ArCH=CH), 6.36 (1 H, d, _J_ = 15.8 Hz, ArCH=CH), 7.11 (2 H, d, _J_ = 7.9 Hz, 2 × ArCH), 7.24 (2 H, d, _J_ = 7.9 Hz, 2 × ArCH), 7.27 - 7.37 (3 H, m, 3 × ArCH), 7.42 - 7.47 (2 H, m, 2 × ArCH).

\(^13\)C NMR (126 MHz, CDCl\(_3\)) δ ppm 21.1 (ArCH\(_3\)), 22.6 (CH\(_2\)), 26.7 (CH\(_2\)), 28.1 (CH\(_3\)), 31.0 (CH\(_2\)), 31.8 (CH\(_2\)), 32.9 (CH\(_2\)), 38.6 (CH), 78.7 (C=CH\(_2\)), 82.9 (C\(_q\)), 110.2 (ArC=C=CH\(_2\)), 125.8 (2 × ArCH), 127.4 (ArCH), 128.4 (2 × ArCH), 128.9 (2 × ArCH), 129.1 (2 × ArCH), 129.2 (ArCH=CH), 130.0 (ArCH=CH), 134.0 (ArC), 134.9 (ArC), 136.5 (ArC), 174.0 (C=O), 207.4 (C=CH\(_2\)).

_\textit{m/z} (ES+) 387.0 [M+H]; HRMS calcd for C\(_{27}\)H\(_{31}\)O\(_2\): 387.2319; found: 387.2310.
$rac-(3R,6S)-3-((E)-5-(4\text{-bromophenyl})\text{pent}-4\text{-en}-1\text{-yl})-6\text{-methyl}-6-(1\text{-phenyl}-2\text{$\lambda^5$-propa}-1,2\text{-dien}-1\text{-yl})\text{tetrahydro}\text{-2H-pyran-2-one (trans-451b)}$

As for general procedure S, reaction of NiI$_2$ (15.6 mg, 0.05 mmol, 8 mol%), SmI$_2$ (28.0 mL, 2.80 mmol, 3.0 eq), ethyl (E)-7-(4-bromophenyl)-2-(3-oxobutyl)hept-6-enoate 436a (317 mg, 0.83 mmol, 1.0 eq), (3-bromoprop-1-yn-1-yl)benzene 420a (179 mg, 0.91 mmol, 1.1 eq) in THF (8 mL). After work-up, purification by column chromatography on silica gel eluting with 0-10% ethyl acetate in petroleum ether (40-60 °C) gave $rac-(3R,6S)-3-((E)-5-(4\text{-bromophenyl})\text{pent}-4\text{-en}-1\text{-yl})-6\text{-methyl}-6-(1\text{-phenyl}-2\text{$\lambda^5$-propa}-1,2\text{-dien}-1\text{-yl})\text{tetrahydro}\text{-2H-pyran-2-one (trans-451b)}$ (combined yield for cis and trans isomers: 30%; for trans: 55.2 mg, 0.12 mmol, 15%) as a colourless oil.

$trans$-diastereomer:

$\nu_{\text{max}}$ (neat)/cm$^{-1}$ 2933, 1947, 1727 (C=O), 1589.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 1.50 - 1.71 (4 H, m, 2 $\times$ CH$_2$), 1.61 (3 H, s, CH$_3$) 1.81 - 1.98 (2 H, m, 1 H from CH$_2$ + 1 H from ArCH=CH$CH_2$), 2.06 - 2.17 (1 H, m, 1 H from CH$_2$), 2.18 - 2.27 (3 H, m, CH$_2$ + 1 H from ArCH=CH$CH_2$), 2.39 - 2.48 (1 H, m, CH), 5.12 (2 H, s, C=CH$_2$), 6.15 - 6.24 (1 H, m, ArCH=CH$CH_2$), 6.28 - 6.36 (1 H, m, ArCH=CH$CH_2$), 7.16 - 7.23 (2 H, m, 2 $\times$ ArCH), 7.28 - 7.47 (7 H, m, 7 $\times$ ArCH).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ ppm 22.6 (CH$_2$), 26.5 (CH$_2$), 28.1 (CH$_3$), 31.0 (CH$_2$), 31.8 (CH$_2$), 32.9 (CH$_2$), 38.6 (CH), 78.7 (C=CH$_2$), 83.0 (C$q$), 110.2 (ArC=C=CH$_2$), 120.5 (ArC), 127.5 (3 $\times$ ArCH), 128.4 (2 $\times$ ArCH), 128.9 (2 $\times$ ArCH), 129.1 (ArCH=CH), 131.1 (ArCH=CH$CH_2$), 131.5 (2 $\times$ ArCH), 134.0 (ArC), 136.6 (ArC), 174.0 (C=O), 207.4 (C=CH$_2$).

$m/z$ (ES$^+$) 485.5 [M+K]; HRMS calcd for C$_{26}$H$_{28}$O$_2$Br: 451.1267; found: 451.1267.
As for general procedure S, reaction of NiI₂ (21 mg, 0.068 mmol, 8 mol%), SmI₂ (34.2 mL, 3.42 mmol, 4.0 eq), ethyl (E)-7-(naphthalen-1-yl)-2-(3-oxobutyl)hept-6-enoate 447a (300 mg, 0.85 mmol, 1.0 eq), (3-bromoprop-1-ynyl)benzene 420a (183 mg, 0.93 mmol, 1.1 eq) in THF (9 mL). After work-up, purification by column chromatography on silica gel eluting with 0-10% ethyl acetate in petroleum ether (40-60 °C) gave rac-(3R,6S)-6-methyl-3-(E)-5-(naphthalen-1-yl)pent-4-en-1-yl)-6-(1-phenyl-2λ₅-propa-1,2-dien-1-yl)tetrahydro-2H-pyran-2-one trans-451c (combined yield for cis and trans isomers: 17%; for trans: 30.0 mg, 71.0 μmol, 8%) as a yellow oil.

trans-diastereomer:

ν_max (neat)/cm⁻¹ 2934, 1727 (C=O), 1589, 1491.

¹H NMR (500 MHz, CDCl₃) δ ppm 1.49 - 1.67 (7 H, m, CH₃ + 2 × CH₂), 1.81 (1 H, dt, J = 14.0, 6.7 Hz, 1 H from CH₂), 1.91 - 1.99 (1 H, m, 1 H from CH₂), 2.07 (1 H, dq, J = 14.1, 6.9 Hz, 1 H from CHCH₂), 2.18 (1 H, ddd, J = 14.1, 7.6, 6.3 Hz, 1 H from CHCH₂), 2.25 - 2.34 (2 H, m, ArCH=CHCH₂), 2.41 (1 H, ddd, J = 7.3, 5.1, 2.4 Hz, CH), 5.05 (2 H, s, C=CH₂), 6.16 (1 H, dt, J = 15.5, 7.0 Hz, ArCH=CH), 7.06 (1 H, d, J = 15.5 Hz, ArCH=CH), 7.19 - 7.23 (1 H, m, ArCH), 7.25 - 7.29 (2 H, m, 2 × ArCH), 7.34 - 7.46 (5 H, m, 5 × ArCH), 7.48 (1 H, d, J = 6.9 Hz, ArCH), 7.68 (1 H, d, J = 8.2 Hz, ArCH), 7.75 - 7.81 (1 H, m, ArCH), 8.05 (1 H, d, J = 8.2 Hz, ArCH).

¹³C NMR (126 MHz, CDCl₃) δ ppm 22.7 (CH₃), 26.7 (CH₂), 28.1 (CH₃), 31.1 (CH₂), 31.9 (CHCH₂), 33.3 (ArCH=CHCH₂), 38.7 (CH), 78.7 (C=CH₂), 83.0 (C₄), 110.3 (ArC=CH=CH), 123.5 (ArCH), 123.9 (ArCH), 125.6 (2 × ArCH), 125.8 (ArC), 127.3 (ArCH), 127.5 (ArCH=CH + ArCH), 128.4 (3 × ArCH), 129.0 (2 × ArCH), 131.1 (ArC), 133.6 (ArCH=CH + ArCH), 134.1 (ArC), 135.5 (ArC), 174.0 (C=O), 207.4 (C=CH₂).
$m/z$ (ES+) 423.1 [M+H]; HRMS calcd for $C_{30}H_{31}O_2$: 423.2319; found: 423.2316.

rac-(3R,6S)-3-(5,5-Diphenylpent-4-en-1-yl)-6-methyl-6-(1-phenyl-2λ^5-propa-1,2-dien-1-yl)tetrahydro-2H-pyran-2-one (trans-451d)

As for general procedure S, reaction of NiI$_2$ (22 mg, 0.070 mmol, 8 mol%), SmI$_2$ (35 mL, 3.5 mmol, 4.0 eq), ethyl 2-(3-oxobutyl)-7,7-diphenylhept-6-enoate 447b (330 mg, 0.87 mmol, 1.0 eq), (3-bromoprop-1-yn-1-yl)benzene 420a (187 mg, 0.96 mmol, 1.1 eq) in THF (9 mL). After work-up, purification by column chromatography on silica gel eluting with 0-10% ethyl acetate in petroleum ether (40-60 °C) gave rac-(3R,6S)-3-(5,5-diphenylpent-4-en-1-yl)-6-methyl-6-(1-phenyl-2λ^5-propa-1,2-dien-1-yl)tetrahydro-2H-pyran-2-one trans-451d (combined yield for cis and trans isomers: 42%; for trans: 40 mg, 0.18 mmol, 21%) as a colourless oil.

**trans-diastereomer:**

$\nu_{\text{max}}$ (neat)/cm$^{-1}$ 2945, 1727 (C=O), 1598, 1493.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 1.42 - 1.67 (5 H, m, CH$_2$ + CH$_3$), 1.78 - 1.96 (3 H, m, CH$_2$ + 1 H from CH$_2$), 1.99 - 2.26 (5 H, m, CH$_2$ + 1 H from CH$_2$ + CH$_2$CH=C), 2.28 - 2.42 (1 H, m, CH), 5.00 - 5.16 (2 H, m, C=q=CH$_2$), 6.08 (1 H, t, $J = 7.3$ Hz, CH=C), 7.13 - 7.49 (15 H, m, 15 × ArCH).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ ppm 22.6 (CH$_2$), 27.1 (CH$_2$), 28.1 (CH$_3$), 29.5 (CH$_2$), 31.1 (CH$_2$), 31.8 (CH$_2$CH=C), 38.5 (CH), 78.6 (C=CH$_2$), 82.9 (C=q), 110.3 (ArC=C=CH$_2$), 126.9 (2 × ArCH), 127.2 (2 × ArCH), 127.4 (ArCH), 128.0 (2 × ArCH), 128.1 (2 × ArCH), 128.4 (2 × ArCH), 129.0 (2 × ArCH), 129.3 (CH=C=q), 129.8 (2 × ArCH), 134.1 (ArC), 140.1 (ArC), 142.0 (CH=C), 142.6 (ArC), 173.9 (C=O), 207.4 (C=CH$_2$).

$m/z$ (ES+) 449.0 [M+H]; HRMS calcd for $C_{32}H_{32}O_2$: 449.2475; found: 449.2461.
rac-(3R,6S)-3-((E)-5-(Furan-2-yl)pent-4-en-1-yl)-6-methyl-6-(1-phenyl-2λ^5^-propa-1,2-dien-1-yl)tetrahydro-2H-pyran-2-one (trans-451e)

As for general procedure S, reaction of NiI₂ (21.0 mg, 0.068 mmol, 8 mol%), SmI₂ (34.2 mL, 3.42 mmol, 4.0 eq), ethyl (E)-7-(furan-2-yl)-2-(3-oxobutyl)hept-6-enoate 447c (250 mg, 0.86 mmol, 1.0 eq), (3-bromoprop-1-yn-1-yl)benzene 420a (183 mg, 0.94 mmol, 1.1 eq) in THF (9 mL). After work-up, purification by column chromatography on silica gel eluting with 0-10% ethyl acetate in petroleum ether (40-60 °C) gave rac-(3R,6S)-3-((E)-5-(furan-2-yl)pent-4-en-1-yl)-6-methyl-6-(1-phenyl-2λ^5^-propa-1,2-dien-1-yl)tetrahydro-2H-pyran-2-one trans-451e (combined yield for cis and trans isomers: 28%; for trans: 41.9 mg, 0.12 mmol, 14%) as a yellow oil.

trans-diastereomer:

ν\textsubscript{max} (neat)/cm\textsuperscript{-1} 2938, 1728 (C=O), 1492.

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ ppm 1.47 - 1.71 (3 H, m, CH\textsubscript{2} + 1 H from CH\textsubscript{2}), 1.61 (3 H, s, CH\textsubscript{3}), 1.80 - 2.00 (2 H, m, CH\textsubscript{2}), 2.03 - 2.28 (5 H, m, ArCH=CHH\textsubscript{2} + CH\textsubscript{2} + 1 H from CH\textsubscript{2}), 2.37 - 2.49 (1 H, m, CH), 5.11 (2 H, s, C=CH\textsubscript{2}), 6.07 - 6.27 (3 H, m, ArCH + 2 × CH=CH), 6.34 (1 H, dd, J = 3.1, 1.8 Hz, ArCH), 7.24 - 7.37 (4 H, m, 4 × ArCH), 7.44 (2 H, d, J = 7.1 Hz, 2 × ArCH).

\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) δ ppm 22.7 (CH\textsubscript{2}), 26.5 (CH\textsubscript{2}), 28.2 (CH\textsubscript{3}), 31.0 (CH\textsubscript{2}), 31.9 (CH\textsubscript{2}), 32.7 (CH\textsubscript{2}CH=C), 38.6 (CH), 78.6 (C=CH\textsubscript{2}), 82.9 (C\textsubscript{q}), 106.1 (ArCH), 110.4 (ArC=C=CH\textsubscript{2}), 111.1 (ArCH), 119.0 (ArCH=CH), 127.5 (ArCH), 128.3 (ArCH=CH), 129.0 (2 × ArCH), 129.3 (2 × ArCH), 134.1 (ArC), 141.2 (ArCH), 153.1 (ArC), 173.9 (C=O), 207.4 (C=CH\textsubscript{2}).

m/z (ES+) 362.0 [M]; HRMS calcd for C\textsubscript{24}H\textsubscript{27}O\textsubscript{3}: 363.1955; found: 363.1960.
6.6.5 SmI$_2$-H$_2$O-mediated cyclisation cascades

$\textit{rac-}(1R,2R,5S,6S,7S)$-6-(Dimethyl(phenyl)silyl)-5,7-dimethyl-2-(5-phenylpent-4-yn-1-yl)-8-oxabicyclo[3.2.1]octan-1-ol (425a)

![Chemical structure of 425a]

As for general procedure S, $\textit{rac-}(3R,6S)$-6-methyl-6-(1-phenyl-2\(^5\)-propa-1,2-dien-1-yl)-3-(5-phenylpent-4-yn-1-yl)tetrahydro-2H-pyran-2-one $\textit{trans-}422a$ (40.0 mg, 93.4 \(\mu\)mol, 1.0 eq) in THF (1.00 mL) and H$_2$O (6.70 mL, 374 mmol, 4000 eq) with SmI$_2$ (0.1 M in THF, 7.5 mL, 0.75 mmol, 8.0 eq) were stirred at room temperature until complete decolourisation had occurred. After work-up, purification by column chromatography on silica gel, eluting with 0-10% ethyl acetate in hexane gave $\textit{rac-}(1R,2R,5S,6S,7S)$-6-(dimethyl(phenyl)silyl)-5,7-dimethyl-2-(5-phenylpent-4-yn-1-yl)-8-oxabicyclo[3.2.1]octan-1-ol 425a (27.0 mg, 62.4 \(\mu\)mol, 67%) as a yellow oil.

\(\nu_{\text{max}}\) (neat)/cm\(^{-1}\) 3083 (O–H), 2951, 1693, 1603, 1495, 1453.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 0.40 (3 H, s, SiCH\(_3\)), 0.47 (3 H, s, SiCH\(_3\)), 1.10 (3 H, s, CH\(_3\)), 1.14 (3 H, d, \(J = 7.5\) Hz, CHCH\(_3\)), 1.30 - 1.38 (1 H, m, 1 H from CH\(_2\)C(O)Me), 1.47 - 1.89 (8 H, m, 3 \(\times\) CH\(_2\) + 1 H from CH\(_2\)COMe + CH), 1.99 (1 H, d, \(J = 13.3\) Hz, CH\(_2\)Si(CH\(_3\))\(_2\)Ph), 2.37 - 2.52 (4 H, m, CHCH\(_3\) + CH\(_2\)C≡C + OH), 7.22 - 7.31 (3 H, m, 3 \(\times\) ArCH), 7.32 - 7.44 (5 H, m, 5 \(\times\) ArCH), 7.49 - 7.59 (2 H, m, 2 \(\times\) ArCH).

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) ppm -0.4 (Si(CH\(_3\))), 0.1 (Si(CH\(_3\))), 12.8 (CHCH\(_3\)), 19.7 (CH\(_2\)C≡C), 22.2 (CH\(_2\)CH\(_2\)C(O)Me), 26.3 (CH\(_2\)), 27.5 (CH\(_2\)), 28.3 (CH\(_3\)), 31.0 (CH\(_2\)C(O)Me), 36.3 (CH), 41.0 (CHSi(CH\(_3\))\(_2\)Ph), 47.8 (CHCH\(_3\)), 80.7 (C≡CAr), 84.2 (C\(_q\)), 90.3 (C≡CAr), 105.8 (CO(OH)), 124.0 (ArC), 127.4 (ArCH), 127.9 (2 \(\times\) ArCH), 128.1 (2 \(\times\) ArCH), 129.0 (ArCH), 131.5 (2 \(\times\) ArCH), 133.7 (2 \(\times\) ArCH), 139.3 (ArC).

\(m/z\) (ES+) 455.5 [M+Na]; HRMS calcd for C\(_{28}\)H\(_{36}\)O\(_2\)SiNa: 455.2382; found: 455.2398.
As for general procedure P, rac-(3R,6S)-6-methyl-6-(1-phenyl-2λ -propa-1,2-dien-1-yl)-3-((E)-5-(p-tolyl)pent-4-en-1-yl)tetrahydro-2H-pyran-2-one 451a (33.0 mg, 85.0 μmol, 1.0 eq) in THF (0.85 mL) and H2O (6.1 mL, 342 mmol, 4000 eq) with SmI2 (0.1 M in THF, 6.8 mL, 0.68 mmol, 8.0 eq) were stirred at room temperature until complete decolourisation had occurred. After work-up, purification by column chromatography on silica gel, eluting with 0-10% ethyl acetate in hexane gave rac-(4S,4aS,5R,6R,7S,9aR)-5,7-dimethyl-4-(4-methylbenzyl)-6-phenyldecahydro-4aH-benzo[7]annulene-4a,7-diol 453a (16.1 mg, 41.0 μmol, 48%) as a white solid.

νmax (neat)/cm−1 2926 (O-H), 2852 (O-H), 1446.

1H NMR (500 MHz, CDCl3) δ ppm 1.11 (3 H, s CH3), 1.12 - 1.18 (1 H, m, 1 H from CH2), 1.20 - 1.37 (3 H, m, CH2 + 1 H from CH2), 1.41 - 1.47 (2 H, m, CH2), 1.45 (3 H, d, J = 7.6 Hz, CHCH2), 1.50 - 1.56 (1 H, m, CH bridgehead), 1.59 - 1.65 (1 H, m, 1 H from CH2), 1.70 - 1.77 (1 H, m, CHCH2Ar), 1.84 (1 H, dd, J = 15.4, 11.7 Hz, 1 H from CH2), 1.97 - 2.11 (3 H, m, 1 H from CH2Ar + CH2), 2.31 (3 H, s, ArCH3), 2.51 (1 H, q, J = 7.6 Hz, CHCH3), 2.82 (1 H, dd, J = 13.4, 3.2 Hz, 1 H from CH2Ar), 3.92 (1 H, s, CHPh), 4.51 (2 H, d, J = 7.9 Hz, 2 × ArCH), 7.05 (2 H, d, J = 7.6 Hz, 2 × ArCH), 7.25 (1 H, s, ArCH), 7.33 (2 H, t, J = 7.6 Hz, 2 × ArCH), 7.41 (2 H, d, J = 7.2 Hz, 2 × ArCH).

13C NMR (101 MHz, CDCl3) δ ppm 13.3 (CHCH3), 21.0 (ArCH3), 25.8 (CH2), 26.4 (CH2), 26.6 (CH2), 28.3 (CH3), 30.9 (CH2), 34.3 (CH2Ar), 43.0 (CHCH3), 43.2 (CH2), 44.4 (CHCH2Ar), 45.2 (CH bridgehead), 49.4 (CHPh), 74.8 (C0OH(CH3)), 77.2 (COH), 126.3 (ArCH), 128.3 (2 × ArCH), 128.9 (2 × ArCH), 129.0 (2 × ArCH), 129.6 (2 × ArCH), 135.1 (ArC), 138.1 (ArC), 145.4 (ArC).

m/z (ES+) 374.2 [M–H2O]; HRMS calcd for C27H36O2Na: 415.2608; found: 415.2612.
As for general procedure P, rac-(3R,6S)-3-((E)-5-(furan-2-yl)pent-4-en-1-yl)-6-methyl-6-(1-phenyl-2γ-propa-1,2-dien-1-yl)tetrahydro-2H-pyran-2-one **4651e** (27.0 mg, 74.4 μmol, 1.0 eq) in THF (0.74 mL) and H₂O (5.4 mL, 298 mmol, 4000 eq) with SmI₂ (0.1 M in THF, 6.0 mL, 0.60 mmol, 8.0 eq) were stirred at room temperature until complete decolourisation had occurred. After work-up, purification by column chromatography on silica gel, eluting with 0-10% ethyl acetate in hexane gave rac-(4S,4aS,5R,6R,7S,9aR)-4-(furan-2-ylmethyl)-5,7-dimethyl-6-phenyldecahydro-4aH-benzo[7]annulene-4a,7-diol **453b** (6.1 mg, 16.6 μmol, 25%) as an opaque oil.

\[\text{\(\nu_{\text{max}}\) (neat)/cm}^{-1}\text{ 2927 (O-H), 2856 (O-H), 1598, 1507.}\]

**1H NMR (400 MHz, CDCl₃)** \(\delta\) ppm 1.10 (3 H, s, CH₃), 1.17 - 1.31 (2 H, m, 1 H from \(CH₂CH₂Ar\) + 1 H from \(CH₂\)), 1.34 - 1.49 (6 H, m, \(CHCH₃\) + \(CH₂\) + 1 H from \(CH₂CH₂\)), 1.49 - 1.63 (3 H, m, CH bridgehead + 2 × OH), 1.63 - 1.71 (2 H, m, \(CH₂\)), 1.78 - 1.94 (2 H, m, 1 H from \(CH₂\) + \(CHCH₂\)), 1.96 - 2.06 (2 H, m, \(CH₂\)), 2.29 (1 H, dd, \(J = 14.8, 10.0\) Hz, 1 H from \(CH₂\)), 2.44 (1 H, q, \(J = 7.8\) Hz, \(CHCH₃\)), 2.75 (1 H, dd, \(J = 14.8, 3.4\) Hz, 1 H from \(CH₂\)), 3.89 (1 H, s, CPh), 5.88 (1 H, d, \(J = 2.8\) Hz, ArCH), 6.24 (1 H, dd, \(J = 2.8, 1.8\) Hz, ArCH), 7.22 - 7.26 (2 H, m, 2 × ArCH), 7.33 (2 H, t, \(J = 7.4\) Hz, 2 × ArCH), 7.37 - 7.44 (2 H, m, 2 × ArCH).

**13C NMR (101 MHz, CDCl₃)** \(\delta\) ppm 13.1 (CH₂CH₂), 25.7 (CH₂), 26.3 (CH₂), 27.3 (CH₂CH₂), 27.5 (CH₂), 28.2 (CH₃), 30.8 (CH₂), 41.8 (CH₂), 43.1 (CH₂), 43.2 (CH₂), 45.1 (CH bridgehead), 49.4 (CPh), 74.7 (C₉OH(CH₃)), 77.2 (COH), 106.3 (ArCH), 110.1 (ArCH), 126.3 (ArCH), 128.3 (2 × ArCH), 129.6 (2 × ArCH), 140.9 (ArCH), 145.3 (ArC), 155.0 (ArC).

**m/z** (ES+) 391.4 [M+Na]; HRMS calcd for C₂₄H₃₂O₃Na: 391.2249; found: 391.2248.
**rac-(1S,2R,3R,4S,5R)-1,3-dimethyl-5-((E)-5-(naphthalen-1-yl)pent-4-en-1-yl)-2-phenylcycloheptane-1,4-diol (454)**

As for general procedure P, **rac-(3R,6S)-6-methyl-3-((E)-5-(naphthalen-1-yl)pent-4-en-1-yl)-6-(1-phenyl-2\(\lambda^2\)-propa-1,2-dien-1-yl)tetrahydro-2\(H\)-pyran-2-one 451c** (30.0 mg, 71.0 \(\mu\)mol, 1.0 eq) in THF (0.80 mL) and \(\text{H}_2\text{O}\) (5.1 mL, 284 mmol, 40 eq) with Sml\(_2\) (0.1 M in THF, 5.7 mL, 0.57 mmol, 8.0 eq) were stirred at room temperature until complete decolourisation had occurred. After work-up, purification by column chromatography on silica gel, eluting with 0-10% ethyl acetate in hexane gave **(1S,2R,3R,4S,5R)-1,3-dimethyl-5-((E)-5-(naphthalen-1-yl)pent-4-en-1-yl)-2-phenylcycloheptane-1,4-diol 454** (16.6 mg, 60.0 \(\mu\)mol, 55%) as a colourless oil.

\(\nu_{\text{max}}\) (neat)/cm\(^{-1}\) 2927 (O-H), 2854, 1727 (C=O), 1705, 1596.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 0.90 (3 H, d, \(J = 6.8\) Hz, CHCH\(_3\)), 0.95 (3 H, s, CH\(_3\)), 1.49 - 1.92 (6 H, m, 1 H from 3 \(\times\) CH\(_2\)), 1.97 - 2.11 (1 H, m, 1 H from CH\(_2\)), 2.29 - 2.44 (3 H, m, CH\(_2\) + 1 H from CH\(_2\)), 2.54 - 2.63 (1 H, m, CH), 2.77 (1 H, br. s, CHPh), 3.77 - 3.84 (1 H, m, CH\(_2\)CH\(_3\)), 6.22 (1 H, dt, \(J = 15.4, 6.9\) Hz, ArCH=CH\(_2\)), 6.95 - 7.01 (1 H, m, ArCH), 7.12 (1 H, d, \(J = 15.6\) Hz, ArCH=CH\(_2\)), 7.19 - 7.40 (3 H, m, 3 \(\times\) ArCH), 7.41 - 7.59 (5 H, m, 5 \(\times\) ArCH), 7.75 (1 H, d, \(J = 8.0\) Hz, ArCH), 7.85 (1 H, d, \(J = 7.3\) Hz, ArCH), 8.12 (1 H, d, \(J = 8.0\) Hz, ArCH).

\(^1\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) ppm 16.3 (CHCH\(_3\)), 23.1 (CH\(_2\)), 26.4 (CH\(_2\)), 32.2 (CH\(_3\)), 33.4 (CH\(_2\)), 35.0 (CH\(_2\)), 38.5 (CH\(_2\)), 42.2 (CHCH\(_3\)), 54.0 (CH), 63.2 (CHPh), 73.8 (C\(_2\)OH(CH\(_3\))), 123.5 (ArCH), 123.9 (ArCH), 125.6 (2 \(\times\) ArCH), 125.8 (ArCH), 127.0 (ArCH), 127.3 (ArCH=CH\(_2\)), 127.3 (ArCH), 127.9 (3 \(\times\) ArCH), 128.4 (ArCH), 130.1 (ArCH), 131.1 (ArC), 133.6 (ArC), 133.7 (ArCH=CH\(_2\)), 135.6 (ArC), 137.6 (ArC), 217.3 (C=O).

\(m/z\) (ES+) 449.5 [M+Na]; HRMS calcd for C\(_{30}\)H\(_{34}\)O\(_2\)Na: 449.2457; found: 449.2453.
6.7 Appendix

X-ray crystal structure of rac-(4S,4aS,5R,6R,7S,9aR)-5,7-dimethyl-4-(4-methylbenzyl)-6-phenyldecahydro-4aH-benzo[7]annulene-4a,7-diol (453a)

Crystal structure and data refinement for s4082na

Empirical formula  \( \text{C}_{27}\text{H}_{36}\text{O}_{2} \)

Formula weight  392.56

Temperature  100(2) K

Wavelength  1.54178 Å

Crystal system Orthorhombic

Space group  Pca2(1)

Unit cell dimensions  
\[ a = 13.4674(3) \text{ Å} \quad \alpha = 90^\circ. \]
\[ b = 12.3593(3) \text{ Å} \quad \beta = 90^\circ. \]
\[ c = 12.9034(3) \text{ Å} \quad \gamma = 90^\circ. \]

Volume  2147.74(9) Å\(^3\)

\( Z \)  4

Density (calculated)  1.214 Mg/m\(^3\)

Absorption coefficient  0.570 mm\(^{-1}\)
F(000) 856

Crystal size 0.29 x 0.20 x 0.10 mm$^3$

Theta range for data collection 3.58 to 72.56°.

Index ranges -16$\leq$h$\leq$16, -15$\leq$k$\leq$15, -15$\leq$l$\leq$13

Reflections collected 12395

Independent reflections 3739 [R(int) = 0.0216]

Completeness to theta = 72.56° 99.6 %

Absorption correction Semi-empirical from equivalents

Max. and min. transmission 0.9452 and 0.856901

Refinement method Full-matrix least-squares on F$^2$

Data / restraints / parameters 3739 / 1 / 270

Goodness-of-fit on F$^2$ 0.984

Final R indices [I>2sigma(I)] R1 = 0.0313, wR2 = 0.0809

R indices (all data) R1 = 0.0318, wR2 = 0.0815

Absolute structure parameter 0.05(16)

Largest diff. peak and hole 0.292 and -0.180 e.Å$^{-3}$
Atomic coordinates \( \times 10^4 \) and equivalent isotropic displacement parameters \( \AA^2 \times 10^3 \) for s4082na. U(eq) is defined as one third of the trace of the orthogonalized \( U_{ij} \) tensor.

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Chiral HPLC of 268

Enantiomeric excess was measured as 41% using chiral HPLC (ChiralPak IA column, 90:10 \( n \)-hexane–EtOH 0.2% TFA, 15 °C, flow rate 1 mL/min, UV detection at 210 nm).
Chiral HPLC of 310

Enantiomeric excess was measured as 15% using chiral HPLC (ChiralPak IA column, 90:10 \(n\)-hexane–EtOH 0.2% TFA, 15 °C, flow rate 1 mL/min, UV detection at 210 nm).
Chiral HPLC of 315

Enantiomeric excess of benzyl ester \((J. \text{ Am. Chem. Soc. 2010, 132, 10920})\) was measured as 14% using chiral HPLC (ChiralPak IA column, 98:2 \(n\)-hexane–\(i\)-PrOH 0.2% TFA, 20 °C, flow rate 1 mL/min, UV detection at 210 nm).

Enantiomeric excess of benzyl ester\(^{155}\) was measured as 14% using chiral HPLC (ChiralPak IA column, 98:2 \(n\)-hexane–\(i\)-PrOH 0.2% TFA, 20 °C, flow rate 1 mL/min, UV detection at 210 nm).
7. References


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