PHD

Recent Advances in Tandem Reductive Processes

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University of Bath
Department of Chemistry
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[B. C. Hartley]
Abstract

The research presented herein is concerned with the exploration of tandem processes initiated by the conjugate reduction of Michael acceptors, encompassing the asymmetric reductive Dieckmann reaction and the two-carbon homologation of aldehydes by two complementary methodologies.

Chapter 1 introduces the area of transition metal catalysed tandem reductive processes as a tool for carbon-carbon bond formation. An extensive discussion of this methodology is included and recent advances in the area are highlighted.

Chapter 2 discusses the initial study into the asymmetric reductive Dieckmann condensation. 3,3’-Disubstituted 4-oxopyrrolidines were synthesised in up to 93% ee using both molybdenum and copper catalysis.

Chapter 3 describes the novel molybdenum-catalysed two-carbon homologation of aldehydes by the reduction of alkylidene Meldrum’s acid derivatives. No over reduction to the corresponding alcohol is observed, as the aldehyde functionality remains protected until hydrolysis.

Chapter 4 discusses the mild, expeditious amine promoted reduction of cyclic malonates to β-substituted propionaldehydes. The synthetic utility of the methodology is demonstrated by the synthesis of γ-substituted propylamines in a one-pot hydrosilylation/reductive amination process.

Chapter 5 describes the synthesis and characterisation for the compounds discussed in chapters 2, 3 and 4.
Acknowledgments

I would like to thank Dr. Chris Frost for the support and guidance he has offered me over the past three years. It has been a great pleasure working for you.

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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>acac</td>
<td>acetylacetonate</td>
</tr>
<tr>
<td>Anal.</td>
<td>analytical (spectrometry)</td>
</tr>
<tr>
<td>app.</td>
<td>apparent</td>
</tr>
<tr>
<td>aq</td>
<td>aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>BINAP</td>
<td>2,2’-bis(diphenylphosphino)-1,1’-binaphthyl</td>
</tr>
<tr>
<td>BINAPO</td>
<td>2,2’-bis(diphenylphosphine oxide)-1,1’-binaphthyl</td>
</tr>
<tr>
<td>BINOL</td>
<td>1,1’-bi-2-naphthol</td>
</tr>
<tr>
<td>BIPHEP</td>
<td>2,2’-bis(diphenylphosphino)-1,1’-biphenyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butylocarbonyl</td>
</tr>
<tr>
<td>br</td>
<td>broad (spectral)</td>
</tr>
<tr>
<td>Bu</td>
<td>normal (primary) butyl</td>
</tr>
<tr>
<td>‘tBu</td>
<td>tert-butyl</td>
</tr>
<tr>
<td>°C</td>
<td>degrees Celsius</td>
</tr>
<tr>
<td>calcd</td>
<td>calculated</td>
</tr>
<tr>
<td>cat.</td>
<td>catalytic quantity</td>
</tr>
<tr>
<td>Cbz</td>
<td>carboxybenzyl</td>
</tr>
<tr>
<td>cm⁻¹</td>
<td>wavenumber(s)</td>
</tr>
<tr>
<td>cod</td>
<td>1,5-cyclooctadiene</td>
</tr>
<tr>
<td>coe</td>
<td>cyclooctene</td>
</tr>
<tr>
<td>δ</td>
<td>chemical shift in parts per million downfield from tetramethylsilane</td>
</tr>
<tr>
<td>COSY</td>
<td>correlation spectroscopy</td>
</tr>
<tr>
<td>cy</td>
<td>cyclohexyl</td>
</tr>
<tr>
<td>d</td>
<td>doublet (spectral)</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undecane</td>
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<tr>
<td>DCC</td>
<td>N,N’-dicyclohexylcarbodiimide</td>
</tr>
<tr>
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<td>1,2-dichloroethane</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>dcpe</td>
<td>1,1’-bis(dicyclohexylphosphino)ethane</td>
</tr>
<tr>
<td>DCU</td>
<td>N,N’-dicyclohexylurea</td>
</tr>
<tr>
<td>°</td>
<td>degrees (angle)</td>
</tr>
<tr>
<td>DIBAL</td>
<td>diisobutylaluminium hydride</td>
</tr>
<tr>
<td>DIFLUO-PHOS</td>
<td>5,5’-bis(diphenylphosphino)-2,2’,2’-tetrafluoro-4,4’-bi-1,3-benzodioxole</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-(N,N’-dimethylamino)pyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide</td>
</tr>
<tr>
<td>DME</td>
<td>dimethoxyethane</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>DOLEFIN</td>
<td>5-benzyl-8-methoxy-1,8-dimethyl-2-(2’-methylpropyl)bicyclo[2.2.2]octa-2,5-diene</td>
</tr>
<tr>
<td>dpm</td>
<td>dipivoyl methane</td>
</tr>
<tr>
<td>dpbb</td>
<td>1,2’-bis(diphenylphosphino)butane</td>
</tr>
<tr>
<td>dppe</td>
<td>1,4’-bis(diphenylphosphino)ethane</td>
</tr>
</tbody>
</table>
dppf 1,1’-bis(diphenylphosphino)ferrocene
dppm bis(diphenylphosphino)methane
DTBM 3,5-di-tert-butyl-4-methoxyphenyl
DuPhos 1,2-bis((2R,5R)-2,5-dimethylphospholano)benzene
ee enantiomeric excess
EI electron impact
ESI electrospray ionisation
Et ethyl
equiv equivalent(s)
fur furyl
g gram(s)
h hour(s)
HMDS hexamethyldisilazide
HMPA hexamethylphosphoramide
HOMO highest occupied molecular orbital
HPLC high-performance liquid chromatography
HRMS high resolution mass spectrometry
Hz hertz
IR infrared
J coupling constant (in NMR spectroscopy)
JOSIPHOS 1-[(S)-2-(diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine
L litre(s)
LDA lithium diisopropylamide
lit. literature
µ micro
m milli; multiplet (spectral)
M molar (moles per litre)
M+ parent molecular ion
MA Meldrum’s acid
Me methyl
MHz megahertz
min minute(s)
mol mole(s)
mp melting point
Ms methanesulfonyl
MS mass spectrometry
MVK methyl vinyl ketone
MW microwave
m/z mass-to-charge ratio (in mass spectrometry)
NMO N-methylmorpholine N-oxide
NMR nuclear magnetic resonance
Ns p-nitrobenzenesulfonyl
PCC pyridinium chlorochromate
Ph phenyl
Phanehos 4,12-bis(diphenylphosphino)-[2.2]-paracyclophepane
Phebox bisoxazolinylphenyl
PMHS polymethylhydrosiloxane
P-Phos 2,2’,6,6’-tetramethoxy-4,4’-bis(diphenylphosphino)-3,3’-bipyridine
ppm part(s) per million
Pr

propyl

‘Pr

iso-propyl

Py

pyridine

q

quartet (spectroscopic)

quin

quintet (spectroscopic)

rac

racemic, racemate

Rf

retention factor (in chromatography)

r.t.

room temperature

s

singlet (spectral)

SEGPHOS

5,5′-bis[diphenylphosphino]-4,4′-bi-1,3-benzodioxole

sept

septet (spectral)

SYNPHOS

5,5′-bis[diphenylphosphino]-4,4′-bi-1,4-benzodioxine

t

triplet (spectral)

TANIA-

PHOS

1-dicyclohexylphosphino-2-[(S)-α-(dimethylamino)-2-(dicyclohexylphosphino)benzyl]ferrocene

TBAB

tetabutylammonium bromide

TBAF

tetabutylammonium fluoride

TBDMS

tert-butyldimethylsilyl

TBS

tributylsilyl

Tf

triflate

TFA

trifluoroacetic acid

THF

tetrahydrofuran

TLC

thin layer chromatography

TMDS

tetramethyldisiloxane

TMS

trimethylsilyl; tetramethylsilane

tol

toluene

tR

retention time (in chromatography)

Ts

p-toluenesulfonyl
Chapter 1 - Tandem Catalytic Reductive Processes

1.1 Introduction

The formation of new carbon-carbon bonds is one of the most important challenges within organic synthesis. Of the numerous methods of carbon-carbon bond formation available to the modern synthetic organic chemist, those involving the nucleophilic attack of silyl enol ethers or silyl ketene acetals on electrophilic carbon centres has proved to be of great importance, especially the Mukaiyama aldol reaction.\(^1\) The 2009 review by Kalesse et al.\(^2\) on the use of highly stereoselective aldol reactions in the total synthesis of natural products highlights the recent progress and applications of the aldol reaction.

Despite being a methodological cornerstone of organic synthesis, enolate chemistry has its limitations. For example, formation of the desired enolate requires either a completely separate synthetic step or the chemo- and regioselective deprotonation of pro-nucleophiles. A particularly attractive method of efficient \textit{in situ} generation of enolates is the use of enones as “latent enolates”.\(^3\) The use of enones as latent enolates enables regioselective enolate formation from relatively robust precursors. These enolates can then react with the desired electrophilic partner (Scheme 1).

\begin{center}
\includegraphics[width=0.8\textwidth]{Scheme1.png}
\end{center}

\textbf{Scheme 1} Tandem processes initiated by the conjugate reduction of enones

Development of catalytic variations of this tandem methodology has greatly focused on the formation of enolates from enones by hydrometallation and has been addressed in a number of reviews.\(^3\)\(^-\)\(^7\) Efficient and highly selective processes have been developed using transition metal salt precatalysts, chiral ligands and stoichiometric reductants. A range of different stoichiometric reductants has been used such as silanes, molecular hydrogen, stannanes and
boranes. The use of chiral ligands results in the formation of chiral metal enolates which allow for the stereoselective nucleophilic attack of the enolate on the carbon electrophile resulting in the formation of new stereogenic centres (Scheme 2).

![Scheme 2 Enantioselective tandem reductive processes](image)

This review will map the recent progress made in tandem reductive processes focusing on those processes initiated by the hydrometallation and hydrosilylation of Michael acceptors.

1.2 Reductive Aldol Reactions

1.2.1 Rhodium-Catalysed Reductive Aldol Reactions

1.2.1.1 Initial Studies

Revis and Hilty reported the first reductive aldol reaction.\(^8\) Catalysed by rhodium chloride, methyl methacrylate 4 was coupled with excess acetone 5 using trimethylsilane as a hydride source giving the \(\beta\)-siloxy ester 6 in a 95% yield (Scheme 3). No aldol product was observed on reacting silyl ketene acetal 7 (synthesised independently) with acetone in the presence of rhodium chloride, suggesting the reaction proceeded via a rhodium ketene acetal (Scheme 3).
Matsuda et al. formed β-siloxy ketone aldols by the reductive coupling of α,β-unsaturated ketones with aldehydes in the presence of Rh$_4$(CO)$_{12}$ and Et$_2$MeSiH; syn-selectivity was observed for this transformation (Scheme 4). It was also found that the addition of MePh$_2$P enabled the reductive coupling of enolisable aldehydes such as hexanal (Scheme 5).

Motherwell and Whitehead reported the rhodium-catalysed intramolecular reductive aldol reaction, it was found that by simply changing the catalyst precursor a switch between cis- and trans-selectivity could be achieved.$^{10,11}$ On using RhCl(PPh$_3$)$_3$ cis-selectivity was observed and using RhH(PPh$_3$)$_4$ trans-selectivity was achieved (Scheme 6). Five-, six- and seven-membered ring products were accessed with substitution on the carbon backbone.
being tolerated. This method also allowed for the synthesis of bicyclic systems. It was also observed that the selectivity of the catalytic precursors was a general, not absolute, trend.\textsuperscript{11} Motherwell and Whitehead applied this methodology to the formal enantioselective synthesis of (–)-carbovir \textsuperscript{20} and (–)-abacavir \textsuperscript{21}.\textsuperscript{12} Exposure of protected diol containing 6-oxohexanoate \textsuperscript{18} to the reductive conditions gave a separable mixture of diastereomers, which, through further manipulations, led to the synthesis of these biologically active targets (Scheme 7).

\begin{center}
\textbf{Scheme 6} Rhodium-catalysed intramolecular reductive aldol reaction
\end{center}

\begin{center}
\textbf{Scheme 7} Key synthetic step towards the synthesis of (–)-carbovir and (–)-abacavir
\end{center}
1.2.1.2 Hydrogen Mediated Processes

Often, transition metal catalysed reduction of Michael acceptors are mediated by a stoichiometric hydride source, such as a silane. The use of molecular hydrogen offers a convenient, atom-economic solution to the use of a stoichiometric reductant, bypassing the removal of undesirable byproducts from the reaction mixture.\textsuperscript{13,14}

Krische has pioneered the reductive aldol reaction mediated by molecular hydrogen, with both \textit{syn}-selective inter- and intramolecular transformations being carried out.\textsuperscript{5,15} Competitive alkene hydrogenation of the Michael acceptor was suppressed by the use of a cationic rhodium precatalyst and an inorganic base (typically KOAc or Li\textsubscript{2}CO\textsubscript{3}).\textsuperscript{16} Mechanistic studies revealed the base converts the rhodium(III)-dihydride species, responsible for alkene hydrogenation via the dihydride cycle (Scheme 8), into the desired rhodium(I)-monohydride species which catalyses the reductive aldol process via the monohydride cycle (Scheme 8).\textsuperscript{5}

![Scheme 8 Competitive alkene hydrogenation and reductive aldol reactions](image)

Early research focused on the intramolecular reductive aldol cyclisation of aldo-enones\textsuperscript{16} and keto-enones\textsuperscript{17,18} with five- and six-membered rings being formed in high yields and with excellent \textit{syn}-selectivity (\textit{syn:anti} >95:5 for all keto-enones). Reactions involving aldo-enones under optimised conditions show trace amounts of alkene hydrogenation product (Scheme 9). However, on moving to keto-enones, increased amounts of alkene hydrogenation occurs due to the decreased electrophilicity of the ketone (Scheme 10).\textsuperscript{17} The efficient reductive aldol cyclisation of keto-enones was achieved using the more
electrophilic 1,3-diones 30 (Scheme 11); no conjugate reduction product was observed for these keto-enones except in the formation of the strained cis-decalone 33.\textsuperscript{18}

\begin{align*}
\text{Scheme 9} & \quad \text{Reductive aldol cyclisation of aldo-enones under hydrogenation conditions} \\
\text{Scheme 10} & \quad \text{Reductive aldol cyclisation of keto-enones via catalytic hydrogenation} \\
\text{Scheme 11} & \quad \text{Reductive aldol cyclisation of enone-diones via catalytic hydrogenation}
\end{align*}

Krische \textit{et al.} also described the challenging intramolecular reductive aldol reaction of enal-ketones (Scheme 12).\textsuperscript{18} Low yields were observed with triphenylphosphine, however, \(\pi\)-acidic ligand tri(2-furyl)phosphine increased yields. Poor to moderate \textit{syn}-selectivity was observed along with varying quantities of undesirable conjugate reduction product.
The intermolecular reductive aldol couplings of vinyl ketones with aryl aldehydes was investigated in Krische’s original paper, however, only poor syn-selectivity was observed (typically syn:anti 2:1).\textsuperscript{16} Further investigation showed that excellent syn-selectivity could be achieved when using the π-acid phosphine ligand tri(2-furyl)phosphine and Li$_2$CO$_3$.\textsuperscript{19}

Hydrometallation is thought to result in a Z-(O)-enolate which undergoes aldolisation via a Zimmerman-Traxler-type transition structure (Scheme 13). The addition of tri(2-furyl)phosphine increases the Lewis acidity of the rhodium centre, therefore promoting the formation of the kinetically favourable syn-diastereomer by the tightening of the chair like transition state and favouring the kinetic pathway by mitigating retro-aldol cyclisation.

Under these conditions, it was found that reduction of normally hydrogen-labile functionalities did not occur; alkynes, alkenes, benzylic ethers and nitroarenes remained intact (Scheme 14).\textsuperscript{19} This reductive coupling was extended from methyl- and ethyl vinyl ketone to the divinyl ketone 41 with chemoselective reduction occurring only at the less substituted alkene; no further reduction of the aldol product was observed (Scheme 15).\textsuperscript{20}
Chapter 1

Scheme 14 Reductive coupling of vinyl ketones and aldehydes containing hydrogen-labile groups

Scheme 15 Regioselective reductive aldol reaction between aldehydes and divinyl ketones

These neutral conditions also allow for the reductive aldol reaction between α,β-unsaturated ketones and chiral N-Boc-α-amino aldehydes without any deprotection of the amine functionality or racemisation of the chiral centre (Scheme 16). In this study Krische et al. attribute the excellent levels of syn-aldol diastereoselectivity and anti-Felkin-Ahn control to the intramolecular hydrogen bonding in the amino aldehyde.

Scheme 16 syn-Diastereoselective hydrogenative aldol coupling between vinyl ketones and α-amino aldehydes

1.2.1.3 Asymmetric Rhodium-Catalysed Reductive Aldol Reactions

Morken et al., in 1999, carried out a catalyst evaluation, screening metal precatalysts, hydride sources and phosphine ligands in an array format. The study revealed that [Rh(cod)Cl]₂, (R,R)-Me-DuPhos 49 and Cl₂MeSiH gave the desired product in both high yields, up to 82% isolated yield, and diastereoselectivity, up to syn:anti 23:1 (Scheme 17).
Further studies by Morken *et al.* into the reductive conditions described above showed that excellent diastereoselectivities of >60:1 (syn:anti) could be achieved in a two step process in which the required aldehyde was added to the reaction mixture after rhodium-catalysed hydrosilylation had occurred.\(^{23}\)

In both Morken’s one- and two-step rhodium-catalysed reductive aldol reactions it is the silyl ketene acetal, formed after hydrosilylation of the Michael acceptor, which is involved in the carbon-carbon bond forming process. Therefore, the chiral rhodium – bisphosphine species is not involved in the key step in which chirality is installed. However, using Et₂MeSiH as the stoichiometric reductant and (R)-BINAP as the bisphosphine ligand Morken *et al.* carried out asymmetric rhodium-catalysed reductive aldol reactions.\(^{24}\) While syn:anti selectivities and yields in this study were moderate, good enantioselectivities were observed for the major syn-diastereomer (Scheme 18). This asymmetric transformation was carried out during the initial arrayed catalyst evaluation, however, a poor yield (4% yield) and enantioselectivity (20% ee) was observed. This was attributed to incomplete complexation during the microscale reaction.

**Scheme 17** Rhodium-catalysed reductive aldol reaction ligated by bisphosphine
Although further studies by Morken et al. into this reactivity of the asymmetric rhodium-catalysed reductive aldol reaction resulted in little improvement in terms of yield and selectivity, greater mechanistic insight was achieved.25 The dinuclear μ-hydride bridged Rh(I) species, [(BINAP)Rh-H/H-Rh(BINAP)] was postulated to be the active hydride species generated \textit{in situ} from (R-BINAP)Rh(COD)BF$_4$ and PhMe$_2$SiH. Morken et al. also showed that without acidic hydrolysis the silyl protected aldol product could be isolated.26 Reductive aldol product 55 was found to be a precursor to the C$_{10}$-C$_{24}$ ketone fragment of the inostamycin family of polyether antibiotics 56 (Scheme 19); synthesis of this fragment also uses a reductive Claisen rearrangement which will be discussed later (\textit{cf}. 1.8).27
Remain ing with the group 9 transition metals, Morken et al. used indane-Pybox 58 in the asymmetric iridium-catalysed reductive aldol reaction (Scheme 20). This showed greater enantio- and diastereoc ontrol than the previously reported rhodium – BINAP system, however, reaction scope was limited to benzaldehyde and α-alkoxy aldehydes.\(^{28}\) The aldol product 57b was used by Morken et al. as a precursor in the synthesis of biologically active macrocyclic borrelidin 59.\(^{29}\) 

![Scheme 20 Asymmetric iridium-catalysed reductive aldol reaction](image)

Both Morken’s rhodium- and iridium-catalysed reductive aldol processes are moderately syn-diastereoselective. Nishiyama et al. developed conditions, formerly used for conjugate reduction,\(^ {30,31}\) to allow for a highly anti-selective rhodium-catalysed reductive aldol reaction to proceed using Rh(Phebox) catalysts 62a and 62b along with a range of alkoxy- and alkylsilanes.\(^ {32}\) With very short reaction times (0.5 – 1 hour), a number of different aldehydes were coupled with tert-butyl acrylate (Scheme 21). Aromatic aldehydes gave consistently high anti-selectivities (up to 98:2) and enantioselectivities (up to 96% ee), while cinnamaldehydes and aliphatic aldehydes proved to be more challenging.
Chapter 1

Although further modifications of the Phebox skeleton resulted in a detrimental effect on the \textit{anti}-selectivity of the process, it did allow for the synthesis of \(\beta\)-hydroxy carboxylic acids by the hydrolysis of the reductive aldol product (Scheme 22).\textsuperscript{33,34}

\begin{center}
\textbf{Scheme 21} Highly \textit{anti}-selective rhodium-catalysed reductive aldol reaction
\end{center}

\begin{center}
\textbf{Scheme 22} Asymmetric synthesis of \(\beta\)-hydroxy carboxylic acids
\end{center}
Using Rh(Phebox-Ph) 62d, Nishiyama et al. were able to couple cyclopentenone and aryl aldehydes with excellent anti-selectivity as well as high yields and enantioselectivities for the favoured anti-product. However, yields and selectivities for this transformation tail away on using other cyclic enones and vinyl methyl ketone (Scheme 23).\(^{35}\)

![Scheme 23 Intermolecular reductive coupling of enones and aldehydes](image)

Nishiyama et al. also observed high yields and selectivities when applying their Rh(Phebox) reductive system to the reductive coupling of acrylates and ketones.\(^{36}\) The reductive coupling of acrylates with both aldehydes and ketones enabled Nishiyama et al. to access both enantiomers of the $\alpha$-chiral dihydroxinnamate 74 using the same chiral ligand.\(^{37}\) Reductive coupling of 71 with $p$-anisaldehyde 72 and subsequent dehydroxyation gave (S)-74, while reductive coupling of 75 with acetone and subsequent dehydration and reduction gave (R)-74 (Scheme 24).
Krische et al. were faced with a number of challenges on attempting asymmetric hydrogenative aldol couplings mediated by molecular hydrogen.\(^{38}\) Firstly, only trace amounts of product were observed when a chelating phosphine ligand was used. Secondly, as seen in prior studies,\(^{18-21}\) \(\pi\)-acidic ligands were required. Finally, commercially available chiral \(\pi\)-acidic phosphine ligands, such as phosphites and phosphoramide ligands derived from BINOL, gave only trace quantities of product; these ligands were considered too \(\pi\)-acidic.

By ligand design and structural optimisation, Krische et al. identified TADDOL-based phosphonite \(82\) to be an effective monodentate ligand for the enantioselective hydrogenative aldol coupling of vinyl ketones with aldehydes (Scheme 25).\(^{38}\) High yields (70-97\%) and excellent enantioselectivities (86-96\%) were observed for reductive coupling of vinyl ketones and \(\alpha\)- and \(\beta\)-heteroatom substituted aldehydes as well as \(\alpha\)-(hetero)aryl substituted aldehydes. When using acrylates only conventional hydrogenation was observed. It was also found that less activated aldehydes could not be tolerated in this reaction.
1.2.2 Copper-Catalysed Reductive Aldol Reactions

Following a number of studies into the copper-catalysed reductive aldol reaction using the phosphine stabilized hexamer Stryker’s reagent, [Ph₃PCuH]₆, and encouraged by the development of the asymmetric copper-catalysed conjugate reduction reaction, Lam et al. reported the diastereo- and enantioselective synthesis of β-hydroxylactones. Lam found Cu(OAc)₂·H₂O to be a convenient copper salt for the transformation along with the inexpensive siloxane 1,1,3,3-tetramethylhydrosiloxane (TMDS) and either DPPF or rac-BINAP. Moderate yields of diastereotopically pure β-hydroxylactones were observed for both five- and six-membered rings, despite the former’s 5-(enolendo)-exo-trig cyclisation being formally disfavoured by Baldwin’s rules (Scheme 26). A range of chiral bisphosphines was screened and enantioselectivities of up to 83% ee were observed when (R)-3,5-xylyl-MeO-BIPHEP 90 was employed as the ligand (Scheme 27).
Scheme 26 Copper-catalysed synthesis of β-hydroxylactones

Scheme 27 Asymmetric copper-catalysed β-hydroxylactone synthesis

Lam proposed a catalytic cycle initiated by the formation of a copper-(I)-bisphosphine hydride complex 91 from Cu(OAc)$_2$, TMDS and a bisphosphine ligand. Hydrometallation of substrate 83 forms the copper enolate 92, carbon-carbon bond formation then occurs to give aldolate 93. Reaction of 93 with TMDS gives copper-(I)-complex 91 and silylated product 94 which undergoes protodesilylation on acidic work-up (Scheme 28).
By moving from an intramolecular reductive aldol reaction using keto-acrylates to those using keto-acrylamides, Lam et al. synthesised 4-hydroxypiperidin-2-ones.⁴⁹ Yields of 4-hydroxypiperidin-2-ones were comparable to those observed for the synthesis of β-hydroxylacones (Scheme 29). The enantioselective synthesis of highly functionalised piperidin-2-ones from enantiomerically enriched substrates was achieved using this methodology; reduction of piperidin-2-ones 96 and 94 gave the potentially biologically active polyhydroxylated piperidines 98 and 99 (Scheme 29).
Lipshutz et al. reported the asymmetric reductive cyclisation of \( \beta,\beta' \)-disubstituted keto-enones, resulting in the generation of 6-membered cyclic products containing three contiguous new stereogenic centres as a single diastereomer with enantiomer excesses of up to 97\% (Scheme 30).\(^5^0\) Yields and selectivities for this impressive transformation were found to be uniformly high and unaffected by the geometry of the enone. The added stereocontrol comes from the formation of the new stereogenic centre after the initial asymmetric conjugate reduction of the enone.

\[
\begin{align*}
103 & : (S,R)-PPF-P(\text{tBu})_2 \\
100a & : R = \text{Me} \\
100b & : R = \text{Ph} \\
101a & : 91\%, 96\% \text{ ee} \\
101b & : 77\%, 97\% \text{ ee} \\
102a & : R = \text{Me} \\
102b & : R = \text{Ph} \\
101a' & : 88\%, 96\% \text{ ee} \\
101b' & : 98\%, 85\% \text{ ee}
\end{align*}
\]

**Scheme 30** Reductive cyclisation to give three contiguous asymmetric stereogenic centres

Riant et al. used the pre-catalyst \([\text{CuF(Ph}_3\text{P)}_3]\).\text{2MeOH}\ for the intermolecular asymmetric copper-catalysed reductive aldol reaction; the chiral copper-hydride species was formed from chiral bisphosphine ligands and PhSiH\(_3\).\(^5^1\) A range of chiral bisphosphines was used to couple methyl acrylate and aromatic ketones. Highest diastereo- and enantioselectivities were achieved with \((R,S)-\text{Cy-TANIAPHOS 106}\); like all ferrocene based ligands screened, \textit{erythro}-selectivity was observed (Scheme 31).
Further development of this reductive process led to the asymmetric reductive coupling of methyl acrylate and a range of aromatic and aliphatic aldehydes; excellent yields and high enantioselectivities were observed for this syn-selective process (Scheme 32). Riant also showed that anti-selectivity could be achieved for the same transformation by using the N-heterocyclic carbene-copper catalyst 110 (Scheme 33). This process was not limited to methyl acrylate as methyl vinyl ketone and acrylonitrile gave comparable results.
Chapter 1

Scheme 33 Riant’s syn-selective coupling of acrylates and aldehydes

By using pinacolborane as a stoichiometric reductant and switching copper precatalysts and bisphosphine ligands, Shibasaki et al. were able to selectively couple allenic esters and ketones either from the α-carbon of the allene, giving the branched product, or the γ-carbon of the allene, giving the linear product (Scheme 34). Cu(OAc)$_2$ and (R)-DTBM-SEGPHOS 116 gave the γ-aldol product 113 with cis-olefin configuration, high enantioselectivities and excellent yields. [CuF(Ph$_3$P)$_3$]$\cdot$2EtOH and TaniaPhos 115 gave the α-aldol product 114 with high diastereoselectivity and moderate to high yields with aromatic ketones.

Scheme 34 Enantio- and regioselective reductive coupling of allenic esters and ketones
1.2.3 Cobalt-Catalysed Reductive Aldol Reactions

Shortly after Revis and Hilty’s original paper on the rhodium-catalysed reduction-aldol reaction,\textsuperscript{8} Isayama and Mukaiyama reported a cobalt-catalysed reductive aldol reaction using $\alpha,\beta$-unsaturated nitriles, amides and esters.\textsuperscript{56} Phenylsilane was used as a hydride source and Co(II)(dpm) was used as a precatalyst, although high yields were observed, selectivity was poor with a syn:anti of 72:28 being achieved at best (Scheme 35).

Later, Krische \textit{et al.} employed Isayama and Mukaiyama’s cobalt-catalysed reductive conditions in an intramolecular reductive aldol reaction giving five-, six- and seven membered cycloreduction products.\textsuperscript{57,58} In contrast to the intermolecular reductive aldol reactions reported by Isayama and Mukaiyama, exceptional \textit{syn}-selectivities (>99:1 for all examples) were reported by Krische \textit{et al.} (Scheme 36). This has been explained on the basis of a Zimmerman-Traxler type transition state.
Lam et al. investigated a cobalt-catalysed alternative to their diastereo- and enantioselective copper-catalysed synthesis of β-hydroxylactones and β-hydroxylactams. A variety of stoichiometric reductants were screened, hydrosilanes gave complex reaction mixtures while, after investigating organometallic reagents with β-hydride-containing alkyl groups (Et₃B and Et₂Zn), efficient reductive cyclisation occurred with the use of diethylzinc. High yields and diastereoselectivities were observed with Co(acac)₂ hydrate when forming 4-hydroxypiperidin-2-ones and CoCl₂ ligated with Cy₂PPh was found to be an effective catalyst system with substrates 123a and 123b; these showed incomplete conversion with Co(acac)₂ hydrate (Scheme 37).

\[
\begin{align*}
\text{Method A} & \text{: Co(acac)₂.H₂O (5 mol\%)} \\
\text{Method B} & \text{: CoCl₂ (5.5 mol\%), Cy₂PPh (5.5 mol\%)}
\end{align*}
\]

Scheme 37 Cobalt-catalysed reductive aldol reaction mediated by Et₂Zn

This cobalt-catalysed reductive aldol reaction was not found to be limited to intramolecular transformations, both N,N'-dimethylacrylamide 118 and 4-acryloylmorpholine 128 were coupled with aliphatic, aromatic and heteroaromatic ketones. Moderate diastereoselectivities were observed, however, ortho-substitution on acetophenone derivatives promoted selectivity to 9:1 (Scheme 38). β-Substitution on the olefin resulted in a large elevation in the diastereoselectivity, with 135 and 136 being accessed with diastereoselectivities of >19:1 (Scheme 39).
To develop an asymmetric variant of this reaction Lam turned to a chiral auxiliary strategy; ligation of cobalt was not an option for asymmetric induction due to it being a zinc-, not a cobalt-, enolate involved in the key carbon-carbon bond forming step.\(^{67}\) N-Acryloyloxazolidine \(137\) was identified as a suitable substrate reacting with acetophenone to give the aldol product \(138\) in 73\% yield and with a 11:1 diastereoselectivity. A range of aromatic and heteroaromatic ketones revealed the aldol product in moderate yields (58-76\%) and good diastereoselectivities (up to 13:1); as with \(\alpha,\beta\)-unsaturated morpholine amides (Scheme 39), substitution on the \(\beta\)-carbon improved reaction yields and selectivities (Scheme 40).
1.2.4 Nickel-Catalysed Reductive Aldol Reactions

Alongside the cobalt catalysis described above, Lam developed a complementary nickel catalysed intramolecular reductive aldol reaction forming β-hydroxylactams and β-hydroxylactones, again using a diethylzinc as a stoichiometric reductant. This nickel-catalysed reductive aldol reaction showed higher reactivity than the cobalt system; substrates which had previously shown little or no reactivity now gave the desired products (Scheme 41).

Scheme 41 Nickel-catalysed reductive aldol reaction mediated by Et₂Zn

A problem encountered with this nickel system is that of competitive alkylative aldol reaction, a side reaction which is not observed under cobalt catalysis. Substrate 143 gave reductive aldol product 144 in 17% yield and alkylative aldol product 145 in 51% yield (Scheme 42). Lam found that this competitive alkylation is eliminated by the addition of α- or β-substituents on the acrylamide.

Scheme 42 Competitive alkylative aldol reaction
The synthesis of six-membered β-hydroxylactones was also successful under nickel catalysis, a transformation which was found not to be possible under the comparable cobalt reductive conditions; the results observed were comparable to those shown with the ketoacrylamides (Scheme 43). However, a significant quantity of the alkylation aldol product was observed with electron-deficient substrates.

Scheme 43 β-Hydroxy lactone synthesis

In this initial study into nickel catalysis, Lam et al. observed the formation of bicyclic product 150, a product of the zinc alkoxy aldol product 149 undergoing lactonisation (Scheme 44). Following this observation Lam et al. carried out a formal synthesis of salinosporamide A 154, a potent 20S proteasome inhibitor and anti-cancer compound.69 Formation of the β-hydroxy-γ-lactam core of 154 required the reductive cyclisation-lactonisation of 151, a much more highly functionalised precursor than previously used. Bicyclic 153a was isolated in 42% yield and was transformed, in a number of steps, to salinosporamide A 154 (Scheme 45).
Prior to work done by Lam et al. on the nickel-catalysed reductive aldol cyclisation, Chrovian and Montgomery reported a similar system in which triethyl borane was used as the terminal reductant. The reaction was found to be initiated by phenyl iodide and only 5% of the Michael aldol side-product was observed. High yield and syn-selectivity was observed for this process with a range of aldehydes (Scheme 46).
1.2.5 Palladium-Catalysed Reductive Aldol Reactions

Little work has been carried out on tandem reductive processes initiated by a palladium-catalysed conjugate reduction. In a rare example, Kiyooka et al. illustrated the substrate dependence of the palladium-catalysed reductive aldol reaction. *Anti*-selectivity (*syn*: *anti* 32:68) was observed in the coupling of N,N'-dimethylacrylamide 118 with benzaldehyde 9, whereas, *syn*-selectivity (*syn*: *anti* 72:28) was observed when using tert-butyl acrylate 60 with a significant depletion of yield (Scheme 47).71

\[
\begin{align*}
\text{O} & \quad \text{O} \\
X &= \text{NMe}_2 & \quad \text{H} & \quad \text{Ph} \\
118 \quad 120 & : 87\% \text{ (syn:anti 32:68)} \\
60 \quad 61a & : 37\% \text{ (syn:anti 72:28)}
\end{align*}
\]

*Scheme 47* Palladium-catalysed reductive aldol reaction

A further example comes from an investigation into the application of dehydroamino acid derivatives in tandem processes. A palladium-catalysed reductive aldol reaction was achieved using *n*-Bu₃SnH as a hydride donor, N-phthaloyl dehydroalanine 155 and benzaldehyde 9 gave a mixture of 156 and 157 (Scheme 48).72

\[
\begin{align*}
\text{EtO} & \quad \text{NPhth} \\
155 \quad 156 & : 65\% \text{ (9:1 dr)} \\
\text{Ph} & \quad \text{O} \\
9 \quad 157 & : 16\%
\end{align*}
\]

*Scheme 48* Reductive coupling of N-phthaloyl dehydroalanine and benzaldehyde
1.2.6 Indium-Catalysed Reductive Aldol Reactions

As with palladium-catalysis, there are few reports of indium-catalysed reductive aldol reactions; however, those few reports disclose highly selective processes. Baba et al. used stoichiometric amounts of InBr$_3$ with $n$-Bu$_3$SnH for the reductive aldol reaction between enones and aromatic aldehydes.$^{73}$ Interestingly, selectivity could be switched by the addition of water to the solvent system (Scheme 49). When carried out in anhydrous THF the thermodynamically favourable product was observed (syn:anti 4:96); addition of water to the solvent system (THF/H$_2$O : 9/1) led to the kinetically favourable product (syn:anti 95:5).

\[
\begin{align*}
\text{InBr}_3 (1.2 \text{ equiv}) & \quad \text{n-Bu}_3\text{SnH (1.2 equiv)} \\
\text{THF/H}_2\text{O (9/1)} & \quad -78^\circ\text{C to r.t., 1 h} \\
\text{O} & \quad \text{HO} \\
\text{Me} & \quad \text{Me} \\
160 : 77\% (\text{syn:anti 95:5}) & \quad 158 159 160 : 89\% (\text{syn:anti 4:96})
\end{align*}
\]

Scheme 49 Indium-promoted reductive aldol reaction

Baba et al. showed that sub-stoichiometric amounts of InBr$_3$ could be used in conjunction with triethyilsilane; this led to excellent syn-selectivity (typically syn:anti >99:1) with aromatic aldehydes and enones.$^{74}$ This high syn-selectivity can be attributed to the formation of a (Z)-indium enolate as conjugate reduction occurs to the s-cis configured enone.

\[
\begin{align*}
\text{InBr}_3 (10 \text{ mol\%}) & \quad \text{Et}_3\text{SiH (1.2 equiv)} \\
\text{EtCN} & \quad 0^\circ\text{C, 4 h} \\
\text{O} & \quad \text{OH} \\
\text{Me} & \quad \text{Me} \\
158 & \quad 9 \\
158 & \quad 159 \\
160 : 78\% (\text{syn:anti 92:8}) & \quad 161
\end{align*}
\]

Scheme 50 Indium-catalysed reductive aldol reaction

Adding to the findings of Baba et al., Miura and Hosomi reported the indium-catalysed conjugate reduction and reductive aldol reaction using In(OAc)$_3$ and PhSiH$_3$.$^{75}$ Reported yields were comparable to those reported by Baba while selectivity was lower for the
Reductive coupling of aryl aldehydes and enones. However, these conditions were adapted for the intramolecular reductive aldol reaction of 163a and 163b. Complete stereocontrol was observed with the six-membered product 164b, while 163a gave five-membered 164a as a 62:38 ratio of the cis:trans isomers (Scheme 51).

\[
\text{In(OAc)}_3 (10 \text{ mol\%}) \quad \text{PhSiH}_3 (1.0 \text{ equiv}) \\
\text{THF/EtOH} \quad 0^\circ\text{C}, 4h
\]

163a : \( n = 1 \)
163b : \( n = 2 \)

\[
\begin{align*}
\text{164a : 85\%} & \quad (\text{cis:trans 62:38}) \\
\text{164b : 90\%} & \quad (\text{cis:trans >99:1})
\end{align*}
\]

Scheme 51 Indium-catalysed intramolecular reductive aldol reaction

### 1.3 Reductive Mannich Reactions

Reductive Mannich reactions offer an efficient route to β-amino esters, which are excellent intermediates in the synthesis of β-amino acids and β-lactams. This challenging transformation requires anhydrous conditions and needs to avoid competitive imine reduction. The majority of examples of reductive Mannich reactions involve the reductive coupling of Michael acceptors to aldimines.

Following a two-step synthesis of β-lactams via a reductive Mannich reaction reported by Isayama,\(^5\) Morken et al. reported the synthesis of β-lactams via an iridium-catalysed reductive Mannich reaction.\(^6\) Under the reductive conditions the Mannich product is cyclised to give the β-lactam in high yields and trans-selectivity. Yields were significantly higher with pentafluorophenyl acrylate; a yield of only 13% was observed with phenyl acrylate (Scheme 52).

\[
\begin{align*}
\text{165} & \quad + \quad \text{166} \\
& \quad \xrightarrow{[\text{Ir(cod)Cl}]_2 (2.5 \text{ mol\%}) \quad \text{P(OPh)}_3 (10 \text{ mol\%}) \quad \text{Et}_2\text{MeSiH} (2.5 \text{ equiv})} \\
& \quad \text{DCE, 60}^\circ\text{C, 6 h}} \\
& \quad \text{167 : 80\%} \quad (\text{trans:cis >20:1}) \\
& \quad \text{168 : 71\%} \quad (\text{trans:cis 5.2:1}) \\
& \quad \text{169 : 58\%} \quad (\text{trans:cis >20:1})
\end{align*}
\]

Scheme 52 Iridium-catalysed β-lactam synthesis
Aldimines were coupled with methyl acrylate using a cationic rhodium complex \([\text{Rh(COD)}\{\text{P(OPh)}_3\}_2] \text{OTf}\) and \(\text{Et}_2\text{MeSiH}\) by Matsuda.\(^{77}\) This synthesis of \(\beta\)-amino esters occurs with slight anti-selectivity and high to excellent yields; highest yields were observed with \(N\)-tosylaldimines. Greater diastereoselectivity was achieved by Nishiyama et al. who applied their \(\text{Rh(Phebox)}\) ligands to the reductive Mannich reaction which, although gave high yields and moderate diastereoselectivities, did not result in any enantios selectivity being observed when a chiral \(\text{Rh(Phebox)}\) complex was used.\(^{78}\) Excellent anti-selectivity was achieved when coupling cinnamate 170 and aldimine 171; such high selectivity was not observed with tert-butyl acrylate 60 (Scheme 53).

![Scheme 53 Rh(Phebox)-catalysed reductive Mannich reaction](image)

Lam applied the cobalt-catalysed conditions developed for the reductive aldol reaction, using diethylzinc as a stoichiometric reductant,\(^{59,66}\) to the coupling \(N\)-tosylaldimines 174 with 4-acryloylmorpholine 128.\(^{79}\) Moderate to good yields and diastereomeric ratios of up to 88:12 (anti:syn) were observed for the transformation which proceeds via a zinc enolate (Scheme 54).

![Scheme 54 Cobalt-catalysed reductive Mannich reaction](image)
After the success of the molecular hydrogen mediated reductive aldol reaction (cf. 1.2.1.2),\textsuperscript{5} Krische reported the rhodium-catalysed reductive Mannich coupling of vinyl ketones to \(N\)-sulfonylimines mediated by hydrogen.\textsuperscript{80} Using the same conditions as the reductive aldol chemistry the reductive coupling of methyl vinyl ketone and \(N\)-arylaldimides gave the Mannich products in excellent yields (88-99\%) but with poor diastereoselectivity (<2:1 dr). To overcome the problem of poor selectivity, caused by the facile geometrical isomerisation of the \(N\)-arylaldimine in the presence of rhodium,\textsuperscript{81,82} \(N\)-sulfonylimines were employed as the reaction electrophile as they are conformationally more stable. Attention was turned to the coupling of vinyl ketones and \(N\)-(o-nitrobenzenesulfonyl)imines \textsuperscript{176} due to the ease of deprotection of the Mannich adducts. Good yields and excellent syn-diastereoselectivities were observed (Scheme 55).

![Scheme 55 Diastereoselective hydrogen-mediated reductive Mannich reaction](image-url)

The only example of transition metal catalysed reductive Mannich reactions to ketimines comes from Shibasaki \textit{et al.} who coupled acrylates with \(N\)-diphenylphosphinoyl ketimines \textsuperscript{179} under copper catalysis.\textsuperscript{83} Initial efforts focused on diastereoselective reductive Mannich reactions. Pinacolborane was used as a stoichiometric reductant and triphenylphosphine as a ligand; excellent yields (up to 94\%) and diastereoselectivities (up to 99:1) were observed. The high yields and diastereoselectivities remained on addition of \((R)\)-DIFLUORPHOS \textsuperscript{181} which, with \((\text{EtO})_3\text{SiH}\), gave the \(\beta\)-amino acids with high enantiomeric excess (Scheme 56). Acid hydrolysis of the diphenylphosphinoyl group gave the free amine with no racemisation or epimerisation.
1.4 Reductive Michael Reactions

Only two reductive systems have been applied to the reductive Michael reaction, both these intramolecular transformations observe complete trans-selectivity of the cyclic products from bis-enones.

Krische et al. reported the cobalt-catalysed intramolecular reductive Michael reaction of bis(enones).\textsuperscript{3,57,58} Interestingly, this reaction gave only the trans-cyclic products in moderate to high yields, a switch in selectivity compared to the related intramolecular reductive aldol reaction. This reaction worked well for symmetrical bis-enones and tolerated heteroatoms in the carboskeleton, which led to the synthesis of cyclic ether 185 (Scheme 57); however, chemoselectivity was poor using non-symmetrical substrates.
Miura and Hosomi’s conditions for the indium-catalysed intramolecular reductive aldol reaction (cf. 1.2.6) also were applicable to the related reductive Michael reaction.\(^{75}\) Like Krische, Miura and Hosomi observed complete \textit{trans}-selectivity, with products being isolated in high yields (Scheme 58).

![Scheme 58 Indium-catalysed reductive Michael reaction](image)

\[ \text{Scheme 58 Indium-catalysed reductive Michael reaction} \]

### 1.5 Morita-Baylis-Hillman Type Reactions

Matsuda \textit{et al.} reported the synthesis of Morita-Baylis-Hillman type products from Michael acceptors and aldehydes.\(^{84-86}\) The process, catalysed by 1 mol\% of either Rh(PPh\(_3\))\(_4\) or RuH\(_2\)(PPh\(_3\))\(_4\), involves the formation of metal-aldolate \(187\). \(187\) undergoes tautomerisation to \(188\) and subsequent \(\beta\)-hydride elimination, regenerating the metal-hydride species, to give the Morita-Baylis-Hillman type product \(186\) (Scheme 59).

![Scheme 59 Synthesis of Morita-Baylis-Hillman type products initiated by conjugate reduction](image)

\[ \text{Scheme 59 Synthesis of Morita-Baylis-Hillman type products initiated by conjugate reduction} \]
1.6 Hydrocarbamoylation Reactions

Matsuda et al. showed aryl isocyanates to be useful coupling partners for rhodium-enolates formed from the hydrometallation of α,β-unsaturated esters.\textsuperscript{87} The hydrocarbamoylation products were formed in high yields regardless of substitution of the Michael acceptor or the aryl isocyanate (Scheme 60). No isocyanate reduction was observed.

\[
\text{MeO} - \text{C} - \text{R} + \text{R'} \text{N}=\text{C}=\text{O} \rightarrow \begin{array}{c}
\text{MeO} - \text{N} - \text{Ph} \\
\text{MeO} - \text{N} - \text{Et} \\
\text{MeO} - \text{N} - \text{Cl}
\end{array}
\]

Scheme 60 Rhodium-catalysed hydrocarbamoylation

1.7 Hydroallylations

Matsuda et al. carried out the rhodium-catalysed hydroallylation of Michael acceptors to give γ,δ-unsaturated esters in high yields by reductive coupling of acrylates and allylic carbonates.\textsuperscript{88,89} Initial studies showed that regioselectivity was poor unless one terminus was sterically disfavoured, for example allylic carbonyl 194 gave 195 and 196 as a 56:44 mixture, whereas, hydroallylation using 197 resulted in a 95:5 mixture of the two regioisomers (Scheme 61).

\[
\text{MeO} - \text{C} - \text{Me} + \text{Ph} \text{OCO}_2\text{Me} \rightarrow \begin{array}{c}
\text{MeO} - \text{C} - \text{Me} - \text{Ph} \\
\text{MeO} - \text{C} - \text{Me} - \text{Me}
\end{array}
\]

Scheme 61 Rhodium-catalysed hydroallylation
To develop this regioselective process further, Matsuda et al. introduced triorganosilyl groups to either end of the allylic termini of the allylic carbonate (Scheme 62).\(^8\)\(^9\) Regioselectivities and yields were uniformly excellent using silylated allylic carbonates. Acidic protodesilylation proceeded in moderate yields.

![Scheme 62 Hydroallylation using silylated allylic carbonates](image)

1.8 Reductive Claisen Rearrangements

The reductive Claisen rearrangement was reported by Morken and Miller.\(^9\)\(^0\) Substituted allyl acrylates underwent rhodium-catalysed hydrosilylation and subsequent Ireland-Claisen rearrangement to give \(\gamma,\delta\)-unsaturated carboxylic acids in good yields and diastereoselectivities (Scheme 63). The reductive Claisen rearrangement of chiral substrate 205 proceeded with little drop in enantiopurity. Product 206 was used as a key intermediate in the total synthesis of inostamycin (cf. 1.2.1.3).\(^2\)\(^7\)

![Scheme 63 Rhodium-catalysed reductive Claisen reaction](image)
1.9 References

Chapter 2 - Initial Studies into the Reductive Dieckmann Condensation

2.1 Dieckmann Condensation

As discussed in chapter 1, catalytic tandem reductive processes have been of great interest over the last two decades. Of particular interest is the use of Michael acceptors as latent enolates enabling reductive aldol, Mannich and Michael reactions to take place. However, to our knowledge there have been no examples of a reductive Dieckmann (or Claisen) condensation in which enolate 208, formed after hydrometallation, attacks the ester, eliminating an alkoxyate group to give a 1,3-dicarbonyl product 209 (Scheme 64).

![Scheme 64 Proposed reductive Dieckmann condensation](image)

The Dieckmann condensation, an intramolecular variant of the Claisen condensation, is a convenient route into the formation of β-keto esters by treatment of a diester with strong base, typically sodium alkoxide (Scheme 65).1

![Scheme 65 Dieckmann condensation](image)

Although there are no examples of reductive Dieckmann condensations, comparable Michael Dieckmann condensations have been reported. For example, a key step in the synthesis of natural product (+/-)-napyradiomycin A1 214 is the Michael Dieckmann condensation of 212 with isobenzofuranone 213 (Scheme 66).2
Scheme 66 Michael Dieckmann condensation as a key step towards the synthesis of (+/-)-napyradiomycin

More recently, Frost et al. have reported the tandem rhodium-catalysed Michael Dieckmann condensation as a route to β-keto esters containing an all-carbon quaternary centre at the α-carbon. In their initial study, five- and six-membered β-keto esters were formed by the rhodium-catalysed conjugate addition of arylzinc chlorides to α-substituted acrylic esters 215a and 215b (Scheme 67). The reaction pathway is unclear with a number of possible routes proposed (Scheme 68).

Scheme 67 Rhodium-catalysed Michael Dieckmann condensation

Scheme 68 Plausible reaction pathways for Frost's Michael Dieckmann reaction
To develop this elegant methodology further, Frost et al. introduced a heteroatom into the carbon backbone of the \( \alpha \)-substituted acrylic ester, enabling the synthesis of 3,3’-disubstituted 4-oxopyrrolidines containing an all carbon quaternary centre.\(^4\) The rhodium-catalysed addition of aryl boronic acids to acrylate \( \text{218} \), derived from sarcosine ethyl ester, was carried out. The desired Michael Dieckmann product \( \text{219} \) was found to be the major product of this process (Scheme 69). An addition/elimination reaction also occurs under these conditions giving acrylate \( \text{220} \), which can also undergo a Michael addition by a second equivalent of aryl boronic acid to give \( \text{221} \) (Scheme 69).

![Scheme 69 Rhodium-catalysed synthesis of 3,3’-disubstituted 4-oxopyrrolidines](image)

After initial studies into the rhodium-catalysed Michael Dieckmann condensation attention was then turned to asymmetric induction at the all-carbon quaternary centre by the introduction of a chiral ligand. After screening a range of chiral bisphosphines \((S)\)-DIFLUORPHOS \( \text{181} \) was found to be the most effective ligand giving 3,3’-disubstituted 4-oxopyrrolidine \( \text{219b} \) in a 69% yield and an excellent 96% ee (Scheme 70). The absolute stereochemistry of \( \text{223a} \) was found to be \( R \) by X-ray crystallography.

![Scheme 70 Asymmetric rhodium-catalysed Michael Dieckmann condensation](image)
Amongst the vast array of conjugate reduction literature is Keinan’s 1987 report on the molybdenum-catalysed conjugate reduction of Michael acceptors, a paper which has received little attention since publication. In this report, a number of Michael acceptors were reduced by molybdenum hexacarbonyl using phenylsilane as the terminal reductant (Scheme 71). By $^1$H NMR and isotope labelling studies, Keinan showed the process proceeded via a silyl enol ether which was protonated on addition of water at the end of the reaction. Excellent conversions were observed for the reduction of $\alpha,\beta$-unsaturated ketones, esters, amides, nitriles and carboxylic acids (75-100% conversion determined by GC and $^1$H NMR analysis).

**Scheme 71** Keinan's molybdenum-catalysed conjugate reduction

It is the availability and low cost of Mo(CO)$_6$ which makes it an attractive catalyst for organic transformations. Mo(CO)$_6$ has many applications within organic chemistry. Mo(CO)$_6$ can be converted into a range of molybdenum complexes by replacement of its carbonyl ligands by both $\pi$- and $\sigma$-donor ligands, but it can also be used as a catalyst in its own right. Beyond its use as a safe, convenient source of carbon monoxide, Mo(CO)$_6$ has been used in asymmetric allylic alkylations, alkyne metathesis, Pauson-Khand reactions, allenic Pauson-Khand reactions, [2+2] cyclisation, N-O bond reduction, cycloisomerisations and conjugate reduction.

The catalytic activity of molybdenum depends on the ease in which coordinatively saturated Mo(CO)$_6$ is converted to coordinatively unsaturated Mo(CO)$_6$-$n$. Typically this is achieved thermally or photochemically. On investigating the thermal displacement of
carbonyl ligands from Mo(CO)$_6$, Keinan showed that, although rapid activation occurs in diglyme between 90-100 °C, efficient activation of Mo(CO)$_6$ can be achieved in THF at reflux.\textsuperscript{5} It was also noted that catalytic activity significantly depended on the physical removal of carbon monoxide from the reaction mixture; reactivity was retarded when the reaction was carried out in a sealed vessel.

### 2.2.1 α-Substituted Acrylic Esters

Of interest to the Frost group is the functionalisation of α-substituted acrylic esters and α-substituted acrylic amides through rhodium-catalysed conjugate additions. Frost has shown that these challenging substrates can be used in the preparation of 2-alkylsuccinates, both α- and β-amino acid derivatives, 2-benzyl pyrrolizidinones, β-keto esters, α,α’-dibenzyl esters and in peptide modifications (Scheme 72).\textsuperscript{3, 52-60}

![Scheme 72 Array of products synthesised from α-substituted acrylate esters by the Frost et al.](image-url)
2.2.2 Conjugate Reduction of $\alpha$-Substituted Acrylic Esters

The use of $\alpha$-substituted Michael acceptors in catalytic tandem reductive processes is a potential route to enantiomerically enriched all-carbon quaternary centres (Scheme 73).

![Scheme 73](image)

To investigate the reduction of $\alpha$-substituted acrylic ester, readily available dimethyl itaconate (DMI) 229 was used as a model substrate. Reduction of DMI was carried out using Keinan’s molybdenum-catalysed conjugate reduction reagents under microwave irradiation. It was found that after 10 minutes at 100 °C, complete conversion to dimethyl 2-methylsuccinate 230 was observed, with a 60% conversion being observed after a period of 5 minutes (Table 1, entry 1). With this result in hand, an additive screen was performed in an attempt to improve the activity of the reductive system. In this regard, 5 mol% of additive was added to the reaction mixture which was heated to 100 °C for 5 minutes (Table 1).

A range of additives was screened and the reaction was either retarded or completely shut down by the addition of both Lewis acids and Lewis bases (Table 1, entries 2-10). However, great success was observed on the addition of $N$-methylmorpholine $N$-oxide (Table 1, entry 11). As discussed above (cf. 2.2), it is the removal of the carbonyl ligands from Mo(CO)$_6$ and subsequent removal of carbon monoxide from the atmosphere which is key to the activation of the molybdenum catalyst. It is therefore unsurprising that the oxidative removal of the carbonyl ligands from Mo(CO)$_6$ by $N$-methylmorpholine $N$-oxide (NMO) greatly increases the rate of reaction for conjugate reduction of DMI.
Table 1 Additive screen for the molybdenum-catalysed reduction of DMI

<table>
<thead>
<tr>
<th>entry</th>
<th>additive</th>
<th>conversion, %$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>no additive</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>DMAP</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>CyNH$_2$</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>triethylamine</td>
<td>18</td>
</tr>
<tr>
<td>5</td>
<td>L-Proline</td>
<td>17</td>
</tr>
<tr>
<td>6</td>
<td>binaphthyl-2,2'-diyl hydrogen phosphate</td>
<td>17</td>
</tr>
<tr>
<td>7</td>
<td>BINOL</td>
<td>55</td>
</tr>
<tr>
<td>8</td>
<td>boric acid</td>
<td>33</td>
</tr>
<tr>
<td>9</td>
<td>BINAP</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>DMSO</td>
<td>20</td>
</tr>
<tr>
<td>11</td>
<td>NMO</td>
<td>100$^c$</td>
</tr>
</tbody>
</table>

$^a$ Reaction conditions: DMI (1 equiv), Mo(CO)$_6$ (5 mol%), additive (5 mol%), PhSiH$_3$ (1.5 equiv), THF (1 mL); reaction mixtures were heated using microwave irradiation, 100 °C, 5 min (100 W).

$^b$ Conversions determined by $^1$H NMR. $^c$ 9 mol% of additive was used.

2.2.3 Optimisation

Complete conversion to 230 was still observed on lowering the reaction temperature to 80 °C, however, reactivity decreased at temperatures below that point (Table 2). When the reduction of DMI was carried out at 80 °C over 5 minutes with one equivalent of NMO to Mo(CO)$_6$ a drop in conversion from >99% to 56% was observed (entry 4, Table 2). Lower catalyst loading also resulted in lower yields (a yield of 22% was observed with a catalyst loading of 2 mol%, no product was observed at 1 mol%). Poor reactivity was observed when PhSiH$_3$ was replaced with less reactive silanes. Ph$_2$SiH$_2$ gave a 3% conversion by $^1$H NMR whilst Cl$_3$SiH, Me(EtO)$_2$SiH, PMHS and Et$_3$SiH did not react at all. It was also found that the reactivity was unaffected when the reaction was heated in an oil bath.
Table 2 Effect of temperature and reaction time on the reduction of DMI

| entry | temperature, °C | time, min | conversion, %
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>5</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>80</td>
<td>10</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>80</td>
<td>5</td>
<td>&gt;99 (95% yield)</td>
</tr>
<tr>
<td>4</td>
<td>80</td>
<td>5</td>
<td>56 INDIRECT</td>
</tr>
<tr>
<td>5</td>
<td>70</td>
<td>5</td>
<td>69</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>5</td>
<td>26</td>
</tr>
<tr>
<td>7</td>
<td>40</td>
<td>5</td>
<td>20</td>
</tr>
</tbody>
</table>

*a Reaction conditions: DMI (1 equiv), Mo(CO)₆ (5 mol%), NMO (9 mol%), PhSiH₃ (1.5 equiv), THF (1 mL); reaction mixtures were heated using microwave irradiation, 5 min (100 W). b Conversions determined by ¹H NMR.

2.2.4 Oxidative Removal of Ligands from Metal Carbonyls

It was Hieber and Lipp who first reported the use of pyridine N-oxides to oxidatively remove carbonyl ligands from Fe(CO)₅.⁶¹ In 1970 Alper and Edward illustrated the generality of this process by the deoxygenation of aliphatic, aromatic and heterocyclic amine N-oxides with Fe(CO)₅; this method of oxidative removal of carbonyl ligands was even carried out with brucine N-oxide (BNO) hydrate 231 (Figure 1).⁶² Alper and Edward were the first to propose a mechanism for the transformation, a mechanism which is still widely accepted. Nucleophilic attack by the oxygen of the amine N-oxide on the carbonyl carbon occurs to form 232 which then eliminates the deoxygenated amine and carbon dioxide (Scheme 74).
With the use of amine N-oxides as oxidative decarboxylating reagents established,\textsuperscript{63,64} Shi \textit{et al.} carried out the first kinetic and mechanistic study into the reaction of trimethylamine N-oxide (TMANO) with the group 6 hexacarbonyls.\textsuperscript{65} Shi \textit{et al.} showed that carbon-oxygen bond making and metal-carbon bond breaking contributed to the energies of the rate determining step. After decarboxylation by TMANO, (CO)\textsubscript{5}MPPh\textsubscript{3} (M = Cr, Mo, W) was formed in the presence of PPh\textsubscript{3} and (CO)\textsubscript{5}MNMe\textsubscript{3} in the absence of phosphine (Scheme 75).

\begin{equation}
\text{Me}_3\text{NO} + \text{M(CO)}_6 \rightarrow \begin{cases} 
(\text{OC})_5\text{M} + \text{C}=\text{O} \\
\text{OC}N\text{Me}_3
\end{cases} \rightarrow \begin{cases} 
(\text{CO})\textsubscript{5}M^* \\
\text{Me}_3\text{N}
\end{cases}
\end{equation}

\textbf{Scheme 75} Oxidative decarboxylation of M(CO)\textsubscript{6} (M = Cr, Mo, W)

The use of amine N-oxides in transition metal catalysed organic transformations has been dominated by the Pauson-Khand reaction (PKR) following the discovery of the accelerating effects amine N-oxides have on this reaction. Amine N-oxides allow PKRs to be carried out at room temperature in high to excellent yields.\textsuperscript{66,67} More recent developments have seen the introduction of recyclable amine N-oxides bound to a solid phase\textsuperscript{68} and also the use of
chiral amine N-oxides in asymmetric PKRs by desymmetrisation of cobalt-alkyne complexes.\textsuperscript{69-75}

### 2.3 Molybdenum-Catalysed Reductive Dieckmann Condensation

Following work by Frost \textit{et al}. on the Michael Dieckmann condensation forming 3,3\textsuperscript{'}-disubstituted 4-oxopyrrolidines (\textit{cf}. 2.1), we set out to develop a reductive Dieckmann condensation using molybdenum catalysis. Scheme 76 shows the envisaged reductive Dieckmann condensation, hydrosilylation of \textsuperscript{234} would give silyl ketene acetal \textsuperscript{235} which would undergo a 5-(enol\textsuperscript{exo})\textsuperscript{exo}-trig cyclisation, this is formally favoured by Baldwin’s rules.\textsuperscript{76} Siloxane elimination gives 3,3\textsuperscript{'}-disubstituted 4-oxopyrrolidine \textsuperscript{237}, a useful intermediate in the synthesis of fluoroquinolone antibacterials and their analogues.

![Scheme 76 Envisaged molybdenum-catalysed reductive Dieckmann condensation](image-url)
2.3.1 Fluoroquinolones

Fluoroquinolones are a potent class of antibacterial agents with a broad spectrum of activity making them a valuable target in synthesis. Following the discovery of Nalidixic acid (a by-product from the synthesis of chloroquine), structure-activity relationship studies soon showed that quinolones fluorinated at the C-6 position with a nitrogen containing heterocycle at the C-7 position showed fewer toxic effects, improved pharmacokinetic properties and extensive and potent activity against Gram-positive and Gram-negative bacteria (Figure 2).

![Fluoroquinolone antibacterials](image)

In 2004, Choi *et al.* synthesised fluoroquinolones 247a and 247b containing a chiral oxylimino pyrrolidine at the C-7 position. These new fluoroquinolones showed excellent *in vitro* antibacterial activities and pharmacokinetic profiles. N-Carboxybenzyl protected 3,3’-disubstituted 4-oxopyrrolidine 243 was prepared by the Dieckmann condensation of glycine derived 241, followed by alkylation by methyl iodine. Optically-enriched products were obtained by resolution: N-tosyl protected L-proline was attached to the primary amine of 244 and diastereomers 246a and 246b were separated by column chromatography. This was followed by the base-catalysed removal of the amino acid (Scheme 77).
Kim et al. synthesised analogues of the pyrrolopiperidine side group of Moxifloxacin 240. Again, access to optically-enriched materials was achieved by the separation of diastereomers 252a and 252b by column chromatography and subsequent removal of the optically active oxazolidinone 251 (Scheme 78).
Although effective, resolution of products obtained from racemic 3,3’-disubstituted 4-oxopyrrolidines 243 and 249 does result in poor atom and step economy. We envisage that, through an asymmetric reductive Dieckmann condensation, optically active 3,3’-disubstituted 4-oxopyrrolidines could be obtained efficiently from α-substituted acrylic esters.

### 2.3.2 Racemic Molybdenum-Catalysed Reductive Dieckmann Condensation

To study the molybdenum-catalysed reductive Dieckmann condensation, a range of α-substituted acrylate esters was synthesised bearing different nitrogen functionalities. Using a synthetic route developed by Greaney et al., substrates were formed by the alkylation of the corresponding \(N\)-protected glycine ethyl or methyl ester with tert-butyl 2-(bromomethyl)acrylate; 218 was formed from the alkylation of sarcosine ethyl ester (Scheme 79).

![Scheme 79 Substrate synthesis](image)

Extended reaction times were required to allow for cyclisation to the desired product (Table 3, entries 1-3). Even with shorter reaction times, acrylate 222 was completely consumed, the corresponding uncyclised, conjugate reduction product was the only other product observed with reaction times of four and eight hours (Table 3, entries 1 and 2). Benzyl substitution on the nitrogen atom gave the most favourable yield with 3,3’-disubstituted 4-oxopyrrolidine 258 being isolated in an 88% yield (Table 3, entry 3). A lower yield was observed with the electron-withdrawing Boc substitution (entry 3) while a number of side products were observed in the reductive Dieckmann condensation of allyl substituted 259.
(entry 5). A low yield was also observed for the formation of methyl substituted 260 (entry 6).

### Table 3 Molybdenum-catalysed reductive Dieckmann Condensation

<table>
<thead>
<tr>
<th>entry</th>
<th>protecting group</th>
<th>R</th>
<th>time, h</th>
<th>product</th>
<th>yield, %&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Benzyl</td>
<td>Et</td>
<td>4</td>
<td>258</td>
<td>57</td>
</tr>
<tr>
<td>2</td>
<td>Benzyl</td>
<td>Et</td>
<td>8</td>
<td>258</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>Benzyl</td>
<td>Et</td>
<td>16</td>
<td>258</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>Boc</td>
<td>Et</td>
<td>16</td>
<td>249</td>
<td>61</td>
</tr>
<tr>
<td>5</td>
<td>Allyl</td>
<td>Me</td>
<td>16</td>
<td>259</td>
<td>51</td>
</tr>
<tr>
<td>6</td>
<td>Methyl</td>
<td>Et</td>
<td>16</td>
<td>260</td>
<td>67</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: Substrate (1 equiv), PhSiH<sub>3</sub> (1.5 equiv), Mo(CO)<sub>6</sub> (5 mol%), NMO (9 mol%), THF, reflux, 16 h. <sup>b</sup> Isolated yields.

### 2.3.3 Asymmetric Reductive Dieckmann Condensation

Having established precedent for the reductive Dieckmann condensation, attention was focused on asymmetric induction at the newly formed quaternary centre. A number of pathways were envisaged to form enantiomerically enriched products (Scheme 80). Firstly, ligation of the transition metal catalyst with a chiral ligand (pathway a), secondly, the formation of a chiral silyl ketene acetal (pathway b), and thirdly, the use of chiral auxiliaries either on the terminal ester (pathway c) or as a chiral amine protecting group (pathway d) were all envisaged.
2.3.3.1 Ligation of Molybdenum

A large amount of research has been focused on the molybdenum-catalysed asymmetric allylic alkylation reaction.\(^{25}\) High enantioselectivities were achieved by the use of nitrogen donor ligands such as pyridylamides 261, bis(dihydrooxazoles) 262 and bipyridines 263 (Figure 3). Unfortunately, there have been no reports of a molybdenum-catalysed asymmetric conjugate reduction. It was envisaged that a chiral molybdenum-hydride species could be accessed on addition of phenylsilane to a molybdenum complex containing chiral N-donor ligands.

![Scheme 80 Possible pathways to an asymmetric reductive Dieckmann condensation](image)

**Figure 3** Common ligands for molybdenum-catalysed asymmetric allylic alkylation reactions
Ligands 264 and 265 (Scheme 81), 1.5 equivalents to molybdenum, were added to a solution of Mo(CO)$_6$ and NMO in THF and stirred for an hour at 80 °C, in both instances a deep red solution was observed. After addition of all other reagents, and a further 16 hours heating, only starting material was observed. Following on from these results, chiral diene 266 was used (1.5 equivalents to molybdenum) giving the desired product in 88% isolated yield as the racemate (Scheme 81). This suggests that either the ligand is not interacting with the metal centre or that it is a silicon, not a molybdenum, enolate which attacks the terminal ester. In light of these results no further attempts were made to induce chirality by ligation of molybdenum.

Scheme 81 Asymmetric molybdenum-catalysed reductive Dieckmann condensation using chiral ligands

2.3.3.2 Ligation of Silicon

Extensive research has been carried out into the use of chiral Lewis acids in organosilicon chemistry which enables the formation of chiral, hypervalent silicon species (the chemistry of hypervalent silicon will be discussed in Chapter 4). In one example from Nakajima et al., lithium binaphtholate 270 enabled an asymmetric Mukaiyama aldol reaction forming syn-269 in 97% ee and anti-269 in 84% ee (Scheme 82).
Chapter 2

Scheme 82 Lithium binaphthol-catalysed asymmetric Mukaiyama aldol reaction

Assuming that the molybdenum reductive Dieckmann condensation proceeds via a silyl ketene acetal, it was proposed that the introduction of a chiral Lewis base would result in a chiral silyl ketene acetal and in turn an enantiomerically enriched product. 50 mol% of \([\text{Li}_2\{((R)\text{-binol})\}^{85} \text{271}\) was added to the reaction mixture which was refluxed for 16 hours. Crude $^1$H NMR and TLC analysis showed the formation of a multitude of compounds from which no products were isolated.

Scheme 83 Lithium binaphthol-directed reductive Dieckmann condensation

2.3.3.3 Chiral Auxiliaries

Although criticised for poor step economy and cost of stoichiometric amounts of auxiliary, the introduction of chirality by the use of chiral auxiliaries still remains a powerful tool in asymmetric organic synthesis.\(^{86}\) An enantioselective version of this reductive Dieckmann condensation could be envisioned by using a chiral auxiliary either on the terminal ester
moiety or on the nitrogen atom (Scheme 84). Attachment of the chiral auxiliary to the terminal ester offers a particularly attractive approach as the directing group would be acting as a traceless chiral auxiliary and could be recovered from the reaction mixture, reducing process cost.

![Scheme 84 Chiral auxiliary directed asymmetric reduction Dieckmann condensation](image)

To investigate the effect of a chiral nitrogen substituent, α-substituted acrylic ester 275 was synthesised using inexpensive, readily available (R)-α-methylbenzylamine. Alkylation of (R)-α-methylbenzylamine 272 by ethyl bromoacetate 273 proceeded smoothly to give 274 in 87% yield, which was alkylated by 255 to give 275 in 46% yield (Scheme 85).

![Scheme 85 Synthesis of 275](image)

275 was exposed to the molybdenum-catalysed reductive conditions described above (cf. 2.3.2) giving 3,3'-disubstituted 4-oxopyrrolidine 276 in 92% isolated yield. $^1$H NMR analysis of 276 showed a 1:1 ratio of diastereomers, suggesting that the α-methylbenzylamino group is too removed from the reaction centre to induce any chirality (Scheme 86).

56
Scheme 86 Rerductive Dieckmann condensation of chiral acrylic ester 275

In a related example from Chemla et al., a chiral α-methylbenzylamino group was used to deliver high levels of diastereoselectivity for the synthesis of 3,4-disubstituted β-prolines via either a carbometalation or domino Michael addition/carbometalation reaction (Scheme 87). The high levels of control are a consequence of zinc(II)-Ar interactions as well as zinc(II) interactions with the carbomethoxy and nitrogen moieties. It is the steric interaction between the methyl and allyl moieties in 281 which makes it less favourable than 280 (Figure 4).

Scheme 87 Diasterocontrolled synthesis of enantioenriched 3,4-disubstituted β-prolines

Figure 4 Origin of the chirality transfer in the carbocyclisation reaction from zinc enolates

In light of the disappointing asymmetric results we next turned to the use of a traceless chiral auxiliary as the terminal ester moiety.
Nagao et al. used traceless chiral auxiliaries in a Dieckmann condensation giving the annihilation product in excellent enantiomeric excess.\textsuperscript{88} Diamide 282 was cyclised under basic conditions and, following methanolysis, gave methyl ester 283 in 69\% overall yield and 96\% ee (Scheme 88).

\begin{center}
\begin{tikzpicture}
\node[shape=circle,draw,fill=black,inner sep=1pt] (a1) at (0,0) {i) KH};
\node[shape=circle,draw,fill=black,inner sep=1pt] (a2) at (1,0) {ii) MeOH, K₂CO₃};
\node[shape=circle,draw,fill=black,inner sep=1pt] (b1) at (2,0) {282};
\node[shape=circle,draw,fill=black,inner sep=1pt] (b2) at (4,0) {283};
\node[shape=circle,draw,fill=black,inner sep=1pt] (c1) at (2,-1) {Xc = \text{Pr} \text{N} \text{S} \text{O}};
\node[shape=circle,draw,fill=black,inner sep=1pt] (c2) at (4,-1) {96\% ee};
\node[shape=circle,draw,fill=black,inner sep=1pt] (d1) at (2,-2) {69\% yield};
\node[shape=circle,draw,fill=black,inner sep=1pt] (d2) at (4,-2) {96\% ee};
\draw[->] (a1) -- (a2);
\draw[->] (a2) -- (b1);
\draw[->] (a2) -- (b2);
\end{tikzpicture}
\end{center}

\textbf{Scheme 88} Asymmetric Dieckmann condensation directed by 4(S)-isopropyl-1,3-thiazolidine-2-thione

Later, Trova and Wang, whilst attempting the asymmetric double alkylation of 284a and 284b, observed Dieckmann products 285a and 285b respectively.\textsuperscript{89} Moderate yields (55\% for both 285a and 285b) were observed and the two diastereomers of 285a were isolated in a 1:1 ratio (Scheme 89).

\begin{center}
\begin{tikzpicture}
\node[shape=circle,draw,fill=black,inner sep=1pt] (a1) at (0,0) {i) NaHMDS};
\node[shape=circle,draw,fill=black,inner sep=1pt] (a2) at (1,0) {THF, -78 °C};
\node[shape=circle,draw,fill=black,inner sep=1pt] (a3) at (2,0) {ii) Mel -78 °C to r.t.};
\node[shape=circle,draw,fill=black,inner sep=1pt] (b1) at (0,-1) {284a : n = 2};
\node[shape=circle,draw,fill=black,inner sep=1pt] (b2) at (0,-2) {284b : n = 3};
\node[shape=circle,draw,fill=black,inner sep=1pt] (c1) at (2,-1) {285a : n = 1};
\node[shape=circle,draw,fill=black,inner sep=1pt] (c2) at (2,-2) {285b : n = 2};
\end{tikzpicture}
\end{center}

\textbf{Scheme 89} Dieckmann condensation directed by oxazolidinones

Sieburth and Chen found that a tandem alkylation Dieckmann reaction of organosilane 286 could be achieved using LDA, giving alkylation Dieckmann product 287 as the syn-product. It was found that on switching to NaHMDS, like Trova and Wang, only Dieckmann condensation product 288 was observed (Scheme 90).\textsuperscript{90}

\begin{center}
\begin{tikzpicture}
\node[shape=circle,draw,fill=black,inner sep=1pt] (a1) at (0,0) {NaHMDS};
\node[shape=circle,draw,fill=black,inner sep=1pt] (a2) at (1,0) {BnBr 68\%};
\node[shape=circle,draw,fill=black,inner sep=1pt] (b1) at (2,0) {LDA BnI 52\%};
\node[shape=circle,draw,fill=black,inner sep=1pt] (c1) at (0,-1) {288};
\node[shape=circle,draw,fill=black,inner sep=1pt] (c2) at (0,-2) {286};
\node[shape=circle,draw,fill=black,inner sep=1pt] (d1) at (2,-1) {287};
\end{tikzpicture}
\end{center}

\textbf{Scheme 90} Alkylation Dieckmann Condensation
Due to its relatively low cost and availability, initial studies into the effect of a chiral terminal ester moiety focused on (+)-menthol ester 292. N-Boc glycine menthol ester 290 was synthesised as described by Franchini. Benzylation of 290 and removal of the Boc protecting group gave N-benzyl glycine menthol ester 291; this was alkylated by acrylic ester 255 to give substrate 292 (Scheme 91).

The reductive Dieckmann condensation of 292 using the conditions described above (cf. 2.3.2) proceeded smoothly forming 258 in 79% isolated yield with a 60% recovery of (+)-menthol 293 (Scheme 92). HPLC analysis of 258 showed a 44% ee for this transformation.

To investigate the effect of the chiral auxiliaries further, esters of (R)-pantolactone 298 and (S)-1-phenylethanol 299 were formed from the coupling with acid 295 and the required alcohol. Carboxylic acid 295 was accessed form the alkylation of N-benzyl glycine 294 by acrylate 255 (Scheme 93).
258 was formed from both 296 and 297 in comparable yields to that observed with the mentholate ester 292, however, poor enantioselectivity was observed: 9% and 2% ee respectively (Scheme 94).

Using menthol ester 292, a silane screen was carried out to see what effect the bulk of the silyl ketene acetal has on the enantioselectivity of the reaction. Knowing that PMHS, (EtO)2MeSiH, Et3SiH and Cl3SiH do not reduce Michael acceptors under molybdenum catalysis (cf. 2.2.2), Ph2SiH2 and Ph3SiH were used. Like the other less reactive silanes, Ph3SiH gave no product, while Ph2SiH2 gave reductive Dieckmann product 258 in 85% isolated yield (Scheme 95). A decrease in enantioselectivity was observed, 20% ee, despite the increased bulk of the silane. It is likely that the decrease in enantioselectivity is a consequence of the increased Lewis acidity of the silicon centre formed after hydrosilylation of 292; this electronic effect is likely to increase the rate of cyclisation.
2.3.4 Proposed Mechanism

In the initial report of the molybdenum-catalysed conjugate reduction using phenylsilane, Keinan et al. showed that the reaction proceeds via a silyl enol ether with a hydride delivered from the silane to the β-carbon and a proton delivered to the α-carbon on hydrolysis (Scheme 96).\(^5\) Unfortunately, no further mechanistic evidence was gathered from this study and the exact role of any molybdenum species formed in this process remains unclear.

![Scheme 96 Keinan's mechanistic insight](image_url)

Another observation from Keinan is that Michael acceptors with fixed transoid conformation were not reduced under these conditions, suggesting that an \(\eta^4\)-1-oxa-1,3-diene molybdenum species are formed with the coordinatively unsaturated molybdenum acting as a Lewis acid activator of the Michael acceptor. The formation, isolation and catalytic activity of a number of molybdenum oxadiene complexes 303 were explored by Schmidt (Scheme 97).\(^92,93\)
The $\eta^2$-coordination of a silicon-hydrogen bond to a metal centre has significant consequences for the activity of the Si-H bond in transition metal catalysed hydrosilylations. Activation of Si-H bonds by $\eta^2$-coordination to molybdenum has been observed for primary, secondary and tertiary silanes, with Si-H bond elongation being observed. These $\sigma$-complexes are often formed by either thermally or photochemical decarboxylation of Mo(CO)$_6$ to give [Mo(CO)$_5$] which reacts with the silane (Scheme 98).

With no evidence of a molybdenum-hydride species being formed form oxidative insertion into a Si-H bond we propose a mechanism in which the molybdenum is coordinated, and therefore activating, both the Michael acceptor and the silane (Scheme 99). Delivery of the hydride to the $\beta$-carbon of the Michael acceptor is followed by reductive elimination giving silyl ketene acetal 304 which undergoes an 5-(enolexo)exo-trig cyclisation to give 3,3'-disubstituted 4-oxopyrrolidine 258.
2.4 Exploring Other Metal Catalysts

Taking 44% ee as the highest achievable selectivity under molybdenum catalysis we looked to other transition metals to catalyse this transformation. The conjugate reduction literature is dominated by the late group transition metals ruthenium, cobalt, rhodium, iridium, nickel, palladium and copper as well as indium. Using menthol ester, we screened a range of catalysts which resulted in the isolation of a number of products.

2.4.1 Indium- and Palladium-Catalysed Reductive Dieckmann Condensation

Both indium- and palladium reductive conditions failed to give the desired reductive Dieckmann product. For indium-catalysis, reductive conditions described by Miura and Hosomi were adapted for this reductive process using In(acac)_3 and In(OAc)_3 as catalysts and PhSiH_3 as the stoichiometric reductant. Only starting material was recovered after the reaction was stirred in THF at 80 °C for 24 h.
Complete consumption of 292 was observed using palladium, however, under these conditions from Keinan and Greenspoon,\textsuperscript{103} the only product observed was \( N \)-benzyl glycine menthol ester as a result of removal of the allyl unit from the amine linker (Scheme 100).\textsuperscript{104}

\[
\begin{align*}
\text{[Rh(cod)Cl]}_2 \quad &\text{PPh}_3 \quad \text{PhMe}_2\text{SiH} \\
&\text{DCE, 60 °C, 16 h} \\
\end{align*}
\]

\textbf{Scheme 101} Rhodium-catalysed reduction of 292

2.4.2 Rhodium-Catalysed Reductive Dieckmann Condensation

As with palladium and indium catalysis, reduction with rhodium did not yield the desired product. The rhodium-catalysed reduction was undertaken using adapted conditions from Morken \textit{et al.},\textsuperscript{105} using \([\text{Rh(cod)Cl}]_2\) ligated by \( \text{PPh}_3 \) with \( \text{Me}_2\text{PhSiH} \) as the stoichiometric reductant. The reaction gave isomerised product 306 in 40% yield and conjugate reduction product 305 in a 9% yield (Scheme 101).

It is proposed that hydrorhodiation of 292 gives organorhodium species 307 and \( \beta \)-hydride elimination results in the formation of enamine 306 (Scheme 102).\textsuperscript{106} Tautomerisation of 307 to rhodium enolate 308, occurring at a slower rate than \( \beta \)-hydride elimination, is followed by \( \sigma \)-bond metathesis to give silyl ketene acetal 309 which is protonated on work up to give conjugate reduction product 305 (Scheme 103).
2.4.3 Cobalt- and Nickel-Catalysed Reductive Dieckmann Condensation

Lam et al. have developed both cobalt- and nickel-catalysed reductive aldol and reductive Mannich reactions which use Et₂Zn as a stoichiometric reductant. The required cobalt- and nickel-hydride species are formed by the transmetallation of an ethyl group onto the cobalt or nickel centre which undergoes β-hydride elimination to give the metal hydride species and ethene.

Reduction of 292 under Lam’s cobalt-catalysed reductive conditions gave the desired reductive Dieckmann product 258 in a 44% isolated yield with a 51% recovery of 292. Analysis of the product showed an enantioselectivity of 29% ee (Scheme 104).
Complete consumption of 292 was observed with the nickel-catalysed reductive Dieckmann condensation using Lam’s conditions,\textsuperscript{109} higher reactivity, relative to the analogous cobalt reductive system, was also observed by Lam. The desired compound was isolated in a 67% yield with an 18% ee; however, the reaction was complicated by the formation of a second product, this was found to be the alkylative Dieckmann product 310, isolated in 29% yield (Scheme 105). This product was formed from the nickel-catalysed conjugate addition of an ethyl group followed by Dieckmann condensation, this observation is unsurprising as Lam et al. reported a competitive alkylative aldol cyclisation when forming both γ-lactams and γ-lactones.\textsuperscript{109}

![Scheme 105 Nickel-catalysed reductive and alkylative Dieckmann condensation](image)

With the complication of the nickel-catalysed reductive Dieckmann condensation by the competitive alkylative Dieckmann condensation and with little scope to improve the disappointing selectivities, cobalt and nickel catalysis were pursued no further.

### 2.4.4 Copper-Catalysed Reductive Dieckmann Condensation

Copper hydride species, CuH, stabilised by phosphine ligands, are excellent catalysts for conjugate reduction and the chemistry of these species has been covered in recent reviews.\textsuperscript{114,115} The use of copper as a catalyst for conjugate reductions grew exponentially from the first application of the hexamer [(Ph\textsubscript{3}P)CuH\textsubscript{6}], Stryker’s reagent.\textsuperscript{116-119} Moving on from Stryker’s reagent, a number of copper salts have been used for the \textit{in situ} generation of CuH, including CuCl (with NaO\textsubscript{t}Bu as an additive), (Ph\textsubscript{3}P)CuF\textsubscript{2}H\textsubscript{2}O, Cu(OAc)\textsubscript{2}, CuCl\textsubscript{2}, CuO\textsubscript{t}Bu and CuF\textsubscript{2}. Predominantly, silanes have been employed as stoichiometric reductants, commonly the inexpensive polymethylhydrosiloxane, PMHS. Switching from triphenylphosphine to chiral bisphosphines leads to the generation of chiral CuH species capable of highly stereoselective 1,2- and 1,4-reductions. This is a very attractive
methodology due to the vast array of commercially available atropisomeric bisphosphines and ferrocenyl bisphosphines ligands.

The initial investigation was into the effect of a range of achiral bisphosphines on the reductive Dieckmann condensation of \( \text{292} \); \( \text{Cu(OAc)}_2 \) was employed as the precatalyst. Higher isolated yields and enantioselectivities were observed on using PMHS as the stoichiometric reductant compared to 1,1,3,3-tetramethylhydrosilane, TMDS (Table 4, entries 1-4). Moderate yields were observed for all ligands with the exception of dppf (entry 2), dppm (entry 5) and dppb (entry 8). The highest enantioselectivity was observed with dppe, 50\% ee (entry 6); changes in the bite angle of the bisphosphine resulted in lower selectivity, particularly Xantphos 311 (Figure 5) whose tricyclic structure results in a notably large bite angle (entry 10). Changing from dppe to the more electron rich and bulkier dcpe resulted in a depletion of enantioselectivity whilst an increase in yield from 68\% to 78\% was observed (entry 9).

\[ \text{TMS} \]

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

\( \text{311 : Xantphos} \)

\textbf{Figure 5 \text{Xantphos}}
Table 4 Ligand screen on achiral bisphosphine ligands

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>yield (%)(^{b})</th>
<th>ee (%)(^{c})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>dppf</td>
<td>5(^{d,e})</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>dppf</td>
<td>43</td>
<td>36</td>
</tr>
<tr>
<td>3</td>
<td>rac-BINAP</td>
<td>20(^{d})</td>
<td>41</td>
</tr>
<tr>
<td>4</td>
<td>rac-BINAP</td>
<td>59</td>
<td>48</td>
</tr>
<tr>
<td>5</td>
<td>dppm</td>
<td>21</td>
<td>44</td>
</tr>
<tr>
<td>6</td>
<td>dppe</td>
<td>68</td>
<td>50</td>
</tr>
<tr>
<td>7</td>
<td>dppp</td>
<td>73</td>
<td>46</td>
</tr>
<tr>
<td>8</td>
<td>dppb</td>
<td>20</td>
<td>43</td>
</tr>
<tr>
<td>9</td>
<td>dcpe</td>
<td>78</td>
<td>40</td>
</tr>
<tr>
<td>10</td>
<td>Xantphos</td>
<td>62</td>
<td>30</td>
</tr>
</tbody>
</table>

\(^{a}\) Reaction conditions: 292 (0.2 mmol), PMHS (1.5 equiv), Cu(OAc)\(_2\) (5 mol\%), Ligand (5 mol\%), THF, 50 °C, 16 h. \(^{b}\) Isolated Yields. \(^{c}\) Determined by HPLC (Chiracel OJ, 1% iPrOH : Hexane, 0.5 mL.min\(^{-1}\)). \(^{d}\) TMDS (1.5 equiv) used in place of PMHS. \(^{e}\) Conversion determined by \(^{1}\)H NMR; product not isolated.

2.4.4.1 Effect of Chiral Ligands on Enantioselectivity

In light of the success of the copper-catalysed reductive Dieckmann condensation using achiral ligands, a range of chiral bisphosphines was screened for the reductive cyclisation of mentholate ester 292.

An initial investigation into the match/mismatch effect between the two isomers of BINAP and the enantiomerically pure mentholate ester of 292 showed that, with esters of (+)-menthol, (R)-BINAP gave the highest selectivity with a 79% ee being observed against a selectivity of 14% being observed with (S)-BINAP (entries 1 and 2, Table 5). Following on from this study, the R-enantiomer of a range of chiral bisphosphines was screened (Table
5). Increasing the bulk of the aryl substituents on BINAP phosphines was found to deplete the selectivity of the reactions (entries 1, 3 and 4); a similar trend is observed with \((R)-^1Pr-DuPhos\) \(315\) and \((R)-Me-DuPhos\) \(314\) (entries 5 and 6). The use of ferrocene derived bisphosphines \((R)-(S)-\) and \((S)-(R)-Josiphos\) \(316\) gave \(258\) in excellent yields, however, poor enantioselectivities were observed in both cases (entries 7 and 8). Very poor selectivity was observed with \((R)-PhanePhos\) \(318\) (entry 9) while moderate selectivity is observed with the BIPHEP derived \((R)-SYNPHOS\) \(317\) (entry 10).

Table 5 Effect of chiral ligands of the copper-catalysed reductive Dieckmann condensation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>((R)-BINAP)</td>
<td>27</td>
<td>79</td>
</tr>
<tr>
<td>2</td>
<td>((S)-BINAP)</td>
<td>62</td>
<td>14</td>
</tr>
<tr>
<td>3</td>
<td>((R)-Tol-BINAP)</td>
<td>45</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>((R)-Xylyl-BINAP)</td>
<td>79</td>
<td>35</td>
</tr>
<tr>
<td>5</td>
<td>((R,R)-^1Pr-DuPhos)</td>
<td>66</td>
<td>46</td>
</tr>
<tr>
<td>6</td>
<td>((R,R)-Me-DuPhos)</td>
<td>68</td>
<td>86</td>
</tr>
<tr>
<td>7</td>
<td>((R)-(S)-Josiphos)</td>
<td>86</td>
<td>45</td>
</tr>
<tr>
<td>8</td>
<td>((S)-(R)-Josiphos)</td>
<td>99</td>
<td>49</td>
</tr>
<tr>
<td>9</td>
<td>((R)-PhanePhos)</td>
<td>53</td>
<td>15</td>
</tr>
<tr>
<td>10</td>
<td>((R)-SYNPHOS)</td>
<td>52</td>
<td>65</td>
</tr>
<tr>
<td>11</td>
<td>((R)-P-Phos)</td>
<td>78</td>
<td>63</td>
</tr>
<tr>
<td>12</td>
<td>((R)-Xylyl-P-Phos)</td>
<td>58</td>
<td>91</td>
</tr>
</tbody>
</table>

\(^a\) Reaction conditions: \(292\) \((0.2 \text{ mmol})\), PMHS \((1.5 \text{ equiv})\), Cu(OAc)_2 \((5 \text{ mol\%})\), Ligand \((5 \text{ mol\%})\), THF, \(50^\circ\text{C}, 16 \text{ h}\). \(^b\) Isolated Yields. \(^c\) Determined by HPLC (Chiracel OJ, 1% \(^1PrOH : \text{Hexane}, 0.5 \text{ mL.min}^{-1}\)).

With \((R)-Me-DuPhos\) \(314\) appearing to be the ligand of choice, our attention turned to dipyridylphosphine ligand \((R)-P-Phos\) \(319\) and its analogue \((R)-Xylyl-P-Phos\) \(320\). Developed by Chan et al., the P-Phos series of ligands has been used in the copper-catalysed asymmetric reduction of ketones with selectivities of up to 98% ee.\(^{120-124}\) A
moderate enantioselectivity of 63% ee was observed with (R)-P-Phos (Table 5, entry 11), while (R)-Xylyl-P-Phos gave 258 in an excellent 91% ee with a decrease in yield being observed (entry 12). Carrying out the reaction at ambient temperature over 3 hours resulted in an increased selectivity, 93% ee, and a slight decrease in yield (Scheme 106).

Scheme 106 Asymmetric copper-catalysed reductive Dieckmann condensation

The asymmetric copper-catalysed reductive Dieckmann condensation of 222, with its terminal ethyl ester, was carried out using both (R,R)-Me-DuPhos 314 and (R,R)-iPr-DuPhos 315 as chiral ligands. Unlike the reductive cyclisation of mentholate ester 292, (R,R)-iPr-DuPhos was found to give an enantiomeric excesses higher than that obtained with the use of (R,R)-Me-DuPhos: 20% ee and 15% ee, respectively (Scheme 107). These results clearly show the strong influence the (+)-menthol chiral auxiliary is having on this transformation, it is little wonder that enantiomeric excesses of up to 50% can be obtained with achiral bisphosphine ligands in conjunction with the chiral auxiliary.
Scheme 107 Copper-catalysed asymmetric reductive Dieckmann condensation of 222

![Scheme 107](image)

**Figure 6** Chiral bisphosphines

### 2.4.4.2 Catalytic Cycle

Scheme 108 shows the proposed catalytic cycle for the copper-catalysed reductive Dieckmann condensation and is adapted from the catalytic cycles proposed for the copper-catalysed reductive aldol reaction.\(^{114,115,125,126}\) *In situ* formation of CuH is followed by coordination of the copper centre to the Michael acceptor, forming π-complex II. The
copper enolate \textbf{III} is formed after delivery of hydride to the $\beta$-carbon atom. Lewis acid activation of the terminal ester and attack by the copper enolate onto the electrophilic centre occurs to give acetal \textbf{IV}. The acetal is then converted to the desired product \textbf{258} generating \textbf{LCuOR V}, an ideal precursor to \textbf{LCuH} which is rapidly reformed on reaction with \textbf{PHMS}.\textsuperscript{114}

![Scheme 108 Catalytic cycle for the copper-catalysed reductive Dieckmann condensation](image)

**2.4.4.3 Prediction of Absolute Stereochemistry**

Unfortunately, attempts to determine the absolute stereochemistry of \textbf{258} by X-ray crystallography failed, as attempts to structurally modify \textbf{258} to give a crystalline derivative resulted in a multitude of products.

In the carbon-carbon bond forming step, attack of the enolate on \textit{re}-face of the terminal ester and elimination of CuOR results in the formation of $(R)$-\textbf{258}, while attack on the $\textit{si}$-face of the terminal ester results in the formation of $(S)$-\textbf{258} (Scheme 109).
In analogous, unpublished work, Frost et al. formed 3,3’-disubstituted 4-oxopyrrolidine (R)-322 by the rhodium-catalysed Michael Dieckmann condensation of 292 (Scheme 110). This suggests that for the rhodium-catalysed Michael Dieckmann reaction, attack of the si-face of the mentholate ester is blocked by the isopropyl group of (+)-menthol.

**Scheme 109** Enantioselectivity in the formation of 258

**Scheme 110** Rhodium-catalysed Michael Dieckmann condensation of mentholate ester 322

### 2.5 Conclusion

A preliminary study has been carried out into the reductive Dieckmann condensation focusing on expeditious synthesis of enantiomerically enriched 3,3’-disubstituted 4-oxopyrrolidines containing an all-carbon quaternary centre.

Initial studies involved molybdenum-catalysis in which activation of the Mo(CO)$_6$ precatalyst occurred by the oxidative removal of carbonyl ligands by NMO. An enantiomeric excess of 44% was achieved when using (+)-menthol as a traceless auxiliary in this process.
Cu(OAc)$_2$ was identified as a suitable precatalyst for the same transformation. Enantiomeric excesses of up to 50% were observed with achiral bisphosphines, while enantiomeric excesses of up to 93% were recorded when (R)-Xylyl-P-Phos was used as a chiral bisphosphine ligand in conjunction with (+)-menthol as a chiral auxiliary.

As stated, this is a preliminary study, due to time constraints a full study into the reductive Dieckmann condensation was not carried out. Substrate scope is broad and a wide variety of chiral auxiliaries are available.
2.6 References

Chapter 3 - Two-Carbon Homologation of Aldehydes by Tandem Molybdenum-Catalysed Hydrosilylations

3.1 Meldrum’s Acid and its Derivatives

Meldrum’s acid 325 (MA) and its derivatives are important reagents in organic chemistry and have been used in the synthesis of a number of natural products and their analogues.\(^1\) The range of chemistry carried out using MA has been covered in a number of reviews,\(^2-5\) including one devoted to the synthetic applications of the pyrolysis of MA derivatives.\(^6\) The unique reactivity of MA and its derivatives comes as a consequence of MA’s remarkable acidity (pK\(_a\) 7.3 in DMSO at 25 °C) compared to the related dimedone 326 and dimethylmalonate 327 (Figure 7),\(^7\) a physical property owing to the fixed E-conformation of the two ester functionalities.\(^8\)-\(^13\)

![Meldrum's Acid and Derivatives](image)

**Figure 7** Comparable equilibrium acidities in DMSO solutions of MA, dimedone and dimethyl malonate

The synthesis of 1,3-dicarbonyl compounds from acyl malonates is one of the most important transformations carried out by MA derivatives. Nucleophilic attack at the one of the ester groups, often by an alcohol or amine, is followed by loss of acetone and carbon dioxide giving the 1,3-dicarbonyl compound which then can be carried through to a vast array of biologically active natural products and their analogues.\(^1\) Beyond 1,3-dicarbonyl compounds, biologically active furanones, pyranones, tetramic acids and their analogues, terpenoids and pyridine alkaloids can be accessed from MA (Scheme 111).
3.1.1 Alkylidene Meldrum’s Acid Derivatives as Michael Acceptors

Alkylidene MA derivatives, synthesised by the Knoevenagel condensation between aldehydes and MA, are of particular interest. Recently, Kaumanns and Mays demonstrated the high electrophilicity of benzylidene MA derivatives by analysing the reaction kinetics of these derivatives with acceptor-substituted carbanions. From this study, benzylidene MA 328a was assigned an electrophilicity parameter comparable to that for carbocation 329 (Figure 8). The high electrophilicity of these substrates has been attributed to, like MA’s high acidity, to the fixed $E$-conformation of the two ester groups.

**Scheme 111** Examples of natural products synthesised from MA

**Figure 8** Electrophilicity parameters of 328 and 329
3.1.2 Synthesis of Alkylidene Meldrum’s Acid Derivatives

The synthesis of alkylidene MA derivatives 328 is achieved by the Knoevenagel condensation of MA and aldehydes. The condensation reaction can be complicated by the Michael addition of another molecule of MA to the newly formed alkylidene MA to give the bis-adduct 330 (Scheme 112).

A number of conditions for this Knoevenagel condensation have been reported with a view to increasing the substrate scope of this reaction. One method of avoiding bis-adduct formation is the addition of a nucleophile, such as a methoxide,15 an amines16 or a thiols,17 to alkylidene MA derivatives; the newly formed adduct is then transformed into the desired alkylidene at the end of the reaction (Scheme 113). Although effective, in light of step and atom economy, this is an unattractive process.

Other methods for the synthesis of alkylidene MA’s include the use of ionic liquids,18,19 microwave irradiation,20 amines supported on silica gel,21 surfactants22 and simply heating the two components in water.23 Fillion et al. reported a general synthesis of alkylidene MA’s using pyrrolidinium acetate as a catalyst (10 mol%) in benzene.24
Fillion successfully synthesised 336 from benzaldehyde in 85% yield, a significant result as under all other conditions 336 undergoes Michael addition of MA (Scheme 114).

Scheme 114 Synthesis of alkylidene MA derivative 336

3.1.3 Michael Addition to Alkylidene Meldrum’s Acid Derivatives

Michael addition to alkylidene MA derivatives has been a key step in a number of multicomponent reactions; MA is reacted with an aldehyde and the desired nucleophile, typically a vinyl ether, enolate or indole. Copper-catalysed additions of Grignard reagents proceeded smoothly, however, more recently, research has focused on the addition of terminal alkynes, dialkylzinc reagents and vinylstannanes to alkylidene MA derivatives.

Alkylation of alkylidene MA derivatives by asymmetric copper-catalysed conjugate addition of diethylzinc was reported by Carreira et al. using BINOL-derived chiral phosphoramidite 341. High yields and enantioselectivities were observed with both aliphatic and aromatic substitutents on the alkylidene MA; aliphatic substitutents were found to be the most favourable (Scheme 115).
Fillion et al. also used copper ligated with BINOL derived chiral phosphoramidites for the asymmetric alkylation of $\beta,\beta'$-disubstituted alkylidene MA derivatives with dialkylzinc reagents; excellent yields and enantioselectivities of up to 95% were observed (Scheme 116). Wilsily and Fillion later reported the expedient preparation of succinimides, succinate esters and acids, $\gamma$-butyrolactones and $\beta$-amino acid derivatives using this methodology (Scheme 117). This process was extended to the 1,6-conjugate addition of dialkylzinc reagents to $\alpha,\beta,\gamma,\delta$-unsaturated MAs which saw a drop in yields and enantioselectivities (Scheme 118).
Fillion et al. synthesised more complex γ-butyrolactones via a sequential Rh(I)/Pd-catalysed 1,4-addition/intramolecular allylation. This process was initiated by the Michael addition of vinylstannanes to alkyldiene MA. This was followed by the palladium-catalysed allylic O-alkylation and ring opening by ethanol to give the desired γ-butyrolactone (Scheme 119).

Alkynylation of alkyldiene MA derivatives was first achieved using trimethylsilylethynyl magnesium bromide and later lithium phenylalkynylide. However, Carreira et al. have developed a powerful technique which enables the direct use of terminal alkynes without the need for a separate metallation step. Copper- and zinc-catalysed conjugate addition of terminal alkynes to alkyldiene MA derivatives have been reported giving adducts in high yields (Scheme 120). Copper-catalysed additions of terminal alkynes are carried out in aqueous media.
Asymmetric alkynylation of alkylidene MA derivatives was not achieved under zinc catalysis, however, excellent enantioselectivities were achieved with copper catalysis. Carreira et al. developed the novel chiral P,N-ligand PINAP (356) from QUINAP for this transformation; excellent enantioselectivities were achieved for the addition of aromatic alkynes to alkylidene MA derivatives (Scheme 121).38,40

3.1.4 Meldrum’s Acids as Acylating Agents

Fillion et al. have pioneered the use of 5-mono- and 5,5′-dialkyl-MAs as acylating agents in the catalytic intramolecular Friedel-Crafts reaction. Initial studies showed scandium triflate to be a suitable Lewis acid catalyst for the synthesis of polysubstituted 1-indanones, while trimethylsilyl triflate and triflic acid were also able to catalyse the transformation.42,43
Substitution at the \(\alpha\)- and/or \(\beta\)-carbons of the substrates were found to be essential for maintaining good yields (Scheme 122). Fillion and Fishlock used this methodology in the synthesis of (±)-taiwaniaquinol B \(362\). The formation of the tricyclic core via a domino trimethylsilyl triflate catalysed Friedel-Crafts acylation/carbonyl \(\alpha\)-\(\text{tert}\)-alkylation reaction was the key step in the synthesis (Scheme 123).

![Scheme 122 Intramolecular Sc(OTf)\(_3\)-catalysed Friedel-Crafts acylation](image)

Scheme 122 Intramolecular Sc(OTf)\(_3\)-catalysed Friedel-Crafts acylation

Fillion and Dumas synthesised fused 4,5-disubstituted indole ring systems by an intramolecular Friedel-Crafts acylation of \(N\)-nosyl-4-substituted indoles. Selective acylation at the 5 position was observed giving the desired tricyclic products under Lewis acid catalysis by boron trifluoride etherate. Both 5-mono and 5,5’-dialkyl MAs cyclised in high yields with pentacyclic \(366\) being accessed in 84% yield from spiro MA derivative \(365\) (Scheme 124).

![Scheme 123 Fillion's synthesis of taiwaniaquinol B](image)

Scheme 123 Fillion's synthesis of taiwaniaquinol B
3.2 Synthesis of Alkylidene Meldrum’s Acid Derivatives

Due to their synthetic utility, a range of alkylidene MA derivatives was synthesised using the convenient procedure proposed by Bigi et al.\textsuperscript{23} This uncatalysed procedure was carried out in water, giving the desired product as a precipitate on cooling of the reaction mixture. All products are easily purified by recrystallisation from hot ethanol giving highly coloured crystalline solids.

Good yields were observed for a range of aldehydes with both electron-donating and electron-withdrawing substituents being tolerated (Table 6). This can be rationalised by considering the transformation as a two step process. Electron-deficient aldehydes favour the initial nucleophilic attack of MA, while electron-rich substituents facilitate the loss of water giving the conjugation stabilised olefin.

Pleasingly, a range of heteroatoms was tolerated under the reaction conditions (Table 6, entries 1-3). A lower yield was observed with sterically bulky 2,3,4-trimethoxybenzaldehyde (entry 9). A disappointing 48% yield was observed for the formation of 328k (entry 11).
Table 6 Synthesis of alkylidene MA’s

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>product</th>
<th>yield, %b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-(OMe)C₆H₄</td>
<td>328a</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>4-(SMe)C₆H₄</td>
<td>328b</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>4-(NMe₂)C₆H₄</td>
<td>328c</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>3,4-(OCH₂O)C₆H₃</td>
<td>328d</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td>2,3-(OCH₂O)C₆H₃</td>
<td>328e</td>
<td>73</td>
</tr>
<tr>
<td>6</td>
<td>C₆H₅CHCH</td>
<td>328f</td>
<td>87</td>
</tr>
<tr>
<td>7</td>
<td>3,4-(OMe)₂C₆H₃</td>
<td>328g</td>
<td>81</td>
</tr>
<tr>
<td>8</td>
<td>2,5-(OMe)₂C₆H₃</td>
<td>328h</td>
<td>73</td>
</tr>
<tr>
<td>9</td>
<td>2,3,4-(OMe)₃C₆H₂</td>
<td>328i</td>
<td>69</td>
</tr>
<tr>
<td>10</td>
<td>4-(NO₂)C₆H₄</td>
<td>328j</td>
<td>83</td>
</tr>
<tr>
<td>11</td>
<td>4-(OBn)C₆H₄</td>
<td>328k</td>
<td>48</td>
</tr>
</tbody>
</table>

*a* Reaction conditions: aldehyde (1 equiv.), Meldrum’s acid (1.1 equiv.), H₂O, 75 °C, 2 h. *b* Isolated yields after recrystallisation.

3.3 Reduction of Meldrum’s Acid Arylidenes

Alkylidene MA 328a was exposed to the molybdenum-catalysed reductive conditions developed for the reduction of dimethyl itaconate (*cf*. 2.2.2). The reaction mixture was heated to 80 °C for 10 minutes by microwave irradiation. After hydrolysis of the reaction mixture, a 29% conversion (determined by ¹H NMR) to 5-monoalkyl MA 367a was observed (Scheme 125).
To investigate this process further the reaction was repeated with an extended reaction time of 16 hours (the reaction being carried in an oil bath). After hydrolysis of the reaction mixture, crude $^1$H NMR analysis did not show the gem-dimethyl peaks of $328\text{a}$ (1.76 ppm) or $367\text{a}$ (1.72 and 1.48 ppm), suggesting complete consumption of $328\text{a}$ and no formation of $367\text{a}$. The major peaks present in the crude $^1$H NMR, along with the two aromatic doublets and the singlet present for the methoxy group, were a 1H triplet at 9.81 ppm ($J = 1.5$ Hz), a 2H triplet at 2.91 ppm ($J = 7.2$ Hz) and a 2H multiplet at 2.78-2.72 ppm suggesting the formation of an aldehyde. Purification by flash column chromatography revealed β-aryl aldehyde $368\text{a}$ as the sole product of the reaction in an 85% yield (Scheme 126). Interestingly, no over-reduction of aldehyde $368\text{a}$ to 3-(4-methoxyphenyl)propan-1-ol was observed. Keinan had previously reported that aldehyde reduction occurs under his molybdenum-catalysed reductive conditions,\textsuperscript{46} suggesting that the aldehyde functionality is protected against reduction until hydrolysis.

Scheme 125 Molybdenum-catalysed conjugate reduction of $328\text{a}$

Scheme 126 Molybdenum-catalysed synthesis of aldehyde $368\text{a}$
This is a completely novel transformation, previous reports of the reduction of benzylidene MAs resulted in high yields of 5-monoalkyl MA derivatives. Reductants for this process include sodium hydrogen telluride,\textsuperscript{47} borane•dimethylamine complex,\textsuperscript{48} triethylammonium formate,\textsuperscript{49} NaBH\textsubscript{4}\textsuperscript{50, 51} and NaBH\textsubscript{3}CN.\textsuperscript{42}

This novel transformation can be described as the two-step, two-carbon homologation of aldehydes.

### 3.3.1 Synthesis of β-Substituted Propionaldehydes

Beyond dihydrocinnamaldehyde, there are few commercially available β-substituted propionaldehydes. Other reported routes to β-substituted propionaldehydes often involve the reduction of dihydrocinnamates using DIBAL-H or the oxidation of 3-substituted propan-1-ols by a Swern oxidation or by PCC.\textsuperscript{52} Reduction of carboxylic acid derivatives to aldehydes using DIBAL-H can be capricious with some substrates lacking reactivity and the over-reduction to the corresponding alcohol being a common drawback. In addition, DIBAL-H ignites upon prolonged exposure to air and reacts violently with water. The oxidising agents mentioned above involve the use of toxic and environmentally damaging reagents.

An alternative route to β-substituted propionaldehydes is the hydroformylation of styrene and its derivatives. Although the oxo process is highly developed, the hydroformylation of styrene often favours the formation of α-phenylpropanal.\textsuperscript{53} A recent paper from Zhang et al.\textsuperscript{54} has reported the highest linear-selectivity for the hydroformylation of styrene with a linear:branched ratio of up to 22:1.

A comparable protocol involving the two-carbon homologation of aldehydes was reported by Lee and Jones in which 1-naphthaldehyde is converted to 3-((1-naphthyl)propanal 373 in three steps.\textsuperscript{55} Weinreb amide 371 was formed from 1-naphthaldehyde and N-methoxy-N-methyl-2-(triphenylphosphoranylidine)acetamide 370.\textsuperscript{56} Alkene hydrogenation and reduction of the Weinreb amide with LiAlH\textsubscript{4} gave the desired aldehyde 373 (Scheme 127).
Chapter 3

**Scheme 127** Three-step, two-carbon homologation of 1-naphthaldehyde

Ylide chemistry was also employed by Wallsgrove et al. in the multi-step synthesis of 3-(4-methylphenyl)propanal 379: the β-substituted propionaldehyde was accessed from 4-methylbenzaldehyde 374 in a 56% overall yield (Scheme 128). This synthetic route was later used by Faber et al. for the synthesis of 3-(4-halophenyl)propanals.

**Scheme 128** Four-step, two-carbon homologation of 4-methylbenzaldehyde
3.3.2 Optimisation

It has already been established that molybdenum-catalysed conjugate reductions require heating in THF for good reaction efficiency, for that reason, no temperature or solvent screen was carried out for this novel transformation (cf. 2.2).

A decrease in aldehyde formation was observed with shorter reaction times (Table 7). In all cases complete consumption of alkylidene MA 328a was observed with 5-monoalkyl MA 367a being the only other product observed.

![Table 7 Time dependence of the molybdenum-catalysed synthesis of aldehydes](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>time, h</th>
<th>yield, %(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>48</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>77</td>
</tr>
<tr>
<td>4</td>
<td>16</td>
<td>85</td>
</tr>
</tbody>
</table>

\(^a\)Reaction conditions: 328a (1.0 equiv.), phenylsilane (3.0 equiv.), Mo(CO)\(_6\) (5 mol%), N-methylmorpholine N-oxide (9 mol%), THF, 80 °C. \(^b\)Isolated yields.

The use of less reactive silanes (Ph\(_2\)SiH\(_2\), Et\(_3\)SiH and PMHS) gave no reduction, while reducing the equivalents of phenylsilane from three to two equivalents led to a lower yield of 49%. A lower yield of 43% and more complex reaction mixture was observed when the additive NMO was removed from the reaction mixture.
3.3.3 Exploring the Scope of the Reaction

Having established the basis for a useful new functional group transformation, different alkylidene MA derivatives were exposed to the reaction conditions (Table 8).

**Table 8** Synthesis of 3-substituted propionaldehydes

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>product</th>
<th>yield, %$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-(OMe)C₆H₄</td>
<td>368a</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>4-(SMe)C₆H₄</td>
<td>368b</td>
<td>66</td>
</tr>
<tr>
<td>3</td>
<td>4-(NMe₂)C₆H₄</td>
<td>368c</td>
<td>81</td>
</tr>
<tr>
<td>4</td>
<td>3,4-(OCH₂O)C₆H₃</td>
<td>368d</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>2,3-(OCH₂O)C₆H₃</td>
<td>368e</td>
<td>78</td>
</tr>
<tr>
<td>6</td>
<td>C₆H₅CHCH</td>
<td>368f</td>
<td>39</td>
</tr>
<tr>
<td>7</td>
<td>3,4-(OMe)₂C₆H₃</td>
<td>368g</td>
<td>59</td>
</tr>
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<td>8</td>
<td>2,5-(OMe)₂C₆H₃</td>
<td>368h</td>
<td>76</td>
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<td>9</td>
<td>2,3,4-(OMe)₃C₆H₂</td>
<td>368i</td>
<td>48</td>
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<tr>
<td>10</td>
<td>4-(NO₂)C₆H₄</td>
<td>368j</td>
<td>37</td>
</tr>
<tr>
<td>11</td>
<td>4-(OBn)C₆H₄</td>
<td>368k</td>
<td>45</td>
</tr>
</tbody>
</table>

$^a$ Reaction conditions: 328 (1.0 equiv.), phenylsilane (3.0 equiv.), Mo(CO)₆ (5 mol%), N-methylmorpholine N-oxide (9 mol%), THF, 80 °C, 16 h. $^b$ Isolated yields.

Pleasingly, a number of heteroatoms were tolerated in this process giving the desired aldehydes in high yields (Table 8, entries 1-3). Isolated yields were consistently good for a range of substrates containing electron-donating aryl substituents, with the exception of the sterically hindered 368i (entry 9). A poor yield was observed for the synthesis of electron-poor 368j, this observation can be rationalised by the inductive deactivation of the alkylidene MA derivative to the initial conjugate reduction by the electron-withdrawing para-nitro group (entry 10). An unexpectedly low yield of 45% was observed for the
formation of 368k (entry 11). A poor yield of 39% and incomplete consumption of starting material was observed with $\alpha,\beta,\gamma,\delta$-unsaturated 328f, however, no hydride addition to the $\delta$-carbon was observed (entry 6).

### 3.3.4 Reduction of 5-Monoalkyl and 5,5’-Dialkyl Meldrum’s Acid Derivatives

To investigate the scope of the reaction further, alkylated MA derivates 367j, 367a and 380 were exposed to the reductive conditions. Nitrophenyl substituted aldehyde 368j, which had previously been isolated in a poor 37% yield, was accessed in 91% yield from 367j (Table 9, entry 1). This suggests that the reduction of 328j is limited by the slow conjugate reduction of its deactivated alkene. Monoalkylated 367a was reduced in good yield (Table 9, entry 2), however, $^1$H NMR analysis showed that 380 was unaffected by the reductive conditions (Table 9, entry 3).

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>$R$</th>
<th>$R'$</th>
<th>product</th>
<th>yield, %$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>367j</td>
<td>NO$_2$</td>
<td>H</td>
<td>368j</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>367a</td>
<td>OMe</td>
<td>H</td>
<td>368a</td>
<td>72</td>
</tr>
<tr>
<td>3</td>
<td>380</td>
<td>OMe</td>
<td>Me</td>
<td>381</td>
<td>0</td>
</tr>
</tbody>
</table>

$^a$ Reaction conditions: Substrate (1.0 equiv.), phenylsilane (3.0 equiv.), Mo(CO)$_6$ (5 mol%), N-methylmorpholine N-oxide (9 mol%), THF, 80 °C, 16 h. $^b$ Isolated yields.
3.3.5 Exploring Other Electrophiles

Following the successful quenching of the reaction mixture with water, a number of different electrophiles were used to quench the reaction mixture using alkyldiene MA 328a as the substrate. Bromination was attempted using both bromine and N-bromosuccinimide, however, after aqueous work-up propionaldehyde 368a was the only observed product with no bromine incorporation. The same result was observed when methyl iodide was added to the reaction mixture after 16 hours.

3.3.6 Mechanistic Studies

The formation of 5-monoalkyl MA when reaction times are shortened shows the synthesis of β-substituted propionaldehydes from alkyldiene MA derivatives is initiated by a molybdenum-catalysed conjugate reduction. It was postulated that the newly formed enolate is the key intermediate for the transformation, which is supported by the study into 5-mono and 5,5-dialkyl MAs. It is, therefore, due to the fixed keto form of 5,5'-dialkyl MA 380 that no aldehyde formation is observed, while easily enolisable 5-monoalkyl MA derivatives readily form the desired product.

3.3.6.1 Deuterium Labelling Studies

To investigate this novel transformation further, deuterium labelling studies were carried out. Firstly, 328a was reduced using trideuteriophenylsilane as the terminal reductant. On hydrolysis of the reaction mixture and isolation of the product, NMR analysis showed that there was no aldehyde peak present in the 1H NMR spectra at 9.81 ppm (Figure 10). However, in the 2D NMR spectra there was a singlet present at 9.75 ppm (Figure 9). 13C NMR analysis showed a triplet at 201.9 ppm (J = 26 Hz) and IR bands were observed at 2081 cm⁻¹ (C-D) and 1712 cm⁻¹ (C=O), suggesting the formation of a deuteroaldehyde. A change in the 1H NMR for the ethyl bridge was also observed (Figure 10 and Figure 11). A 1H multiple was observed at 2.92-2.86 ppm and at 2.74 ppm a 2H doublet (J = 7.9 Hz)
were observed. $^2$H NMR analysis of the product also showed a singlet at 2.81 ppm suggesting deuteration at the $\beta$-carbon indicative of the conjugate reduction of 328a (Figure 9). This analysis suggests the formation of the deuterio-aldehyde 382a (Scheme 129); this was confirmed by $^1$H-, $^2$D- and $^{13}$C NMR, mass spectrometry and IR analysis.

Scheme 129 Reduction of 328a using trideuterophenylsilane

Figure 9 $^2$D NMR 1,3-dideutero-3-(4-methoxyphenyl)propanal 382a

Figure 10 $^1$H NMR of 1,3-dideutero-3-(4-methoxyphenyl)propanal 382a
Following the deuterium labelling using trideuteriophenylsilane, the reduction of 328a with phenylsilane and hydrolysis with deuterium oxide was carried out. The isolated product showed a 1H singlet at 9.81 ppm in the 1H NMR (Figure 13), this is a change from the 1H triplet observed for 368a at 9.81 ppm (Figure 14), this suggests a α,α’-dideuterated product. The 2D NMR showed only a singlet at 2.64 ppm (Figure 12), confirming deuteration at the α-carbon. The 1H NMR did not show cleanly either mono- or di-deuteration at the α-carbon, a singlet was observed at 2.90 ppm and a multiplet was observed at 2.74-2.71 ppm, these peaks integrated in a ratio of ~5:1 (Figure 13). Mass spectrometry showed the presence of dideuterated 383a, monodeuterated 384a and 368a in a 73:20:7 ratio, which concurs with the integration values (Scheme 130).
Figure 12 $^2$D NMR of $\alpha$,\(^{\prime}\)-dideutero-3-(4-methoxyphenyl)propanal 383a

Figure 13 $^1$H NMR of $\alpha$,\(^{\prime}\)-dideutero-3-(4-methoxyphenyl)propanal 383a

Figure 14 $^1$NMR of 3-(4-methoxyphenyl)propanal 368a
3.3.7 Proposed Mechanism

In light of the mechanistic studies, we propose a mechanism in which hydride is delivered to the \( \beta \)-carbon of 328a by a molybdenum-catalysed hydrosilylation giving dioxinone 386 (Scheme 131). On heating, rapid cycloreversion occurs, eliminating acetone to reveal ketene 387. It is proposed that the newly formed ketene undergoes hydrosilylation by a second equivalent to phenylsilane to afford enol silane 388. This intermediate remains in solution, protecting the aldehyde functionality from further reduction, until hydrolysis at the end of reaction. As shown by the deuterium labelling studies, hydrolysis delivers two protons to the \( \alpha \)-carbon. The elimination of carbon dioxide on hydrolysis was confirmed by limewater test.

Scheme 131 Proposed mechanism for the two-carbon homologation of aldehydes
Attempts to observe reaction intermediates by NMR were unsuccessful; however, disappearance of the isopropylene group of MA and appearance of acetone in the reaction mixture was observed when the reaction was carried out in deuterated THF, in a sealed NMR tube. Along with the positive limewater test, this clearly suggests that acetone is eliminated prior to protonation, while carbon dioxide is eliminated on protonation.

A number of important transformations undertaken by Meldrum’s acid derivatives can also be attributed to the cyclic malonate’s ability to undergo cycloreversion giving $\alpha$-oxoketenes after elimination of acetone. The synthesis of ketenes from MA derivatives using flash vacuum pyrolysis is well established, however, it was not until 1997 that an efficient, mild method of generating $\alpha$-oxoketenes was reported by Sato et al.\textsuperscript{59} IR and $^1$H NMR spectroscopy provided direct evidence of ketene formation from enolised MA derivatives in the synthesis of linear malonates (Scheme 132).

![Scheme 132 Generation of $\alpha$-oxoketenes from enolised MA derivatives](image)

As well as the synthesis of linear malonates, intermediate $\alpha$-oxoketenes have been used in cyclocondensations with imines in the synthesis of both bicyclic sulfur-containing 2-pyridones and multi-ring fused 2-pyridones (Scheme 133).\textsuperscript{60-63} Almqvist et al. showed that, under acid conditions 2-pyridones could be synthesised in excellent yields.
An alternative mechanism, in keeping with the deuterium-labelling studies, can be envisaged in which \( \alpha \)-oxoketene 387 is not formed. Hydrosilylation of the ester moiety of dioxinone 386 could occur to give disilylated 395, which then undergoes cycloreversion to give intermediate 388 (Scheme 134).

![Scheme 134 Alternative mechanism for two-carbon homologation of aldehydes](image)

### 3.4 Conclusion

We have reported a expeditious two-carbon homologation of aldehydes, catalysed by the cheap, stable Mo(CO)\(_6\). Moderate to good isolated yields have been observed for a range of alkylidene MA derivatives with the highest yields being observed with electron-rich olefins. It is proposed that this novel transformation is initiated by the hydrosilylation of the \( \alpha,\beta \)-unsaturated ester, followed by cycloreversion which reveals an \( \alpha \)-oxoketene which is, in turn, hydrosilylated. On termination of the reaction, decarboxylative protonation furnishes the desired 3-substituted propionaldehyde.
The proposed mechanism is supported by deuterium labelling studies in which deuterium has been used as both an electrophile, in the form of deuterium oxide, and as a nucleophile, in the form of trideuteriophenylsilane.
3.5 References

Chapter 4 - Amine Promoted Reduction of Malonic Esters to β-Substituted Propionaldehydes and γ-Substituted Propylamines

4.1 Lewis Base Catalysis

In a recent, comprehensive review, Denmark and Beutner define Lewis base catalysis as:

“…the process by which an electron-pair donor increases the rate of a given chemical reaction by interacting with an acceptor atom in one of the reagents or substrates. The binding event may enhance either the electrophilic or nucleophilic character of the bound species. Furthermore, the Lewis base should not be consumed or altered during the course of the reaction – a hallmark of any catalytic process.”

One key application of Lewis base catalysis is the activation of silicon reagents enabling efficient ligand transfer to acceptor electrophiles.

4.1.1 Hypervalent Silicon

In 1809 Gay-Lussac discovered SiF₄·2NH₃, the first reported hypervalent silicon reagent. However, it was not until the late 20th century and into the 21st century that the synthetic utility of hypervalent silicon reagents was fully explored. A vast range of stereoselective transformations have been reported with particular attention being paid to Lewis base catalysis, where, through coordination of optically active organic compounds to tetrahedral silicon reagents, highly selective transformations have been achieved.

Unlike carbon, in the presence of Lewis bases, silicon can form five-, six- and even seven-coordinated silicon species. Two explanations have been proposed for the formation of hypervalent silicon species; firstly, it is due to the participation of silicon’s 3d orbitals,
and secondly, it is due to “hypervalent bonding” and the formation of 3-centre-4-electron molecular bonds.\textsuperscript{9}

If hypervalency is a consequence of 3d orbital participation then the five-coordinate species would be sp\textsuperscript{3}d hybridised with trigonal-bipyramidal geometry whilst the six-coordinate species would be sp\textsuperscript{3}d\textsuperscript{2} hybridised with octahedron geometry (Scheme 135). As the s-character of the silicon centre decreases, the Lewis acidity increases and the Si-R bond is elongated leading to efficient hydride or carbon nucleophile transfer to a donor molecule.

\textbf{Scheme 135} Participation of 3d-orbitals in hypervalent silicon species

It was Denmark et al. who proposed that it is the participation of “hypervalent bonding” and the formation of one (pentavalent) or two (hexavalent) 3-centre-4-electron bonds which enables the formation of hypervalent silicon species, ruling out the participation of the 3d orbitals.\textsuperscript{9} The 3-centre-4-electron molecular bonds are formed from a silicon p-orbital and two orbitals from two electronegative ligands, the remaining silicon p-orbitals and s-orbital hybridise and form more conventional covalent bonding. In the case of the hypervalent bonds, the majority of the electron density is placed on the ligands due to the HOMO being a non-bonding interaction. The silicon centre, therefore, increases in s-character and Lewis acidity as the number of hypervalent bonds increases (Scheme 136).
Three different reaction modes are possible with hypervalent silicon reagents. Firstly, it can act as a Lewis acid, activating a substrate to attack from an external nucleophile (Scheme 137, pathway a). Secondly, the nucleophilic ligand of the silicon reagent is transferred to the substrate with no substrate-silicon interaction (Scheme 137, pathway b). The final reaction pathway involves substrate activation by the Lewis acidic silicon reagent with nucleophilic ligand transfer occurring at the same time (Scheme 137, pathway c).
Corriu et al. first recognised the tendency of hypervalent silanes to release hydrides on addition of a Lewis base when he demonstrated the reduction of acetophenone to phenyl ethanol 396 using triethoxysilane and CsF (Scheme 138). The addition of CsF was found to be essential as ketones are chemically inert to trialkoxysilanes.

![Scheme 138](image)

**Scheme 138** Fluoride promoted reduction of acetophenone

Activation of silanes by alkoxy ligands enabled the development of asymmetric Lewis base catalysed reductions. The first example of catalytic asymmetric reduction of ketones by trialkoxysilanes was promoted by the dilithium salts of chiral diols or amino alcohols (Scheme 139).

![Scheme 139](image)

**Scheme 139** The first asymmetric reduction of ketones using trialkoxysilanes

Since the example above (Scheme 139), the development of asymmetric organocatalysis has exploded within organic chemistry. Recent examples of asymmetric ketone reductions give the desired products in excellent yields and enantioselectivities (Scheme 140). Trichlorosilane is often employed in these transformations as a cheap stoichiometric reductant.
4.1.3 Lewis Base Promoted Conjugate Reduction by Silanes

Nakajima et al. reported the first example of a Lewis base catalysed conjugate reduction and a reductive aldol reaction.\textsuperscript{15} Hexamethylphosphoramide (HMPA) and aryl phosphine oxides, including (S)-BINAPO 405, enabled highly selective asymmetric transformations (Scheme 141). The one-pot reductive aldol reaction is particularly pleasing as benzaldehyde reduction was scarcely observed under the reaction conditions described. The observed stereoselectivities are competitive with many asymmetric transition metal catalysed reductive aldol reactions (\textit{cf.} 1.2).
4.2 Reduction of 5-Monoalkyl Meldrum's Acid Derivatives

During previous work into the molybdenum-catalysed two-carbon homologation of aldehydes (cf. Chapter 3), it was shown that β-substituted propionaldehydes 368 could be formed by the reduction of both alkylidene MA derivatives 328 and 5-monoalkyl MA derivatives 367 (Scheme 142). In the latter example the reaction was initiated by enolisation, not a molybdenum-catalysed conjugate reduction.

![Scheme 142 Molybdenum-catalysed synthesis of β-substituted propionaldehydes](image)

It was proposed that the reaction proceeded via α-oxoketene 387, formed from the cycloreversion of 386 (Scheme 143). This ketene was hydrosilylated to give 388 which, after decarboxylative protonation, gave of the desired aldehyde.

![Scheme 143 Proposed mechanism for the molybdenum-catalysed synthesis of β-substituted propionaldehydes](image)
In light of this work, it was postulated that a metal-free variant of this transformation could be carried out using a hypervalent silicon reagent to reduce the cyclic malonate to the desired β-substituted propionaldehyde. In an initial investigation into this Lewis base promoted transformation, 5-monoalkyl MA derivative 367a was stirred, with phenylsilane and triethylamine, in THF at 80 °C for 16 hours. \(^1\)H NMR analysis of the reaction mixture showed complete conversion of 367a to 3-(4-methoxyphenyl)propanal 368a. In the absence of triethylamine no reaction was observed. Pleasingly, complete consumption of 367a was achieved after two hours at ambient temperature giving 368a in an 84% isolated yield (Scheme 144).

![Scheme 144 Triethylamine promoted reduction of 367a](image)

### 4.2.1 Optimisation

#### 4.2.1.1 Lewis Base Screen

A number of different Lewis bases were screened for this reaction (Table 10). 50 mol% of Lewis base was used in the additive screen, however, it was found that no turnover of catalyst was observed (all conversions were below 50%). Reactivity was observed with all amine bases, excellent conversions were observed for triethylamine and N,N-dimethylaminopyridine, DMAP (Table 10, entries 1 and 2). Due to increased steric bulk, lower conversions were observed for Hunig’s base and diazabicycloundec-7-ene, DBU (entries 4 and 5). A good conversion was observed using N-methylmorpholine N-oxide (entry 3); activation of silanes using amine-N-oxides has been documented in a number of recent reviews.\(^4\) No reactivity was observed on using dicyclohexylurea (DCU), triphenylphosphine, dimethylsulfoxide (DMSO) or dimethylformamide (DMF) as Lewis bases (entries 6-9). Importantly, no reactivity was observed when using potassium...
carbonate, illustrating that the role of the base is not only the deprotonation of the substrate but also the activation of the silane (entry 10).

Due to cost and ease of handling, triethylamine was chosen as the preferred Lewis base promoter for this transformation.

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<th>entry</th>
<th>Lewis base</th>
<th>conversion, %$^b$</th>
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</tr>
<tr>
<td>2</td>
<td>DMAP</td>
<td>49</td>
</tr>
<tr>
<td>3</td>
<td>NMO</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>DIPEA</td>
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</tr>
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<td>DBU</td>
<td>30</td>
</tr>
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<tr>
<td>7</td>
<td>PPh$_3$</td>
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</tr>
<tr>
<td>8</td>
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</tbody>
</table>

$^a$ Reaction conditions: 367a (1 equiv), phenylsilane (3 equiv), Lewis base (0.5 equiv), THF, r.t., 2 h.

$^b$ Conversion determined by $^1$H NMR.

### 4.2.1.2 Silane Screen

As with the molybdenum-catalysed synthesis of $\beta$-substituted aldehydes, less reactive silanes did not result in successful product synthesis. Diphenylsilane, triethylsilane, diethoxymethylsilane and polymethylhydrosiloxane showed no reactivity. The use of trichlorosilane resulted in the formation of 368a in an 8% conversion (Scheme 145).
Lower yields were observed on decreasing the equivalents of phenylsilane (Table 11), a yield of less than 50% was observed on using equimolar amounts of 5-monoalkyl MA derivative 367a and phenylsilane suggesting that 2 equivalents of phenylsilane is required for this transformation.

Table 11 Effect of phenylsilane equivalents on yield

<table>
<thead>
<tr>
<th>entry</th>
<th>equivalents of PhSiH₃</th>
<th>yield, %&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>41</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>67</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>84</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: 367a (1 equiv), phenylsilane (1-3 equiv), triethylamine (2 equiv), THF, r.t., 2 hours. <sup>b</sup> Isolated yields.

4.2.2 Exploring the Scope of the Reaction

A range of 5-monoalkyl MA derivatives 367 were synthesised in excellent yields from alkylidene MA derivatives 328 by reduction with NaBH₄ in high yield. Optically active substrate 329o was accessed by the reductive coupling MA and Boc-L-Proline 406.
The 5-monoalkyl MA derivatives were exposed to the mild reductive conditions described above resulting in the synthesis of the desired β-substituted propionaldehydes (Table 12), with the exception of 367m (entry 8). An insoluble salt, which underwent no further transformation, was formed on addition of triethylamine to 367m, a contrast to its regioisomer 367l which proceeds smoothly (entry 7).

Moderate to high yields were observed for a range of functionalities. Electron poor 368j was isolated in the highest yield (entry 2), however, only a moderate yield was observed with aryl halide 368n (entry 9). A yield of 74% was observed for benzyloxy substituted 368k (entry 6); this aldehyde was accessed in only 45% yield from the corresponding alkylidene MA derivative 328k using molybdenum-catalysed reductive conditions (cf. 3.3.3).
Table 12 Triethylamine promoted reduction of 5-monoalkyl MA derivatives 367

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>product</th>
<th>yield, %&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-(OMe)C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>368a</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>2,3-(OCH&lt;sub&gt;2&lt;/sub&gt;O)C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;3&lt;/sub&gt;</td>
<td>368e</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;CHCH</td>
<td>368f</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>3,4-(OMe)&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;3&lt;/sub&gt;</td>
<td>368g</td>
<td>61</td>
</tr>
<tr>
<td>5</td>
<td>4-(NO&lt;sub&gt;2&lt;/sub&gt;)C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>368j</td>
<td>92</td>
</tr>
<tr>
<td>6</td>
<td>4-(OBn)C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>368k</td>
<td>74&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td>2-naphthyl</td>
<td>368l</td>
<td>65</td>
</tr>
<tr>
<td>8</td>
<td>1-naphthyl</td>
<td>368m</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>4-BrC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>368n</td>
<td>56</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>368o</td>
<td>75</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: 367 (1 equiv), phenylsilane (3 equiv), triethylamine (2 equiv), THF, r.t., 2 h.
<sup>b</sup> Reaction was stirred for 4 h. <sup>c</sup> Isolated yields.

Pleasingly, chiral γ-amino aldehyde 368o was isolated in good yield (entry 10). This γ-amino aldehyde could be used in the synthesis of a range of potent and selective indole based 5-HT<sub>6</sub> receptor agonists and antagonists via a palladium-catalysed indole formation with o-haloanilines (Scheme 147).

Scheme 147 Proposed synthetic route to biologically active indole derivatives from 368o

In addition to 5-monoalkylated MA derivatives, 5,5’-disubstituted MA derivative 380 was exposed to these reductive conditions. Analysis of the reaction mixture showed that, even
after a prolonged period of heating, 5,5′-disubstituted MA derivative 380 underwent no reduction, only unreacted 380 was observed in the reaction mixture (Scheme 148).

![Scheme 148 Reduction of 5,5′-dialkyl MA 380](image)

### 4.2.2.1 Synthesis of Aminoaldehydes

Following the formation of chiral γ-amino aldehyde 368o, N-Boc-L-phenylalanine derivative 367p was synthesised by the same method as 367o (Scheme 149).

![Scheme 149 Synthesis of 367p](image)

Exposure of this secondary carbamate to the reductive conditions described above did not result in the formation of any amino aldehyde: crude 1H NMR analysis showed no peaks between 9 and 10 ppm. Following purification by flash column chromatography, one and two dimensional NMR studies showed the primary product of the reaction was chiral 2-pyrrolidinone 410; no other products were isolated from the reaction mixture (Scheme 150).

![Scheme 150 Reduction of 367p](image)
No reaction was observed when either triethylamine or phenylsilane were removed from the reaction mixture. It is proposed that the reaction is initiated by the nucleophilic attack of the nitrogen on the electrophilic ester of the MA group; subsequent elimination of acetone and carbon dioxide results in the formation of enolate 411 (Scheme 151). The eliminated acetone, activated by the Lewis acidic silane species, then undergoes condensation at the 3-position to give 410.

4.2.2.2 Reduction of Michael Acceptors

Reduction of alkylidene MA derivative 328a by triethylamine and phenylsilane was achieved with prolonged heating, and aldehyde 368a was isolated in a 36% yield (Scheme 152). This transformation is unsurprising in light of high electrophilicity of 328a\(^21\) and the ability of silanes to reduce Michael acceptors in the presence of Lewis bases (removal of triethylamine from the reaction mixture resulted in no reaction).\(^15\) When less reactive dimethyl itaconate was exposed to the same reductive conditions no conversion to dimethyl 2-methyl succinate was observed.
4.2.3 Mechanistic Studies

As with the molybdenum-catalysed reduction of arylidene MA derivatives, deuterium labelling studies were carried out to gain insight into the reaction mechanism. Deuterium was used as a nucleophile and an electrophile in the form of trideuteriophenylsilane\textsuperscript{22} and deuterium oxide.

Reduction of 367a with trideuteriophenylsilane followed by hydrolysis with water proceeded smoothly with the product isolated in 85\% yield. \textsuperscript{1}H NMR analysis showed no aldehyde peak at 9.80 ppm (Figure 16) and a singlet at 9.75 ppm was observed in the \textsuperscript{2}H NMR (Figure 15), no other peaks were observed in the \textsuperscript{2}H NMR. Furthermore, a triplet at 201.9 ppm was observed in the \textsuperscript{13}C NMR and bands at 2079 cm\textsuperscript{-1} (C-D) and 1712 cm\textsuperscript{-1} (C=O) were observed in the IR spectra confirming the formation of a deuteroaldehyde. The \textsuperscript{1}H NMR also showed a 2H triplets at 2.91 ppm and 2.74 ($J = 7.5$ Hz); a 2H multiplet is observed at 2.77-2.72 ppm in the \textsuperscript{1}H NMR spectra of 268a (Figure 17). This analysis suggests the formation of the deuteroaldehyde 412a (Scheme 153), this was confirmed by \textsuperscript{1}H-, \textsuperscript{2}D-, and \textsuperscript{13}C NMR, mass spectrometry and IR analysis.

![Scheme 153 Reduction of 367a using trideuterophenylsilane](image)

![Figure 15 \textsuperscript{2}D NMR of 1-deutero-3-(4-methoxyphenyl)propanal 412a](image)
Reduction of 367a with phenylsilane, followed by hydrolysis with deuterium oxide gave the same mixture of products as the molybdenum-catalysed reduction of alkylidene MA derivative 328a hydrolysed with deuterium oxide (cf. 3.3.6.1). Again incomplete deuteration at the α-carbon occurred, however, the α,α'-dideuterated product 383a was the major product of the reaction.

Scheme 154 Reduction of 367a quenched by deuterium oxide
4.2.4 Proposed Mechanism

There are two possible reaction pathways for the amine promoted reduction of 5-monoalkyl Meldrum’s acid derivatives. Both proposed pathways are initiated by the deprotonation of 367 on addition of triethylamine and subsequent silylation by phenylsilane to give 386 (Scheme 155). In pathway a the cycloreversion of 386 gives $\alpha$-oxoketene 387 which undergoes hydrosilylation to intermediate 388 and this remains in solution until decarboxylative protonation at the end of the reaction (decarboxylation confirmed by limewater test). In pathway b the ester moiety of 386 is hydrosilylated to give 395; this then undergoes cycloreversion to give, like pathway a, 388.

Scheme 155 Proposed reaction pathways for the triethylamine promoted reduction of 5-monoalkyl MAs
Attempts to isolate intermediate 388 were unsuccessful. However, $^1$NMR analysis of the reaction mixture prior to protonation showed loss of acetone is occurring prior to decarboxylative protonation.

### 4.3 Application of Aldehyde Synthesis in Multi-Step Syntheses

Multiple-step syntheses carried out in one pot are of interest as they can increase efficiency by avoiding repeated isolation and purification processes. It was envisaged that the mild, expeditious synthesis of $\beta$-substituted propionaldehydes, described above, could be used as the first step in a one-pot multi-step synthesis due to the synthetic utility of the newly formed aldehyde functionality.

To explore the synthetic utility of the amine promoted $\beta$-substituted propionaldehyde synthesis, a one-pot malonate reduction/reductive amination was proposed to access $\gamma$-substituted propylamines 414 directly from 5-monoalkyl Meldrum’s acid derivatives (Scheme 156). Decarboxylative protonation would reveal the protected aldehyde functionality; this would undergo imine formation on addition of a primary or secondary amine. Reduction of the imine would result in the formation of the desired $\gamma$-substituted propylamines.

![Scheme 156](image)

Scheme 156 Envisaged process for $\gamma$-substituted propylamine synthesis from 367

Methanol proved to be a suitable proton source giving the aldehyde before imine formation on addition of a suitable amine. Imine reduction was, as expected, achieved with both Pd/C with 1 atmosphere of molecular hydrogen$^{23}$ and NaBH(OAc)$_3$ $^{24}$ (Table 13, entries 1 and 2). Higher yields were observed with the palladium-catalysed hydrogenation.
Table 13 One-pot reduction/reductive amination of 367a

<table>
<thead>
<tr>
<th>entry</th>
<th>amine</th>
<th>product&lt;sup&gt;a&lt;/sup&gt;</th>
<th>yield, %&lt;sup&gt;b&lt;/sup&gt;</th>
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<tbody>
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<td>63</td>
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<td><img src="image2" alt="product_414aa" /></td>
<td>31&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td><img src="image1" alt="amine_415b" /></td>
<td><img src="image2" alt="product_414ab" /></td>
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<td>6</td>
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<td>8</td>
<td><img src="image1" alt="amine_415g" /></td>
<td><img src="image2" alt="product_414ag" /></td>
<td>37</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: (i) Substrate 367a (1 equiv), phenylsilane (3 equiv), triethylamine (2 equiv), THF, r.t., 2 h, (ii) methanol, amine (2 equiv), r.t. 1 h, (iii) Pd/C, H<sub>2</sub> (1 atm), r.t. 16 h. Isolated yields.<br><sup>b</sup> NaBH(OAc)<sub>3</sub> (2 equiv) used.

This one-pot process was carried out with a range of primary and secondary amines and alkylidene MA derivative 367a, products were isolated in moderate yields (Table 13).
Despite high steric hindrance, diisopropylamine gave the highest yield of 63%, a pleasing yield for this multi-step process (entry 1). Yields varied little for other secondary amines (entries 3, 6 and 7) with the exception of the less nucleophilic morpholine 415d (entry 5). A poor yield was observed with the use of benzylamine 415g (entry 8); it is likely that this is a consequence of the dialkylation of the amine. Aniline 415c gives the reductive amination product in 48% yield (entry 4).

Table 14 One-pot reduction/reductive amination of 5-monoalkyl MAs

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>product$^a$</th>
<th>yield, %$^b$</th>
</tr>
</thead>
<tbody>
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<td>1</td>
<td><img src="image" alt="substrate_367g" /></td>
<td><img src="image" alt="product_414ga" /></td>
<td>56</td>
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<tr>
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<td>57</td>
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<td>3</td>
<td><img src="image" alt="substrate_367k" /></td>
<td><img src="image" alt="product_414ka" /></td>
<td>32$^c$</td>
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<td><img src="image" alt="substrate_367l" /></td>
<td><img src="image" alt="product_414la" /></td>
<td>41</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="substrate_367o" /></td>
<td><img src="image" alt="product_414oa" /></td>
<td>61</td>
</tr>
</tbody>
</table>

$^a$ Reaction conditions: (i) Substrate 367 (1 equiv), phenylsilane (3 equiv), triethylamine (2 equiv), THF, r.t., 2 h, (ii) methanol, diisopropylamine (2 equiv), r.t. 1 h, (iii) Pd/C, H$_2$ (1 atm), r.t. 16 h. $^b$ Isolated yields. $^c$ NaBH(OAc)$_3$ (2 equiv) used.
This one-pot process tolerated a range of 5-monoalkyl MA derivatives (Table 14). Of note is the synthesis of 416ka and 414ka from the common substrate 367k, by adjusting the reductive conditions the benzyl protecting group can be either removed or left unchanged (entries 2 and 3, Table 14). The trend in reactivity for this multi-step process is the same as the synthesis of β-substituted propionaldehydes with the exception of 414la which was isolated in a poor 41% yield (entry 4).

**4.4 Conclusion**

A triethylamine promoted reduction of 5-monoalkyl MA derivatives to β-substituted aldehydes by phenylsilane has been reported. Good yields have been observed with a range of substrates using these mild, expeditious reductive conditions. Evidence towards a proposed mechanism has been acquired through deuterium labelling studies and a limewater test.

This reductive system has been used in a one-pot reductive aldehyde formation/reductive amination for the synthesis of γ-substituted propylamines directly from 5-monoalkyl MA derivatives. Moderate yields were observed for this one-pot process.

Under more forcing conditions it was possible to access β-aryl aldehydes directly from alkylidene MA derivatives; an amine promoted conjugate reduction is the initiating step of this reaction.
4.5 References

Chapter 5 - Experimental

5.1 General Information

Commercially available solvents and reagents were obtained from Sigma Aldrich Company Ltd, Lancaster Synthesis Ltd, Fisher Scientific Ltd and Strem Chemicals UK and were used without further purification. Solvents and were deoxygenated where necessary by purging with nitrogen. ‘Petrol’ refers to the fraction of petroleum ether boiling in the range of 40-60 °C. For catalytic experiments, HPLC-grade solvent was passed through an Innovative Technology Pure-Solv solvent purification system. Microwave reactions were performed using a CEM Discover 300W laboratory microwave instrument.

NMR spectra were recorded on Bruker AV 250, AV300 or AV 500 spectrometers at 298 K unless otherwise stated. Chemical shifts (δ) are expressed in parts per million (ppm). $^1$H NMR spectra were referenced internally to residual protio-solvent (CHCl$_3$ at 7.26 ppm), $^{13}$C NMR spectra were referenced to deuterio-solvent resonance (CDCl$_3$ at 77.0 ppm) and $^2$H NMR were referenced to deuterio-solvent (CDCl$_3$ at 7.26 ppm). Assignments were supported by $^{13}$C PENDANT NMR and homo- and heteronuclear, one- and two-dimensional experiments as appropriate. The multiplicities of the spectroscopic data are presented in the following manner: singlet (s), broad singlet (br s), doublet (d), doublet of doublets (dd), double of doublet of doublets (ddd), doublet of doublet of triplets (ddt), triplet (t), triplet of doublets (td), quartet (q), quintet (quin), septet (sept) and multiplet (m). Coupling constants (J) are expressed in Hertz (Hz). The assignment of aromatic proton resonances for para disubstituted benzene rings has been simplified by assuming an AB system, however, the characteristic features of an AA’BB’ system were observed in the NMR spectra.

IR spectra were recorded on either a Nicolet-Nexus FTIR spectrometer, over the range 4000-600 cm$^{-1}$ and averaged over 32 scans, using KBr discs or NaCl plates. Melting points were determined using a Buchi 535 melting point apparatus and are uncorrected. Electrospray Ionisation (ESI) and Electron Impact (EI) mass spectra were obtained at the
EPSRC National Mass Spectrometry Service Centre at Swansea University or on a Bruker MicroTOF spectrometer at the mass spectrometry service at the University of Bath.

High Performance Liquid Chromatography (HPLC) was performed on an Agilent 1100 Series system, using a Chiralpak OJ column by Daicel Chemical Industries Ltd. Elemental analyses were recorded on a Micromass Autospec Spectrometer at the University of Bath.

5.2 Molybdenum-Catalysed Conjugate Reduction

5.2.1: Dimethyl 2-methylsuccinate 230

An oven dried microwave vial was charged with a solution dimethyl itaconate (79.1 mg, 0.5 mmol), molybdenum hexacarbonyl (6.6 mg, 0.025 mmol, 5 mol%) and N-methylmorpholine N-oxide monohydrate (5.9 mg, 0.044 mmol, 9 mol%) in tetrahydrofuran (1.0 mL). Phenylsilane (92 µL, 0.75 mmol) was added to the solution and the vial was sealed under an atmosphere of nitrogen. The solution was heated to 80 °C (100 W) in a microwave reactor for 5 minutes and allowed to cool to room temperature. After cooling to room temperature, water (0.5 mL) was added to the reaction mixture and the resulting solution was stirred at ambient temperature for 15 minutes. The solution was diluted with diethyl ether (25 mL) and washed with water (2 x 25 mL) followed by saturated brine (25 mL). The organic phase was extracted, dried over MgSO₄ and concentrated in vacuo. Methanol (20 mL) was added to the residue, the solution was filtered through celite and concentrated in vacuo to afford the desired compound as a colourless oil (147.4 mg, 95%).

¹H NMR (300 MHz, CDCl₃) δ 3.70 (3H, s, OCH₃), 3.68 (3H, s, OCH₃), 3.00-2.89 (1H, m, MeO₂CCH₂), 2.74 (1H, dd, J₁ = 16.2 Hz, J₂ = 8.3 Hz, CH₂CO₂Me), 2.41 (1H, dd, J₁ = 16.2 Hz, J₂ = 6.0 Hz, CH₂CO₂Me), 1.22 (3H, d, J = 7.2 Hz); ¹³C NMR (75.5 MHz, CDCl₃) δ 176.1, 172.7, 52.5, 52.4, 37.9, 36.0, 17.4; HRMS (ESI) calcd for C₇H₁₂NaO₄ [M+Na]⁺: m/z 183.0628, found 183.0623. Data identical to literature values.¹
5.3 Synthesis of α-Substituted Acrylic Esters

5.3.1: General Procedure for the Synthesis of α-Substituted Acrylic Esters

\[ \text{PG}-\text{H} \to \text{O} \quad \text{+} \quad \text{OtBuO} \to \text{Br} \quad \text{N} \quad \text{PG} \quad \text{OR} \quad \text{NaH} \quad \text{THF, 0 o-r.t., 24 h} \quad \text{OtBuO} \quad \text{N} \quad \text{PG} \quad \text{OR} \]

\( N \)-Protected glycine methyl or ethyl ester 254 was added to a stirred solution of sodium hydride (60% dispersion in mineral oil) in tetrahydrofuran at 0 °C. The subsequent solution was stirred for 1 hour at 0 °C. tert-Butyl 2-(bromomethyl)acrylate 255 was then added to the reaction mixture and the resulting solution was stirred at ambient temperature for 24 hours. The reaction mixture was quenched with water and dissolved in diethyl ether. The organic phase was washed with water and saturated brine. The organic phase was extracted, dried over MgSO₄, concentrated \textit{in vacuo} and purified by flash column chromatography.

5.3.2: tert-butyl 2-((benzyl(2-ethoxy-2-oxoethyl)amino)methyl)acrylate 222

\[ \text{OtBuO} \quad \text{N} \quad \text{Bn} \quad \text{OEt} \quad \text{O} \quad \text{N} \quad \text{Benzyl glycine ethyl ester} \quad \text{254a} \quad (1.93 \text{ g, 10.0 mmol}), \text{NaH} \quad (0.48 \text{ g, 12.0 mmol}), \text{OtBuO} \quad \text{N} \quad \text{PG} \quad \text{OR} \quad \text{tert-butyl 2-(bromomethyl)acrylate} \quad 255 \quad (2.42 \text{ g, 11.0 mmol)} \text{and tetrahydrofuran (50 mL) were reacted under the standard protocol and purified by flash column chromatography (9:1 petrol:ethyl acetate) to give the desired compound as a colourless oil (2.15 g, 64%); Rf (9:1 petrol:ethyl acetate) 0.24; IR (neat, cm}^{-1} \text{) v 2978, 2932 (C-H), 1736, 1711 (C=O), 1636 (C=C); }^{1} \text{H NMR (300 MHz, CDCl}_3 \text{) } \delta 7.32-7.17 \text{ (5H, m, Ar-H), 6.13 (1H, s, C=CH}_2 \text{), 5.76 (1H, s, C=CH}_2 \text{), 4.11 (2H, q, J = 7.2 Hz, OCH}_2\text{CH}_3 \text{), 3.80 (2H, s, NCH}_2\text{Ph), 3.50 (2H, s, NCH}_2\text{C=C), 3.28 (2H, s, NCH}_2\text{CO}_2\text{Et), 1.46 (9H, s, C(CH}_3)_3 \text{), 1.22 (3H, t, J = 7.2 Hz, OCH}_2\text{CH}_3 \text{); }^{13} \text{C NMR (75.5 MHz, CDCl}_3 \text{) } \delta 171.9, 166.7, 139.9, 139.4, 129.2, 128.7, 127.5, 125.7, 81.0, 60.6, 57.8, 55.0, 53.9, 28.5, 14.7; \text{HRMS (ESI) calcd for C}_{19}\text{H}_{27}\text{NNaO}_4 [\text{M+Na}]^+ : m/z 356.1838, found 356.1833; Anal. calcd for C}_{19}\text{H}_{27}\text{NO}_4: C 68.4, H 8.16, N 4.20, found: C 68.5, H 8.27, N 4.25. \]
5.3.3: *tert*-butyl 2-((*tert*-butoxycarbonyl(2-ethoxy-2-oxoethyl)amino)methyl)acrylate

256

\[
\begin{align*}
\text{N-Boc glycine ethyl ester} \ 254b & \ (2.25 \text{ g, } 15 \text{ mmol}), \ \text{sodium hydride} \ (0.72 \text{ g, } 18 \text{ mmol}), \ \text{*tert*-butyl 2-(bromomethyl)acetate} \ 255 & \ (3.63 \text{ g, } 16.5 \text{ mmol}) \ \text{and tetrahydrofuran} \ (75 \text{ mL}) \ \text{were reacted under standard conditions and purified by flash column chromatography} \ (9:1 \ \text{petrol:ethyl acetate}) \ \text{to give the desired compound, a colourless oil, as a 1:1 mixture of rotamers (4.11 g, 80\%); } R_f \ (9:1 \ \text{petrol:ethyl acetate}) \ 0.27; \ \text{IR} \ (\text{neat, cm}^{-1}) \ \nu \ 2980, \ 2935 \ (\text{C-H}), \ 1753, \ 1706 \ (\text{C=O}), \ 1638 \ (\text{C=C}); \ \text{^1H NMR} \ (300 \text{ MHz, CDCl}_3) \ \delta \ 6.19 \ \text{and} \ 6.17 \ (1H, s, \ \text{C=C}_2H_2), \ 5.67 \ \text{and} \ 5.60 \ (1H, s, \ \text{C=C}_2H_2), \ 4.17 \ \text{and} \ 4.16 \ (2H, q, J = 7.2 \text{ Hz, OCH}_2CH_3), \ 4.11 \ \text{and} \ 4.06 \ (2H, s, \text{NCH}_2C=\text{C}), \ 3.99 \ \text{and} \ 3.88 \ (2H, s, \text{NCH}_2CO_2\text{Et}), \ 1.48 \ \text{and} \ 1.47 \ (9H, s, \text{C(CH}_3)_3), \ 1.44 \ \text{and} \ 1.42 \ (9H, s, \text{C(CH}_3)_3), \ 1.26 \ \text{and} \ 1.25 \ (3H, t, J = 7.2 \text{ Hz, OCH}_2CH_3); \ \text{^13C NMR} \ (75.5 \text{ MHz, CDCl}_3) \ \delta \ 170.4 \ \text{and} \ 170.3, \ 165.9, \ 156.2 \ \text{and} \ 155.5, \ 138.4 \ \text{and} \ 138.1, \ 126.1 \ \text{and} \ 125.3, \ 81.6 \ \text{and} \ 81.4, \ 80.9 \ \text{and} \ 80.8, \ 61.3, \ 50.0 \ \text{and} \ 49.5, \ 49.3 \ \text{and} \ 49.2, \ 28.7 \ \text{and} \ 28.6, \ 28.4, \ 14.6 \ \text{and} \ 14.5; \ \text{HRMS (ESI) calcd for C}_{17}H_{30}NO_6 [M+H]^+: m/z 344.2073, found 344.2063.\
\end{align*}
\]

5.3.4: *tert*-butyl 2-((allyl(2-methoxy-2-oxoethyl)amino)methyl)acrylate

257

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\begin{align*}
\text{N-allyl glycine methyl ester} \ 254c & \ (1.29 \text{ g, } 10 \text{ mmol}), \ \text{sodium hydride} \ (0.48 \text{ g, } 12.0 \text{ mmol}), \ \text{*tert*-butyl 2-(bromomethyl)acetate} \ 255 & \ (2.42 \text{ g, } 11.0 \text{ mmol}) \ \text{and tetrahydrofuran} \ (50 \text{ mL}) \ \text{were reacted under standard conditions and purified by flash column chromatography} \ (9:1 \ \text{petrol:ethyl acetate}) \ \text{to give the desired compound as a colourless oil (1.43 g, 53\%); } R_f \ (9:1 \ \text{petrol:ethyl acetate}) \ 0.22; \ \text{IR} \ (\text{neat, cm}^{-1}) \ \nu \ 2979, \ 2954, \ 2845 \ (\text{C-H}), \ 1741, \ 1715 \ (\text{C=O}), \ 1641 \ (\text{C=C}); \ \text{^1H NMR} \ (300 \text{ MHz, CDCl}_3) \ \delta \ 6.14 \ (1H, s, \ \text{C=C}_2H_2), \ 5.81 \ (1H, ddt, J^1 = 17.3 \text{ Hz, } J^2 = 10.2 \text{ Hz, } J^3 = 6.4 \text{ Hz, NCH}_2CHCH_2), \ 5.71 \ (1H, s, \text{C=CH}_2), \ 5.18 \ (1H, ddt, J^1 = 17.3 \text{ Hz, } J^2 = 1.9 \text{ Hz, } J^3 = 1.5 \text{ Hz, NCH}_2CHCH_2), \ 5.13 \ (1H, ddt, J^1 = 10.2 \text{ Hz, } J^2 = 1.9 \text{ Hz, } J^3 = 1.1 \text{ Hz, NCH}_2CHCH_2), \ 3.67 \ (3H, s, \text{CO}_2\text{H}), \ 3.44 \ (2H, s, \text{NCH}_2C=\text{C}), \ 3.35 \ (2H, s, \text{NCH}_2CO_2\text{Me}), \ 3.26 \ (2H, ddd, J^1 = 6.4 \text{ Hz, } J^2 = 1.5 \text{ Hz, } J^3 = 1.1 \text{ Hz, NCH}_2CHCH_2), \ 1.48
\end{align*}
\]
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(9H, s, C(CH₃)₃); ¹³C NMR (75.5 MHz, CDCl₃) δ 172.4, 166.6, 139.7, 136.0, 125.9, 118.1, 81.1, 57.3, 54.6, 54.11, 51.7, 28.5; HRMS (ESI) calcd for C₁₄H₂₃NNaO₄ [M+Na]⁺: m/z 292.1525, found 292.1519.

5.3.5: tert-butyl 2-(((2-ethoxy-2-oxoethyl)methylamino)methyl)acrylate 218

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\begin{align*}
\text{Sarcosine ethyl ester hydrochloride 254d} & (694 \text{ mg, 4.53 mmol}), \text{ sodium hydride (422 mg, 10.5 mmol)}, \text{ tert-butyl 2-(bromomethyl)acetate 255 (1 g, 4.53 mmol)} \text{ and tetrahydrofuran (50 mL)} \text{ were reacted under standard conditions and purified by flash column chromatography (4:1 petrol:ethyl acetate)} \text{ to give the desired compound as a colourless oil (932 mg, 80%); } R_f (4:1 \text{ petrol:ethyl acetate})0.27; \text{ IR (neat, cm}^{-1}) \nu 2980 (\text{C-H}), 1740, 1713 (\text{C=O}), 1636 (\text{C=C}); ¹H (300 MHz, CDCl₃) \delta 6.08 (1H, s, C=C-H-H), 5.61 (1H, s, C=CH-H), 4.07 (2H, q, J = 7.2 Hz, OCH₂CH₃), 3.28 (2H, s, NCH₂C=C), 3.20 (2H, s, CH₂CO₂Et), 2.30 (3H, s, NCH₃), 1.40 (9H, s, C(CH₃)₃), 1.18 (3H, t, J = 7.2 Hz, OCH₂CH₃); ¹³C NMR (75.5 MHz, CDCl₃) δ 171.3, 166.4, 139.2, 126.0, 80.9, 60.5, 58.1, 57.1, 42.3, 28.3, 14.6; HRMS (ESI) calcd for C₁₃H₂₁NNaO₄ [M+Na]⁺: m/z 280.1524, found 280.1522.
\end{align*}
\]

5.3.6: (R)-ethyl 2-((1-phenylethylamino)acetate 274

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\begin{align*}
(R)-1-\text{Phenylethylamine 272} & (1.05 \text{ mL, 8.25 mmol}) \text{ was added to a stirred solution of sodium hydride (60% dispersion in mineral oil) (330 mg, 8.25 mmol) in tetrahydrofuran (25 mL)} \text{ at 0 °C. The subsequent solution was stirred for 1 hour at 0 °C. Ethyl 2-bromoacetate 273 (457 µL, 4.13 mmol)} \text{ was then added to the reaction mixture and the resulting solution was stirred at ambient temperature for 24 hours. The reaction mixture was quenched with water and dissolved in diethyl ether (50 mL). The organic phase was washed with water (50 mL) and saturated brine (50 mL). The organic phase was extracted, dried over MgSO₄, concentrated in vacuo and purified by flash column chromatography (4:1 petrol:ethyl acetate) to give the desired compound as a colourless oil (746 mg, 87%); } R_f (4:1 \text{ petrol:ethyl acetate}) 0.20; ¹H NMR (300 MHz, CDCl₃) δ 7.31 (5H, m, ArH), 4.13 (2H, q, J = 7.2 Hz, CO₂CH₂CH₃), 3.77 (1H, q, J = 6.4 Hz, NCH₂), 3.27 (1H, d, J = 17.3 Hz, J) \]

130
NCH$_2$CO$_2$Et), 3.19 (1H, d, $J = 17.3$ Hz, NCH$_2$CO$_2$Et), 1.90 (1H, s, NH), 1.36 (3H, d, $J = 6.4$ Hz, NCHCH$_3$), 1.22 (3H, t, $J = 7.2$ Hz, CO$_2$CH$_2$CH$_3$); $^{13}$C (75.5 MHz, CDCl$_3$) $\delta$ 173.0, 145.0, 128.9, 127.6, 127.2, 61.1, 58.1, 49.3, 24.6, 14.6; HRMS (ESI) calcd for C$_{12}$H$_{17}$N$\text{NaO}_2$ [M+Na]$^+$: $m/z$ 230.1152, found 230.1142. Data identical to literature values.$^2$

5.3.7: (R)-tert-butyl 2-(((2-ethoxy-2-oxoethyl)(1-phenylethyl)amino)methyl)acrylate 275

2-((R)-1-Phenylethlamino)acetate 274 (711 mg, 3.43 mmol), sodium hydroxide (137 mg, 3.43 mmol), tert-butyl 2-(bromomethyl)acetate 255 (663 mg, 3.43 mmol) and tetrahydrofuran (20 mL) were reacted under standard conditions and purified by flash column chromatography (10:1 petrol:ethyl acetate) to give the desired compound as a colourless oil (544 mg, 46%); $R_f$ (10:1 petrol:ethyl acetate) 0.24; $[\alpha]_D^{24}$ -1.3 (c = 0.8, CDCl$_3$); IR (neat, cm$^{-1}$) ν 2980, 2935 (C-H), 1735, 1708 (C=O), 1639 (C=C); $^1$H NMR (300 MHz, CHCl$_3$) $\delta$ 7.40-7.19 (5H, m, Ar), 6.13 (1H, s, C=CHH), 5.87 (1H, s, C=CHH), 4.12 (2H, q, $J = 7.2$ Hz, OCH$_2$CH$_3$), 4.10 (1H, q, $J = 6.8$ Hz, NCH), 3.49 (1H, d, $J = 16.2$ Hz, NCH$_2$C=C), 3.45 (1H, d, $J = 16.2$ Hz, NCH$_2$C=C), 3.40 (1H, d, $J = 17.3$ Hz, NCH$_2$CO$_2$Et), 3.25 (1H, d, $J = 17.3$ Hz, NCH$_2$CO$_2$Et), 1.48 (9H, s, C(CH$_3$)$_3$), 1.36 (3H, d, $J = 6.8$ Hz, CHCH$_3$), 1.24 (3H, t, 7.2 Hz, OCH$_2$CH$_3$); $^{13}$C NMR (75.5 MHz, CDCl$_3$) $\delta$ 172.5, 166.7, 144.7, 140.4, 128.6, 127.9, 127.3, 125.4, 81.0, 60.7, 60.6, 52.1, 51.8, 28.5, 19.3, 14.6; HRMS (ESI) calcd for C$_{20}$H$_{29}$NO$_4$Na [M+Na]$^+$: $m/z$ 370.1994, found 370.1994.

5.3.8: (1S,2R,5S)-2-isopropyl-5-methylcyclohexyl 2-(tert-butoxycarbonylamino)acetate 290

To a stirred solution of N-Boc glycine 289 (3.50 g, 20.2 mmol) in dichloromethane (110 mL) was added dicyclohexylcarbodiimide (4.18 g, 20.2 mmol), and dimethylaminopyridine (110 mg, 0.9 mmol) at 0 °C. The resulting solution was stirred for 1 hour before the addition of (+)-menthol (3.78 g, 24.2 mmol) and then stirred for a further 24 hours after
reaching ambient temperature. The reaction mixture was dissolved in DCM (100 mL) and washed with water (200 mL) and saturated brine (200 mL); the organic phase was extracted and concentrated in vacuo. The residue was dissolved in ethyl acetate and filtered through celite, the filtrate was concentrated in vacuo and purified by flash column chromatography (12:1 petrol:diethyl ether) to give the desired product as a colourless oil (5.09 g, 80%); \( R_f \) (12:1 petrol:diethyl ether) 0.21; [\( \alpha \)]\( _D \) +75.3 (c = 0.9, CHCl\(_3\)); IR (neat, cm\(^{-1}\)) \( \nu \) IR 3034 (N-H), 2958, 2871 (C-H), 1740, 1701 (C=O); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 5.02 (1H, br s, N\( H \)), 4.74 (1H, td, \( J^1 = 10.9 \) Hz, \( J^2 = 4.5 \) Hz, OCH\(_2\)), 3.87 (2H, d, \( J = 5.3 \) Hz, NCH\(_2\)), 2.01-1.94 (1H, m, mentholate), 1.90-1.75 (1H, m, mentholate), 1.73-1.63 (2H, m, mentholate), 1.53-1.32 (2H, m, mentholate), 1.44 (9H, s, C(C\(_{\text{Me}}\)\(_3\))), 1.11-0.79 (3H, m, mentholate), 0.89 (3H, d, \( J = 6.5 \) Hz, CHC(C\(_{\text{Me}}\)\(_3\))), 0.87 (3H, d, \( J = 6.5 \) Hz, CHC(C\(_{\text{Me}}\)\(_3\))), 0.74 (3H, d, \( J = 6.8 \) Hz, CHCH\(_3\)); \(^{13}\)C NMR (75.5 MHz, CDCl\(_3\)) \( \delta \) 170.3, 156.0, 80.2, 75.8, 47.3, 43.0, 41.2, 34.5, 31.8, 28.7, 26.6, 23.8, 22.4, 21.1, 16.7; HRMS (ESI) calcd for C\(_{17}\)H\(_{32}\)NO\(_4\) [M+H]\(^+\) : m/z 314.2331, found 314.2330.

5.3.9: (1S,2R,5S)-2-isopropyl-5-methylcyclohexyl 2-(benzylamino)acetate 291

(1S,2R,5S)-2-Isopropyl-5-methylcyclohexyl 2-(tert-butoxycarbonylamino)acetate 289 (3.0 g, 9.57 mmol) was added to a stirred solution of sodium hydride (60% dispersion in mineral oil) (460 mg, 11.48 mmol) in tetrahydrofuran (100 mL) at 0 °C. The resulting solution was stirred at 0 °C for 1 hour then benzyl bromide (1.71 mL, 14.36 mmol) was added and the solution stirred at ambient temperature for 24 hours. The reaction mixture was dissolved in diethyl ether (100 mL) and washed with saturated sodium hydrogen carbonate solution (2 x 150 mL), water (150 mL) and saturated brine (150 mL). The organic phase was extracted and concentrated in vacuo and the residue was reacted further without isolation of the product. The residue was dissolved in dichloromethane (30 mL) and stirred at 0 °C. Trifluoacetic acid (7.5 mL) added to the solution drop wise, the reaction mixture was then stirred at ambient temperature for 3 hours. The reaction mixture was concentrated in vacuo and the residue dissolved in diethyl ether (100 mL). The organic phase was washed with saturated sodium hydrogen carbonate solution (3 x 100 mL), water (100 mL) and brine.
(100 mL). The organic phase was extracted, concentrated \textit{in vacuo} and purified by flash column chromatography (10:1 petrol:ethyl acetate) to give the desired compound as a colourless oil (1.34 g, 46%); $R_f$ (10:1 petrol:ethyl acetate) 0.28; $\left[\alpha\right]_D^{24} +34.6$ (c = 7.5, CHCl$_3$); \textit{IR} (neat, cm$^{-1}$) ν 3030 (N-H), 2957, 2870 (C-H), 1732 (C=O); \textit{$^1$H NMR} (300 MHz, CDCl$_3$) δ 7.30-7.19 (5H, m, Ar), 4.74 (1H, td, $J^1 = 10.9$ Hz, $J^2 = 4.5$ Hz, OCH), 3.77 (2H, s, NCH$_2$Ph), 3.35 (2H, s, NCH$_2$CO$_2$X$_c$), 2.01-1.96 (1H, m, mentholate), 1.87-1.74 (1H, m, mentholate), 1.70-1.61 (2H, m, mentholate), 1.39-1.29 (1H, m, mentholate), 1.11-0.80 (4H, m, mentholate), 0.88 (3H, d, $J = 6.5$ Hz, CH(CH$_3$)$_2$), 0.86 (3H, d, $J = 6.5$ Hz, CH(CH$_3$)$_2$), 0.75 (3H, d, $J = 7.2$ Hz, CHCH$_3$); \textit{$^{13}$C NMR} (75.5 MHz, CDCl$_3$) δ 172.4, 140.0, 128.8, 128.7, 127.5, 75.1, 53.7, 50.7, 47.4, 41.4, 34.6, 31.8, 26.7, 23.8, 22.4, 21.1, 16.7; \textit{HRMS} (ESI) calcd for C$_{19}$H$_{30}$NO$_2$ [M+H]$^+$: m/z 304.2277, found 304.2270.

5.3.10: \textit{tert}-butyl 2-((benzyl(2-((1S,2R,5S)-2-isopropyl-5-methylcyclohexyloxy)-2-oxoethyl)amino)methyl)acrylate 292

(1S,2R,5S)-2-Isopropyl-5-methylcyclohexyl 2-(benzylamino)acetate 291 (500 mg, 1.65 mmol) was added to a solution of sodium hydride (60% dispersion in mineral oil) (72.5 mg, 1.81 mmol) in tetrahydrofuran (20 mL) at 0 °C. The subsequent solution was stirred for at 0 °C for 1 hour before the addition of \textit{tert}-butyl 2-(bromomethyl)acrylate 255 (750 mg, 1.81 mmol). The reaction mixture was stirred at ambient temperature for 24 hours. The reaction mixture was dissolved in diethyl ether (50 mL) and washed with saturated sodium hydrogen carbonate solution (2 x 50 mL), water (50 mL) and brine (50 mL). The organic phase was extracted, dried over MgSO$_4$ and \textit{concentrated in vacuo}. The mixture was purified by flash column chromatography (15:1 petrol:diethyl ether) to give the desired product as a colourless oil (185 mg, 66% yield); $R_f$ (15:1 petrol:diethyl ether) 0.25; $\left[\alpha\right]_D^{24} +56.1$ (c = 1.8, CHCl$_3$); \textit{IR} (neat, cm$^{-1}$) ν 2957, 2870 (C-H), 1738, 1712 (C=O), 1637 (C=C); \textit{$^1$H NMR} (300 MHz, CDCl$_3$) δ 7.38-7.23 (5H, m, Ar), 6.19 (1H, d, $J = 6.19$ Hz, C=C,H), 5.81 (1H, d, $J = 1.9$ Hz, C=CH,H), 4.78 (1H, td, $J^1 = 10.9$ Hz, $J^2 = 4.5$ Hz, OCH), 3.87 (2H, s, NCH$_2$Ph), 3.58 (2H, s, NCH$_2$C=C), 3.32 (2H, s, NCH$_2$CO$_2$X$_c$), 2.07-2.00 (1H,
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m, mentholate, 1.94-1.79 (1H, m, mentholate), 1.74-1.67 (2H, m, mentholate), 1.61-1.47 (1H, m, mentholate), 1.53 (9H, s, C(CH_{3})_{3}), 1.44-1.34 (1H, m, mentholate), 1.17-0.88 (3H, m, mentholate), 0.94 (3H, d, J = 6.5 Hz, CH(CH_{3})_{2}), 0.92 (3H, d, J = 6.5 Hz, CH(CH_{3})_{2}), 0.81 (3H, d, J = 6.8 Hz, CHCH_{3}); ^{13}C NMR (75.5 MHz, CDCl_{3}) \delta 170.0, 165.2, 138.7, 138.0, 127.7, 127.2, 126.0, 124.3, 124.0, 79.5, 73.1, 56.4, 53.7, 52.6, 46.0, 40.0, 33.2, 29.9, 27.1, 25.2, 21.3, 19.7, 15.3; HRMS (ESI) calcd for C_{27}H_{42}NO_{4} [M+H]^+ : m/z 444.3114, found 444.3099; Anal. calcd for C_{27}H_{41}NO_{4}: C 73.1, H 9.32, N 3.16, found: C 73.4, H 9.41, N 3.27.

5.3.11: 2-(benzyl(2-(tert-butoxycarbonyl)allyl)amino)acetic acid 295

\[
\begin{align*}
\text{BnHN} & \xrightarrow{\text{NaH}} \xrightarrow{\text{THF, 0 \degree C to r.t.}} \text{BnHN} & \xrightarrow{\text{\text{BuO}}} \xrightarrow{\text{NaH}} \xrightarrow{\text{THF, 0 \degree C to r.t.}} \text{BnHN} & \xrightarrow{\text{\text{BuO}}} \\
& \xrightarrow{\text{\text{\text{BuO}}}} \xrightarrow{\text{\text{\text{BuO}}}} \\
& \xrightarrow{\text{\text{\text{BuO}}}} \xrightarrow{\text{\text{\text{BuO}}}} \\
& \xrightarrow{\text{\text{\text{BuO}}}} \xrightarrow{\text{\text{\text{BuO}}}} \\
& \xrightarrow{\text{\text{\text{BuO}}}} \xrightarrow{\text{\text{\text{BuO}}}} \\
& \xrightarrow{\text{\text{\text{BuO}}}} \xrightarrow{\text{\text{\text{BuO}}}} \\
& \xrightarrow{\text{\text{\text{BuO}}}} \xrightarrow{\text{\text{\text{BuO}}}} \\
& \xrightarrow{\text{\text{\text{BuO}}}} \xrightarrow{\text{\text{\text{BuO}}}} \\
& \xrightarrow{\text{\text{\text{BuO}}}} \xrightarrow{\text{\text{\text{BuO}}}} \\
& \xrightarrow{\text{\text{\text{BuO}}}} \xrightarrow{\text{\text{\text{BuO}}}} \\
\end{align*}
\]

\(N\)-Benzylglycine 294 (250 mg, 1.51 mmol) was added to a solution of sodium hydride (60% dispersion in mineral oil) (121 mg, 3.26 mmol) in tetrahydrofuran (15 mL) at 0 \degree C. The resulting solution was stirred at 0 \degree C for 1 hour before the addition of tert-butyl 2-(bromomethyl)acrylate 255 (266 mg, 1.38 mmol). The reaction mixture was allowed to stir for 24 hours at ambient temperature. The reaction mixture was dissolved in DCM (50 mL) and acidified with 1 M HCl (aq) (10 mL). The organic phase was extracted, dried over MgSO_{4} and concentrated \textit{in vacuo}. The residue was purified by column chromatography (10:1 ethyl acetate:methanol) to give the desired product as a colourless viscous oil (115 mg, 25%); \(R_f\) (10:1 ethyl acetate:methanol) 0.15; IR (neat, cm\(^{-1}\)) \(\nu\) 3238 (O-H), 1702 (C=O), 1636 (C=C); \(^1\)H NMR (300 MHz, CDCl_{3}) \(\delta\) 10.40 (1H, br s, CO\(_2\)H), 7.35-7.22 (5H, m, Ar), 6.28 (1H, s, C=CHH), 5.79 (1H, s, C=CHH), 3.70 (2H, s, NCH\(_2\)C=C), 3.45 (2H, s, NCH\(_2\)Ph), 3.25 (2H, s, NCH\(_2\)CO\(_2\)H), 1.54 (9H, s, C(CH\(_3\))\(_3\)); ^{13}C NMR (75.5 MHz, CDCl_{3}) \(\delta\) 172.3, 166.4, 137.8, 137.0, 129.9, 129.4, 129.2, 128.3, 82.6, 58.1, 57.7, 55.7, 28.4; HRMS (ESI) calcd for C\(_{17}\)H\(_{22}\)NO\(_4\) [M-H]^- : m/z 304.1549, found 304.1535.
5.3.12: General Procedure for the Coupling of Chiral Auxiliaries and 295

\[
\begin{array}{ccc}
\text{Bn} & \text{N} & \text{CO}_2\text{H} \\
\text{BuO} & \text{BuO} & \text{O} \\
\text{Xc} & \text{O} & \text{Bn} \\
\end{array}
\xleftarrow{\text{DCM, 0 °C - r.t.}}
\xrightarrow{16 \text{ h}}
\begin{array}{ccc}
\text{Bn} & \text{N} & \text{Xc} \\
\text{BuO} & \text{BuO} & \text{O} \\
\end{array}
\]

To a stirred solution of 2-(benzyl(2-(tert-butoxycarbonyl)allyl)amino)acetic acid 295 (611 mg, 2 mmol) in dichloromethane (10 mL) was added dicyclohexycarbodiimide (413 mg, 2 mmol) and \(N, N\)-dimethylaminopyridine (12.2 mg, 0.1 mmol, 5 mol%). The resulting solution was stirred at 0 °C for 1 hour before the addition of alcohol (2.2 mmol). The reaction mixture was stirred at ambient temperature for 16 hours. The reaction mixture was dissolved in DCM (100 mL) and washed with water (2 x 100 mL) and saturated brine solution (100 mL). The organic phase was extracted, dried over MgSO$_4$ and concentrated in vacuo. The mixture was purified by flash column chromatography.

5.3.13: (\textit{R}-)\textit{tert}-butyl 2-((benzyl(2-(4,4-dimethyl-2-oxotetrahydrofuran-3-yloxy)-2-oxoethyl)amino)methyl)acrylate 296

\[
\begin{array}{ccc}
\text{BuO} & \text{Bn} & \text{O} \\
\text{O} & \text{O} & \text{BuO} \\
\text{O} & \text{O} & \text{O} \\
\end{array}
\]

\((\textit{R})\)-Pantolactone 298 (286 mg, 2.2 mmol) was reacted under the general procedure and purified by flash column chromatography (10:1 petrol:ethyl acetate) to give the desired compound as a colourless oil (500 mg, 60%); \(R_f\) (10:1 petrol:ethyl acetate) 0.09; \([\alpha]_D^{14} +2.0\) (c 1.6, CHCl$_3$); IR (neat, cm$^{-1}$) \(v\) 2977, 2933 (C-H), 1794, 1756, 1709 (C=O), 1636 (C=C); $^1$H NMR (300 MHz, CDCl$_3$) \(\delta\) 7.37-7.22 (5H, m, Ar), 6.19 (1H, d, \(J = 1.9\) Hz, C=CH$_2$), 5.80 (1H, d, \(J = 1.9\) Hz, C=CHH), 5.41 (1H, s, OCH), 4.05 (2H, s, NCH$_2$COX$_c$), 3.88 (2H, s, NCH$_2$Ph), 3.59 (2H, s, NCH$_2$C=C), 3.54 (1H, d, \(J = 17.3\) Hz, OCH$_2$C(CH$_3$)$_2$), 3.46 (1H, d, \(J = 17.3\) Hz, OCH$_2$C(CH$_3$)$_2$), 1.52 (9H, s, C(CH$_3$)$_3$), 1.23 (3H, s, C(CH$_3$)$_2$), 1.10 (3H, s, C(CH$_3$)$_2$); $^{13}$C NMR (75.5 MHz, CDCl$_3$) \(\delta\) 171.1, 169.2, 165.2, 138.4, 137.6, 127.8, 127.3, 126.2, 124.4, 79.7, 75.2, 73.9, 56.3, 53.6, 52.0, 39.1, 27.1, 22.0, 19.0; HRMS (ESI) calcd for C$_{23}$H$_{31}$NNaO$_6$ [M+Na] : \(m/z\) 440.2049, found 440.2044.
5.3.14: (S)-tert-butyl 2-((benzyl(2-oxo-2-(1-phenylethoxy)ethyl)amino)methyl)acrylate

(S)-1-Phenylethanol 299 (266 µL, 2.2 mmol) was reacted under the general procedure and purified by flash column chromatography (15:1 petrol:ethyl acetate) to give the desired compound as a colourless oil (398 mg, 49%); \( R_f (10:1 \text{ petrol:ethyl acetate}) = 0.30; [\alpha]^D_{24} = -29.7 \) (c 1.7, CHCl₃); IR (neat, cm⁻¹) ν 2981, 2933 (C-H), 1745, 1711 (C=O), 1636 (C=C); \(^1\)H NMR (300 MHz, CDCl₃) \( \delta \) 7.39-7.20 (10H, m, Ar), 6.14 (1H, s, C=CHH), 5.93 (1H, q, \( J = 6.8 \) Hz, OCH(Ph)Me), 5.75 (1H, s, C=CHH), 3.81 (2H, s, NCH₂Ph), 3.53 (2H, s, NCH₂C=C), 3.37 (1H, d, \( J = 17.3 \) Hz, NCH₂COXₗ), 3.31 (1H, d, \( J = 17.3 \) Hz, NCH₂COXₗ), 1.54 (3H, d, \( J = 6.8 \) Hz, CHCH₃), 1.49 (9H, s, C(CH₃)₃); \(^{13}\)C NMR (75.5 MHz, CDCl₃) \( \delta \) 171.1, 166.7, 142.0, 140.0, 139.4, 129.2, 129.0, 128.6, 128.3, 127.5, 126.5, 125.6, 81.0, 72.7, 57.8, 55.1, 54.1, 28.5, 22.7; HRMS (ESI) calcd for C₂₅H₃₁NNaO₄ \([\text{M+Na}]^+\) : \( m/z \) 432.2151, found 432.2146.
Chapter 5

5.4 Molybdenum-Catalysed Reductive Dieckmann Condensation

5.4.1: General Procedure for the Molybdenum-Catalysed Reductive Dieckmann Condensation

To a solution of molybdenum hexacarbonyl (6.6 mg, 0.025 mmol, 5 mol%) and \(N\)-methylmorpholine \(N\)-oxide monohydrate (5.9 mg, 0.044 mmol, 9 mol%) in tetrahydrofuran (3 mL) was added β-substituted acrylate (0.5 mmol) followed by phenylsilane (92 µL, 0.75 mmol). The reaction mixture was stirred at 80 °C for 16 hours. After cooling to room temperature the reaction mixture was dissolved in diethyl ether (25 mL) and washed with water (2 x 25 mL) and saturated brine (25 mL). The organic phase was extracted, dried over \(\text{MgSO}_4\) and concentrated in vacuo. The residue was purified by flash column chromatography.

5.4.2: tert-butyl 1-benzyl-3-methyl-4-oxopyrrolidine-3-carboxylate 258

tert-Butyl 2-((benzyl(2-ethoxy-2-oxoethyl)amino)methyl)acrylate 222 (167 mg, 0.5 mmol) was reacted under the general procedure and purified by flash column chromatography (12:1 petrol:diethyl ether) to give the desired product as a colourless oil (128 mg, 88%); \(R_f\) (12:1 petrol:diethyl ether) 0.19; IR (neat, cm\(^{-1}\)) ν 2979, 2935, 2797 (C-H), 1766, 1729 (C=O); \(^1\)H NMR (300 MHz, CDCl\(_3\)) δ 7.34-7.24 (5H, m, Ar), 3.71 (2H, s, NCH\(_2\)Ph), 3.33 (1H, d, \(J = 9.4\) Hz, NCH\(_2\)C(Me)CO\(_2\)tBu), 3.20 (1H, d, \(J = 17.0\) Hz, NCH\(_2\)C=O), 3.00 (1H, d, \(J = 17.0\) Hz, NCH\(_2\)C=O), 2.68 (1H, d, \(J = 9.4\) Hz, NCH\(_2\)C(Me)CO\(_2\)tBu), 1.44 (9H, s, C(CH\(_3\))\(_3\)), 1.35 (3H, s, CH\(_3\)); \(^{13}\)C NMR (75.5 Hz, CDCl\(_3\)) δ 210.9, 170.7, 138.0, 128.9, 128.8, 127.8, 82.4, 62.9, 61.3, 60.3, 58.4, 28.3, 18.2; HRMS (ESI) calcd for C\(_{17}\)H\(_{23}\)NNaO\(_3\) [M+Na]\(^+\): \(m/z\) 312.1576, found 312.1560; Anal. calcd for C\(_{17}\)H\(_{23}\)NO\(_3\): C 70.6, H 8.01, N 4.84, found: C 70.4, H 8.09, N 4.81; Diacel Chiralcel OJ, hexane/propan-2-ol (99:1), 0.5 mL min\(^{-1}\), \(t_R\) = 15.3 and 16.6 mins.
5.4.3: di-tert-butyl 3-methyl-4-oxopyrrolidine-1,3-dicarboxylate 249

![Chemical structure of di-tert-butyl 3-methyl-4-oxopyrrolidine-1,3-dicarboxylate]

tert-Butyl 2-((tert-butoxycarbonyl(2-ethoxy-2-oxoethyl)amino)methyl)acrylate 256 (172 mg, 0.5 mmol) was reacted under the general procedure and purified by flash column chromatography (10:1 petrol:ethyl acetate) to give the desired product, a colourless oil, a 1:1 mixture of rotamers (91.4 mg, 61%); \( R_f \) (10:1 petrol:ethyl acetate) 0.28; IR (neat, cm\(^{-1}\)) \( v \) 2977, 2928 (C-H), 1753, 1723, 1699 (C=O); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 4.18 and 4.16 (1H, d, \( J = 12.1 \) Hz, NC\( \text{H}_2\)C(Me)CO\(_2\)tBu), 4.03 and 3.98 (1H, d, \( J = 19.2 \) Hz, NC\( \text{H}_2\)C=O), 3.71 (1H, d, \( J = 19.2 \) Hz, NC\( \text{H}_2\)C=O), 3.36 (1H, d, \( J = 12.1 \) Hz, NC\( \text{H}_2\)C(Me)CO\(_2\)tBu), 1.45 (9H, s, C(CH\(_3\))\(_3\)), 1.40 (9H, s, C(CH\(_3\))\(_3\)), 1.30 (3H, s, CH\(_3\)); \(^{13}\)C NMR (75.5 Hz, CDCl\(_3\)) \( \delta \) 209.0 and 208.3, 169.5, 154.5, 83.2, 81.0, 57.5 and 56.9, 55.1 and 54.4, 53.1 and 52.6, 28.8, 28.1, 17.7; HRMS (ESI) calcd for C\(_{15}\)H\(_{25}\)NNaO\(_5\) [M+Na]\(^+\) \( m/z \) 322.1630, found 322.1632.

5.4.4: tert-butyl 1-allyl-3-methyl-4-oxopyrrolidine-3-carboxylate 259

![Chemical structure of tert-butyl 1-allyl-3-methyl-4-oxopyrrolidine-3-carboxylate]

tert-Butyl 2-((allyl(2-methoxy-2-oxoethyl)amino)methyl)acrylate 257 (134.7 mg, 0.5 mmol) was reacted under the general procedure and purified by flash column chromatography (20:1 petrol:ethyl acetate) to give the desired product as a colourless oil (61.0 mg, 51%); \( R_f \) (20 petrol:ethyl acetate) 0.26; IR (neat, cm\(^{-1}\)) \( v \) 2983, 2936, 2800 (C-H), 1764, 1725 (C=O); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 5.84 (1H, ddt, \( J_1 = 17.0 \) Hz, \( J_2 = 10.2 \) Hz, \( J_3 = 6.4 \) Hz, NCH\(_2\)C=CH\(_2\)), 5.23 (1H, dd, \( J_1 = 17.0 \) Hz, \( J_2 = 1.9 \) Hz, NCH\(_2\)CH=CH\(_2\)), 5.15 (1H, dd, \( J_1 = 10.2 \) Hz, \( J_2 = 1.9 \) Hz, NCH\(_2\)CH=CH\(_2\)), 3.28 (1H, d, \( J = 9.4 \) Hz, NCH\(_2\)C(Me)CO\(_2\)tBu), 3.15 (2H, d, \( J = 6.4 \) Hz, NCH\(_2\)CH=CH\(_2\)), 3.12 (1H, d, \( J = 17.0 \) Hz, NCH\(_2\)C=O), 3.0 (1H, d, \( J = 17.0 \) Hz, NCH\(_2\)C=O), 2.70 (1H, d, \( J = 9.4 \) Hz, NCH\(_2\)C(Me)CO\(_2\)tBu), 1.42 (9H, s, C(CH\(_3\))\(_3\)), 1.33 (3H, s, CH\(_3\)); \(^{13}\)C NMR (75.5 MHz, CDCl\(_3\)) \( \delta \) 211.0, 170.7, 134.8, 118.1, 82.4, 62.9, 61.2, 59.1, 58.2, 28.2, 18.4; HRMS (ESI) calcd for C\(_{13}\)H\(_{21}\)NNaO\(_3\) [M+Na]\(^+\) \( m/z \) 262.1419, found 262.1417.
5.4.5: tert-butyl 1,3-dimethyl-4-oxopyrrolidine-3-carboxylate 260

![Chemical Structure](image)

tert-Butyl 2-(((2-ethoxy-2-oxoethyl)methylamino)methyl)acrylate 218 (129 mg, 0.5 mmol) was reacted under the general procedure and purified by flash column chromatography (4:1 petrol:ethyl acetate) to give the desired product as a colourless oil (71.8 mg, 67%); $R_f$ (4:1 petrol:ethyl acetate) 0.26; IR (neat, cm$^{-1}$) ν 2979, 2937, 2783 (C-H), 1766, 1729 (C=O); $^1$H NMR (300 MHz, CDCl$_3$) δ 3.23 (1H, d, $J = 9.4$ Hz, NCH$_2$C(Me)CO$_2$Bu), 3.10 (1H, d, $J = 17.0$ Hz, NCH$_2$C=O), 2.99 (1H, d, $J = 17.0$ Hz, NCH$_2$C=O), 2.68 (1H, d, $J = 9.4$ Hz, NCH$_2$C(Me)CO$_2$Bu), 2.40 (3H, s, NCH$_3$), 1.43 (9H, s, C(CH$_3$)$_3$), 1.33 (3H, s, CH$_3$); $^{13}$C NMR (75.5, CDCl$_3$) δ 211.3, 170.5, 82.4, 65.2, 63.2, 58.8, 43.0, 28.2, 18.6; HRMS (ESI) calcd for C$_{11}$H$_{19}$NNaO$_3$ [M+Na]$^+$ : $m/z$ 236.1263, found 236.1259.
5.5 Asymmetric Molybdenum-Catalysed Reductive Dieckmann Condensation

5.5.1: Ligation of molybdenum

A solution of molybdenum hexacarbonyl (6.6 mg, 0.025 mmol), N-methylmorpholine N-oxide monohydrate (5.9 mg, 0.044 mmol) and (+)-dolefin 266 (15.5 mg, 0.05 mmol) was stirred in tetrahydrofuran (1 mL) for 45 minutes at 80 °C. After cooling to ambient temperature tert-butyl 2-(((2-ethoxy-2-oxoethyl)(1-phenylethyl)amino)methyl)acrylate 222 (167 mg, 0.5 mmol) and phenylsilane (92 µL, 0.75 mmol). The reaction mixture was stirred at 80 °C for 16 hours. After cooling to room temperature the reaction mixture was dissolved in diethyl ether (25 mL) and washed with water (2 x 25 mL) and saturated brine (25 mL). The organic phase was extracted, dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (12:1 petrol:diethyl ether) to give the desired product 258 as a colourless oil (127 mg, 88%); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 °C): tᵣ = 15.3 min, tᵣ = 16.5 min, 0% ee. Spectroscopic data identical to that previously reported (cf. 5.9.1).

5.5.2: tert-butyl 3-methyl-4-oxo-1-((R)-1-phenylethyl)pyrrolidine-3-carboxylate 276

To a solution of molybdenum hexacarbonyl (6.6 mg, 0.025 mmol, 5 mol%) and N-methylmorpholine N-oxide monohydrate (5.9 mg, 0.044 mmol, 9 mol%) in tetrahydrofuran (3 mL) was added (R)-tert-butyl 2-(((2-ethoxy-2-oxoethyl)(1-phenylethyl)amino)
methyl)acrylate 275 (174 mg, 0.5 mmol) followed by phenylsilane (92 µL, 0.75 mmol). The reaction mixture was stirred at 80 °C for 16 hours. After cooling to room temperature the reaction mixture was dissolved in diethyl ether (25 mL) and washed with water (2 x 25 mL) and saturated brine (25 mL). The organic phase was extracted, dried over MgSO4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (12:1 petrol:ethyl acetate) to give the desired product, a colourless oil, as an inseparable 1:1 mixture of diastereomers (140.1 mg, 92%); *Rf* (12:1 petrol:ethyl acetate) 0.22; IR (neat, cm⁻¹) ν 2976, 2934 (C-H), 1764, 1728 (C=O). ¹H NMR (300 MHz, CDCl₃) δ 7.33-7.22 (5H, m, Ar), 3.36 (0.5H, q, *J* = 6.8 Hz, NCH₂), 3.33 (0.5H, q, *J* = 6.8 Hz, NCH₂), 3.30 (0.5H, d, *J* = 17.0 Hz, NCH₂CO), 3.27 (0.5H, d, *J* = 9.4 Hz, NCH₂(C(Me)CO₂)²Bu), 3.23 (0.5H, d, *J* = 9.4 Hz, NCH₂(C(Me)CO₂)²Bu), 3.07 (1H, s, NCH₂CO), 2.87 (0.5H, d, *J* = 17.0 Hz, NCH₂CO), 2.58 (0.5H, d, *J* = 9.4 Hz, NCH₂(C(Me)CO₂)²Bu), 2.54 (0.5H, d, *J* = 9.4 Hz, NCH₂(C(Me)CO₂)²Bu), 1.44 (4.5H, s, C(CH₃)₃), 1.43 (4.5H, s, C(CH₃)₃), 1.36 (1.5H, d, *J* = 6.8 Hz, NCHCH₃), 1.35 (1.5H, d, *J* = 6.8 Hz, NCHCH₃), 1.32 (1.5H, s, C(CO₂)²BuCH₃), 1.29 (1.5H, s, C(CO₂)²BuCH₃); ¹³C NMR (75.5 MHz, CDCl₃) δ 211.1 (2C), 170.8 and 170.7, 144.3 (2C), 128.9 (2C), 127.7 (2C), 127.4 (2C), 82.3 and 82.2, 65.3 and 65.2, 61.7 and 61.6, 60.5 and 60.4, 58.3 (2C), 28.5 and 28.3, 22.8 (2C), 18.1 and 17.9; HRMS (ESI) calcd for C₁₈H₂₆NO₃ [M+H]+: *m/z* 304.1913, found 304.1912.

5.5.3: Reductive Dieckmann Condensation of 292

To a solution of molybdenum hexacarbonyl (6.6 mg, 0.025 mmol, 5 mol%) and N-methylmorpholine N-oxide monohydrate (5.9 mg, 0.044 mmol, 9 mol%) in tetrahydrofuran (3 mL) was added tert-butyl 2-((benzyl(2-((1S,2R,5S)-2-isopropyl-5-methylecyclohexyloxy)-2-oxoethyl)amino)methyl) acrylate 292 (222 mg, 0.5 mmol) followed by phenylsilane (92 µL, 0.75 mmol). The reaction mixture was stirred at 80 °C for 16 hours. After cooling to room temperature the reaction mixture was dissolved in diethyl ether (25 mL) and washed with water (2 x 25 mL) and saturated brine (25 mL). The organic phase was extracted, dried over MgSO₄ and concentrated *in vacuo*. The residue was
purified by flash column chromatography (12:1 petrol:diethyl ether) to give the desired product 258 as a colourless oil (115 mg, 79%), followed by (+)-menthol 293 as colourless crystals (93.3 mg, 60%).

Data for 258: HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 °C): $t_R$ (minor) = 18.4 min, $t_R$ (major) = 20.4 min, 44% ee. All other spectroscopic data identical to that previously reported (cf. 5.9.1).

Data for 293: $^1$H NMR (300 MHz, CDCl$_3$) δ 3.38-3.30 (1H, m), 2.15 (1H, sept.d, $J^1$ = 6.8 Hz, $J^2$ = 2.6 Hz), 1.95-1.88 (2H, m), 1.64-1.53 (2H, m), 1.45-1.29 (1H, m), 1.11-1.02 (1H, m), 0.99-0.81 (3H, m), 0.88 (3H, d, $J = 6.8$ Hz), 0.87 (3H, d, $J = 6.8$ Hz), 0.76 (3H, d, $J = 7.2$ Hz); $^{13}$C NMR (75.5 MHz, CDCl$_3$) δ 71.3, 50.0, 45.0, 34.5, 31.6, 25.6, 23.0, 22.1, 20.9, 16.0. 293 is commercially available.

### 5.5.4: Reductive Dieckmann Condensation of 296

To a solution of molybdenum hexacarbonyl (5.4 mg, 0.02 mmol, 5 mol%) and N-methylmorpholine $N$-oxide monohydrate (4.8 mg, 0.033 mmol, 9 mol%) in tetrahydrofuran (3 mL) was added (R)-tert-butyl 2-((benzyl(2-(4,4-dimethyl-2-oxotetrahydrofuran-3-yloxy)-2-oxoethyl)amino)methyl)acrylate 296 (170 mg, 0.41 mmol) followed by phenylsilane (75 µL, 0.62 mmol). The reaction mixture was stirred at 80 °C for 16 hours. After cooling to room temperature the reaction mixture was dissolved in diethyl ether (25 mL) and washed with water (2 x 25 mL) and saturated brine (25 mL). The organic phase was extracted, dried over MgSO$_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (12:1 petrol:diethyl ether) to give the desired product 258 as a colourless oil (76.4 mg, 65%); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 °C): $t_R$ (minor) = 15.8 min, $t_R$ (major) = 17.3 min, 9% ee. Spectroscopic data identical to that previously reported (cf. 5.9.1).
5.5.5: Reductive Dieckmann Condensation of 297

![Reductive Dieckmann Condensation of 297](image)

To a solution of molybdenum hexacarbonyl (6.6 mg, 0.025 mmol, 5 mol%) and N-methylmorpholine N-oxide monohydrate (5.9 mg, 0.044 mmol, 9 mol%) in tetrahydrofuran (3 mL) was added tert-butyl (S)-tert-butyl 2-((benzyl(2-oxo-2-(1-phenylethoxy)ethyl)amino)methyl)acrylate 292 (205 mg, 0.5 mmol) followed by phenylsilane (92 µL, 0.75 mmol). The reaction mixture was stirred at 80 °C for 16 hours. After cooling to room temperature the reaction mixture was dissolved in diethyl ether (25 mL) and washed with water (2 x 25 mL) and saturated brine (25 mL). The organic phase was extracted, dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (12:1 petrol:diethyl ether) to give the desired product 258 as a colourless oil (94.9 mg, 66%); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 °C): tᵣ (minor) = 15.3 min, tᵣ (major) = 16.7 min, 2% ee. Spectroscopic data identical to that previously reported (cf. 5.9.1).

5.5.6: Reductive Dieckmann Condensation of 292 Mediated by Diphenylsilane

![Reductive Dieckmann Condensation of 292 Mediated by Diphenylsilane](image)

To a solution of molybdenum hexacarbonyl (6.6 mg, 0.025 mmol, 5 mol%) and N-methylmorpholine N-oxide monohydrate (5.9 mg, 0.044 mmol, 9 mol%) in tetrahydrofuran (3 mL) was added tert-butyl 2-((benzyl(2-((1S,2R,5S)-2-isopropyl-5-methylocyclohexyloxy)-2-oxoethyl)amino)methyl)acrylate 292 (222 mg, 0.5 mmol) followed by diphenylsilane (139 µL, 0.75 mmol). The reaction mixture was stirred at 80 °C for 16 hours. After cooling to room temperature the reaction mixture was dissolved in diethyl ether (25 mL) and washed with water (2 x 25 mL) and saturated brine (25 mL). The organic phase was extracted, dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (12:1 petrol:diethyl ether) to give the desired...
product 258 as a colourless oil (127 mg, 85%), followed by (+)-menthol 293 as colourless crystals (96.8 mg, 62%).

Data for 258: HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 °C): $t_R$ (minor) = 16.1 min, $t_R$ (major) = 17.6 min, 20% ee. All other spectroscopic data identical to that previously reported (cf. 5.9.1).

Data for 293: All data identical to that previously reported (cf. 5.5.3).
5.6 Palladium-Catalysed Deallylation

5.6.1: (1S,2R,5S)-2-isopropyl-5-methylcyclohexyl 2-(benzylamino)acetate 291

To a solution of tert-butyl 2-((benzyl(2-((1S,2R,5S)-2-isopropyl-5-methylcyclohexyloxy)-2-oxoethyl)amino)methyl) acrylate 292 (88.7 mg, 0.2 mmol) in chloroform (2 mL) was added diphenylsilane (76 µL, 0.3 mmol), zinc chloride (13.6 mg, 0.1 mmol) and Pd(PPh$_3$)$_4$ (4.6 mg, 0.004 mmol). The reaction mixture was stirred at ambient temperature for 20 hours. The reaction mixture was filtered through a short silica column and concentrated in vacuo to give the desired product as a colourless oil (84.9 mg, 96% yield). Spectroscopic data identical to that previously reported (cf. 5.3.8).
5.7 Rhodium-Catalysed Reduction

5.7.1: tert-butyl 3-(benzyl(2-((1S,2R,5S)-2-isopropyl-5-methylocyclohexyloxy)-2-oxoethyl)amino)-2-methylpropanoate 305 and tert-butyl 3-(benzyl(2-((1S,2R,5S)-2-isopropyl-5-methylocyclohexyloxy)-2-oxoethyl)amino)-2-methylacrylate 306

A solution of [Rh(cod)Cl]2 (2.5 mg, 0.01 mmol, 5 mol% Rh) and triphenylphosphine (6.8 mg, 0.026 mmol 13 mol%) in dichloromethane (2 mL) was stirred under an atmosphere of argon for 30 minutes. tert-Butyl 2-((benzyl(2-((1S,2R,5S)-2-isopropyl-5-methylocyclohexyloxy)-2-oxoethyl)amino)methyl) acrylate 292 (88.7 mg, 0.2 mmol) was added to the solution, followed by dimethylphenylsilane (46 µL, 0.3 mmol) and the resultant mixture was stirred at 60 °C for 16 hours. After cooling to room temperature, water (0.5 mL) was added and was left to stir for 15 minutes before the reaction mixture was dissolved in DCM, dried over MgSO4, concentrate in vacuo. The residue was purified by flash column chromatography (17:1 petrol:diethyl ether) to give 305 as a colourless oil (8.1 mg, 9%) followed by 306 as a colourless oil (34.5 mg, 40%).

Data for 305: RF (17:1 petrol:diethyl ether) 0.28; IR (neat, cm⁻¹) ν 2955, 2979 (C-H), 1730 (C=O); 1H NMR (300 MHz, CDCl3) δ 7.36-7.21 (5H, m, Ar), 4.72 (1H, td, J1 = 10.9 Hz, J2 = 4.5 Hz, OCH), 3.83 (2H, s, NCH2Ph), 3.27 (2H, s, NCH2COXc), 3.00 (1H, dd, J1 = 12.8 Hz, J2 = 9.0 Hz, NCH2CH(Me)CO2tBu), 2.78 (1H, dd, J1 = 12.8 Hz, J2 = 6.4 Hz, NCH2CH(Me)CO2tBu), 2.64-2.52 (1H, m, CH(Me)CO2tBu), 2.03-1.96 (1H, m, mentholate), 1.87-1.75 (1H, m, mentholate), 1.71-1.63 (2H, m, mentholate), 1.50-1.21 (3H, m, mentholate), 1.45 (9H, s, C(CH3)3), 1.03 (3H, d, J = 7.2 Hz, tBuO2CCHCH3), 1.04-0.83 (2H, m, mentholate), 0.91 (3H, d, J = 6.5 Hz, CH(CH3)2), 0.88 (3H, d, J = 6.5 Hz, CH(CH3)2), 0.77 (3H, d, J = 6.8 Hz, CHCH3); 13C NMR (75.5 MHz, CDCl3) δ 176.9, 166.0, 137.0, 129.4, 128.6, 127.5, 80.6, 74.6, 60.1, 59.8, 56.2, 47.4, 41.5, 40.5, 34.6, 31.8, 28.5, 26.6, 23.7, 22.4, 21.2, 16.6, 15.7; HRMS (ESI) calcd for C27H44NO4 [M+H]+: m/z 446.3270, found 446.3271.
Data for 306: $R_f$ (17:1 petrol:diethyl ether) 0.09; $[\alpha]_D^{24} +55.5$ (c 1.4, CHCl$_3$); IR (neat, cm$^{-1}$) v 2956, 2929, 2870 (C-H), 1740, 1683 (C=O), 1628, 1605 (C=C); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.40 (1H, s, C=CHN) 7.39-7.23 (5H, m, Ar), 4.74 (1H, td, $J^1 = 10.9$ Hz, $J^2 = 4.5$ Hz, OCH), 4.48 (2H, s, NCH$_2$Ph), 3.87 (2H, s, NCH$_2$COX$_x$), 3.00 (1H, dd, $J^1 = 12.8$ Hz, $J^2 = 9.0$ Hz, NCH$_2$CH(Me)CO$_2$Bu), 2.78 (1H, dd, $J^1 = 12.8$ Hz, $J^2 = 6.4$ Hz, NCH$_2$CH(Me)CO$_2$Bu), 2.64-2.52 (1H, m, CH(Me)CO$_2$Bu), 2.01-1.94 (1H, m, mentholate), 1.85 (3H, s, CH$_3$C=C), 1.87-1.74 (1H, m, mentholate), 1.70-1.64 (2H, m, mentholate), 1.55-1.26 (2H, m, mentholate), 1.46 (9H, s, C(CH$_3$)$_3$), 1.11-0.83 (3H, m, mentholate), 0.91 (3H, d, $J = 6.5$ Hz, CH(CH$_3$)$_2$), 0.88 (3H, d, $J = 6.5$ Hz, CH(CH$_3$)$_2$), 0.75 (3H, d, $J = 6.8$ Hz, CHCH$_3$); $^{13}$C NMR (75.5 MHz, CDCl$_3$) $\delta$ 170.5, 170.1, 148.0, 137.5, 129.2, 129.0, 128.1, 97.4, 79.1, 75.9, 58.9, 52.8, 47.4, 41.2, 34.5, 31.8, 28.8, 26.6, 23.7, 22.4, 21.1, 16.6, 11.7; HRMS (ESI) calcd for C$_{27}$H$_{44}$NO$_4$ [M+H]$^+$ : m/z 444.3114, found 446.3124.
5.8 Cobalt-Catalysed Reductive Dieckmann Condensation

5.8.1: tert-butyl 1-benzyl-3-methyl-4-oxopyrrolidine-3-carboxylate 258

A solution of Co(acac)$_2$ (2.7 mg, 0.01 mmol, 5 mol%) and tert-butyl 2-((benzyl(2-((1S,2R,5S)-2-isopropyl-5-methylcyclohexyloxy)-2-oxoethyl)amino)methyl)acrylate 292 (88.7 mg, 0.2 mmol) in tetrahydrofuran (3 mL) was stirred at room temperature for 15 minutes before cooling to 0 °C. Diethylzinc (1 M in hexanes) (400 µL, 0.4 mmol) was added to the solution, the reaction mixture was stirred at ambient temperature for 16 hours. 1 M HCl$_{\text{aq}}$ (1 mL) was added to the reaction mixture and the resulting solution was stirred for 15 minutes. The reaction mixture was dissolved in diethyl ether (25 mL) and washed with saturated sodium hydrogen carbonate (2 x 25 mL), water (25 mL) and saturated brine (25 mL). The organic phase was extracted, dried over MgSO$_4$ and concentrated in vacuo. The residue was purified by flashed column chromatography (12:1 petrol:diethyl ether) to give 258 as a colourless oil (25.6 mg, 44%); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 °C): $t_R$ (minor) = 15.4 min, $t_R$ (major) = 16.6 min, 29% ee. All other spectroscopic data identical to that previously reported ($\text{cf.}$ 5.9.1).
5.9 Nickel-Catalysed Reductive Dieckmann Condensation

5.9.1: tert-butyl 1-benzyl-4-oxo-3-propylpyrrolidine-3-carboxylate 310 and tert-butyl 1-benzyl-4-oxo-3-propylpyrrolidine-3-carboxylate 258

A solution of Ni(acac)$_2$ (2.7 mg, 0.01 mmol, 5 mmol%) and tert-butyl 2-((benzyl(2-((1S,2R,5S)-2-isopropyl-5-methylcyclohexyloxy)-2-oxoethyl)amino)methyl)acrylate 292 (88.7 mg, 0.2 mmol) in tetrahydrofuran (3 mL) was stirred at room temperature for 15 minutes before cooling to 0 °C. Diethylzinc (1 M in hexanes) (400 µL, 0.4 mmol) was added to the solution, the reaction mixture was stirred at ambient temperature for 16 hours. 1 M HCl$_{\text{aq}}$ (1 mL) was added to the reaction mixture and the resulting solution was stirred for 15 minutes. The reaction mixture was dissolved in diethyl ether (25 mL) and washed with saturated sodium hydrogen carbonate (2 x 25 mL), water (25 mL) and saturated brine (25 mL). The organic phase was extracted, dried over MgSO$_4$ and concentrated in vacuo. The residue was purified by flashed column chromatography (12:1 petrol:diethyl ether) to give tert-butyl 1-benzyl-4-oxo-3-propylpyrrolidine-3-carboxylate 310 as a colourless oil (18.3 mg, 29% yield) followed by 258 as a colourless oil (38.7 mg, 67%).

Data for 310: $R_f$ (12:1 petrol:diethyl ether) 0.24; IR (neat, cm$^{-1}$) ν 2963, 2933, 2874, 2797 (C-H), 1762, 1725 (C=O); $^1$H NMR (300 MHz, CDCl$_3$) δ 7.31-7.20 (5H, m, Ar-H), 3.70 (1H, d, $J = 13.2$ Hz, NC$_2$H$_2$Ph), 3.64 (1H, d, $J = 13.2$ Hz, NCH$_2$), 3.37 (1H, d, $J = 9.4$ Hz, NCH$_2$C($^\text{Pr}$)CO$_2$Bu), 3.19 (1H, d, $J = 17.0$ Hz, NCH$_2$CO), 2.88 (1H, d, $J = 17.0$ Hz, NCH$_2$CO), 2.64 (1H, d, $J = 9.4$ Hz, NCH$_2$C($^\text{Pr}$)CO$_2$Bu), 1.81 (1H, ddd, $J = 13.9$ Hz, 12.4 Hz, 4.5 Hz, C(CO$_2$Bu)CH$_2$CH$_2$CH$_3$), 1.64 (1H, ddd, $J = 13.9$ Hz, 12.4 Hz, 4.5 Hz, C(CO$_2$Bu)CH$_2$CH$_2$CH$_3$), 1.51-1.34 (1H, m, C(CO$_2$Bu)CH$_2$CH$_2$CH$_3$), 1.42 (9H, s, C(CH$_3$)$_3$), 1.27-1.12 (1H, m, C(CO$_2$Bu)CH$_2$CH$_2$CH$_3$), 0.87 (3H, t, $J = 7.2$ Hz, C(CO$_2$Bu)CH$_2$CH$_2$CH$_3$); $^{13}$C NMR (75.5 MHz, CDCl$_3$) δ 210.1, 169.6, 138.0, 129.3, 128.8, 127.7, 82.3, 62.6, 61.6, 60.4, 60.3, 35.1, 28.3, 18.7, 14.9; HRMS (ESI) calcd for C$_{19}$H$_{28}$NO$_3$ [M+H]$^+$: m/z 318.2069, found 318.2074.
Data for 258: HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 °C): \( t_R \) (minor) = 14.6 min, \( t_R \) (major) = 15.6 min, 18% ee. All other spectroscopic data identical to that previously reported (cf. 5.9.1).
5.10 Copper-Catalysed Reductive Dieckmann Condensation

5.10.1: Reductive Dieckmann Condensation of 292 Mediated by Tetramethyldisiloxane

A solution of Cu(OAc)$_2$ (1.8 mg, 0.01 mmol, 5 mol%) and rac-BINAP (6.4 mg, 0.01 mmol, 5 mol%) in tetrahydrofuran (1 mL) was stirred at ambient temperature for 15 minutes before the addition of tetramethyldisiloxane (53 µL, 0.3 mmol). The resulting solution was stirred for a further 10 minutes, after which, a solution of tert-butyl 2-(((benzyl(2-((1S,2R,5S)-2-isopropyl-5-methylcyclohexyloxy)-2-oxoethyl)amino)methyl) acrylate 292 (88.7 mg, 0.2 mmol) in tetrahydrofuran (2 mL) was added via syringe. The reaction was stirred at 50 °C for 16 hours. The crude reaction mixture was concentrated in vacuo and purified by flash column chromatography (12:1 petrol:diethyl ether) to give 258 as a colourless oil (11.5 mg, 20%); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 °C): $t_R$ (minor) = 17.2 min, $t_R$ (major) = 18.6 min, 41% ee. All other spectroscopic data identical to that previously reported (cf. 5.9.1).

5.10.2: Reductive Dieckmann Condensation of 292 Using Achiral Bisphosphine Ligands

A solution of Cu(OAc)$_2$ (1.8 mg, 0.01 mmol, 5 mol%) and achiral bisphosphine ligand (0.01 mmol, 5 mol%) in tetrahydrofuran (1 mL) was stirred at ambient temperature for 15 minutes before the addition of polymethylhydrosiloxane (20 µL, 0.3 mmol). The resulting solution was stirred for a further 10 minutes, after which, a solution of tert-butyl 2-(((benzyl(2-((1S,2R,5S)-2-isopropyl-5-methylcyclohexyloxy)-2-oxoethyl)amino)methyl) acrylate 292 (88.7 mg, 0.2 mmol) in tetrahydrofuran (2 mL) was added via syringe. The reaction was stirred at 50 °C for 16 hours. The crude reaction mixture was concentrated in vacuo.
vacuo and purified by flash column chromatography (12:1 petrol:diethyl ether) to give 258 as a colourless oil.

5.10.2.1: dppf

dppf (5.7 mg, 0.01 mmol) was reacted under the standard procedure to give the desired product as a colourless oil (24.8 mg, 43% yield); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 °C): $t_R$ (minor) = 17.3 min, $t_R$ (major) = 19.0 min, 36% ee. All other spectroscopic data identical to that previously reported (cf. 5.9.1).

5.10.2.2: rac-BINAP

rac-BINAP (6.2 mg, 0.01 mmol) was reacted under the standard procedure to give the desired product as a colourless oil (34.3 mg, 59% yield); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 °C): $t_R$ (minor) = 14.8 min, $t_R$ (major) = 16.0 min, 48% ee. All other spectroscopic data identical to that previously reported (cf. 5.9.1).

5.10.2.3: dppm

dppm (3.8 mg, 0.01 mmol) was reacted under the standard procedure to give the desired product as a colourless oil (12.3 mg, 21% yield); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 °C): $t_R$ (minor) = 17.1 min, $t_R$ (major) = 18.7 min, 44% ee. All other spectroscopic data identical to that previously reported (cf. 5.9.1).

5.10.2.4: dppe

dppe (4.0 mg, 0.01 mmol) was reacted under the standard procedure to give the desired product as a colourless oil (39.4 mg, 68% yield); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 °C): $t_R$ (minor) = 15.0 min, $t_R$ (major)
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= 16.2 min, 50% ee. All other spectroscopic data identical to that previously reported (cf. 5.9.1).

5.10.2.5: dppp

dppp (4.1 mg, 0.01 mmol) was reacted under the standard procedure to give the desired product as a colourless oil (52.1 mg, 73% yield); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 °C): \( t_R \) (minor) = 15.0 min, \( t_R \) (major) = 16.2 min, 46% ee. All other spectroscopic data identical to that previously reported (cf. 5.9.1).

5.10.2.6: dppb

dppb (4.3 mg, 0.01 mmol) was reacted under the standard procedure to give the desired product as a colourless oil (11.8 mg, 20% yield); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 °C): \( t_R \) (minor) = 17.5 min, \( t_R \) (major) = 19.2 min, 43% ee. All other spectroscopic data identical to that previously reported (cf. 5.9.1).

5.10.2.7: dcpe

dcpe (4.2 mg, 0.01 mmol) was reacted under the standard procedure to give the desired product as a colourless oil (45.3 mg, 78% yield); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 °C): \( t_R \) (minor) = 15.1 min, \( t_R \) (major) = 16.2 min, 40% ee. All other spectroscopic data identical to that previously reported (cf. 5.9.1).

5.10.2.8: Xantphos

Xantphos 311 (5.8 mg, 0.01 mmol) was reacted under the standard procedure to give the desired product as a colourless oil (36.1 mg, 62% yield); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 °C): \( t_R \) (minor) = 15.2 min, \( t_R \) (major)
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= 16.4 min, 30% ee. All other spectroscopic data identical to that previously reported (cf. 5.9.1).

5.10.3: Reductive Dieckmann Condensation of 292 Using Chiral Bisphosphine Ligands

A solution of Cu(OAc)$_2$ (1.8 mg, 0.01 mmol, 5 mol%) and chiral bisphosphine ligand (0.01 mmol, 5 mol%) in tetrahydrofuran (1 mL) was stirred at ambient temperature for 15 minutes before the addition of polymethylhydrosiloxane (20 µL, 0.3 mmol). The resulting solution was stirred for a further 10 minutes, after which, a solution of tert-butyl 2-((benzyl(2-((1S,2R,5S)-2-isopropyl-5-methylcyclohexyloxy)-2-oxoethyl)amino)methyl)acrylate 292 (88.7 mg, 0.2 mmol) in tetrahydrofuran (2 mL) was added via syringe. The reaction was stirred at 50 °C for 16 hours. The crude reaction mixture was concentrated in vacuo and purified by flash column chromatography (12:1 petrol:diethyl ether) to give 258 as a colourless oil.

5.10.3.1: (R)-BINAP

(R)-BINAP (R)-52 (6.2 mg, 0.01 mmol) was reacted under the standard procedure to give the desired product as a colourless oil (15.5 mg, 27% yield); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 °C): $t_R$ (minor) = 15.4 min, $t_R$ (major) = 16.8 min, 79% ee. All other spectroscopic data identical to that previously reported (cf. 5.9.1).

5.10.3.2: (S)-BINAP

(S)-BINAP (S)-52 (6.2 mg, 0.01 mmol) was reacted under the standard procedure to give the desired product as a colourless oil (36.1 mg, 62% yield); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 °C): $t_R$ (minor) = 15.5 min, $t_R$ (major)
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= 16.8 min, 14% ee. All other spectroscopic data identical to that previously reported (cf. 5.9.1).

5.10.3.3: \((R)-\text{Tol-BINAP}\)

\((R)-\text{Tol-BINAP} 312\) (6.8 mg, 0.01 mmol) was reacted under the standard procedure to give the desired product as a colourless oil (26.1 mg, 45% yield); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 °C): \(t_R\) (minor) = 15.1 min, \(t_R\) (major) = 16.3 min, 75% ee. All other spectroscopic data identical to that previously reported (cf. 5.9.1).

5.10.3.4: \((R)-\text{Xylyl-BINAP}\)

\((R)-\text{Xylyl-BINAP} 313\) (7.4 mg, 0.01 mmol) was reacted under the standard procedure to give the desired product as a colourless oil (46.0 mg, 79% yield); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 °C): \(t_R\) (minor) = 14.8 min, \(t_R\) (major) = 15.9 min, 35% ee. All other spectroscopic data identical to that previously reported (cf. 5.9.1).

5.10.3.5: \((R,R)-\text{iPr-DuPhos}\)

\((R,R)-\text{iPr-DuPhos} 315\) (4.2 mg, 0.01 mmol) was reacted under the standard procedure to give the desired product as a colourless oil (38.2 mg, 66% yield); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 °C): \(t_R\) (minor) = 17.7 min, \(t_R\) (major) = 19.4 min, 46% ee. All other spectroscopic data identical to that previously reported (cf. 5.9.1).

5.10.3.6: \((R,R)-\text{Me-DuPhos}\)

\((R,R)-\text{Me-DuPhos} 314\) (3.1 mg, 0.01 mmol) was reacted under the standard procedure to give the desired product as a colourless oil (39.5 mg, 68% yield); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 °C): \(t_R\) (minor) = 15.2 min, \(t_R\)
(major) = 16.3 min, 86% ee. All other spectroscopic data identical to that previously reported (cf. 5.9.1).

5.10.3.7: \((R)-(S)-\text{Josiphos}\)

\((R)-(S)-\text{Josiphos} \) 316 (6.4 mg, 0.01 mmol) was reacted under the standard procedure to give the desired product as a colourless oil (49.7 mg, 86% yield); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 °C): \(t_R\) (minor) = 16.0 min, \(t_R\) (major) = 17.3 min, 45% ee. All other spectroscopic data identical to that previously reported (cf. 5.9.1).

5.10.3.8: \((S)-(R)-\text{Josiphos}\)

\((S)-(R)-\text{Josiphos} \) 317 (6.4 mg, 0.01 mmol) was reacted under the standard procedure to give the desired product as a colourless oil (57.6 mg, 99% yield); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 °C): \(t_R\) (minor) = 137 min, \(t_R\) (major) = 14.8 min, 48% ee. All other spectroscopic data identical to that previously reported (cf. 5.9.1).

5.10.3.9: \((R)-\text{PhanePhos}\)

\((R)-\text{PhanePhos} \) 318 (5.8 mg, 0.01 mmol) was reacted under the standard procedure to give the desired product as a colourless oil (30.4 mg, 53% yield); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 °C): \(t_R\) (minor) = 15.3 min, \(t_R\) (major) = 16.7 min, 15% ee. All other spectroscopic data identical to that previously reported (cf. 5.9.1).

5.10.3.10: \((R)-\text{SYNPHOS}\)

\((R)-\text{SYNPHOS} \) 317 (6.4 mg, 0.01 mmol) was reacted under the standard procedure to give the desired product as a colourless oil (30.3 mg, 52% yield); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 °C): \(t_R\) (minor) = 14.8 min, \(t_R\) (major)
= 16.0 min, 65% ee. All other spectroscopic data identical to that previously reported (cf. 5.9.1).

5.10.3.11: (R)-P-Phos

(R)-P-Phos 319 (6.4 mg, 0.01 mmol) was reacted under the standard procedure to give the desired product as a colourless oil (44.9 mg, 78% yield); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 °C): t<sub>R</sub> (minor) = 17.7 min, t<sub>R</sub> (major) = 19.5 min, 63% ee. All other spectroscopic data identical to that previously reported (cf. 5.9.1).

5.10.3.12: (R)-Xylyl-P-Phos

(R)-Xylyl-P-Phos 320 (7.6 mg, 0.01 mmol) was reacted under the standard procedure to give the desired product as a colourless oil (33.7 mg, 58% yield); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 °C): t<sub>R</sub> (minor) = 15.2 min, t<sub>R</sub> (major) = 16.4 min, 91% ee. All other spectroscopic data identical to that previously reported (cf. 5.9.1).

5.10.4: Room Temperature Reductive Dieckmann Condensation of 292

A solution of Cu(OAc)<sub>2</sub> (1.8 mg, 0.01 mmol, 5 mol%) and (R)-Xylyl-P-Phos 320 (6.4 mg, 0.01 mmol, 5 mol%) in tetrahydrofuran (1 mL) was stirred at ambient temperature for 15 minutes before the addition of polymethylhydrosiloxane (20 μL, 0.3 mmol). The resulting solution was stirred for a further 10 minutes, after which, a solution of tert-butyl 2-((benzyl((1S,2R,5S)-2-isopropyl-5-methylcyclohexyloxy)-2-oxoethyl)amino)methyl)acrylate 292 (88.7 mg, 0.2 mmol) in tetrahydrofuran (2 mL) was added via syringe. The reaction was stirred at ambient temperature for 3 hours. The crude reaction mixture was concentrated in vacuo and purified by flash column chromatography (12:1 petrol:diethyl ether) to give 258 as a colourless oil (27.1 mg, 47%); HPLC Diacel Chiralpak OJ,
hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 °C): $t_R$ (minor) = 15.2 min, $t_R$ (major) = 16.4 min, 93% ee; $[\alpha]^D_{24} +19.6$ (c = 1.1, CHCl$_3$). All other spectroscopic data identical to that previously reported (cf. 5.9.1).

5.10.5: Reductive Dieckmann Condensation of 222 Using Chiral Bisphosphine Ligands

![Chemical structure](image)

A solution of Cu(OAc)$_2$ (1.8 mg, 0.01 mmol, 5 mol%) and chiral bisphosphine ligand (0.01 mmol, 5 mol%) in tetrahydrofuran (1 mL) was stirred at ambient temperature for 15 minutes before the addition of polymethylhydrosiloxane (20 µL, 0.3 mmol). The resulting solution was stirred for a further 10 minutes, after which, a solution of tert-butyl 2-((benzyl(2-ethoxy-2-oxoethyl)amino)methyl) acrylate 222 (66.7 mg, 0.2 mmol) in tetrahydrofuran (2 mL) was added via syringe. The reaction was stirred at 50 °C for 16 hours. The crude reaction mixture was concentrated in vacuo and purified by flash column chromatography (12:1 petrol:diethyl ether) to give 258 as a colourless oil.

5.10.5.1: (R,R)-Pr-DuPhos

(R,R)-Pr-DuPhos 315 (4.2 mg, 0.01 mmol) was reacted under the standard procedure to give the desired product as a colourless oil (15.3 mg, 26% yield); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 °C): $t_R$ (minor) = 15.0 min, $t_R$ (major) = 16.3 min, 20% ee. All other spectroscopic data identical to that previously reported (cf. 5.9.1).

5.10.5.2: (R,R)-Me-DuPhos

(R,R)-Me-DuPhos 314 (3.1 mg, 0.01 mmol) was reacted under the standard procedure to give the desired product as a colourless oil (45.6 mg, 79% yield); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 °C): $t_R$ (minor) = 15.3 min, $t_R$
(major) = 16.6 min, 15% ee. All other spectroscopic data identical to that previously reported (cf. 5.9.1).
5.11 General Procedure for the Synthesis of Alkylidene Meldrum’s Acid Derivatives

To a solution of Meldrum’s acid (1.1 equiv) in water was added aldehyde (1.0 equiv). The resulting solution was stirred at 75 °C for 2 hours. After cooling the reaction mixture was filtered via Buckner filtration and washed with water (100 mL) and petrol (100 mL). The resulting solid was recrystallised from hot ethanol to give the desired compound.

5.11.1: 5-(4-methoxybenzylidene)-2,2-dimethyl-[1,3]dioxane-4,6-dione 328a

Meldrum’s acid (4.66 g, 32.3 mmol), p-anisaldehyde (3.58 mL, 29.4 mmol) and water (50 mL) were reacted under the standard procedure to give the desired compound as a yellow crystalline solid (5.58g, 72%); mp (EtOH) 125-126 °C (lit = 127-128 °C); 1H NMR (300 MHz, CDCl₃) δ 8.34 (1H, s, C=CH), 8.19 (2H, d, J = 9.0 Hz, ArH), 6.95 (2H, d, J = 9.0 Hz, ArH), 3.88 (3H, s, OCH₃), 1.76 (6H, s, C(CH₃)₂); 13C NMR (75.5 MHz, CDCl₃) δ 165.0, 164.4, 160.8, 158.3, 138.0, 125.1, 115.0, 111.3, 104.5, 56.1, 27.9; HRMS (ESI) calcd for C₁₄H₁₄NaO₅ [M+Na]^+: m/z 285.0739, found 285.0725. Data identical to literature values.

5.11.2: 5-(4-(Methylthio)benzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione 328b

Meldrum’s acid (1.59 g, 11.0 mmol) and 4-(methylthio)benzaldehyde (1.52 g, 10.0 mmol) and water (20 mL) were reacted under the standard protocol to desired compound as a yellow crystalline solid (2.10 g, 75%); mp (EtOH) 126-128 °C; IR (KBr, cm⁻¹) ν 3099, 2986, 2939 (C-H); 1750, 1711 (C=O); 1H NMR (300 MHz, CDCl₃) δ 8.39 (1H, s, C=CH); 8.11 (2H, d, J 6.8 Hz, ArH); 7.32 (2H, d, J 6.8 Hz, ArH); 2.58 (3H, s, SCH₃), 1.83 (6H, s, C(CH₃)₂); 13C NMR (75.5 MHz, CDCl₃) δ 163.6, 160.1, 157.4, 148.4, 134.6, 127.7, 124.7, 112.4, 104.2, 27.5, 14.4; HRMS (ESI) calcd for C₁₄H₁₃NO₄S
[M+NH₄]⁺: m/z 296.0951, found 296.0951; Anal. calcd for C₁₄H₁₄O₄S: C 60.4, H 5.07, found: C 60.7, H 5.16.

5.11.3: 5-(4-dimethylaminobenzylidene)-2,2-dimethyl-[1,3]dioxane-4,6-dione 328c

Meldrum’s acid (793 mg, 5.5 mmol), 4-dimethylaminobenzaldehyde (746 mg, 5.0 mmol) in water (10 mL) was reacted under standard protocol to give the desired compound as an orange crystalline solid (1.26 g, 92%); mp (EtOH) 174-175 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.31 (1H, s, C=CH), 8.25 (2H, d, J = 9.4 Hz, ArH), 6.70 (2H, d, J = 9.4 Hz, ArH), 3.15 (6H, s, N(CH₃)₂), 1.76 (6H, s, C(CH₃)₂); ¹³C NMR (75.5 MHz, CDCl₃) δ 165.6, 161.9, 158.4, 155.0, 139.4, 120.5, 111.6, 105.4, 103.8, 40.5, 27.7; HRMS (ESI) calcd for C₁₅H₁₈NO₄ [M+H]⁺: m/z 276.1236, found 276.1230. Data identical to literature values.⁵

5.11.4: 5-(benzo-[1,3]dioxol-5-ylmethylene)-2,2-dimethyl-[1,3]dioxane-4,6-dione 328d

Meldrum’s acid (1.25 g, 10.4 mmol), piperonal (1.50 g, 10.0 mmol) in water (20 mL) was reacted under standard protocol to give the desired compound as a yellow crystalline solid (2.54 g, 82%); mp (EtOH) 178-180 °C (lit = 179-180 °C)⁶; ¹H NMR (300 MHz, CDCl₃) δ 8.31 (1H, s, C=CH), 8.06 (1H, d, J = 1.9 Hz, ArH), 7.54 (1H, dd, J¹ = 8.3 Hz, J² = 1.9 Hz, ArH), 6.90 (1H, d, J = 8.3 Hz, ArH), 6.09 (2H, s, OCH₂O), 1.78 (6H, s, C(CH₃)₂); ¹³C NMR (75.5 MHz, CDCl₃) δ 164.3, 160.7, 158.3, 153.6, 148.7, 134.6, 126.8, 112.8, 111.7, 108.9, 104.7, 102.8, 27.9; HRMS (EI) calcd for C₁₄H₁₂NaO₆ [M+Na]⁺: m/z 299.0532, found 299.0534. Data identical to literature values.⁶
5.11.5: 5-(benzo-[1,3]dioxol-4-ylmethylene)-2,2-dimethyl-[1,3]dioxane-4,6-dione 328e

Meldrum’s acid (1.25 g, 10.4 mmol), 2,3-(methyleneedioxy)benzaldehyde (1.50 g, 10.0 mmol) in water (20 mL) was reacted under the standard protocol to give the desired compound as a yellow crystalline solid (2.03 g, 73%); mp (EtOH) 172-174 °C; IR (KBr, cm^{-1}) ν 1740, 1710 (C=O), 1561 (C=C), 1382, 1248 (C-O); ^1H NMR (300 MHz, CDCl₃) δ 8.43 (1H, s, C=C₃H), 7.50 (1H, dd, J₁ = 7.5 Hz, J₂ = 1.5 Hz, ArH), 6.95 (1H, dd, J₁ = 7.5 Hz, J₂ = 1.5 Hz, ArH), 6.88 (1H, t, J = 7.5 Hz, ArH), 6.06 (2H, s, OCH₂O), 1.80 (6H, s, C(CH₃)₂); ^13C NMR (75.5 MHz, CDCl₃) δ 163.2, 160.0, 149.8, 149.6, 148.2, 124.1, 122.1, 166.4, 115.4, 113.1, 105.1, 102.1, 28.0; HRMS (ESI) calcd for C₁₄H₁₂NaO₆ [M+Na]^+: m/z 299.0532, found 299.0530; Anal. calcd for C₁₄H₁₀O₆: C 70.0, H 4.42.

5.11.6: 2,2-dimethyl-5-(3-phenyl-allylidene)-[1,3]dioxane-4,6-dione 328f

Meldrum’s acid (793 mg, 5.5 mmol), cinnamaldehyde (629 µL, 5.0 mmol) and water (10 mL) was reacted under the standard protocol to give the desired product as a yellow crystalline solid (1.12 g, 87%); mp (EtOH) 98-99 °C (lit 101 °C); ^1H NMR (300 MHz, CDCl₃) δ 8.32 (1H, dd, J₁ = 15.1 Hz, J₂ = 12.1 Hz, PhCH₂H), 8.19 (1H, d, J = 12.1 Hz, C=CH), 7.68-7.64 (2H, m, ArH), 7.46-7.39 (4H, m, ArH and PhCH), 1.76 (6H, s, CH₃); ^13C NMR (75.5 MHz, CDCl₃) δ 163.4, 161.2, 158.4, 154.9, 135.3, 132.2, 129.7, 129.6, 124.9, 111.8, 105.2, 28.1; HRMS (ESI) calcd for C₁₅H₁₂NaO₄ [M+Na]^+: m/z 281.0790, found 281.0792. Data identical to literature values.
5.11.7: 5-(3,4-dimethoxybenzylidene)-2,2-dimethyl-[1,3]dioxane-4,6-dione 328g

Meldrum’s acid (1.59 g, 11.0 mmol), 3,4-dimethoxybenzaldehyde (1.66 g, 10 mmol) and water (20 mL) was reacted under the standard protocol to give the desired product as a yellow/orange crystalline solid (2.38 g, 81 %); mp (EtOH) 160-161 °C (lit = 156-158 °C);\(^4\) \(\text{\textsuperscript{1}H NMR (300 MHz, CDCl}_3\text{)} \delta 8.34 \text{ (1H, s, C}=\text{C}=\text{H}), 8.28 \text{ (1H, d, J}= 2.3 \text{ Hz, ArH}), 7.62 \text{ (1H, dd, J}^1 = 8.3 \text{ Hz, J}^2 = 2.3 \text{ Hz, ArH}), 6.92 \text{ (1H, d, J} = 8.3 \text{ Hz, ArH}), 3.97 \text{ (3H, s, OCH}_3\text{), 3.94 (3H, s, OC}=\text{H}_3\text{), 1.77 (6H, s, C}(CH}_3\text{)}_2\text{); 13}\text{C NMR (75.5 MHz, CDCl}_3\text{)} \delta 164.5, 161.0, 158.6, 155.1, 149.1, 133.1, 125.5, 116.1, 111.1, 111.0, 104.6, 56.6, 56.4, 27.9; HRMS (EI) calcd for C\textsubscript{15}H\textsubscript{17}O\textsubscript{6} [M+H\textsuperscript{+}]: m/z 293.1020, found 293.1017. Data identical to literature values.\(^4\)

5.11.8: 5-(2,5-dimethoxybenzylidene)-2,2-dimethyl-[1,3]dioxane-4,6-dione 328h

Meldrum’s acid (1.59 g, 11.0 mmol), 2,5-dimethoxybenzaldehyde (1.66 g, 10 mmol) and water (20 mL) was reacted under standard protocol to give the desired compound as an orange crystalline solid (2.15 g, 73 %); mp (EtOH) 124-125 °C (lit = 120-121 °C);\(^8\) \(\text{\textsuperscript{1}H NMR (300 MHz, CDCl}_3\text{)} \delta 8.72 \text{ (1H, s, C}=\text{C}=\text{H}), 7.67 \text{ (1H, d, J}= 3.0 \text{ Hz, ArH}), 7.08 \text{ (1H, dd, J}^1 = 9.0 \text{ Hz, J}^2 = 3.0 \text{ Hz, ArH}), 6.90 \text{ (1H, d, J} = 9.0 \text{ Hz, ArH}), 3.85 \text{ (3H, s, OCH}_3\text{), 3.79 (3H, s, OCH}_3\text{), 1.80 (6H, s, C}(CH}_3\text{)}_2\text{); 13}\text{C NMR (75.5 MHz, CDCl}_3\text{)} \delta 163.7, 160.5, 154.8, 153.3, 152.8, 122.5, 121.9, 116.5, 115.4, 112.4, 104.8, 56.5, 56.3, 27.9; HRMS (EI) calcd for C\textsubscript{15}H\textsubscript{16}NaO\textsubscript{6} [M+Na\textsuperscript{+}]: m/z 315.0845, found 315.0856. Data identical to literature values.\(^8\)
5.11.9: 5-(2,3,4-trimethoxybenzylidene)-2,2-dimethyl-[1,3]dioxane-4,6-dione 328i

Meldrum’s acid (793 mg, 5.5 mmol), 2,3,4-trimethoxybenzaldehyde (9.81 g, 5.5 mmol) and water (10 mL) was reacted under standard protocol to give the desired compound as a yellow crystalline solid (1.11 g, 69 %); mp (EtOH) 127-128 °C (lit = 123-124)\(^9\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.72 (1H, s, C=CH), 8.16 (1H, d, \(J = 9.0\) Hz, ArH), 6.72 (1H, d, \(J = 9.0\) Hz, ArH), 3.99 (3H, s, OC\(_3\)H), 3.94 (3H, s, OC\(_3\)H), 3.84 (3H, s, OCH\(_3\)), 1.78 (6H, s, C(CH\(_3\))\(_2\)); \(^1\)C NMR (75.5 MHz, CDCl\(_3\)) \(\delta\) 164.1, 161.0, 159.6, 156.4, 153.0, 141.8, 129.6, 119.4, 112.6, 107.3, 104.6, 62.5, 61.4, 56.7, 27.9; HRMS (EI) calcd for C\(_{16}\)H\(_{18}\)NaO\(_7\) [M+Na]\(^+\): \(m/z\) 345.0950, found 345.0931. Data identical to literature values.\(^9\)

5.11.10: 5-(4-nitrobenzylidene)-2,2-dimethyl-[1,3]dioxane-4,6-dione 328j

Meldrum’s acid (4.66 g, 32.3 mmol), 4-nitrobenzaldehyde (4.44 g, 29.4 mmol) and water (50 mL) was reacted under the standard protocol to give the desired product as a pale orange solid (6.78 g, 83 %); mp (EtOH) 140-142 °C (lit 142-143 °C)\(^3\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.45 (1H, s, C=CH), 8.30 (2H, d, \(J = 8.7\) Hz, ArH), 8.06 (2H, d, \(J = 8.7\) Hz, ArH), 1.84 (6H, s, C(CH\(_3\))\(_2\)); \(^1\)C NMR (75.5 MHz, DMSO-d\(_6\)) \(\delta\) 162.0, 159.3, 154.2, 149.0, 138.9, 132.8, 123.5, 119.5, 105.5, 27.6; HRMS (ESI) calcd for C\(_{13}\)H\(_{11}\)NNaO\(_6\) [M+Na]\(^+\): \(m/z\) 300.0484, found 300.0482. Data identical to literature values.\(^3\)
5.11.11: 5-(4-benzyloxybenzylidene)-2,2-dimethyl-[1,3]dioxane-4,6-dione 328k

Meldrum’s acid (6.34 g, 44.0 mmol), 4-benzyloxybenzaldehyde (8.49 g, 40.0 mmol) and water (100 mL) was reacted under the standard protocol to give the desired compound as a yellow crystalline solid (6.43 g, 48%); mp (EtOH) 118-120 °C; IR (KBr, cm\(^{-1}\)) \(\nu\) 1721, 1754 (C=O), 1216 (C-O); \(^1\)H NMR (250 MHz, CDCl\(_3\)) \(\delta\) 8.37 (1H, s, C=CH), 8.22 (2H, d, \(J = 8.9\) Hz, ArH), 7.45–7.31 (5H, m, ArH), 7.03 (2H, d, \(J = 8.9\) Hz, ArH), 5.17 (2H, s, OCH\(_2\)Ph), 1.78 (6H, s, C(CH\(_3\))\(_2\)); \(^13\)C NMR (75.5 MHz, CDCl\(_3\)) \(\delta\) 164.5, 164.2, 160.9, 158.3, 138.0, 136.1, 129.2, 128.8, 12.9, 125.3, 115.6, 111.4, 104.6, 70.8, 27.9; HRMS (ESI) calcd for C\(_{20}\)H\(_{18}\)O\(_5\) [M+Na]\(^+\): \(m/z\) 361.1052, found 361.1048; Anal. calcd for C\(_{20}\)H\(_{18}\)O\(_5\): C 71.0, H 5.36, found: C 70.8, H 5.44.

5.11.12: 2,2-dimethyl-5-(naphthalene-2-ylmethylene)-1,3,-dioxane-4,6-dione 328l

Meldrum’s acid (793 mg, 5.5 mmol), 2-naphthaldehyde (781 mg, 5.0 mmol) and water (10 mL) was reacted under the standard protocol to give the desired product as a pale yellow crystalline solid (462 mg, 33 %); mp (EtOH) 148-150 °C; IR (KBr, cm\(^{-1}\)) \(\nu\) 1760, 1731, (C=O) 1607 (C=C); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.58 (1H, s, C=CH), 8.54 (1H, s, ArH), 8.13 (1H, dd, \(J^1 = 8.7\) Hz, \(J^2 = 1.9\) Hz, ArH), 7.94 (1H, d, \(J = 7.9\) Hz, ArH), 7.88 (1H, d, \(J = 8.7\) Hz, ArH), 7.86 (1H, d, \(J = 7.9\) Hz, ArH), 7.63 (1H, ddd, \(J^1 = 7.9\) Hz, \(J^2 = 6.8\) Hz, \(J^3 = 1.5\) Hz, ArH), 7.55 (1H, ddd, \(J^1 = 7.9\) Hz, \(J^2 = 6.8\) Hz, \(J^3 = 1.5\) Hz, ArH), 1.84 (6H, s, C(CH\(_3\))\(_2\)); \(^13\)C NMR (75.5 MHz, CDCl\(_3\)) \(\delta\) 163.9, 160.4, 158.6, 137.5, 136.0, 133.0, 130.2, 129.9, 129.8, 128.7, 128.5, 128.2, 127.4, 114.8, 105.0, 28.1; HRMS (ESI) calcd for C\(_{17}\)H\(_{14}\)NaO\(_4\) [M+Na]\(^+\): \(m/z\) 305.0790, found 305.0786; Anal. calcd for C\(_{17}\)H\(_{12}\)O\(_4\): C 72.3, H 5.00, found: C 72.5, H 5.40.
5.11.13: 2,2-dimethyl-5-(naphthalen-1-ylmethylene)-1,3-dioxane-4,6-dione 328m

Meldrum’s acid (4.66 g, 32.3 mmol), 1-naphthaldehyde (4.0 mL, 29.4 mmol) and water (50 mL) was reacted under the standard protocol to give the desired product as a pale yellow crystalline solid (6.4 g, 77 %); mp (EtOH) 140-141 °C; IR (KBr, cm\(^{-1}\)) \(\nu\) 1728 (C=O), 1608 (C=C); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 9.22 (1H, s, C=CH\(_2\)), 8.03-7.90 (4H, m, Ar\(_H\)), 7.65-7.51 (3H, m, Ar\(_H\)), 1.86 (6H, s, C(CH\(_3\))\(_2\)); \(^{13}\)C NMR (75.5 MHz, CDCl\(_3\)) \(\delta\) 163.2, 159.9, 156.9, 133.7, 133.7, 132.1, 130.4, 129.6, 129.4, 128.2, 127.1, 125.3, 124.0, 117.4, 105.2, 28.2; HRMS (ESI) calcd for C\(_{17}\)H\(_{18}\)NO\(_4\) [M+NH\(_4\)]\(^+\) : m/z 300.1230, found 300.1234.
5.12 General Procedure for the Synthesis of 5-Monoalkyl Meldrum’s Acid Derivatives

To a solution of 5-arylidene Meldrum’s acid derivative and glacial acetic acid in dichloromethane at 0 °C was added sodium borohydride portion wise. The resulting solution was allowed to reach ambient temperature and stirred for 2 hour. The solution was dissolved in dichloromethane and washed with brine and water. The organic phase was extracted, dried over MgSO₄ and concentrated in vacuo to give the desired product.

5.12.1: 5-(4-methoxybenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione 367a

5-(4-methoxybenzylidene)-2,2-dimethyl-[1,3]dioxane-4,6-dione 328a (1.00 g, 3.82 mmol), glacial acetic acid (4.0 mL), sodium borohydride (0.43 g, 11.4 mmol) and dichloromethane (25 mL) was reacted under the standard procedure to give the desired product as a white solid (994 mg, 98%); mp (EtOAc) 82-85 °C (lit = 85-86 °C)¹⁰; IR (KBr, cm⁻¹) ν 3006, 2961, 2915 (C-H), 1787, 1746 (C=O); ¹H NMR (300 MHz, CDCl₃) δ 7.24 (2H, d, J = 8.7 Hz, ArH), 6.82 (2H, d, J = 8.7 Hz, ArH), 3.77 (3H, s, OCH₃), 3.72 (1H, t, J = 4.9 Hz, CH₂CH), 3.44 (2H, d, J = 4.9 Hz, ArCH₂), 1.72 (3H, s, CH₃), 1.48 (3H, s, CH₃); ¹³C NMR (75.5 MHz, CDCl₃) δ 165.9, 159.1, 131.4, 129.4, 114.3, 105.6, 55.6, 48.7, 31.9, 28.9, 27.8; HRMS (ESI) calcd for C₁₄H₁₅O₅ [M-H]⁻: m/z 263.0919, found 263.0912. Anal. calcd for C₁₄H₁₆O₅: C 63.6, H 6.10, found: C 63.1, H 6.06. Data identical to literature data.¹⁰
5.12.2: 5-(benzo[d][1,3]dioxol-4-ylmethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione 367e

5-(benzo[d][1,3]dioxol-4-ylmethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione 328e (615 mg, 2.23 mmol), glacial acetic acid (2.0 mL), dichloromethane (10 mL) and sodium borohydride (168 mg, 4.45 mmol) was reacted under the standard protocol to give the desired compound as a white solid (569 mg, 92%); mp (EtOAc) 127-128 °C; IR (KBr, cm⁻¹) ν 1755, 1725 (C=O), 1276 (C-O); ¹H NMR (300 MHz, CDCl₃) δ 6.81 (1H, d, J = 2.3 Hz, ArH), 6.77 (1H, d, J = 6.8 Hz, ArH), 6.72 (1H, dd, J¹ = 6.8 Hz, J² = 2.3 Hz, ArH), 5.92 (2H, s, O-CH₂-O), 4.00 (1H, t, J = 5.7 Hz, CH₂CH), 3.40 (2H, d, J = 5.7 Hz, ArCH₂), 1.79 (3H, s, C(CH₃)₂), 1.71 (3H, s, C(CH₃)₂); ¹³C NMR (75.5 MHz, CDCl₃) δ 165.4, 147.6, 145.6, 123.6, 122.2, 119.5, 107.8, 105.5, 101.1, 46.4, 29.0, 27.0, 26.7; HRMS (ESI) calcd for C₁₄H₁₃O₆ [M-H]⁻: m/z 277.0712, found 277.0694. Anal. calcd for C₁₄H₁₂O₆: C 60.9, H 4.40, found: C 59.9, H 4.30.

5.12.3: 5-cinnamyl-2,2-dimethyl-1,3-dioxane-4,6-dione 367f

2,2-dimethyl-5-(3-phenyl-allylidene)-[1,3]dioxane-4,6-dione 328f (233 mg, 0.90 mmol), glacial acetic acid (1.0 mL), dichloromethane (10 mL) and sodium borohydride (0.10 g, 2.71 mmol) was reacted under standard protocol to give the desired compound as a white solid (203 mg, 87%); mp (EtOAc) 85-86 °C; ¹H NMR (250 MHz, CDCl₃) δ 7.41-7.21 (5H, m, Ar), 6.63 (1H, d, J = 15.8 Hz, PhCH), 6.29 (1H, dt, J¹ = 15.8 Hz, J² = 7.3 Hz, PhCHCH), 3.70 (1H, t, J = 5.1 Hz, CH₂CH), 3.05 (2H, dd, J¹ = 7.3 Hz, J² = 5.1 Hz, CHCH₂CH), 1.81 (3H, s, C(CH₃)₂), 1.77 (3H, s, C(CH₃)₂); ¹³C NMR (75.5 MHz, CDCl₃) δ 165.4, 137.2, 135.1, 128.9, 128.0, 126.7, 124.3, 105.5, 47.0, 30.0, 28.8, 27.3; HRMS (ESI) calcd for C₁₅H₁₅O₄ [M-H]⁺: m/z 259.0970, found 259.0970. Data identical to literature values.¹¹
5.12.4: 5-(3,4-dimethoxybenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione 367g

5-(3,4-dimethoxybenzylidene)-2,2-dimethyl-[1,3]dioxane-4,6-dione 328g (585 mg, 2.0 mmol), glacial acetic acid (2.0 mL), dichloromethane (15 mL) and sodium borohydride (151 mg, 4.0 mmol) was reacted under the standard protocol to give the desired compound as a white solid (495 mg, 84%); mp (EtOAc) 138-140 °C (lit = 136-137 °C);\(^\text{12}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) 6.84 (1H, d, \(J = 9.0\) Hz, ArH), 6.83 (1H, s, ArH), 6.76 (1H, d, \(J = 9.0\) Hz, ArH), 3.84 (3H, s, OC\(_3\)H\(_3\)), 3.83 (3H, s, OC\(_3\)H\(_3\)), 3.74 (1H, t, \(J = 4.9\) Hz, CH\(_2\)C), 3.43 (2H, d, \(J = 4.9\) Hz, CH\(_2\)C), 1.71 (3H, s, CH\(_3\)), 1.47 (3H, s, CH\(_3\)); \(^{13}\)C NMR (75.5 MHz, CDCl\(_3\)) 165.9, 149.1, 148.5, 129.9, 122.4, 113.5, 111.5, 105.6, 56.3, 56.2, 48.7, 32.3, 28.9, 27.8; HRMS (ESI) calcd for C\(_{15}\)H\(_{18}\)NaO\(_6\) [M+Na\(^+\)]: \(m/z\) 317.1001, found 317.0989. Data identical to literature values.\(^\text{12}\)

5.12.5: 5-(4-nitrobenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione 367j

5-(4-nitrobenzylidene)-2,2-dimethyl-[1,3]dioxane-4,6-dione 328j (1.00 g, 3.61 mmol), glacial acetic acid (4.0 mL), dichloromethane (25 mL) and sodium borohydride (0.43 g, 11.4 mmol) was reacted under the standard protocol to give the desired compound as a pale yellow solid (881 mg, 87%); mp (EtOAc) 111-112 °C; IR (KBr, cm\(^{-1}\)) \(v\) 1758, 1730 (C=O), 1517, 1342 (N-O); \(^1\)H NMR (300 MHz, CDCl\(_3\)) 8.13 (2H, d, \(J = 8.7\) Hz, ArH), 7.53 (2H, d, \(J = 8.7\) Hz, ArH), 3.83 (1H, t, \(J = 5.3\) Hz, CH\(_2\)CH), 3.44 (2H, d, \(J = 5.3\) Hz, CH\(_2\)CH), 1.79 (3H, s, C(CH\(_3\))\(_2\)), 1.67 (3H, s, C(CH\(_3\))\(_2\)); \(^{13}\)C NMR (75.5 MHz, CDCl\(_3\)) 165.0, 147.5, 145.1, 131.3, 124.1, 105.8, 48.1, 31.8, 28.8, 27.4; HRMS (ESI) calcd for C\(_{13}\)H\(_{12}\)NO\(_6\) [M-H] : \(m/z\) 278.0665, found 278.0674; Anal. calcd for C\(_{13}\)H\(_{13}\)NO\(_6\): C 55.9, H 4.69, N 5.02, found: C 55.7, H 4.75, N 4.98.
5.12.6: 5-(4-benzyloxybenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione 367k

5-(4-benzyloxybenzylidene)-2,2-dimethyl-[1,3]dioxane-4,6-dione 328k (2.26 g, 6.68 mmol), glacial acetic acid (8.0 mL), dichloromethane (50 mL) and sodium borohydride (0.75 g, 20.0 mmol) was reacted under the standard protocol to give the desired compound as a white solid (2.10 g, 93%); mp (EtOAc) 92-94 °C; IR (KBr, cm\(^{-1}\)) \(\nu\) 3020, 2945, 2872 (C-H), 1785, 1748 (C=O); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.43-7.29 (5H, m, ArH), 7.24 (2H, d, \(J = 8.7\) Hz, ArH), 6.89 (2H, d, \(J = 8.7\) Hz, ArH), 5.03 (2H, s, O-CH\(_2\)-Ph), 3.73 (1H, t, \(J = 4.9\) Hz, CH\(_2\)CH), 3.44 (2H, d, \(J = 4.9\) Hz, CH\(_2\)CH), 1.72 (3H, s, C(CH\(_3\))\(_2\)), 1.46 (3H, s, C(CH\(_3\))\(_2\)); \(^{13}\)C NMR (75.5 MHz, CDCl\(_3\)) \(\delta\) 165.9, 158.3, 137.3, 131.4, 129.8, 129.0, 128.4, 127.9, 115.3, 105.7, 70.3, 48.7, 31.9, 28.9, 27.8; HRMS (ESI) calcd for C\(_{20}\)H\(_{20}\)NaO\(_5\) [M+Na]\(^+\): m/z 363.1208, found 363.1203; Anal. calcd for C\(_{20}\)H\(_{20}\)O\(_5\), C 70.6, H 5.92, found: C 71.3, H 5.88.

5.12.7: 2,2-dimethyl-5-(naphthalen-2-ylmethyl)-1,3-dioxane-4,6-dione 367l

5-(naphthalene-2-methylidene)-2,2-dimethyl-[1,3]dioxane-4,6-dione 328l (201 mg, 0.71 mmol), glacial acetic acid (1.0 mL), dichloromethane (10 mL) and sodium borohydride (80.7 mg, 2.13 mmol) was reacted under the standard protocol to give the desired compound as a white solid (190 mg, 94%); mp (EtOAc) 128-129 °C; IR (KBr, cm\(^{-1}\)) \(\nu\) 3050, 2984, 2870 (C-H), 1790, 1745 (C=O); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.82-7.77 (4H, m, ArH), 7.50-7.41 (3H, m, ArH), 3.84 (1H, t, \(J = 4.9\) Hz, CH\(_2\)CH), 3.65 (2H, d, \(J = 4.9\) Hz, CH\(_2\)CH), 1.73 (3H, s, C(CH\(_3\))\(_2\)), 1.50 (3H, s, C(CH\(_3\))\(_2\)); \(^{13}\)C NMR (75.5 MHz, CDCl\(_3\)) \(\delta\) 165.7, 135.2, 133.8, 132.9, 129.0, 128.7, 128.3, 128.2, 128.0, 126.5, 126.3, 105.6, 48.7, 32.6, 28.8, 27.6; HRMS (ESI) calcd for C\(_{17}\)H\(_{15}\)O\(_4\) [M-H]\(^-\): m/z 283.0970, found 283.0964.
5.12.8: 2,2-dimethyl-5-(naphthalen-1-ylmethyl)-1,3-dioxane-4,6-dione 367m

5-(naphthalene-1-methylidene)-2,2-dimethyl-[1,3]dioxane-4,6-dione 328m (1.15 g, 4.09 mmol), glacial acetic acid (2.5 mL), dichloromethane (25 mL) and sodium borohydride (464 mg, 12.3 mmol) was reacted under the standard protocol to give the desired compound as a white solid (1.12 g, 97%); m.p (EtOAc) 135-137 °C; IR (KBr, cm⁻¹) 3057, 3000, 2869 (C-H); 1781, 1750 (C=O); 1H NMR (300 MHz, CDCl₃) δ 8.08 (1H, dd, J₁ = 8.3 Hz, J₂ = 1.1 Hz, ArH), 7.89 (1H, dd, J₁ = 8.3 Hz, J₂ = 1.5 Hz, ArH), 7.79 (1H, d, J = 8.3 Hz, ArH), 7.65 (1H, dd, J₁ = 7.2 Hz, J₂ = 1.1 Hz, ArH), 7.57 (1H, ddd, J₁ = 8.3 Hz, J₂ = 6.8 Hz, J₃ = 1.5 Hz, ArH), 7.51 (1H, ddd, J₁ = 8.3 Hz, J₂ = 6.8 Hz, J₃ = 1.5 Hz, ArH), 7.44 (1H, dd, J₁ = 8.3 Hz, J₂ = 7.2 Hz, ArH), 3.93 (1H, t, J = 5.3 Hz, CHCH₂Ar), 3.80 (2H, d, J = 5.3 Hz, CHCH₂Ar), 1.70 (3H, s, C(CH₃)₂), 1.69 (3H, s, C(CH₃)₂); 13C NMR (75.5 MHz, CDCl₃) δ 165.7, 134.5, 134.4, 131.7, 129.6, 128.8, 128.3, 127.1, 126.2, 126.0, 123.2, 105.6, 48.2, 29.2, 29.0, 26.9; HRMS (ESI) calcd for C₁₇H₁₅O₄ [M-H]⁻: m/z 283.0970, found 283.0972. Data identical to literature values.¹³

5.12: 5-(4-benzyloxybenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione 367n

4-bromobenzaldehyde (537 mg, 2.9 mmol) was added to a solution of Meldrum’s acid (470 mg, 3.19 mmol) in water (10 mL). The solution was stirred at 75 °C for 2 h. After cooling the precipitate was filtered via Buckner filtration and washed with water (100 mL) and petrol (100 mL) and dried. The resulting solid was dissolved in dichloromethane (10 mL), acetic acid (2 mL) was added and the solution cooled to 0 °C. Sodium borohydride (219 mg, 5.8 mmol) was added portionwise, the solution allowed to warm to ambient temperature and was stirred for 2 h. The reaction mixture was dissolved in DCM (50 mL) and washed with water (3 x 50 mL) and brine (50 mL). The organic phase was separated, dried over MgSO₄ and concentrated in vacuo to give the desired product as a white solid (426 mg, 47%); mp (EtOAc) 143-144 °C (lit = 142-144 °C)¹⁴; 1H NMR (300 MHz, CDCl₃) δ 7.41 (2H, d, J = 8.3 Hz, ArH), 7.21 (2H, d, J = 8.3 Hz, ArH), 3.73 (1H, t, J = 5.3 Hz, CHCH₂Ar), 3.69 (2H, d, J = 5.3 Hz, CHCH₂Ar), 1.70 (3H, s, C(CH₃)₂), 1.69 (3H, s, C(CH₃)₂); 13C NMR (75.5 MHz, CDCl₃) δ 165.7, 134.5, 134.4, 131.7, 129.6, 128.8, 128.3, 127.1, 126.2, 126.0, 123.2, 105.6, 48.2, 29.2, 29.0, 26.9; HRMS (ESI) calcd for C₁₇H₁₅O₄ [M-H]⁻: m/z 283.0970, found 283.0972. Data identical to literature values.¹³
CH$_2$CH), 3.43 (2H, d, $J$ = 4.9 Hz, CH$_2$CH), 1.75 (3H, s, C(CH$_3$)$_2$), 1.59 (3H, s, C(CH$_3$)$_2$);
$^{13}$C NMR (75.5 MHz, CDCl$_3$) δ 165.4, 136.5, 132.1, 121.7, 105.6, 48.3, 31.8, 28.8, 27.6;
HRMS (ESI) calcd for C$_{13}$H$_{14}$BrO$_4$ [M+H]$^+$: $m/z$ 313.0075, found 313.0081. Data identical to literature values.$^{14}$

5.13 The Reductive Coupling of N-Boc Protected Amino Acids and Meldrum’s Acid

To a solution of N-Boc amino acid (20.0 mmol) and Meldrum’s acid (3.02 g, 20.9 mmol) in dichloromethane (100 mL) was added 4-(dimethylamino)pyridine (3.85 g, 31.5 mmol). The solution was cooled to 0 °C and a solution of N,N’-dicyclohexylcarbodiimide (4.74 g, 23.0 mmol) in dichloromethane (50 mL) was added dropwise over 1 hour. After warming to room temperature the reaction mixture was left to stir for 20 hours. The reaction mixture was filtrated and the filtrate washed with 5% KHSO$_4$ (3 x 100 mL) and saturated brine (1 x 100 mL). The organic phase was extracted and dried over MgSO$_4$ at 0 °C for 5 hours. The solution was filtered, glacial acetic acid (13.3 mL, 220 mmol) was added to the filtrate and the solution was cooled to 0 °C. Sodium borohydride (1.85 g, 50 mmol) was added portion wise over 1 hour before the reaction mixture was stirred for 16 hours at room temperature. The reaction mixture was washed with water (2 x 100 mL) and saturated brine (100 mL). The organic phase was extracted, dried over MgSO$_4$ and concentrated in vacuo. The mixture was purified by flash column chromatography to a give the desired compound.
5.13.1: (S)-tert-butyl 2-((2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)methyl)pyrrolidine-1-carboxylate 367o

N-Boc-L-proline (4.31 g, 20.0 mmol) was reacted under the standard protocol. The reaction mixture was purified by flash column chromatography (4:1 petrol:ethyl acetate) to give the desired compound as a white solid (5.10 g, 78%); Rf (4:1 petrol:ethyl acetate) 0.32; mp 122-123 °C; [α]D24 -22.6 (c 0.40, CHCl₃); IR (KBr, cm⁻¹) ν 2976, 2915 (C-H), 1784, 1749, 1675 (C=O); ¹H NMR (300 MHz, CDCl₃) δ 4.66 (1H, d, J = 4.5 Hz, NC₃H), 4.32 (1H, t, J = 7.9 Hz, CH malonate), 3.33 (2H, m, NCH₂), 2.32-2.23 (1H, CHCH₂CH), 2.12-1.87 (4H, m), 1.83 (3H, s, C(CH₃)₂), 1.74 (3H, s, C(CH₃)₂), 1.72-1.62 (1H, m), 1.41 (9H, s, C(CH₃)₃); ¹³C NMR (75.5 MHz, CDCl₃) δ 165.5, 157.0, 105.3, 79.9, 55.8, 47.0, 45.6, 32.1, 32.0, 29.1, 28.8, 26.0, 24.0; HRMS (ESI) calcd for C₁₆H₂₄NO₆ [M-H]⁻ : m/z 326.1604, found 326.1590.

5.13.2: (R)-tert-butyl 1-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-3-phenylpropan-2-ylcarbamate 367p

N-Boc-L-phenylalanine (5.32 g, 20.0 mmol) was reacted under the standard protocol. The reaction mixture was purified by flash column chromatography (2:1 petrol:ethyl acetate) to give the desired compound as a white solid (6.75 g, 90%); Rf (2:1 petrol:ethyl acetate) 0.24; [α]D24 +4.6 (c = 1.8, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.37-7.17 (5H, m, ArH), 4.57-4.42 (1H, m, CH Meldrum’s acid), 4.37-4.09 (1H, m, NHCH), 3.91 (1H, brs, NH), 3.00-2.74 (2H, m, ArCH₂), 2.38-2.03 (2H, m, CHCH₂), 1.78 (3H, s, C(CH₃)₂), 1.74 (3H, s, C(CH₃)₂), 1.36 (9H, s, C(CH₃)₃); ¹³C NMR (75.5 MHz, CDCl₃) δ 165.7, 165.6, 156.5, 137.2, 129.3, 128.6, 126.7, 105.1, 79.6, 50.0, 44.2, 41.8, 31.4, 28.5, 28.2, 26.0. Data identical to literature values.¹⁵
5.14 Alkylation of 5-Monoalkyl Meldrum’s Acid Derivatives

5.14.1: 5-(4-methoxybenzyl)-2,2,5-trimethyl-1,3-dioxane-4,6-dione 380

To a solution of 5-(4-methoxybenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione 367a (529 mg, 2 mmol) and potassium carbonate (304 mg, 2.2 mmol) in N,N’-dimethylformamide (5 mL) was added methyl iodide (125 µL, 2mmol). The reaction mixture was stirred at room temperate for 1 hour. The reaction mixture was dissolved in ethyl acetate (50 mL) and washed with water (3 x 50 mL) and saturated brine (50 mL). The organic phase was extracted, dried over MgSO₄ and concentrated \textit{in vacuo} to give the desired compound as a colourless solid (545 mg, 98%); mp (ethyl acetate) 86-88 °C (lit = 84 °C);¹⁶ ¹H NMR (300 MHz, CDCl₃) δ 7.08 (2H, d, \( J = 9.0 \) Hz, ArH), 6.78 (2H, d, \( J = 9.0 \) Hz, ArH), 3.75 (3H, s, OCH₃), 3.26 (2H, s, ArCH₂), 1.72 (3H, s, C(CH₃)₂), 1.60 (3H, s, C(CH₃)₂), 0.97 (3H, s, C(CH₃));¹³C NMR (75.5 MHz, CDCl₃) δ 170.4, 159.5, 131.6, 127.8, 114.5, 105.6, 55.62, 52.8, 44.6, 29.8, 28.8, 26.1; HRMS (ESI) calcd for C₁₅H₁₈NaO₅ [M+Na]⁺: \( m/z \) 301.1052, found 301.1051. Data identical to literature values values.¹⁶
5.15 General Preparation of 3-Aryl Propionaldehydes

**Method A**

![Chemical Structure]

To a solution of alkylidene Meldrum’s acid derivative (0.5 mmol), molybdenum hexacarbonyl (6.6 mg, 5 mol%) and N-methylmorpholine N-oxide monohydrate (5.9 mg, 9 mol%) in tetrahydrofuran (3.0 mL) was added phenylsilane (185 µL, 1.5 mmol). The resulting solution was stirred under an atmosphere of nitrogen at 80 °C for 16 h. After cooling to room temperature water (0.5 mL) was added and the solution stirred for 15 minutes. The solution was dissolved in ether (50 mL) was washed with 1 M NaOH (3 x 50 mL) followed by saturated brine (2 x 50 mL). The organic phase was extracted, dried over MgSO₄ and concentrated *in vacuo*. The desired product was purified by flash column chromatography.

**Method B**

![Chemical Structure]

To a solution of 5-monoalkyl Meldrum’s acid derivative (0.5 mmol), molybdenum hexacarbonyl (6.6 mg, 5 mol%) and N-methylmorpholine N-oxide monohydrate (5.9 mg, 9 mol%) in tetrahydrofuran (3.0 mL) was added phenylsilane (185 µL, 1.5 mmol). The resulting solution was stirred under an atmosphere of nitrogen at 80 °C for 16 h. After cooling to room temperature water (0.5 mL) was added and the solution stirred for 15 minutes. The solution was dissolved in ether (50 mL) was washed with 1 M NaOH (3 x 50 mL) followed by saturated brine (2 x 50 mL). The organic phase was extracted, dried over MgSO₄ and concentrated *in vacuo*. The desired product was purified by flash column chromatography.
Method C

To a solution of 5-alkyl Meldrum’s acid derivative (0.5 mmol) in tetrahydrofuran (3 mL) was added triethylamine (139 µL, 1.0 mmol) followed by phenylsilane (185 µL, 1.5 mmol). The resulting solution was stirred for 2 hours at room temperature. Water (0.5 mL) was added to the solution and stirred for 15 minutes. The reaction mixture was dissolved in diethyl ether (50 mL) and washed with water (2 x 50 mL) then with saturated brine (50 mL). The organic phase was extracted, dried over MgSO\(_4\) and concentrated \textit{in vacuo} and purified by column chromatography to give the desired product.

Method D

To a solution of alkylidene Meldrum’s acid derivative (0.5 mmol) tetrahydrofuran (3.0 mL) was added triethylamine (139 µL, 1.0 mmol) and phenylsilane (185 µL, 1.5 mmol). The resulting solution was stirred at 80 °C for 16 h. After cooling to room temperature water (0.5 mL) was added and the solution stirred for 15 minutes. The solution was dissolved in ether (25 mL) was washed with water (2 x 25 mL) followed by saturated brine (25 mL). The organic phase was extracted, dried over MgSO\(_4\) and concentrated \textit{in vacuo}. The desired product was purified by flash column chromatography.
**5.15.1: 3-(4-methoxyphenyl)-propanal 368a**

5-(4-methoxybenzylidene)-2,2-dimethyl-[1,3]dioxane-4,6-dione 328a (131 mg, 0.5 mmol) was reacted using method A to give the desired product, purified by flash column chromatography (petrol:ethyl acetate 11:1), as a colourless oil (70.1 mg, 85%).

5-(4-methoxybenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione 367a (132 mg, 0.5 mmol) was reacted using method B to give the desired product, purified by flash column chromatography, as a colourless oil (59.4 mg, 72%).

5-(4-methoxybenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione 367a (132 mg, 0.5 mmol) was reacted using method C to give the desired product, purified by flash column chromatography, as a colourless oil (68.9 mg, 84%).

5-(4-methoxybenzylidene)-2,2-dimethyl-[1,3]dioxane-4,6-dione 328a (131 mg, 0.5 mmol) was reacted using method D to give the desired product, purified by flash column chromatography, as a colourless oil (29.4 mg, 36%).

$R_f$ (11:1 petrol:ethyl acetate) 0.21; IR (neat, cm$^{-1}$) $v$ 2840, 2730 (C-H), 1716 (C=O), 1246 (C-O); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.80 (1H, t, $J = 1.5$ Hz, CHO), 7.11 (2H, d, $J = 8.7$ Hz, ArH), 6.84 (2H, d, $J = 8.7$ Hz, ArH), 3.78 (3H, s, CH$_3$), 2.91 (2H, t, $J = 7.2$ Hz, ArCH$_2$), 2.77-2.72 (2H, m, CH$_2$CHO); $^{13}$C NMR (75.5 MHz, CDCl$_3$) $\delta$ 202.3, 158.5, 132.7, 129.7, 114.4, 55.7, 46.0, 27.7; HRMS (ESI) calcd for C$_{10}$H$_{12}$NaO$_2$ [M+Na]$^+$ : $m/z$ 187.0735, found 187.0738. Data identical to literature values.$^{17}$

**5.15.2: 3-(4-thiomethylbenzene)-propanal 368b**

5-(4-thiomethylbenzylidene)-2,2-dimethyl-[1,3]dioxane-4,6-dione 328b (139 mg, 0.5 mmol) was reacted using method A to give the desired product, purified by flash column chromatography (11:1 petrol:ethyl acetate), as a colourless oil (44 mg, 66%); $R_f$ (11:1 petrol:ethyl acetate) 0.24; IR (neat, cm$^{-1}$) $v$ 2824, 2727 (C-H), 1722 (C=O); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.81 (1H, t, $J = 1.5$ Hz, CHO), 7.20 (2H, d, $J = 8.7$ Hz, Ar), 7.12 (2H, d, $J = 8.7$ Hz, Ar), 2.92 (2H, t, $J = 7.2$ Hz, ArCH$_2$), 2.79-2.73 (2H, m, CH$_2$CHO); $^{13}$C NMR
(75.5 MHz, CDCl$_3$) $\delta$ 201.9, 137.7, 136.5, 129.3, 127.5, 45.7, 31.4, 28.0, 16.6, HRMS (EI) calcd for C$_{10}$H$_{16}$NOS [M+NH$_4^+$]$: m/z$ 198.0947, found 198.948; Anal. calcd for C$_{10}$H$_{12}$OS: C 66.6, H 6.71, found: C 66.3, H 6.88.

5.15.3: 3-(4-dimethylaminobenzene)-propanal 368c

[Chemical structure image]

5-(4-dimethylaminobenzylidene)-2,2-dimethyl-[1,3]dioxane-4,6-dione 328c (126 mg, 0.5 mmol) was reacted using method A to give the desired product, purified by flash column chromatography (10:1 petrol:ethyl acetate), as a colourless oil (71.8 mg, 81%); $R_f$ (10:1 petrol:ethyl acetate) 0.19; IR (neat, cm$^{-1}$) $\nu$ 2826, 2729 (C-H); 1722 (C=O); $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 9.82 (1H, t, $J$ = 1.5 Hz, CH$_O$), 7.07 (2H, d, $J$ = 8.7 Hz, ArH), 6.70 (2H, d, $J$ = 8.7 Hz, ArH), 2.92 (6H, s, N(CH$_3$)$_2$), 2.89 (2H, t, $J$ = 7.2 Hz, ArCH$_2$), 2.76-2.70 (2H, m, CH$_2$CHO); $^{13}$C NMR (75.5 MHz, CDCl$_3$) $\delta$ 202.7, 149.7, 129.3, 128.6, 113.4, 46.1, 41.2, 27.6; HRMS (EI) calcd for C$_{11}$H$_{16}$NO [M+H]$^+$: $m/z$ 178.1232, found 178.1228.

5.15.4: 3-(benzo[1,3]dioxol-5-yl)propanal 368d

[Chemical structure image]

5-(benzo[1,3]dioxol-5-ylmethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione 328d (138.1 mg, 0.5 mmol) was reacted using method A to give the desired product, purified by column chromatography (petrol : ethyl acetate 6:1), as a colourless oil (58.3 mg, 65%); $R_f$ (6:1 petrol:ethyl acetate) 0.29; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.79 (1H, t, $J$ = 1.5 Hz, CH$_O$), 6.72 (1H, d, $J$ = 7.8 Hz, ArH), 6.68-6.62 (2H, m, ArH), 5.91 (2H, s, OCH$_2$O), 2.87 (2H, t, $J$ = 7.3 Hz, ArCH$_2$), 2.74-2.70 (2H, m, CH$_2$CHO); $^{13}$C NMR (75.5 MHz, CDCl$_3$) $\delta$ 202.2, 148.1, 146.4, 134.5, 121.5, 109.2, 108.7, 101.3, 46.0, 28.3; HRMS (EI) calcd for C$_{10}$H$_{10}$NaO$_3$ [M+Na]$^+$: $m/z$ 201.0528, found 201.0532. Data identical to literature values.$^{18}$
5.15.5: 3-(benzo[1,3]-dioxol-4-yl)-propanal 368e

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

5-(benzo[\text{d}][1,3]dioxol-4-ylmethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione 328e (138 mg, 0.5 mmol) was reacted using method A to give the desired product, purified by flash column chromatography (petrol : ethyl acetate 11:1), as a colourless oil (69.4 mg, 78%).

5-(benzo[\text{d}][1,3]dioxol-4-ylmethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione 367e (139 mg, 0.5 mmol) was reacted using method C to give the desired product, purified by flash column chromatography, as a colourless oil (69.2 mg, 78%).

\[
R_f \ (11:1 \text{ petrol:ethyl acetate}) \ 0.24; \ IR \ (\text{neat}, \ cm^{-1}) \ \nu \ 2828, 2729 \ (C-H); \ 1724 \ (C=O); \ 1252 \ (C-O); \ \text{H NMR} \ (300 \ MHz, \ CDCl_3) \ \delta \ 9.81 \ (1H, \ t, \ J = 1.3 \ Hz, \ CHO), \ 6.79-6.65 \ (3H, \ m, \ Ar H), \ 5.93 \ (2H, \ s, \ -OC\text{H}_2O-), \ 2.92 \ (2H, \ t, \ J = 7.3 \ Hz, \ ArC\text{H}_2), \ 2.82-2.75 \ (2H, \ m, \ CH_2CHO); \ 13C \ NMR \ (75.5 \ MHz, \ CDCl_3) \ \delta \ 202.0, \ 147.6, \ 145.8, \ 128.2, \ 122.8, \ 122.1, \ 107.4, \ 101.0, \ 43.7, \ 22.7; \ HRMS \ (ESI) \ \text{calcd for C}_{10}H_{10}NaO_3 \ [M+Na]^+ : m/z \ 201.0528, \ \text{found 201.0524.}
\]

5.15.6: (\text{E})-5-phenylpent-4-enal 367f

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\begin{align*}
\text{Ph} & \quad \text{O} \\
\text{H}
\end{align*}
\]

2,2-dimethyl-5-(3-phenyl-allylidene)-[1,3]dioxane-4,6-dione 328f (129 mg, 0.5 mmol) was reacted using method A to give the desired product, purified by flash column chromatography (12:1 petrol:ethyl acetate), as a colourless oil (31.2 mg, 39%).

5-cinnamyl-2,2-dimethyl-[1,3]dioxane-4,6-dione 367f (130 mg, 0.5 mmol) was reacted using method C to give the desired product, purified by flash column chromatography (petrol : ethyl acetate 12:1), as a colourless oil (64.2 mg, 80%).

\[
R_f \ (12:1 \text{ petrol:ethyl acetate}) \ 0.26; \ \text{H NMR} \ (300 \ MHz, \ CDCl_3) \ \delta \ 9.83 \ (1H, \ t, \ J = 1.3 \ Hz, \ CHO), \ 7.36-7.28 \ (4H, \ m, \ Ar H), \ 7.24-7.19 \ (1H, \ m, \ Ar H), \ 6.4 \ (1H, \ dt, \ J^1 = 15.8 \ Hz, \ J^2 = 1.3 \ Hz, \ PhCH), \ 6.21 \ (1H, \ dt, \ J^1 = 15.8 \ Hz, \ J^2 = 6.4 \ Hz, \ PhCHCH), \ 2.66-2.61 \ (2H, \ m, \ CHCHCH_2), \ 2.59-2.51 \ (2H, \ m, \ CH_2CHO); \ 13C \ NMR \ (75.5 \ MHz, \ CDCl_3) \ \delta \ 202.2, \ 137.6, \ 131.5, \ 129.0, \ 128.6, \ 127.7, \ 126.5, \ 43.7, \ 25.9; \ HRMS \ (ESI) \ \text{calcd for C}_{11}H_{12}NaO \ [M+Na]^+ : m/z \ 183.0786, \ \text{found 183.0790. Data identical to literature values.}^{19}
\]
5.15.7: 3-(3,4-dimethoxyphenyl)-propanal 368g

\[
\begin{align*}
&\text{MeO} \\
&\text{MeO} \\
&\text{O} \\
&\text{H}
\end{align*}
\]

5-(3,4-dimethoxybenzylidene)-2,2-dimethyl-[1,3]dioxane-4,6-dione 328g (146 mg, 0.5 mmol) was reacted using method A to give the desired product, purified by flash column chromatography (4:1 petrol:ethyl acetate), as a colourless oil (51.2 mg, 53%).

5-(3,4-dimethoxybenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione 367g (147 mg, 0.5 mmol) was reacted using method C to give the desired product, purified by flash column chromatography, as a colourless oil (59.5 mg, 61%).

\( R_f \) (4:1 petrol:ethyl acetate) 0.30; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 9.79 (1H, t, \( J = 1.5 \) Hz, CHO), 6.80 (1H, d, \( J = 8.5 \) Hz, ArH), 6.74-6.71 (2H, m, ArH), 3.87 (3H, s, OCH\(_3\)), 3.85 (3H, s, OCH\(_3\)), 2.90 (2H, t, \( J = 7.2 \) Hz, ArCH\(_2\)), 2.78-2.71 (2H, m, CH\(_2\)CHO); \(^{13}\)C NMR (75.5 MHz, CDCl\(_3\)) \( \delta \) 202.1, 149.4, 147.9, 133.3, 120.5, 112.1, 111.8, 56.3, 56.2, 45.9, 28.2; HRMS (EI) calcd for C\(_{11}\)H\(_{14}\)NaO\(_3\) [M+Na]\(^+\) : \( m/z \) 217.0841, found 217.0840. Data identical to literature values.\(^{20}\)

5.15.8: 3-(2,5-dimethoxyphenyl)-propanal 368h

\[
\begin{align*}
&\text{MeO} \\
&\text{O} \\
&\text{H}
\end{align*}
\]

5-(2,5-dimethoxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione 328h (146 mg, 0.5 mmol) was reacted using method A to give the desired product, purified by flash column chromatography (11:1 petrol:ethyl acetate), as a colourless oil (73.4 mg, 76%); \( R_f \) (11:1 petrol:ethyl acetate) 0.20; IR (neat, cm\(^{-1}\)) \( \nu \) 2836, 2729 (C-H); 1723 (C=O); 1225 (C-O); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 9.80 (1H, t, \( J = 1.5 \) Hz, CHO), 6.78-6.69 (3H, m, ArH), 3.77 (3H, s, OCH\(_3\)), 3.75 (3H, s, OCH\(_3\)), 2.92 (2H, t, \( J = 7.2 \) Hz, ArCH\(_2\)), 2.74-2.68 (2H, m, CH\(_2\)CHO); \(^{13}\)C NMR (75.5 MHz, CDCl\(_3\)) \( \delta \) 202.7, 153.9, 147.9, 133.3, 120.5, 112.1, 111.8, 56.1, 56.1, 44.3, 24.1; HRMS (EI) calcd for C\(_{11}\)H\(_{15}\)O\(_3\) [M+H]\(^+\) : \( m/z \) 195.1021, found 195.1021.
5.15.9: 3-(2,3,4-trimethoxyphenyl)-propanal 367i

\[
\text{MeO} \quad \text{OMe} \quad \text{O} \quad \text{H}
\]

5-(2,3,4-trimethoxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione 328i (161 mg, 0.5 mmol) was reacted using method A to give the desired product, purified by column chromatography (11:1 petrol:ethyl acetate), as a colourless oil (53.3 mg, 48%); \( R_f \) (11:1 petrol:ethyl acetate 0.26); IR (neat, cm\(^{-1}\)) \( v \) 2826, 2728 (C-H); 1723 (C=O); 1248, 1232 (C-O); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 9.78 (1H, t, \( J = 1.5 \) Hz, CHO), 6.80 (1H, d, \( J = 8.7 \) Hz, ArH), 6.57 (1H, d, \( J = 8.7 \) Hz, ArH), 3.87 (3H, s, OCH\(_3\)), 3.84 (3H, s, OCH\(_3\)), 3.81 (3H, s, OCH\(_3\)), 2.86 (2H, t, \( J = 7.5 \) Hz, ArCH\(_2\)), 2.72-2.66 (2H, m, CH\(_2\)CHO); \(^{13}\)C NMR (75.5 MHz, CDCl\(_3\)) \( \delta \) 202.7, 152.9, 152.2, 142.6, 126.6, 124.2, 107.5, 61.2, 61.1, 56.4, 45.1, 23.2; HRMS (El) calcd for C\(_{12}\)H\(_{16}\)NaO\(_4\) [M+Na]\(^+\) : \( m/z \) 247.0946, found 247.0937.

5.15.10: 3-(4-nitrophenyl)-propanal 368j

\[
\text{O}_2\text{N} \quad \text{H}
\]

5-(4-nitrobenzylidene)-2,2-dimethyl-[1,3]dioxane-4,6-dione 328j (139 mg, 0.5 mmol) was reacted using method A to give the desired product, purified by flash column chromatography (6:1 petrol:ethyl acetate), as a colourless crystalline solid (32.8 mg, 37%).

5-(4-nitrobenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione 367j (140 mg, 0.5 mmol) was reacted using method B to give the desired product, purified by flash column chromatography, as a colourless crystalline solid (81.6 mg, 91%).

5-(4-nitrobenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione 367j (140 mg, 0.5 mmol) was reacted using method C to give the desired product, purified by flash column chromatography, as a colourless crystalline solid (82.2 mg, 92%).

\( R_f \) (6:1 petrol:ethyl acetate) 0.19; mp (EtOH) 106-108 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 9.82 (1H, t, \( J = 1.1 \) Hz, CHO), 8.14 (2H, d, \( J = 8.7 \) Hz, ArH), 7.36 (2H, d, \( J = 8.7 \) Hz, ArH), 3.05 (2H, t, 7.2 Hz, ArCH\(_2\)), 2.88-2.83 (2H, m, CH\(_2\)CHO); \(^{13}\)C NMR (75.5 MHz, CDCl\(_3\)) \( \delta \) 200.6, 148.7, 147.0, 129.7, 124.2, 44.9, 28.2; HRMS (ESI) calcd for C\(_9\)H\(_{10}\)NO\(_3\) [M+H]\(^+\) : \( m/z \) 180.0661, found 180.0660; Anal. calcd for C\(_9\)H\(_9\)NO\(_3\): C 60.3, H 5.06, N 7.82, found: C 60.0, H 5.25, N 7.69. Data identical to literature values.\(^{21}\)
5.15.11: 3-(4-benzyloxyphenyl)-propanal 368k

5-(4-benzyloxybenzylidene)-2,2-dimethyl-[1,3]dioxane-4,6-dione 328k (169 mg, 0.5 mmol) was reacted using method A to give the desired product, purified by flash column chromatography (9:1 petrol:ethyl acetate), as a white solid (54.4 mg, 45%).

5-(4-benzyloxybenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione 367k (170 mg, 0.5 mmol) was reacted using method C to give the desired product, purified by flash column chromatography, as a white solid (88.5 mg, 74% yield).

\[ R_f \text{ (9:1 petrol:ethyl acetate) 0.27; } \]
\[ \text{mp (petrol) 87-88}^\circ \text{C; } ^1\text{H NMR (300 MHz, CDCl}_3\text{) } \delta 9.82 (1\text{H, t, } J=1.5 \text{ Hz, CHO}), 7.45-7.29 (5\text{H, m, ArH}), 7.11 (2\text{H, d, } J=8.7 \text{ Hz, ArH}), 6.91 (2\text{H, d, } J=8.7 \text{ Hz, ArH}), 5.05 (2\text{H, s, PhCH}_2\text{O}), 2.91 (2\text{H, t, } J=7.5 \text{ Hz, ArCH}_2\text{}), 2.75 (2\text{H, m, CH}_2\text{CHO}); ^{13}\text{C NMR (75.5 MHz, CDCl}_3\text{) } \delta 202.1, 157.7, 137.5, 133.0, 129.7, 129.0, 128.3, 127.9, 115.4, 70.5, 45.9, 27.7; \]
\[ \text{HRMS (ESI) calcd for C}_{16}\text{H}_{16}\text{NaO}_2 \text{ [M+Na]}^+: m/z 263.1048, \text{found } m/z 263.1041; \]
\[ \text{Anal. calcd for C}_{16}\text{H}_{16}\text{O}_2: C 80.0, \text{H 6.71, found: C 80.8, H 6.66. Data identical to literature values.}^{22} \]

5.15.12: 3-(2-naphthyl)-propanal 368l

5-(2-naphthalen-2-methyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione 367l (139 mg, 0.5 mmol) was reacted using method C to give the desired product, purified by flash column chromatography (12:1 petrol:ethyl acetate), as a yellow oil (58.5 mg, 65%); \[ R_f \text{ (12:1 petrol:ethyl acetate) 0.24; } ^1\text{H NMR (300 MHz, CDCl}_3\text{) } \delta 9.85 (1\text{H, t, } J=1.4 \text{ Hz, CHO}), 7.85-7.77 (3\text{H, m, ArH}), 7.65 (1\text{H, s, ArH}), 7.53-7.42 (2\text{H, m, ArH}), 7.34 (1\text{H, dd, } J^1=8.5 \text{ Hz, } J^2=1.9 \text{ Hz, ArH}), 3.13 (2\text{H, d, } J=7.6 \text{ Hz, ArCH}_2\text{}), 2.90-2.83 (2\text{H, m, CH}_2\text{CHO}); ^{13}\text{C NMR (75.5 MHz, CDCl}_3\text{) } \delta 201.9, 138.3, 134.0, 132.6, 128.7, 128.1, 127.9, 127.3, 126.9, 126.6, 125.9, 45.6, 28.7; \]
\[ \text{HRMS (ESI) calcd for C}_{13}\text{H}_{11}\text{O } \text{[M-H]}^-: m/z 183.0810, \text{found } 183.0810. \]
\[ \text{Data identical to literature values.}^{23} \]
5.15.13: 3-(4-bromophenyl)-propanal 368n

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

5-(4-bromobenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione 367n (157 mg, 0.5 mmol) was reacted using method C to give the desired product, purified by flash column chromatography (12:1 petrol:ethyl acetate), as a colourless oil (84.3 mg, 79%); \( R_f \) (12:1 petrol:ethyl acetate) 0.28; IR (neat, cm\(^{-1}\)) 2826, 2728 (CHO); 1723 (C=O); 650 (C-Br); \(^1\)H NMR (250 MHz, CDCl\(_3\)) \( \delta \) 9.80 (1H, t, \( J = 1.3 \) Hz, CHO), 7.39 (2H, d, \( J = 8.5 \) Hz, ArH), 7.07 (2H, d, \( J = 8.5 \) Hz, ArH), 2.91 (2H, t, \( J = 7.3 \) Hz, ArCH\(_2\)), 2.77 (2H, m, CH\(_2\)CHO); \(^{13}\)C NMR (75.5 MHz, CDCl\(_3\)) \( \delta \) 199.9, 138.3, 130.6, 129.0, 119.0, 44.0, 26.4; HRMS (ESI) calcd for C\(_9\)H\(_9\)BrNaO [M+Na]\(^+\): \( m/z \) 234.9729, found 234.9735.

5.15.14: (S)-\( \text{tert} \)-butyl 2-(3-oxopropyl)pyrrolidine-1-carboxylate 368o

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

To a solution of (S)-\( \text{tert} \)-butyl 2-((2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)methyl)pyrrolidine-1-carboxylate 367o (818.4 mg, 2.5 mmol) in tetrahydrofuran (15 mL) was added triethylamine (700 \( \mu \)L, 5 mmol) followed by phenylsilane (925 \( \mu \)L, 7.5 mmol). The solution was allowed to stir for 2 hours at room temperature before water (5 mL) was added. The reaction mixture was dissolved in diethyl ether (100 mL) and washed with water (2 x 100 mL) followed by saturated brine (100 mL). The organic phase was extracted, dried over MgSO\(_4\) and concentrated in vacuo. The residue was purified by flash column chromatography (10:1 petrol:ethyl acetate) to give the desired product, a mixture of rotamers, as a colourless oil (428 mg, 75%); \( R_f \) (10:1 petrol:ethyl acetate) 0.21; \([\alpha]_D^{24}\) +160.3 (c 0.56, CHCl\(_3\)); IR (neat, cm\(^{-1}\)) \( \nu \) 2880, 2722 (C-H), 1724, 1690 (C=O); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 9.72 (1H, brs, CHO), 3.80 (1H, brs, BocNCH\(_2\)), 3.38-3.20 (2H, m, BocNCH\(_2\) and BocNCH), 2.53-2.37 (2H, m, CH\(_2\)CHO), 2.00-1.55 (6H, m), 1.41 (9H, s, C(CH\(_3\))\(_3\)); \(^{13}\)C NMR (75.5 MHz, CDCl\(_3\)) \( \delta \) 202.6 and 202.2, 155.25, 79.8 and 79.5, 56.8, 46.9 and 46.6, 41.2, 31.2 and 30.6, 28.9, 27.4, 24.1 and 23.3; HRMS (ESI) calcd for C\(_{12}\)H\(_{21}\)NNaO\(_3\) [M+Na]\(^+\): \( m/z \) 250.1419, found : \( m/z \) 250.1417.
5.16 Synthesis of 3,5-Disubstituted Pyrrolidines

5.16.1: (S)-tert-butyl 5-benzyl-2-oxo-3-(propan-2-ylidene)pyrrolidine-1-carboxylate

To a solution of (R)-tert-butyl 1-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-3-phenylpropan-2-ylcarbamate 367p (189 mg, 0.5 mmol) in tetrahydrofuran (3 mL) was added triethylamine (139 µL, 1.0 mmol) followed by phenylsilane (185 µL, 1.5 mmol). The reaction mixture allowed to stir at ambient temperature for 20 hours. The reaction mixture was dissolved in ethyl acetate (50 mL) and washed with water (2 x 50 mL) and saturated brine (50 mL). The organic phase was extracted, dried over MgSO$_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (12:1 petrol:ethyl acetate) to give the desired compound as a colourless oil (71.4 mg, 45%); $R_f$ (12:1 petrol:ethyl acetate) 0.20; IR (neat, cm$^{-1}$) ν 2979, 2932 (C-H), 1772, 1707 (C=O), 1662 (C=C); $^1$H NMR (300 MHz, CDCl$_3$) δ 7.33-7.17 (5H, m, ArH), 4.34-4.26 (1H, m, NC$_{H}$), 3.18 (1H, dd, $J^1 = 13.2$ Hz, $J^2 = 3.4$ Hz, ArCH$_2$), 2.53 (1H, dd, $J^1 = 13.2$ Hz, $J^2 = 9.4$ Hz, ArCH$_2$), 2.47-2.37 (2H, m, CCH$_2$CH), 2.21 (3H, s, C(CH$_3$)$_2$), 1.75 (3H, s, C(CH$_3$)$_2$), 1.59 (9H, s, C(CH$_3$)$_3$); $^{13}$C NMR (75.5 MHz, CDCl$_3$) δ 167.3, 151.3, 149.2, 137.7, 129.8, 129.0, 127.1, 123.4, 82.9, 55.4, 41.3, 29.0, 28.6, 24.5, 20.3; HRMS (ESI) calcd for C$_{19}$H$_{25}$NNaO$_3$ [M+Na]$^+$: m/z 338.1732, found 338.1715.
5.17 Deuterium Labelling Studies

5.17.1: 1,3-dideuterated-3-(4-methoxyphenyl) propionaldehyde 382a

To a solution of 5-(4-methoxybenzylidene)-2,2-dimethyl-[1,3]dioxane-4,6-dione 328a (131 mg, 0.5 mmol), molybdenum hexacarbonyl (6.6 mg, 5 mol%) and N-methylmorpholine N-oxide (5.9 mg, 0.044 mmol, 9 mol%) in tetrahydrofuran (3 mL) was added trideuteriophenylsilane (185 µL, 1.5 mmol). The resulting solution was stirred under an atmosphere of nitrogen at 80 °C for 16 h. After cooling to room temperature water (0.5 mL) was added and the solution stirred for 15 minutes. The solution was dissolved in ether (50 mL) was washed with 1 M NaOH (3 x 50 mL) followed by brine (2 x 50 mL). The organic phase was extracted, dried over MgSO\textsubscript{4} and concentrated \textit{in vacuo}. The desired product was isolated by flash column chromatography (11:1 petrol:ethyl acetate) as a colourless oil (65.1 mg, 79%); 100% deuterium incorporation; \(R_f\) (11:1 petrol:ethyl acetate) 0.21; IR (neat, cm\textsuperscript{-1}) \(v\) 2081 (C-D), 1709 (C=O), 1246 (C-O); \(^1\)H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 7.11 (2H, d, \(J = 8.7\) Hz, ArH), 6.84 (2H, d, \(J = 8.7\) Hz, ArH), 3.79 (3H, s, OCH\textsubscript{3}), 2.92-2.86 (1H, m, CH\textsubscript{D}), 2.74 (2H, d, \(J = 7.9\) Hz, CH\textsubscript{2}CDO); \(^2\)H NMR (77 MHz, DCM) \(\delta\) 9.75 (s, CDO), 2.84 (s, ArCHD); \(^13\)C NMR (75.5 MHz, CDCl\textsubscript{3}) \(\delta\) 201.9 (t, \(J = 26.0\) Hz), 158.5, 132.7, 129.6, 114.4, 55.7, 45.7, 29.3 (t, \(J = 19.6\) Hz); HRMS (EI) calcd for C\(_{10}\)H\(_{14}\)D\(_2\)NO [M+NH\(_4^+\)]: \(m/z\) 189.0855, found: \(m/z\) 189.0855.

5.17.2: Preparation of \(\alpha,\alpha\)-dideuterated-3-(4-methoxyphenyl) propionaldehyde 383a

Procedure A: To a solution of 5-(4-methoxybenzylidene)-2,2-dimethyl-[1,3]dioxane-4,6-dione 328a (131 mg, 0.5 mmol), molybdenum hexacarbonyl (6.6 mg, 5 mol%) and N-methylmorpholine N-oxide monohydrate (5.9 mg, 0.044 mmol, 9 mol%) in tetrahydrofuran (3 mL) was added phenylsilane (185 µL, 1.5 mmol). The resulting solution was stirred under an atmosphere of nitrogen at 80 °C for 16 h. After cooling to room temperature deuterium oxide (0.5 mL) was added and the solution stirred for 15 minutes.
Procedure B: To a solution of 5-(4-methoxybenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione 367a (132 mg, 0.5 mmol) in tetrahydrofuran (3 mL) was added triethylamine (139 µL, 1.0 mmol) and phenylsilane (183 µL, 1.5 mmol). The reaction mixture was allowed to stir for 2h at room temperature under an atmosphere of nitrogen. Deuterium oxide (1.0 mL) was added to the reaction mixture and stirred for 15 minute.

Work-up: The reaction mixture was dissolved in diethyl ether (50 mL) and washed with water (50 mL) and brine (50 mL). The organic phase was extracted, dried over MgSO\textsubscript{4} and concentrated \textit{in vacuo}. The desired product was isolated by flash column chromatography (11:1 petrol:ethyl acetate) as a colourless oil (Procedure A: 61.5 mg, 75%; Procedure B: 68.0 mg, 82% yield); 73% deuterium incorporation; \(R_f\) (11:1 petrol:ethyl acetate) 0.21; IR (neat, cm\(^{-1}\)) \(v\) 2836, 2725 (C-H), 1723 (C=O), 1249 (C-O); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 9.81 (1H, s, CHO), 7.11 (2H, d, \(J = 8.7\) Hz, ArH), 6.84 (2H, d, \(J = 8.7\) Hz, ArH), 3.78 (3H, s, OC\(_3\)H\(_3\)), 2.89 (2H, s, ArCH\(_2\)) \(\delta\) 2.64 (s); \(^1\)C NMR (75.5 MHz, CDCl\(_3\)) \(\delta\) 202.3, 158.5, 132.7, 129.6, 114.4, 55.7, 45.5 (t, \(J = 28.5\) Hz CD\(_2\)), 27.6; HRMS (EI) calcd for C\(_{10}\)H\(_{10}\)D\(_2\)NaO [M+Na]\(^+\): \(m/z\) 189.0855, found: \(m/z\) 189.0858.

5.17.3: Preparation of 1-deuterated-3-(4-methoxyphenyl) propionaldehyde 412a

To a solution of 5-(4-methoxybenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione 467a (132 mg, 0.5 mmol) in tetrahydrofuran (3 mL) was added triethylamine (139 µL, 1.0 mmol) and trideuterophenylsilane\(^{24}\) (190 µL, 1.5 mmol). The reaction mixture was allowed to stir for 2h at room temperature under an atmosphere of nitrogen. Water (1.0 mL) was added to the reaction mixture and stirred for 15 minute. The reaction mixture was dissolved in diethyl ether (50 mL) and washed with water (50 mL) and brine (50 mL). The organic phase was extracted, dried over MgSO\textsubscript{4} and concentrated \textit{in vacuo}. The desired product was isolated by flash column chromatography (11:1 petrol:ethyl acetate) as a colourless oil (70.4 mg, 85%); 100% deuterium incorporation; \(R_f\) (11:1 petrol:ethyl acetate) 0.21; IR (neat, cm\(^{-1}\)) \(v\) 2279 (C-D), 1712 (C=O), 1247 (C-O); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.11 (2H, d, \(J = 8.7\) Hz, ArH), 6.84 (2H, d, \(J = 8.7\) Hz, ArH), 3.78 (3H, s, OCH\(_3\)), 2.91 (2H, t, \(J = 7.5\) Hz, ArCH\(_2\)) 2.74 (2H, t, \(J = 7.5\) Hz, CH\(_2\)CDO); \(^2\)H NMR (77 MHz, DCM) \(\delta\) 9.75 (s); \(^1\)C NMR
(75.5 MHz, CDCl$_3$) $\delta$ 201.9 (t, $J = 26.0$ Hz), 158.5, 132.8, 129.6, 114.4, 55.7, 45.8, 27.7; HRMS (EI) calcd for C$_{10}$H$_{10}$DNaO [M+Na]$^+$: $m/z$ 187.0855, found: $m/z$ 187.0854.

5.18 One-Pot Aldehyde Formation Reductive Amination

Method A: Using Pd/C, H$_2$

\[
\begin{align*}
\text{R'} & \quad \text{O} \\
\text{O} & \quad \text{R''}
\end{align*}
\]

To a solution of 5-monoalkyl Meldrum’s acid (0.5 mmol) in tetrahydrofuran (3 mL) was added triethylamine (139 $\mu$L, 1 mmol) followed by phenylsilane (185 $\mu$L, 1.5 mmol). The reaction mixture was stirred for 2 hours at room temperature. Methanol (1 mL) was added to the reaction mixture and stirred for 15 minutes before amine was added (1 mmol) and stirred for a further hour. 10% palladium on activated carbon (50 mg) was added and hydrogen gas bubbled through the solution. The reaction mixture was left for 16 hours. The reaction mixture was then passed through a pad of celite and concentrated in vacuo. The residue was dissolved in ethyl acetate (25 mL) and washed with 1 M HCl$_{aq}$ (3 x 25 mL). The aqueous phase was basified with 1 M NaOH$_{aq}$ and washed with DCM (3 x 50 mL). The combined organic phases were dried over MgSO$_4$ and concentrated in vacuo.

Method B: Using Na(OAc)$_3$BH

\[
\begin{align*}
\text{R'} & \quad \text{O} \\
\text{O} & \quad \text{R''}
\end{align*}
\]

To a solution of 5-substituted Meldrum’s acid derivative (0.5 mmol) in tetrahydrofuran (3 mL) was added triethylamine (139 $\mu$L, 1.0 mmol) followed by phenylsilane (185 $\mu$L, 1.5 mmol). The reaction mixture was stirred for 2 hours at room temperature. Methanol (1 mL) was added to the reaction mixture and stirred for 15 minutes before amine was added (1 mmol) and stirred for a further hour. Sodium triacetoxyborohydride (212 mg, 1.0 mmol) was added and the reaction mixture was left to stir for 16 hours. The reaction mixture was dissolved in ethyl acetate (25 mL) and the organic phase was then extracted with 1 M HCl$_{aq}$ (3 x 25 mL). The combined aqueous phases basified with 1 M NaOH$_{aq}$ and extracted with
DCM (3 x 50 mL). The combined organic phases were dried over MgSO₄ and concentrated in vacuo.

5.18.1: N,N-diisopropyl-3-(4-methoxybenzene)propan-1-amine 414aa

5-(4-methoxybenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione 367a (132 mg, 0.5 mmol) and diisopropylamine 415a (140 µL, 1.0 mmol) were reacted using method A to give the desired product as a colourless oil (77.7 mg, 63%).

IR (neat, cm⁻¹) ν 3001, 2968, 2875 (C-H), 1245 (C-O);

1H NMR (300 MHz, CDCl₃) δ 7.11 (2H, d, J = 8.7 Hz, ArH), 6.83 (2H, d, J = 8.7 Hz, ArH), 3.79 (3H, s, OCH₃), 3.04 (2H, sept, J = 6.4 Hz, CH(CH₃)₂), 2.55 (2H, t, J = 7.5 Hz, ArCH₂), 2.45 (2H, t, J = 7.5 Hz, CH₂N), 1.74 (2H, quin, J = 7.5 Hz, CH₂CH₂CH₂), 1.01 (12H, d, J = 6.4 Hz, CH(CH₃)₂);

13C NMR (75.5 MHz, CDCl₃) δ 156.5, 133.6, 128.2, 112.6, 54.2, 47.7, 44.0, 31.9, 31.7, 19.5; HRMS (ESI) calcd for C₁₆H₂₈NO [M+H]⁺: m/z 250.2171, found 250.2177.

5.18.2: N,N-dimethyl-3-(4-methoxybenzene)propan-1-amine 414ab

5-(4-methoxybenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione 367a (132 mg, 0.5 mmol) and dimethylamine (2M solution in THF) 415b (1 mL, 1.0 mmol) were reacted using method A to give the desired product, purified by flash column chromatography (98:2 ethyl acetate:methanol), as a colourless oil (50.0 mg, 52%); RF (98:2 ethyl acetate:methanol) 0.18; 1H NMR (300 MHz, CDCl₃) δ 7.10 (2H, d, J = 8.7 Hz, ArH), 6.82 (2H, d, J = 8.7 Hz, ArH), 3.78 (3H, s, OCH₃), 2.58 (2H, t, J = 7.5 Hz, ArCH₂), 2.28 (2H, t, J = 7.5 Hz, NCH₂), 2.22 (6H, s, N(CH₃)₂), 1.76 (2H, quin, J = 7.5 Hz, CH₂CH₂CH₂);

13C NMR (75.5 MHz, CDCl₃) δ 158.1, 134.7, 129.6, 114.1, 59.7, 55.6, 45.9, 33.1, 30.1; HRMS (ESI) calcd for C₁₂H₂₀NO [M+H]⁺: m/z 194.1545, found 194.1540. Data identical to literature values.²⁵
5.18.3: N-phenyl-3-(4-methoxybenzene)propane-1-amine 414ac

![Chemical Structure]

5-(4-methoxybenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione 367a (132 mg, 0.5 mmol) and aniline 415c (91 µL, 1.0 mmol) were reacted using method A to give the desired product, purified by flash column chromatography (ethyl acetate), as a colourless oil (57.9 mg, 48%); $R_f$ (ethyl acetate) 0.22; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.23 (2H, dd, $J^1$ = 8.7 Hz, $J^2$ = 7.5 Hz, ArH), 7.18 (2H, d, $J$ = 8.7 Hz, ArH), 6.91 (2H, d, $J$ = 8.7 Hz, ArH), 6.76 (1H, t, $J$ = 7.5 Hz, ArH), 6.64 (2H, d, $J$ = 7.5 Hz, ArH), 3.85 (3H, s, OCH$_3$), 3.32 (1H, brs, NH), 3.18 (2H, t, $J$ = 7.2 Hz, ArCH$_2$), 2.74 (2H, t, $J$ = 7.2 Hz, NCH$_2$), 1.97 (2H, quin, $J$ = 7.2 Hz, CH$_3$CH$_2$CH$_2$); $^{13}$C NMR (75.5 MHz, CDCl$_3$) $\delta$ 156.8, 147.3, 132.7, 128.3, 128.2, 116.1, 112.8, 111.7, 54.2, 42.3, 31.4, 30.2; HRMS (ESI) calcd for C$_{16}$H$_{20}$NO [M+H]$^+$ : $m/z$ 242.1545, found 242.1528. Data identical to literature values.$^{26}$

5.18.4: 4-(3-(4-methoxyphenyl)propyl)morpholine 414ad

![Chemical Structure]

5-(4-methoxybenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione 367a (132 mg, 0.5 mmol) and morpholine 415d (88 µL, 1.0 mmol) were reacted using method A to give the desired product, purified by flash column chromatography (ethyl acetate), as a colourless oil (48.0 mg, 41%); $R_f$ (ethyl acetate) 0.23; IR (neat, cm$^{-1}$) $\nu$ 3011, 2944, 2859, 2813 (C-H), 1246, 1117 (C-O); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.09 (2H, d, $J$ = 8.7 Hz, ArH), 6.81 (2H, d, $J$ = 8.7 Hz, ArH), 3.77 (3H, s, OCH$_3$), 3.70 (4H, t, $J$ = 4.5 Hz, O(CH$_2$)$_2$), 2.58 (2H, t, $J$ = 7.5 Hz, ArCH$_2$), 2.42 (4H, t, $J$ = 4.5 Hz, N(CH$_2$)$_2$), 2.34 (2H, t, $J$ = 7.5 Hz, NCH$_2$) 1.77 (2H, quin, $J$ = 7.5 Hz, CH$_2$CH$_2$CH$_2$); $^{13}$C NMR (75.5 MHz, CDCl$_3$) $\delta$ 158.2, 134.5, 129.7, 114.1, 67.4, 58.7, 55.6, 54.1, 33.1, 28.9; HRMS (ESI) calcd for C$_{14}$H$_{22}$NO$_2$ [M+H]$^+$ : $m/z$ 236.1651, found 236.1638.
5.18.5: 1-(3-(4-methoxyphenyl)propyl)piperidine 414ae

5-(4-methoxybenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione 367a (132 mg, 0.5 mmol) and piperidine 415e (0.1 mL, 1.0 mmol) were reacted using method A to give the desired product, purified by flash column chromatography (ethyl acetate), as a colourless oil (57.9 mg, 50%); \( R_f \) (ethyl acetate) 0.24; IR (neat, \( \text{cm}^{-1} \)) \( v \) 2938, 2855, 2804, 2769 (C-H), 1245 (C-O); \( ^{1} \text{H} \) NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.09 (2H, d, \( J = 8.7 \text{ Hz} \), ArH), 6.81 (2H, d, \( J = 8.7 \text{ Hz} \), ArH), 3.77 (3H, s, OC\(_3\)H\(_3\)), 2.56 (2H, t, \( J = 7.9 \text{ Hz} \), ArCH\(_2\)), 2.38-2.28 (6H, m, N(CH\(_2\))\(_3\)) 1.79 (2H, quin, \( J = 7.9 \text{ Hz} \), CH\(_2\)CH\(_2\)CH\(_2\)), 1.58 (4H, quin, \( J = 5.7 \text{ Hz} \), CH\(_2\)), 1.46-1.38 (2H, m, CH\(_2\)); \( ^{13} \text{C} \) NMR (75.5 MHz, CDCl\(_3\)) \( \delta \) 158.1, 134.8, 129.6, 114.1, 59.3, 55.6, 55.0, 33.4, 29.3, 26.4, 24.9; HRMS (ESI) calcd for C\(_{15}\)H\(_{24}\)NO [M+H]\(^+\) : \( m/z \) 234.1858, found 234.1857.

5.18.6: N-benzyl-N-methyl-3-(4-methoxybenzene)propane-1-amine 414af

5-(4-methoxybenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione 367a (132 mg, 0.5 mmol) and N-benzyl-N-methylamine 415f (0.1 mL, 1.0 mmol) were reacted using method A to give the desired product, purified by flash column chromatography (ethyl acetate), as a colourless oil (68.1 mg, 52%); \( R_f \) (ethyl acetate) 0.18; IR (neat, \( \text{cm}^{-1} \)) \( v \) 3028, 2939, 2836, 2790 (C-H), 1246 (C-O); \( ^{1} \text{H} \) NMR (250 MHz, CDCl\(_3\)) \( \delta \) 7.36-7.27 (5H, m, ArH), 7.10 (2H, d, \( J = 8.5 \text{ Hz} \), ArH), 6.83 (2H, d, \( J = 8.5 \text{ Hz} \), ArH), 3.80 (3H, s, OCH\(_3\)), 3.52 (2H, s, NCH\(_2\)Ph), 2.60 (2H, t, \( J = 7.6 \text{ Hz} \), ArCH\(_2\)), 2.43 (2H, t, \( J = 7.6 \text{ Hz} \), CH\(_2\)N), 2.21 (3H, s, NCH\(_3\)), 1.83 (2H, quin, \( J = 7.9 \text{ Hz} \), CH\(_2\)CH\(_2\)CH\(_2\)); \( ^{13} \text{C} \) NMR (75.5 MHz, CDCl\(_3\)) \( \delta \) 158.1, 140.0, 134.9, 129.7, 129.5, 128.6, 127.3, 114.1, 62.7, 57.2, 55.7, 42.6, 33.1, 29.8; HRMS (EI) calcd for C\(_{18}\)H\(_{24}\)NO [M+H]\(^+\) : \( m/z \) 270.1858, found 270.1853.
5.18.7: *N*-benzyl-3-(4-methoxybenzene)propane-1-amine 414ag

5-(4-methoxybenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione 367a (132 mg, 0.5 mmol) and benzylamine 415g (0.11 mL, 1.0 mmol) were reacted using method A to give the desired product (47.8 mg, 37%); IR (neat, cm$^{-1}$) $\nu$ 3064 (N-H), 3030, 3004, 2955, 2836 (C-H) 1249 (C-O); $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 7.28-7.14 (5H, m, ArH), 7.01 (2H, d, $J = 8.8$ Hz, ArH), 6.74 (2H, d, $J = 8.8$ Hz, ArH), 3.70 (5H, s, OCH$_3$ and NCH$_2$Ph), 2.58 (2H, t, $J = 7.3$ Hz, ArCH$_2$), 2.52 (2H, t, $J = 7.3$ Hz, CH$_2$N), 2.25 (1H, brs, NH), 1.72 (2H, quin, $J = 7.3$ Hz, CH$_2$CH$_2$CH$_2$); $^{13}$C NMR (75.5 MHz, CDCl$_3$) $\delta$ 156.7, 139.4, 133.2, 128.2, 127.4, 127.1, 125.9, 112.7, 54.2, 53.0, 47.9, 31.7, 30.9; HRMS (EI) calcd for C$_{17}$H$_{22}$NO $[M+H]^+$: $m/z$ 256.1701, found 256.1686.

5.18.8: *N,N*-diisopropyl-3-(3,4-dimethoxyphenyl)propan-1-amine 414ga

5-(3,4-dimethoxybenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione 367g (147 mg, 0.5 mmol) and diisopropylamine 415a (140 µL, 1.0 mmol) was reacted using method A to give the desired product, purified by flash column chromatography (4:1 petrol:ethyl acetate), as a colourless oil (81.2 mg, 56%); $R_f$ (4:1 petrol:ethyl acetate) 0.27; IR (neat, cm$^{-1}$) $\nu$ 2963, 2902, 2877 (C-H), 1261, 1235 (C-O); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 6.80-6.70 (3H, m, ArH), 3.87 (3H, s, OCH$_3$), 3.86 (3H, s, OCH$_3$), 3.03 (2H, sept, $J = 6.4$ Hz, NCH(CH$_3$)$_2$), 2.55 (2H, t, $J = 7.9$ Hz, ArCH$_2$), 2.44 (2H, t, $J = 7.9$ Hz, CH$_2$N), 1.74 (2H, quin, $J = 7.5$ Hz, CH$_2$CH$_2$CH$_2$), 1.00 (12H, d, $J = 6.4$ Hz, NCH(CH$_3$)$_2$); $^{13}$C NMR (75.5 MHz, CDCl$_3$) $\delta$ 149.2, 147.4, 135.6, 120.5, 112.0, 111.5, 56.3, 56.2, 48.8, 45.5, 33.6, 21.0, 18.6; HRMS (ESI) calcd for C$_{17}$H$_{30}$NO$_2$ [M+H]$^+$: $m/z$ 280.2277, found 280.2259.
5.18.9: \( N,N\)-diisopropyl-3-(4-hydroxyphenyl)propan-1-amine 416ka

\[
\begin{align*}
\text{HO} &-\text{N} \\
\text{5-(4-benzyloxybenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione 367k} &\text{ (170 mg, 0.5 mmol) and} \\
\text{diisopropylamine 415a} &\text{ (140 \( \mu \text{L}, 1.0 \text{ mmol}) was reacted using method A to give the desired} \\
\text{product as a colourless oil (67.3 mg, 57\%); IR (neat, cm}^{-1} \text{) \( \nu \) 3414 (O-H), 2945, 2853 (C-H);} \\
\text{\( ^1\text{H NMR (300 MHz, CDCl}_3 \text{) } \delta \) 7.00 (2H, d, \( J = 8.7 \text{ Hz, ArH} \)), 6.75 (2H, d, \( J = 8.7 \text{ Hz, ArH} \)), 3.09 (2H, sept, \( J = 6.4 \text{ Hz, NCH(CH}_3}_2 \)), 2.50 (2H, t, \( J = 7.5 \text{ Hz, ArCH}_2 \)), 2.47 (2H, t, \( J = 7.5 \text{ Hz, CH}_2\text{N} \)), 1.77 (2H, quin, \( J = 7.5 \text{ Hz, CH}_2\text{CH}_2\text{CH}_2 \)), 1.04 (12H, d, \( J = 6.4 \text{ Hz, NCH(CH}_3}_2 \));} \\
\text{\( ^{13}\text{C NMR (75.5 MHz, CDCl}_3 \text{) } \delta \) 154.6, 134.2, 129.7, 116.2, 49.3, 45.6, 33.3, 33.0, 20.8; HRMS (ESI) calcd for C_{15}H_{26}NO \ [M+H]^+ : m/z 236.2014, found 236.2004.} \end{align*}
\]

5.18.10: \( N,N\)-diisopropyl-3-(4-benzyloxyphenyl)propan-1-amine 414ka

\[
\begin{align*}
\text{BnO} &-\text{N} \\
\text{5-(4-benzyloxybenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione 367k} &\text{ (170 mg, 0.5 mmol) and} \\
\text{diisopropylamine 415a} &\text{ (140 \( \mu \text{L}, 1.0 \text{ mmol}) was reacted using method B to give the desired} \\
\text{product as a colourless oil (52.8 mg, 32\%); IR (neat, cm}^{-1} \text{) \( \nu \) 2968, 2855 (C-H) 1238 (C-O);} \\
\text{\( ^1\text{H NMR (300 MHz, CDCl}_3 \text{) } \delta \) 7.46-7.30 (5H, m, ArH), 7.12 (2H, d, \( J = 8.7 \text{ Hz, ArH} \)), 6.91 \text{ (2H, d, \( J = 8.7 \text{ Hz, ArH} \)), 5.05 (2H, s, PhCH}_2\text{O), 3.05 (2H, sept, \( J = 6.4 \text{ Hz, NCH(CH}_3}_2 \)),} \\
\text{2.56 (2H, t, \( J = 7.9 \text{ Hz, ArCH}_2 \)), 2.46 (2H, t, \( J = 7.9 \text{ Hz, CH}_2\text{N} \)), 1.76 (2H, quin, \( J = 7.9 \text{ Hz, CH}_2\text{CH}_2\text{CH}_2 \)), 1.03 \text{ (12H, d, \( J = 6.4 \text{ Hz, NCH(CH}_3}_2 \)); \} \\
\text{\( ^{13}\text{C NMR (75.5 MHz, CDCl}_3 \text{) } \delta \) 155.8, 136.2, 133.9, 128.2, 127.5, 126.8, 126.45, 113.6, 69.0, 49.0, 47.9, 44.0, 31.7, 19.5;} \\
\text{HRMS (ESI) calcd for C}_{22}\text{H}_{32}\text{NO} \ [M+H]^+ : m/z 326.2484, found 326.2483.} \end{align*}
\]
5.18.11: \(\text{N,\text{N-diisopropyl-3-(2-Naphthyl)propan-1-amine 414la}\)

\[
\text{N,\text{N-diisopropyl-3-(2-Naphthyl)propan-1-amine 414la}}
\]

\[
5-(2\text{-naphthalen-2-methyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione 367l \ (139 \text{ mg, 0.5 mmol})}
\]

and diisopropylamine \(415a\) (140 \(\mu\text{L, 1.0 mmol}\)) was reacted using method A to give the desired product, purified by flash column chromatography (4:1 petrol:ethyl acetate), as a yellow oil (55.1 mg, 41%); \(R_f\) (4:1 petrol:ethyl acetate) 0.25; IR (neat, cm\(^{-1}\)) \(\nu \text{ 2978, 2912, 1845, (C-H)}; \)

\(\text{1H NMR (300 MHz, CDCl}_3\): \(\delta \text{ 7.84-7.65 (3H, m, ArH), 7.65 (1H, s, ArH), 7.50-7.40 (2H, m, ArH), 7.37 (1H, dd, \(J^1 = 8.7 \text{ Hz, } J^2 = 1.9 \text{ Hz, ArH}), 3.06 (2H, sept, \(J = 6.6 \text{ Hz, NCH(CH}_3\}_2\)), 2.80 (2H, t, \(J = 7.5 \text{ Hz, ArCH}_2\)), 2.52 (2H, t, \(J = 7.5 \text{ Hz, } CH_2N\)), 1.87 (2H, quin, } J = 7.5 \text{ Hz, } CH_2CH_2CH_2, 1.04 (12H, d,} \(J = 6.6 \text{ Hz, NCH(CH}_3\}_3\)); \(\text{13C NMR (75.5 MHz, CDCl}_3\):} \(\delta 140.7, 134.1, 132.4, 128.2, 128.0, 127.8, 126.7, 126.4, 126.2, 125.4, 49.0, 45.4, 34.3, 33.1, 21.1; HRMS (ESI) calcd for } C_{19}H_{28}N [M+H]^+ : m/z 270.2222, found : m/z 270.2204. \)

5.18.12: \(\text{(R)-tert-butyl 2-(3-(diisopropylamino)propyl)pyrrolidine-1-carboxylate 414o}\)

\[
\text{(R)-tert-butyl 2-(3-(diisopropylamino)propyl)pyrrolidine-1-carboxylate 414o}}
\]

\(\text{(S)-tert-butyl 2-((2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)methyl)pyrrolidine-1-carboxylate 367o \ (164 mg, 0.5 mmol) and diisopropylamine 415a (140 \(\mu\text{L, 1.0 mmol}) was reacted using method A to give the desired product, purified by flash column chromatography (ethyl acetate), as a colourless oil (95.1 mg, 61%); } \(\text{R}_f\) (ethyl acetate) 0.28; \([\alpha]_D^{24} +383.3 (c 0.06, CHCl}_3); \text{ IR (neat, cm}^{-1}\) 2971, 2875 (C-H), 1680 (C=O); \text{1H NMR (300 MHz, CDCl}_3\):} \(\delta 3.70 (1H, brs, BocNC}_H}_2\), 3.40-3.25 (2H, m, BocNC}_H}_2 and BocNC}_H), 2.99 (2H, sept, } J = 6.4 \text{ Hz, NCH(CH}_3\}_2\), 2.45 (2H, m, NCH}_2\), 2.00-1.59 (5H, m), 1.46 (9H, s, C(CH}_3\}_3\), 1.44-1.18 (3H, m), 1.00 (12H, d, } J = 6.4 \text{ Hz, N(CH(CH}_3\}_3\)); \(\text{13C NMR (75.5 MHz, CDCl}_3\):} \(\delta 155.1, 79.3, 57.7, 48.9, 46.5, 45.8, 32.9, 31.1, 29.0, 24.2, 23.5, 21.1; HRMS (ESI) calcd for } C_{18}H_{37}N_2O_2 [M+H]^+ : m/z 313.2855, found : m/z 313.2844. \)
5.19 References