New Synthetic Methodologies for Hypervalent Iodine(III)-Mediated Atom-transfer Reactions

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Hypervalent iodine(III) compounds are attractive reagents in organic synthesis. The main advantages include their low cost and low toxicity. In particular, they have been used as atom-transfer reagents to introduce nucleophiles such as chloride and fluoride into organic compounds. In chapter two, a one-pot synthetic method was designed to introduce a variety of nucleophiles into the 2-position of 1,3-dicarbonyl compounds using fluoroiodane. Chloride, methoxy and ethoxy groups were introduced into a series of 1,3-dicarbonyl compounds in moderate to high yields (32-90 %). The advantage of this method is that only one hypervalent iodine(III) reagent is required to introduce a range of different nucleophiles into the 2-position of 1,3-dicarbonyl compounds, whereas previous methods required a different hypervalent iodine(III) reagent for each nucleophile. Unfortunately, the introduction of either a trifluoromethyl or a trifluoroethoxy group proved unsuccessful due to the low nucleophilicity and steric bulk of these nucleophiles.

In chapter three a catalytic method was developed to introduce chlorine into 1,3-dicarbonyl compounds using 2-(2-iodophenyl)propan-2-ol under mild reaction conditions and in good yields (73-76 %). This methodology was applied to the tosyloxylation and fluorination of a *β*-ketoester with limited success. However, when hexafluoroisopropanol (HFIP) was employed as a solvent, the stoichiometric fluorination was possible. A range of 2-fluoro-1,3-dicarbonyl compounds was synthesised in good to excellent yields using fluoroiodane in HFIP, without the need for $Et_3N.3HF$. ^1H NMR studies provided evidence for the activation of fluoroiodane by hydrogen bonding, due to the formation of a hydrogen bonding adduct between fluoroiodane and HFIP.

Finally, three chiral iodoarenes were synthesised in chapter four and investigated in the enantioselective chlorination of 1,3-dicarbonyl compounds. Only a small enantiomeric excess was obtained due to issues with background chlorination and hydroxylation. The Gilmour system, employing cesium choride and Selectfluor was explored and preliminary work showed no evidence of a competing background reaction.

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Statement

This thesis is based on work conducted by the author in the Department of Chemistry at the University of Leicester, during the period between October 2015 and September 2019. All the work described in the thesis is original unless otherwise stated. This work is not being presented for any other degree.

Signed: _____ Date: _____

Table of Contents

Abstract……..……...i

Acknowledgements.....ii

Abbreviations vii

Chapter 1 Introduction..... 1

1.1 Hypervalent Iodine 1

1.2 Tosyloxylation..... 2

1.2.1 Synthesis of [Hydroxy(tosyloxy)iodo]benzene HTIB 2

1.2.2 Synthetic Applications of HTIBs 5

1.3 Chlorination..... 9

1.3.1 The Importance of Chlorination..... 9

1.3.2 Iodine(III) Chlorinating Reagents 11

1.4 Fluorination 15

1.4.1 The Importance of Fluorination 15

1.4.2 (Difluoroiodo)arenes 17

1.4.3 Togni's Reagents 26

1.4.4 Fluoroiodane..... 30

1.5 References for Chapter 1..... 39

Chapter 2 Atom Transfer Reactions using Fluoroiodane 43

2.1 Project Aims 43

2.2 Synthesis of Fluoroiodane 43

2.3 Synthesis of 1,3-Dicarbonyl Substrates..... 46

2.4 Chlorination of 1,3-Dicarbonyl Substrates..... 48

2.4.1 Chlorination of Ethyl 3-oxo-phenylpropanoate 48

2.4.2 Chlorination of Ethyl 3-(4-methoxyphenyl)-3-oxopropanoate..... 50

2.4.3 Chlorination of Dibenzoylmethane..... 51

2.4.4 Chlorination of *N,N*-Diethyl-3-oxo-3-phenylpropanamide 53

2.4.5 Chlorination of Ethyl 1-oxo-2,3-indanone-2-carboxylate..... 54

2.5 Chlorination of 1,3 Dicarbonyl Substrates using Hydroxyiodane..... 59

2.6 Trifluoromethylation of 1,3-Dicarbonyl Substrates..... 60

2.7 Methoxylation of 1,3-Dicarbonyl Compounds..... 63

2.7.1 Methoxylation of Ethyl 3-(4-methoxyphenyl)-3-oxopropanoate using Hydroxyiodane 67

2.8 Ethoxylation of 1,3-Dicarbonyl Compounds 68

2.9 Trifluoroethoxylation of 1,3-Dicarbonyl Substrates..... 71

2.10 Amination of 1,3-Dicarbonyl Compounds 75
2.10.1 Literature Procedure for the Amination of Ethyl 3-oxo-3-phenylpropanoate . 75
2.10.2 Amination of Ethyl 3-oxo-3-phenylpropanoate 77
2.10.3 Amination using *p*-Toluenesulfonamide 80
2.11 Conclusions and Future Work 82
2.12 References for Chapter 2 84
Chapter 3 Catalytic Chlorination of 1,3-Dicarbonyl Compounds 86
3.1 Introduction 86
3.2 Project Aims 88
3.3 Catalytic Chlorination of 1,3-Dicarbonyl Compounds 89
3.3.1 Catalytic Chlorination of 1,3-Ketoesters using 2-(2-Iodophenyl)propan-2-ol 89
3.3.2 Catalytic Chlorination of *N*,*N*-Diethyl-3-oxo-3-phenylpropanamide using 2-(2-Iodophenyl)propan-2-ol 94
3.4 Catalytic Tosyloxylations 95
3.4.1 Tosyloxylation of Ethyl 3-oxo-3-phenylpropanoate using 1-Fluoro-3,3-dimethyl-1,3-dihydro-λ^3-benzo[*d*][1,2]iodoxole 95
3.4.2 Tosyloxylation of Ethyl 3-oxo-3-phenylpropanoate using 2-(2-Iodophenyl)propan-2-ol 96
3.5 Stoichiometic Fluorinations using 2-(2-Iodophenyl)propan-2-ol 101
3.5.1 Catalytic Fluorinations using 2-(2-Iodophenyl)propan-2-ol 101
3.5.2 Stoichiometric Fluorinations using 2-(2-Iodophenyl)propan-2-ol 102
3.6 Fluorinations in 1,1,1,3,3,3-Hexafluoroisopropanol using 1-Fluoro-3,3-dimethyl-1,3-dihydro-λ^3-benzo[*d*][1,2]iodoxole 106
3.6.1 Fluorination of Ethyl 3-oxo-3-phenylpropanoate in HFIP 106
3.6.2 Synthesis of *N*,*N*-Diethyl-3-(4-methoxyphenyl)-3-oxopropanamide 108
3.6.3 Fluorination of 1,3-Dicarbonyl Compounds in Hexafluoroisopropanol 109
3.6.4 Fluorination of 1,3-Diketones 113
3.6.5 HFIP Mechanistic Studies 116
3.7 Conclusions and Future Work 120
3.8 References for Chapter 3 122
Chapter 4 Enantioselective Chlorination of 1,3-Dicarbonyl Compounds 124
4.1 Enantioselective Chlorinations 124
4.1.1 Metal-Catalysed Enantioselective Chlorinations 124
4.1.2 Organocatalysed Enantioselective Chlorinations 130
4.2 Chiral Hypervalent Iodine Reagents 137
4.3 Project Aims 147
4.4 Preparation of Chiral Iodoarenes 148

4.4.1 Synthesis of Dimethyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))(2*R*, 2'*R*)-dipropionate 148

4.4.2 Synthesis of Dibenzyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))(2*R*,2'*R*)-bis(3-phenylpropanoate) 150

4.4.3 Synthesis of di-*tert*-Butyl 2,2'-((2-iodo-1,3-phenylene)bis)oxy))(2*R*,2'*R*)-dipropionate 153

4.5 Enantioselective Chlorination using *m*-CPBA and HCl 155

4.5.1 Chlorination of Ethyl 1-oxo-2,3-indanone-2-carboxylate 155

4.5.2 Enantioselective Chlorination of Ethyl 1-oxo-2,3-indanone-2-carboxylate using Dimethyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))(2*R*, 2'*R*)-dipropionate 158

4.5.3 Enantioselective Chlorination of Ethyl 1-oxo-2,3-indanone-2-carboxylate using Derivatives of Dimethyl 2,2-((2-iodo-1,3-phenylene)bis(oxy))(2*R*, 2'*R*)-dipropionate 167

4.5.4 Enantioselective Chlorination of *tert*-Butyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate 169

4.5.5 Enantioselective Fluorination of Ethyl 1-oxo-2,3-indanone-2-carboxylate 173

4.5.6 Control Reactions 175

4.6 Enantioselective Chlorination using Selectfluor and CsCl 176

4.7 Conclusions 179

4.8 References for Chapter 4 180

Chapter 5 Conclusions and Future Work 183

Chapter 6 Experimental Section 185

6.1 General Information 185

6.2 Experimental for Chapter 2 186

6.3 Experimental for Chapter 3 204

6.4 Experimental for Chapter 4 214

6.5 References for Chapter 6 228

Abbreviations

Ac Acetyl

ASAP Atmospheric Solids Probe

Bn Benzyl

BOC *tert*-butyloxycarbonyl

D Doublet

DCE Dichloroethane

DCM Dichloromethane

DIAD Diisopropyl azodicarboxylate

DMF Dimethylformamide

DMI Diaminomethylmalonitrile

DSC Differential Scanning Calorimetry

ee Enantiomeric excess

EI Electron Impact

Eq. Equivalents

e.r. Enantiomeric Ratio

ES Electrospray

Et Ethyl

h Hours

HFIP 1,1,1,3,3,3-hexafluoroisopropanol

HPLC High Pressure Liquid Chromatography

HTIB [Hydroxy(tosyloxy)iodo]benzene

iPr Isopropanol

J Coupling Constant

LCD Liquid Crystal Display

m Multiplet

*m*CPBA metachloroperbenzoic acid

m/z Mass/charge ratio

Me Methyl

MeCN Acetonitrile

mp Melting Point

MS Mass spectrometry

NBS *N*-Bromosuccinimide

NCS *N*-Chlorosuccinimide

NFSI *N*-fluorobenzenesulfonimide

NMR Nuclear Magnetic Resonance

PET Positron Emission Tomography

Ts Tosyl

Ph Phenyl

ppm Parts per million

q Quartet

RT Room Temperature

s Singlet

t Triplet

^{t}Bu *tert*-Butyl

TClCA Trichloroisocyanuric Acid

TEMPO 2,2,6,6-Tetra-1-piperidinyloxy

TFA Trifluoroacetic acid

TFE Trifluoroethanol

THF Tetrahydrofuran

$TMSCF_3$ Trimethyl(trifluoromethylsilane)

TREAT-HF Triethylamine Trihydrofluoride

Chapter 1 Introduction

1.1 Hypervalent Iodine

Hypervalent iodine compounds have seen a recent resurgence in interest due to their applications in a wide variety of synthetic transformations and most prominently as selective oxidants.[1] They are used as a replacement for first- and second-row transition metal catalysts as well as over toxic metals because of their low cost, low toxicity and environmentally benign nature making them attractive compounds.[2]

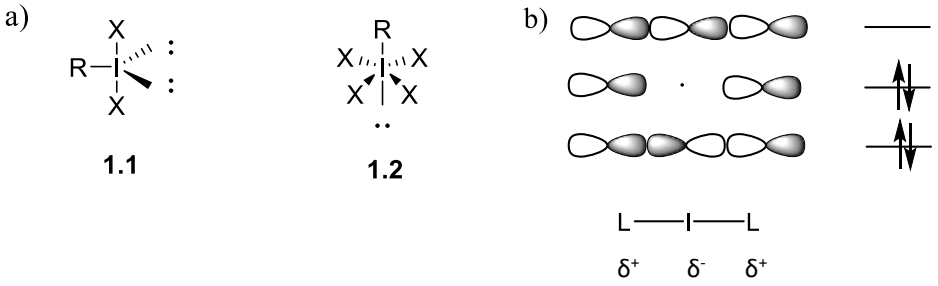
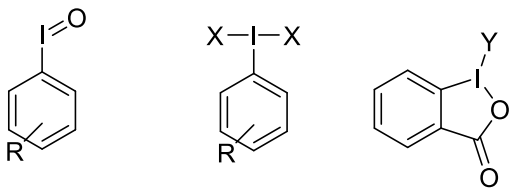


Figure 1.1 a) *Structure of hypervalent iodine compounds b) orbitals in the hypervalent bond*[3]

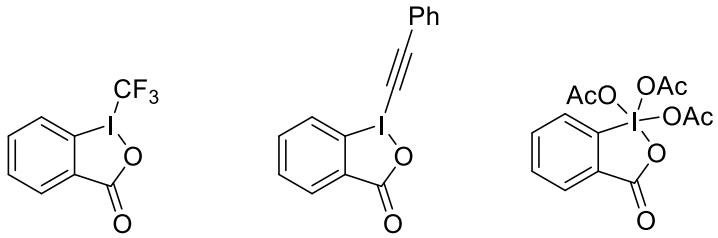
Iodine(III) compounds have a three centre four electron bond (3c-4e) bond, L-I-L, which is formed as a result of the overlap of the iodine 5p orbital with the orbitals of the ligand. These compounds are highly polarised which results in a longer and weaker covalent bond and they are electrophilic at the iodine because of a node in the non-bonding orbital of the hypervalent bond.[2] Iodine(III) compounds with two heteroatom ligands have a T-shape and adopt a distorted trigonal bipyramidal structure **1.1** (Figure 1.1). The heteroatoms are situated in the apical positions and the least electronegative ligand, the carbon ligand, is positioned in the equatorial position, as well as the two lone pairs.[3] Examples of iodine(III) reagents include linear compounds such as (dichloroiodo)toluene, (difluoroiodo)toluene, aryl iodonium salts and cyclic benzoiodoxoles **1.5** such as Togni's reagent (Y = CF_3) (Figure 1.2).[4] Other interesting examples of benzoiodoxoles include Waser's ethynylbenzoiodoxoles,[5] which are acetylene transfer reagents.



1.3 **1.4** **1.5**

Figure 1.2 *Iodine(III) reagents; X, Y = Cl, F, O, CF_3, N, -C≡C-R', R= H, CH_3*

Iodine(V) compounds adopt a distorted octahedral shape **1.2** (Figure 1.1). The organic ligand and the lone pair of electrons lie in the apical position and the 4 electronegative atoms occupy the equatorial positions. The most famous example of an iodine(V) reagent is Dess-Martin periodinane (DMP) (Figure 1.3). DMP is a benzoiodoxole derived compound in which the iodine atom is present within a ring and is a mild, non-toxic and powerful oxidant, widely used in organic synthesis.[6,7] These cyclic reagents are much more stable than linear hypervalent iodine reagents.[8]



Togni's Reagent Ethynylbenzoiodoxole DMP

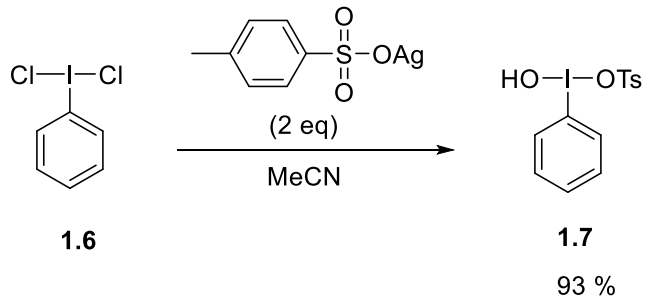
Figure 1.3 *Hypervalent iodine reagents*

1.2 Tosyloxylation

1.2.1 Synthesis of [Hydroxy(tosyloxy)iodo]benzene HTIB

Based on initial work by Alcock and Waddington in 1963 generating (diacetoxyiodo)benzene from (dichloro)iodobenzene **1.6** and silver acetate, Koser proposed the synthesis of the ditosylate analogue.[9,10] (Dichloroiodo)benzene **1.6** was reacted with 2 equivalents of silver tosylate in acetonitrile and interestingly instead of

forming the ditosylate, [hydroxy(tosyloxy)iodo]benzene (HTIB) **1.7** was generated in a 93 % yield (Scheme 1.1). HTIB had been synthesised previously by Neiland in 1970.[11]



1.6 **1.7**

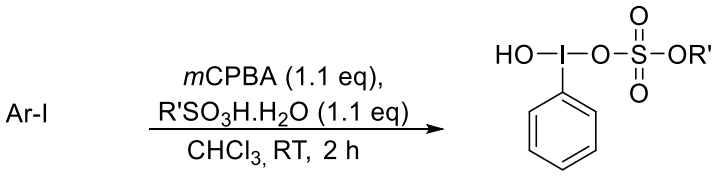
93 %

Scheme 1.1 *Synthesis of [hydroxy(tosyloxy)iodo]benzene*[11]

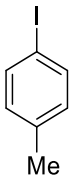
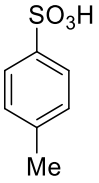
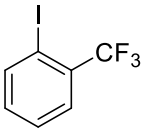
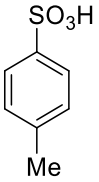
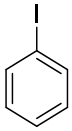
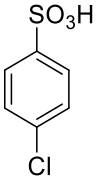
Yamamoto and Togo reported an improved one-pot synthesis of [hydroxy(tosyloxy)iodo]arenes from iodoarenes using *m*-chloroperbenzoic acid in chloroform, at room temperature for 2 hours affording HTIB in an excellent 95 % yield (Table 1.1). This methodology was applied to a range of derivatives, with electron-withdrawing and donating groups on the iodoarene ring and sulfonic acid derivatives containing nitro groups and chlorine atoms, were tolerated in very good to excellent yields (75-99 %).[12]

In 2013 Olofsson and coworkers synthesised a variety of [hydroxy(tosyloxy)iodo]benzene HTIB derivatives using a similar method. This methodology tolerated both electron withdrawing and donating groups on the aromatic ring of the iodoarene and the reaction was conducted under mild conditions and fast reaction times. In most cases the reaction was completed in 30 minutes (Scheme 1.2).[13]

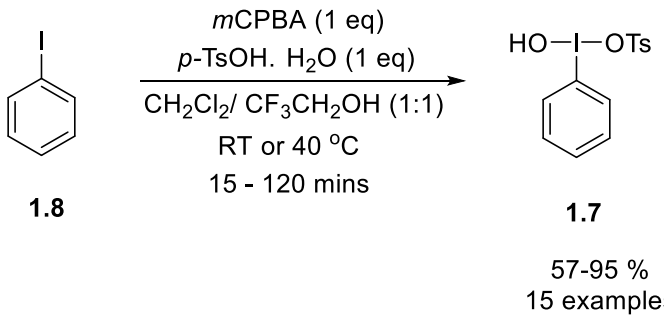
Table 1.1 *One-pot synthesis of HTIB*[12]



75-100 %
15 examples

Entry	Ar	R'SO$_3$H	Yield (%)
1			100
2			85
3			88

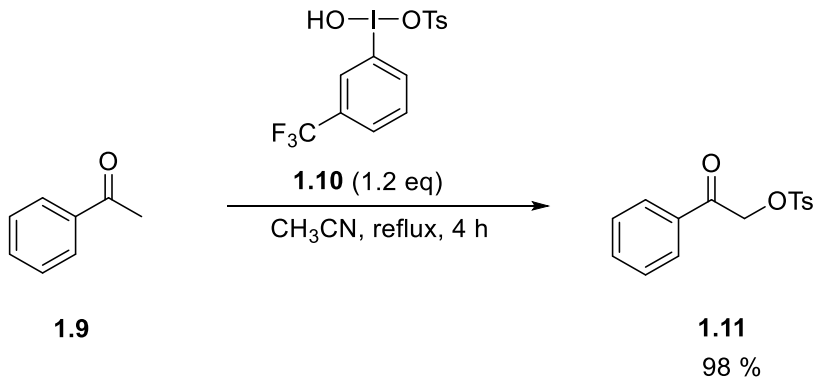
Yusubov and Wirth reported a solvent free method for preparing HTIB and its derivatives by grinding (diacetoxyiodo)arenes with the corresponding acid in the solid state for several minutes and then evaporating off the acetic acid generated as a by-product of the reaction.[14] A 93 % yield of HTIB was obtained which was comparable to Koser's original yield of 93 %.[15]



Scheme 1.2 *Synthesis of [hydroxy(tosyloxy)iodo]benzene using m-CPBA*[13]

1.2.2 Synthetic Applications of HTIBs

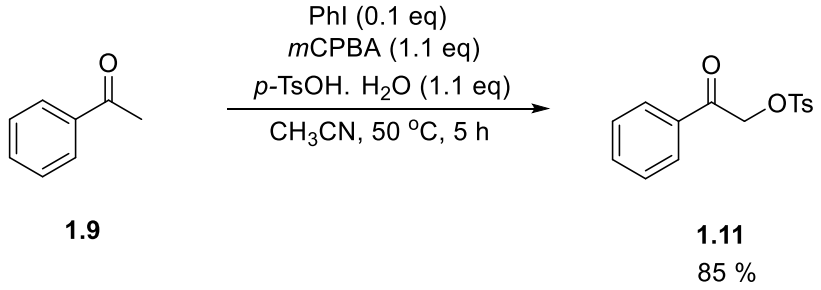
[Hydroxy(tosyloxy)iodo]benzene (HTIB) **1.7** has been widely investigated for the α-tosyoxylation of ketones and the methodology has then been extended to 1,3-dicarbonyl compounds. Since this early work, other methods have been reported for the synthesis of HTIB and its derivatives. Nabana *et al.* investigated the synthesis of a range of modified [hydroxy(tosyloxy)iodo]arenes for the α-tosyloxylation of ketones. Interestingly, it was found that installing a CF_3 group at the *meta*-position of the aromatic ring **1.10** afforded a slightly improved 98 % yield for the α-tosyloxylation of ketones compared to 93 % for HTIB (Scheme 1.3).[16]



Scheme 1.3 *α-Tosyloxylation of carbonyl compounds*[16]

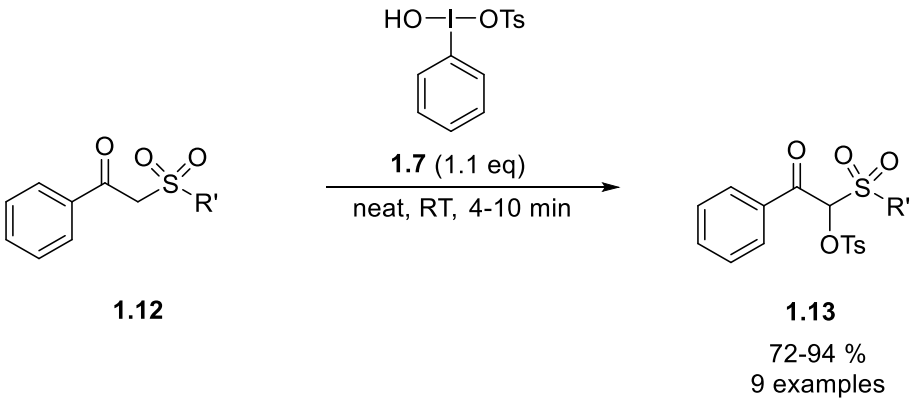
The *in-situ* generation of HTIB has also been explored. Yamamoto and coworkers reported the catalytic formation of HTIBs when investigating the synthesis of α-tosyloxyketones (Scheme 1.4). Starting from iodobenzene (0.1 equivalent) with *m*-CPBA (1.1 equivalents) as the oxidant and *p*-toluenesulfonic acid monohydrate (1.1 equivalents)

in acetonitrile at 50 °C for 5 hours, the corresponding products were formed in good yields (63-88 %).[17]



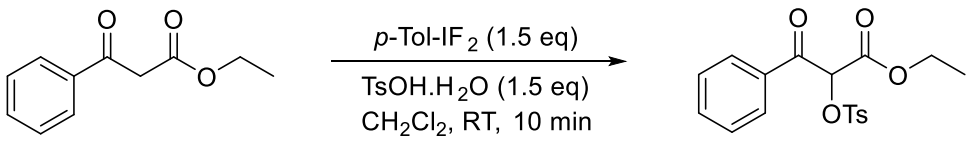
Scheme 1.4 *α-Tosyloxylation of ketones*[17]

Yusubov and Wirth conducted a solvent free α-tosyloxylation of a series of 1,3-dicarbonyl compounds including 1,3-diketones, with the *in situ* generation of HTIB using (diacetoxyiodo)benzene and *p*-toluenesulfonic acid monohydrate (2.2 equivalents) and the α-tosyloxylated products were obtained in moderate to excellent yields (32-92 %) after only 10 minutes.[14] Varma and coworkers reported a similar solvent free method α-tosyloxylation of *β*-keto sulfones using [hydroxy(tosyloxy)iodo]benzene at room temperature for 4-10 minutes affording the corresponding products in good to excellent yields (72-94 %) (Scheme 1.5).[18]



Scheme 1.5 *Solvent free α-tosyloxylation of β-keto sulfones*[18]

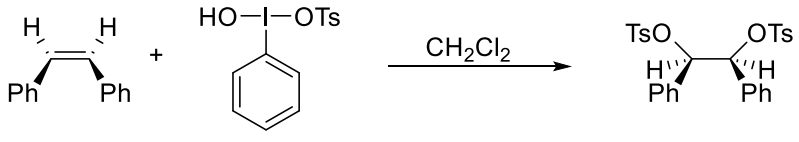
Zhang and coworkers reported the α-tosyloxylation of a series of *β*-ketoesters mediated by (difluoroiodo)toluene using *p*-toluenesulfonic acid in dichloromethane at room temperature in 10 minutes or less, affording the tosyloxylated 1,3-dicarbonyl compounds in excellent yields (82-98 %). This was a mild and efficient method for introducing a tosylate group and other oxygen nucleophiles, such as an acetyl group into the α-position of 1,3-dicarbonyl compounds (Scheme 1.6).[19]



1.14 **1.15** 90 %

Scheme 1.6 *α-Tosyloxylation of β-ketoesters*[19]

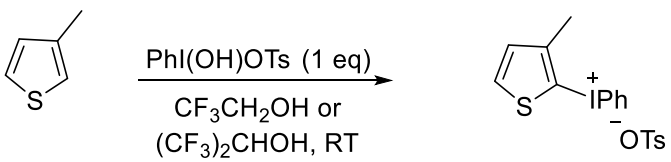
Koser reported the ditosyloxylation of alkenes using HTIB in 1984 (Scheme 1.7).[20] A range of bis(tosyloxy)alkanes were synthesised under mild reaction conditions and in most cases short reaction times (0.5 – 24 h) with moderate to good yields (18-70%).



1.16 (1 eq) **1.17** 26 %

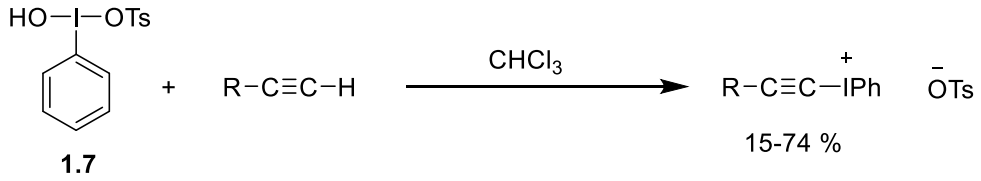
Scheme 1.7 *Ditosyloxylation of alkenes*[20]

HTIB has also been used for the preparation of diaryliodonium salts and alkynyliodonium salts. HTIB was used in 2,2,2-trifluoroethanol or 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) to synthesise diaryliodonium salts of thiophenes in excellent yields (71-98 %) in 3 hours (Scheme 1.8).[21] Alkynyliodonium salts can also be generated by reacting HTIB with terminal alkynes in chloroform to form an alkynyliodonium tosyloxylate (Scheme 1.9).[22] Iodonium salts can be used for a wide variety of synthetic transformations such as Michael type conjugate additions and Diels-Alder reactions, and so are synthetically important.



1.18 **1.19** 98 %

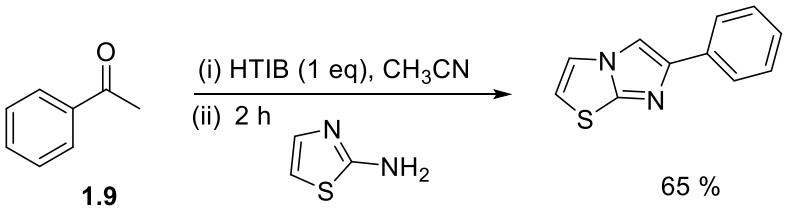
Scheme 1.8 *Synthesis of diaryliodonium salts of thiophenes*[21]



R= *i*-Pr, *i*-Bu, *s*-Bu, *t*-Bu. cyclopentyl, cyclohexyl, Ph, *p*-Tol

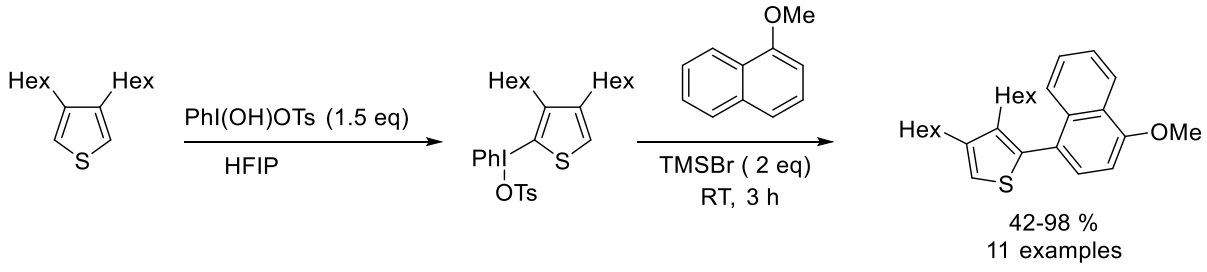
Scheme 1.9 *Synthesis of alkynyliodonium salts*[22]

A one-pot synthesis of 6-arylimidazo[2,1-b]thiazoles was generated by Aggarwal and coworkers using HTIB (Scheme 1.10) under mild reaction conditions with short reaction times and in good yields (57-70 %). These are inhibitors of mitochondrial NADH dehydrogenase and are known to display anti-inflammatory properties and anti-tumour properties, demonstrating the necessity of reagents such as HTIB.[23]



Scheme 1.10 *Synthesis of 6-arylimidazo[2,1-b]thiazoles*[23]

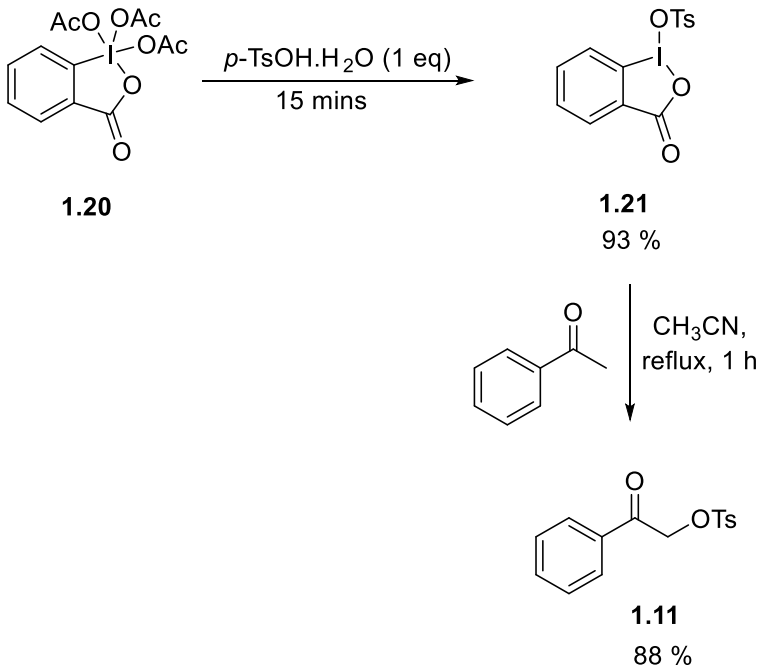
Interestingly, a metal-free cross coupling of heteroaromatic compounds has been promoted using HTIB and bromotrimethylsilane (TMSBr) in HFIP in 42-98 % yields.[24] Using this method a range of mixed biaryls was generated under mild reaction conditions, and avoided unwanted oligomerisation which is produced in cross coupling reactions employing metals (Scheme 1.11).



Scheme 1.11 *Metal-free cross coupling of heteroaromatic compounds*[24]

Karade and coworkers synthesised a DMP derivative **1.21** for α-tosyloxylation of acetophenone. It was synthesised in an excellent 93 % yield reacting DMP **1.20** with *p*-toluenesulfonic acid under solvent free conditions (Scheme 1.12). **1.21** was then reacted

with the acetophenone to form the α-tosyloxylated product **1.11** in a comparable yield (63-88 %) to Yamamoto and Togo. The synthesis of α-tosyloxyacetophenone by Karade and coworkers gave an 88 % in just 1 hour,[25] whilst Yamamoto and Togo reported the same reaction under catalytic conditions in a similar 85 % yield in 5 hours.



Scheme 1.12 *DMP derivatives for α-tosyloxylation*[25]

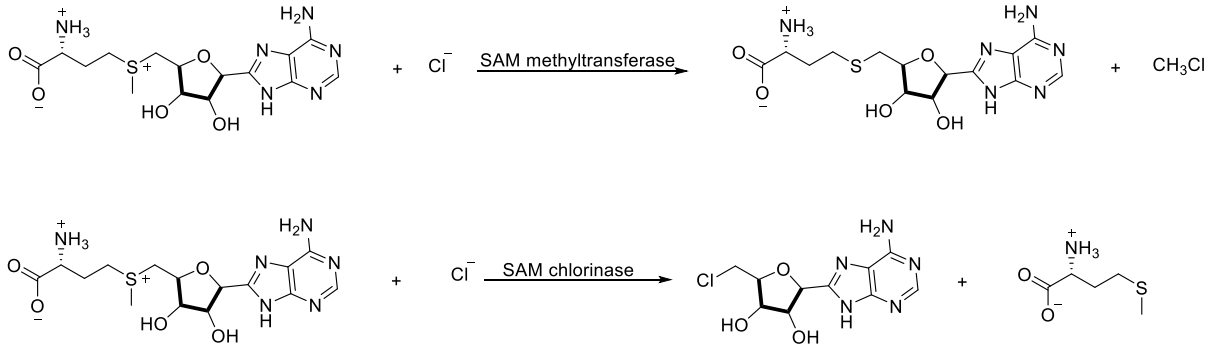
1.3 Chlorination

1.3.1 The Importance of Chlorination

Chlorine is the 20th most abundant element in the earth's crust and the main form of chlorine is in sodium, potassium and magnesium minerals such as halite, as well as chloride dissolved in the ocean. Elemental chlorine is produced industrially by electrolysis and is used for the synthesis of organochlorine compounds including chlorinated herbicides, antimicrobial agents, plastics and degreasing agents.[26]

Organochlorine compounds in nature include volatile haloalkanes formed by algae, fungi and bacteria. Halogenated compounds are also produced in biosynthesis, and the first halogenase enzyme, chloroperoxidase, was discovered in the 1960s from the fungus *Caldariomyces fumago.*[27] Chloroperoxidase uses hydrogen peroxide to catalyse

electrophilic halogenation reactions forming mono, di, or tri-chloroacetic acid and polychlorinated alkanes such as chloroform. Haloperoxidases in biology are able to emulate the formal umpolung, Cl^- to Cl^+.[28] The enzyme *S-adenosyl*-L-methionine (SAM) is used as a cosubstrate in halogenation and works via two different mechanisms. The first mechanism involves a SAM dependent methyl transferase which facilitates the transfer of a methyl group from SAM by the nucleophilic attack of a chloride anion forming chloromethane and the second mechanism involves a halide bound in the enzyme hydrophobic pocket which displaces the L-methionine group (Scheme 1.13).[28]



Scheme 1.13 *SAM mechanism*

The physiochemical properties that arise as a result of the introduction of a chlorine atom include an increase in lipophilicity and high electrophilicity of the carbon atom bound to the chlorine atom. In addition, the electronic effects of more remote carbon atoms are affected due to an increase in electrophilic reactivity and low bond energy in alkyl chlorides resulting in higher reactivity. The stereo and electronic effects of introducing a chlorine atom into the binding pocket of a protein can be altered. Local steric interference of the chlorine atom with amino acids can arise, as well as local electronic attraction or repulsion.[29] This can result in stronger or weaker interactions of chlorine with amino acids, which can affect the function of the target protein.

The introduction of a chlorine atom alone does not always lead to an increase in the biological activity of the compound it is inserted into, the position of the chlorine substituent can affect the activity of the compound. In the case of dichlorodiphenyltrichloroethane (DDT), an insecticide with a CCl_3 which is required for its activity (Figure 1.4). The two chlorine atoms need to be at the 4 and 4' positions for the compound to be active. The isomers with the chlorine substituents at the 2, 2' positions or the 3, 3' positions are inactive. In other cases, the chlorine atoms are responsible for

the increased biological activity of a compound. This is the case for a plethora of compounds including the anticancer agent Salinosporamide A and antibiotics vancomycin,[27] chloroamphenicol[27] and clindamycin[30] and the anti-tumour compounds rebeccamycin,[31] astin A[32] and cryptophycin (Figure 1.4).

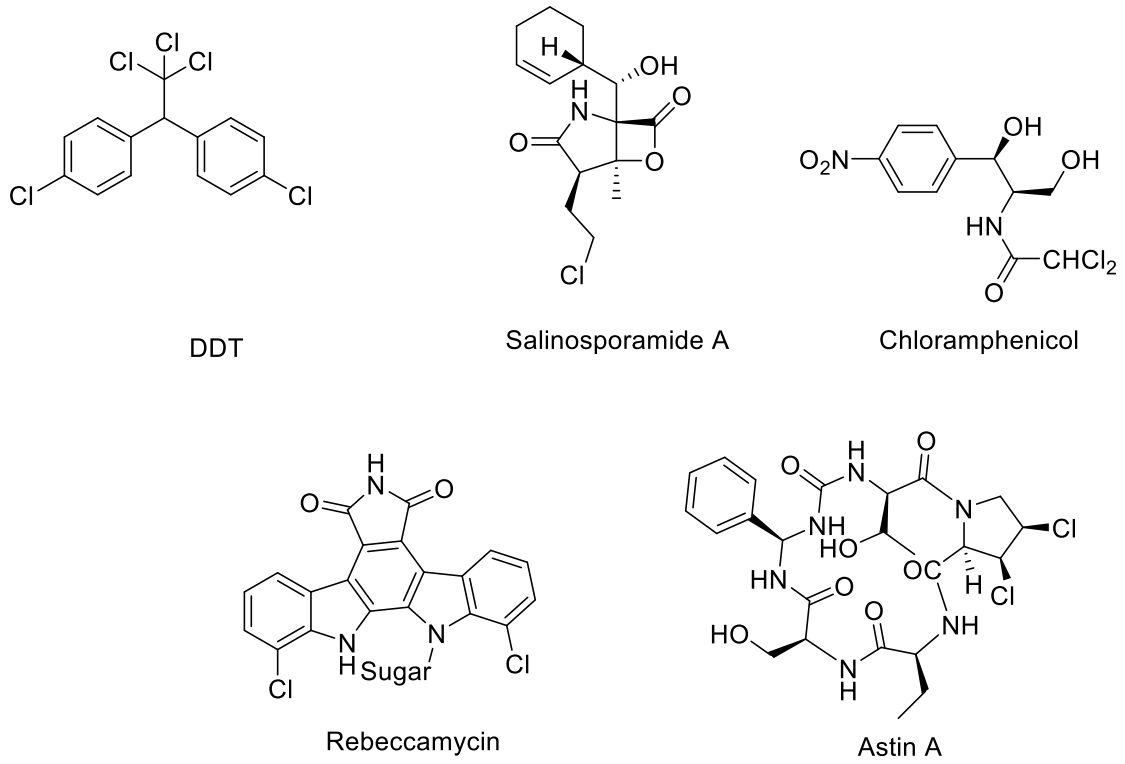
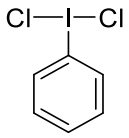


Figure 1.4 *Important chlorinated compounds*

1.3.2 Iodine(III) Chlorinating Reagents

In 1886 Willgerodt reported the preparation of (dichloroiodo)benzene **1.6**, $PhICl_2$, by passing chlorine gas through cooled solutions of iodobenzene in chloroform. This was the first example of a hypervalent iodine chlorinating reagent.[33] This method is still used today for the large scale 20 kg preparation of crude (dichloroiodo)benzene (Figure 1.5) in a 94 % yield.[34] Since then, new synthetic methodologies have been developed to avoid the use of corrosive chlorine gas in the preparation of (dichloroiodo)arenes. A two-phase method using CCl_4/ concentrated aqueous HCl provides (dichloroiodo)benzene in excellent yields (> 90 %) and other examples include using $Na_2S_2O_8$.[35, 36]

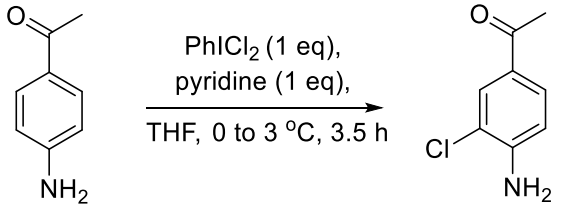


1.6

Figure 1.5 (*Dichloroiodo)benzene*

(Dichloro)iodoarenes ($ArICl_2$) are mild reagents which are capable of selective chlorination and they are better than using $Cl_{2\ (g)}$ which has high reactivity and poor selectivity, making it unsuitable for enantioselective transformations. Although (dichloroiodo)arenes are easy to handle, they are light and heat sensitive and so they are unable to be stored. (Dichloroiodo)benzene and other (dichloroiodo)arenes undergo decomposition to Cl_2 and the aryl iodide in polar solvents, such as acetic acid, but also in non-polar solvents, such as carbon tetrachloride as well as in the presence of a strong Bronstead acid such as trifluoroacetic acid.[37] The position of the substituents on the aryl ring is also important and *ortho* Lewis basic groups, such as a nitro group, increase the rate of decomposition.[38]

Early uses of (dichloroiodo)arenes include the chlorination of aromatic compounds. 4-Aminoacetophenone **1.22** was chlorinated in an 87 % yield under mild reaction conditions. This process was also applied to a large 19.5 kg scale (Scheme 1.14).

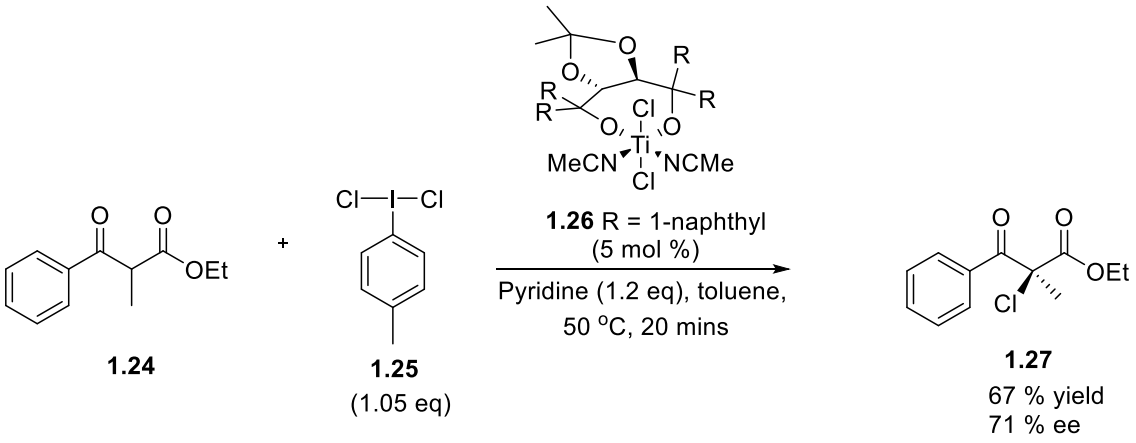


1.22 **1.23** 87 %

Scheme 1.14 *Chlorination of 4-aminoacetophenone*[34]

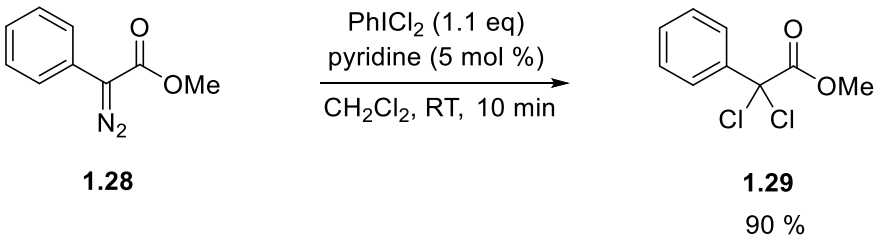
In 2004 Togni *et al.* expanded on their work with [$TiCl_2$(TADDOLato)] complexes and carried out the catalytic asymmetric chlorination of 1,3-dicarbonyl compounds in combination with (dichloroiodo)toluene (Scheme 1.15). A range of acyclic 1,3-dicarbonyl compounds were chlorinated using [$TiCl_2$(TADDOLato)] **1.26** (5 mol %), (dichloroiodo)toluene **1.25** and pyridine as the base at 50 °C for 20 minutes to give the

chlorinated products in good yields (37-83 % yields) and low to good enantiomeric excesses (< 10 – 71 % ee).[39]



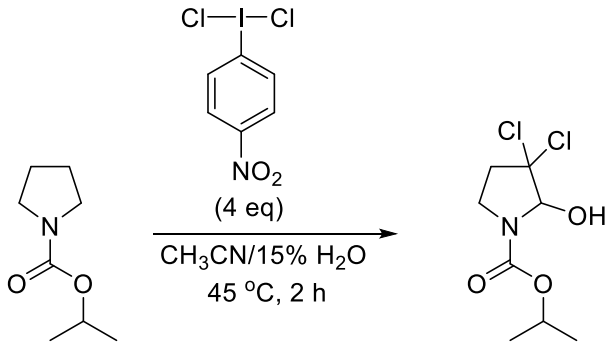
Scheme 1.15 *Catalytic and stereoselective chlorination of 1,3-dicarbonyl compounds using (dichloroiodo)toluene and [$TiCl_2$(TADDOLato)]*[39]

Murphy and coworkers reported the synthesis of α,α-dichlorinated esters from diazoesters in good to excellent yields (67-95 %) using (dichloroiodo)toluene in rapid reaction times (Scheme 1.16).[40] This was expanded upon to generate 3,3-dichloro-2-oxindoles and a α, α-dichlorodicarbonyls in 12-96 % yields.[40, 41]



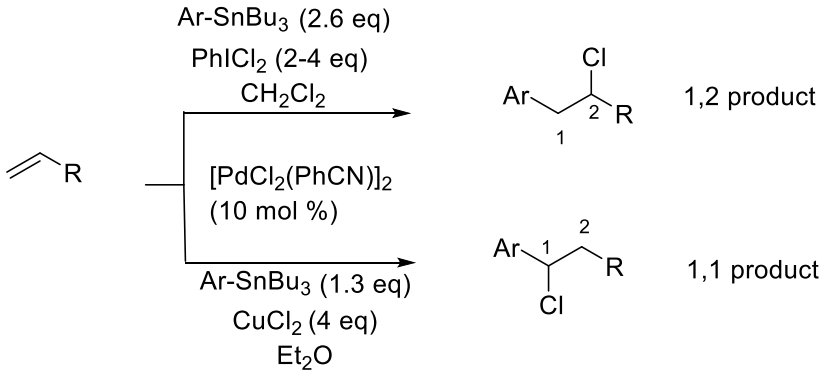
Scheme 1.16 *Synthesis α,α-dichlorinated esters from diazoesters*[40]

The *α,α,β*-oxidation of carbamates (Scheme 1.17) was reported using (dichloroiodo)benzene with a nitro group at the *para*-postion. A series of nitrogen heterocycles were chlorinated in good to excellent yields (42-92 %) with the *N* protecting group remaining intact.



Scheme 1.17 *α, α, β-Oxidation of carbamates using iodotoluene dichloride*[42]

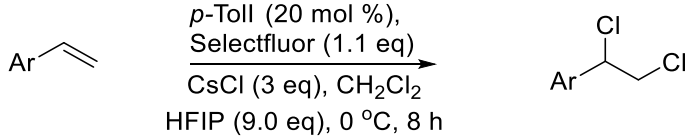
Sanford reported the generation of aryl chlorinated products from alkenes using a palladium catalyst, $[PdCl_2(PhCN)]_2$ and (dichloroiodo)toluene in a Mizoroki-Heck reaction. The 1,2-product was generated in excellent yields (72-96 %) and there was high selectivity for the 1,2 product over the 1,1-product (Scheme 1.18).[43]



Scheme 1.18 *Synthesis of aryl chlorinated products*[43]

Another example of chlorination using iodine(III) reagents includes Gilmour's synthesis of a Willgerodt type reagent, (dichloroiodo)toluene *in situ* for the vicinal dichlorination of unactivated alkenes. The alkenes were reacted with iodotoluene (20 mol %), Selectfluor (1.1 equivalent) as the oxidant, cesium chloride (3 equivalents) and HFIP (9 equivalents) in dichloromethane at 0 °C for 8 hours affording the vicinal dichlorinated products in moderate to high yields (53-76 %) (Scheme 1.19).[44] A variety of groups were tolerated on the alkene substrate including unprotected alcohols, free acids, sulfate,

tosyloxylate, phosphate groups and styrenes. This section demonstrates the synthetic versatility of (dichloroiodo)arenes.



Scheme 1.19 *Chlorination of alkenes*[44]

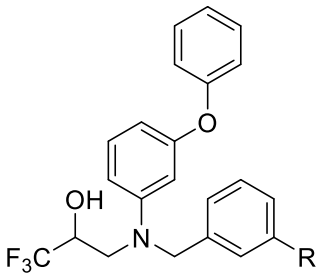
1.4 Fluorination

1.4.1 The Importance of Fluorination

The fluorine atom has unique effects on the chemical and biological activity of the compounds it is introduced into, such as altering the pKa and increasing the biological activity. It is due to these effects that fluorine has broad applications in the pharmaceutical and agrochemical industries, as well as being employed in materials chemistry, for example for the generation of liquid crystals for LCDs. Currently 25-30 % of drugs contain at least one fluorine atom, and fluorine is also used to generate ^{18}F-labelled radiotracers for positron emission tomography (PET). It is these important applications that demonstrate the need to develop new and efficient methodologies of introducing fluorine into organic compounds.[45, 46]

The fluorine atom is highly electronegative (Pauling electronegativity 4.0) and has a small Van der Waals radius (1.35 Å), which enables the formation of very stable hydrogen bonds with hydrogen bond donors. The high electronegativity of the fluorine atom also means that carbon-fluorine bonds are highly polarised and therefore they are more electrostatic in nature as opposed to covalent. This characteristic increases the binding affinity of a molecule with a target receptor. The introduction of a trifluoromethyl group into a compound can result in a more significant steric demand as the Van der Waals radius is closer to that of an ethyl group. This in combination with the high electronegativity can lead to changes in the preferred molecular conformation. In the case of the cholesteryl transfer protein inhibitor, methoxybenzene has a planar conformation whilst the OCF_3 group of trifluoromethoxybenzene is out of the plane. The conformational change observed was used to design inhibitors of cholesteryl transfer protein for treatment against coronary heart disease. Molecular modelling showed that

the tetrafluoroethyl group sits out of the plane with respect to the phenyl ring and results in more efficient binding to the target protein. When the R group was altered from a tetrafluoroethoxy group to an ethoxy group, it led to an 8-fold loss in potency (Figure 1.6).[47]



R = OCF_2CF_2H
R = OCH_2CH_3
R = OCH_3
R = OCF_3

Figure 1.6 *Cholesteryl transfer protein inhibitor*[47]

Fluorine is relatively small in size (1.47 Å) and sits between oxygen (1.57 Å) and hydrogen (1.2 Å). Consequently, the substitution of a hydrogen atom for a fluorine atom has minimal steric effect. This replacement does however have significant effect on electronics as it alters the pKa of the functional groups adjacent to the fluorine atom. The pharmacokinetic properties of a molecule can be altered by changing the pKa as well as by changing the binding affinity of a molecule.[48]

The lipophilicity of a molecule can also be tuned by the introduction of a fluorine atom. According to Lipinski's rules, a log P of 5 or below is required in order for a drug compound to pass through the cell membrane. Aromatic fluorination always increases lipophilicity because of excellent overlap between the 2s and 2p orbitals of fluorine with the orbitals of the adjacent carbon atoms. Per/polyfluorination also increases lipophilicity however, monofluorination and trifluoromethylation of saturated alkyl groups is known to decrease lipophilicity, due to the polarity of these compounds as a result of strong carbon-fluorine and carbon-trifluoromethyl bond dipoles.[48]

The metabolic stability can be increased by substituting a C-H bond with a C-F bond. This is a result of the cytochrome P450 monooxygenase in the liver being unable to metabolise the fluorinated compound. This is beneficial as it increases the biological half-

life of the drug compound because it is metabolised slower and therefore leads to greater therapeutic efficacy.[48, 49]

The statin, Lipitor, is one of the biggest selling drugs globally. It is responsible for reducing the amount of cholesterol synthesised by the body and is an important example of a fluorinated drug. Lipitor is a potent competitive inhibitor of the enzyme 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA reductase), which is the rate limiting enzyme in the biosynthesis of cholesterol (Figure 1.7).[50]

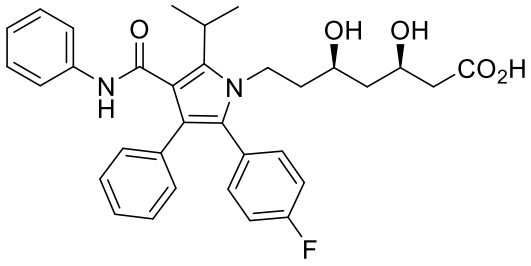
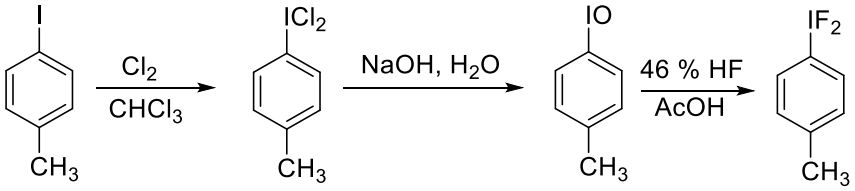


Figure 1.7 *Atorvastatin (Lipitor)*[50]

1.4.2 (Difluoroiodo)arenes

1.4.2.1 Preparation of (Difluoroiodo)arenes



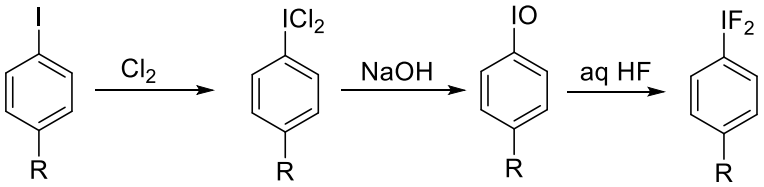
Scheme 1.20 *Preparation of difluoroiodotoluene*[56]

An early example of the synthesis of (difluoroiodo)toluene **1.34** came from work conducted by Allen and Garvey (Scheme 1.20).[51] *p*-Iodotoluene **1.32** was reacted with chlorine gas in chloroform at room temperature to generate (dichloro)iodotoluene **1.25** in a 90 % yield. (Dichloroiodo)toluene was hydrolysed with sodium hydroxide in water affording (iodoso)toluene **1.33** in an 85 % yield, which was then reacted with glacial acetic acid and 46 % HF in water to give (difluoroiodo)toluene (Scheme 1.20). Sawaguchi and Hara used a similar method to synthesise (difluoroiodo)toluene, the final step involved the reaction of the iodosoarene with aqueous HF to generate

(difluoroiodo)toluene in an 86 % yield (Table 1.2).[52] This method was applied to synthesise a range of (difluoroiodo)arenes with electron withdrawing groups (NO_2, Cl) and electron donating groups (CH_3) on the aromatic ring.

In order to generate a more direct route, Carpenter and coworkers developed a one-pot synthesis of (difluoroiodo)arenes by reacting mercuric oxide and 48 % aqueous HF with (dichloroiodo)toluene at room temperature for one minute to generate the (difluoroiodo)arene (Scheme 1.21).[53] Other examples of the synthesis of difluoroiodoarenes include the use of xenon difluoride and anhydrous HF. Hori and coworkers moved away from using these methods to avoid using either toxic mercury salts or toxic XeF_2 which cannot be used in standard glassware. Iodosobenzene **1.35** was treated with 46 % aqueous HF to afford (difluoroiodo)benzene **1.36** in an 86 % yield (Scheme 1.22).[54] However, these methods still require the use of aqueous HF which is extremely corrosive.

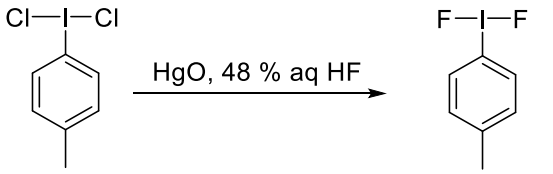
Table 1.2 *Difluoroiodoarenes*[52]



a: R = CH_3
b: R = H
c: R = Cl
d: R = NO_2

Entry	R	Yield of $ArICl_2$[a] (%)	Yield of ArIO[a] (%)	Yield of $ArIF_2$[a] (%)
1	CH_3	96	81	86
2	H	96	73	86
3	Cl	92	61	79
4	NO_2	81	81	85[b]

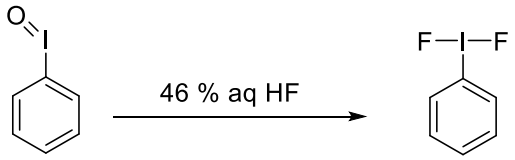
[a] Isolated yield; [b] Isolated without recrystallisation.



1.25 **1.34**

60-90 %

Scheme 1.21 *One-pot synthesis of (difluoroiodo)toluene*

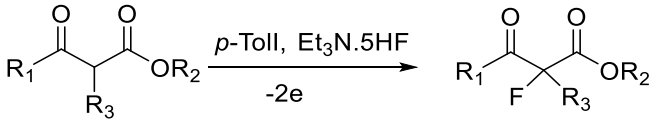


1.35 **1.36**

86 %

Scheme 1.22 *Synthesis of (difluoroiodo)benzene*

An electrochemical synthesis of (difluoroiodo)arenes was reported using $Et_3N.3HF$ but was limited in its methodology, and (difluoroiodo)toluene could not be generated.[55] This work was expanded upon by Hara and coworkers to generate (difluoroiodo)toluene *in situ* using $Et_3N.5HF$ to monofluorinate 1,3-dicarbonyl substrates (Scheme 1.23).[56]



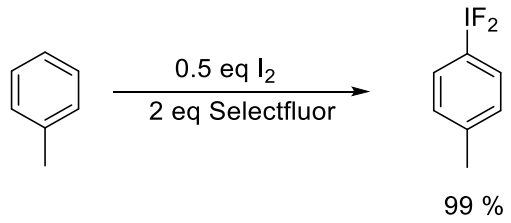
1.37 **1.38**

50-79 %

8 examples

Scheme 1.23 *Electrochemical fluorination of 1,3-dicarbonyl compounds $Et_3N.5HF$*[56]

Shreeve and coworkers generated (difluoroiodo)arenes under mild conditions by reacting toluene derivatives with Selectfluor (Scheme 1.24) in good yields (64-83 %). Trace amounts of $Et_3N.3HF$ were added to overcome the low instability of the (difluoroiodo)arenes and it was proposed that the HF may stabilise the (difluoroiodo)arenes.[57]



Scheme 1.24 *Synthesis of (difluoroiodo)toluene using Selectfluor*

1.4.2.2 Stoichiometric Fluorination

The fluorination of 1,3-dicarbonyl compounds at the 2- position is useful for the preparation of building blocks of blockbuster drug molecules containing a fluorine atom. The installation of the fluorine atom into the 2-position of 1,3-dicarbonyl compounds has been conducted previously using elemental fluorine and electrophilic fluorinating reagents such as *N*-fluorobenzenesulfonimide (NFSI) and Selectfluor (Figure 1.8). However, these reagents require elemental fluorine for their synthesis and are expensive. (Difluoroiodo)toluene and its derivatives have also been investigated as fluorinating reagents, because they can be prepared from cheap and readily available sources of fluoride. (Difluoroiodo)toluene has been utilised for a wide variety of transformations.

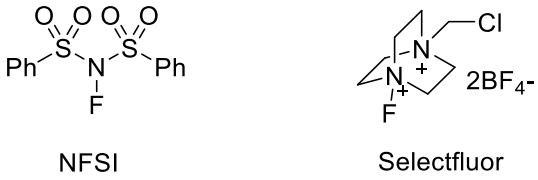
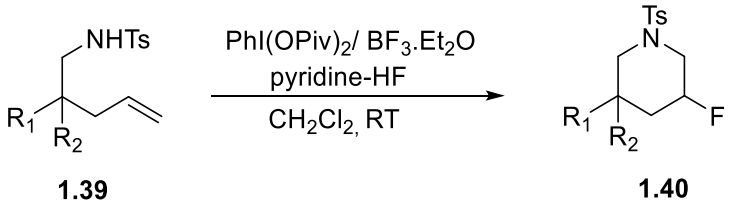


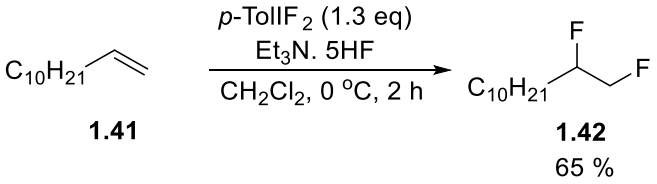
Figure 1.8 *Fluorinating reagents*

The regioselective metal-free aminofluorination of alkenes has been reported by Meng and Li (Scheme 1.25), employing di-(pivaloyloxy)iodobenzene (PIDP) (1.2 equivalents) and pyridine- HF (10 equivalents) with the Lewis acid, boron trifluoride etherate (10 equivalents) as the promoter in good yields (59-85 %).[58] Zhang *et al.* also reported the aminofluorination of homoallylic alkenes using iodosobenzene (2 equivalents) and $BF_3.OEt_2$ (1 equivalent) in dichloromethane. The fluorinated products were obtained in moderate to very good yields (32-88 %) without the need for hazardous pyridine-HF.[59]

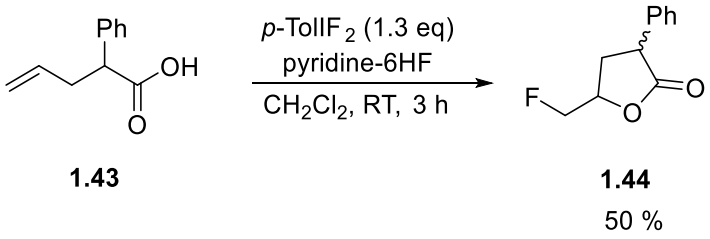


Scheme 1.25 *Aminofluorination of alkenes*[58]

The vicinal difluorination of alkenes was achieved using $Et_3N.5HF$ and (difluoroiodo)toluene (Scheme 1.26).[60] A variety of functionalities such as an ester, acetoxy, chloro and hydroxyl groups were tolerated. Alkenes containing a substituted ester group were found to be less reactive with a terminal double bond. Fluorocyclisations using (difluoroiodo)toluene were conducted using pyridine-6HF in short reaction times 1-4 hours (Scheme 1.27).

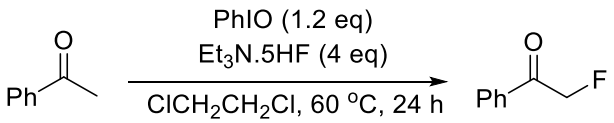


Scheme 1.26 *Vicinal difluorination of alkenes*[60]



Scheme 1.27 *Fluorocyclisation using (difluoroiodo)toluene*

Another interesting application of using either iodosobenzene or iodotoluene in combination with $Et_3N.5HF$ was the fluorination of acetophenone derivatives (Scheme 1.28). The monofluorinated products were obtained in good yields (62-84 %) from the reaction with cyclic and acyclic ketones at 60 °C for 24 hours. α-Fluoroketones can also be obtained using silyl enol ethers of the corresponding ketone using (difluoroiodo)toluene, using $BF_3.OEt_2$ as the activator and $Et_3N.2HF$ as the fluoride source.[61]



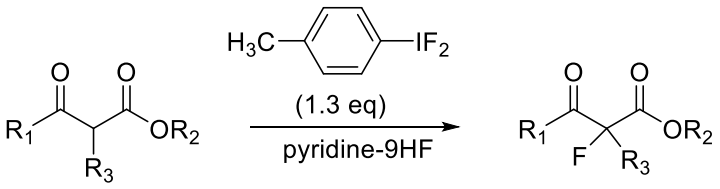
1.45 **1.46**

79 %

Scheme 1.28 *Fluorination of acetophenone derivatives*[61]

In 1996 Hara and coworkers used (difluoroiodo)toluene for the mild and selective mono-fluorination of acyclic *β*-ketoesters in the presence of an amine-HF complex (Table 1.3).[62] Pyridine-9HF (1 equivalent) was used in combination with (difluoroiodo)toluene (1.3 equivalents) to afford the monofluorinated products in good yields (50-80 %). Interestingly, it was reported that in the absence of an amine-HF complex, the reaction was unable to proceed. Bulkier tert-butyl ester groups were tolerated as well as an aryl or alkyl group at the 2- position, although a reduction in yield was observed. The same group prepared (difluoroiodo)toluene under electrochemical conditions using a 1:1:1 mixture of $Et_3N.5HF$, iodotoluene and the substrate, affording the mono-fluorinated products in similar yields (Table 1.4)[56]

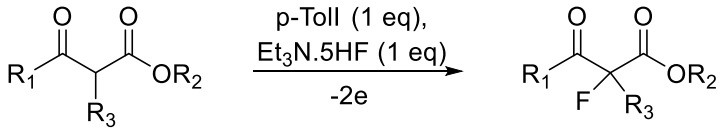
Table 1.3 *Fluorination of β-ketoesters*[62]



1.37 **1.38**

Entry	R_1	R_2	R_3 (%)	Yield (%)
1	CH_3	Et	H	80
2	CH_3	Bu	H	79
3	Ph	Et	H	73
4	CH_3	Bu	CH_3	62
5	Ph	Et	Ph	50

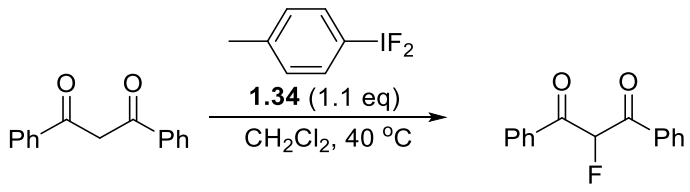
Table 1.4 *Electrochemical fluorination of β-ketoesters*[56]



1.37 **1.38**

Entry	R_1	R_2	R_3 (%)	Yield (%)
1	CH_3	Bu	H	79
2	Ph	Et	H	72
3	C_6H_{10}	Et	H	70
4	CH_3	Bu	CH_3	56
5	Ph	Ph	H	50

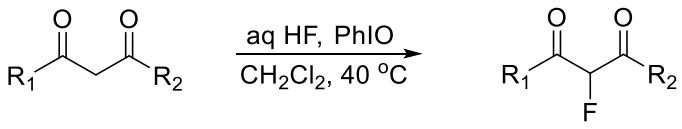
Hara *et al.* developed the methodology for the direct fluorination of 1,3-dicarbonyl compounds without the need for the amine-HF complex, but these reactions required longer reaction times and higher temperatures (Scheme 1.29). The 1,3-dicarbonyl compounds were reacted with a stoichiometric amount of (difluoroiodo)toluene in dichloromethane at 40 °C for 10-24 hours affording the fluorinated products in good yields (55-82 %) for a range of acyclic *β*-ketoesters, *β*-ketoamides and *β*-diketones.[63] Under neutral conditions the fluorination of 1,3-diketones afforded high yields and a 71 % yield was achieved for 2-fluoro-1,3-diphenylpropane-1,3-dione.



1.47 **1.48**
71 %

Scheme 1.29 *Fluorination using (difluoroiodo)toluene without amine-HF* [63]

Hori and coworkers developed a one-pot α-fluorination of 1,3-dicarbonyl compounds, using iodosylbenzene in combination with 55 % aqueous HF (Scheme 1.30). The α-fluorinated products were obtained in moderate to excellent yields (25-93 %) over a broad range of acyclic substrates including *β*-ketoesters, *β*-ketoamides and *β*-diketones.[54]



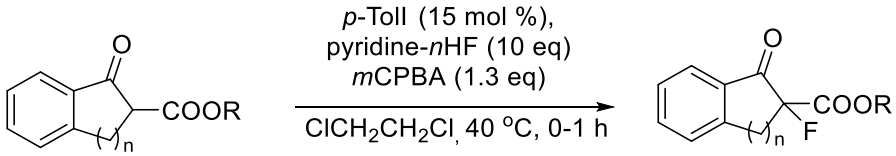
1.49 **1.50**
25-93 %

R^1 = Alkyl, Aryl: R^2 = OEt, Alkyl, Ph, NR_2

Scheme 1.30 *One-pot α-fluorination of 1,3-dicarbonyl compounds*[54]

1.4.2.3 Catalytic Fluorination

The use of (difluoroiodo)arenes provided efficient and selective fluorination but required being used in a stoichiometric amount. Shibata *et al.* reported the catalytic fluorination of *β*-dicarbonyl compounds using an iodoarene (Scheme 1.31). The fluorination was conducted using 4-iodotoluene (15 mol %), Pyridine-*n*HF (10 equivalents) and *m*CPBA (1.3 equivalents) in dichloroethane at 40 ℃ for 0.5 – 1 hour in most cases. A range of cyclic and acyclic *β*-ketoesters and amides were fluorinated in 25-98 % yields and even the enantioselective fluorinations of 1,3-dicarbonyl compounds were reported with moderate enantiomeric excesses.[64] This methodology was also applied to the aminofluorination of alkenes in good yields (31 -73 %). Kitamura also developed a catalytic fluorination procedure (Table 1.5) using either *o*-iodotoluene **1.53**, iodobenzene **1.8** or *o*-iodoanisole **1.54** as the iodoarene catalyst in combination with 55 % aqueous HF and *m*CPBA (1.5 equivalents) in dichloroethane at 40 ℃. The fluorinated products were obtained in good yields (44-82 %) but required aqueous HF.[65]

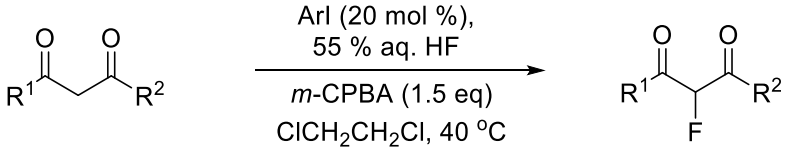


1.51 **1.52**

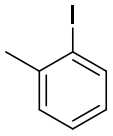
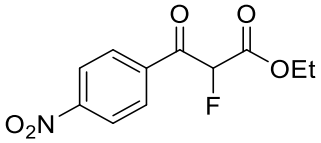
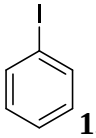
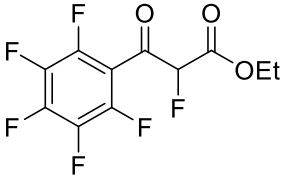
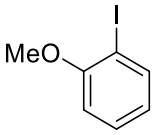
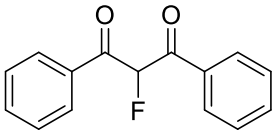
R = ^{t}Bu, *n* = 1, 76 %
R = Ad, *n* = 1, 71 %
R = L-Men, *n* = 1, 66 %
R = Ad, *n* = 2, 88 %

Scheme 1.31 *Catalytic fluorination of 1,3-dicarbonyl compounds*[64]

Table 1.5 *Catalytic fluorination of 1,3-dicarbonyl compounds using iodoarenes*



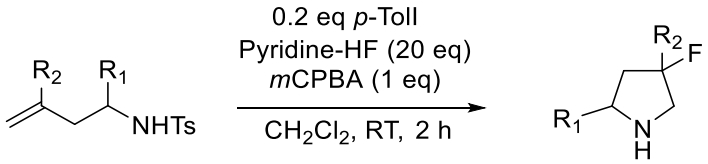
1.49 **1.50**

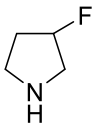
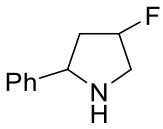
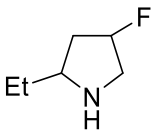
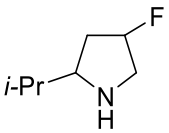
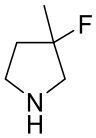
Entry	ArI	Time (h)	Product	Yield (%)
1	 **1.53**	24		82
2	 **1.8**	24		75
3[a]	 **1.54**	24		70

[a] At room temperature

The intramolecular aminofluorination of homoallylamines has also been reported by Oyamada and coworkers (Table 1.6), using iodotoluene (20 mol %), pyridine-HF (20 equivalents) and *m*CPBA (1 equivalent) to generate 3-fluoropyrrolidines in very good yields and in rapid reaction times (60-86 %).[66]

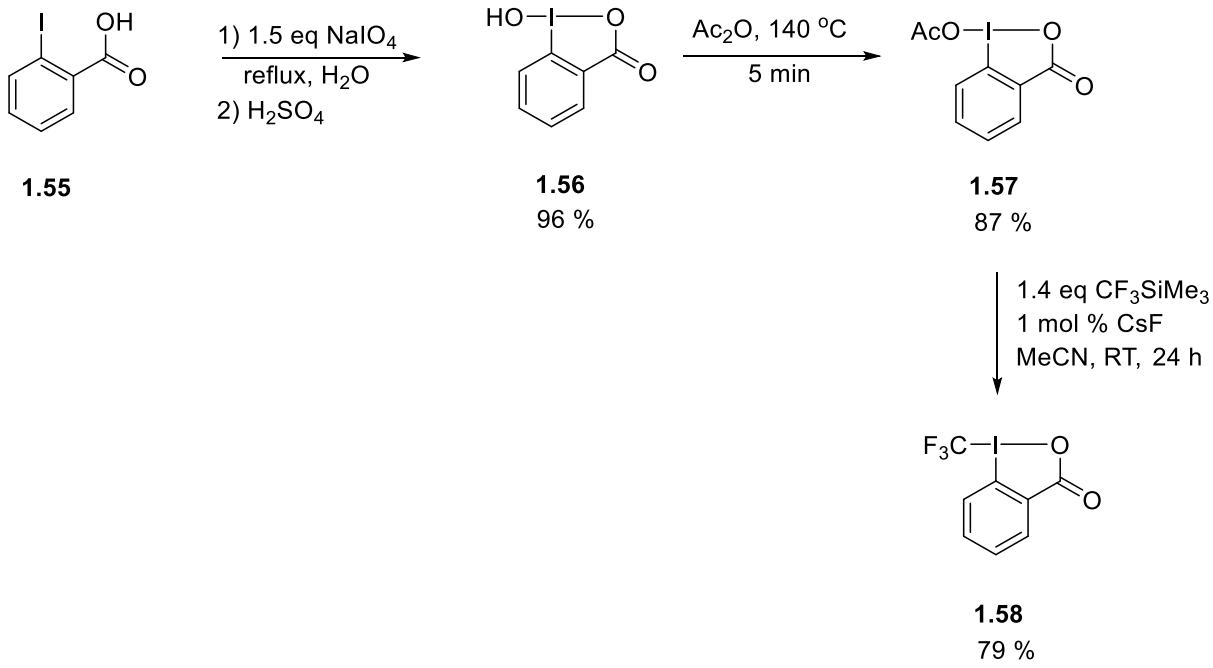
Table 1.6 *Aminofluorination using (difluoroiodo)toluene*[66]



Entry 1	Product	Yield (%)
1		74
2		71 (*cis:trans* = 65:35)
3		78 (*cis:trans* = 70:30)
4		86 (*cis:trans* = 70:30)
5		60

1.4.3 Togni's Reagents

In 2006 Togni developed two hypervalent iodine(III) trifluoromethylating reagents based on a cyclic hypervalent iodine core skeleton.[4] The initial synthesis of Togni's acid reagent began from 2-iodobenzoic acid **1.55** using 1.5 equivalents of sodium periodate and water which was refluxed overnight, followed by the addition of dilute sulphuric acid to deliver hydroxyiodobenzoiodoxolone **1.56** in an excellent 96 % yield. Hydroxyiodobenzoiodoxolone **1.56** was then acetylated in an acetic anhydride mixture at 140 °C. In the final step acetoxyiodane **1.57** was reacted with Ruppert-Prakash reagent ($TMSCF_3$) and cesium fluoride to generate the acid form of Togni's reagent **1.58** (Scheme 1.32).



1.55

1.56
96 %

1.57
87 %

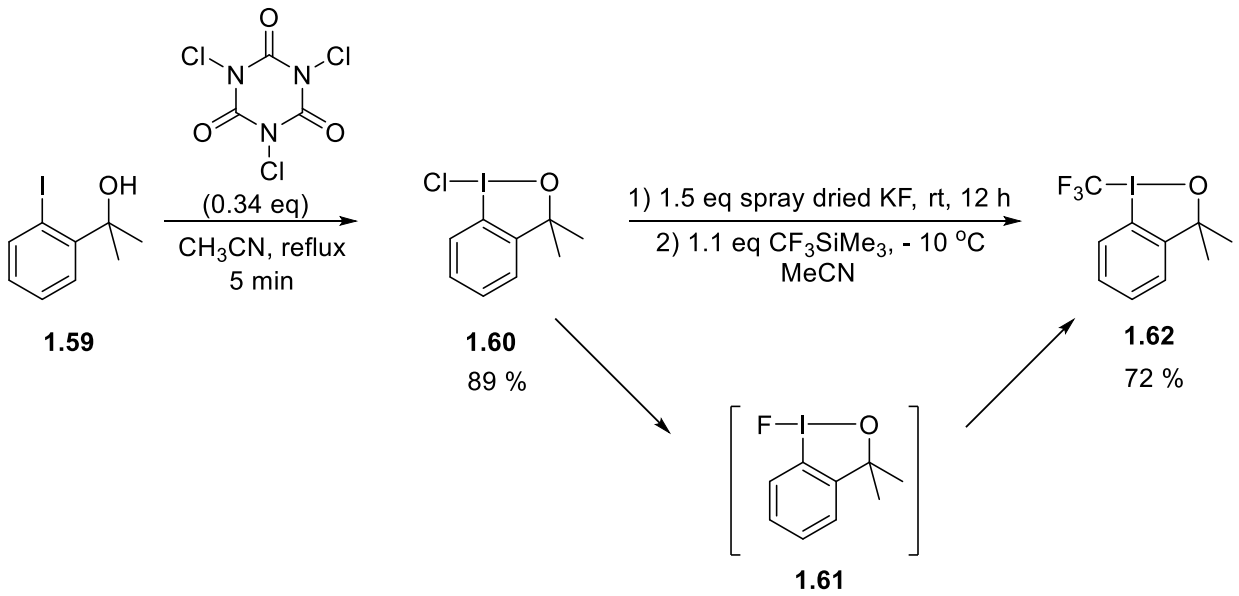
1.58
79 %

Scheme 1.32 *Synthesis of Togni's reagent (acid form)*[67,68]

A more direct route to Togni's acid reagent was developed by forming the chloroiodane from 2-iodobenzoic acid **1.55** and trichloroisocyanuric acid (TClCA). Chloroiodane was then treated with KOAc and Ruppert-Prakash reagent. The two-step synthesis was performed on a large scale (30 g).

The alcohol form of Togni's reagent was synthesised from 2-(2-iodophenyl)propan-2-ol **1.59** which was reacted with TClCA to generate chloroiodane **1.60**. Chloroiodane was reacted with spray dried KF to generate fluoroiodane *in situ* and subsequently reacted with Ruppert-Prakash reagent to form the alcohol form of Togni's reagent **1.62** in a 72 % yield (Scheme 1.33).

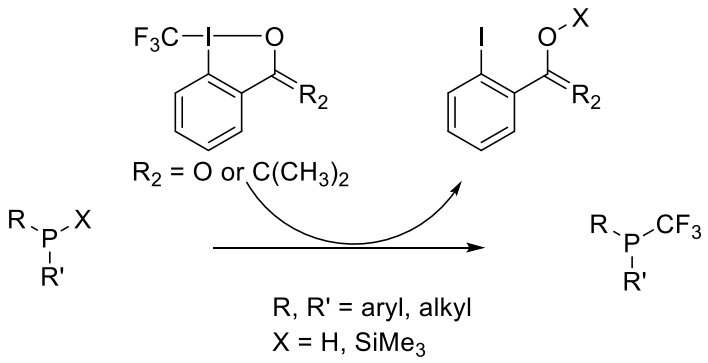
Togni's reagent is a widely used electrophilic trifluoromethylating reagent, due to its broad synthetic applications and a complete overview of its scope would not be possible. A detailed discussion of the application of Togni's reagent can be found in his review.[69] A brief summary of the scope of Togni's reagent will be discussed here.



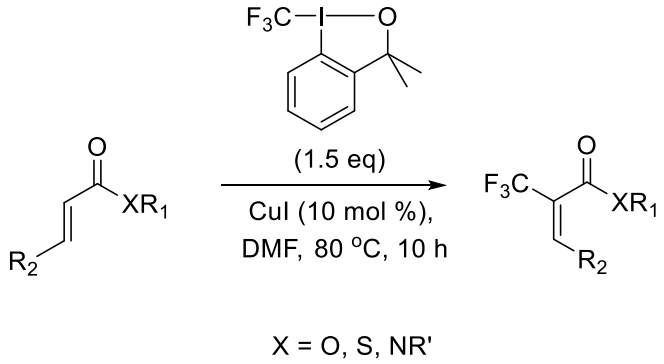
Scheme 1.33 *Synthesis of Togni's reagent (alcohol form)*[68]

The first nucleophiles investigated for trifluoromethylation were sulphur and phosphorus centred nucleophiles. Thiols were able to undergo direct electrophilic trifluoromethylation and a wide variety of functional groups on the thiols were tolerated, including amines, amides, carboxylic acid, thioacetals and alkynes in good to excellent yields (51-99 %). The reaction was conducted at low temperature which helped to avoid competing side reactions.[70] These conditions were then applied to biologically relevant compounds including cysteine. Phosphorus centred nucleophiles were also investigated (Scheme 1.34) and the trifluoromethylated products were obtained in good yields (36-78 %) starting with alkyl and aryl phosphines.[71] Trifluoromethylated 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) derived ligands were also formed and have been subsequently used in enantioselective reactions.[72]

Copper(I) catalysis was used for the trifluoromethylation of *α,β*-unsaturated carbonyls using Togni's reagent (Scheme 1.35). A wide range of functional groups were tolerated and good to excellent yields were obtained (50-92 %).

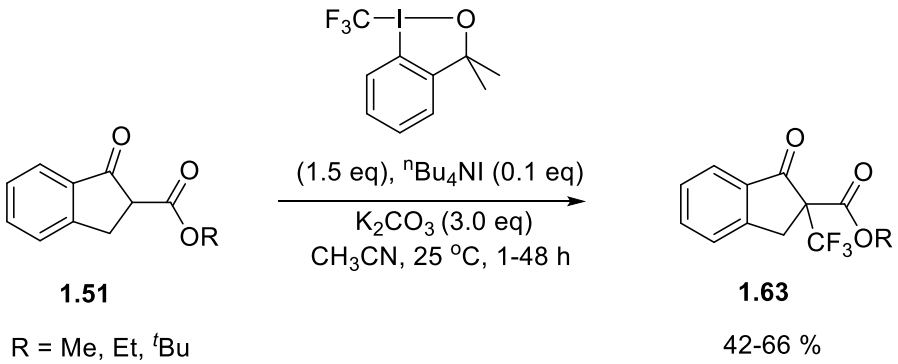


Scheme 1.34 *Trifluoromethylation of phosphorus nucleophiles*[71]



Scheme 1.35 *Trifluoromethylation of α, β-unsaturated carbonyls*[73]

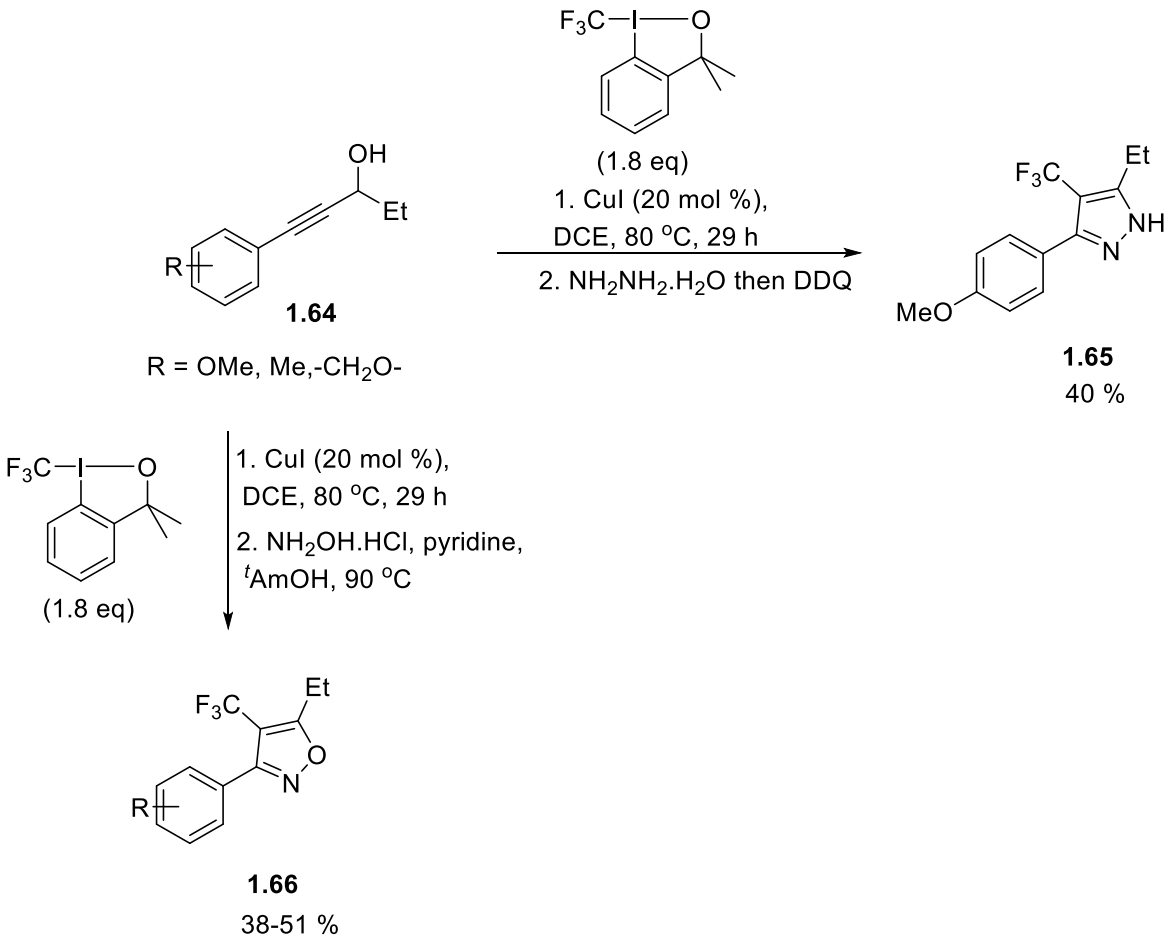
The trifluoromethylation of cyclic *β*-ketoesters was investigated using phase transfer catalysis with Togni's reagent (the alcohol form) and tetrabutylammonium iodide. The trifluoromethylated *β*-ketoesters were delivered in good yields (42-66 %) but could only be applied to a small series of cyclic *β*-ketoesters (Scheme 1.36).[67]



Scheme 1.36 *Trifluoromethylation of cyclic β-ketoesters*

A one-pot synthesis of trifluoromethylated heterocycles from propargylic alcohols was synthesised by the reaction of Togni's reagent with CuI followed by the addition of

hydrazine or hydroxylamine hydrochloride and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) forming pyrazoles **1.65** and isoxazoles **1.66** containing a CF_3 group, which are important for the synthesis of pharmaceuticals.[74]



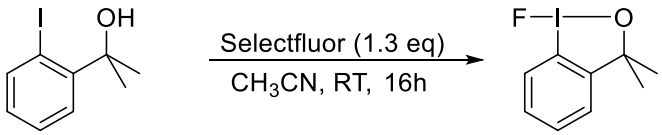
Scheme 1.37 *One-pot synthesis of trifluoromethylated heterocycles*[74]

1.4.4 Fluoroiodane

1.4.4.1 Synthesis of Fluoroiodane

The drawbacks of linear iodine(III) compounds include their low stability and high reactivity, whereas cyclic hypervalent iodine reagents are more stable. The stability of cyclic iodine(III) reagents stems from the incorporation of an iodine atom into a five membered ring. The presence of an electronegative atom, oxygen, provides additional stability.[75]

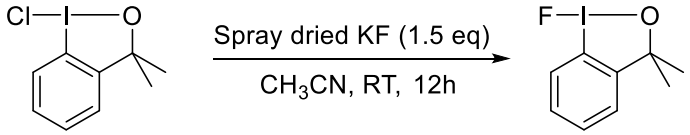
The first synthesis of fluoroiodane was reported by Legault in 2012 by an electrophilic fluorination of 2-(2-iodophenyl)propan-2-ol using Selectfluor (Scheme 1.38).[76] This synthetic route is not applicable for large scale synthesis as Selectfluor is expensive.



1.60 **1.61**

Scheme 1.38 *Synthesis of fluoroiodane using Selectfluor*[76]

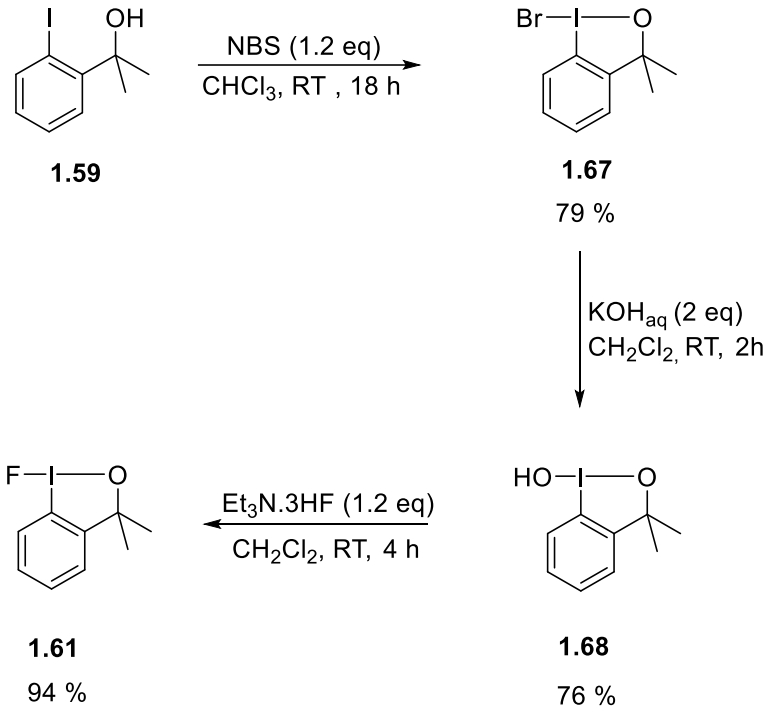
Togni synthesised fluoroiodane employing a nucleophilic route by reacting chloroiodane with spray-dried potassium fluoride (1.5 equivalents) in acetonitrile under argon. This method is not suitable for large scale synthesis either as it would be costly (Scheme 1.39).



1.60 **1.61**
94 %

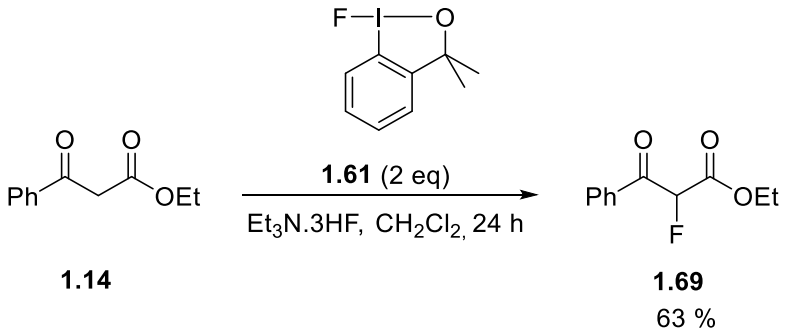
Scheme 1.39 *Synthesis of fluoroiodane by nucleophilic fluorination*[74]

Stuart and coworkers developed a synthetic route to fluoroiodane in three steps from 2-(2-iodophenyl)propan-2-ol. Bromoiodane was synthesised by reacting 2-(2-iodophenyl)propan-2-ol with 1.2 equivalents of *N*-bromosuccinimide. Bromoiodane **1.67** was then reacted with 2 equivalents of potassium hydroxide affording hydroxyiodane **1.68** following a nucleophilic substitution. Finally, fluoroiodane **1.61** was formed by reacting hydroxyiodane with 1.2 equivalents of triethylamine trihydrofluoride in an excellent 94 % yield. Stuart's method is advantageous as it does not require time consuming purifications by column chromatography and the reactions do not require inert conditions (Scheme 1.40).[77]

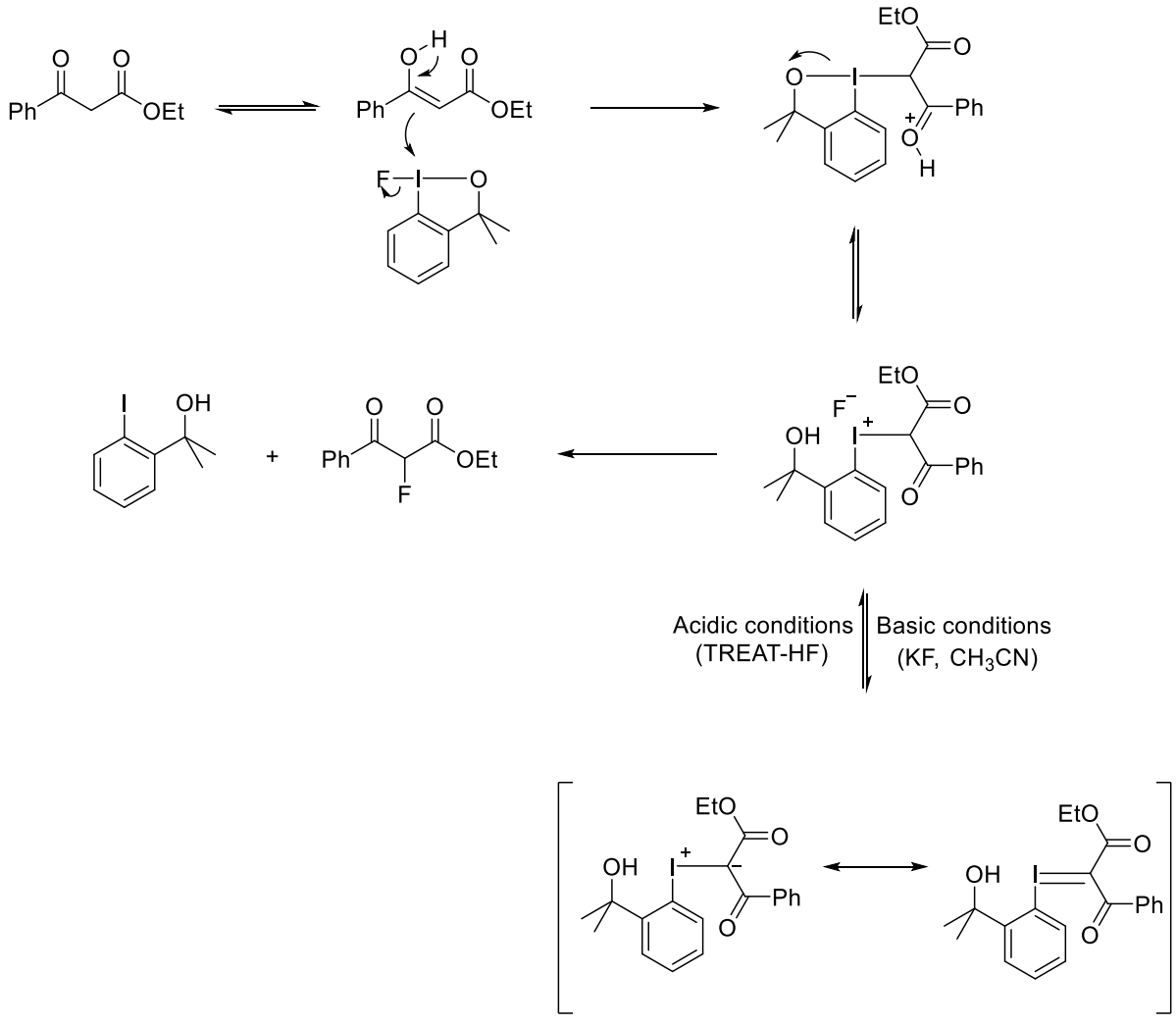


Scheme 1.40 *Synthesis of fluoroiodane using triethylamine trihydrofluoride*[77]

Stuart and coworkers developed the fluorination of 1,3-dicarbonyl compounds using fluoroiodane and triethylamine trihydrofluoride as a Bronstead acid activator. Starting with ethyl 3-oxo-3-phenylpropanoate as the model substrate, the optimum conditions were fluoroiodane in 2 equivalents, 2.7 equivalents of $Et_3N.3HF$ at 40 °C for 24 hours (Scheme 1.41). There was an 89 % conversion to the monofluorinated product **1.69** with a 63 % yield after purification by column chromatography. A 6 % yield of the difluorinated product was also observed. These optimal conditions were applied to a small series of 1,3-dicarbonyl compounds including 1,3-ketoesters, 1,3-diketones and a cyclic 1,3-ketoester in good yields. The *β*-diketones preferentially formed the difluorinated product as a result of the higher enol content of the substrate.



Scheme 1.41 *Fluorination of 1,3-dicarbonyl compounds using fluoroiodane*[77]



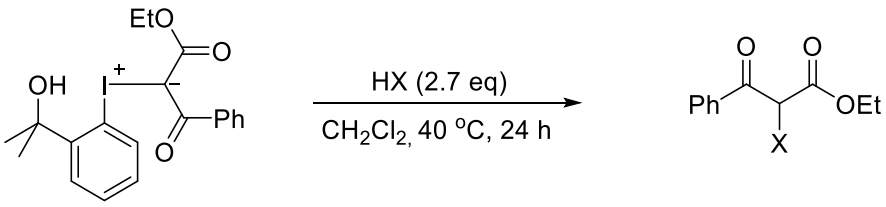
Scheme 1.42 *Mechanism of fluorination using fluoroiodane*[77,78]

Treatment of ethyl 3-oxo-3-phenylpropanoate with fluoroiodane under basic conditions with potassium fluoride (1.2 equivalents) in acetonitrile at 40 ℃ afforded 18 % of the iodonium ylide, which had not been observed previously and increasing the amount of

KF to 5.6 equivalents at 60 ℃ gave a 100 % conversion to the iodonium ylide. Iodonium intermediates have been proposed to form upon the reaction of 1,3-dicarbonyl compounds with iodine(III) reagents.[54] This reaction was proposed to proceed via a similar mechanism. The mechanism shows the enol tautomer reacting with the electropositive iodine (Scheme 1.42). Ring opening of the intermediate followed by proton transfer generates the iodonium fluoride. The final step of the mechanism was proposed to proceed via a reductive elimination with fluoride.

The iodonium ylide was then treated with $Et_3N.3HF$ in the first instance to observe whether fluorination was able to take place. The treatment of the iodonium ylide with $Et_3N.3HF$ (2.7 equivalents) in dichloromethane at 40 ℃ for 24 hours afforded 100 % conversion to the monofluorinated product with a 36 % isolated yield and no evidence of difluorination. These conditions were then applied to other nucleophiles and the iodonium ylide was reacted with HCl, acetic acid and *para*-toluenesulfonic acid to give the corresponding products in very good yields (Table 1.7).

Table 1.7 *Introduction of nucleophiles into the 2-position of 1,3-dicarbonyl compounds*



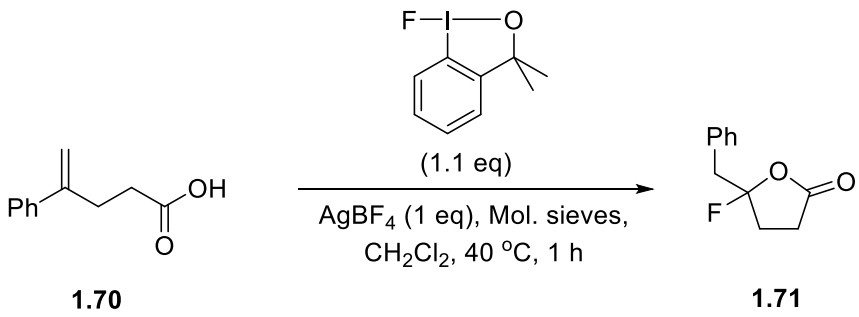
Entry	X	Product[a] (%)
1	Cl	100 (83)
2	OAc	100 (93)
3	OTs	100 (72)

[a]Isloated yields in parenthesis.

1.4.4.2 Scope of Fluorinations

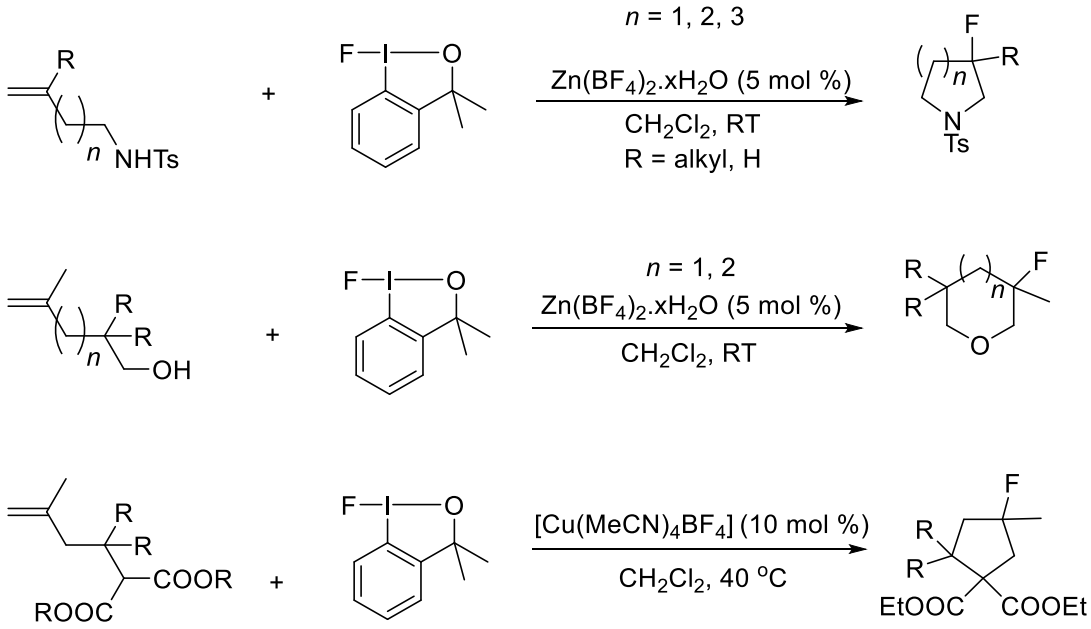
Since its synthesis in 2012, fluoroiodane has demonstrated its ability to carry out a wide variety of synthetic transformations. In late 2015 Stuart and coworkers reported the

intramolecular fluorolactonisation of unsaturated carboxylic acids using fluoroiodane, $AgBF_4$ and 4Å molecular sieves forming a tertiary alkyl fluoride (Scheme 1.43).[79] A cyclisation, aryl migration and fluorination occurred in one step to form γ-lactones which were not previously accessible using fluoraza reagents. This unusual selectivity has however been reported previously by Wirth and coworkers when using hypervalent iodine(III) reagents.[80] A series of fluorinated lactones were obtained in 32-86 % yields and the reaction tolerated electron withdrawing and donating groups. The reaction was also conducted in the absence of $AgBF_4$ for 1 hour affording a small series of fluorocyclised products in good yields (50-54 %) demonstrating that this method is amenable to PET chemistry.[79]



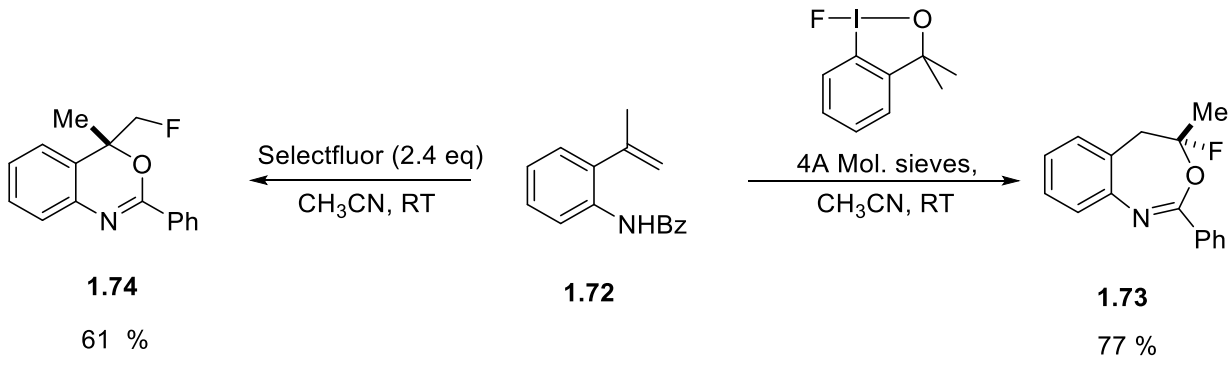
Scheme 1.43 *Intramolecular fluorolactonisation of unsaturated carboxylic acids*

Szabó reported the use of fluoroiodane for the intramolecular fluorocyclisation of unsaturated amines, malonates and alcohols employing a transition metal catalyst. Fluoroiodane in combination with $Zn(BF_4)_2.xH_2O$ (5 mol %) afforded a series of aminofluorinated and oxyfluorinated products in good yields (55-84 %) under mild reaction conditions (Scheme 1.44).[81]



Scheme 1.44 *Intramolecular fluorocyclisation using fluoroiodane*[81]

Gulder and coworkers also investigated cyclisations using fluoroiodane and developed a chemodivergent fluorocyclisation to generate benzoxazepines in good yields (61-85 %) under metal-free conditions (Scheme 1.45). The fluorination of styrenes with an amide group at the *ortho* position **1.72**, were reacted with fluoroiodane and 4Å molecular sieves affording a varied series of benzoxazepines, including activated and non-activated benzene groups as well as a trisubstituted double bond in the starting material. Fluoroiodane promoted a 7 membered ring formation and a shift in the aryl group, in comparison to previous work, where Selectfluor generated benzoxazine.[82]



1.74
61 %

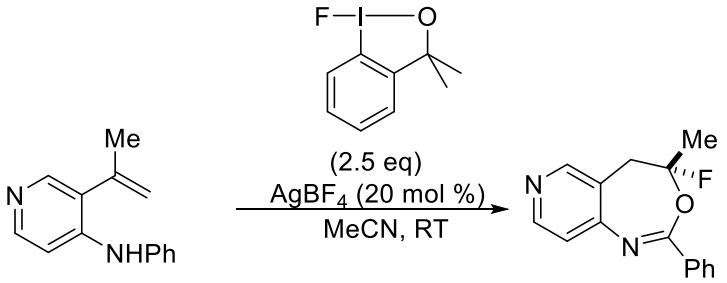
1.72

1.73
77 %

Scheme 1.45 *Synthesis of benzoxazepines*[82]

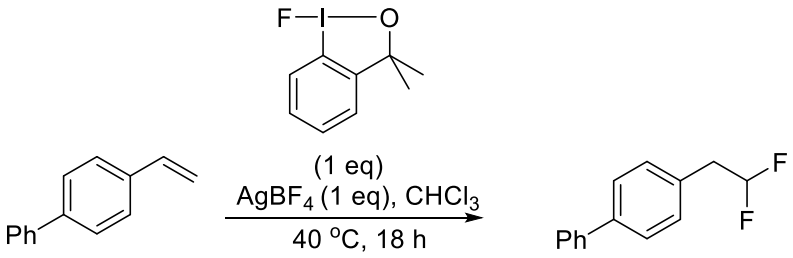
Additionally, Gulder explored the use of fluoroiodane for the synthesis of fluoro-aza-benzoxazepines. Using 2.5 equivalents of fluoroiodane and 20 mol % of $AgBF_4$ in

acetonitrile generated a series of fluoro-aza-benzoxazepines in moderate to good yields (25-78 %) regardless of the substituents on the benzene ring (Scheme 1.46).[83]



1.75 **1.76**
78 %

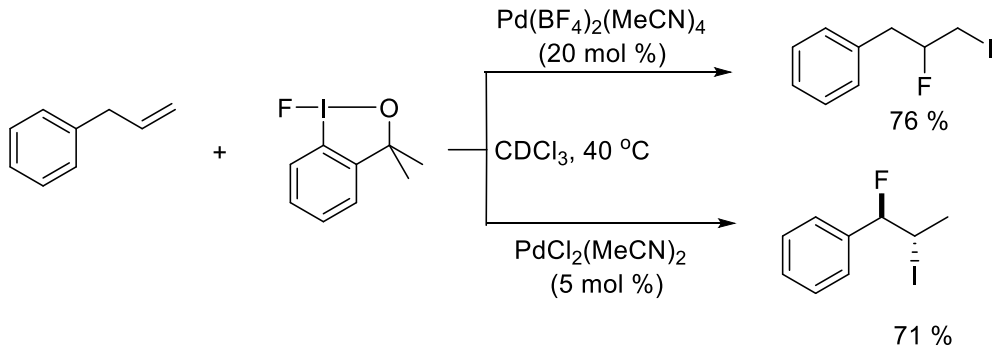
Scheme 1.46 *Synthesis of fluoro-aza-benzoxazepines*[83]



1.77 **1.78**
73 %

Scheme 1.47 *Geminal difluorination of styrenes*[84]

Other interesting applications of fluoroiodane include the geminal difluorination of styrenes reported by Szabó and a range of 1,1-difluoro products were generated in good yields (55-88 %) (Scheme 1.47). Interestingly, one fluorine originated from fluoroiodane, following transfer of the electrophilic fluorine of fluoroiodane and the second fluoride is from the tetrafluoroborate counterion.[84] Szabó and coworkers also reported an interesting vicinal iodofluorination of carbon-carbon double bonds in the presence of a palladium catalyst. Using either $Pd(BF_4)_2(MeCN)_4$ or $PdCl_2(MeCN)_2$ and fluoroiodane, a series of 1,2-iodofluorinated products were obtained in good yields (40-86 %). Interestingly, the catalyst was found to affect the regioselectivity. $PdCl_2(MeCN)_2$ triggered isomerisation of the double bond prior to reacting with fluoroiodane to form the *anti*-product (Scheme 1.48).



Scheme 1.48 *Vicinal iodofluorination* [85]

Another interesting application of fluoroiodane includes the ring opening of cyclopropanes mediated by a silver catalyst to form 1,3-difluorinated products. Using 2 equivalents of fluoroiodane and 1 equivalent of $AgBF_4$ at room temperature afforded a range of 1,3-difluorinated products. Aliphatic and aromatic substrates were investigated with electron donating groups on the aromatic ring accelerating the rate of reaction and electron withdrawing groups slowing the reaction down from 1 hour to 24 hours.[86]

In summary, fluoroiodane has shown broad applications in fluorocyclisation reactions and geminal difluorinations. A major advantage of fluoroiodane is the new chemoselectivity which enables access to a wider variety of products.

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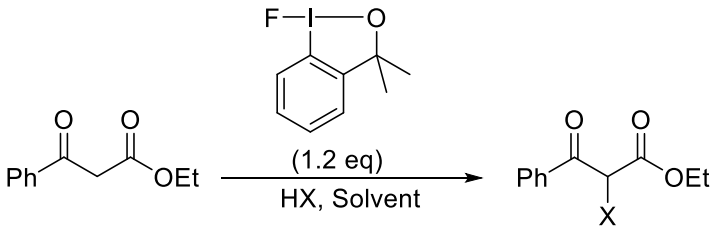
Chapter 2 Atom Transfer Reactions using Fluoroiodane

2.1 Project Aims

Hypervalent iodine reagents such as (difluoroiodo)benzene, (dichloro)iodobenzene and [hydroxy(tosyloxy)iodo]benzene (HTIB) can be prepared from cheap and readily available starting materials. The use of these reagents is limited due to their instability, in the case of (difluoroiodo)toluene and they require being prepared *in situ.* In addition, the introduction of a nucleophile such as a fluoride requires the synthesis of a specific hypervalent iodine reagent, containing that nucleophile. For example, introducing fluoride requires the synthesis of either (difluoroiodo)benzene or fluoroiodane. Fluoroiodane is an air and moisture stable reagent and one main advantage is that it can be prepared from cheap and readily available sources of fluoride and has already been demonstrated by Stuart and coworkers to fluorinate *β*-ketoesters, *β*-ketoamides and *β*-diketones in good yields. The aim of this project is to expand upon this work and develop a one-pot synthetic method to introduce a variety of different nucleophiles such as chloride, methoxide, ethoxide, trifluoromethyl and aromatic amines into 1,3-dicarbonyl into the 2-position of a range of 1,3-dicarbonyl compounds, using one reagent, fluoroiodane (Scheme 2.1).



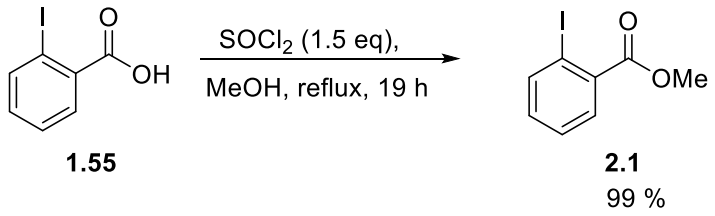
X = Cl, OMe, OEt, OCH_2CF_3, CF_3, R-NH_2

Scheme 2.1 *Atom transfer reactions using fluoroiodane*

2.2 Synthesis of Fluoroiodane

The hypervalent fluoroiodane reagent, 1-fluoro-3,3-dimethyl-1,3-dihydro-λ^3-benzo[*d*][1,2]iodoxole **1.61**, was prepared from 2-iodobenzoic acid **1.55**. Following the five step synthetic route developed by the Stuart group in 2013.[1] In the first step 2-iodobenzoic acid underwent an esterification reaction using thionyl chloride in methanol

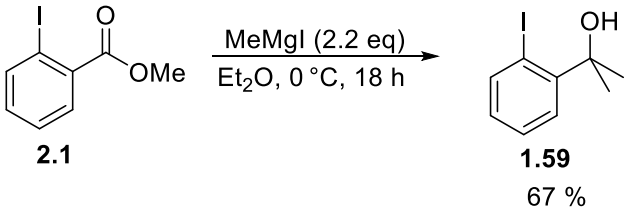
(Scheme 2.2). After refluxing the reaction mixture for 19 hours, methyl-2-iodobenzoate **2.1** was isolated in a 99 % yield. The appearance of a singlet at 3.81 ppm in the ^{1}H NMR spectrum, corresponding to the OCH_3 group confirmed the formation of methyl 2-iodobenzoate. This reaction required no purification and was carried out on a 15-25 g scale multiple times. The reaction was reliable and gave consistently high yields of 94 to 99 %.



1.55 **2.1** 99 %

Scheme 2.2 *Synthesis of methyl-2-iodobenzoate*

In order to synthesise 2-(2-iodophenyl)propan-2-ol **1.59**, a Grignard reaction was carried out, with methyl-2-iodobenzoate following the experimental procedure reported by Togni *et al.* (Scheme 2.3).[2] The Grignard reaction generated methylmagnesium iodide *in situ* by reacting magnesium turnings with methyl iodide in dry diethyl ether. Methyl-2-iodobenzoate **2.1** was added to the methyl magnesium iodide solution in dry diethyl ether at 0 °C and the reaction was warmed to room temperature and stirred for 18 hours. The literature method reported that the reaction mixture required refluxing for 1.5 hours after stirring the reaction for 18 hours,[3] however thin layer chromatography (TLC) analysis showed that the reaction did not require further heating and so the reaction was quenched after 18 hours.

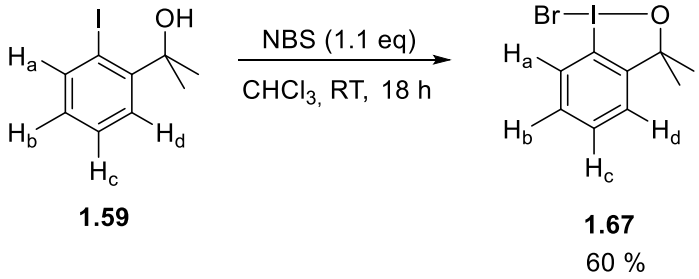


2.1 **1.59** 67 %

Scheme 2.3 *Synthesis of 2-(2-iodophenyl)propan-2-ol*

The crude product was purified by flash column chromatography on silica gel due to the presence of starting material. Furthermore, the formation of by-products within the Grignard reaction had been documented in the literature and also confirmed the need for purification.[4] The reaction was repeated a number of times on a large scale (10 –15 g) affording good yields following flash column chromatography where starting material

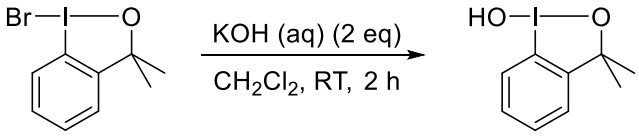
was present (66 -67 %). The ^{1}H NMR spectrum showed the absence of the OCH_3 singlet at 3.81 ppm, indicating that **2.1** was consumed. The presence of a 6H singlet at 1.63 ppm was observed for the two methyl groups in **1.59** and the appearance of the distinctive broad singlet for the hydroxyl group at 2.72 ppm confirmed the formation of the alcohol.



1.59 **1.67** 60 %

Scheme 2.4 *Synthesis of 1-bromo-3,3-dimethyl-1,3-dihydro-λ^3-benzo[d][1,2]iodoxole*

The preparation of bromoiodane **1.67** was carried out by reacting 2-(2-iodophenyl)propan-2-ol **1.59** with *N*-bromosuccinimide in chloroform at room temperature for 18 hours (Scheme 2.4). The crude product was recrystallized from warm ethyl acetate yielding 1-bromo-3,3-dimethyl-1,3-dihydro-λ^3-benzo[*d*][1,2]iodoxole **1.67**. During recrystallisation the temperature was not taken above 35 ^{o}C to avoid degradation of **1.67** back to iodoalcohol **1.59**. The reaction was carried out multiple times resulting in good yields, ranging from 57 – 60 %. ^{1}H NMR spectroscopy confirmed the formation of 1-bromo-3,3-dimethyl-1,3-dihydro-λ^3-benzo[*d*][1,2]iodoxole **1.67** by the downfield shift of H_b from 6.77 ppm in **1.59** to 7.47 ppm in **1.67**. The change in oxidation state was also apparent in the ^{13}C NMR spectrum of **1.67**, where the chemical shift of the carbon – iodine bond in **1.59** was at 93.2 ppm and, upon oxidation to iodine(III) the C-I bond shifted downfield to 112.0 ppm.

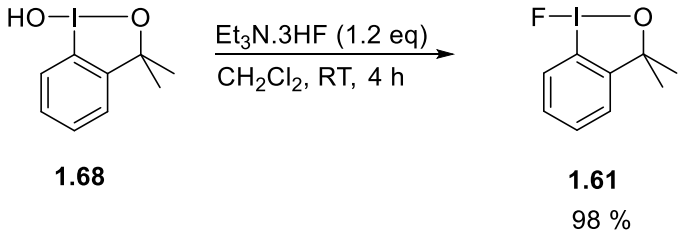


1.67 **1.68** 78 %

Scheme 2.5 *Synthesis of 1-hydroxy-3,3-dimethyl-1,3-dihydro-λ^3-benzo[d][1,2]iodoxole*

Bromoiodane **1.67** was next reacted in a biphasic reaction of dichloromethane and aqueous potassium hydroxide (Scheme 2.5). The nucleophilic substitution, generated hydroxyiodane **1.68** in a very good 78 % yield and no purification was needed due to the

100 % conversion from bromoiodane to hydroxyiodane. ^{1}H NMR spectroscopy confirmed the formation of **1.68** because the chemical shifts of the aromatic protons changed and the aromatic proton adjacent to the alcohol side arm was at 7.14 ppm in **1.67** but shifted downfield to 7.23 ppm for the hydroxyiodane **1.68**.



1.68 **1.61** 98 %

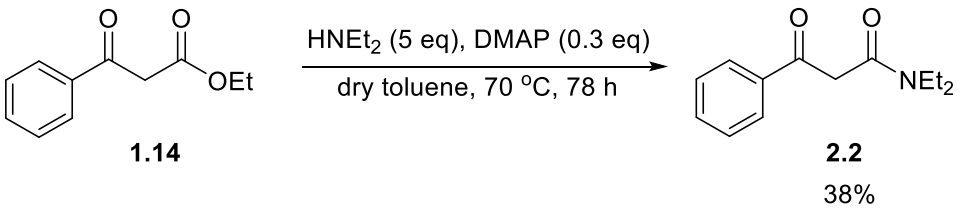
Scheme 2.6 *Synthesis of 1-fluoro-3,3-dimethyl-1,3-dihydro-λ^3-benzo[d][1,2]iodoxole*

In the final step fluoroiodane **1.61** was synthesised by reacting hydroxyiodane with TREAT-HF in dichloromethane for 4 hours at room temperature affording an excellent 98 % yield (Scheme 2.6). The product was coevaporated in toluene to remove any remaining water. It is not possible to dry fluoroiodane over magnesium sulphate as sulphate exchanges with fluoride and hence this method was avoided. The ^{19} F NMR spectrum confirmed the formation of **1.61** through the presence of a singlet at -143.1 ppm.

2.3 Synthesis of 1,3-Dicarbonyl Substrates

A range of 1,3-dicarbonyl substrates was selected to functionalise at the 2- position and the substrates included 1,3-ketoesters, a 1,3-ketoamide and a 1,3-diketone. The 1,3-dicarbonyl substrates required for the chlorination reactions that were not commercially available were synthesised prior to the chlorination reactions.

Initially *N,N*-diethyl-3-oxo-3-phenylpropanamide was synthesised by refluxing ethyl 3-oxo-phenylpropanoate with diethylamine and 4-dimethylaminopyridine in dry toluene for 26 hours. Only a 20 % conversion was obtained and the crude product was purified by column chromatography to give the product in a 5 % yield. The low conversion may have been a consequence of the reaction requiring more equivalents of amine to push the reaction to completion.

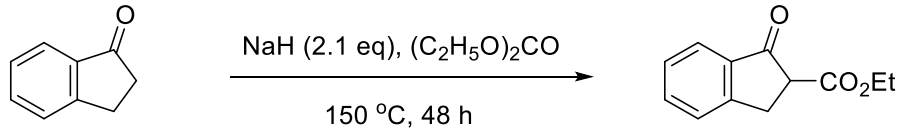


1.14 **2.2**

38%

Scheme 2.7 *Synthesis of N,N-diethyl-3-oxo-3-phenylpropanamide*

The reaction was repeated and monitored by thin layer chromatography (TLC). After 26 hours TLC showed the presence of starting material and in order to push the reaction to completion a further 2 equivalents of diethylamine was added and the reaction was refluxed for a further 26 hours. Since there was still starting material present, the reaction was stirred for a further 48 hours at 70 °C. Following a total of 78 hours a 63% conversion was obtained and a 38% isolated yield was achieved (Scheme 2.7). The lower isolated yield was probably a consequence of the presence of an unknown by-product being formed which was isolated by column chromatography, but was unable to be identified. ^{1}H NMR spectroscopy confirmed the formation of **2.2** by the appearance of a 6H triplet at 1.13 ppm corresponding to the 2 x CH_3 groups for the keto tautomer as well as a 6H triplet at 1.18 ppm for the 2 x CH_3 groups for the enol tautomer. Furthermore, two distinctive singlets were observed at 4.04 ppm and 5.72 ppm and corresponded to the CH_2 group in the keto tautomer as well as the CH group in the enol tautomer respectively.



2.3 **2.4**

82 %

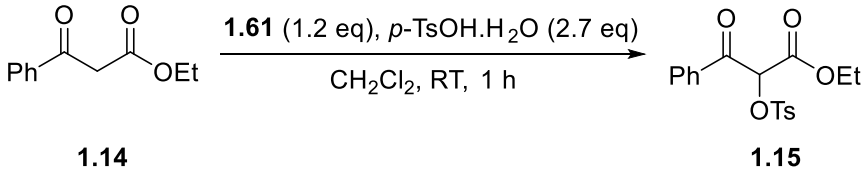
Scheme 2.8 *Synthesis of ethyl 1-oxo-2,3-indanone-2-carboxylate*

Ethyl 1-oxo-2,3-indanone-2-carboxylate was initially synthesised by refluxing 1-indanone with sodium hydride in dry diethyl carbonate for 48 hours resulting in a 100 % conversion and an 82% isolated yield after purification by column chromatography. An 83:17 ratio of keto:enol was observed by ^{1}H NMR spectroscopy before and after purification. The diethyl carbonate was dried over calcium chloride for 1 hour before being used in the reaction.

The disappearance of the two 2 H multiplets at 2.69 ppm and 3.15 ppm corresponding to the protons on the 5 membered ring of indanone demonstrated the consumption of starting material. The formation of the product was confirmed by two 3H triplets at 1.30 ppm and 1.37 ppm corresponding to the keto and enol tautomers of the ethoxy CH_3 group respectively. The 2H multiplet at 4.24 ppm and the 2H quartet of doublets at 4.31 ppm corresponded to the OCH_2 of the keto and enol tautomers, indicating the addition of the CO_2Et group. The 1H doublet of doublets at 3.73 ppm corresponds to the $CHCO_2Et$ proton. The ^{13}C NMR spectrum showed the presence of two CH_3 groups at 14.2 ppm and 14.5 ppm for the keto and enol tautomers of the ethoxy moiety and CH at 53.3 ppm for the 1H adjacent to the ethoxy moiety on the indanone ring.

2.4 Chlorination of 1,3-Dicarbonyl Substrates

2.4.1 Chlorination of Ethyl 3-oxo-phenylpropanoate

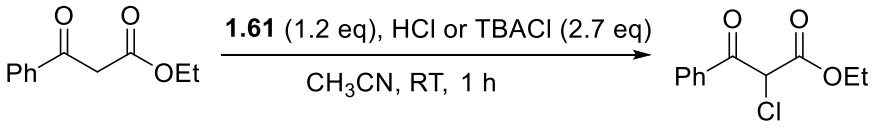


1.14 **1.15**

Scheme 2.9 *Tosyloxylation of ethyl 3-oxo-3-phenylpropanoate using fluoroiodane*

The aim of this section was to develop a one-pot synthesis to generate a range of 2-chloro-1,3-dicarbonyl compounds using the hypervalent fluoroiodane reagent **1.61**. Previously within the Stuart group the tosyloxylation of 1,3-dicarbonyl compounds using fluoroiodane and *p*-toluenesulfonic acid monohydrate was investigated (Scheme 2.9). Ethyl-3-oxo-3-phenylpropanoate was reacted with fluoroiodane (1.2 equivalents), *p*-toluenesulfonic acid monohydrate (2.7 equivalents) at room temperature for 1 hour. After purification by column chromatography the monotosyloxylated product was isolated in an 80 % yield. These conditions were used as a starting point for the chlorination of 1,3-dicarbonyl compounds using ethyl 3-oxo-phenylpropanoate **1.14** as the model substrate (Table 2.1). In addition, hydrochloric acid and tetrabutylammonium chloride were investigated as the source of chloride, to determine whether an acid was required for these reactions.

Table 2.1 *Optimisation of the chlorination of ethyl 3-oxo-3-phenylpropanoate*



1.14 **2.5**

Entry	Chloride Source	Concentration (M)	Conversion[a] (%)	Isolated yield (%)
1	HCl	0.31	> 95	63
2	HCl	0.63	39	-[c]
3	TBACl	0.31	93	17
4	TBACl	0.63	91	20
5[b]	TBACl	0.31	91	-[c]

[a] Conversion was determined by ^{1}H NMR spectroscopy of the crude product; [b] reaction was carried out for 2 hours; [c] the crude product was not purified.

The chlorination reactions were carried out at 0.31 M and 0.63 M in acetonitrile to observe the effects of changing the concentration on the reaction. Firstly, the concentration was investigated using hydrochloric acid as the source of chloride. The reaction was carried out under dry conditions using a Schlenk line and a 95 % conversion was obtained under more dilute conditions (entry 1), whereas only a 39 % conversion was obtained under more concentrated reaction conditions (entry 2).

The consumption of starting material was confirmed by the disappearance of the 2H singlet at 4.00 ppm corresponding to the aliphatic CH_2 within ethyl 3-oxo-3-phenylpropanoate. The product **2.5** was confirmed by the presence of a 1H singlet at 5.62 ppm corresponding to the CHCl proton. The isolated yield for entry 1 was quite low in comparison to the conversion because the Rf values of the starting material and the iodoalcohol by-product are very similar to the product, leading to a challenging purification by column chromatography.

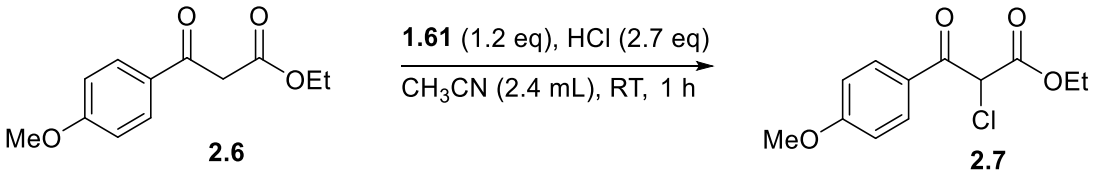
When tetrabutylammonium chloride (TBACl) was used as the chloride source, there was no difference between the conversions for the reactions carried out at 0.31 M and 0.63 M (entries 3 and 4). Unfortunately, the monochlorinated product was only isolated in a 17-

20 % yield because a number of by-products were produced in this reaction making it more difficult to isolate the monochlorinated product. From Table 2.1 it was clear that the best results were obtained using HCl (2.7 equivalents) as the chloride source with a 95 % conversion and a 63 % isolated yield (entry 1).

During the chlorination of ethyl 3-oxo-3-phenylpropanoate using fluoroiodane there was no evidence of fluorinated products being produced. Stuart and coworkers reported the fluorination of 1,3-dicarbonyl compounds at 40 °C for 20 hours in the presence of $Et_3N.3HF$. The corresponding chlorination of ethyl 3-oxo-3-phenylpropanoate was conducted under shorter reaction times and milder conditions and consequently, the fluorinated product was not expected to be produced under these conditions.

2.4.2 Chlorination of Ethyl 3-(4-methoxyphenyl)-3-oxopropanoate

Table 2.2 *Chlorination of ethyl-3-(4-methoxyphenyl)-3-oxopropanoate*



Entry	Chloride source (eq)	Conversion (%)	Isolated yield (%)
1	HCl	90	50
2	TBACl	93	38

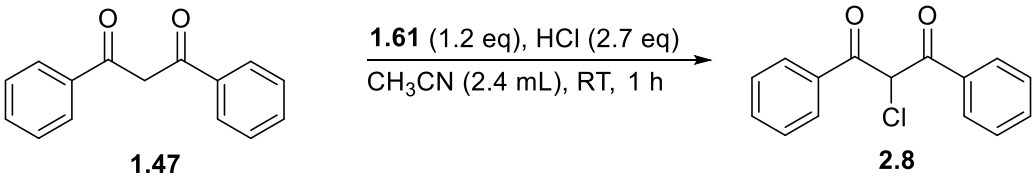
The chlorination of ethyl 3-(4-methoxyphenyl)-3-oxopropanoate was initially carried out using HCl (2.7 equivalents) as the source of chloride and fluoroiodane (1.2 equivalents) for 1 hour at room temperature giving a 90% conversion. Following purification by column chromatography, a 50% isolated yield was obtained (entry 1). The low isolated yield was a result of the similarity in Rf values of **2.7** and iodoalcohol **1.59**, resulting in a challenging separation. A very slow, non-polar solvent system was used in order to obtain optimum separation.

The reaction was repeated using tetrabutylammonium chloride (2.7 equivalents) as the chloride source and a 93% conversion was obtained after 1 hour, with a 38% isolated yield after purification by column chromatography (entry 2). The low isolated yield was attributed to the difficulty in purification, due to the tetrabutylammonium chloride being present and **2.7** and iodoalcohol **1.59** having a similar Rf value. In addition, the reactions using HCl were cleaner as more by-products were produced when TBACl was used as the source of chloride.

^{1}H NMR spectroscopy confirmed the consumption of the starting material through the disappearance of the 2H singlet of the aliphatic CH_2 at 3.94 ppm. The formation of product was confirmed by the presence of a 1H singlet at 5.57 ppm corresponding to the CHCl group of **2.7**, as well as a 3H triplet at 1.25 ppm corresponding to the CH_3 within the ethyl group and a singlet at 3.89 ppm belonging to the OCH_3 of the methoxy group. Within the ^{13}C NMR spectrum the presence of a singlet at 57.9 ppm for CHCl confirmed formation of **2.7**. The isotope pattern for chlorine was also observed in the mass spectrum, where an *m/z* of 257.05710 was observed for the ^{35}Cl isotope, $C_{12}H_{14}O_4{}^{35}Cl$ (100 %) and an *m/z* of 259.05557 was obtained for the ^{37}Cl isotope, $C_{12}H_{14}O_4{}^{37}Cl$ (40 %).

2.4.3 Chlorination of Dibenzoylmethane

Table 2.3 *Chlorination of dibenzoylmethane*



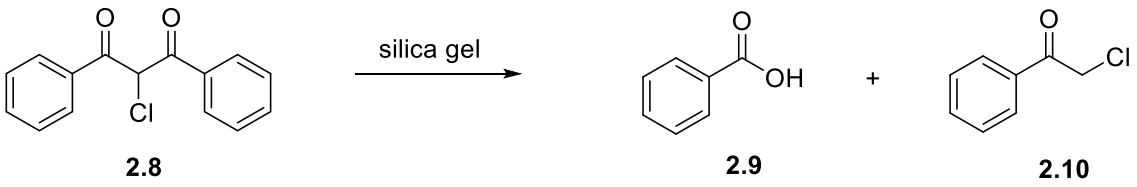
1.47 **2.8**

Entry	Conversion (%)	Isolated yield (%)
1	100	Degraded
2	> 95	Degraded
3	> 95	56

The optimum reaction conditions were applied to a 1,3-diketone, dibenzoylmethane **1.47**. Dibenzoylmethane was chlorinated using HCl (2.7 eq) and fluoroiodane (1.2 eq) in acetonitrile for 1 hour at room temperature (Table 2.3). In entry 1 a 100 % conversion was achieved, however an isolated yield was not obtained because the 2-chloro-1,3-diphenylpropan-1,3-dione **2.8** degraded to 1-chloroacetophenone **2.10**. The degradation could have resulted from the hydrochloric acid becoming more concentrated when the solvent was removed by rotary evaporation. After purification of entry 2 by column chromatography, 1-chloroacetophenone **2.10** was obtained in a 25 % yield and was identified by the distinct 2H singlet at 4.71 ppm for the CH_2Cl group. The isotope pattern for chlorine was also obtained in the mass spectrum of **2.10**, where an *m/z* of 155.0259 was observed for the ^{35}Cl isotope, $C_8H_8O^{35}Cl$ and the ^{37}Cl isotope gave an *m/z* of 157.0247 ($C_8H_8O^{37}Cl$). 2-Chloro-1,3-diphenylpropane-1,3-dione **2.8** was therefore being hydrolysed into benzoic acid **2.9** and 1-chloroacetophenone **2.10** upon purification by column chromatography on silica gel (Scheme 2.10) and not in the reaction.

To overcome the degradation issue, the reaction was repeated and an aqueous work up was carried out (entry 3). ^1H NMR spectroscopy of the crude product confirmed that no degradation had taken place in the reaction and 2-chloro-1,3-diphenylpropane-1,3-dione **2.8** was purified by column chromatography on silica gel. An isolated yield was not achieved as a consequence of the product degrading on the column. The reaction was then repeated and a > 95 % conversion was achieved. The product was purified by precipitation in petroleum spirit (40 – 60 °C) resulting in a 56 % isolated yield.

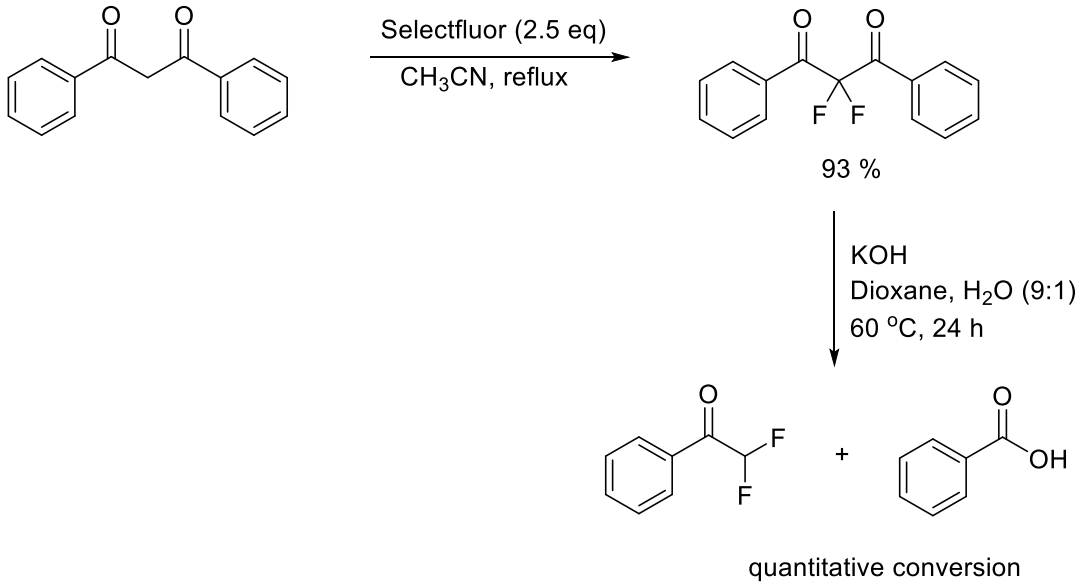
The ^1H NMR spectrum of product **2.8** confirmed that there was no starting material present by the absence of the 1H singlet at 6.86 ppm corresponding to the alkene proton for dibenzoylmethane in the enol form. The presence of the 1H singlet at 6.41 ppm for the CHCl proton of the product confirmed that the monochlorinated product was formed. Within the ^{13}C NMR spectrum a peak at 63.0 ppm was observed for CHCl. The isotope pattern of chlorine was also obtained in the mass spectrum, where an *m/z* of 259.0531 was observed corresponding for the ^{35}Cl isotope, $C_{15}H_{12}O_2{}^{35}Cl$ and the ^{37}Cl isotope gave an *m/z* of 261.0513 for $C_{15}H_{12}O_2{}^{37}Cl$.



2.8 **2.9** **2.10**

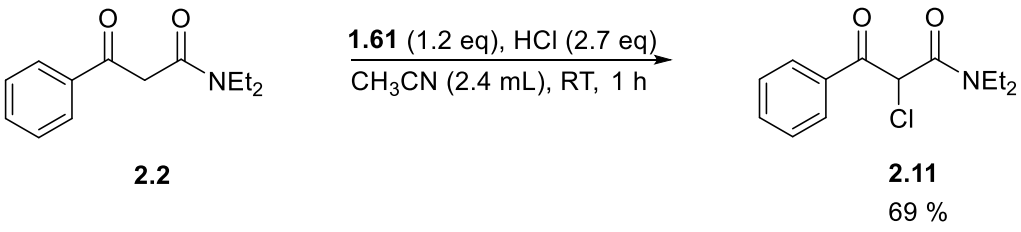
Scheme 2.10 *Hydrolysis of 2-chloro-1,3-diphenylpropanedione*

A similar hydrolysis of 2,2-difluoro-1,3-diphenylpropanedione to form a series of difluoromethyl ketones was reported in the literature by Pattison.[5] In the first step dibenzoylmethane was difluorinated by refluxing with 2.5 equivalents of Selectfluor in acetonitrile. The difluorinated product was then treated with KOH and water to form the corresponding difluoromethyl ketone and benzoic acid in a quantitative conversion (Scheme 2.11).



Scheme 2.11 *Hydrolysis of 2,2-difluoro-1,3-diketones*[5]

2.4.4 Chlorination of *N,N*-Diethyl-3-oxo-3-phenylpropanamide

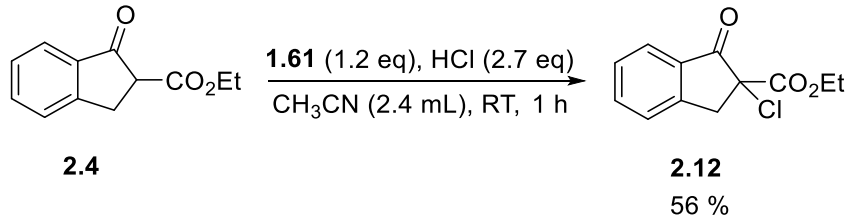


2.2 **2.11**
69 %

Scheme 2.12 *Chlorination of N,N-diethyl-3-oxo-3-phenylpropanamide*

N,N-Diethyl-3-oxo-3-phenylpropanamide was chlorinated using the same optimum reaction conditions; HCl (2.7 equivalents), fluoroiodane (1.2 equivalents) for 1 hour at room temperature in acetonitrile (Scheme 2.12). A 100 % conversion was obtained and the product was isolated in a good 69 % yield after purification by column chromatography. ^{1}H NMR spectroscopy confirmed the consumption of starting material by the absence of the 2H singlet at 4.06 ppm corresponding to the aliphatic CH_2, and by the absence of the 1H singlet corresponding to the alkene proton for the enol tautomer at 5.72 ppm. The formation of product **2.11** was also confirmed by ^{1}H NMR spectroscopy by the presence of a 1H singlet for the CHCl group at 5.84 ppm. The isotope pattern for chlorine was also obtained in the mass spectrum of **2.11**, where an *m/z* of 254.0948 was observed for the ^{35}Cl isotope, $C_{13}H_{17}NO_2{}^{35}Cl$ and the ^{37}Cl isotope gave an *m/z* of 256.0922 for $C_{13}H_{17}NO_2{}^{37}Cl$.

2.4.5 Chlorination of Ethyl 1-oxo-2,3-indanone-2-carboxylate

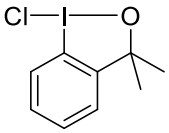


2.4 **2.12** 56 %

Scheme 2.13 *Chlorination of ethyl 1-oxo-2,3-indanone-2-carboxylate*

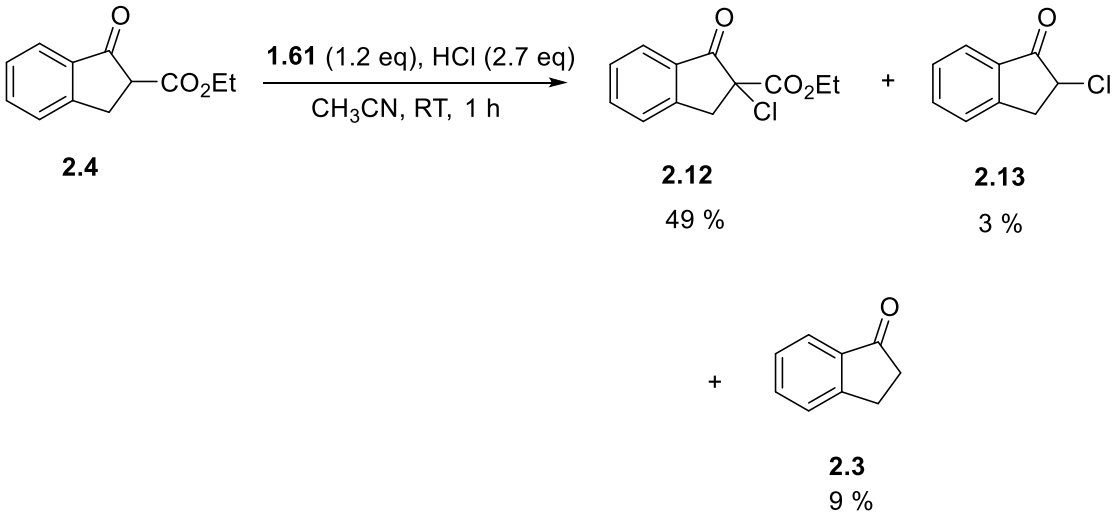
The chlorination of ethyl 1-oxo-2,3-indanone-2-carboxylate (Scheme 2.13) was carried out using fluoroiodane (1.2 equivalents) and HCl (2.7 equivalents) in acetonitrile at room temperature for 1 hour. Although an 88% conversion was obtained, the monochlorinated product **2.12** was only isolated in a low 18% yield. 1-Indanone was present in the ^{1}H NMR spectrum of the crude product, indicating that decarboxylation of ethyl 1-oxo-2,3-indanone-2-carboxylate had occurred during the reaction. Since 1-indanone was not present in the ^{1}H NMR spectrum of the starting material, ethyl 1-oxo-2,3-indanone-2-carboxylate, it must be formed in the reaction. It was also observed that ethyl 2-chloro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate **2.12** decarboxylated on the silica column to form 2-chloroindanone (Scheme 2.14). The 2-chloroindanone **2.13** was identified by ^{1}H NMR spectroscopy, giving a 1H doublet of doublets at 3.30 ppm and a 1H doublet of doublets at 3.79 ppm corresponding to the diastereotopic protons of the CH_2 group, as well as a 1H doublet of doublets at 4.57 ppm corresponding to the CHCl proton.

Interestingly, chloroiodane **1.60** was also produced in the reaction and was isolated in a 63 % yield (Figure 2.1).



1.60

Figure 2.1 *1-Chloro-3,3-dimethyl-1,3-dihydro-λ^3-benzo[d][1,2]iodoxole (chloroiodane)* ***1.60***



2.4

2.12
49 %

2.13
3 %

2.3
9 %

Scheme 2.14 *Degradation of ethyl 2-chloro-1-oxo-2,3-dihydro-1H-indene-2-carboxylate* ***2.12***

In order to determine if ethyl 2-chloro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate was light sensitive, the reaction was repeated twice under the same reaction conditions. However, one reaction was carried out exposed to ambient light and the other reaction was kept in the dark and was wrapped in aluminium foil.

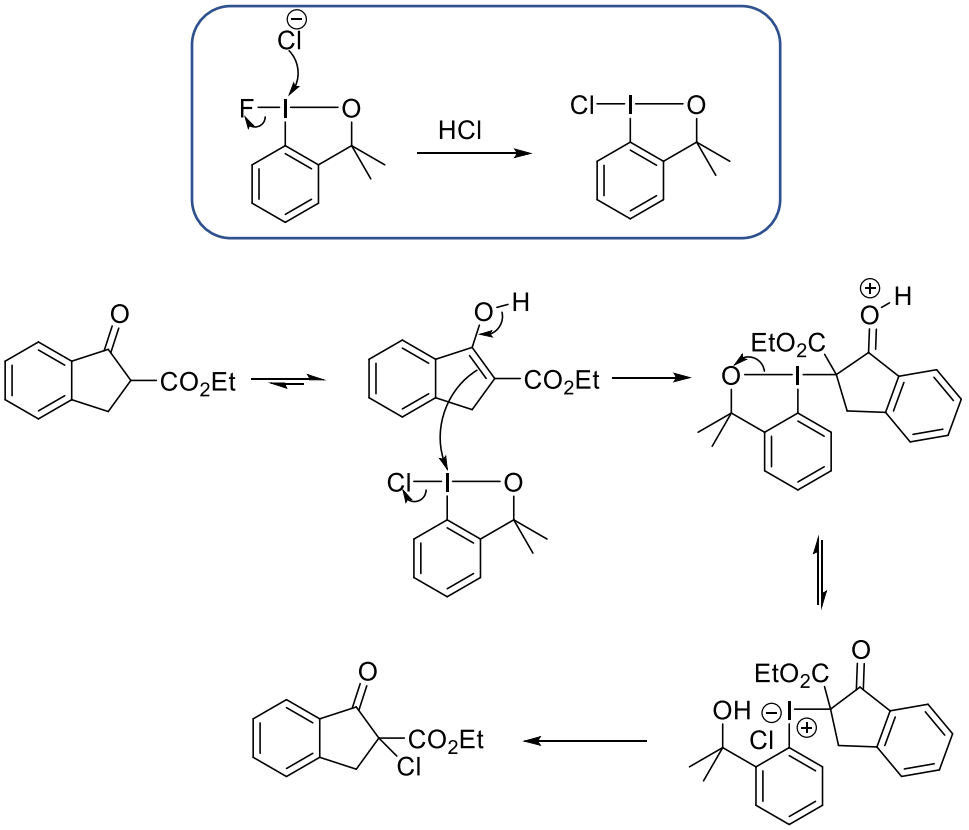
The chlorination of ethyl 1-oxo-2,3-indanone-2-carboxylate in ambient light showed the presence of 1-indanone **2.3** and the monochlorinated product **2.12** by ^{1}H NMR spectroscopy. In this reaction there was only a 10% conversion to product and no starting material was present. A small quantity of the starting material had been chlorinated, but the majority of the starting material had decarboxylated to form 1-indanone **2.3**.

The reaction wrapped in aluminium foil afforded an 88% conversion to product **2.12**. The ^{1}H NMR spectrum of the crude product also showed the presence of chloroiodane **1.60**

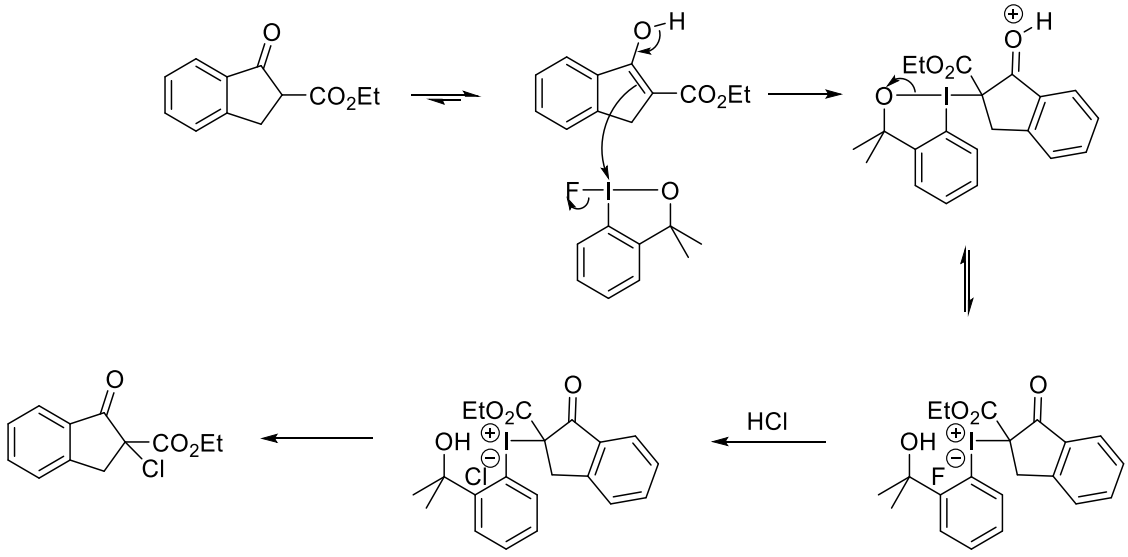
and 1-indanone **2.3**. The crude product was purified by column chromatography to give **2.12** in a 56% isolated yield. The low isolated yield was due to degradation of the product **2.12** to **2.13** on the silica column as well as the formation of an unidentified by-product. Since the degradation products had a similar Rf to that of the monochlorinated product **2.12**, it made isolating the product more challenging.

The ^{1}H NMR spectrum of product **2.12** showed the presence of a 3H triplet at 1.27 ppm corresponding to the CH_3 within the ethyl group and a 2H multiplet at 4.27 ppm belonging to the CH_2 of the ethyl group. In addition, the presence of a 1H doublet at 3.56 ppm and a 1H doublet at 4.10 ppm corresponds to the two CH_2 protons on the ring. The ^{13}C NMR spectrum also revealed the presence of a singlet at 68.0 ppm for the CCl carbon. In addition, the formation of product was confirmed by mass spectrometry where the parent ion peak at *m/z* 239.0481 corresponded to the ^{35}Cl isotope, and the parent ion peak at *m/z* of 241.0471 for the ^{37}Cl isotope.

The isolation of chloroiodane brought into question the mechanism for these reactions. Evidence of chloroiodane could suggest that a chlorine atom was displacing the fluorine atom in fluoroiodane by a nucleophilic substitution. Upon synthesis of chloroiodane, the reaction could proceed via the proposed reaction mechanism shown in Scheme 2.15, whereby the enol tautomer of the 1,3-dicarbonyl substrate reacts with chloroiodane to form an iodonium intermediate.[6] The mechanism shows the enol tautomer reacting with the electropositive iodine. Ring opening of the intermediate followed by proton transfer generates the iodonium chloride. The final step of the mechanism was proposed to proceed via a reductive elimination with chloride (Scheme 2.15).



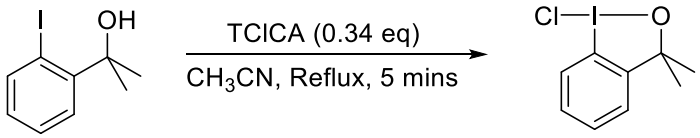
Scheme 2.15 *Proposed chlorination mechanism I*



Scheme 2.16 *Proposed chlorination mechanism II*

An alternative mechanism is shown in Scheme 2.16. Here, the enol reacted directly with fluoroiodane at the electropositive iodine and displaced the fluoride anion to form an intermediate which undergoes ring opening to give an iodonium fluoride. The iodonium

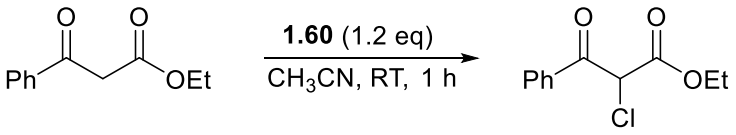
fluoride could then undergo anion exchange with the excess HCl to form the iodonium chloride, followed by reductive elimination to yield the desired monochlorinated product and iodoalcohol.



1.59 **1.60** 83%

Scheme 2.17 *Synthesis of 1-chloro-3,3-dimethyl-1,3-dihydro-λ^3-benzo[d][1,2]iodoxole*

From the results so far, it was not possible to distinguish between the two proposed mechanisms. Hence, the chloroiodane was prepared in order to investigate its reactivity in the direct chlorination of ethyl 3-oxo-3-phenylpropanoate and to compare its reactivity with the fluoroiodane / HCl system. 2-(2-Iodophenyl)propan-2-ol **1.59** was synthesised and purified by column chromatography, before reacting it with trichloroisocyanuric acid in acetonitrile for 5 minutes. After purification by recrystallisation, chloroiodane was isolated in an 83 % yield (Scheme 2.17).



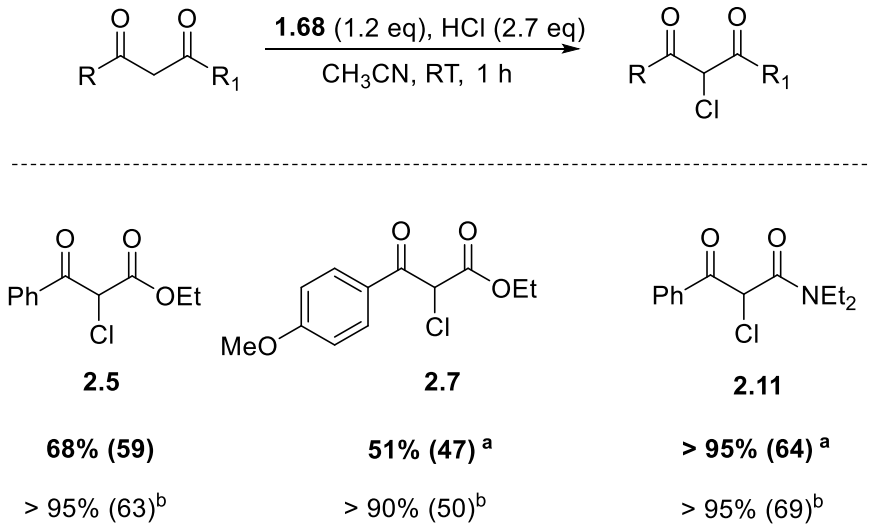
1.14 **2.5** 11%

Scheme 2.18 *Chlorination using 1-chloro-3,3-dimethyl-1,3-dihydro-λ^3-benzo[d][1,2]iodoxole*

Ethyl 3-oxo-3-phenylpropanoate was reacted with chloroiodane (1.2 equivalents) in acetonitrile at room temperature for 1 hour, but the reaction only reached an 11 % conversion to the monochlorinated product **2.5** and unreacted starting material was observed (Scheme 2.18). These initial results indicated that the reaction proceeded much slower through the chloroiodane mechanism (Scheme 2.15) and when the reaction was repeated using chloroiodane for 24 hours an 80 % conversion to product was observed. However, when the reaction was repeated in the presence of HCl (2.7 equivalents), using chloroiodane in acetonitrile at room temperature for 1 hour, a 91 % conversion and a 78

% isolated yield was achieved. Here, the reaction gave a similar result to the previous reaction using fluoroiodane in the presence of HCl (2.7 equivalents) to give a 100 % conversion and a 63 % isolated yield.

2.5 Chlorination of 1,3 Dicarbonyl Substrates using Hydroxyiodane



Scheme 2.19 *Chlorination reactions using hydroxyiodane **1.68**; [a] after 2 hours; [b]reaction carried out using **1.61** (1.2 equivalents)*

Hydroxyiodane **1.68** the precursor to fluoroiodane, was investigated as an alternative hypervalent iodine reagent for the chlorination of 1,3-dicarbonyl substrates. Ethyl 3-oxo-3-phenylpropanoate was the initial substrate studied using the optimum reaction conditions; HCl (2.7 equivalents) and **1.68** (1.2 equivalents) in acetonitrile. The reaction was carried out at room temperature for 1 hour in the first instance giving a 68% conversion and a 59% isolated yield. The reaction with hydroxyiodane proceeded slower than the same reaction using fluoroiodane **1.61** (1.2 equivalents), where a 100 % conversion was achieved, with a 63% isolated yield.

The chlorination was repeated under the same conditions but for 2 hours, to investigate whether the yield could be improved. An 85% conversion and a 61% isolated yield was obtained. This data showed that fluoroiodane was a better reagent for the chlorination as it allowed the reaction to reach completion after just 1 hour, whereas only an 85 % conversion was obtained using hydroxyiodane for 2 hours.

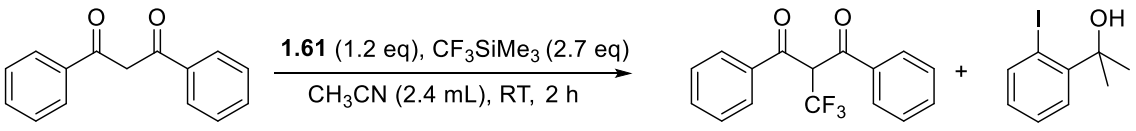
The chlorination of ethyl 3-(4-methoxyphenyl)-oxopropanoate was carried out using hydroxyiodane under the same reaction conditions. After 2 hours a 51% conversion was obtained with a 47% isolated yield. This chlorination proceeded at a much slower rate than when using fluoroiodane, where a 90% conversion was achieved after just 1 hour.

N,N-Diethyl-3-oxo-3-phenylpropanamide was chlorinated with hydroxyiodane **1.68** (1.2 equivalents), HCl (2.7 equivalents) and acetonitrile at room temperature for 2 hours. A 100 % conversion was obtained and the monochlorinated product was isolated in a 64 % yield. This result was similar to that using fluoroiodane (1.2 equivalents) where a 100 % conversion was achieved, with a 69 % isolated yield in 1 hour.

In conclusion, the chlorination of 1,3-dicarbonyl substrates proceeded at a slower rate using hydroxyiodane instead of fluoroiodane. It is therefore worth preparing fluoroiodane instead of completing the synthesis at hydroxyiodane.

2.6 Trifluoromethylation of 1,3-Dicarbonyl Substrates

Fluoroiodane is a successful fluorinating reagent, capable of fluorinating a range of 1,3-dicarbonyl compounds. It has also been used to introduce nucleophiles into the 2-position of 1,3-dicarbonyl compounds, through tosyloxylation and chlorination.[7] The aim of this section was to investigate the ability of fluoroiodane to trifluoromethylate a range of 1,3-dicarbonyl compounds.

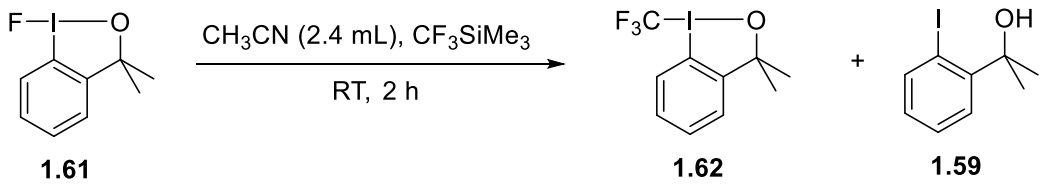


1.47 **2.14** **1.59**

Scheme 2.20 *Synthesis of 1,3-diphenyl-2-(trifluoromethyl)propane-1,3-dione*

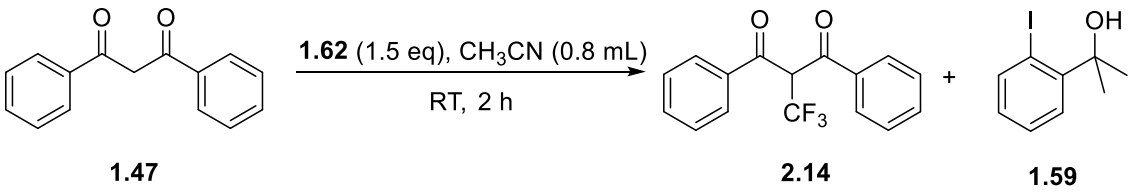
The trifluoromethylation of dibenzoylmethane was investigated using fluoroiodane (1.2 equivalents) and Ruppert's reagent (trimethyl(trifluoromethyl)silane) in acetonitrile at room temperature for 2 hours. The ^{19}F NMR spectrum of the crude product showed that Togni's reagent was formed *in situ*,[8] with a singlet at -39.9 ppm, and there was no fluoroiodane present as the singlet at -143.1 ppm had disappeared. The ^{1}H NMR spectrum showed the presence of iodoalcohol **1.59** (Scheme 2.20) which would be formed upon

trifluoromethylation occurring. Comparing the ^{1}H NMR spectrum of the crude product to the starting material, dibenzoylmethane, it was apparent that a new compound was formed. There was a 2H aromatic triplet at 6.90 ppm, a 1H aromatic triplet at 7.05 ppm and a 2H aromatic doublet at 7.32 ppm, matching up with the expected splitting pattern and number of protons within the aromatic region of the starting material. However, the signals were shifted much further upfield than the starting material with a 2H aromatic triplet at 7.49 ppm, a 1H aromatic triplet at 7.55 ppm and a 2H aromatic doublet at 7.99 ppm. This was a promising sign that the dibenzoylmethane had been trifluoromethylated. In the ^{19}F and ^{1}H NMR spectra there were numerous unidentifiable peaks and it was apparent that the reaction did not proceed cleanly. The crude product was purified by column chromatography but, the potential product was not isolated. The column was extremely difficult as the crude sample contained a multitude of peaks, resulting in a challenging purification and analysis.



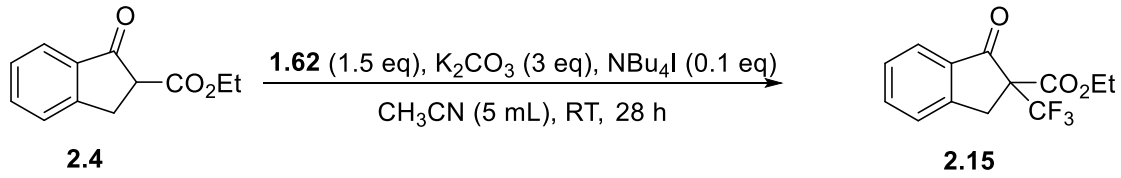
Scheme 2.21 *Synthesis of Togni's reagent* [2, 15]

In light of this result, Togni's reagent was prepared prior to the trifluoromethylation, by reacting fluoroiodane with Ruppert's reagent (2.7 equivalents) in acetonitrile at room temperature for 2 hours following Togni's literature procedure (Scheme 2.21).[2] A 95% yield was obtained in a mixture with iodoalcohol (13 %). The synthesis of Togni's reagent was repeated under the same conditions and Togni's reagent was precipitated in pentane to remove the iodoalcohol, leaving a colourless filtrate, which was concentrated to afford an 85% yield with an 11% iodoalcohol impurity. The precipitations were repeated in order to remove iodoalcohol but very little was removed by this method. Consequently, the trifluoromethylations were carried out using Togni's reagent with the iodoalcohol impurity because it would not be expected to react.



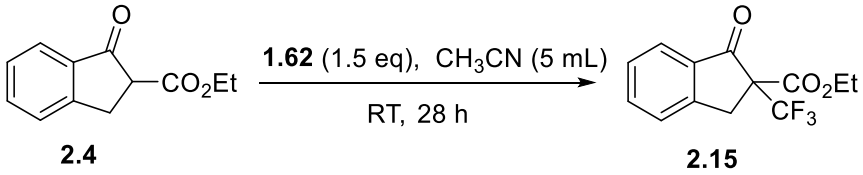
Scheme 2.22 *Trifluoromethylation of dibenzoylmethane using Togni's reagent*

The trifluoromethylation of dibenzoylmethane was attempted using Togni's reagent (1.5 equivalents) in acetonitrile at room temperature for 2 hours (Scheme 2.22). After 2 hours there was no evidence of product, or the formation of new peaks within the ^{19}F NMR spectrum. Despite this, all of Togni's reagent was consumed with only iodoalcohol and dibenzoylmethane observed in the ^{1}H NMR spectrum of the crude reaction mixture.



Scheme 2.23 *Trifluoromethylation of ethyl 3-oxo-3-phenylpropanoate with additives*[8]

Togni's literature procedure for the trifluoromethylation of ethyl 1-oxo-2,3-indanone-2-carboxylate was used to prepare ethyl 1-oxo-2-(trifluoromethyl)-2,3-dihydro-1*H*-indene-2-carboxylate **2.15**.[8] The synthesis involved reacting ethyl 1-oxo-2,3-indanone-2-carboxylate with Togni's reagent, potassium carbonate and tetra-*n*-butylammonium iodide in acetonitrile at room temperature for 28 hours (Scheme 2.23). ^{19}F NMR spectroscopy of the crude mixture showed the presence of Togni's reagent at -40.7 ppm and a peak at -69.2 ppm, which matched the literature value for the trifluoromethylated product.[15] In the ^{1}H NMR spectrum iodoalcohol was observed, alongside Togni's reagent and the trifluoromethylated ethyl 1-oxo-2,3-indanone-2-carboxylate, but the product could not be isolated.



Scheme 2.24 *Trifluoromethylation of ethyl 1-oxo-2,3-indanone-2-carboxylate without additives*

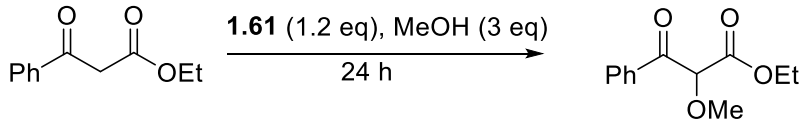
The reaction was repeated without potassium carbonate and tetra-*n*-butylammonium iodide (Scheme 2.24). The ^{19}F NMR spectrum of the crude product showed the presence of multiple peaks but in this case Togni's reagent was consumed as there was no peak present at -40.7 ppm. Also, the peak corresponding to product at -69.2 ppm was observed and was much more prevalent than in the reaction with additives. In contrast, the reaction without additives was much messier, with a multitude of peaks being observed in the ^{19}F NMR spectrum. The ^{1}H NMR spectrum showed the presence of iodoalcohol as well as unidentifiable peaks. The crude product was purified by column chromatography but the desired product was not isolated and many different compounds were observed in the ^{19}F and ^{1}H NMR spectra.

The trifluoromethylation reactions investigated showed very little evidence of trifluoromethylation despite attempting to use different substrates to test its capability. The reactions resulted in complicated ^{1}H NMR spectra which showed the formation of a multitude of products, and they also resulted in very difficult purifications. As a result of this, it was decided to investigate other atom transfer reactions.

2.7 Methoxylation of 1,3-Dicarbonyl Compounds

With the aim of expanding the scope of fluoroiodane through the introduction of a variety of nucleophiles at the α-position of a number of 1,3-dicarbonyl substrates, methanol was explored as a nucleophile. The initial substrate investigated for the introduction of a methoxy group was ethyl 3-oxo-3-phenylpropanoate.

Table 2.4 *Methoxylation of ethyl 3-oxo-3-phenylpropanoate*

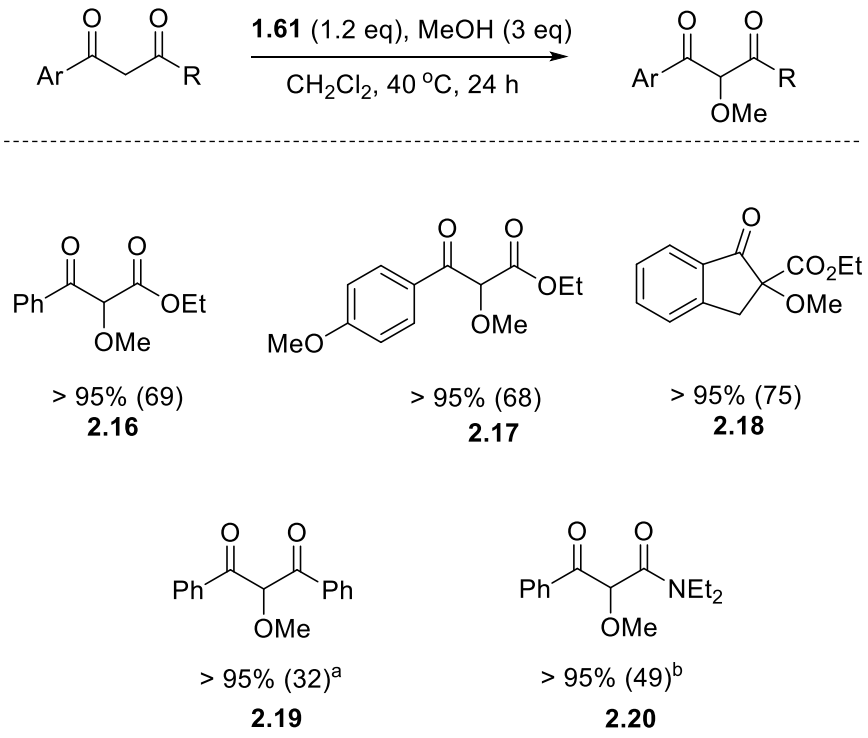


1.14 **2.16**

Entry	Temperature	Solvent	Conversion[a] (%)	Isolated yield (%)
1	RT	CH_3CN	0	0
2	RT	CH_2Cl_2	100	52
3	40	CH_2Cl_2	100	67[b]
4	40	CH_2Cl_2	100	69

[a]Conversion denoted by the consumption of starting material; [b] as a mixture with iodoalcohol.

A preliminary investigation into the methoxylation of ethyl 3-oxo-3-phenylpropanoate was investigated, starting with room temperature reactions, as the chlorinations were able to proceed under mild conditions. Fluoroiodane (1.2 equivalents) and methanol (3 equivalents) were reacted with ethyl 3-oxo-3-phenylpropanoate in acetonitrile at room temperature for 24 hours (entry 1), unfortunately, the ^{1}H NMR spectrum showed no evidence of methoxylation. The reaction was repeated in dichloromethane and a significantly improved 100 % conversion was achieved and after purification by column chromatography, a 52 % yield of the methoxylated product was obtained (entry 2). When the reaction was heated to 40 °C for 24 hours a 100 % conversion was obtained and the crude product was purified by column chromatography on silica gel. When a graduated solvent system of 0-10% ethyl acetate in petroleum spirit (40-60 ^{o}C) was used, the product was not isolated but was obtained in a 67% yield as a mixture with iodoalcohol, the by-product of the reaction.



Scheme 2.25 *Methoxylation of 1,3-dicarbonyl compounds; [a] Reaction carried out at room temperature for 24 hours wrapped in aluminium foil; [b] reaction carried out at 30 °C for 24 hours in neat methanol, wrapped in aluminium foil.*

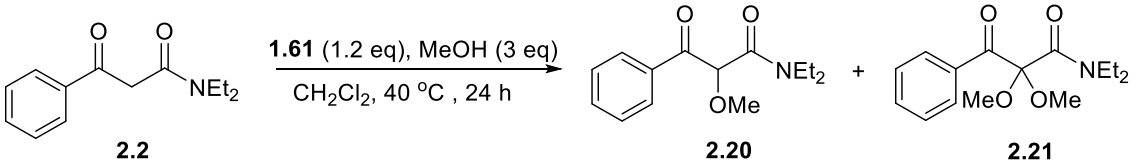
In an attempt to isolate the product from iodoalcohol, various solvent systems were investigated using TLC. The reaction was repeated with the aim of improving the isolated yield using a new solvent system, 0.5% methanol in dichloromethane, and a 69% isolated yield was achieved. ^{1}H NMR spectroscopy showed the presence of a 1H singlet corresponding to the CHOMe at 4.93 ppm and the presence of a 3H singlet corresponding to the OMe peak at 3.54 ppm confirming the formation of product **2.16**.

The methoxylation of ethyl 3-(4-methoxyphenyl)-3-oxopropanoate was investigated using the optimum reaction conditions (Scheme 2.25) and a 68% isolated yield was obtained following purification by column chromatography. The formation of **2.17** was confirmed by ^{1}H NMR spectroscopy by the appearance of a 3H singlet at 3.51 ppm corresponding to OMe of the CHOMe, a second 3H singlet at 3.86 ppm corresponded to the OMe on the phenyl ring and a 1H singlet at 4.88 ppm belonged to the aliphatic CH proton within the CHOMe group.

Ethyl 1-oxo-2,3-indanone-2-carboxylate was also methoxylated under the same reaction conditions and a 75% isolated yield was obtained after purification by column

chromatography. The reaction was wrapped in aluminium foil to prevent decarboxylation upon exposure to light as observed during chlorination of the same substrate.

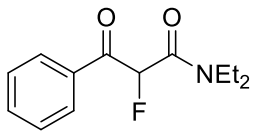
The methoxylation of dibenzoylmethane was conducted at room temperature for 24 hours in dichloromethane, due to its high enol content (Scheme 2.25) and the reaction was wrapped in aluminium foil to prevent hydrolysis due to exposure to light, but despite this the product degraded to 2-methoxy-1-phenylethanone in a 5% yield following purification and a lower 32% isolated yield of 2-methoxy-1,3-diphenylpropane-1,3-dione was obtained as a mixture of keto:enol (37:63) tautomers. The isolation of **2.19** was confirmed by ^{1}H NMR spectroscopy by the presence of a 3H singlet at 3.24 ppm corresponding to the OMe in the enol form, as well as a 1H broad singlet at 15.80 ppm for the OH of the enol. The appearance of a 3H singlet at 3.54 ppm corresponded to the OMe in the keto form, as well as a 1H singlet for the CHOMe group at 3.24 ppm.



Scheme 2.26 *Methoxylation of N,N-diethyl-3-oxo-3-phenylpropanamide*

The methoxylation of *N,N*-diethyl-3-oxo-3-phenylpropanamide was conducted initially using the optimised conditions (Scheme 2.26) and a greater than 95% conversion was obtained. ^{1}H NMR spectroscopy revealed the presence of mono- **2.20** and di-methoxylated **2.21** products in a 77 : 23 ratio respectively.

In order to prevent the dimethoxylation occurring, the reaction was repeated using fluoroiodane (1.2 equivalents) in neat methanol, at room temperature for 24 hours. The ^{1}H NMR spectrum of the crude product showed 71 % conversion to the mono-methoxylated product. The reaction was then repeated at 30 °C and the ^{1}H NMR spectrum of the crude product showed an 82 % conversion to the mono-methoxylated product **2.20**, which was isolated in a 49 % yield. Interestingly, the ^{1}H NMR spectrum of the crude product showed a 17 % conversion to the monofluorinated product **2.22** (Figure 2.2) and this was the first time that the fluorinated product was observed in these atom transfer reactions, presumably due to the longer and higher temperature reaction.



2.22

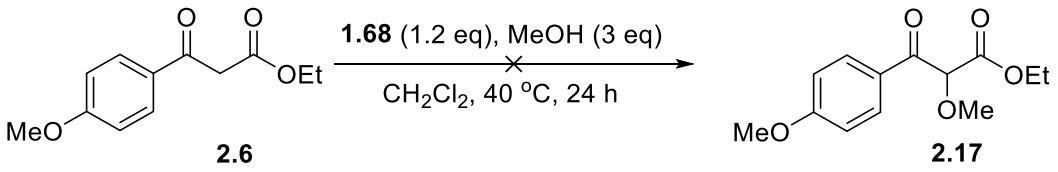
Figure 2.2 *N,N-Diethyl-2-fluoro-3-oxo-3-phenylpropanamide*

^{1}H NMR spectroscopy confirmed the formation of **2.20** due to the appearance of two sets of 3H triplets at 1.06 ppm and 1.11 ppm that correspond to the CH_3 of the diethyl groups and the appearance of the 2H multiplets at 3.24-3.39 ppm and 3.41-3.49 ppm that correspond to the CH_2 groups of the diethyl functionality. Also present was a 3H singlet at 3.51 ppm corresponding to the OMe protons and a 1H singlet at 5.21 ppm corresponding to the CH of the CHOMe group. The presence of only one OMe group and a 1H singlet of the CHOMe as well as the integration of the aromatic protons in a 2:1:2 ratio, indicated that **2.20** was only in the keto form.

The formation of **2.22** was easily identified by the distinctive doublet at 6.12 ppm with a $^{2}J_{HF}$ coupling constant of 50.0 Hz for the CHF group. The ^{1}H NMR spectrum also contained two 3H triplets at 1.11 ppm and 1.19 ppm belonging to the two CH_3 groups within the diethyl functionality, as well as the 2H quartet at 3.39 ppm corresponding to a CH_2 within the *N*CH_2CH_3 and the second CH_2 appeared as diastereotopic protons with two 1H multiplets at 3.42-3.48 ppm and 3.49-3.56 ppm respectively.

2.7.1 Methoxylation of Ethyl 3-(4-methoxyphenyl)-3-oxopropanoate using Hydroxyiodane

The methoxylations were also investigated using hydroxyiodane under the standard reaction conditions to compare the results directly with using fluoroiodane. Using ethyl 3-(4-methoxyphenyl)-3-oxopropanoate as the model substrate, the reaction was carried out using hydroxyiodane (1.2 equivalents) and methanol (3 equivalents) in dry dichloromethane at 40 ^{o}C for 24 hours (Scheme 2.27). Unfortunately, the reaction did not work using hydroxyiodane and, the unreacted starting material was recovered, as well as hydroxyiodane. Therefore, fluoroiodane was required to methoxylate 1,3-dicarbonyl substrates.

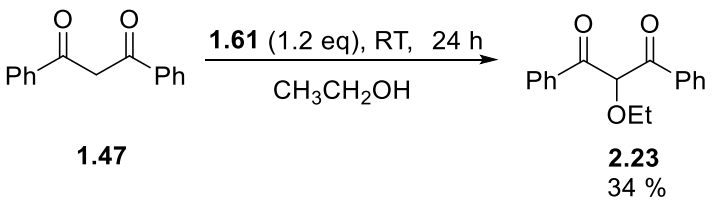


Scheme 2.27 *Attempted methoxylation ethyl 3-(4-methoxyphenyl)-3-oxopropanoate using 1-hydroxy-3,3-dimethyl-3,3-dimethyl-1,3-dihydro-λ^3-benzo[d][1,2]iodoxole*

Using fluoroiodane it was possible to introduce a methoxy group into the 2- position of a small range of 1,3-dicarbonyl substrates in good yields and under mild reaction conditions. However, these reactions required higher temperatures in order to push the reaction to completion compared to the chlorination reactions and a competing fluorination was observed for the first time. In contrast to the chlorinations, these reactions did not work with hydroxyiodane and demonstrated that fluoroiodane was essential for these reactions to proceed.

2.8 Ethoxylation of 1,3-Dicarbonyl Compounds

Following the successful introduction of the methoxy group into the 2- position of a range of 1,3-dicarbonyl substrates, ethoxylation was also investigated. The ethoxylation of dibenzoylmethane was carried out using fluoroiodane in neat ethanol at room temperature for 24 hours (Scheme 2.28). The reaction did not reach completion as a 52 % consumption of starting material was observed and following purification by column chromatography an isolated yield was not obtained due to degradation of the diketone on silica to 2-ethoxy-1-phenylethan-1-one **2.23** (Figure 2.3) in a 17 % isolated yield. ^{1}H NMR spectroscopy confirmed formation of **2.23** by the appearance of a 2H singlet at 4.74 ppm belonging to the $COCH_2$ as well as a 3H triplet at 1.29 ppm corresponding to the CH_3 group and a 2H quartet at 3.63 ppm for the CH_2 of the ethoxy group. ^{13}C NMR spectroscopy showed the presence of the $COCH_2$ group at 73.5 ppm.



Scheme 2.28 *Ethoxylation of dibenzoylmethane*

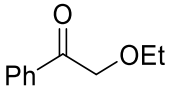
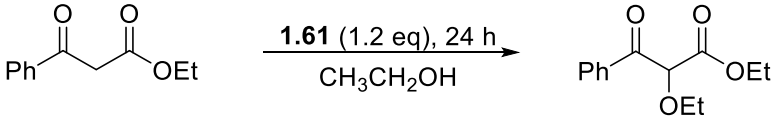


Figure 2.3 *2-ethoxy-1-phenylethan-1-one* ***2.24***

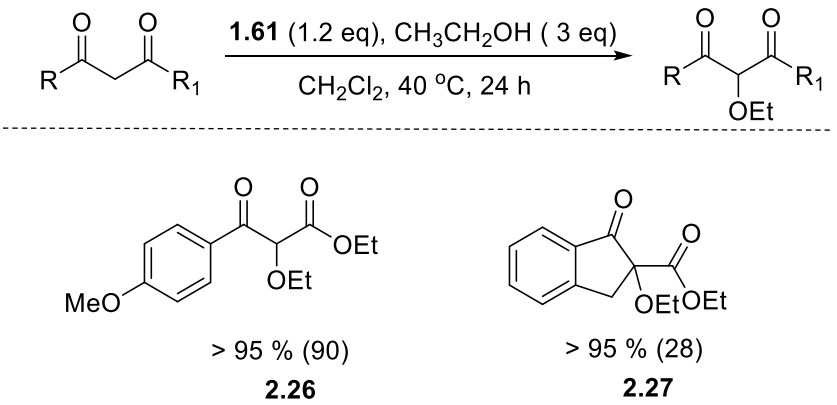
The ethoxylation was then investigated using ethyl 3-oxo-3-phenylpropanate under exactly the same reaction conditions used for dibenzoylmethane (Table 2.5). Ethyl 3-oxo-3-phenylpropanote was ethoxylated and a 59 % conversion to product was achieved. In order to push the reaction to completion the reaction was repeated at 40 °C for 24 hours, giving a 100 % consumption of starting material. The ^{1}H NMR spectrum of the crude product showed evidence of multiple products being formed in the reaction and so the reaction did not proceed cleanly. The ethoxylation of the ethyl 3-oxo-3-phenylpropanate was repeated in dichloromethane and the amount of ethanol was reduced to 3 equivalents (entry 3). The crude ^{1}H NMR spectrum of the crude product showed a greater than 95 % consumption of starting material and following purification by column chromatography a 34 % isolated yield was obtained. The low isolated yield was a result of the formation of by-products within the reaction and a low conversion of the starting material to product.

Table 2.5 *Ethoxylation of ethyl 3-oxo-3-phenylpropanoate*



1.14 **2.25**

Entry	Solvent (0.6 M)	Temp. (^{0}C)	Conversion (%)	Yield (%)
1	CH_3CH_2OH	RT	59	-
2	CH_3CH_2OH	40	> 95	-
3	CH_3CH_2OH (3 eq), CH_2Cl_2	40	> 95	34



Scheme 2.29 *Ethoxylation of 1,3-dicarbonyl substrates; conversion was denoted by the consumption of starting material*

The ethoxylation of ethyl 3-(4-methoxyphenyl)-3-oxopropanoate was also investigated and the optimum reaction conditions for the ethoxylation of ethyl 3-oxo-3-phenyl propanoate were applied (Scheme 2.29). Using fluoroiodane (1.2 equivalents) and ethanol (3 equivalents) in dry dichloromethane at 40 °C for 24 hours afforded a 100 % conversion to the monoethoxylated product **2.26**. After purification by column chromatography **2.26** was isolated in a 90% yield.

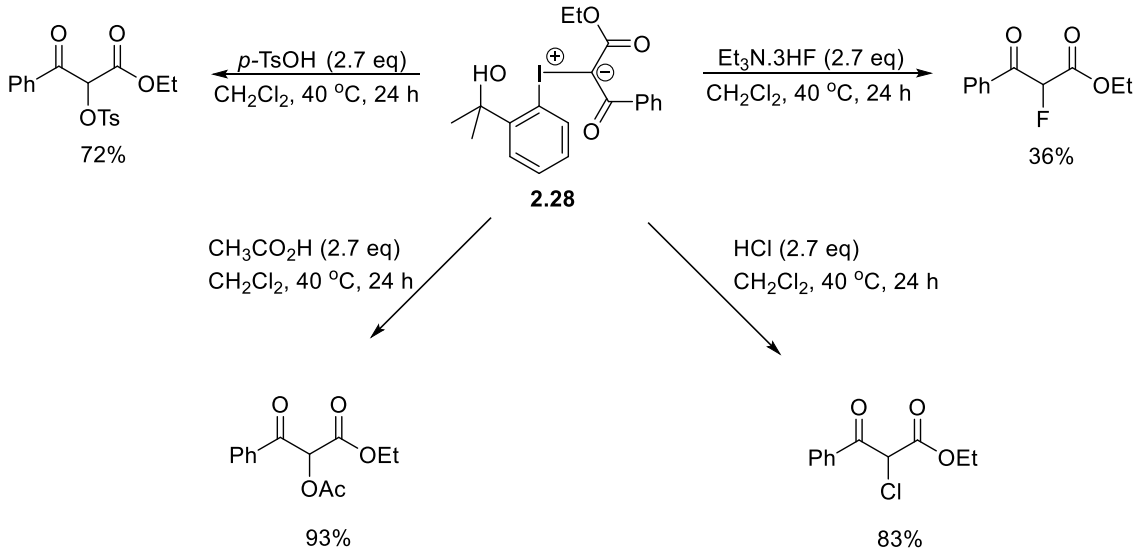
Ethyl 1-oxo-2,3-indanone-2-carboxylate was also investigated as a substrate for the ethoxylation reactions using the same reaction conditions but only a 28 % isolated yield was obtained following purification by column chromatography.

From these results it was possible to show proof of concept and ethoxylate a small series of 1,3-dicarbonyl substrates. The ethoxylation of ethyl-3-(4-methoxyphenyl)-3-oxopropanoate proceeded in a high conversion and gave an excellent isolated yield. The ethoxylation did not work well using a diketone and hydrolysis of the product was observed on silica gel. On the other hand, ethyl 3-oxo-3-phenylpropanaote and ethyl 1-oxo-2,3-indanone-2-carboxylate were also ethoxylated but much lower isolated yields were obtained. The ethoxylations did not work as well as the methoxylations possibly because it is a weaker nucleophile as a consequence of steric hindrance in comparison to methanol.

2.9 Trifluoroethoxylation of 1,3-Dicarbonyl Substrates

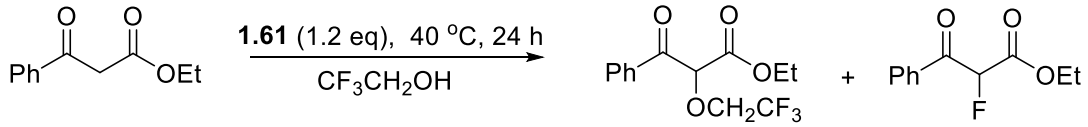
Previous work conducted within the Stuart group involved reacting the iodonium ylide **2.28** with the a small series of acids with the aim of developing a one pot synthetic route to introduce a number of different nucleophiles into the 2-position of a range of 1,3-dicarbonyl substrates (Scheme 2.30).[6,7] The nucleophiles investigated were *para*-toluenesulfonic acid, triethylamine trihydrofluoride, hydrochloric acid and acetic acid. The tosyloxylation, acetoxylation and chlorination of **2.28** resulted in high yields whilst the fluorination gave a moderate yield.

The aim of this section was to develop the trifluoroethoxylation of 1,3-dicarbonyl compounds either by using fluoroiodane **1.61** in combination with trifluoroethanol or by reacting an iodonium ylide with trifluoroethanol.



Scheme 2.30 *Atom transfer reactions from the iodonium ylide* ***2.28***[6]

Table 2.6 Trifluoroethoxylation of ethyl 3-oxo-3-phenylpropanoate

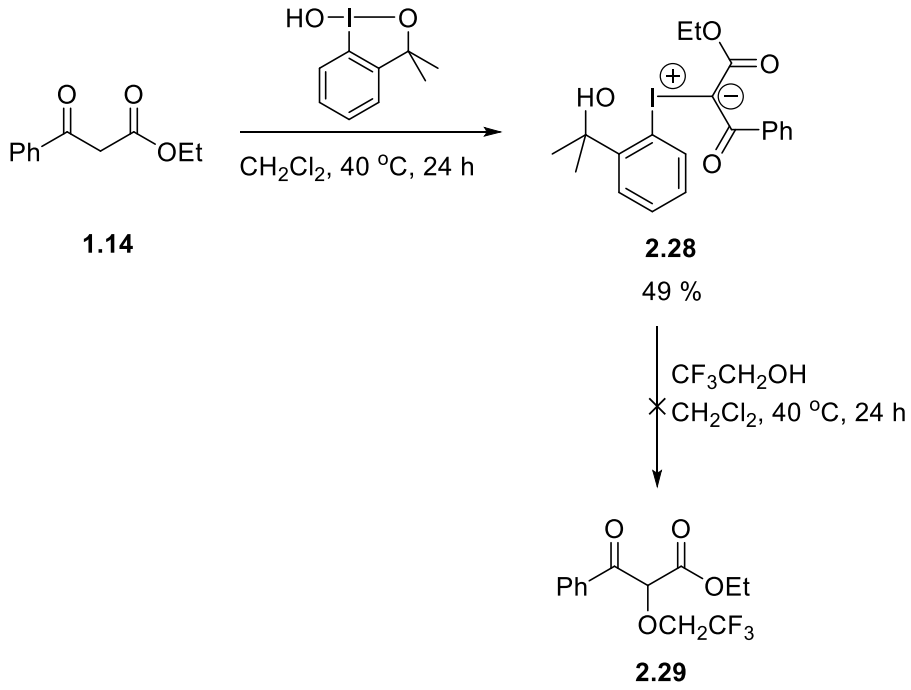


1.14 **2.29** **1.69**

Entry	Solvent (0.6 M)	Conversion to 2.29[a] (%)	Conversion to 1.69[b] (%)
1	CH_3CH_2OH	> 90	26 %
2	CF_3CH_2OH (3 eq), CH_2Cl_2	76	20 %
3	CF_3CH_2OH, CH_2Cl_2 (1:1 v/v)	87	-[c]

[a] Conversion denoted by the consumption of starting material and determined by ^{1}H NMR spectroscopy; [b] Isolated yield; [c] Undetermined.

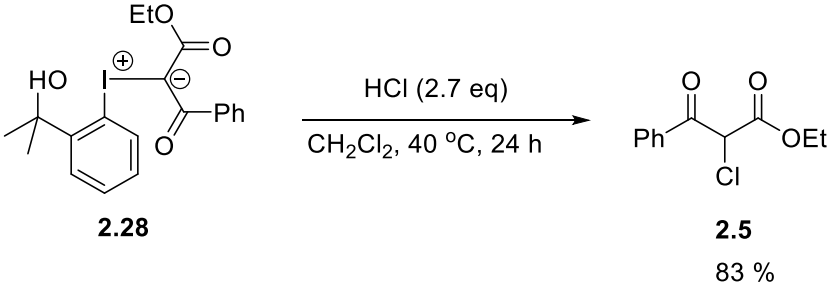
Ethyl 3-oxo-3-phenyl propanoate was used as the model substrate for the optimisation of the trifluoroethoxylation reactions. The conditions initially used were fluoroiodane (1.2 equivalents) in neat trifluoroethanol at 40 °C for 24 hours affording a greater than 90 % consumption of starting material. Purification by column chromatography showed the presence of 26 % ethyl 2-fluoro-3-oxo-3-phenylpropanoate as well as multiple by products with no evidence of trifluoroethoxylation. The reaction was repeated using 3 equivalents of trifluoroethanol in dichloromethane at 40 °C for 24 hours to attempt to reduce the number of side products being formed. A 76 % consumption of starting material was obtained and following purification by column chromatography, ethyl 2-fluoro-3-oxo-3-phenyl propanoate was isolated in a 20 % yield. Again, there was no clear evidence of trifluoroethoxylation occuring. The reaction was finally repeated using a 50:50 v/v mixture of dry dichloromethane and trifluoroethanol and an 87 % consumption of starting material was obtained, but there was no indication of trifluoroethoxylation occuring by ^{1}H NMR spectroscopy.



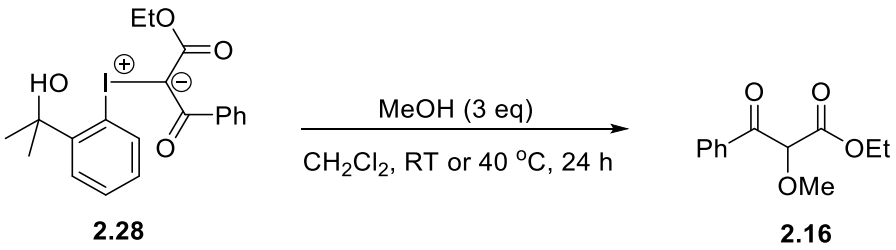
Scheme 2.31 *Synthesis of the iodonium ylide ethyl-2-((2-(2-hydroxypropan-2-yl)phenyl)-λ^3-iodaneylidene)-3-oxo-3-phenylpropanoate* ***2.28***

The iodonium ylide of ethyl 3 oxo-3-phenylpropanoate was prepared by reacting ethyl 3-oxo-3-phenylpropanoate with hydroxyiodane (2 equivalents) in dry dichloromethane at 40 °C for 24 hours. The reaction was carried out on a 1-2 g scale with a 100 % consumption of starting material achieved in all cases. After purification by column chromatography and a slow recrystallisation in diethyl ether, the iodonium ylide **2.28** was isolated in a 31-49 % yield.

A test reaction was carried out initially to ensure that the reaction worked using the iodonium ylide. Chlorination of the iodonium ylide was conducted using HCl (2.7 equivalents) in dichloromethane at 40 °C for 24 hours and an 83 % isolated yield was obtained after purification by column chromatography (Scheme 2.32).



Scheme 2.32 *Chlorination of the ylide*

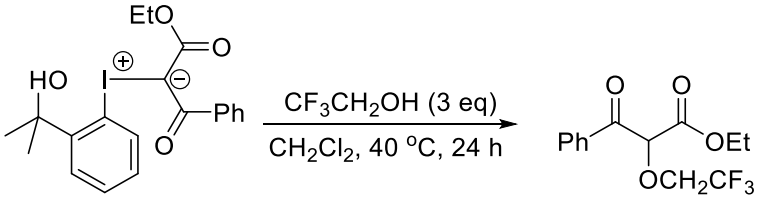


2.28 **2.16**

Scheme 2.33 *Methoxylation of the ylide*

The reaction of the ylide **2.28** was investigated further using methanol as the nucleophile. The methoxylation was carried out by reacting the iodonium ylide **2.28** with 3 equivalents of methanol in dry dichloromethane at room temperature for 24 hours which gave a 100 % consumption of starting material, but there was no evidence that methoxylation had ocurred in the reaction. The reaction was repeated by heating at 40 °C for 24 hours and again a 100 % consumption of starting material was obtained. The ^{1}H NMR spectrum showed the formation of several products which were not identified.

Although the methoxylation of **2.28** was unsuccessful, the trifluoroethoxylation was investigated by reacting the iodonium ylide **2.28** with 3 equivalents of trifluoroethanol in dry dichloromethane at 40 °C for 24 hours where a 50 % consumption of starting material was obtained (Scheme 2.34).



2.28 **2.29**

Scheme 2.34 *Trifluoroethoxylation of ethyl 3-oxo-3-phenylpropanoate*

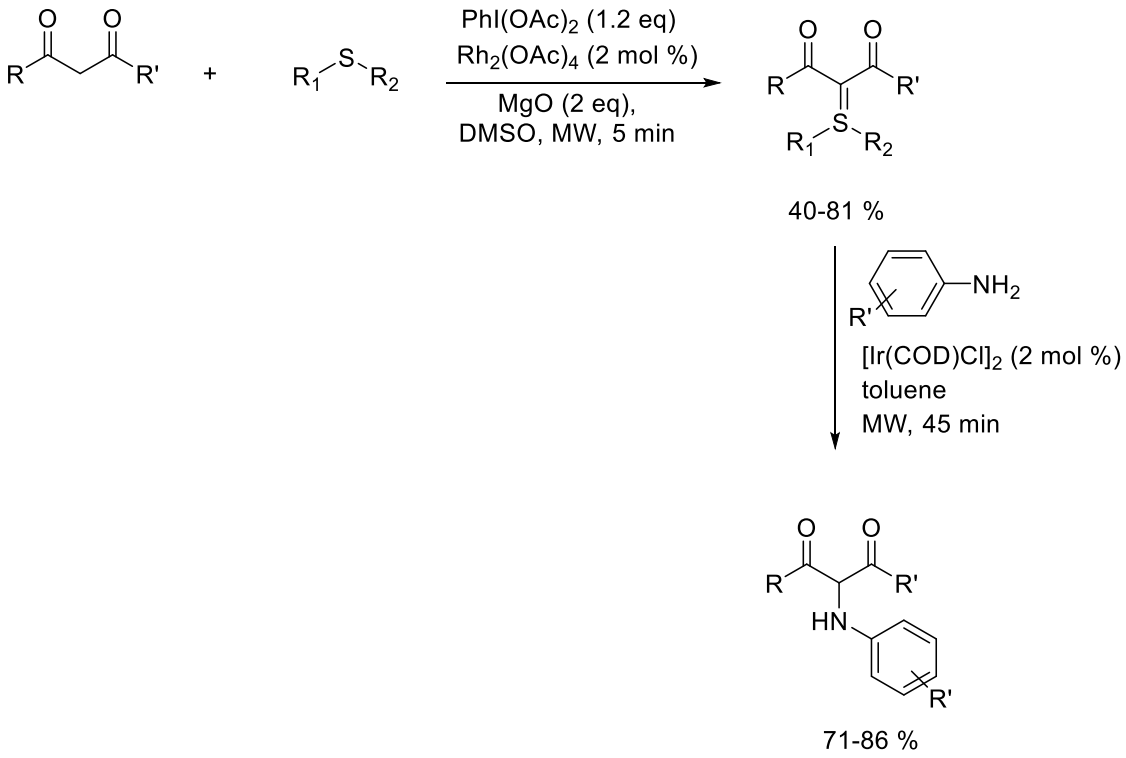
The reaction was repeated in neat trifluoroethanol at room temperature for 24 hours and a 58 % consumption of starting material was obtained. However, ^{1}H and ^{19}F NMR spectra showed no evidence of trifluoroethoxylation. Finally, the reaction was repeated in neat trifluoroethanol at 40 °C for 24 hours. This time there was a 100 % consumption of starting material but trifluoroethoxylation was not detected by ^{1}H and ^{19}F NMR spectroscopy. These reactions produced many by-products that could not be separated by column chromatography.

2.10 Amination of 1,3-Dicarbonyl Compounds

2.10.1 Literature Procedure for the Amination of Ethyl 3-oxo-3-phenylpropanoate

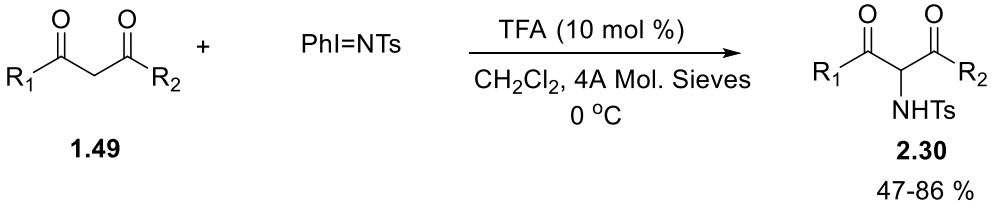
α-Amido *β*-dicarbonyl compounds are important building blocks in organic synthesis and they are useful intermediates for the synthesis of heterocycles,[9] and unnatural α-amino acids,[10] as well as being used as precursors in the synthesis of pharmaceuticals and natural products.[11,12] Direct α-amination of 1,3-ketoesters and 1,3-ketoamides can be synthetically challenging. Current methods include N–C acyl migration,[13] N-H insertion using rhodium,[14] acylation of an α-amino ester Schiff-base[15] and the rhodium catalysed synthesis of sulfur ylides, generating iodonium ylides *in situ* followed by N-H insertion.[16] All of these methods suffer disadvantages such as requiring multistep synthesis or the need for a strong base. Current methods of direct *α*-amination of 1,3-ketoesters and 1,3-ketoamides include copper(II) triflate catalysed amination using PhI=NTs as the nitrogen source,[17] Lewis acid catalysed amination using PhI=NTs,[18] and iodosobenzene mediated amination using perchlorate zinc hexahydrate.[19]

Vaitla *et al.* conducted the amination of ethyl 3-oxo-3-phenylpropanoate using rhodium chemistry to synthesise sulfur ylides which were then able to undergo N-H insertion (Scheme 2.35). This method of amination firstly required generating the sulfur ylide using phenyliodonium diacetate (1.2 equivalents), rhodium(II) acetate dimer (2 mol %) and magnesium oxide (2 equivalents) as the base in DMSO, under microwave conditions for 5 minutes. The sulfur ylide was then able to undergo N-H insertion, by reacting the ylide wth an iridium catalyst, aniline, chloro(1,5-cyclooctadiene)iridium(II) dimer (2 mol %) and toluene under microwave conditions for 45 minutes a series of N-H insertion products were synthesised in good yields (40-81 %).[16]



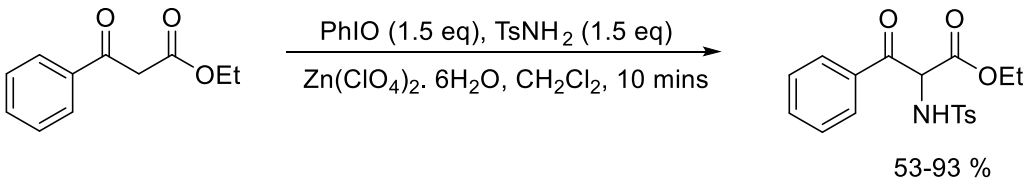
Scheme 2.35 *Rhodium-catalysed synthesis of sulfoxonium ylides for N-H insertion*[16]

Chan and co-workers synthesised **2.30** using Brønsted acid catalysis using ethyl 3-oxo-3-phenylpropanoate as the model substrate. The amination of ethyl 3-oxo-3-phenylpropanoate was conducted by firstly activating the 1,3-dicarbonyl compound using trifluoroacetic acid to generate the enolate, followed by using PhI=NTs, which activates the amine facilitating the reaction progression (Scheme 2.36).[18]



Scheme 2.36 *Brønsted acid catalysed amination of 1,3-dicarbonyl compounds*

Zhang *et al.* also conducted the α-amination of ethyl 3-oxo-3-phenylpropanoate using iodosobenzene to generate PhI=NTs *in situ* and perchlorate zinc hexahydrate to activate the 1,3-dicarbonyl compound enabling the reaction to proceed (Scheme 2.37).[19] The literature indicated that an activated 1,3-dicarbonyl compound and an active amine are required to help aid the reaction.



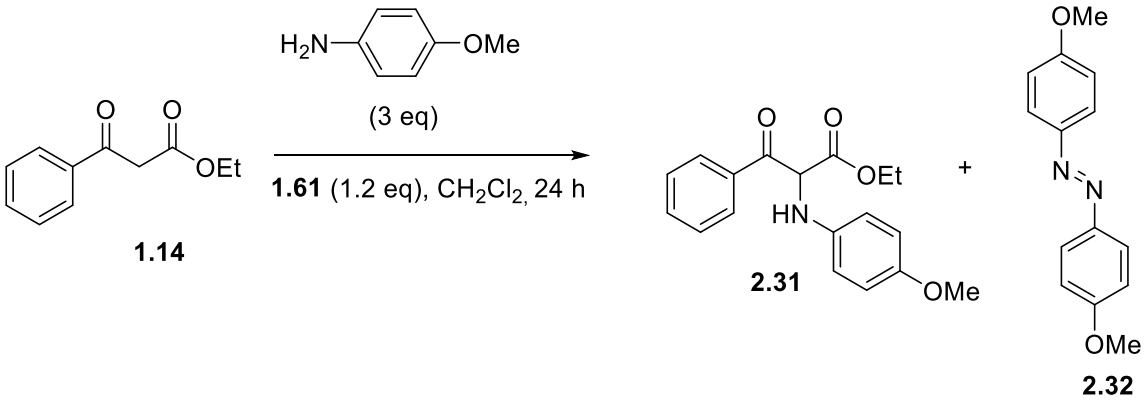
Scheme 2.37 *α-Amination of 1,3-dicarbonyl compounds using iodosobenzene and p-toluenesulfonamide*

2.10.2 Amination of Ethyl 3-oxo-3-phenylpropanoate

The amination of ethyl 3-oxo-3-phenylpropanoate was based on the work reported by Bayer and coworkers into the rhodium-catalysed synthesis of sulfoxonium ylides for N-H insertion.[16] In this work the amination using *p*-anisidine was initially carried out using 1-fluoro-3,3-dimethyl-1,3-dihydro-λ^3-benzo[*d*][1,2]iodoxole **1.61** (1.2 equivalents), *p*-anisidine (3 equivalents) in dichloromethane at room temperature for 24 hours. The ^{1}H NMR spectrum of the crude product showed a 20 % conversion to the product **2.31** (entry 1). The appearance of product was confirmed by the 3H singlet at 3.70 ppm corresponding to the OCH_3 moiety of *p*-anisidine, as well as the 3H triplet at 1.32 ppm and a 2H quartet at 4.20 ppm corresponding to the CH_3 and the CH_2 of the ethoxy moiety respectively. The 1H singlet at 4.93 ppm corresponded to the CH adjacent to *p*-anisidine, and a 4H singlet at 6.63 ppm belonged to the four aromatic CH protons of *p*-anisidine and a 1H broad singlet at 10.22 ppm was observed for the NH group. ^{13}C NMR spectroscopy also confirmed the formation of **2.31** by the presence of a singlet at 55.5 ppm corresponding to the OCH_3 group, as well as two singlets at 14.6 ppm and 59.2 ppm belonging to the CH_3 and CH_2 of the ethoxy moiety. In addition to this, the singlet at 89.5 ppm corresponded to the α-CH carbon. There was 5 singlets in the aromatic region corresponding to the 5 aromatic CH signals in the product. An *m/z* of 314.1391 was also observed in the mass spectrum for $C_{18}H_{20}NO_4$.

In addition, the ^{1}H NMR spectrum of the crude product showed evidence of the formation of a dimer with two molecules of *p*-anisidine forming an aromatic azo compound **2.32**. The ^{1}H NMR spectrum showed a 6H singlet at 3.89 ppm corresponding to the two OCH_3 groups, a 4H doublet at 7.01 ppm with a $^3J_{HH}$ coupling constant of 9.0 Hz belonging to the four aromatic CH protons and another 4H doublet at 7.88 ppm with a $^3J_{HH}$ coupling constant of 9.0 Hz, corresponding to the other four aromatic CH protons of the dimer **2.32**.[20] An *m/z* of 243.1138 was also observed for $C_{14}H_{15}N_2O_2$.

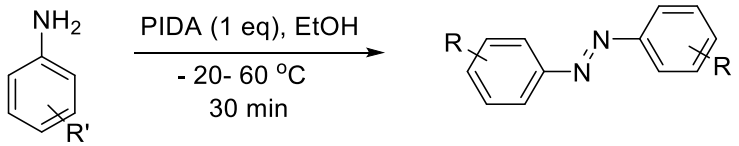
Table 2.7 *Attempted amination of ethyl 3-oxo-3-phenylpropanoate using p-anisidine*



[a]Conversion denoted by the formation of product **2.31** determined by ^{1}H NMR spectroscopy; [b] Isolated yield in parenthesis, [c] **1.61** (1 equivalent) used in the reaction; [d] 5 equivalents of *p*-anisidine used in the reaction; [e] **1.61** (1.5 equivalents) used in the reaction; [f] dichloromethane 2.6 mL (0.28 M); [g] reaction conducted in the microwave, pressure = 250 psi, μλ = 150 W, premix = 30 seconds, temperature 80 °C, time 30 minutes.

Entry	Solvent	Temperature (°C)	Conv. to 2.31 [a, b] (%)	Conv. to 2.32 (%)
1	CH_2Cl_2	RT	20	10
2	CH_2Cl_2	40	54 (40)	10 (5)
3[c]	CH_2Cl_2	40	32	8
4[d, e]	CH_2Cl_2	40	32	11
5[e]	CH_2Cl_2	40	11	11
6[e]	CH_2Cl_2	RT-40	11	10
7[f]	CH_2Cl_2	40	11	11
8	CH_3CN	40	16	9
9	$ClCH_2CH_2Cl$	60	21	15
10[g]	CH_2Cl_2	80	27	12

The dimerization of anilines to form azo compounds is known in the literature and often occurs in systems containing hypervalent iodine reagent.[21,22,23,24] For example, Hajra *et al.* used phenyliodine(III) diacetate to synthesise aromatic azo compounds (Scheme 2.38).[20] A series of *ortho*-, *meta*- and *para*-substituted anilines were used to form azo compounds in good yields (51-76 %).



Scheme 2.38 *Synthesis of azobenzenes*[20]

In order to increase the conversion, the temperature was increased to 40 °C for 24 hours and a 54 % conversion to **2.31** was achieved, as well as a 10 % conversion to **2.32** (entry 2). Following purification by column chromatography a 40 % isolated yield of **2.31** and a 5 % yield of **2.32** was obtained. In order to reduce the dimerization occurring within the reaction, the number of equivalents of *p*-anisidine was reduced to 1 equivalent, but only a 32 % conversion to **2.31** was achieved and an 8 % conversion to the dimer (entry 3). In entry 4 the number of equivalents of **1.61** was increased to 1.5 equivalents and the number of equivalents of *p*-anisidine was increased, to 5 equivalents, however, the conversion to **2.31** remained at 32 % and the dimer at 11 %. When entry 2 was repeated with 1.5 equivalents of fluoroiodane, the conversion to **2.31** and **2.32** both dropped to 11 % (entry 5).

In the original reaction conditions (entry 2), fluoroiodane was reacted with *p*-anisidine in dichloromethane at room temperature before adding ethyl 3-oxo-3-phenylpropanoate and then heating the reaction mixture to 40 °C for 24 hours. In entry 6 fluoroiodane (1.5 equivalents) was reacted with *p*-anisidine (3 equivalents) in dichloromethane for 1 hour before adding ethyl-3-oxo-3-phenylpropanoate and then heating the reaction mixture to 40 °C for 24 hours but there was only a 10 % conversion to **2.31** and a 10 % conversion to **2.32**. Unfortunately, there was no improvement when more dilute conditions, 0.28 M instead of 0.6 M were used in entry 7 or when the solvent was changed to acetonitrile in entry 8. The reaction was then conducted in dichloromethane at 60 °C, but ^{1}H NMR spectroscopy showed a lower 21 % conversion to **2.31** and a 15 % conversion to the dimer **2.32**. Finally, the reaction was performed at 80 °C in the microwave for 30 minutes but this only resulted in only a 27 % conversion to **2.31** (entry 10).

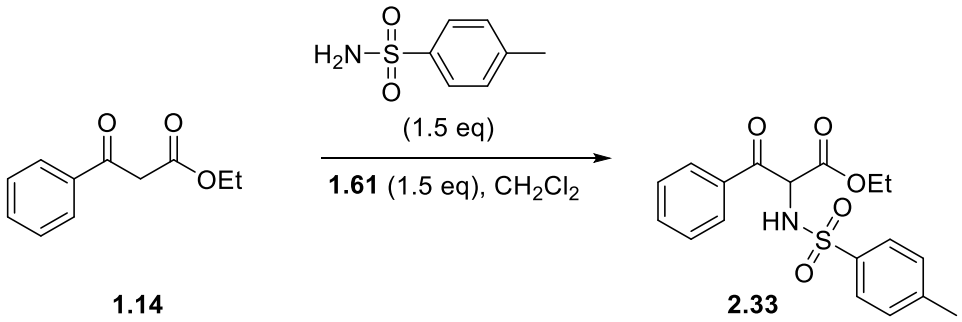
2.10.3 Amination using *p*-Toluenesulfonamide

p-Toluenesulfonamide was also investigated as the nitrogen nucleophile, to determine whether it could be amenable to the atom-transfer chemistry as it is electron withdrawing in comparison to *p*-anisidine. *p*-Toluenesulfonamide is less nucleophilic in nature and could therefore be less susceptible to homodimerization and react more readily with the enol. The amination of ethyl 3-oxo-3-phenylpropanoate was based on the conditions employed by Zhang *et al.* reacting a 1,3-dicarbonyl compound with *p*-toluenesulfonamide in the presence of a Lewis acid catalyst.

Ethyl 3-oxo-3-phenylpropanoate was reacted with *p*-toluenesulfonamide (1.5 equivalents), **1.61** (1.5 equivalents) in dichloromethane at room temperature for 2 hours (entry 1). The ^{1}H NMR spectrum of the crude product showed no evidence of product formation. The reaction was repeated using a Lewis acid catalyst, zinc tetrafluoroborate hexahydrate (0.25 equivalents), in dichloromethane at room temperature for 2 hours, but there was no still evidence of product formation (entry 2). The reaction was repeated at room temperature for 2 hours however the solvent was altered to hexafluoroisopropanol and again there was no evidence of product formed (entry 3). The reaction in hexafluoroisopropanol did promote the fluorination of ethyl 3-oxo-3-phenylpropanoate, and 28 % of the monofluorinated *β*-ketoester was isolated. In entry 4 the reaction was repeated using zinc tetrafluoroborate hexahydrate (0.25 equivalents) but the ^{1}H NMR spectrum showed no evidence of product. However, 40 % of the fluorinated *β*-ketoester was obtained.

The reaction was then conducted in dichloromethane at 40 °C for 24 hours and the ^{1}H NMR spectrum showed a low 11 % conversion to **2.33** (entry 5). The product formation was confirmed by the appearance of a 3H singlet at 2.38 ppm corresponding to the methyl of the *p*-toluenesulfonamide, as well as a 1H doublet at 5.58 ppm belonging to the CH adjacent to the *p*-toluenesulfonamide group and a 1H doublet at 5.94 ppm arising due to the NH proton coupling to the neighbouring α-CH proton. The ^{13}C NMR spectrum showed the presence of two singlets at 13.7 ppm and 21.5 ppm corresponding to the CH_3 within the ethoxy group and the CH_3 of the *p*-toluenesulfonamide respectively. In addition to this the α-CH appeared at 60.9 ppm and an *m/z* of 362.1062 for $C_{18}H_{20}NO_5S$ was obtained.

Table 2.8 *Amination of ethyl 3-oxo-3-phenylpropanoate using p-toluenesulfonamide*



1.14 **2.33**

Entry	Solvent	Temperature (°C)	Time (h)	Catalyst (0.25 eq)	Conversion[a] (%)
1	CH_2Cl_2	RT	2	No catalyst	0
2	CH_2Cl_2	RT	2	$Zn(BF_4)_2.\ xH_2O$	0
3	$(CF_3)_2CHOH$	RT	2	No catalyst	0
4	$(CF_3)_2CHOH$	RT	2	$Zn(BF_4)_2.\ xH_2O$	0
5	CH_2Cl_2	40	24	No catalyst	11
6	CH_2Cl_2	40	24	$Zn(BF_4)_2.\ xH_2O$	30
7	CH_2Cl_2	60	24	$Zn(BF_4)_2.\ xH_2O$	13
8[b]	CH_2Cl_2	40	24	$Zn(BF_4)_2.\ xH_2O$	28
9[c]	CH_2Cl_2	40	24	$Zn(BF_4)_2.\ xH_2O$	14
10	CH_3CN	40	24	$Zn(BF_4)_2.\ xH_2O$	2

[a]Conversion denoted by the formation of product determined by ^{1}H NMR spectroscopy; [b] *p*-toluenesulfonamide (3 equivalents); [c] $Zn(BF_4)_2.xH_2O$ (1 equivalent).

The reaction was then conducted using **1.61** (1.5 equivalents), *p*-toluenesulfonamide (1.5 equivalents) and zinc tetrafluoroborate hexahydrate (0.25 equivalents) in dichloromethane at 40 °C for 24 hours. The crude ^{1}H NMR spectrum showed a 30 % conversion to **2.33** (entry 6). In order to push the reaction further, the reaction was repeated at 60 °C for 24 hours but only a 13 % conversion to product was achieved (entry 7). When the reaction was repeated at 40 °C for 24 hours with 3 equivalents of *p*-toluenesulfonamide the yield did not improve and a 28 % conversion to **2.33** was obtained

(entry 8). Using a stoichiometric quantity of zinc tetrafluoroborate hexahydrate in entry 9 did not improve the reaction and only showed a 14 % conversion to the aminated product. Finally, the reaction was performed in acetonitrile using **1.61** (1.5 equivalents), *p*-toluenesulfonamide (1.5 equivalents), zinc tetrafluoroborate hexahydrate (0.25 equivalents) at 40 °C for 24 hours (entry 10). The ^{1}H NMR of the crude product showed a 2 % conversion to **2.33**, and therefore acetonitrile was not an appropriate solvent.

The amination of ethyl 3-oxo-3-phenylpropanoate using fluoroiodane was challenging and proved unsuccessful. The amination of using *p*-anisidine was possible but only in a 40 % yield. This showed proof of principle of introducing nitrogen nucleophiles into 1,3-dicarbonyl compounds, but unfortunately the yield could not be improved. *p*-Toluenesulfonamide was then investigated as a nucleophile in combination with a zinc Lewis acid catalyst but disappointingly only a 30 % conversion to the desired product was achieved. In both cases homodimerization of the nitrogen nucleophile was an issue and due to the weak nucleophilicity and bulky nature of the nucleophile the aminations were unsuccessful.

2.11 Conclusions and Future Work

A one-pot synthetic method was developed to introduce a range of nucleophiles into the 2-position of a number of 1,3-dicarbonyl substrates. The chlorinations proceeded successfully under mild reaction conditions at room temperature for 1 hour to afford chlorination of a diverse range of substrates including a 1,3-diketone, acyclic 1,3-ketoesters, a cyclic 1,3-ketoester and a 1,3-ketoamide in good yields. Methoxylation of a range of substrates was also successful but, required heating to 40 °C for 24 hours. The ethoxylation reactions investigated afforded give ethyl 2-ethoxy-3-(4-methoxyphenyl)-3-oxopropanoate in a high yield, but the substrate scope was much more limited and the reaction was much more difficult. The trifluoroethoxylation and trifluoromethylation of ethyl 3-oxo-3-phenylpropanoate were both challenging reactions and ultimately proved unsuccessful.

Hydroxyiodane **1.68** was investigated as an alternative hypervalent iodine reagent in the chlorinations and methoxylations. It was possible to use hydroxyiodane for the chlorination but these reactions proceeded at a slower rate than using fluoroiodane **1.61**.

Unfortunately, the hydroxyiodane did not promote the methoxylation of 1,3-dicarbonyl substrates and fluoroiodane was required for these reactions.

The aminations of ethyl 3-oxo-3-phenylpropanoate with *p*-anisidine and *p*-toluenesulfonamide were unsuccessful. In particular, the amination using *p*-anisidine suffered from homodimerisation of the aniline to form the aromatic azo compound as well as the reaction forming multiple by-products. *p*-Anisidine is a poor nucleophile and is sterically bulky which could contribute to the amination being unable to take place. Using *p*-toluenesulfonamide as the nucleophile also resulted in poor conversions to the corresponding aminated product. Employing a Lewis acid catalyst, $Zn(BF_4)_2.xH_2O$ improved the conversion to product, but altering the reaction conditions did not result in any further improvements.

2.12 References for Chapter 2

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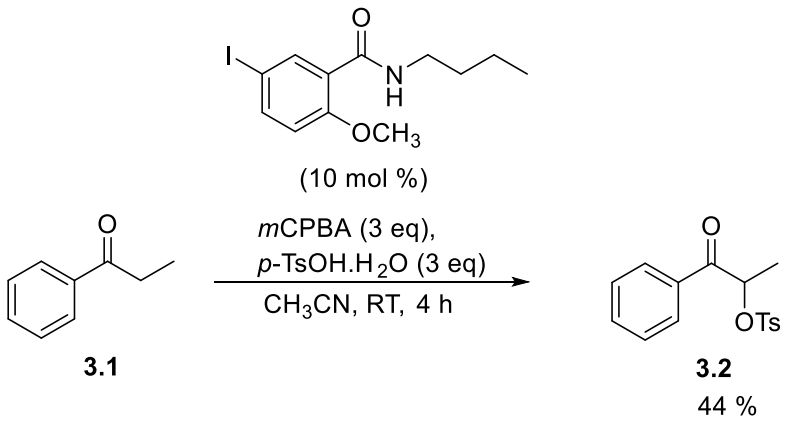
Chapter 3 Catalytic Chlorination of 1,3-Dicarbonyl Compounds

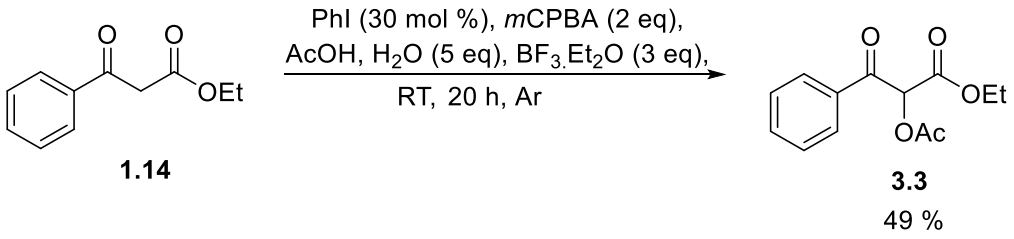
3.1 Introduction

The catalytic introduction of nucleophiles into the α-position of carbonyl compounds employing hypervalent iodine reagents has been conducted within the literature.[1,2] Whitehead and coworkers reported the *α*-tosyloxylation of propiophenone using 10 mol % of benzamide iodoarene catalyst, with *m*CPBA and *p*-toluensulfonic acid in a good 44 % yield (Scheme 3.1). A range of propiophenone derivatives were reacted under similar conditions at 50 ^{o}C for 4-24 hours, affording the tosyloxylated products in high yields (72-99 %).[3]



Scheme 3.1 *α-Tosyloxylation of propiophenone*[3]

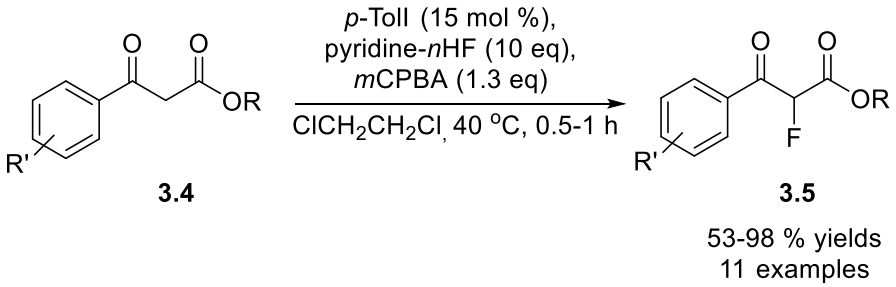
Other examples of using catalytic quantities of iodoarene for atom-transfer reactions include the *α*-acetoxylation of ketones and a 1,3-ketoester by Ochiai and coworkers (Scheme 3.2). Iodobenzene (30 mol %), *m*CPBA (2 equivalents) and $BF_3.Et_2O$ (3 equivalents) were used for the *α*-acetoxylation of ethyl 3-oxo-3-phenylpropanoate delivering the product in a good 49 % yield.[4]



Scheme 3.2 *α-Acetoxylation of ethyl 3-oxo-3-phenylpropanoate*[4]

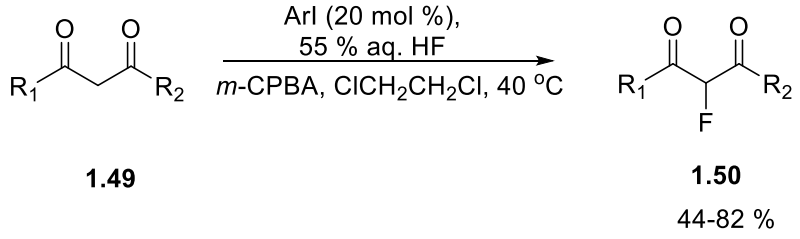
The catalytic fluorination of 1,3-dicarbonyl compounds has also been reported in the literature. Shibata and coworkers reported the catalytic fluorination of *β*-ketoesters using

iodotoluene (15 mol %) and *m*-chloroperbenzoic acid (1.3 equivalents) and pyridine-HF (10 equivalents). Under these conditions good to high yields (53-98 %) of the monofluorinated products were achieved (Scheme 3.3).



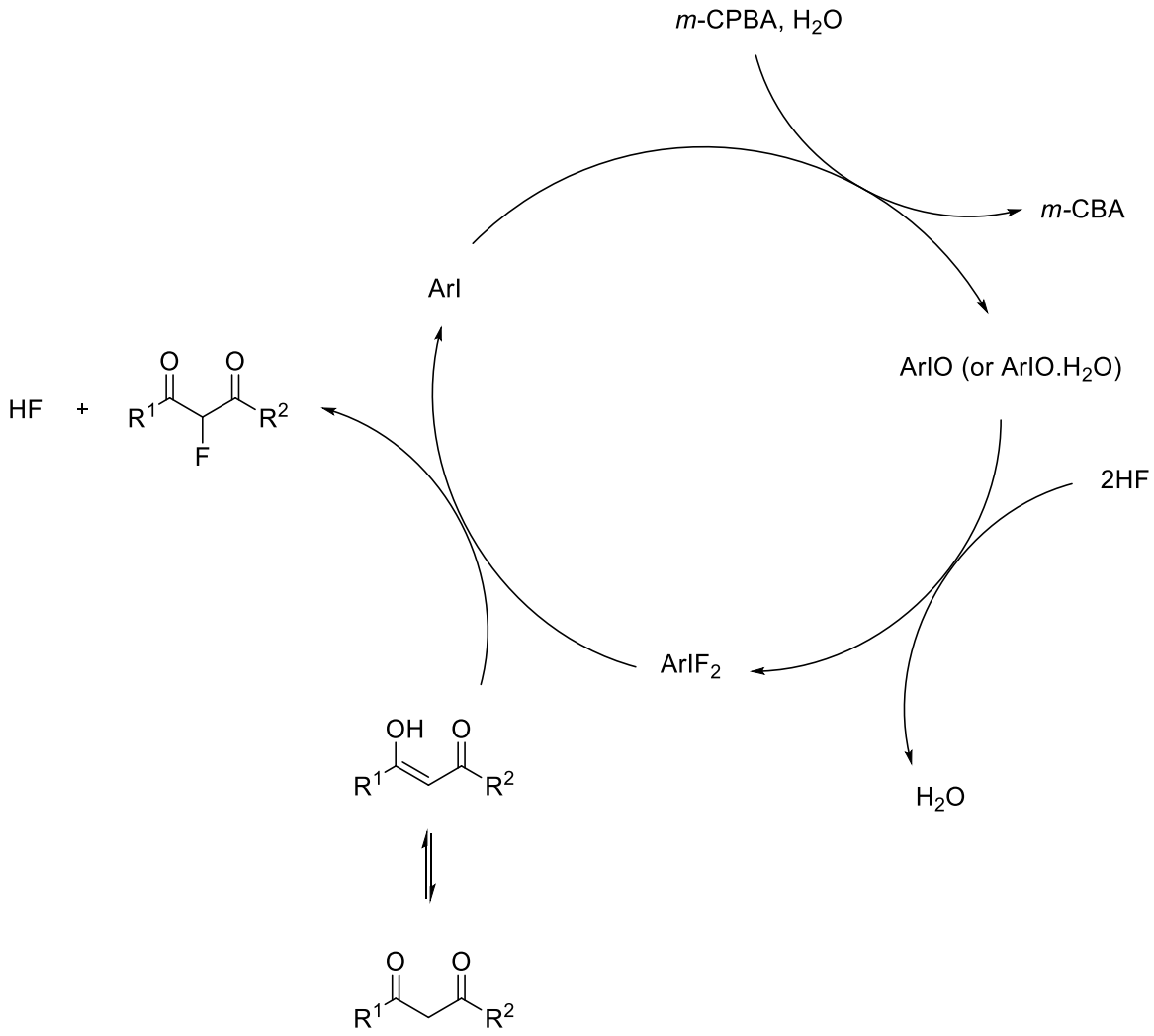
Scheme 3.3 *Catalytic fluorination of 1,3-dicarbonyl compounds using iodotoluene*[2]

Kitamura also developed a method for the catalytic fluorination of 1,3-dicarbonyl compounds using iodoarenes such as *o*-iodotoluene, *o*-iodoanisole and *o*-ethyliodobenzene (Scheme 3.4). A catalytic amount of the iodoarene (20 mol %) was used with 55 % aqueous HF and *m*CPBA (1.5 equivalents) in dichloroethane to give the fluorinated products in good yields (44-82 %).



Scheme 3.4 *Catalytic fluorination of 1,3-dicarbonyl compounds*[5]

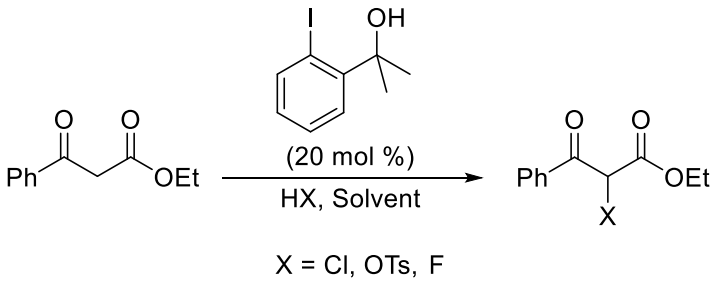
Kitamura and coworkers proposed a mechanism for the catalytic fluorination of 1,3-dicarbonyl compounds using iodoarenes (Scheme 3.5). The fluorination mechanism was proposed to proceed firstly by the oxidation of the iodoarene by *m*-chloroperbenzoic acid to an iodosylarene. The iodosylarene is then converted to (difluoro)iodoarene when reacted with HF and the (difluoro)iodoarene subsequently reacts with the enol tautomer of the 1,3-dicarbonyl compound affording the 2-fluorinated 1,3-dicarbonyl products and regenerates the iodoarene catalyst.[5]



Scheme 3.5 *Catalytic fluorination mechanism*

3.2 Project Aims

The catalytic introduction of nucleophiles such as fluoride into the 2-position of 1,3-dicarbonyl compounds has been widely explored in the literature and involved the oxidation of iodine(I) to iodine(III). In Chapter 3 I propose to develop a one-pot method to introduce different nucleophiles such as chloride, fluoride and tosylate into the 2-position of 1,3-dicarbonyl substrates by employing a catalytic amount of 2-(2-iodophenyl)propan-2-ol **1.59**.



Scheme 3.6 *Catalytic atom-transfer reactions using 2-(2-iodophenyl)propan-2-ol*

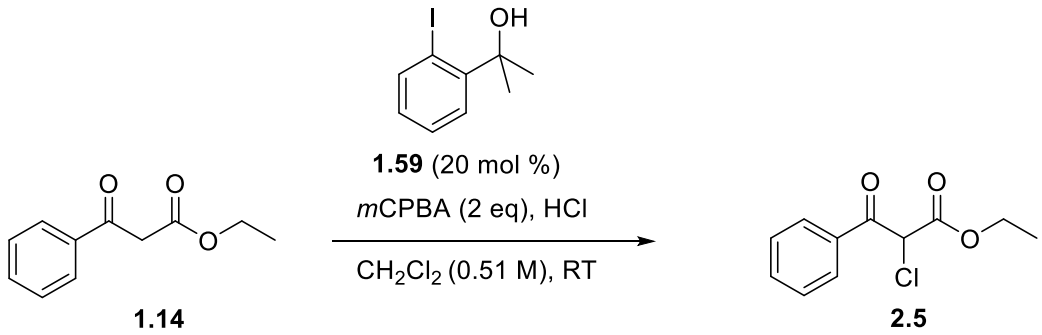
Fluorinated solvents such as trifluoroethanol and 1,1,1,3,3,3-hexafluoroisopropanol have been shown in the literature to act as a hydrogen bond donors. I propose to investigate the use of fluorinated solvents such as 1,1,1,3,3,3-hexafluoroisopropanol for the activation of the fluoroiodane reagent. The overall aim is to develop mild and more efficient methodology to fluorination 1,3-dicarbonyl compounds.

3.3 Catalytic Chlorination of 1,3-Dicarbonyl Compounds

3.3.1 Catalytic Chlorination of 1,3-Ketoesters using 2-(2-Iodophenyl)propan-2-ol

Initially, the catalytic chlorination was investigated using ethyl 3-oxo-3-phenylpropanoate **1.14** as the model substrate with 2-(2-iodophenyl)propan-2-ol **1.59** (20 mol %), hydrochloric acid (3.5 equivalents) as the source of chloride and *m*-chloroperbenzoic acid (2 equivalents) as the oxidant. The reaction was carried out in dry dichloromethane at room temperature for 2.5 hours to give an 80 % conversion to the monochlorinated product (entry 1). The consumption of starting material was confirmed by the reduction in the 2H singlet at 4.00 ppm corresponding to the aliphatic CH_2 protons within ethyl 3-oxo-3-phenylpropanoate. The formation of product **2.5** was confirmed by the appearance of a 1H singlet at 5.62 ppm corresponding to the CHCl proton.

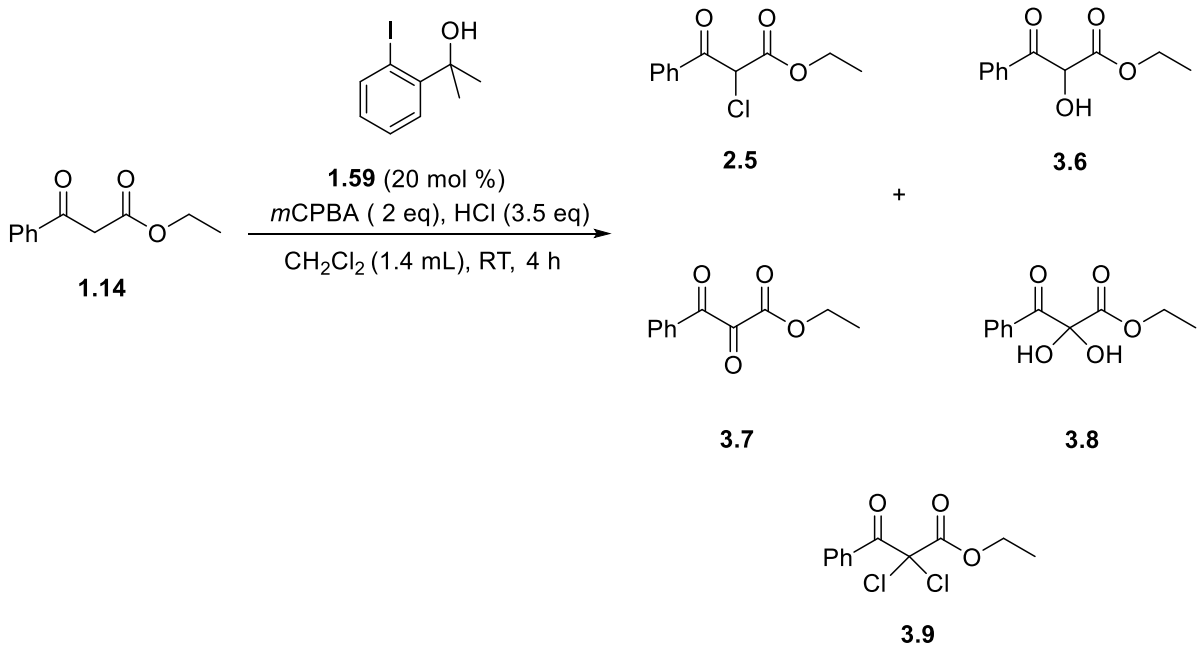
Table 3.1 *Optimisation of the catalytic chlorination of ethyl 3-oxo-3-phenylpropanoate*



Entry	HCl (eq)	Time (h)	Conversion[a] (%)	Isolated Yield (%)
1	3.5	2.5	80	-[b]
2	3.5	4	83	38
3[c]	3.5	4	46	37
4	5.0	4	100	76

[a] Conversion was determined by ^{1}H NMR spectroscopy of the crude product; [b] not isolated; [c] Reaction carried out in CH_3CN.

In order to improve the conversion, the reaction was repeated under identical conditions, but the reaction time was increased to 4 hours giving an 83 % consumption of starting material (entry 2). The reaction was purified by column chromatography and ethyl 2-chloro-3-oxo-3-phenylpropanoate **2.5** was obtained in a 38 % isolated yield. However, the mono-hydroxylated product **3.6** was also isolated in a 9 % yield and was identified by the 1H singlet at 5.60 ppm corresponding to the CH adjacent to the hydroxy group. The dihydroxylated product **3.8** and vicinal tricarbonyl product **3.7** were also isolated in a 16 % and 2 % yield respectively. The dihydroxylated product was characterised by the 2H singlet at 5.30 ppm for the 2 hydroxy protons, whilst the tricarbonyl product **3.7** was identified by the 2H quartet at 4.43 ppm for the OCH_2 group.

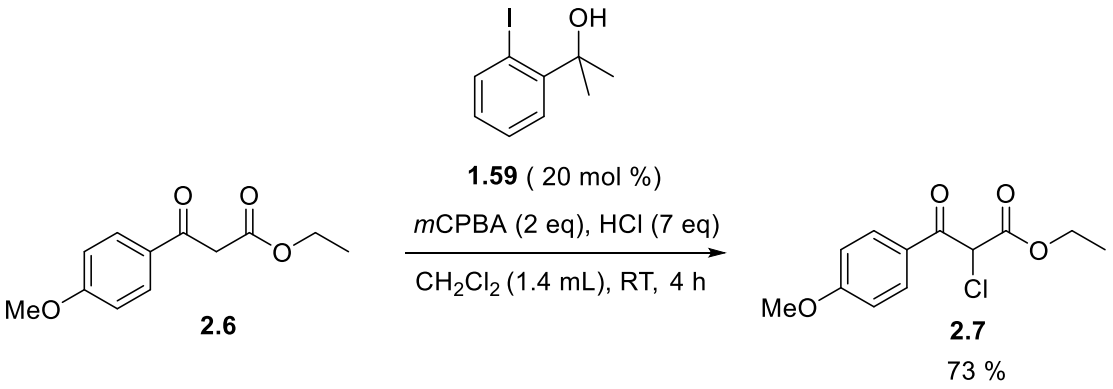


Scheme 3.7 *α-Hydroxylation of ethyl 3-oxo-3-phenylpropanoate*

When the reaction was repeated in acetonitrile, as this was the best solvent in the stoichiometric chlorination, the conversion dropped to 46 % (entry 3). Upon purification a 37 % isolated yield of the monochlorinated product was obtained, along with 3 % of the monohydroxylated product, 8 % of the dihydroxylated product **3.8** and 4 % of the vicinal tricarbonyl product **3.7**.

Increasing the amount of hydrochloric acid to 5 equivalents in entry 4 delivered a 100 % conversion. After purification by column chromatography the monochlorinated product was isolated in a 76 % yield and the dichlorinated product **3.9** was obtained in an 18 % yield.

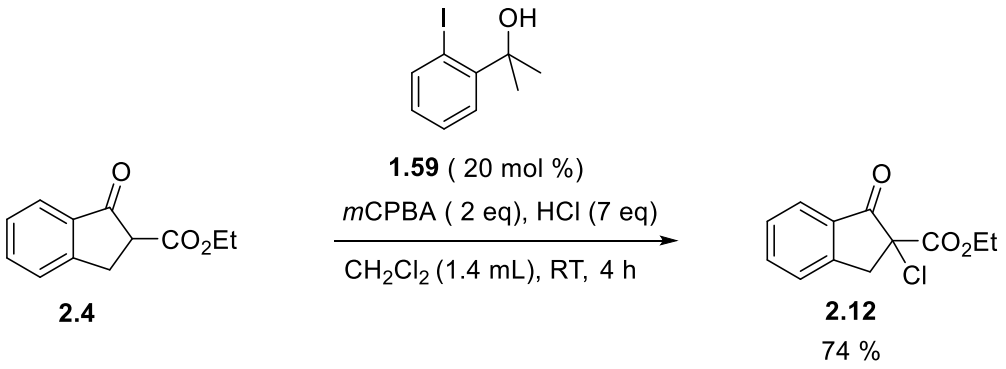
The dichlorinated product **3.9** was identified by the 3H triplet at 1.20 ppm and the 2H quartet at 4.33 ppm corresponding to the ethoxy group in the ^{1}H NMR spectrum. The presence of a singlet in the ^{13}C NMR spectrum at 81.9 ppm corresponded to the CCl_2 carbon and confirmed the formation of product. There was no sign of any hydroxylated products in this reaction.



Scheme 3.8 *Catalytic chlorination of ethyl 3-(4-methoxyphenyl)-3-oxopropanoate using 2-(2-iodophenyl)-propan-2-ol*

Ethyl 3-(4-methoxyphenyl)-3-oxopropanoate was chlorinated under the optimum conditions developed for ethyl 3-oxo-3-phenylpropanoate, using *m*-chloroperbenzoic acid (2 equivalents), hydrochloric acid (5 equivalents) and 2-(2-iodophenyl)propan-2-ol (20 mol %) in dry dichloromethane at room temperature for 4 hours (Scheme 3.8). The ^{1}H NMR spectrum of the crude product showed a 64 % conversion by the appearance of a 3H singlet at 3.89 ppm corresponding to the OCH_3 group, as well as the 1H singlet at 5.57 ppm belonging to the CHCl proton. Following purification by column chromatography, a 54 % yield of the monochlorinated product was obtained. The ^{13}C NMR spectrum of the product had a singlet at 57.9 ppm corresponding to the CHCl and confirmed formation of **2.7**. The isotope pattern of chlorine was also obtained in the mass spectrum of **2.7**, where an *m/z* of 257.0571 was observed for the ^{35}Cl isotope, $C_{12}H_{14}O_4{}^{35}Cl$ (100 %) and an *m/z* of 259.05557 was obtained for the ^{37}Cl isotope, $C_{12}H_{14}O_4{}^{37}Cl$ (40 %).

The reaction was repeated using a larger excess of hydrochloric acid (7 equivalents) under the same reaction conditions in order to improve the conversion to product. The crude ^{1}H NMR spectrum showed a 74 % conversion to the monochlorinated product **2.7** and following purification by column chromatography, a 73 % isolated yield of the product was achieved. There was no evidence of dichlorination or hydroxylation in this reaction.

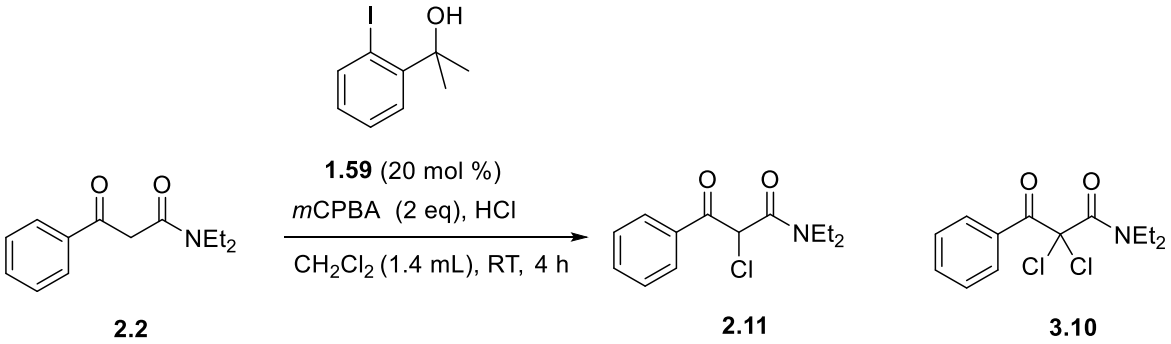


Scheme 3.9 *Catalytic chlorination of ethyl 1-oxo-2,3-indanone-2-carboxylate using 2-(2-iodophenyl)-propan-2-ol*

Ethyl-1-oxo-2,3-indanone-2-carboxylate was chlorinated using *m*-chloroperbenzoic acid (2 equivalents), hydrochloric acid (7 equivalents) and iodoalcohol (20 mol %) in dry dichloromethane at room temperature for 4 hours (Scheme 3.9). The crude ^{1}H NMR spectrum showed a 100 % consumption of starting material, indicated by the disappearance of the 1H doublet of doublets at 3.36 ppm and the 1H doublet of doublets at 3.54 ppm corresponding to the CH_2 within the 5 membered indanone ring. The 2H singlet at 3.51 ppm for the CH_2 of the enol tautomer also disappeared.

Following purification by column chromatography, a 74 % isolated yield of ethyl 2-chloro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate **2.12** was achieved. The ^{1}H NMR spectrum showed the presence of a 3H triplet at 1.27 ppm corresponding to the CH_3 within the ethoxy group and a 2H multiplet at 4.27 ppm belonging to the OCH_2 of the ethoxy group. In addition, the presence of a 1H doublet at 3.56 ppm and a 1H doublet at 4.10 ppm corresponded to the two CH_2 protons on the indanone ring. The ^{13}C NMR spectrum contained a singlet at 68.0 ppm for the CCl carbon. The formation of product was confirmed by mass spectrometry where there was a *m/z* 239.0481 for the parent ion peaks with the ^{35}Cl isotope, $C_{12}H_{12}O_3{}^{35}Cl$ and *m/z* 241.0471 for the ^{37}Cl isotope, $C_{12}H_{12}O_3{}^{37}Cl$.

3.3.2 Catalytic Chlorination of *N,N*-Diethyl-3-oxo-3-phenylpropanamide using 2-(2-Iodophenyl)propan-2-ol



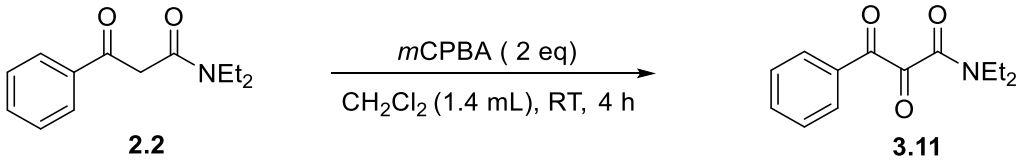
Scheme 3.10 *Catalytic chlorination of N,N-diethyl-3-oxo-3-phenylpropanamide using 2-(2-iodophenyl)-propan-2-ol*

The chlorination of *N,N*-diethyl-3-oxo-3-phenylpropanamide was investigated initially using *m*-chloroperbenzoic acid (2 equivalents), hydrochloric acid (5 equivalents) and 2-(2-iodophenyl)propan-2-ol (20 mol %) in dry dichloromethane at room temperature for 4 hours (Scheme 3.10). The ^{1}H NMR spectrum of the crude product revealed a 70 % consumption of starting material by the reduction in the 2H singlet at 4.04 ppm corresponding to the aliphatic CH_2 group of the keto tautomer, as well as the reduction in the 1H singlet at 5.72 ppm corresponding to the alkene CH of the enol tautomer. The ^{1}H NMR spectrum of the crude product also showed the formation of multiple by-products. After purification by column chromatography, the dichlorinated product **3.10** was isolated in a 12 % yield and was identified by the two 3H triplets at 1.05 and 1.07 ppm and the two 2H quartets at 3.34 ppm and 3.38 ppm belonging to the two sets of CH_3 and CH_2 groups respectively within the diethyl moiety. The *m/z* of 288.0552 was observed for the ^{35}Cl isotope, $C_{13}H_{16}NO_2{}^{35}Cl_2$, 290.0539 corresponded to the $^{35}Cl^{37}Cl$ isotope, $C_{13}H_{16}NO_2{}^{35}Cl^{37}Cl$ and 292.0556 for the ^{37}Cl isotope, $C_{13}H_{16}NO_2{}^{37}Cl^{37}Cl$.

There was no evidence of the monochlorinated product in the ^{1}H NMR spectrum. Interestingly, the vicinal tricarbonyl product **3.11**, was produced in an 18 % yield and was identified in the ^{1}H NMR spectrum by the appearance of two 3H triplets at 1.25 ppm and 1.31 ppm corresponding to the two sets of CH_3 groups within the diethyl moiety and a 4H multiplet at 3.44-3.54 ppm belonging to the two aliphatic CH_2 groups within the same moiety. The ^{13}C NMR spectrum also revealed the presence of three carbonyl groups at 165.4 ppm, 185.6 ppm and 192.3 ppm confirming the presence of the three different

carbonyl groups. In addition, the formation of the vicinal tricarbonyl was also confirmed by mass spectrometry where the *m/z* 234.0021 corresponding to $C_{13}H_{16}NO_3$ was obtained.

In order to prevent the second chlorination from occurring, the reaction was repeated using 3.5 equivalents of hydrochloric acid. The ^{1}H NMR spectrum of the crude product showed a 100 % consumption of starting material. After purification by column chromatography the vicinal tricarbonyl product **3.11**, was isolated in a 40 % yield and there was only a 7 % yield of the dichlorinated product.



2.2 **3.11**

Scheme 3.11 *Control reaction; reaction of N,N-diethyl-3-oxo-3-phenylpropanamide in the presence of mCPBA*

With the aim of investigating the background reactions taking place within this system, a control experiment was conducted whereby *N,N*-diethyl-3-oxo-3-phenylpropanamide was reacted with *m*-chloroperbenzoic acid (2 equivalents) in dry dichloromethane at room temperature for 4 hours (Scheme 3.11). The ^{1}H NMR spectrum of the crude product showed a 100 % consumption of starting material and the formation of multiple by-products.

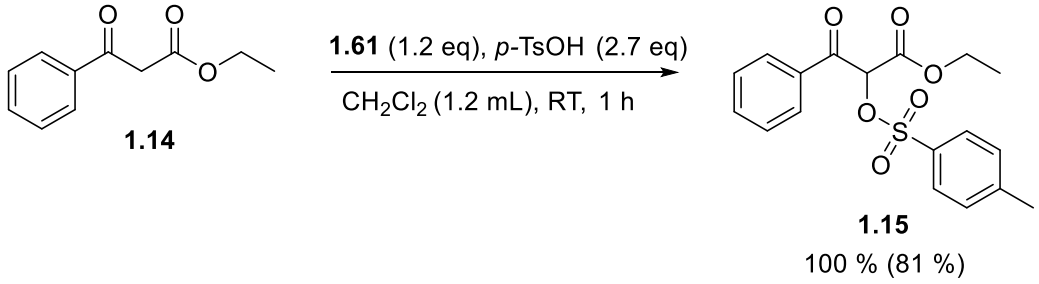
Unfortunately, purification by column chromatography was extremely difficult and the multiple by-products could not be separated. The vicinal tricarbonyl product was isolated in only a 5 % yield.

3.4 Catalytic Tosyloxylations

3.4.1 Tosyloxylation of Ethyl 3-oxo-3-phenylpropanoate using 1-Fluoro-3,3-dimethyl-1,3-dihydro-λ^3-benzo[*d*][1,2]iodoxole

To expand upon the established catalytic methodology developed in the chlorination system, *para*-toluenesulfonic acid was investigated as a nucleophile. The tosyloxy group was first introduced into the 2-position of ethyl 3-oxo-3-phenylpropanoate using 1-fluoro-3,3-dimethyl-1,3-dihydro-λ^3-benzo[*d*][1,2]iodoxole **1.61** in combination with *p*-toluenesulfonic acid at room temperature for 1 hour (Scheme 3.12).[6] Ethyl 3-oxo-3-phenyl-2-(tosyloxy)propanoate **1.15** was isolated by column chromatography on silica

gel in an 81 % yield. This is an extremely similar result to the initial report which gave an 80 % yield under the same reaction conditions.



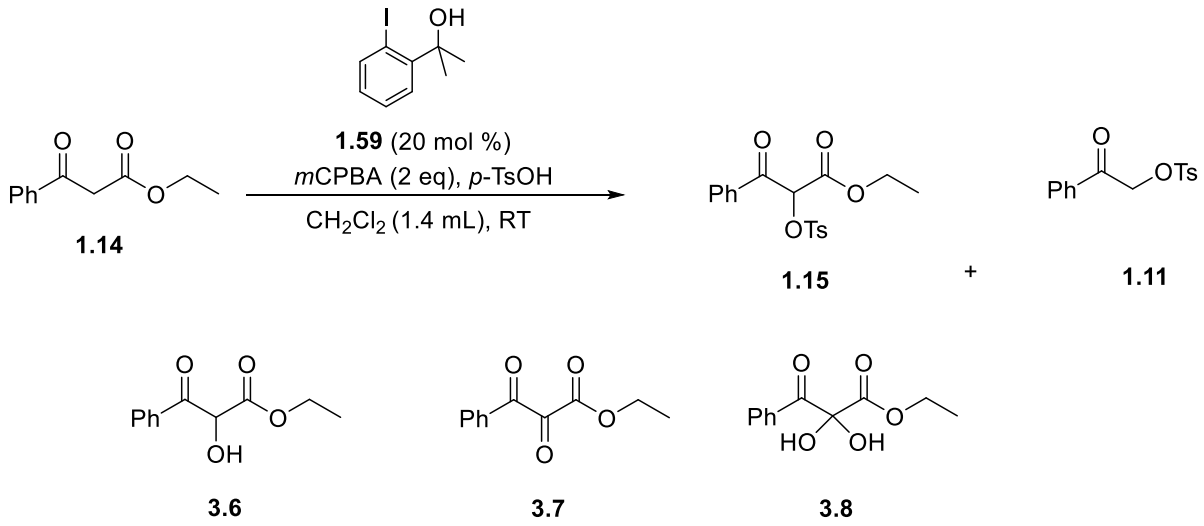
Scheme 3.12 *Synthesis of ethyl 3-oxo-3-phenyl-2-(tosyloxy)propanoate using 1-fluoro-3,3-dimethyl-1,3-dihydro-λ^3-benzo[d][1,2]iodoxole* ***1.61***

The formation of **1.15** was confirmed by the 1H singlet at 5.98 ppm in the ^{1}H NMR spectrum for the α-proton adjacent to the tosyloxy group and a 3H singlet corresponding the methyl group of the tosyloxy group (Scheme 3.12). The integration of the aromatic protons in a 2:1:2 ratio indicated the phenyl ring and two sets of AB doublets were observed for the 4 aromatic protons of the tosyloxy group. Within the ^{13}C NMR spectrum there was a singlet at 21.7 ppm corresponding to the methyl group within the tosyloxy group which was in agreement with the literature.[7]

3.4.2 Tosyloxylation of Ethyl 3-oxo-3-phenylpropanoate using 2-(2-Iodophenyl)propan-2-ol

Ethyl 3-oxo-3-phenylpropanoate **1.14** was reacted with *p*-toluenesulfonic acid (5 equivalents) in the presence of a catalytic amount of 2-(2-iodophenyl)propan-2-ol **1.59** and *m*-CPBA (2 equivalents) in dichloromethane at room temperature for 4 hours giving a 55 % conversion to the tosyloxylated product **1.15** (entry 1). Also apparent within the ^{1}H NMR spectrum was the formation of a the monohydroxylated product **3.6** (8 % conversion) which was identified by the 1H singlet at 5.27 ppm corresponding to the CH adjacent to the hydroxyl group and as well as the 3H singlet at 2.46 ppm belonging to the CH_3 on the tosyloxy group.

Table 3.2 *Tosyloxylation of ethyl 3-oxo-3-phenylpropanoate using 2-(2-iodophenyl)propan-2-ol* ***1.59***



Entry	*p*-TsOH (eq)	Temp. (°C)	Time (h)	1.15[a] (%)	1.11[a] (%)	3.6[a] (%)	3.7[a] (%)	3.8[a] (%)
1	5	RT	4	55	3	8	1	2
2	7.5	0	2	70 (14)	16 (23)	0	6	0
3	7.5	RT	2	64 (28)	16 (32)	2	6	2
4	7.5	40	2	55	24	1	0	1
5[b]	7.5	RT	1	28	1	17	12	1
6[b]	7.5	RT	2	30	0	25	6	0
7[b,c]	7.5	RT	2	43	11	8	0	2

[a] Conversion determined by ^{1}H NMR spectroscopy; [b] *p*-toluenesulfonic acid dried at 50 °C under vacuum for 4 hours prior to use; [c] reaction carried out in HFIP (1.4 mL).

The amount of *p*-toluenesulfonic acid was increased to 7.5 equivalents in entry 2 and the reaction was performed at 0 °C for 2 hours. The ^{1}H NMR spectrum of the crude product showed a 70 % conversion to the tosyloxylated product **1.15**, but unfortunately it was

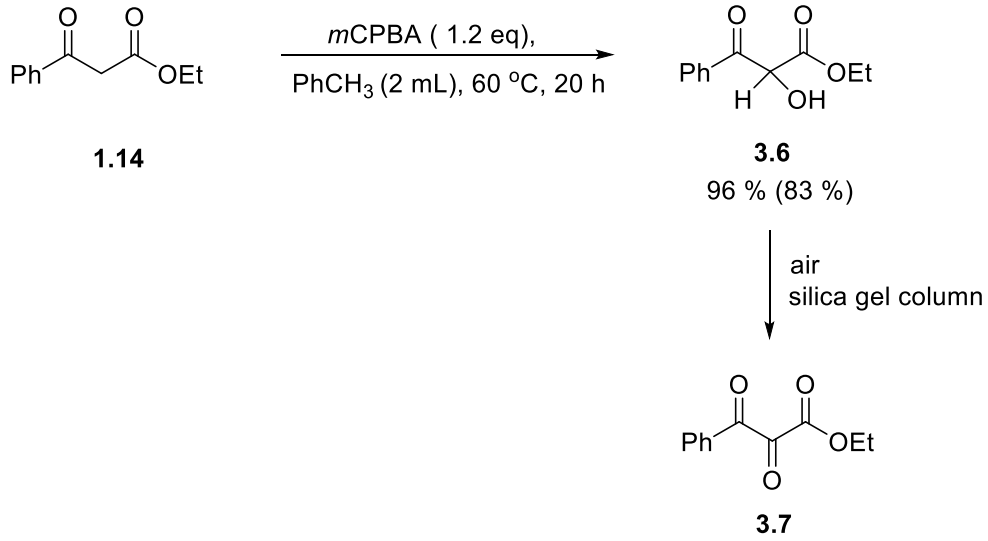
hydrolysed to form α-(tosyloxy)acetophenone **1.11** in a 16 % conversion. α-(Tosyloxy)acetophenone **1.11** was identified by the 2H singlet at 5.27 ppm corresponding to the CH_2 group. Disappointingly the desired monotosyloxylated product **1.15** was only isolated in a 14 % yield, along with its hydrolysis product **1.11** in a 23 % yield, after purification by column chromatography. When the reaction was repeated at room temperature, there was a similar 64 % conversion to the mono-tosyloxylated product **1.15** and a 16 % conversion to α-(tosyloxy)acetophenone **1.11**. After purification by column chromatography, the monotosyloxylated product **1.15** was obtained in a 28 % yield and its hydrolysis product **1.11** was isolated in a 32 % yield. The higher isolated yield of the hydrolysis product **1.11** suggested that not only is the product hydrolysing within the reaction, but also during purification by column chromatography. Increasing the reaction temperature to 40 ^oC (entry 4), resulted in a lower 55 % conversion to **1.15** and a higher 24 % conversion to the hydrolysed product **1.11**.

In order to minimise the hydrolysis of the tosyloxylated product **1.15**, the *para*-toluenesulfonic acid was dried prior to use by heating to 50 °C under vacuum for 4 hours, in an attempt to reduce the water content. In entry 5 the reaction was repeated using the dried *p*-toluenesulfonic acid at room temperature for 1 hour. A lower 28 % conversion to **1.15** was obtained and there was a significant reduction in the conversion (1 %) to the hydrolysed product. Disappointingly, the ^1H NMR spectrum of the crude product showed 17 % conversion to the monohydroxylated product **3.6** and a 12 % conversion to the vicinal tricarbonyl **3.7**. In entry 6 the reaction was repeated for 2 hours and a similar 30 % conversion to **1.15** was obtained with a greater 25 % conversion the to monohydroxylated product **3.6** and 6 % conversion to **3.7**.

When the reaction was repeated in HFIP an improved 43 % conversion to the tosyloxylated product was achieved, but unfortunately the amount of the hydrolysis product **1.11** increased to 11 %. There was however, a reduction in the amount of hydroxylation with an 8 % conversion to the monohydroxylated product **3.6**.

Entry 3 gave the most promising reaction conditions with a high conversion 64 % to the monotosyloxylated product **1.15** and a moderate 16 % conversion to the hydrolysed product **1.11**. This result validated that the tosyloxylation was possible under these reaction conditions however, issues with hydrolysis resulted in low isolated yields of the desired product.

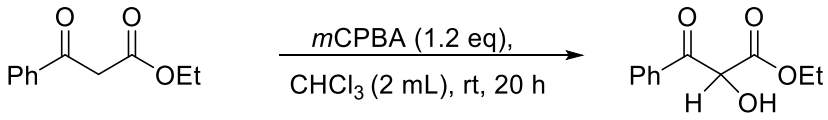
3.4.3 Investigating the Effect of *m*-CPBA



1.14 **3.6** 96 % (83 %) **3.7**

Scheme 3.13 *α-Hydroxylation of ethyl 3-oxo-3-phenylpropanoate*

The hydroxylation of *β*-ketoesters and *β*-ketoamides using *m*-chloroperbenzoic acid as the oxidant is established in the literature.[8,9] Nishiwaki *et al.* developed a metal free hydroxylation of *β*-ketoesters and *β*-ketoamides using *m*-chloroperbenzoic acid under mild reaction conditions.[7] Here, it was found that varying the solvent enabled higher yields to be achieved with aprotic solvents proving the most effective for hydroxylation. In this case toluene, which upon heating the reaction at 60 °C for 20 hours using 1.2 equivalents of *m*-CPBA achieved a 96 % conversion to the α-hydroxylated product and an 83 % isolated yield. Furthermore, the α-hydroxylated *β*-ketoester was unstable to air oxidation and to column chromatography on silica gel which led to the formation of the vicinal tricarbonyl product **3.7** (Scheme 3.13).

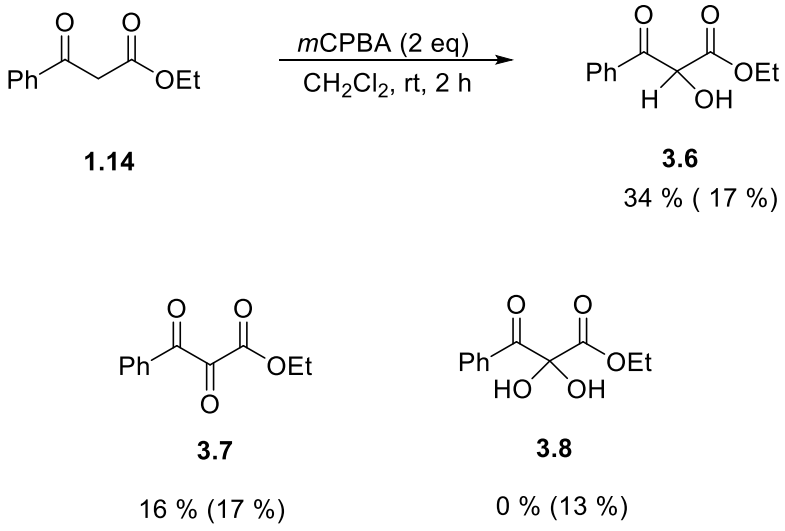


1.14 **3.6** 53 %

Scheme 3.14 *α-Hydroxylation of ethyl 3-oxo-3-phenylpropanoate using m-chloroperbenzoic acid in chloroform*[9]

Nishiwaki and coworkers also reported the reaction of ethyl 3-oxo-3-phenylpropanoate with *m*-CPBA (1.2 equivalents) in $CHCl_3$ at room temperature for 20 hours which resulted in a 53 % conversion to the α-hydroxylated product (Scheme 3.14).[9] This result provided

evidence that the *m*-chloroperbenzoic acid in my system is responsible for the hydroxylation within the tosyloxylation reaction under mild conditions.



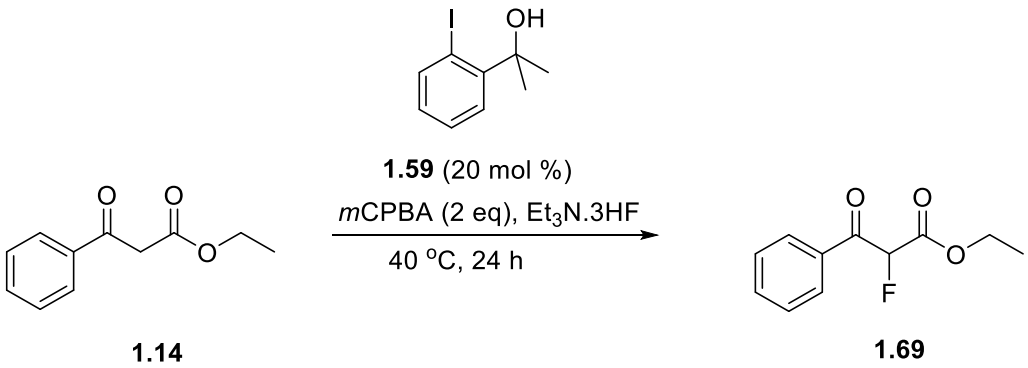
Scheme 3.15 *Investigating the effect of m-chloroperbenzoic acid*

In order to investigate the effect of *m*-CPBA in the tosyloxylation reaction, ethyl 3-oxo-3-phenylpropanoate was reacted with *m*-chloroperbenzoic acid (2 equivalents) in dry dichloromethane at room temperature for 2 hours, under identical conditions to the optimum tosyloxylation conditions (Table 3.2, entry 3). The ^{1}H NMR spectrum of the crude reaction mixture showed a 50 % consumption of starting material. There was 34 % conversion to the monohydroxylated product **3.6** and 16 % conversion to the tricarbonyl product **3.7**. Following purification by column chromatography on silica gel, a 17 % isolated yield of the mono-hydroxylated product was obtained, as well as 17 % of the vicinal tricarbonyl product and 13 % of the dihydroxylated product. These results show that 50 % oxidation is occurring within the reaction to form the mono-hydroxylated product **3.6** and the vicinal tricarbonyl product **3.7**. Furthermore, during purification by column chromatography and in the presence of air, the ratios of **3.6**, **3.7** and **3.8** are able to interconvert due to the formation of the vicinal tricarbonyl product **3.7** from the monohydroxylated product, which is then subsequently able to form the hydrate **3.8**.

3.5 Stoichiometic Fluorinations using 2-(2-Iodophenyl)propan-2-ol

3.5.1 Catalytic Fluorinations using 2-(2-Iodophenyl)propan-2-ol

Table 3.3 *Catalytic fluorination of ethyl 3-oxo-3-phenylpropanoate*



1.14 **1.69**

Entry	$Et_3N.3HF$ (eq)	*m*CPBA (eq)	Solvent	Conversion (%)
1	3.5	2	CH_2Cl_2	0
2	3.5	2	CH_3CN	4
3	10	2	CH_2Cl_2	3
4	10	2	CH_3CN	3

With the aim of testing the scope of the catalytic reactions, fluorine was investigated next using triethylamine trihydrofluoride as the fluoride source. The catalytic fluorinations were investigated in the first instance using 2-(2-iodophenyl)propan-2-ol (20 mol %), *m*-chloroperbenzoic acid (2 equivalents), triethylamine trihydrofluoride (3.5 equivalents) at 40 °C for 24 hours using ethyl 3-oxo-3-phenylpropanoate as the model substrate. The fluorinations were investigated at higher temperatures and longer reaction times because previous work within the Stuart group indicated that the fluorinations required harsher conditions than the tosyloxylations and chlorinations.[10] The ^{1}H NMR spectrum of the crude product showed no evidence of the fluorinated product **1.69** (Table 3.3, entry 1) and ethyl 3-oxo-3-phenylpropanoate was still present. 2-(2-Iodophenyl)propan-2-ol was also present in the ^{1}H NMR spectrum with a 6H singlet at 1.76 ppm corresponding to the two methyl groups.

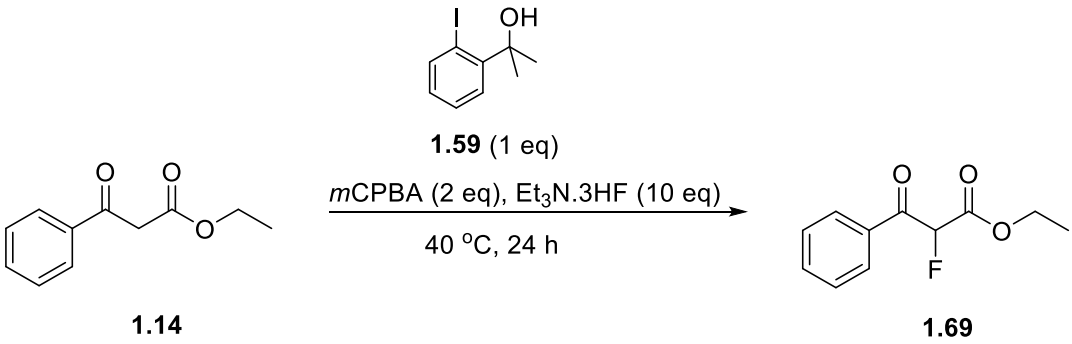
The reaction was repeated under identical conditions using acetonitrile as the solvent and a 4 % conversion to the monofluorinated product **1.69** was obtained (Table 3.3, entry 2). Ethyl 2-fluoro-3-oxo-3-phenylpropanoate was identified by the characteristic 1H doublet at 5.87 ppm in the ^{1}H NMR spectrum with a $^{2}J_{HF}$ coupling constant of 50.0 Hz and a singlet in the ^{19}F{^{1}H} NMR spectrum at -190.4 ppm. These initial reactions were conducted by reacting 2-(2-iodophenyl)propan-2-ol with *m*-chloroperbenzoic acid and triethylamine trihydrofluoride at room temperature for 15 minutes to allow oxidation of 2-(2-iodophenyl)propan-2-ol and the formation of 1-fluoro-3,3-dimethyl-1,3-dihydro-λ^{3}-benzo[*d*][1,2]iodoxole **1.61**, before adding the substrate to the reaction mixture and heating to 40 °C for 24 hours.

The reaction was repeated, but the method was altered in order to allow a longer period for the oxidation of 2-(2-iodophenyl)propan-2-ol and generation of fluoroiodane *in situ*. The reaction was conducted by reacting 2-(2-iodophenyl)propan-2-ol (20 mol %), with *m*-chloroperbenzoic acid (2 equivalents) and triethylamine trihydrofluoride (10 equivalents) at room temperature for 1 hour to allow oxidation of 2-(2-iodophenyl)propan-2-ol and formation of 1-fluoro-3,3-dimethyl-1,3-dihydro-λ^{3}-benzo[*d*][1,2]iodoxole **1.61** before adding the substrate to the reaction mixture and heating to 40 °C for 24 hours in either dichloromethane or acetonitrile (entries 3 and 4). In both cases the crude ^{1}H NMR spectrum showed a 3 % conversion to the monofluorinated product **1.69**.

3.5.2 Stoichiometric Fluorinations using 2-(2-Iodophenyl)propan-2-ol

Since the fluorination of ethyl 3-oxo-3-phenylpropanoate did not work with a catalytic amount of 2-(2-iodophenyl)propan-2-ol (20 mol %), the same reaction was investigated using a stoichiometric amount of 2-(2-iodophenyl)propan-2-ol (Table 3.4). Initially, the fluorination of ethyl 3-oxo-3-phenylpropanoate was conducted using *m*-chloroperbenzoic (2 equivalents), 2-(2-iodophenyl)propan-2-ol (1 equivalent), triethylamine trihydrofluoride (10 equivalents) in dichloromethane at 40 °C for 24 hours. The ^{1}H NMR spectra showed a 21 % conversion to the monofluorinated product **1.69**. When the reaction was repeated in acetonitrile (Table 3.4, entry 2), only a 12 % conversion was obtained.

Table 3.4 *Stoichiometric fluorination of ethyl 3-oxo-3-phenylpropanoate*



1.14 1.69

Entry	mCPBA (eq)	Solvent (mL)	Temperature (^{o}C)	Conversion[a] (%)
1	2	CH_2Cl_2	40	21
2	2	CH_3CN	40	12
3	2	CF_3CH_2OH	40	47 (44)
4[b]	2	CF_3CH_2OH	40	13
5	2	-	40	24
6	2	CF_3CH_2OH	60	44
7	3	CF_3CH_2OH	40	48
8[c]	2	CF_3CH_2OH	40	30

[a]Isolated yield in parenthesis; [b]Iodoalcohol (20 mol %); [c]Triethylamine trihydrofluoride (20 equivalents).

In my previous work on the trifluoroethoxylation of ethyl 3-oxo-3-phenylpropanoate, the monofluorinated product **1.69** was produced unexpectedly in a 26 % yield. Therefore, trifluoroethanol was investigated as the solvent in entry 3 and resulted in an improved 47 % conversion to the monofluorinated product which was isolated in a 44 % yield. The reaction was repeated using a catalytic amount of **1.59** (20 mol %) but the conversion to the monofluorinated product dropped to 13 % (Table 3.4, entry 4). When the reaction was

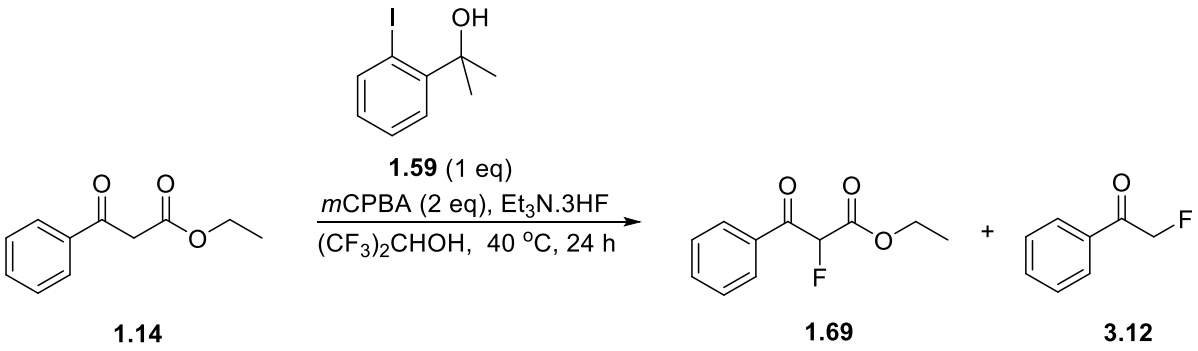
repeated under solvent free conditions in entry 5, a 24 % conversion to the monofluorinated product **1.69** was observed.

The reaction was repeated in trifluoroethanol at 60 °C for 24 hours (Table 3.4, entry 6). The ^{1}H NMR spectrum of the crude product showed a 44 % conversion to the monofluorinated product, which showed no significant temperature effect on the conversion to the product. When the amount of *m*-chloroperbenzoic acid was increased to 3 equivalents, the ^{1}H NMR spectrum showed a 48 % conversion to the monofluorinated product, which concluded that the oxidant was not the limiting factor in this system. Finally, the reaction was repeated with 20 equivalents of triethylamine trihydrofluoride, but only a 30 % conversion to the monofluorinated product was achieved.

The fluorination of ethyl 3-oxo-3-phenylpropanoate in trifluoroethanol gave better conversions (47 %) to the monofluorinated product **1.69** than using either dichloromethane (21 %) or acetonitrile (12 %). We were therefore interested to examine the effect of using hexafluoroisopropanol as the solvent to see if it improved the reaction further (Table 3.5). Initially, the conversion to the monofluorinated product increased to 55 % when the reaction was performed in hexafluoroisopropanol at 40 ^{o}C for 4 hours (entry 1) using *m*-CPBA (2 equivalents), 2-(2-iodophenyl)propan-2-ol (1 equivalent) and TREAT-HF (10 equivalents).

Previous work in the Stuart group had shown that the concentration of the fluorination reaction was important and that the amount of fluorination was reduced under more dilute conditions. Since the best results were obtained with a reaction concentration of 0.48 M.[10] The reaction was repeated at 0.48 M by decreasing the equivalents of triethylamine trihydrofluoride to 7.5 equivalents and using 0.6 mL of HFIP (Table 3.5). Although a lower 52 % conversion to the monofluorinated product was obtained, there was also a 14 % conversion to 2-fluoroacetophenone. The hydrolysis to 2-fluoroacetophenone **3.12** was confirmed by the distinct 2H doublet at 5.52 ppm and a singlet in the ^{19}F NMR spectrum at -230.9 ppm. The reaction was repeated at 0.48 M using 5 equivalents of triethylamine trihydrofluoride (6 mL) and HFIP (0.9 mL) (Table 3.5, entry 3). The conversion to the monofluorinated product **1.69** dropped further to 43 %, but the conversion to 2-fluoroacetophenone increased to 27 %.

Table 3.5 *Stoichiometric fluorination of ethyl 3-oxo-3-phenylpropanoate in 1, 1, 1, 3, 3, 3, -hexafluoroisopropanol*



Entry	$Et_3N.3HF$ (eq)	HFIP (mL)	Temperature (°C)	Conv. to 1.69[a] (%)	Conv. to 3.12[a] (%)
1	10	1.4	40	55	0
2[b]	7.5	0.6	40	52	14
3[b]	5	0.9	40	43	27
4[c]	5	0.9	40	0	0

[a] Conversion to product; [b] 0.48 M; [c] Reaction conducted with 4Å powdered molecular sieves.

In entry 4, the same reaction was conducted using powdered molecular sieves with the aim of preventing the hydrolysis of ethyl 2-fluoro-3-oxo-3-phenylpropanoate, but the ^1H NMR spectrum of the crude product showed no evidence of fluorination of ethyl 3-oxo-3-phenylpropanoate.

The fluorination of ethyl 3-oxo-3-phenylpropanoate using a catalytic amount of 2-(2-iodophenyl)propan-2-ol proved challenging. When stoichiometric quantities of **1.59** were employed in trifluoroethanol, the fluorination was possible in moderate yields. The reaction was improved by using HFIP as the solvent, but the competing hydrolysis of **1.69** unfortunately led to low isolated yields.

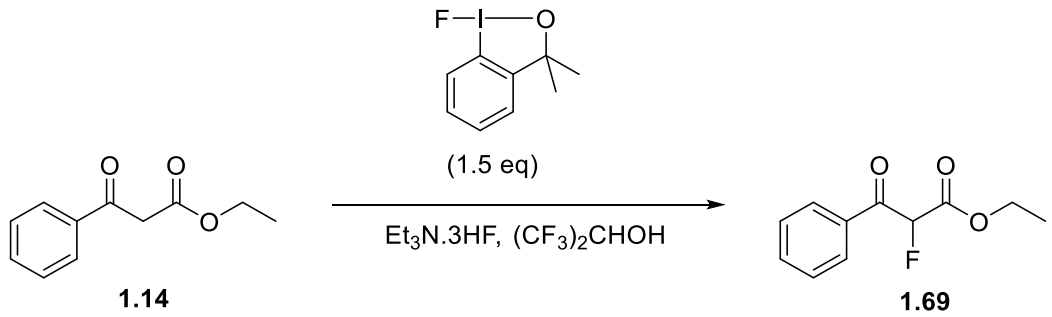
3.6 Fluorinations in 1,1,1,3,3,3-Hexafluoroisopropanol using 1-Fluoro-3,3-dimethyl-1,3-dihydro-λ^3-benzo[*d*][1,2]iodoxole

3.6.1 Fluorination of Ethyl 3-oxo-3-phenylpropanoate in HFIP

Szabó and coworkers used fluoroiodane and $AgBF_4$ for fluorocyclisations.[11] Density functional theory (DFT) calculations showed that this mechanism proceeds through the activation of fluoroiodane using a Lewis acid.[12] The Lewis acid activated the fluoroiodane reagent by coordinating to its fluorine atom, which elongates the I-F bond. Recent work proposed that the fluorocyclisation of unsaturated amides proceeded without a Lewis acid catalyst because the amide functionality acted a hydrogen bond donor to activate the fluoroiodane, by hydrogen bonding to its fluorine atom.[12] In the previous section hexafluoroisopropanol gave promising results for the fluorination of ethyl 3-oxo-3-phenylpropanoate. Fluorinated solvents such as trifluoroethanol and hexafluoroisopropanol are useful solvents in synthetic organic chemistry, due to their ability to form strong hydrogen bonds and because of their low nucleophilicity.[13] For example HFIP has been shown to activate benzylic fluorides by hydrogen bonding and Gulder has also reported the use of HFIP to activate *N*-halosuccinimides by hydrogen bonding, for halogenation.[14] The aim of this section was to investigate whether hexafluoroisopropanol could be used to activate fluoroiodane by hydrogen bonding and eliminate the need for the TREAT-HF activator.

Ethyl 3-oxo-3-phenylpropanoate was fluorinated using 1-fluoro-3,3-dimethyl-1,3-dihydro-λ^3-benzo[*d*][1,2]iodoxole (1.5 equivalents) and triethylamine trihydrofluoride (2.7 equivalents), in HFIP at 40 °C for 6 hours (Table 3.6, entry 1). The crude ^{1}H NMR spectrum showed a 98 % conversion and after purification by column chromatography, a 98 % isolated yield of the monofluorinated product **1.69** was achieved. This is a much better yield than performing the reaction in dichloromethane using 2 equivalents of fluoroiodane **1.61** for 24 hours which gave a 63 % yield of the monofluorinated product. However, when the reaction was repeated in HFIP for 4 hours the conversion decreased to 82 % (Table 3.6, entry 2).

Table 3.6 *Fluorination of ethyl 3-oxo-3-phenylpropanoate*



1.14 1.69

Entry	$Et_3N.3HF$ (eq)	Temperature (°C)	Time (h)	Conversion[a,b] (%)
1	2.7	40	6	98 (98)
2	2.7	40	4	82
3	0.5	40	6	87 (87)
4	0.5	40	8	80
5	0	40	6	70 (58)
6	0	60	6	79 (77)
7	0	80	6	69
8	0	60	4	76 (73)

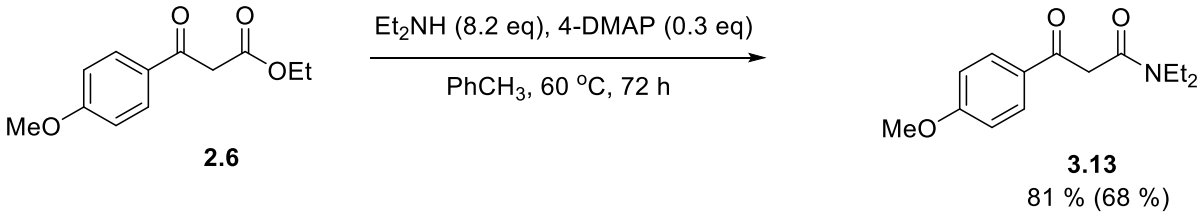
[a] Determined by ^1H NMR spectroscopy; [b] Isolated yield in parenthesis.

The amount of triethylamine trihydrofluoride was then reduced to 0.5 equivalents and the monofluorinated product was obtained in an excellent 87 % yield, but the reaction was not improved by extending the reaction time to 8 hours (Table 3.6, entries 3 and 4).

In the final set of experiments the reaction was investigated without using any triethylamine trihydrofluoride to activate the fluoroiodane. In entry 5 the reaction was conducted at 40 ℃ for 6 hours giving a 70 % conversion which improved to 79 % when the reaction temperature was increased to 60 ℃ (entry 6). Unfortunately, the conversion dropped back to 69 % when the reaction temperature was further increased to 80 ℃. Finally, the reaction was repeated at 60 ℃ for just 4 hours forming the monofluorinated

product in 73 % isolated yield. All of these reactions formed predominantly the monofluorinated product with only trace amounts of the difluorinated products (< 2 %) was observed in the ^{19}F NMR spectrum at -107.7 ppm. This result in contrast to the original reactions conducted in dichloromethane with Et_3N. 3HF where the difluorinated product was observed in a 6 % conversion at 40 °C and a 25 % conversion at 60 °C.

3.6.2 Synthesis of *N,N*-Diethyl-3-(4-methoxyphenyl)-3-oxopropanamide

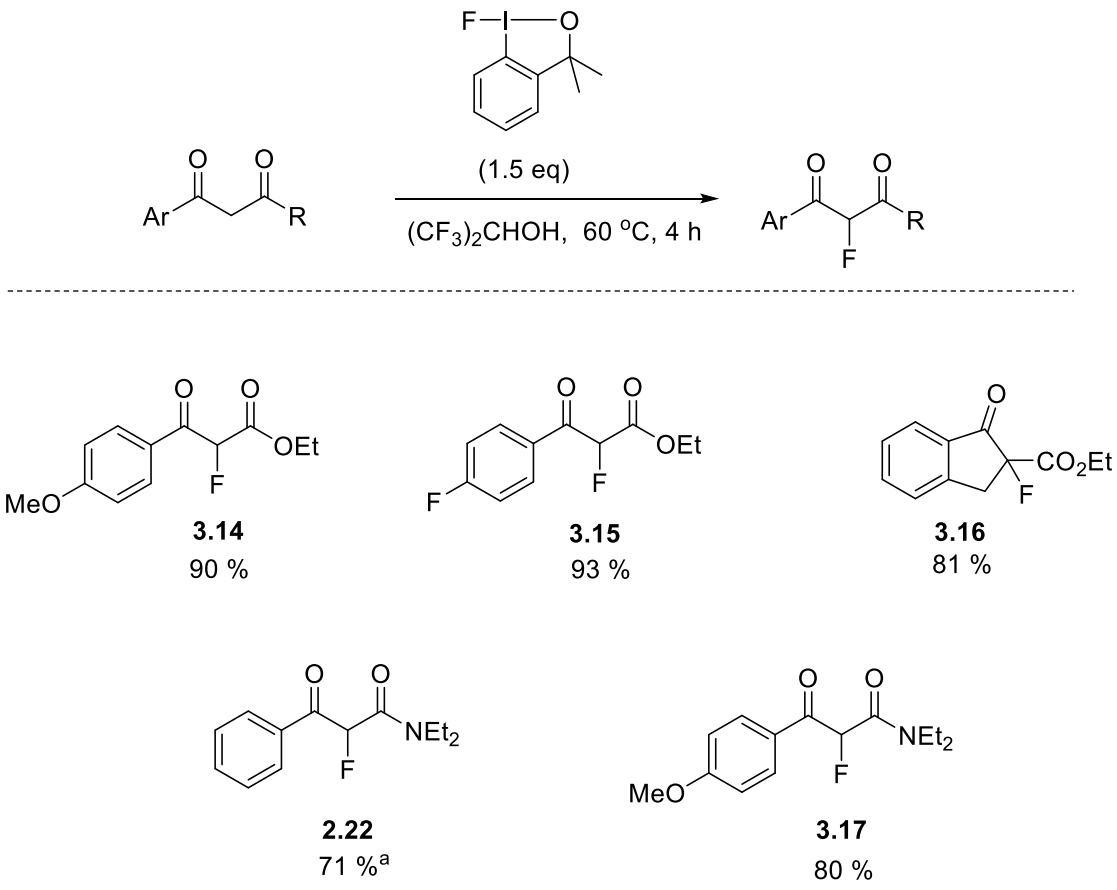


Scheme 3.16 *Synthesis of N,N-diethyl-3-(4-methoxyphenyl)-3-oxopropanamide*

N,N-Diethyl-3-(4-methoxyphenyl)-3-oxopropanamide **3.13** is not commercially available and was synthesised by reacting ethyl 3-(4-methoxyphenyl)-3-oxopropanoate with 4-dimethylaminopyridine (0.3 equivalents) and diethylamine (5 equivalents) in dry toluene at 60 °C for 24 hours. A further quantity of diethylamine (3.2 equivalents) was added to the reaction and the reaction mixture was heated to 60 °C for a further 48 hours. An 81 % conversion to *N,N*-diethyl-3-(4-methoxyphenyl)-3-oxopropanamide **3.13** was obtained and the crude product was purified by column chromatography to give the pure product in a 68 % isolated yield (Scheme 3.16).

^1H NMR spectroscopy confirmed the formation of product **3.13** by the appearance of a 3H singlet at 3.85 ppm corresponding to the OCH_3 of the enol tautomer and a 3H singlet at 3.87 ppm for the OCH_3 of the keto tautomer, a singlet at 5.65 ppm belonging to the 1H singlet of the enol tautomer, a 2H singlet at 4.01 ppm for the CH_2 of the keto tautomer as well as a 12H multiplet at 1.12-1.23 ppm corresponding to the two NCH_3 groups of the keto and enol tautomers in the diethyl moiety and a second 8 H multiplet at 3.36-3.46 ppm belonging to the two CH_2 groups of the keto and enol tautomers in diethyl moiety. The product was isolated in a 25 % enol : 75 % keto ratio.

3.6.3 Fluorination of 1,3-Dicarbonyl Compounds in Hexafluoroisopropanol



Scheme 3.17 *Fluorination of 1,3-dicarbonyl substrates in hexafluoroisopropanol;* [a]*Reaction carried out at room temperature for 1 hour*

With the aim of expanding the substrate scope, the optimum reaction conditions were applied to a small series of 1,3-dicarbonyl compounds. Ethyl 3-(4-methoxyphenyl)-3-oxo-3-phenylpropanoate was fluorinated using 1-fluoro-3,3-dimethyl-1,3-dihydro-λ^3-benzo[*d*][1,2]iodoxole (1.5 equivalents) in HFIP at 60 °C for 4 hours. The crude ^{1}H NMR spectrum showed a > 95 % conversion to the monofluorinated product. After purification by column chromatography a 90 % isolated yield was achieved. The formation of product **3.14** was determined by the presence of a 1H doublet at 5.82 ppm corresponding to the CHF, with a $^2J_{HF}$ coupling constant of 48.9 Hz and the presence of a 3H singlet at 3.86 ppm corresponding to the OCH_3 group. ^{19}F NMR spectroscopy showed the presence of a singlet at -189.6 ppm belonging to the monofluorinated product. The ^{13}C NMR spectrum

contained a doublet at 90.1 ppm belonging to the CHF carbon, with a $^{1}J_{CF}$ of 196.8 Hz. The formation of product was also confirmed by mass spectrometry where the *m/z* 241.0888 corresponding to $C_{12}H_{14}FO_4$ was obtained.

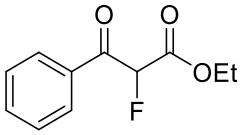
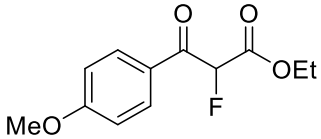
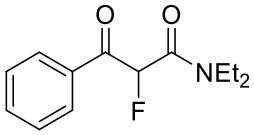
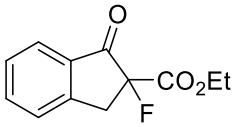
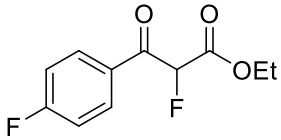
Ethyl 3-(4-fluorophenyl)-3-oxo-3-phenylpropanoate was fluorinated under the same reaction conditions and a 93 % isolated yield was achieved after purification by column chromatography. The ^{1}H NMR spectrum showed the formation of product **3.15** through the presence of a 1H doublet at 5.89 ppm corresponding to the CHF with a $^{2}J_{HF}$ coupling constant of 48.9 Hz. The ^{19}F NMR spectrum showed two 1F singlets at -189.6 ppm for CHF and at -101.8 ppm for ArF. The formation of product was confirmed by mass spectrometry where the *m/z* 229.0679 corresponding to $C_{11}H_{12}F_2O_3$ was obtained. Under the same conditions ethyl 1-indanone-2-fluoro-2-carboxylate was obtained in an 81 % yield. The formation of product **3.16** was determined by the appearance of a 1H doublet of doublets at 3.44 ppm corresponding to the CH_2 within the indanone ring with a $^{2}J_{HH}$ coupling constant of 17.6 Hz and a $^{3}J_{HF}$ coupling constant of 22.6 Hz, and a 1H doublet of doublets at 3.80 ppm corresponding to the CH_2 within the indanone ring, with a $^{2}J_{HH}$ coupling constant of 17.6 Hz and a $^{3}J_{HF}$ coupling constant of 11.7 Hz. The ^{19}F NMR spectrum showed a singlet at -164.4 ppm. The ^{13}C NMR spectrum showed a doublet at 38.3 ppm corresponding to the same CH_2 of the indanone ring, with a $^{2}J_{CF}$ coupling constant of 24.0 Hz, as well as a doublet at 94.5 ppm for the CF carbon with a $^{1}J_{CF}$ with a coupling constant of 202.7 Hz.

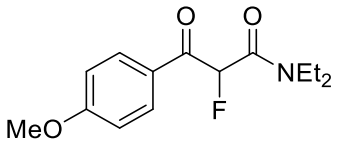
N,N-Diethyl-3-oxo-3-phenylpropanamide was fluorinated under the same conditions and a > 95 % consumption of starting material was achieved, but after purification by column chromatography only a 54 % isolated yield was obtained. The low isolated yield was a result of other by-products being formed in the reaction. The reaction was repeated at room temperature for 4 hours and the crude ^{1}H NMR spectrum showed a 95 % conversion but it also showed the presence of by-products being formed in the reaction. The reaction was repeated for 1 hour at room temperature affording a 71 % isolated yield of the monofluorinated product **2.22**. The formation of **2.22** was confirmed by the appearance of a 1H doublet at 6.12 ppm in the ^{1}H NMR spectrum corresponding to the CHF with a $^{2}J_{HF}$ coupling constant of 49.1 Hz. The ^{19}F NMR spectrum showed a singlet at -186.8 ppm for the monofluorinated product.

Finally, *N*,*N*-diethyl-3-(4-methoxyphenyl)-3-oxopropanamide was fluorinated at 60 ºC for 4 hours in an 80 % isolated yield. The formation of product **3.17** was confirmed by the appearance of a 1H doublet at 6.08 ppm in the ^{1}H NMR spectrum corresponding to the CHF, with a $^{2}J_{HF}$ coupling constant of 49.1 Hz and the presence of a 3H singlet at 3.87 ppm belonging to the OCH_3. ^{19}F NMR spectroscopy showed a singlet at -186.1 ppm corresponding to the monofluorinated product. The ^{13}C NMR spectrum contained a doublet at 92.8 ppm corresponding to the CHF carbon, with a $^{1}J_{CF}$ of 188.4 Hz. The formation of product was also confirmed by mass spectrometry where the *m/z* 268.1343 corresponding to $C_{14}H_{19}NFO_3$ was obtained.

Previous work conducted within the Stuart group carried out the fluorination of the 1,3-dicarbonyl substrates using **1.61** (2 equivalents) and triethylamine trihydrofluoride (2.7 equivalents) in dichloromethane at 40 ºC for 24 hours. In this work I have demonstrated that the fluoroiodane reagent can be activated by HFIP and $Et_3N.3HF$ is no longer required in these reactions. Furthermore, the reaction time has been decreased from 24 hours to 6 hours and the amount of fluoroiodane has been reduced from 2 equivalents to 1.5 equivalents. Entries 1,2 and 4 in Table 3.7. demonstrate clearly that the monofluorinated products were obtained in better yields in HFIP than using $Et_3N.3HF$ in dichloromethane. The cyclic *β*-ketoester was also fluorinated in an excellent 81 % yield in HFIP in just 4 hours compared to a moderate 55 % yield using $Et_3N.3HF$ and dichloromethane for 48 hours. Finally, the 1,3-ketoamides were fluorinated in 71-80 % yields in HFIP and **2.22** was obtained under much milder reaction conditions (1 h at RT).

Table 3.7 *Comparison of the fluorination of 1,3-dicarbonyl compounds using* ***1.61*** *with and without triethylamine hydrofluoride*

Entry	Product	Yield with $Et_3N.3HF$ [a,b] (%)	Yield in HFIP [b,c] (%)
1	 **1.69**	63[d]	73
2	 **3.14**	67[d]	90
3	 **2.22**	88[g]	71[h]
4	 **3.16**	55[d,f]	81
5	 **3.15**	-[e]	93

6	 **3.17**	-[e]	80

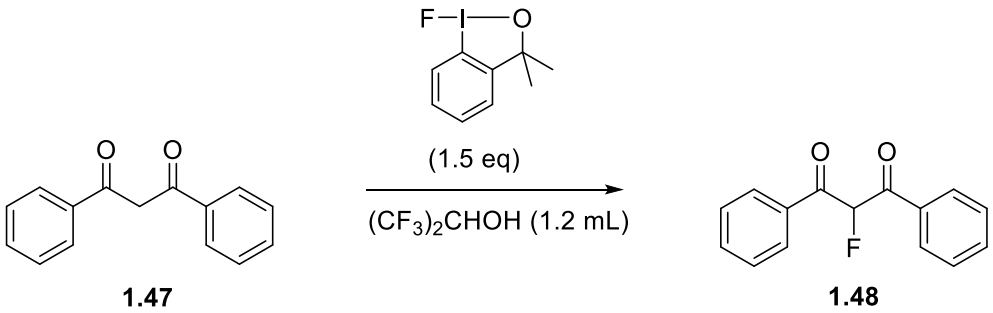
[a] Reaction conditions (0.72 mmol), fluoroiodane **1.61** (1.44 mmol), $Et_3N.3HF$ (1.94 mmol) and dry CH_2Cl_2 (1.2 mL) at 40 °C for 24 h; [b] Isolated yield; [c] Reaction conditions: substrate (0.72 mmol), fluoroiodane **1.61** (1.08 mmol) and HFIP (1.2 mL) at 60 °C for 4 h; [d] Result taken from ref 10; [e] Not part of original study; [f] 60 °C for 48 h; [g]Result taken from reference 21; [h] RT for 1 h.

3.6.4 Fluorination of 1,3-Diketones

Dibenzoylmethane was fluorinated using 1-fluoro-3,3-dimethyl-1,3-dihydro-λ^3-benzo[*d*][1,2]iodoxole (1.5 equivalents) in HFIP at 60 °C for 4 hours (Table 3.8, entry 1) and a 95 % consumption of starting material was achieved. Evidence of the monofluorinated product was observed by ^{19}F NMR spectroscopy with a singlet at -186.8 ppm and a very minor peak at -102.6 ppm corresponding to the difluorinated product. After column chromatography, the product was unable to be separated. The ^1H NMR spectrum of the crude reaction showed the presence of multiple products being formed. Despite lowering the temperature to 40 °C in entry 2, the product was still unable to be isolated.

The reaction was then conducted under much milder conditions, at room temperature for 4 hours and 1 hour. Although there was evidence of the monofluorinated product being formed, it unfortunately degraded during purification by column chromatography. The reaction was performed at 0 °C for 1 hour and the crude ^1H NMR spectrum showed a 51 % conversion to the monofluorinated product **1.48**. However, the reaction was not clean and this may be due to the degradation of dibenzoylmethane (entry 5). Furthermore, dibenzoylmethane exists as the enol tautomer, which is the reactive part of the 1,3-diketone, and this could have accelerated background reactions or decomposition.

Table 3.8 *Fluorination of dibenzoylmethane*



1.47 **1.48**

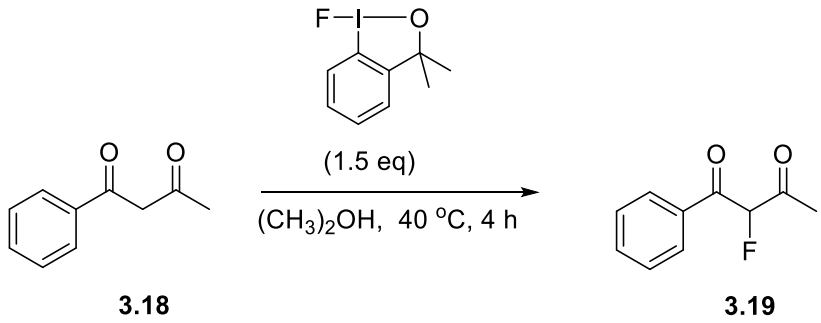
Entry	Solvent	Temperature (°C)	Time (h)	Conversion[a] (%)
1[b]	$(CF_3)_2CHOH$	60	4	95 (0)
2[b]	$(CF_3)_2CHOH$	40	4	95 (0)
3[b]	$(CF_3)_2CHOH$	RT	4	95
4[b]	$(CF_3)_2CHOH$	RT	1	95 (0)
5[c]	$(CF_3)_2CHOH$	0	1	51
6[c]	CH_2Cl_2[d]	RT	4	52
7[c]	CH_2Cl_2[d]	RT	1	44
8[c]	CH_3CN	RT	20	10
9[c]	CH_3CN	40	20	13
10[c]	CF_3CH_2OH	-20	1	2

[a]Isolated yield in parenthesis; [b]Conversion denoted by the consumption of starting material; [c] Conversion denoted by formation of product; [d]HFIP (5 equivalents).

In order to slow the reaction down, the reaction was repeated using dichloromethane as the solvent, with 5 equivalents of HFIP to activate, 1-fluoro-3,3-dimethyl-1,3-dihydro-λ^3-benzo[*d*][1,2]iodoxole (1.5 equivalents) at room temperature for 4 hours (entry 6). A 52 % conversion was achieved but multiple by-products were still being formed. The reaction was repeated at room temperature for 1 hour and a lower 44 % conversion was

achieved with no improvement in the selectivity of the reaction to form the monofluorinated product and **1.48** was unable to be recovered following purification. Acetonitrile and trifluoroethanol were also investigated as the solvent but these reactions only gave low conversions to monofluorinated product (entries 8-10).

Unfortunately, the fluorination of dibenzoylmethane was unsuccessful due to the high reactivity of the starting material and its susceptibility to degradation. Despite altering the solvent, reaction times and temperature the reaction was not clean and the monofluorinated product was not isolated.



Scheme 3.18 *Optimisation of the fluorination of 1-phenylbutane-1,3-dione*

1-Phenylbutane-1,3-dione was also fluorinated using 1-fluoro-3,3-dimethyl-1,3-dihydro-λ^3-benzo[*d*][1,2]iodoxole (1.5 equivalents) in hexafluoroisopropanol and the reaction was carried out at 40 °C for 4 hours (Scheme 3.18). The ^{1}H NMR spectrum of the crude product showed a 95 % consumption of starting material, and there was evidence of the desired fluorinated product **3.19** in the ^{19}F NMR spectrum at – 189.4 ppm (keto) and – 169.9 ppm (enol) but multiple products were formed. Consequently, the product could not be isolated following purification by column chromatography. The reaction was repeated under milder reaction conditions, at room temperature for 1 hour. The ^{1}H NMR spectrum of the crude product showed 95 % consumption of starting material but the reaction was very messy due to the presence of multiple by-products and there was no evidence of the monofluorinated product **3.19** being formed.

3.6.5 HFIP Mechanistic Studies

3.6.5.1 NMR Investigation into the Activation of 1-Fluoro-3,3-dimethyl-1,3-dihydro-λ^3-benzo[*d*][1,2]iodoxole by Hydrogen Bonding to 1,1,1,3,3,3-Hexafluoroisopropanol

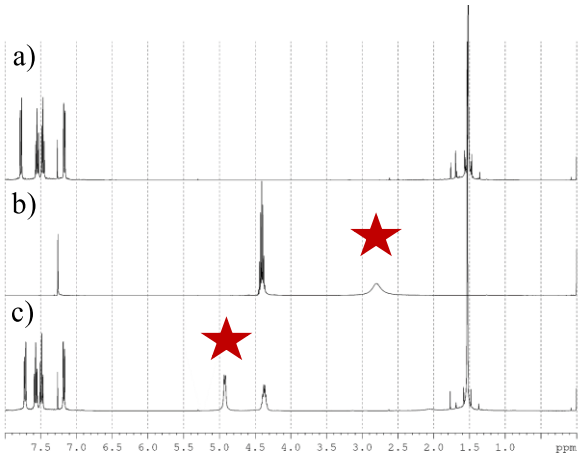
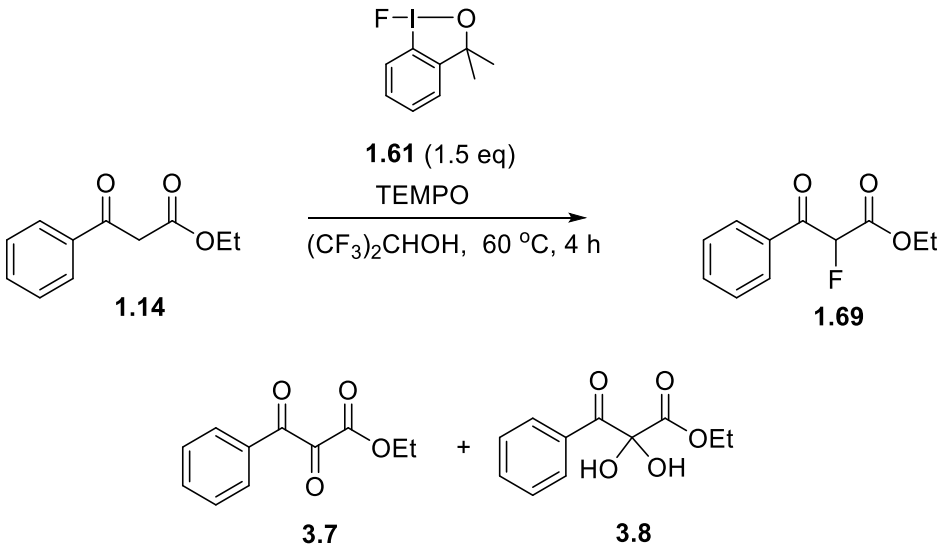


Figure 3.1 ^{1}H NMR spectra of (a) fluoroiodane **1.61**, (b) HFIP and (c) a 1:1 mixture of fluoroiodane:HFIP, showing a plausible structure of an adduct. The deshielded OH signal is indicated by the red star.

An investigation into the mechanism of the fluorinations using HFIP was conducted in the Stuart group by William Riley.[15] Employing the use of ^{1}H, ^{13}C and ^{19}F NMR spectroscopy, the spectra for a) fluoroiodane, b) HFIP and c) a 1:1 mixture of fluoroiodane: HFIP were recorded (Figure 3.1). The ^{1}H NMR spectra of the c) 1:1 mixture of HFIP: fluoroiodane showed a downfield shift in the OH singlet from 2.80 ppm in b) HFIP, to 4.92 ppm in the 1:1 mixture. The broad OH singlet observed for HFIP changed to a doublet in the 1:1 mixture of HFIP: fluoroiodane, with a $^{3}J_{HH}$ coupling constant of 7.5 Hz. The doublet was due to the OH proton coupling to the adjacent CH proton in HFIP. This downfield shift for the OH proton provided evidence for the formation of a 1:1 adduct between fluoroiodane and HFIP, as a result of hydrogen bonding. The ^{19}F NMR spectrum of the 1:1 adduct showed broadening of the singlet at -143.0 ppm which is not present in the ^{19}F NMR spectrum of fluoroiodane and also gave evidence for hydrogen bonding occurring.[14] It is therefore proposed that the fluoroiodane reagent is activated by hydrogen bonding to the OH proton within HFIP and this resulted in elongation of the I-F bond, making the iodine more electropositive.

3.6.5.2 TEMPO Studies

Table 3.9 *Mechanistic investigation using TEMPO*



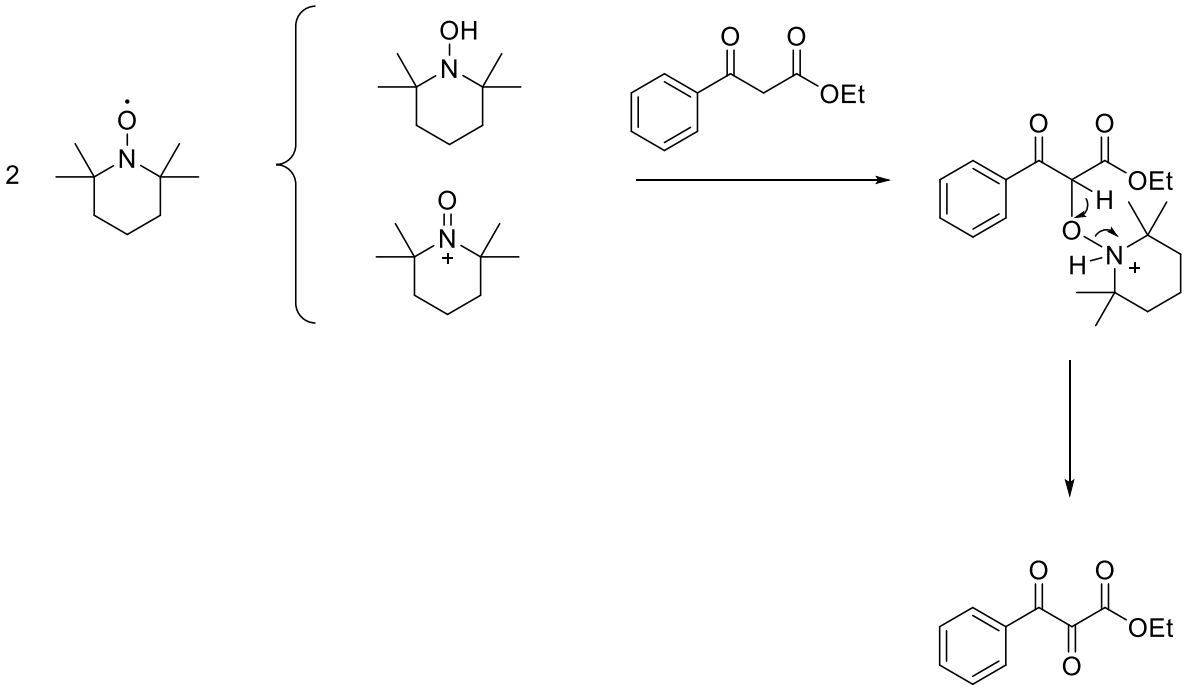
Entry	TEMPO (eq)	Conv. to 1.69[a] (%)	Conv. to 3.7[a]	Conv. to 3.8[a] (%)
1	0.1	87 (70)	3 (0)	3 (0)
2	1	11 (11)	22 (8)	57 (70)
3[b]	1	0	0 (4)	42 (16)

[a] Isolated yields in parenthesis; [b] No fluoroiodane, **1.61**.

In order to glean whether the mechanism for fluorination was proceeding through a radical based mechanism, TEMPO was employed as a radical trap. Ethyl 3-oxo-3-phenylpropanoate was reacted with **1.61** in HFIP at 60 °C for 4 hours in the presence of TEMPO (0.1 equivalent). An 87 % conversion to the monofluorinated product **1.69** was achieved and a 70 % yield was obtained following purification by column chromatography, which is a very similar result to the 73 % yield obtained in the absence

of TEMPO. There was no evidence of a TEMPO-bound adduct which indicated that the reaction was not proceeding through a radical based mechanism.

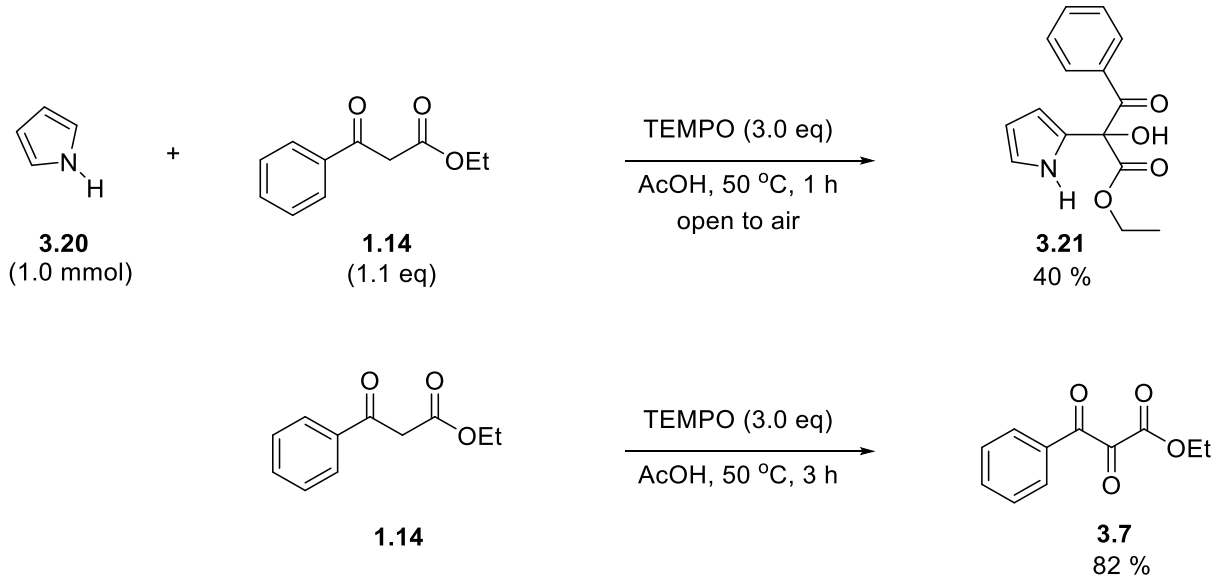
The reaction was then repeated using 1 equivalent of TEMPO and an 89 % consumption of starting material was achieved. After purification by column chromatography, the monofluorinated product **1.69** was isolated in only a 11 % yield, along with 70 % of the dihydroxylated product **3.8** and 8 % of the tricarbonyl product **3.7**. This result showed that TEMPO promoted the oxidation of the 1,3-dicarbonyl compound. The reaction was also carried out using 1 equivalent of TEMPO in the absence of fluoroiodane and the ^{1}H NMR spectrum of the crude product showed a 42 % conversion to the dihydroxylated product **3.8** only. Following purification by column chromatography, 16 % of the dihydroxylated product was isolated with 4 % of the tricarbonyl product. This result showed that the hypervalent 1-fluoro-3,3-dimethyl-1,3-dihydro-λ^3-benzo[*d*][1,2]iodoxole reagent promoted the oxidation of the 1,3-dicarbonyl compound in the presence of TEMPO as a lower conversion to the oxidation products was obtained in the absence of **1.61**.



Scheme 3.19 *Proposed mechanism*

A plausible mechanism for this system involves the generation of a *N*-oxopiperidinium ion and *N*-hydroxypiperidine (TEMPOH) under acidic conditions (Scheme 3.19). The

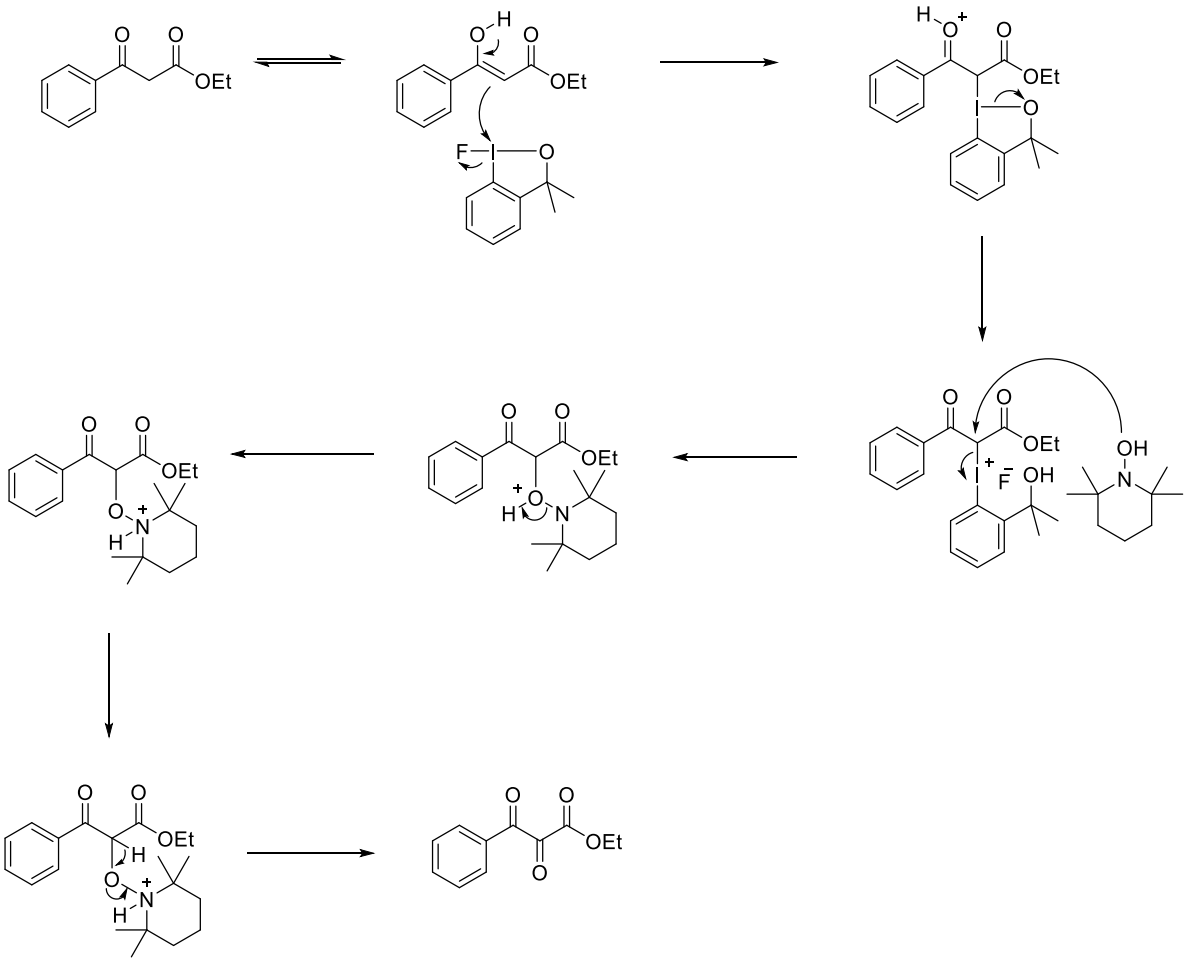
substrate then forms an adduct upon reacting with the *N*-oxopiperidinium ion. Deprotonation of the α-proton leads to the loss of tetramethylpiperidine to form the vicinal tricarbonyl product.[16, 17]



Scheme 3.20 *TEMPO mediated oxidation*

Zhang *et al.* reported the reaction of indoles and pyrroles with 1,3-dicarbonyl compounds, in which a vicinal tricarbonyl compound **3.7** was generated *in situ* due to the presence of TEMPO, affording indole substituted tertiary alcohols **3.21**. Using pyrrole as an example, the oxidation of ethyl 3-oxo-3-phenylpropanoate was conducted using TEMPO, acetic acid at 50 °C for 1 hour generating an oxidised acylated product, which was also applied to a series of indoles (Scheme 3.20). The reaction was conducted in the absence of pyrrole for 3 hours and an 82 % conversion to the tricarbonyl was obtained.[12]

The observation of the acceleration of the formation of a vicinal tricarbonyl product as a result of the hypervalent iodine reagent **1.61**, could proceed by the enol of ethyl 3-oxo-3-phenylpropanoate reacting at the electropositive iodine, displacing fluoride. Ring opening of the intermediate followed by proton transfer generated the iodonium fluoride which undergoes nucleophilic attack from the oxygen of *N*-hydroxypiperidine to displace 2-(2-iodophenyl)propan-2-ol. A proton transfer followed by deprotonation of the α-proton leads to the loss of tetramethylpiperidine to form the vicinal tricarbonyl product **3.7** (Scheme 3.21). Hypervalent iodine mediated oxidations with TEMPO have been demonstrated within the literature.[16, 18, 19, 20]



Scheme 3.21 *Proposed mechanism*

3.7 Conclusions and Future Work

A catalytic procedure was developed for the chlorination of 1,3-ketoesters using 20 mol % of 2-(2-iodophenyl)propan-2-ol. A small series of 1,3-ketoesters were successfully chlorinated under mild reaction conditions and short reaction times in very good yields (73-76 %).

The tosyloxylation of ethyl 3-oxo-3-phenylpropanoate was carried out using 20 mol % of 2-(2-iodophenyl)propan-2-ol to give the monotosyloxylated product. Unfortunately, hydrolysis of the tosyloxylated product was a problem in this reaction and during the purification of the product on silica gel to form α-(tosyloxy)acetophenone.

HFIP is an excellent solvent for promoting the fluorination of 1,3-carbonyl compounds using fluoroiodane. ^{1}H NMR studies provided evidence for the formation of a hydrogen bonding adduct between fluoroiodane and HFIP. This validated our proposal that HFIP could be used to activate fluoroiodane by hydrogen bonding and promote fluorination. A range of 1,3-ketoesters and 1,3-ketoamides were fluorinated in good to excellent yields, under mild reaction conditions using fluoroiodane and importantly, without the need for $Et_3N.3HF$.

3.8 References for Chapter 3

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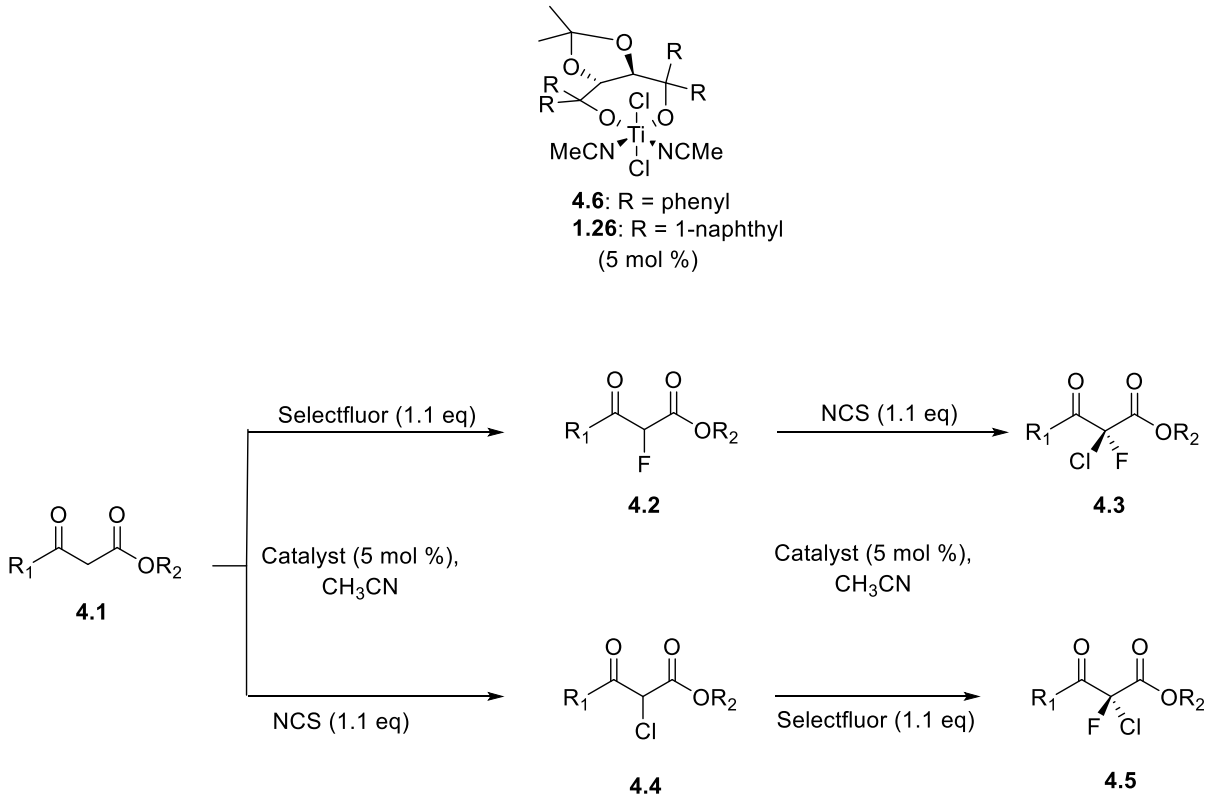
Chapter 4 Enantioselective Chlorination of 1,3-Dicarbonyl Compounds

4.1 Enantioselective Chlorinations

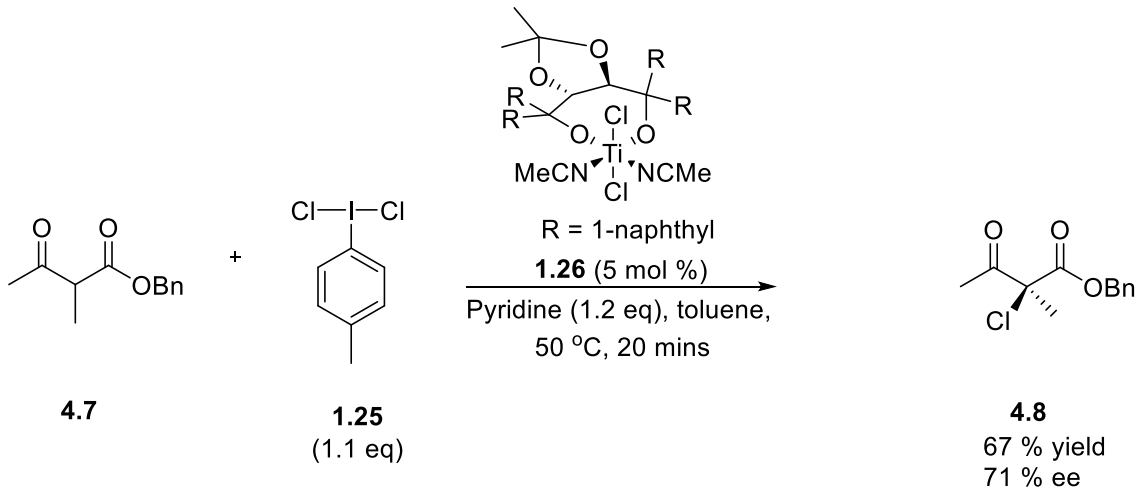
4.1.1 Metal-Catalysed Enantioselective Chlorinations

The importance of the α-halogenation of 1,3-dicarbonyl compounds stems from their usefulness as intermediates for building blocks in organic synthesis and for modern drug discovery. In 2003 Togni and coworkers pioneered the chlorination of 1,3-dicarbonyl compounds.[1] A one-pot titanium catalysed stereoselective fluorination and chlorination of 1,3-dicarbonyl compounds was developed using *R,R*-[$TiCl_2$(TADDOLato)] **4.6** or **1.26** with Selectfluor and *N*-chlorosuccinimide (NCS) in acetonitrile (Scheme 4.1). Interestingly, varying the order of addition of the halogenating agents determined the chiral induction. The (*S*) enantiomer was generated when first fluorinating with Selectfluor and then chlorinating using NCS, and the (*R*) enantiomer was obtained following the chlorination then fluorination sequence. Moderate to good yields (45-80 %) of the α-chloro-α-fluoro-*β*-ketoesters was achieved with moderate enantiomeric excess (24-65 % ee) of the acyclic products.

In 2004 Togni *et al.* expanded on their work with [$TiCl_2$(TADDOLato)] complexes and carried out the catalytic asymmetric chlorination of 1,3-dicarbonyl compounds with (dichloroiodo)toluene (Scheme 4.2).[2] A range of acyclic 1,3-dicarbonyl compounds were chlorinated using the *R,R*-[$TiCl_2$(TADDOLato)] complex **1.26** and (dichloroiodo)toluene **1.25** in toluene which gave the chlorinated products in good yields (37-83 % yields) but with low to good enantiomeric excess (< 10 – 71 % ee).[2] No examples of the chlorination of cyclic *β*-ketoesters were reported using this method.



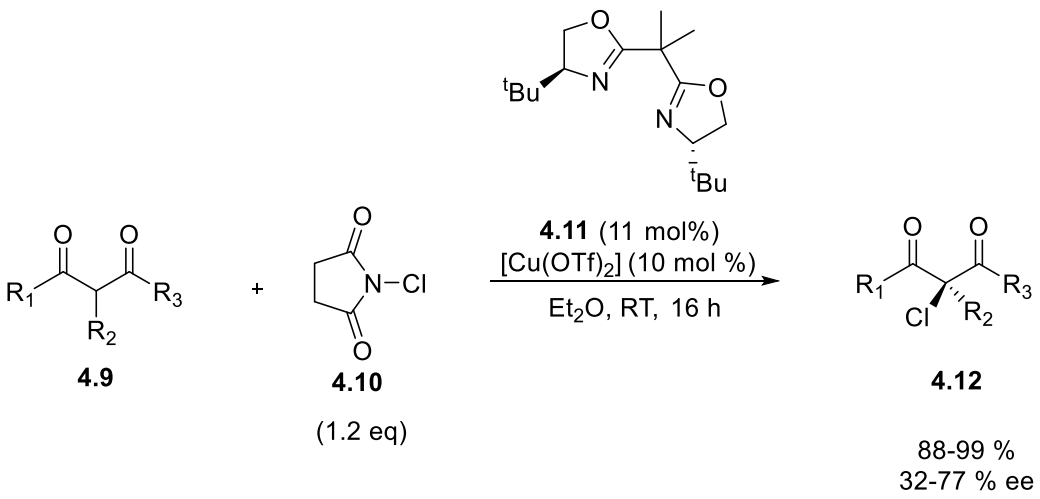
Scheme 4.1 *Stereoselective tandem chlorination and fluorination of 1,3-dicarbonyl compounds*[1]



Scheme 4.2 *Stereoselective chlorination of 1,3-dicarbonyl compounds using (dichloroiodo)toluene and [TiCl*$_2$*(TADDOLato)]*[2]

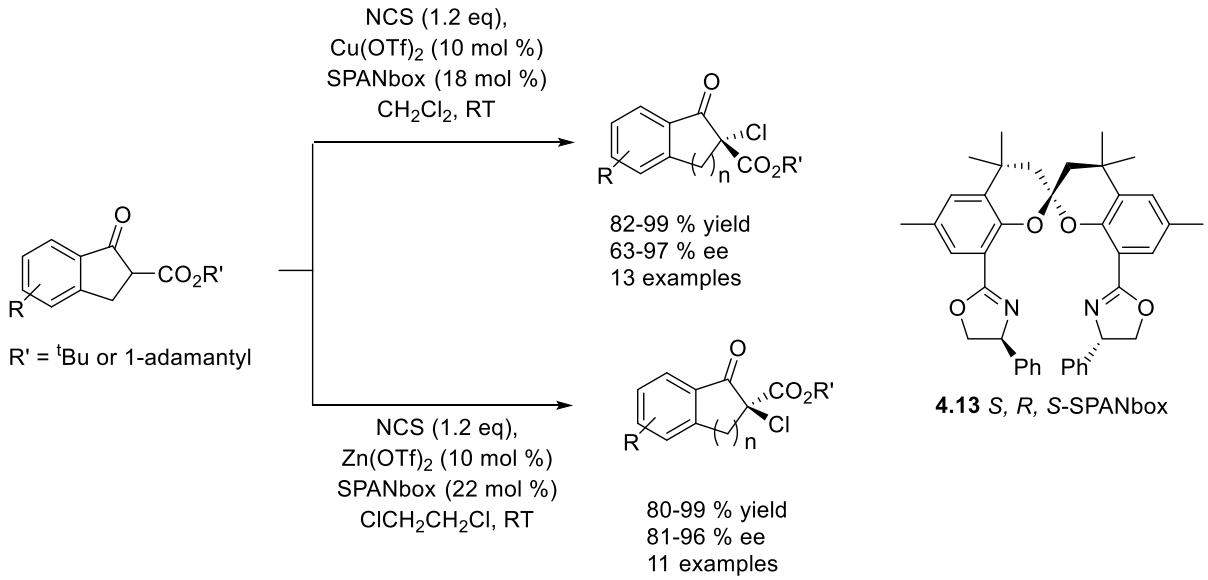
The application of Lewis acid catalysts for the chlorination of *β*-ketoesters was investigated further. Jorgensen and coworkers reported the asymmetric chlorination of 1,3-dicarbonyl compounds with NCS, catalysed by chiral bisoxazoline copper(II) complexes (Scheme 4.3). This work was promising because high yields (88-99 %) and

good enantiomeric excesses (32-77 %) were obtained with both cyclic and acyclic 1,3-dicarbonyl substrates.



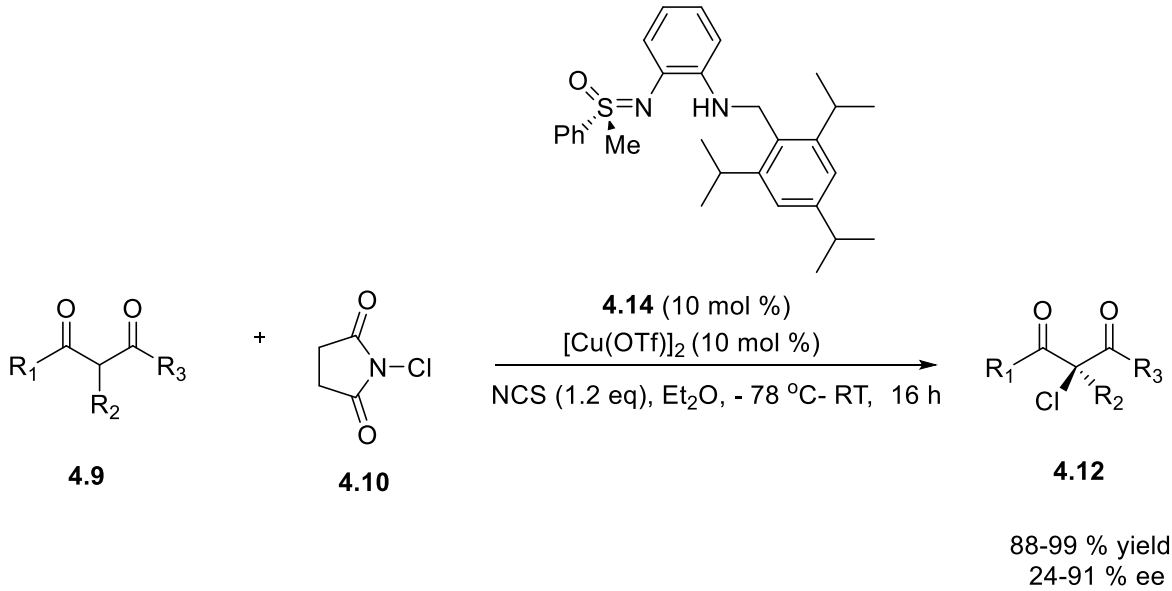
Scheme 4.3 *Chlorination of 1,3-dicarbonyl compounds using [Cu(OTf)$_2$\{(S)-^{t}Bu-BOX\}] and N-chlorosuccinimide*[3]

Bisoxazoline ligands were also used by Ding and coworkers for the chlorination of 1,3-dicarbonyl compounds. Copper and zinc complexes of spiro-2,2'-bichroman-based bisoxazoline ligand (SPANbox) **4.13** were synthesised and used in a catalytic amount to chlorinate cyclic *β*-ketoesters in high yields and good to high enantiomeric excesses (Scheme 4.4).[4] Shibata and coworkers used a similar phenyl bisoxazoline ligand with a nickel catalyst, $Ni(ClO_4)_2.6H_2O$. A small series of 7 cyclic substrates afforded good yields (61-93 %) and good to high enantiomeric excesses (60-98 %).[5]



Scheme 4.4 *Chlorination of β-ketoesters using SPANbox*[4]

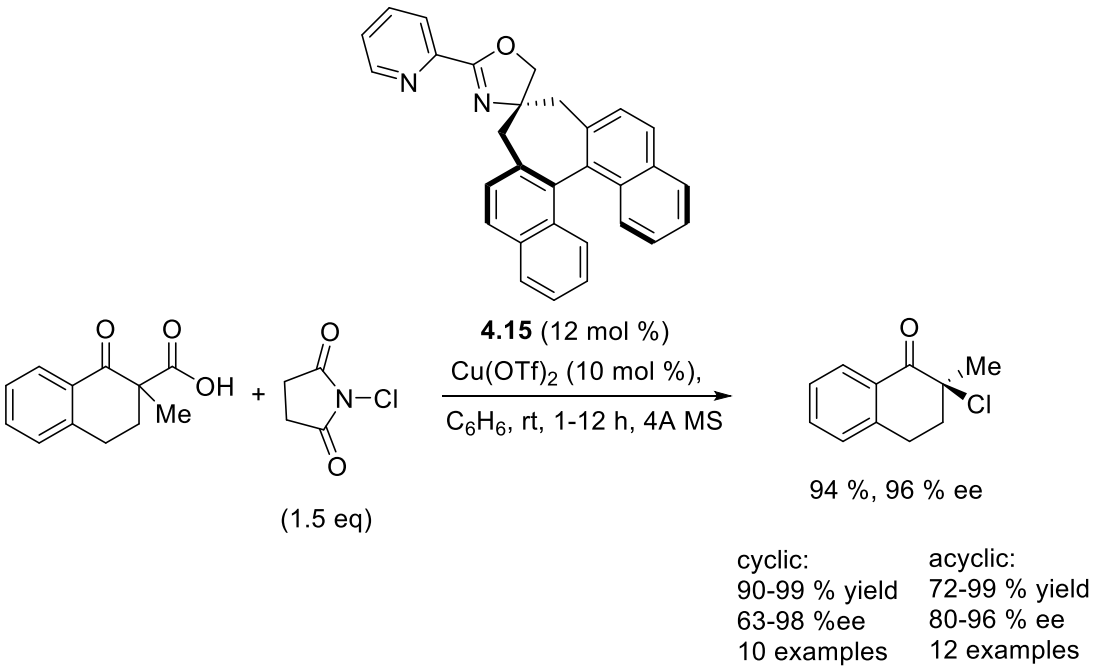
The enantioselective chlorination of 1,3-dicarbonyl compounds using a C_1 chiral sulfoximine-copper complex was reported by Bolm and coworkers (Scheme 4.5).[6] Using $Cu(OTf)_2$, NCS and the chiral sulfoximine *(S)*-**4.14** in diethyl ether gave the corresponding chlorinated products in high 88-99 % yields and moderate to high enantioselectivities (24-91 % ee).[6]



Scheme 4.5 *Chiral sulfoximine (S)-**4.14** catalysed enantioselective chlorination*[6]

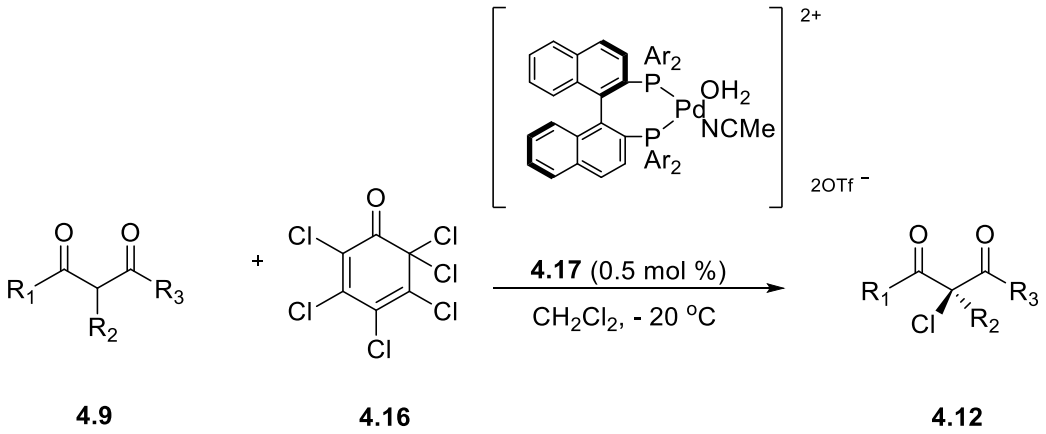
Other examples of asymmetric chlorination include the Lewis acid Cu(I) catalysed chlorination of acyclic 1,3-dicarbonyl compounds using chiral phosphine-Schiff base

type ligand (10 mol %) with $[Cu(OTf)]_2$. The chlorinated products were obtained in very good yields, with 10 acyclic products affording a 78-99 % yield with 50-82 % enantiomeric excesses and three examples of chlorination of cyclic substrates with good to excellent yields (63-99 %) but with low enantiomeric excesses (12-34 % ee).[7]



Scheme 4.6 *Enantioselective chlorination of carbonyl compounds using a chiral pyridyl spirooxazoline ligand (SPYMOX)*[8]

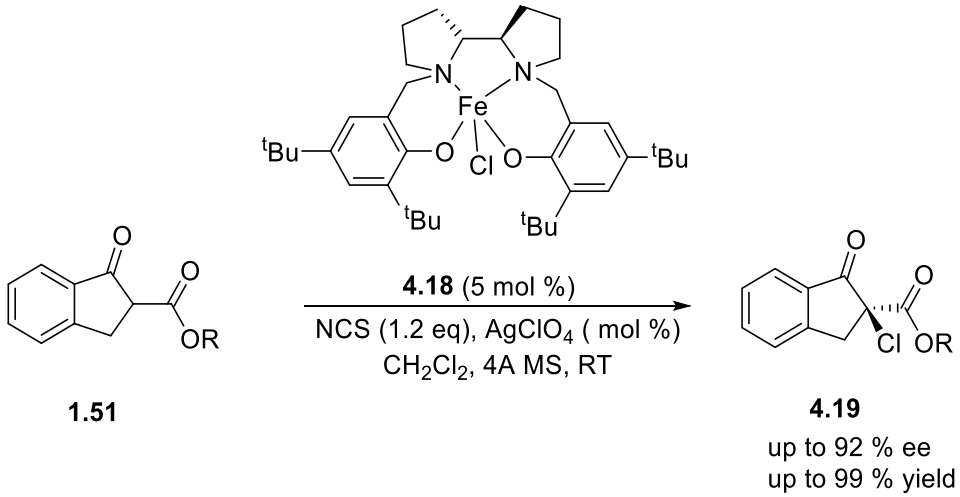
Pyridyl spirooxazoline ligands (SPYMOX) **4.15** have also been explored for the chlorination of carbonyl compounds (Scheme 4.6). Iwasa and coworkers synthesised a spirooxazoline ligand with a quinoline backbone, to induce higher enantioselectivities due to the steric repulsion between the substrate and the introduced benzene ring, in order to push the reaction site closer to the binaphthyl backbone, which did afford a higher enantioselectivity. The acyclic and cyclic chlorinated carbonyl compounds were obtained in high 72-99 % yields with good to high 63-98 % enantiomeric excesses. In the case of more challenging substrates including a cyanoacetate and *β*-ketophosphonates poor enantioselectivities (0-37 % ee) were achieved.[8]



4.9 **4.16** **4.12**

Scheme 4.7 *Enantioselective chlorination of cyclic 1,3-dicarbonyl compounds using chiral palladium(II) complexes*[9]

Other metal complexes have been explored for the chlorination of 1,3-dicarbonyl compounds including palladium and iron complexes. The chiral palladium complex **4.17** was used to chlorinate a cyclic and acyclic *β*-ketoesters by Kang and coworkers (Scheme 4.7). The cyclic ketoesters were obtained in excellent yields (92-95 %) and high enantiomeric excesses (87-92 %) with a *tert*-butyl group ester group and lower enantiomeric excesses for the products with an ethoxy group (60 % ee) and methoxy group (27 % ee) with low catalytic loading (0.5 mol %).[9] The Iron(III)-BP salan complex **4.18** could only chlorinate cyclic substrates but in high yields (81-99 %) and high enantioselectivities (48-92 % ee).[10]

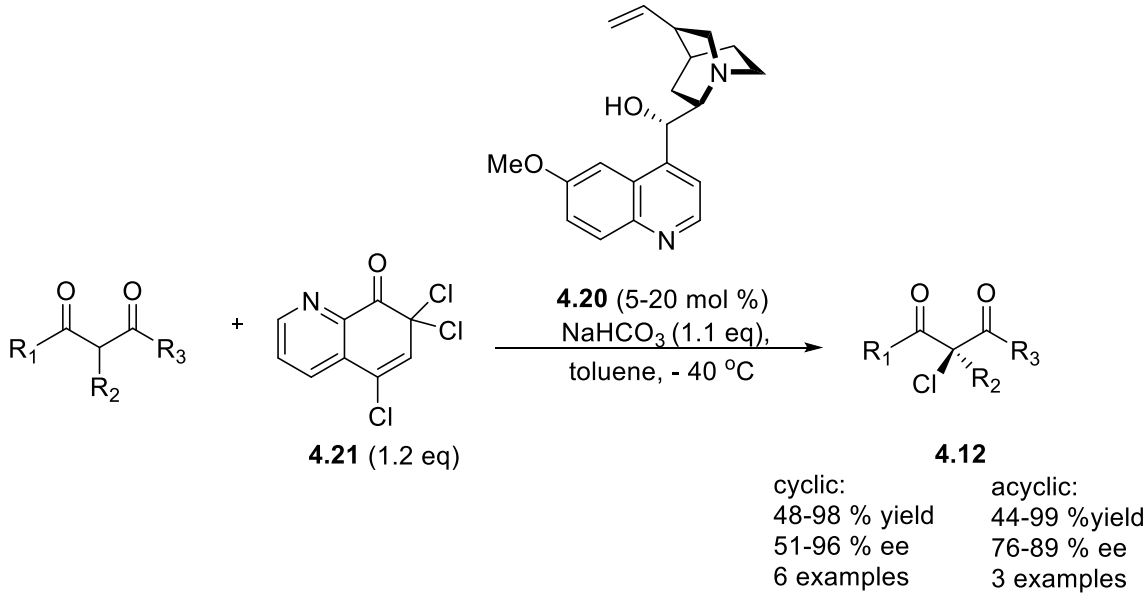


Scheme 4.8 *Asymmetric chlorination of cyclic 1,3-dicarbonyl compounds catalysed by Iron(III)-BPsalan complexes*[10]

Spymox **4.15** and SPANbox **4.13** were effective in the chlorination of 1,3-dicarbonyl compounds. Spymox **4.15** enabled acyclic and cyclic chlorinated products to be accessed, but required argon conditions for its synthesis. SPANbox could only be applied to cyclic 1,3-ketoesters. Che *et al.* were able to afford chlorinated 1,3-dicarbonyl compounds in high yields (81-99 %) and reasonably high enantioselectivity (48-92 % ee) but these reactions required an argon atmosphere (Scheme 4.8).

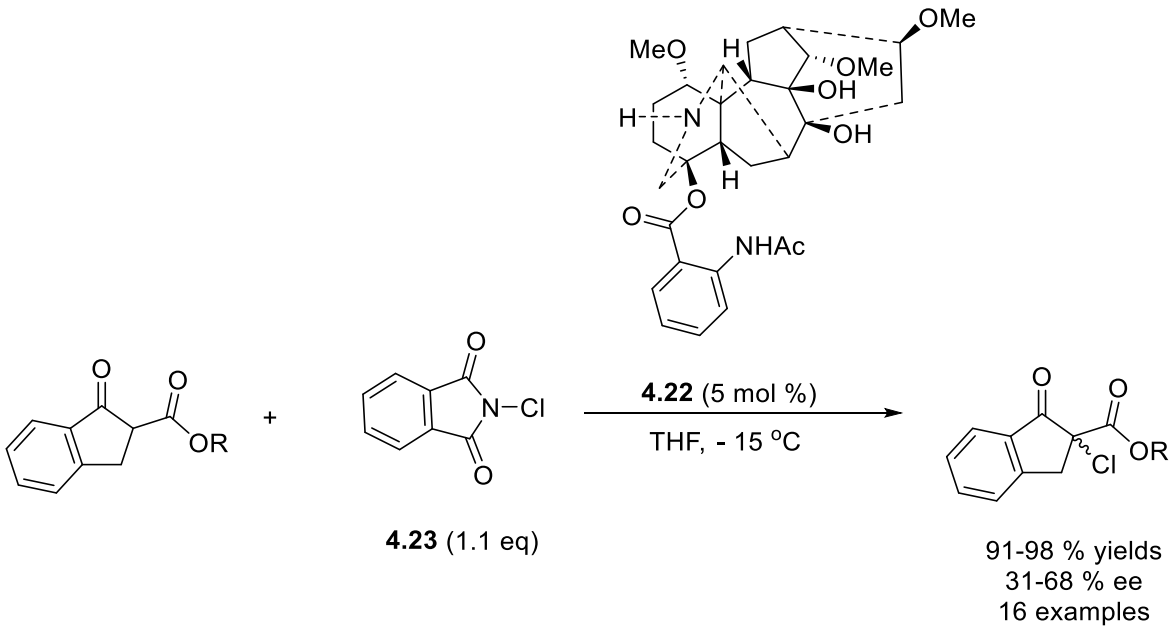
4.1.2 Organocatalysed Enantioselective Chlorinations

Alternatively, an organocatalytic approach can be used for the enantioselective chlorination of 1,3-dicarbonyl compounds. In 2005 Sambri and coworkers reported the first organocatalytic chlorination of 1,3-dicarbonyl compounds using a cinchona alkaloid derivative (Scheme 4.9).[11] The chinchona alkaloid derivative **4.20** acted as a chiral base to generate the enolate before halogenation using polyhalogenated quinolinones. The chlorination of the substrates was carried out using benzoylquinidine as the catalyst with sodium hydrogen carbonate. The corresponding cyclic and acyclic products were achieved in moderate to high yields (44-99 %) and moderate to high enantiomeric excesses (51-96 %).[11]

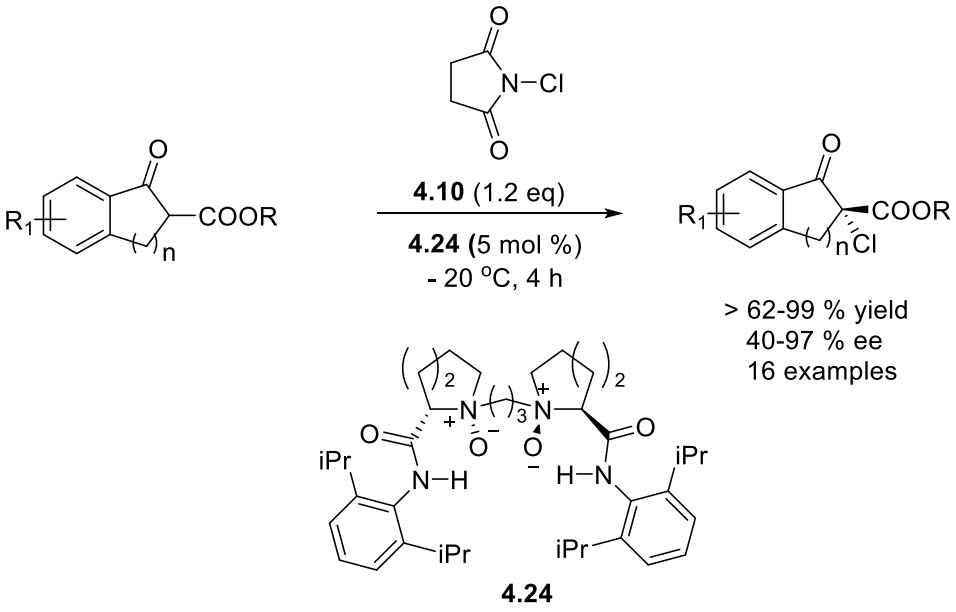


Scheme 4.9 *Enantioselective chlorination of 1,3-dicarbonyl compounds using a cinchona alkaloid derivative*[11]

The use of diterpenoid alkaloid derivatives for enantioselective chlorination was reported by Gao and coworkers (Scheme 4.10). Using **4.22** (5 mol %) and **4.23** as the chlorine source in THF, the cyclic products were achieved in high yields (91-98 %) but moderate enantiomeric excesses (31-68 %).[12] In 2010 Feng and coworkers reported the highly enantioselective α-chlorination of cyclic 1,3-dicarbonyl compounds using an *N,N'*-dioxide organocatalyst **4.24** derived from (*S*)-pipecolic acid (Scheme 4.11). The chlorinated products were afforded mostly in excellent yields of up to 99 % and up to 98 % enantiomeric excesses with 16 examples.[13] This methodology was extremely efficient and high yielding, but a limiting factor was the method only worked well with cyclic substrates.



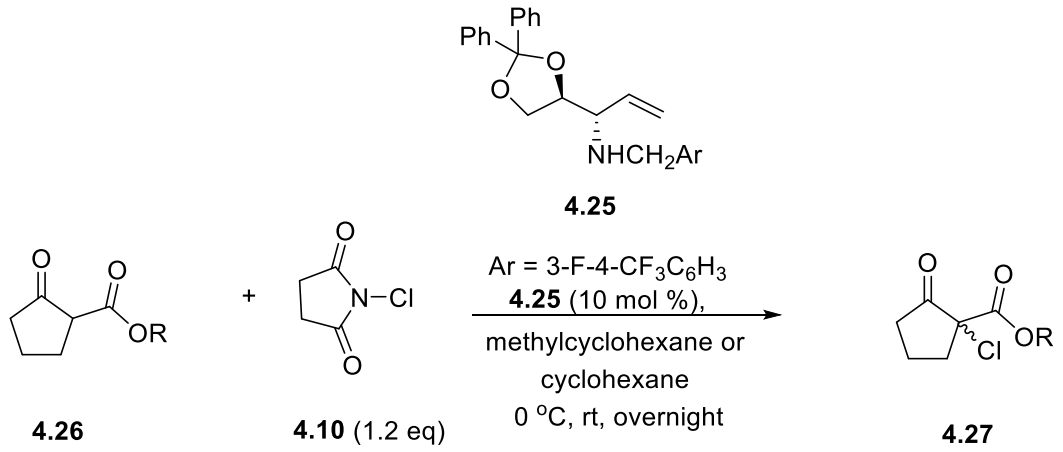
Scheme 4.10 *α-Chlorination of 1,3-dicarbonyl compounds using chiral diterpenoid alkaloid derivatives*[12]



Scheme 4.11 *Enantioselective α-chlorination of cyclic 1,3-dicarbonyl compounds using an N,N'-dioxide organocatalyst*[13]

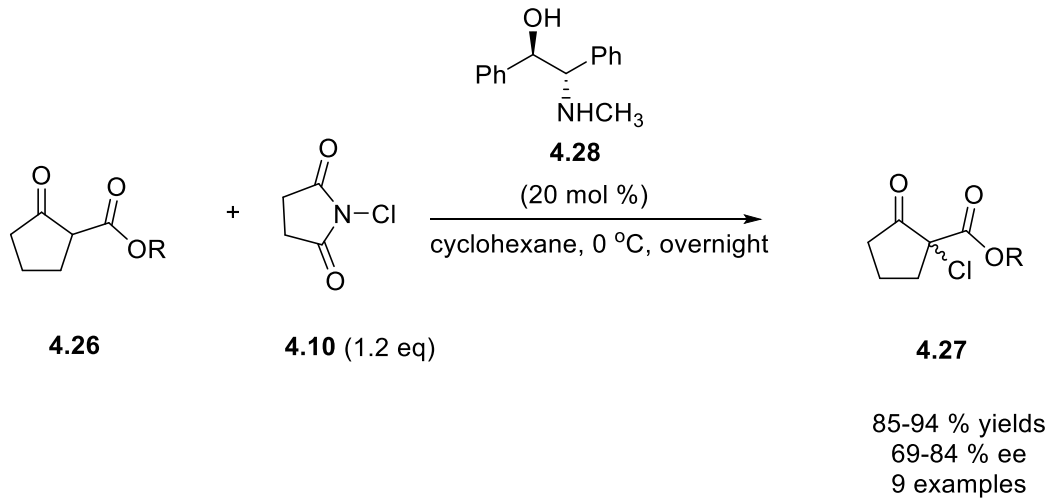
Galvez *et al.* developed a new approach for the enantioselective chlorination of 1,3-dicarbonyl compounds using chiral amino diol derivatives as the organocatalyst (Scheme 4.12). The chiral amino diol **4.25** and NCS **4.10** were used to chlorinate cyclic *β*-ketoesters in high yields (71-99 %) and good to excellent enantiomeric excesses (84-96

% ee).[14] Bulkier isopropyl groups were tolerated as the ester functionality. Acyclic substrates were not investigated using this methodology.



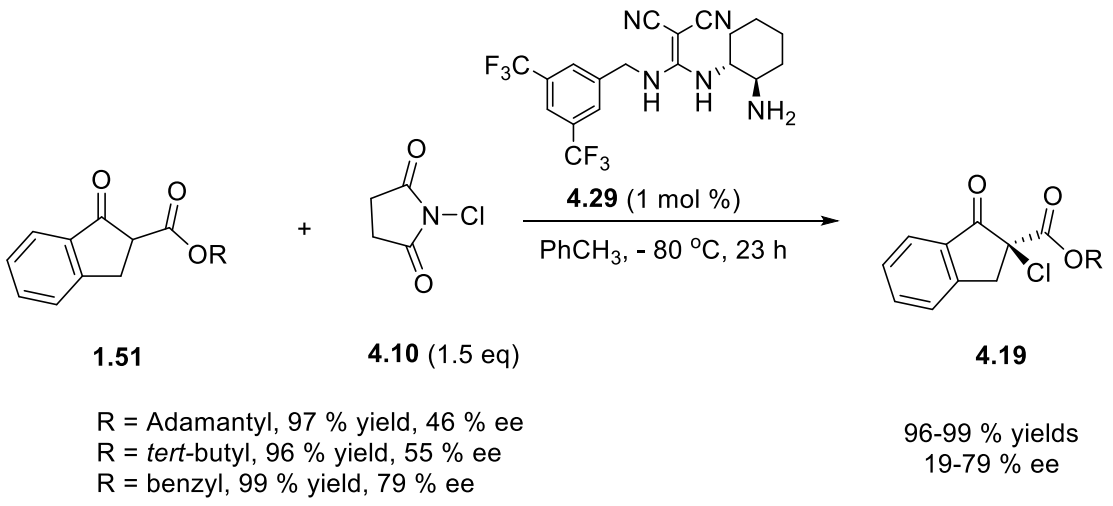
Scheme 4.12 *Enantioselective chlorination of 1,3-dicarbonyl compounds employing chiral amino diol derivatives*[14]

Other interesting examples of the α-chlorination of 1,3-dicarbonyl compounds include the use of commercially available chiral 2-amino alcohol derivatives by Li *et al.* (Scheme 4.13). Using a catalytic amount of the chiral 2-amino alcohol **4.28** (20 mol %) and NCS in cyclohexane, the cyclic products were obtained in high yields (85-94 %) and good enantiomeric excesses (69-84 %).[15] This methodology was not applied to acyclic substrates. Alonso and coworkers reported the chlorination of 1,3-dicarbonyl compounds using NCS and 2-aminobenzimidazole derivatives, which afforded the cyclic chlorinated products in high yields (92-99 %) but only poor enantiomeric excess (5-50 %).[16]

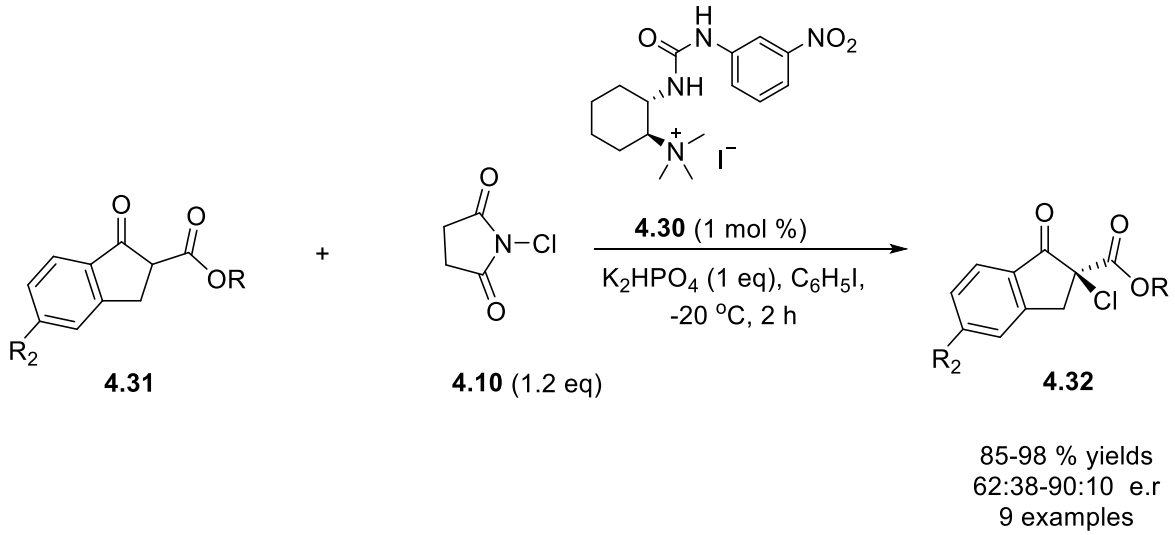


Scheme 4.13 *α-Chlorination of 1,3-dicarbonyl compounds using a chiral 2-amino alcohol derivative*[15]

Additional examples include Muira and coworkers who conducted the catalytic chlorination of 1,3-dicarbonyl compounds facilitated by diaminomethylenemalonitrile (DMI) as an organocatalyst **4.29**. The use of the DMI organocatalyst (1 mol %), with NCS as the chlorine source delivered the α-chlorinated cyclic 1,3-dicarbonyl compounds in high yields (96-99 %) but in moderate to good enantiomeric excesses (19-79 % ee) (Scheme 4.14). The acyclic product was obtained in a low yield and the enantiomeric excess was not determined. Bulkier ester groups were investigated including an adamantyl group, benzyl group and a *tert*-butyl group, which were tolerated but only the benzyl ester group afforded a good enantiomeric excess (79 % ee).[17] In 2016 Waser *et al.* conducted the α-chlorination of 1,3-dicarbonyl compounds using bifunctional ammonium salt catalysis (Scheme 4.15). Employing a chiral urea quarternary ammoniuim salt hybrid as the organocatalyst **4.30** (1 mol %) with NCS afforded the cyclic products in high yields (85-98 %) and moderate to high enantiomeric ratios (62:38 to 90:10).[18]

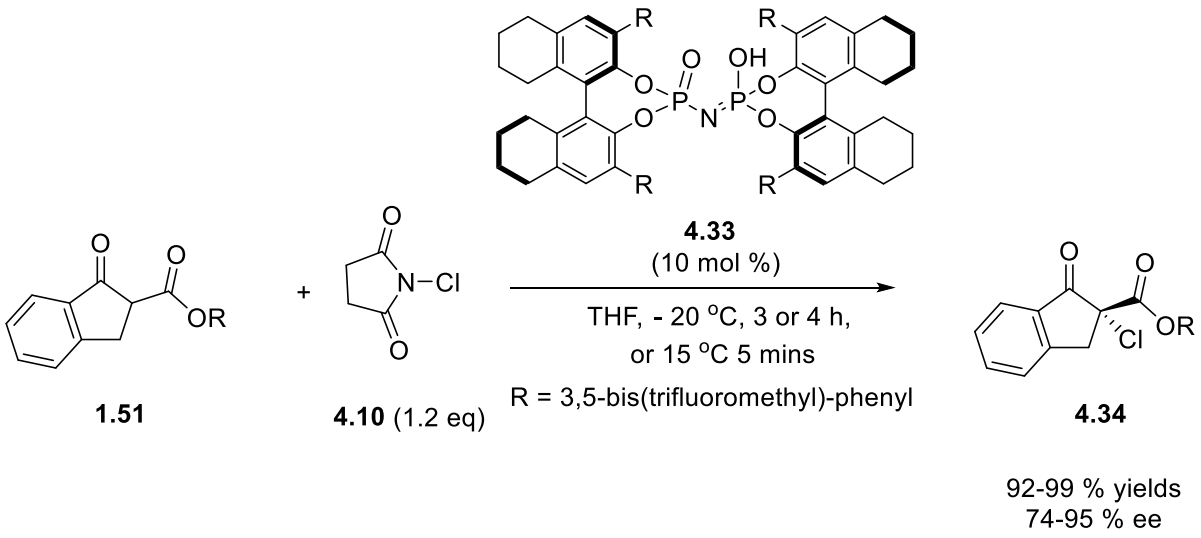


Scheme 4.14 *General scheme for the α-chlorination of 1,3-dicarbonyl compounds facilitated by diaminomethylenemalonitrile*[17]



Scheme 4.15 *2-Chlorination of 1,3-dicarbonyl compounds employing bifunctional ammonium salt catalysis*[18]

In 2018 Zhang *et al.* reported the first enantioselective α-chlorination of 1,3-dicarbonyl compounds using a chiral acid (Scheme 4.16). Using NCS and catalyst **4.33** (10 mol %), in THF afforded 18 cyclic chlorinated products in excellent yields (92-99 %) and good to high enantiomeric excesses (74-95 % ee).[19] Bulky substrates were tolerated and overall provided higher enantiomeric excesses.



Scheme 4.16 *Enantioselective α-chlorination of 1,3-dicarbonyl compounds using a chiral acid*[19]

The enantioselective chlorination of 1,3-dicarbonyl compounds has been widely explored using metal catalysts and organocatalysts. The drawbacks of these methods include the multistep synthesis of the catalyst and the complex catalyst structures. The transformation often requires high catalyst loading and complex sources of chloride, as well as requiring bulky ester units on the substrate to obtain high enantioselectivities. The chlorination of cyclic and acyclic substrates often cannot occur under the same reaction conditions. Hence, there is a drive for more efficient, mild and straightforward methodology for the enantioselective chlorination of 1,3-dicarbonyl compounds.

4.2 Chiral Hypervalent Iodine Reagents

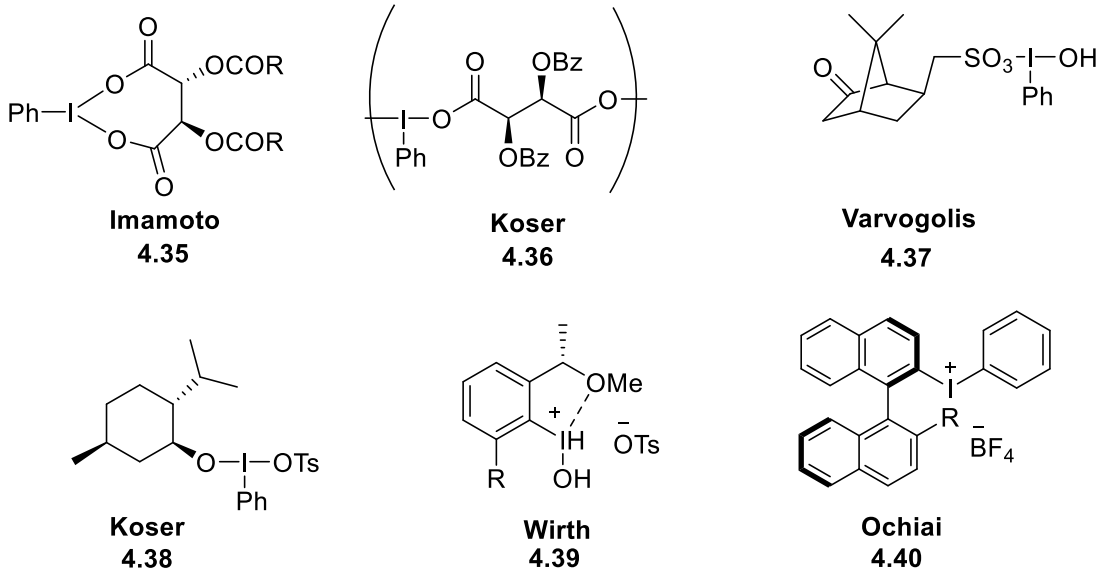
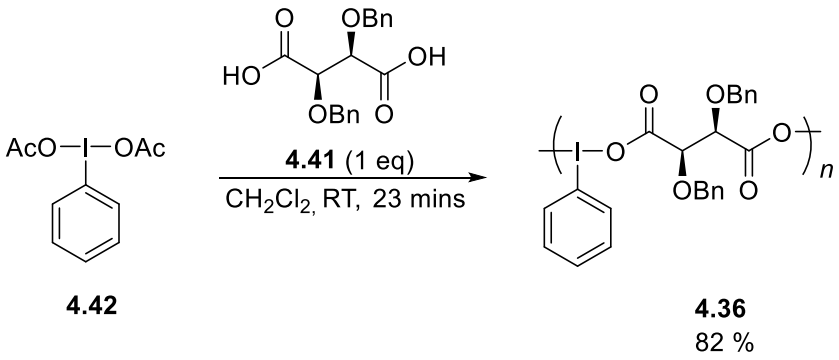
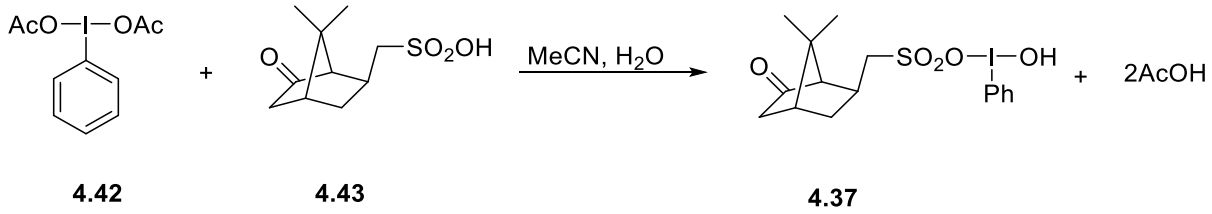


Figure 4.1 Chiral iodoarenes[20,21]

Current strategies for the synthesis of chiral hypervalent iodine reagents include using ligand exchange to attach chiral acids or alcohols to the iodine centre and the introduction of axial chirality through the iodoarene backbone (Figure 4.1). In 1986 Imamoto introduced a new class of chiral hypervalent iodine reagents, by reacting iodosylbenzene with derivatives of L-tartaric acid anhydrides in acetone at room temperature affording **4.35**.[22] These chiral λ^3-iodanes were used for the oxidation of sulfides to sulfoxides with moderate enantiomeric excesses (30-53 % ee). It was discovered that the chiral unit required C_2 symmetry to obtain good enantioselectivity in the direct α-((10-camphorsulfonyl)oxylation of various ketones and carbonyl compounds with an active methylene group.[23] Koser *et al.* also investigated the synthesis of chiral sulfoxides using chiral L-tartrate polymers **4.36**. The hypervalent iodine polymers were generated by reacting dibenzoyl-L-tartaric acid **4.41** with bis(acetoxyiodobenzene) **4.42** (Scheme 4.17).[24] Varvogolis synthesised [hydroxy(((+)-10-camphorsulfonyl)oxy)iodo]benzene **4.37** by reacting (diacetoxyiodo)benzene **4.42** and (+)-10-camphorsulfonic acid **4.43** in acetonitrile (Scheme 4.18). This hypervalent iodine reagent was then used by Chen and coworkers for the oxidation of sufhides to sulfoxides with poor enantioselectivity.[25]



Scheme 4.17 *Synthesis of a polymeric chiral iodoarene*[24]

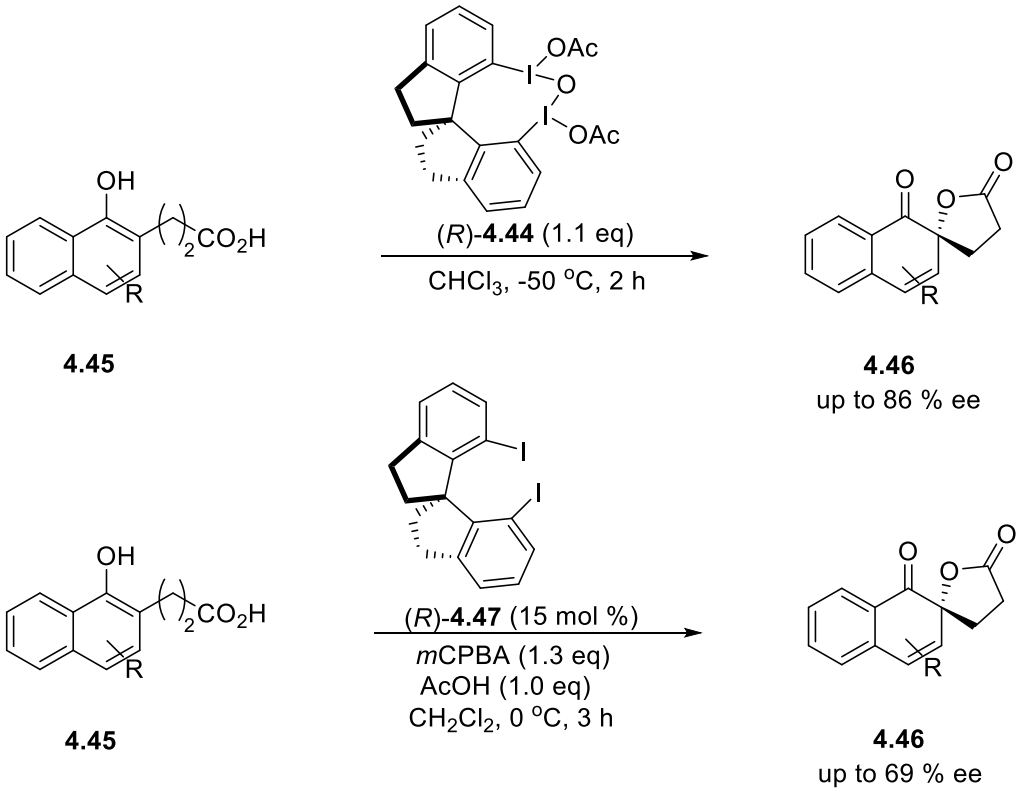


Scheme 4.18 *[Hydroxy(((+)-10-camphorsulfonyl)oxy)iodo]benzene synthesis*[23]

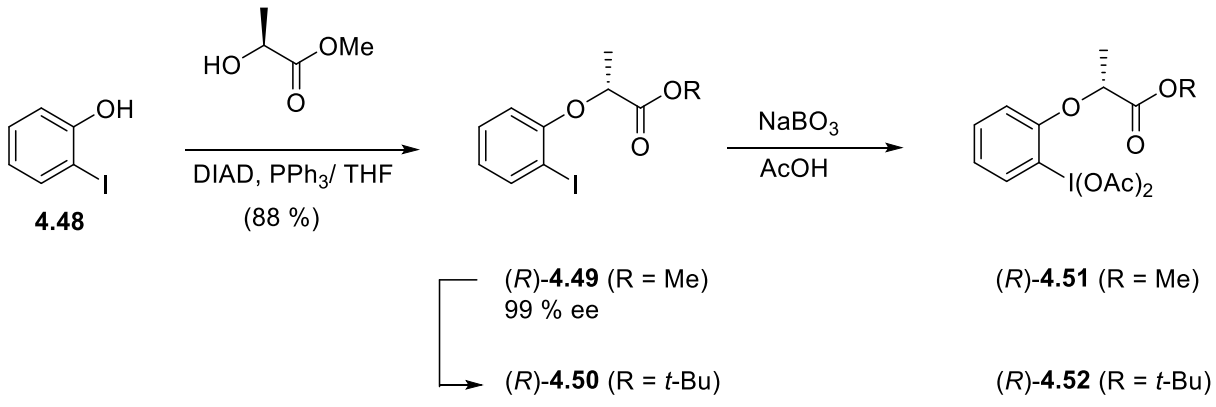
In 1997 Wirth *et al.* developed a chiral hypervalent iodine compound **4.39**, with the stereogenic centre situated closer to the iodine atom.[26] The oxytosyloxylations of ketones were investigated with good yields (40-70 %) and enantiomeric excesses of up to 15 % in their early work.[26] Building on this work, new molecules with the chiral moiety *ortho* to the iodine on the aromatic ring were developed and applied to the enantioselective oxygenation of ketones and alkenes with up to 65 % enantiomeric excess.[27] In 1999 Ochiai *et al.* synthesised the first chiral binaphthyl diaryliodonium salt **4.40**, for the α-phenylation of *β*-ketoester enolates (up to 53 % ee).[28]

In 2013 Kita reported the highly enantioselective spirolactonisation of naphthols based on a chiral hypervalent iodine reagent with a conformationally rigid spirobiindane backbone (Scheme 4.19).[29] This was based off work published by Kita in 2008 which was the first procedure for the enantioselective *ortho* spirocyclisation of napthols with a carboxylic acid moiety, with 78-86 % enantiomeric excesses obtained using a stoichiometric quantity of the chiral iodine(III) reagent **4.44** (Scheme 4.19).[30] All previous formation of spirolactones reported in the literature gave racemic prodocuts. The chiral spirobiindane **4.44** was reacted with a stoichiometric amount of oxidant, *m*CPBA to furnish the product in with good enantioselectivity (up to 86 % ee). This reaction was

conducted generating **4.44** *in-situ* from **4.47** using *m*CPBA (1.3 equivalents), in the presence of acetic acid (1.0 equivalent), but this reduced the enantiomeric excess to 69 % due to the reduction in temperature. When the reaction was conducted for 8 hours, high yields (50-96 %) and enantiomeric excesses (80-92 %) were reported. This work consolidated the importance of introducing a chirality at the *ortho* position of the iodoarene rings to improve enantiocontrol by introducing steric effects.

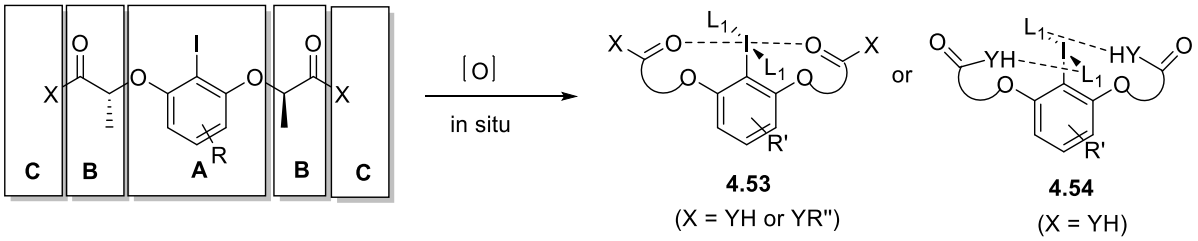


Scheme 4.19 *Spirolactonisation of naphthols*[29]

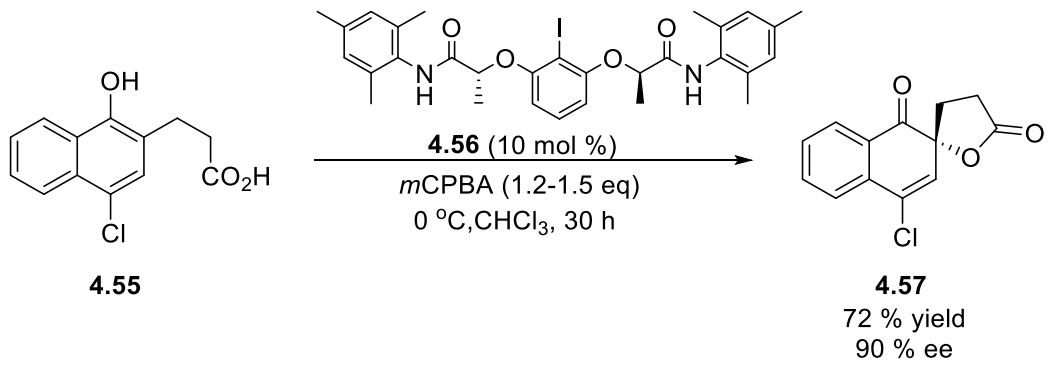


Scheme 4.20 *Synthesis of chiral iodoarenes* [31]

The introduction of chiral lactate groups as the *ortho* ring substituent for developing a chiral environment around the iodine centre was developed by Fujita in 2007 (Scheme 4.20).[31] This was instrumental in the development of chiral iodine(III) reagents with improved enantiomeric excesses. The lactate moiety was introduced in a Mitsunobu reaction with **4.48**, followed by oxidation of the chiral iodoarene to iodine(III) using acetic acid and sodium perborate. In 2010 Ishihara developed conformationally flexible C_2 symmetric chiral iodoarenes, which consisted of three units, an iodoaryl moiety (A), chiral linkers (B) and subfunctional groups (C) (Scheme 4.21). The iodosylarenes were generated *in situ* from the corresponding iodoarenes. The electron deficient iodine(III) centre is thought to form intramolecular n-σ^* interactions between the iodine and the Lewis basic group of the subfunctional group C, i.e the carbonyl groups (**4.53**). Intramolecular hydrogen bonding between the acidic hydrogen of the subfunctional group C and the carbonyl group of the iodine(III) ligand, such as an acetoxy ligand, could also be generated (**4.54**).[32] Ishihara used the C_2 symmetric chiral iodoarenes for the enantioselective spirooxylactonisation of 1-naphthols to deliver the products in good yields and excellent enantiomeric excesses (Scheme 4.22).[32] This seminal work by Ishihara and coworkers pioneered the synthesis of a wide array of C_2 symmetric hypervalent iodine(III) reagents with a lactate moiety, which generated greater enantiocontrol in a wide range of reactions.

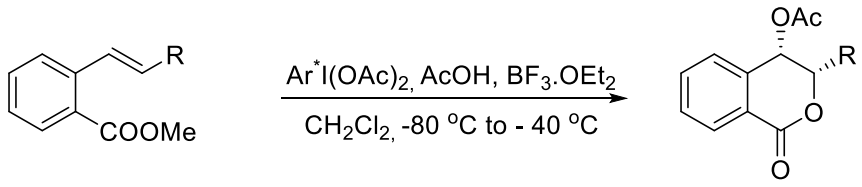


Scheme 4.21 *Conformationally flexible C_2 symmetric chiral iodoarenes*[32]

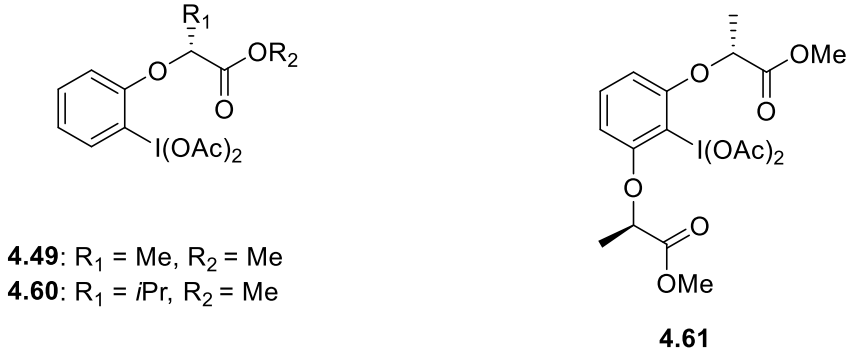


Scheme 4.22 *Oxidative spirolactonisation catalysed by C_2-symmetric iodoarenes*

In the same year Sugimura applied the lactate based chiral iodoarenes in Scheme 4.23 to the *endo*-selective oxylactonisation of *ortho*-alk-1-enylbenzoate **4.60** in good yields (57-84 %) and high enantiomeric excesses (75-97 % ee). High facial selectivity of the hypervalent iodine reagents suggested that the iodine atom of the reactive site may be strongly affected by the chirality of the lactic acid moiety.[33] Overall **4.61** gave the best enantiomeric excesses but in some cases at detriment to the yield. **4.49** and **4.60** generally afforded higher yields than **4.61** but most cases slightly lower enantiomeric excesses.

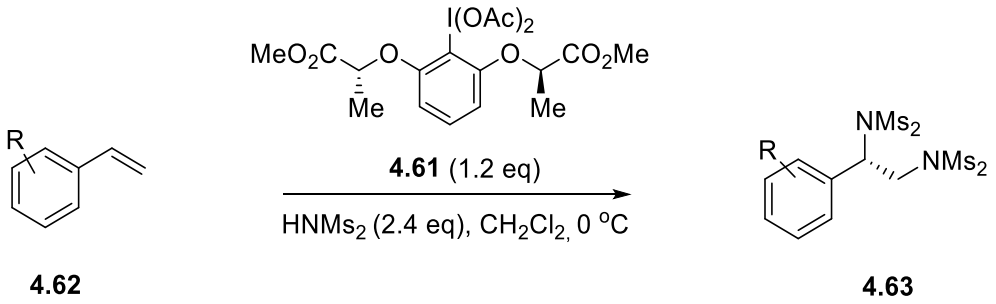


a: R = H, b: R = CH_2OMe, c: R= CH_2OH, d: R = nC_5H_{11}



Scheme 4.23 *Endo-selective oxylactonisation of ortho-alkyl-1-enylbenzoate*[33]

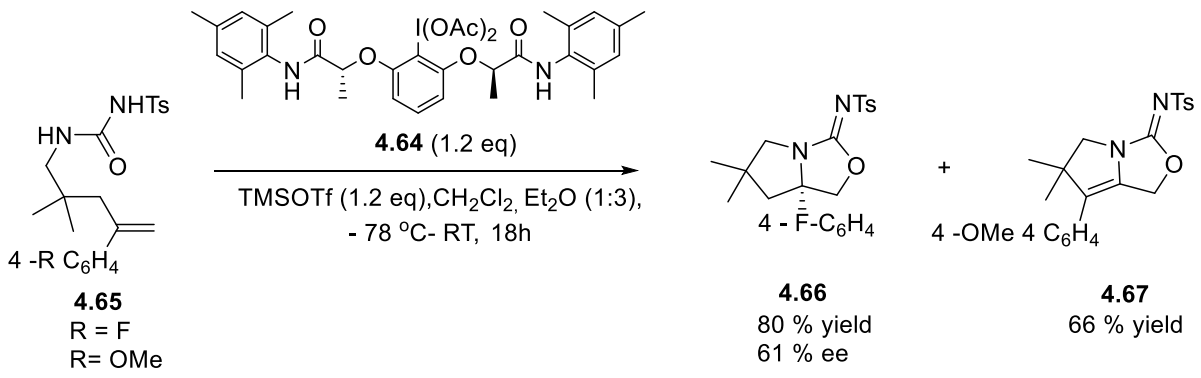
Structural studies of the hypervalent iodine reagents in solution were conducted using mass spectrometry. Solvated clusters of cationic iodonium salts were generated and analysed. Electrospray ionisation mass spectra of (diacetoxyiodo)arenes were measured and the data was obtained in aqueous acetonitrile containing trifluoroacetic acid. A signal corresponding to the aryl(hydroxy)iodonium ion ($M^+ = ArI^+(OH)$ was observed, as was $H_3O^+.(MeCN)_n$ (n = 1,2,3) in the range m/z <150. The iodonium ion solvated by acetonitrile, $M^+.(MeCN)_n$ (n = 1,2) was observed for 1-(diacetoxyiodo)-2,4,6-trimethylbenzene, which has no oxy substituent on the aryl group and one or two molecules of solvent were seen to coordinate to the iodonium ion. Mass spectrometry of reagent **4.61** showed minimal solvation by acetonitrile. The mono-functionalised iodine reagent **4.49** showed no evidence of a signal corresponding to $M^+.(MeCN)_2$, but a small signal corresponding to M^+.MeCN was observed, where only one molecule of solvent coordinated to the iodonium species. This showed that the 1-(methoxycarbonyl)ethoxy lactate side chain of **4.49** and **4.61** prevented the interaction of acetonitrile molecules with the iodonium ion. These results indicate that the lactate side chain interacts with the hypervalent iodine moiety even when in solution and this interaction is therefore responsible for the enantiodifferentiation of the hypervalent iodine reagent.[33]



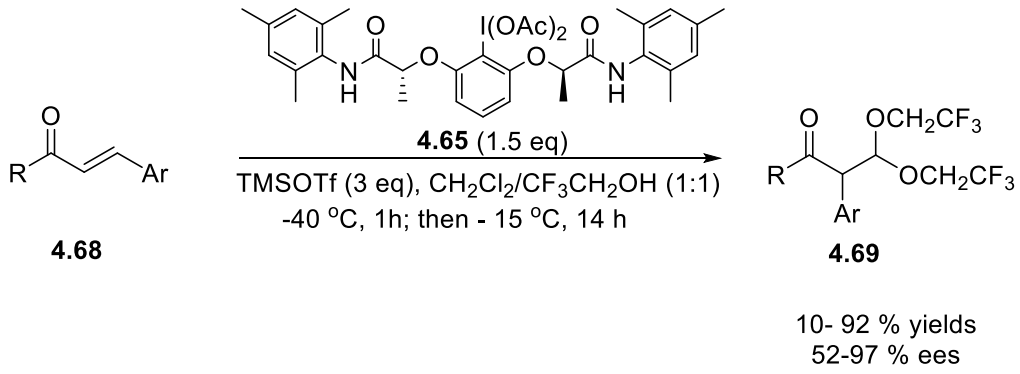
Scheme 4.24 *Intermolecular enantioselective diamination of styrenes*[34]

Muniz *et al.* used similar C_2 symmetric chiral iodoarenes for the intermolecular enantioselective diamination of styrenes, in good yields and high enantiomeric excesses (up to 99 %) (Scheme 4.24). [34] Wirth also used lactate based hypervalent iodine reagents for the metal-free oxyamination of alkenes (Scheme 4.25). Moderate to good yields (17-80 %) of the products were obtained but with varying enantiomeric excesses (21-66 % ee). The α-arylation of carbonyl compounds was the first report (Scheme 4.26) of chiral

hypervalent iodine compounds in highly stereoselective rearrangements in moderate to good yields (10-92 %) and moderate to high enantiomeric excesses (52 – 97 % ee).[35,36]



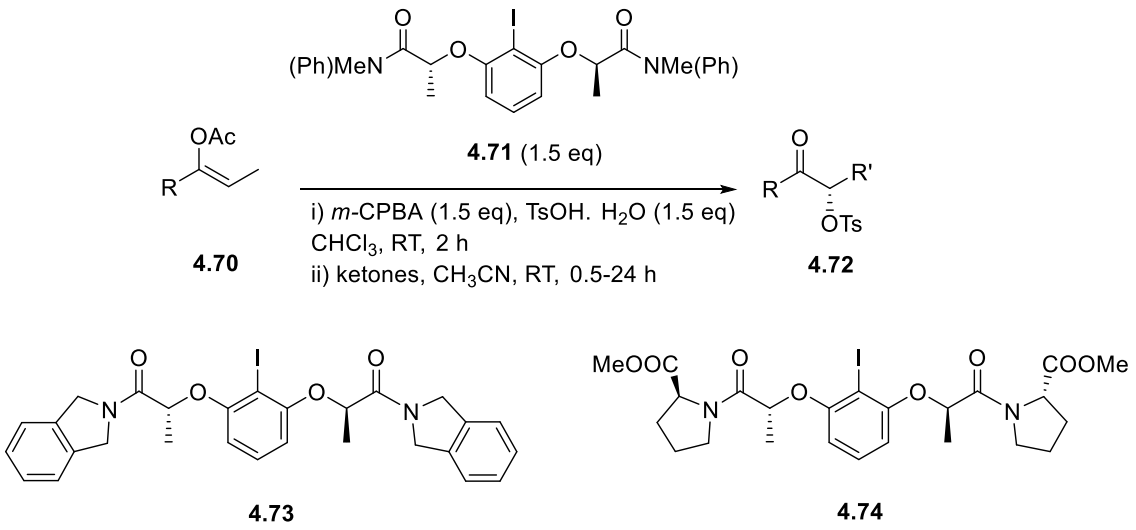
Scheme 4.25 *Transformations using C_2 symmetric chiral iodine(III) reagents*



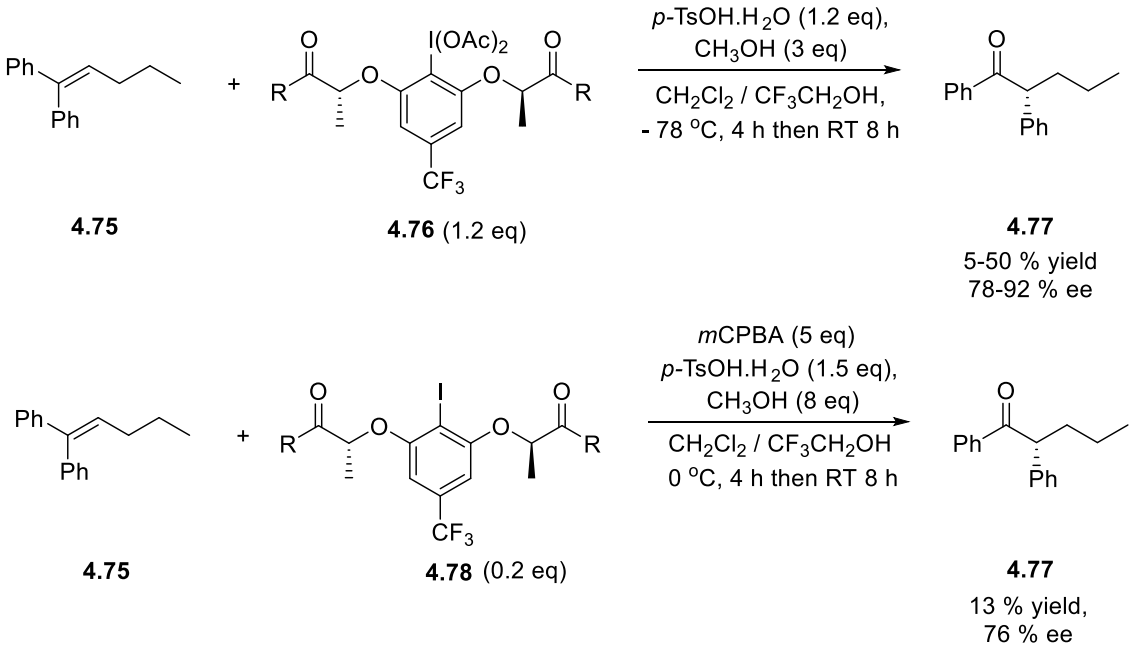
Scheme 4.26 *α-Arylation of carbonyl compounds*

High enantioselectivities were achieved in the α-tosyloxylation of ketones by Legault and coworkers, using C_2 symmetric chiral iodoarene precatalysts **4.71** (Scheme 4.27).[37] The addition of a methyl group to the amide nitrogen lead to enhanced enantioselectivity, due to the constrained rotation of the phenyl group with respect to the methyl group on the lactate arms. By using iodolinyl moieties **4.73** on the amide lead to a drastic loss of reactivity and selectivity. Benzylic and aliphatic groups on the amide nitrogen atoms of iodoarene **4.71** led to good yields (55-94 %) of the α-tosyloxy ketones and acceptable enantioselectivities (18-96 %). Introducing a second source of chirality into the iodoarene was investigated by creating amides from chiral amines **4.74**, which showed overall good

enantioselectivity (78-84 % ee) but the iodoarenes were challenging to purify due to their high polarity.[37]



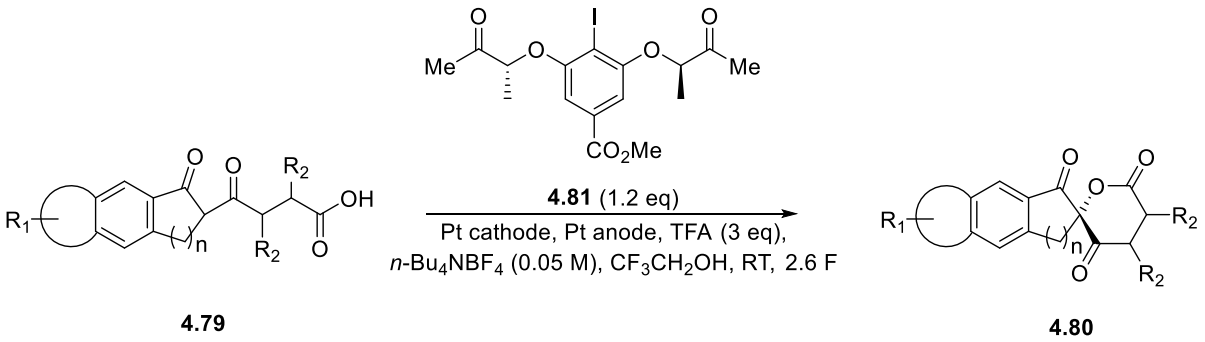
Scheme 4.27 *α-Tosyloxylation of ketones*[37]



Scheme 4.28 *Electron deficient chiral lactic acid based iodoarenes for the enantioselective oxidative rearrangement of 1,1-disubstituted alkenes*[38]

More recently, Wirth attached a electron withdrawing group (CF_3) to the aromatic ring to enhance the electrophilicity of the iodine. The rearrangement of 1,1-disubstituted alkenes using *p*-toluenesulfonic acid monohydrate and methanol delivered the products in moderate yields but with good enantioselectivities. This transformation was also

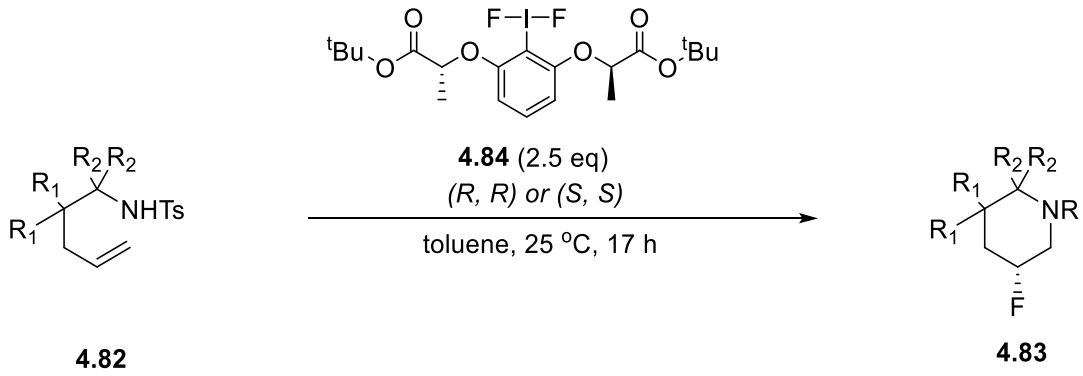
investigated using a catalytic amount of iodoarene **4.78** (0.2 equivalents), but the enantioselective rearrangement had to be performed at higher temperatures as the oxidation to iodine(III) was too slow at low temperature.[38]



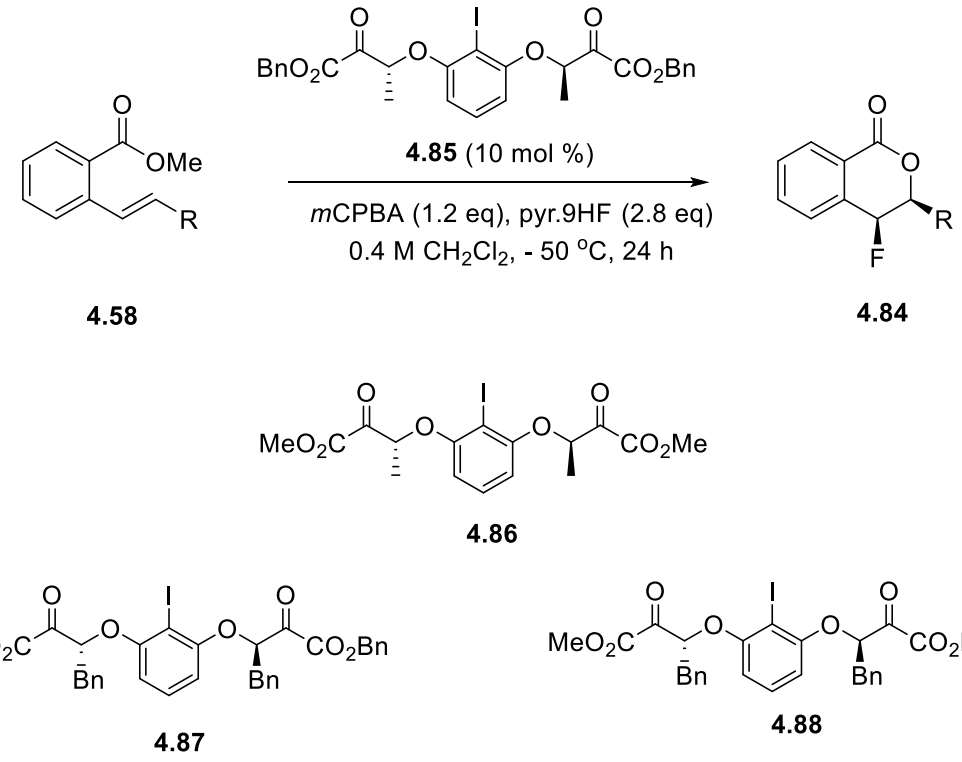
Scheme 4.29 *Enantioselective electrochemical lactonization of diketo acid*[39]

Wirth *et al.* conducted the first enantioselective reaction in an electrochemical flow microreactor (Scheme 4.29). The enantioselective electrochemical lactonization of diketo acid derivatives **4.80** were conducted using chiral iodoarenes. Conducting this chemistry under electrochemical conditions avoided using excess chemical oxidants and reducing agents. A range of substrates underwent lactonization in moderate to good yields (40-87 %), and good enantiomeric excesses (47-71 %) using **4.81**. The substrate without an aryl group gave only a 36 % yield and was racemic.[39]

The regio and enantioselective aminofluorination of alkenes was achieved using ^{t}Bu-lactate derivitised (difluoroiodo)arene **4.84** which was generated using Selectfluor (Scheme 4.30).[40] The metal free aminofluorination gave the *endo* cyclised product, using 2.5 equivalents of the chiral hypervalent iodine(III) reagent **4.84** with good yields (64-90 %) and good enantiomeric excesses (61-88 % ee). The enantiomeric excesses improved to > 90 % following recrystallisation. Approximately 50-60 % of the chiral iodoarene was recovered with the initial enantiomeric purity (99 %) despite requiring 2.5 equivalents of the reagent in the reaction.[40]



Scheme 4.30 *Metal free aminofluorination*[40]

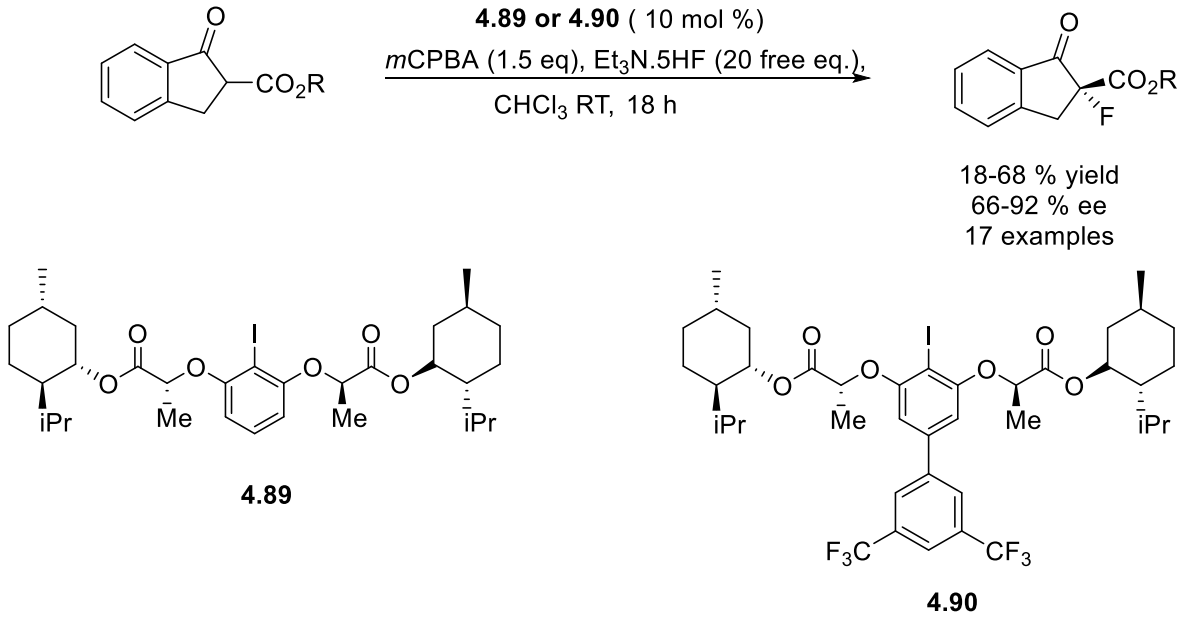


Scheme 4.31 *Enantioselective fluorolactonisation for the preparation of 4-fluoroisochromanones*[41]

Jacobsen and co-workers developed an enantioselective lactonization for the synthesis of 4-fluoroisochromanones (Scheme 4.31). A variety of aryl iodides were investigated for their ability to carry out the fluorolactonisation reaction. The substrate was reacted with a chiral iodoarene (10 mol %), using *m*CPBA (1.2 equivalents) as the oxidant and pyridine.9HF (2.8 equivalents) in dichloromethane. The catalysts **4.86** and **4.85** provided similar enantioselectivities (-87 % ee and -94 % ee respectively) compared to the benzyl

substituted iodoarenes **4.87** and **4.88** (87 % ee and 95 % ee respectively) but **4.85** affords the highest yield (86 %).[41]

In 2018 Rueping *et al.* developed a metal-free asymmetric fluorination of 1,3-dicarbonyl compounds using chiral iodoarenes (Scheme 4.32). The enantioselective fluorination was conducted using either catalyst **4.89** or **4.90** (10 mol %), *meta*-chloroperbenzoic acid (1.5 equivalents and $Et_3N.5HF$ (5 equivalents) in chloroform. The corresponding fluorinated products were obtained in moderate to good yields (18-68 %) with high enantiomeric ratios of up to 92 %.[42]

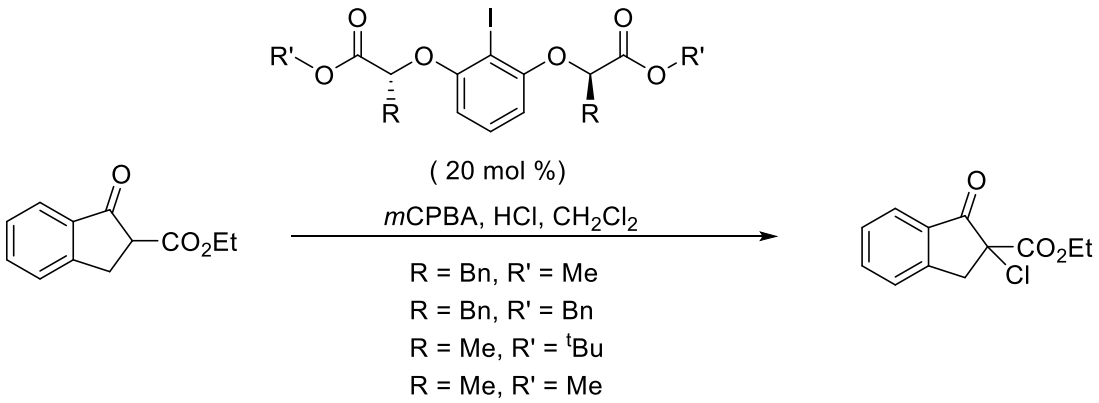


Scheme 4.32 *Metal-free asymmetric fluorination of 1,3-dicarbonyl compounds*[42]

4.3 Project Aims

The enantioselective fluorination of 1,3-dicarbonyl compounds has been established within the literature and the use of C_2 symmetric chiral iodoarenes with a lactate side arm has shown to improve the enantiomeric excess of the systems it has been introduced into. The corresponding enantioselective chlorination has not been reported in the literature and the use of hypervalent iodine(III) reagents for enantioselective chlorination is limited. The aim of this research was to synthesise a small series of chiral lactic acid based hypervalent iodine(III) reagents following the synthetic route by Sugimura *et al.*, and

explore their application for the enantioselective chlorination of 1,3-dicarbonyl compounds.



Scheme 4.33 *Enantioselective chlorination of ethyl 1-oxo-2,3-indanone-2-carboxylate*

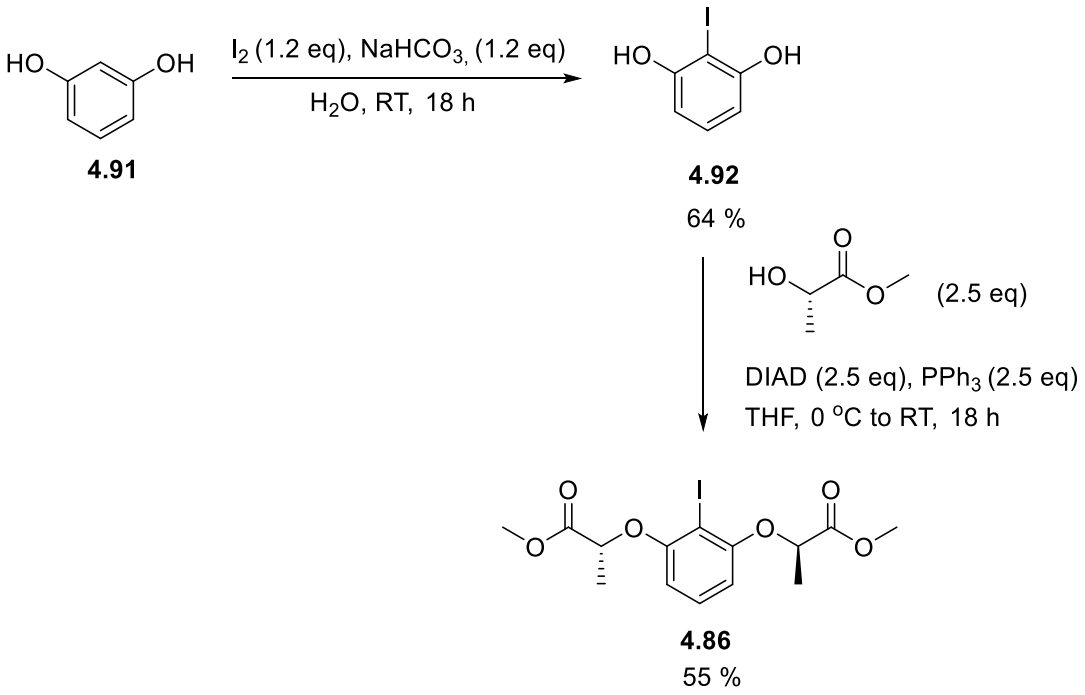
4.4 Preparation of Chiral Iodoarenes

4.4.1 Synthesis of Dimethyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))(2*R*, 2'*R*)-dipropionate

The chiral iodoarene dimethyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))(2*R*, 2'*R*)-dipropionate **4.86** was prepared following the synthetic route by Sugimura *et al.*, (Scheme 4.34). 2-Iodoresorcinol **4.92** was synthesised by adding iodine to resorcinol **4.91** and sodium hydrogen carbonate in water at 0 °C, warming the reaction mixture to room temperature and stirring for 18 hours. The ^{1}H NMR spectrum showed the consumption of starting material by the disappearance of a 2H singlet at 4.73 ppm corresponding to the hydroxyl protons and the disappearance of a 1H singlet at 6.36 ppm corresponding to the proton between the two hydroxyl groups. The ^{1}H NMR spectrum of 2-iodoresorcinol showed the appearance of a 2H doublet at 6.56 ppm, a 1H triplet at 7.11 ppm and a 2H singlet at 5.23 ppm which confirmed the formation of 2-iodoresorcinol in a good 64 % yield. The ^{13}C NMR spectrum showed the appearance of a singlet at 77.7 ppm corresponding to the new carbon-iodine bond.

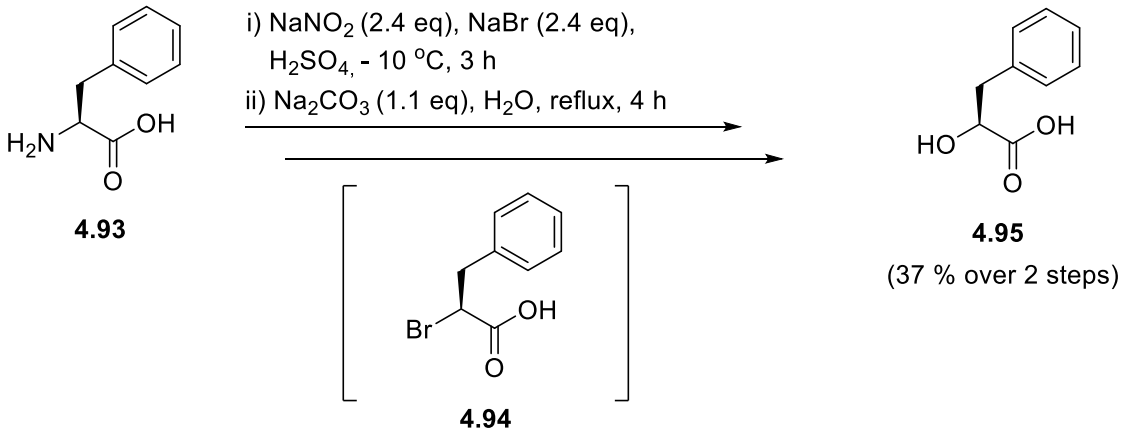
Following a procedure by Ishihara *et al.*, a Mitsunobu reaction was used to convert 2-iodoresorcinol **4.92** to dimethyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))(2*R*, 2'*R*)-dipropionate **4.86** (Scheme 4.34).[33] Diisopropylazodicarboxylate (2.5 equivalents) was added to a mixture of 2-iodoresorcinol, triphenylphosphine (2.5 equivalents) and (*S*)-methyl lactate (2.5 equivalents) stirring at 0 °C in dry THF. After warming the reaction

mixture to room temperature, it was stirred overnight. After purification by column chromatography a good 55 % yield of the product **4.86** was obtained. ^{1}H NMR spectroscopy confirmed the consumption of starting material by the absence of the 2H singlet at 5.23 ppm corresponding to the two protons belonging to the hydroxyl groups, as well as the disappearance of the 2H doublet at 6.56 ppm and 1H triplet at 7.11 ppm. The formation of product **4.86** was confirmed by the appearance of a 6H doublet at 1.71 ppm corresponding to the 2 x CH_3 groups of the (*S*)-methyl lactate, as well as a 6H singlet at 3.75 ppm belonging to the 2 x OCH_3 groups and a 2H quartet at 4.77 ppm corresponding to the two CH groups. Also, a 2H aromatic doublet at 6.37 ppm and a 1H aromatic triplet at 7.14 ppm corresponded to the protons on the aromatic ring. The ^{13}C NMR spectrum showed the presence of a carbon-iodine bond at 80.6 ppm which is shifted downfield in comparison to the C-I bond in 2-iodoresorcinol at 77.1 ppm. Also present are two CH_3 groups at 18.7 ppm and 52.4 ppm corresponding to the methyl and methoxy groups of the lactate moiety respectively and a singlet at 74.2 ppm for the CH of the lactate moiety. An optical rotation of -21.1 (c = 1.0, $CHCl_3$) was obtained, which was in agreement with the literature value of -20.0 (c = 1.0, $CHCl_3$).[33,39]



Scheme 4.34 *Synthesis of dimethyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))(2R, 2'R)-dipropionate*

4.4.2 Synthesis of Dibenzyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))(2*R*,2'*R*)-bis(3-phenylpropanoate)



Scheme 4.35 *Synthesis of (S)-2-hydroxy-3-phenylpropanoic acid*

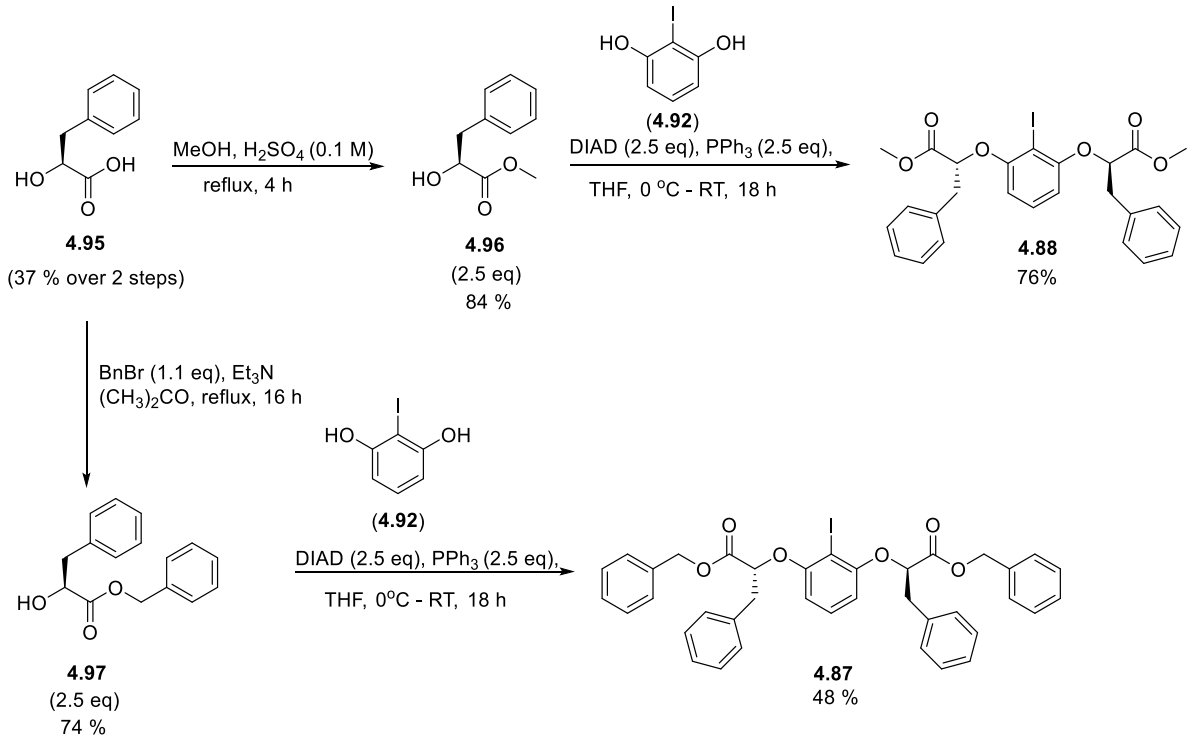
The lactate moiety was altered to L-(-)-3-phenyllactic acid **4.95** in order to introduce a bulkier benzyl group rather than a methyl group. Using a method by Gendron and coworkers, L-phenylalanine **4.93** was diazotised with sodium nitrite in sulfuric acid at – 10 °C and then reacted with sodium bromide to give (*S*)-2-bromo-3-phenylpropanoic acid.[44] After purification by flash column chromatography, (*S*)-2-bromo-3-phenylpropanoic acid **4.94** was dissolved in water with sodium carbonate (1.1 equivalents) and the reaction mixture was refluxed for 4 hours (Scheme 4.35). The crude product was recrystallised from diethyl ether and hexane to give (*S*)-2-hydroxy-3-phenylpropanoic acid **4.95** in a moderate 37 % yield over 2 steps. ^{1}H NMR spectroscopy confirmed the formation of product by the presence of two 1H doublet of doublets at 2.91 ppm and 3.12 ppm respectively corresponding to the benzylic CH_2 group, as well as a 1H doublet of doublets at 4.35 ppm belonging to the aliphatic CH, a 1H multiplet at 7.18-7.24 ppm and a 4H doublet at 7.28 ppm which confirmed the presence of the aromatic ring. The product was observed in the mass spectrum with an *m/z* of 165.0552 for the parent ion M-H$^-$, and an optical rotation of -26.8 (*c* = 1.0, acetone) was consistent with the literature value, - 26.7 (*c* = 0.9, acetone) and confirmed the (*S*) stereochemistry.[43,44]

(*S*)-2-Hydroxy-3-phenylpropanoic acid **4.95** was reacted with methanol and a catalytic amount of sulphuric acid (0.1 equivalents) at reflux for 4 hours to give methyl (*S*)-2-hydroxy-3-phenylpropanoate **4.96** in an excellent 84 % yield (Scheme 4.36). ^{1}H NMR spectroscopy confirmed the formation of the product through the appearance of a 1H

doublet at 2.70 ppm corresponding to the OH, two 1H doublet of doublets at 2.97 ppm and 3.13 ppm corresponding to the CH_2 of the benzyl group and a 3H singlet at 3.78 ppm corresponding to the OCH_3. ^{13}C NMR spectroscopy showed the presence of a singlet at 52.5 ppm corresponding to the new OCH_3 group.

Methyl (*S*)-2-hydroxy-3-phenylpropanoate **4.96** (2.5 equivalents) was then reacted with 2-iodoresorcinol **4.92**, triphenylphosphine (2.5 equivalents) and diisopropyl azodicarboxylate (2.5 equivalents) in dry THF in a Mitsunobu reaction. After purification by column chromatography, dimethyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))(2*R*,2'*R*)-bis(3-phenylpropanoate) **4.88** was obtained in a very good 76 % yield. ^1H NMR spectroscopy confirmed the formation of product **4.88** through the presence of a 2H doublet of doublets corresponding to the two CH_AH_B groups at 2.97 ppm and 3.31 ppm belonging to the two benzyl groups, as well as a 6H singlet at 3.66 ppm corresponding to the two OCH_3 groups on the lactate moiety. A 2H doublet at 6.21 ppm and a 1H triplet at 7.04 ppm were also observed for the three aromatic protons on the aromatic ring. The parent ion peak was observed in the mass spectrum at *m/z* of 561.0770. The ^{13}C NMR spectrum showed the presence of a CH_2 at 39.1 ppm corresponding to the CH_2 of the benzyl group and a singlet at 52.3 ppm corresponding to the methoxy group. An optical rotation of 68.5 was obtained (c = 1.0, $CHCl_3$). The optical rotation of **4.88** was not reported in the literature.

Dibenzyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))(2*R*, 2'*R*)-bis(3-phenylpropanoate) **4.87** was then synthesised. In the first step (*S*)-2-hydroxy-3-phenylpropanoic acid **4.95** was reacted with benzyl bromide and triethylamine in acetone and the reaction mixture was refluxed for 16 hours to give benzyl (*S*)-2-hydroxy-3-phenylpropanoate in a good 74 % yield. ^1H NMR spectroscopy confirmed the formation of product through the appearance of a 1H singlet at 2.74 ppm corresponding to the OH group as well as a 2H singlet at 5.18 ppm corresponding to the new benzyl OCH_2 group, and two 1H doublet of doublets at 2.98 ppm and 3.12 ppm corresponding to the CH_AH_B of the original benzyl group. The product **4.87** was observed in the mass spectrum with an *m/z* of 279.1003 for the sodiated product.

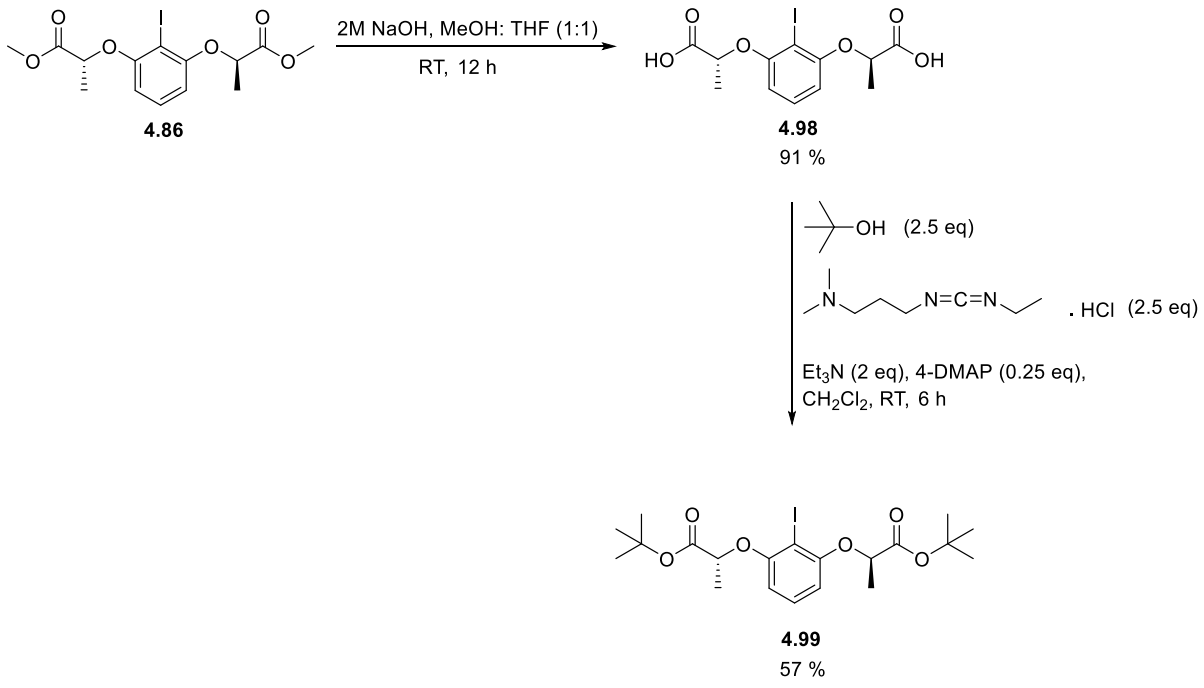


Scheme 4.36 *Synthesis of the chiral iodoarenes; dimethyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))(2R, 2'R)-bis(3-phenylpropanoate)* ***4.88*** *and dibenzyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))(2R, 2'R)-bis(3-phenylpropanoate)* ***4.87***

Benzyl (*S*)-2-hydroxy-3-phenylpropanoate **4.97** was reacted with 2-iodoresorcinol, triphenylphosphine (2.5 equivalents) and diisopropyl azodicarboxylate (2.5 equivalents) in dry THF in a Mitsunobu reaction. ^{1}H NMR spectroscopy confirmed formation of the product by the presence of a two doublet of doublets at 3.32 ppm and 4.84 ppm corresponding to the two benzyl CH_AH_B protons and a 4H singlet at 5.07 ppm corresponding to the two sets of aliphatic CH_2 protons of the benzyloxy groups, as well as the aromatic protons with a 2H doublet at 6.16 ppm and a 1H triplet at 6.89 ppm and a 20H multiplet at 7.13-7.39 ppm corresponding to the benzyl aromatic protons. The product **4.87** was observed in the mass spectrum with an *m/z* of 713.1385 corresponding to the parent ion. The ^{13}C NMR spectrum showed two CH_2 groups at 39.1 ppm and 67.2 ppm corresponding to the benzyl and benzyloxy CH_2 groups respectively. An optical rotation of 26.8 was obtained (c = 1.0, $CHCl_3$). The optical rotation of **4.87** was not reported in the literature.

4.4.3 Synthesis of di-*tert*-Butyl 2,2'-((2-iodo-1,3-phenylene)bis)oxy))(2*R*,2'*R*)-dipropionate

To generate bulkier derivatives of the chiral iodoarene and introduce diversity into the lactate moiety, the ester functionality was removed from dimethyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))(2*R*, 2'*R*)-dipropionate **4.86**. Following a procedure by Ishihara and coworkers, dimethyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))(2*R*, 2'*R*)-dipropionate was reacted with methanol and sodium hydroxide in dry tetrahydrofuran and the reaction was stirred at room temperature overnight to give (2*R*,2'*R*)-2,2'-((2-iodo-1,3-phenylene)bis(oxy))dipropionic acid **4.98** in an excellent 91 % yield (Scheme 4.37). ^{1}H NMR spectroscopy confirmed the formation of product through the presence of a 6H doublet at 1.55 ppm corresponding to the two methyl groups on the lactate arm, as well as the 2H singlet at 13.1 ppm corresponding to the two hydroxyl groups. The optical rotation of the product was observed to be - 11.7 (*c* = 1.0, THF), compared to Uyanik *et al.* with an optical rotation of -6.4 (*c* = 1.0, THF), which was consistent with the literature.[32]



Scheme 4.37 *Synthesis of di-tert-butyl 2,2'-((2-iodo-1,3-phenylene)bis)oxy))(2R, 2'R)-dipropionate **4.99***

Following a procedure by Nevado and coworkers, (2*R*,2'*R*)-2,2'-((2-iodo-1,3-phenylene)bis(oxy))dipropionic acid **4.98** was reacted with *tert*-butanol (2.5 equivalents), triethylamine (2 equivalents), 4-dimethylaminopyridine (0.25 equivalents) and *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (2.5 equivalents) and the reaction was stirred at room temperature for 6 hours (Scheme 4.37).[41] After purification by column chromatography di-*tert*-butyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))(2*R*, 2*'R*)-dipropionate **4.99** was obtained in a good 57 % yield. ^{1}H NMR spectroscopy confirmed formation of the product but as a mixture of diastereoisomers. The appearance of two 18 H singlets at 1.43 ppm and 1.44 ppm showed the presence the two sets of *tert*-butyl groups, corresponding to two diastereoisomers as well as a 12H doublet at 1.68 ppm corresponding to the four methyl groups of the lactate moiety of both isomers, which are overlapping. Further evidence of the diastereoisomers is the appearance of the 4H multiplet at 6.37-6.41 ppm and two overlapping 2 H triplets at 7.14 ppm corresponding to the 2 protons on the resorcinol aromatic rings of both isomers. An optical rotation of -20.4 (c = 1.0, $CHCl_3$) was obtained, whereas Wirth *et al.* reported an optical rotation of -31 (*c* = 1.0, $CHCl_3$). This confirmed the mixture of diastereoisomers and therefore **4.99** could not be used in the enantioselective chlorination.[39]

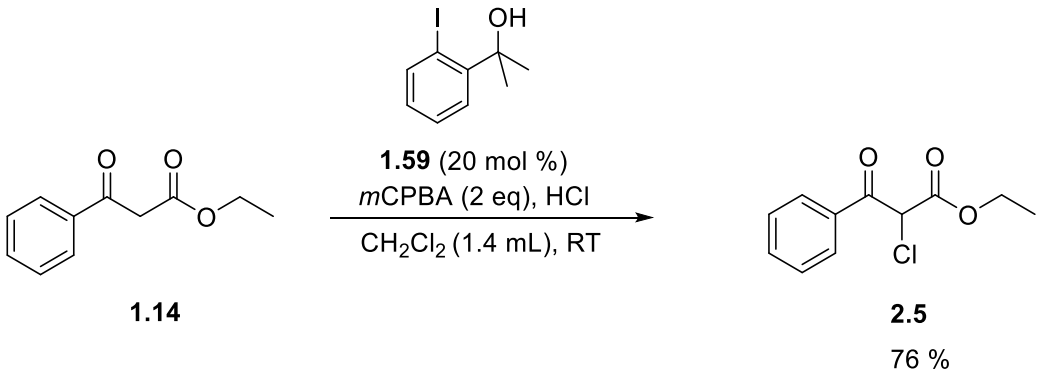
There was no evidence of the formation of a second diastereoisomer during the synthesis of **4.98** and the optical rotation obtained, - 11.7 (*c* = 1.0, THF), was concordant with the literature value of -6.5 (*c* = 1.0, THF).[32] Di-*tert*-butyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))(2*R*, 2*'R*)-dipropionate **4.99** was then generated by reacting **4.98** with *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC.HCl) and *tert*-butanol. The optical rotation of -20.4 (c = 1.0, $CHCl_3$) was obtained for **4.99**, which was significantly different to that obtained by Wirth and coworkers (-31 (*c* = 1.0, $CHCl_3$)).[39] The ^{1}H NMR spectrum of **4.99** also showed the presence of two diastereoisomers which was not apparent in ^{1}H NMR spectrum of **4.98**. EDC.HCl is known to cause racemisation in amide bond formation and so evidence showed that epimerisation occurred during the coupling of *tert*-butanol to form di-*tert*-butyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))(2*R*, 2*'R*)-dipropionate **4.99**.

4.5 Enantioselective Chlorination using *m*-CPBA and HCl

4.5.1 Chlorination of Ethyl 1-oxo-2,3-indanone-2-carboxylate

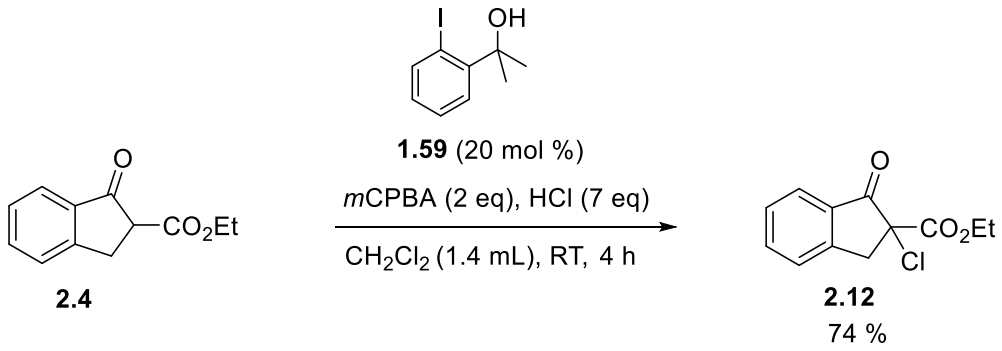
The aim of this research was to develop a system for the enantioselective chlorination of 1,3-dicarbonyl compounds. Ethyl 1-oxo-2,3-indanone-2-carboxylate was used as the model substrate as it had been well reported in the literature for its use as a model substrate in similar systems. The initial testing of the chlorination of ethyl 1-oxo-2,3-indanone-2-carboxylate **2.4** was conducted using 4-iodotoluene as it is cheap and commercially available reagent and is capable of being oxidised from iodine(I) to iodine(III).

In my previous work the catalytic chlorination of 1,3-dicarbonyl compounds was investigated. Using ethyl 3-oxo-3-phenylpropanoate as the model substrate, the chlorination proceeded under the following optimum conditions; 2-(2-iodophenyl)-propan-2-ol **1.59** (20 mol %), *m*CPBA (2 equivalents) and HCl (5 equivalents) in dichloromethane at room temperature for 4 hours. The chlorinated product was obtained in a 100 % conversion with a 76 % isolated yield (Scheme 4.38).



Scheme 4.38 *Catalytic chlorination of ethyl 3-oxo-3-phenylpropanaote*

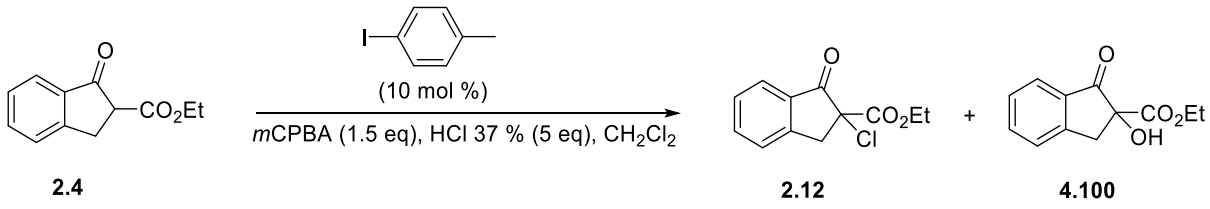
The catalytic chlorination of ethyl 1-oxo-2,3-indanone-2-carboxylate was possible under the same conditions but using a larger excess of HCl (7 equivalents). Under these conditions the *β*-ketoester was chlorinated in a 100 % conversion with a good 74 % isolated yield (Scheme 4.39).



Scheme 4.39 *Catalytic chlorination of* ethyl 1-oxo-2,3-indanone-2-carboxylate

The catalytic chlorination of ethyl 1-oxo-2,3-indanone-2-carboxylate **2.4** using iodotoluene was investigated based on these optimum conditions. As the chlorination of ethyl 3-oxo-3-phenylpropanoate was possible using 5 equivalents of HCl this was used as a starting point and only 10 mol % of iodotoluene was used as it undergoes oxidation easily.

Table 4.1 *Chlorination of ethyl 1-oxo-2,3-indanone-2-carboxylate using 4-iodotoluene*



Entry	Temperature (°C)	Time (h)	Conversion[a] (%)	2.12 (%)	4.100 (%)
1	RT	4	100	41	59
2	0	4	100	53	47
3[c]	0	4	100	48	52
4	0	1	100	54 (44)[b]	46 (28)[b]
5	-20	4	100	51	49

[a] Conversion denoted by the consumption of starting material; [b] Isolated yield in parenthesis; [c] *m*CPBA (1.05 equivalents).

4-Iodotoluene (10 mol %), *meta*-chloroperbenzoic acid (1.5 equivalents) and hydrochloric acid (5 equivalents) in dichloromethane was stirred at room temperature for

15 minutes before adding ethyl 1-oxo-2,3-indanone-2-carboxylate **2.4** and stirring for a further 4 hours (Table 4.1). ^{1}H NMR spectroscopy showed a 100 % consumption of starting material, through the disappearance of the 1H doublet of doublets at 3.73 ppm corresponding to the $CHCO_2Et$ proton and a 41 % conversion to the product **2.12** and 59 % of the hydroxylated product **4.100** (Table 4.1, entry 1). Formation of the product was confirmed by the appearance of a 3H triplet at 1.27 ppm corresponding to the CH_3 of the ethyl group and a 2H multiplet at 4.27 ppm belonging to the CH_2 of the ethyl group. Also, the presence of a 1H doublet at 3.56 ppm and a 1H doublet at 4.10 ppm corresponded to the CH_2 on the indanone ring. ^{1}H NMR spectroscopy also showed the presence of the hydroxylated product **4.100** through the appearance of a 3H triplet at 1.18 ppm corresponding to the CH_3 of the ethyl moiety, as well as a 2H multiplet at 4.18-4.25 ppm corresponding to the CH_2 of the ethyl group. In addition, the presence of two 1H doublets at 3.25 ppm and 3.73 ppm belonging to the CH_2 on the indanone ring and a 1H singlet at 3.99 ppm corresponding to the OH proton, confirmed the formation of product. The product **4.100** was observed in the mass spectrum and an *m/z* of 221.0817 was obtained for the parent ion peak.

In order to prevent the background hydroxylation from occurring, the reaction was repeated at 0 °C for 4 hours using dried *meta*-chloroperbenzoic acid (Table 4.1, entry 2). The crude ^{1}H NMR spectrum showed a 100 % consumption of starting material with an improved 53 % conversion to the chlorinated product **2.12** and a 47 % conversion to the hydroxylated product **4.100**. The reaction was then repeated under the same conditions but the amount of *meta*-chloroperbenzoic acid was reduced to 1.05 equivalents to reduce the amount of hydroxylation. The crude ^{1}H NMR spectrum showed a 100 % conversion was achieved, with a reduced 48 % conversion to the chlorinated product and a 52 % conversion to the hydroxylated product (entry 3). The reaction was then conducted for 1 hour at 0 °C using *meta*-chloroperbenzoic acid (1.5 equivalents). The crude ^{1}H NMR spectrum showed a 100 % consumption of starting material, with a 54 % conversion and a 44 % isolated yield of the chlorinated product **2.12** and a 46 % conversion to the hydroxylated product **4.100** and a 28 % isolated yield (entry 4). Following the increased chlorination and reduced hydroxylation at 0 °C, the reaction was repeated at – 20 °C for 4 hours. A 100 % consumption of starting material was achieved with a 51 % conversion

to the chlorinated product and a similar 49 % conversion to the hydroxylated product (Table 4.1, entry 5).

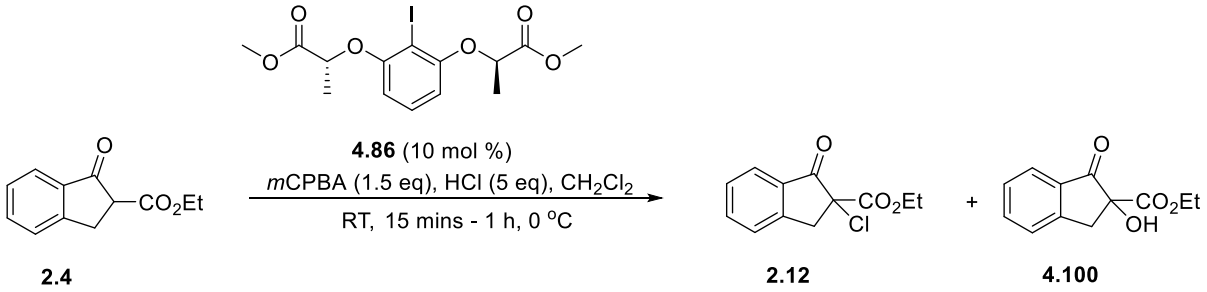
The catalytic chlorination of ethyl 1-oxo-2,3-indanone-2-carboxylate using iodotoluene (10 mol %) afforded a 41 % conversion to the chlorinated product **2.12** and 59 % conversion to the hydroxylated product **4.100**, whereas the catalytic chlorination of ethyl 1-oxo-2,3-indanone-2-carboxylate using iodoalcohol (20 mol %) afforded 100 % consumption of starting material with a 74 % isolated yield. This could be a consequence of the iodotoluene being easier to oxidise to iodosotoluene, and rapidly reacting with the *β*-ketoester preferentially to form the hydroxylated product **4.100**.

4.5.2 Enantioselective Chlorination of Ethyl 1-oxo-2,3-indanone-2-carboxylate using Dimethyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))(2*R*, 2'*R*)-dipropionate

Rueping *et al.* established methodology for the enantioselective fluorination of 1,3-dicarbonyl compounds using chiral iodoarenes (Scheme 4.32). The enantioselective fluorination of ethyl 1-oxo-2,3-indanone-2-carboxylate was conducted using iodoarene**s** **4.89** or **4.90** and a range of *β*-ketoesters were fluorinated in moderate to good yields (18-74 %) and high enantiomeric ratios (83:17 to 96:4 e.r). In this work ethyl 1-oxo-2,3-indanone-2-carboxylate was also employed as the model substrate and the aim was to develop conditions for its enantioselective chlorination.

The enantiomers of ethyl 2- chloro-1-oxo-2,3-dihyro-1*H*-indene-2-carboxylate **2.12** were separated by HPLC on a chiralcel OJ column. The flow rate of the mobile phase was set at 0.7 mL/min using 10 % isopropanol in hexane. The retention times; t_R = 16.373 minutes 48 %, t_R = 25.378 minutes 52 %, showed that **2.12** had a slight enantiomeric excess (4 % ee). These conditions were subsequently used to determine the e.r. of **2.12** in each of the chiral reactions.

Table 4.2 *Enantioselective Chlorination of ethyl 1-oxo-2,3-indanone-2-carboxylate using dimethyl 2,2-((2-iodo-1,3-phenylene)bis(oxy))(2R, 2'R)-dipropionate*



2.4 **2.12** **4.100**

Entry	Temp. (°C)	Conc. (M)	Conv.[a] (%)	2.12[b] (%)	4.100[b] (%)	e.r of 2.12[c] (%)
1[d]	0	0.51	100	60	40	-
2	0	0.51	100	65 (43)	35 (29)	48:52
3	0	0.25	100	70 (70)	30 (22)	48:52
4	0	0.1	100	69 (53)	31 (28)	48:52
5[e]	-20	0.1	100	19 (16)	81 (54)	48:52
6	-20	0.1	100	64 (49)	36 (27)	48:52
7[f]	-20	0.25	100	65	35	-
8	-40	0.1	100	38 (17)	62 (41)	51:49

[a]Determined by ^{1}H NMR spectroscopy; [b]isolated yields in parenthesis; [c]determined by chiral HPLC; [d]Wet *m*CPBA; [e] addition of iodoarene **4.86** (10 mol %), *m*CPBA (1.5 equivalents), HCl (5 equivalents) and **2.4** in dichloromethane at – 20 °C and stirred for 1 hour; [f]addition of **2.4**, iodoarene **4.86** (10 mol %), HCl (5 equivalents) and *m*CPBA (1.5 equivalents) in dichloromethane at room temperature and the reaction cooled to – 20 °C for 1 hour.

The enantioselective chlorination of ethyl 1-oxo-2,3-indanone-2-carboxylate **2.4** was initially tested using the model chiral iodoarene, dimethyl 2,2-((2-iodo-1,3-phenylene)bis(oxy))(2*R*, 2'*R*)-dipropionate **4.86**. In Table 4.2, entry 1, dimethyl 2,2-((2-iodo-1,3-phenylene)bis(oxy))(2*R*, 2'*R*)-dipropionate (10 mol %) was reacted with *meta*-chloroperbenzoic acid (1.5 equivalents), hydrochloric acid (5 equivalents) in

dichloromethane (0.51 M) and the reaction mixture was stirred at room temperature for 15 minutes before cooling the reaction mixture to 0 °C and then adding the substrate, ethyl 1-oxo-2,3-indanone-2-carboxylate. The *meta*-chloroperbenzoic acid in this entry had not been dried prior to use. The crude ^{1}H NMR spectrum showed a 100 % conversion was achieved with 60 % conversion to the chlorinated product **2.12** and a 40 % conversion to the hydroxylated product **4.100**. The reaction was then repeated using *meta*-chloroperbenzoic acid which had been dried under vacuum for 4 hours, to reduce the moisture content with the aim of reducing the amount of hydroxylation. A 100 % conversion was achieved with an improved 65 % conversion to the chlorinated product **2.12** and a reduced 35 % conversion to the hydroxylated product **4.100**. After purification by column chromatography a 43 % of **2.12** and a 29 % yield of **4.100** was obtained. Chiral HPLC of the chlorinated product showed that it was racemic (Table 4.2, entry 2).

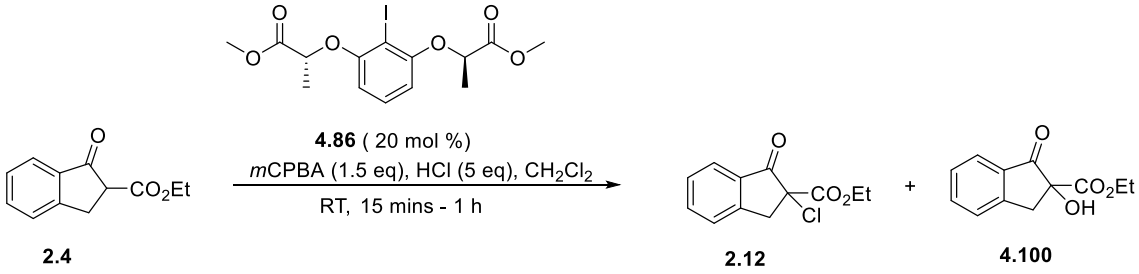
The reaction was repeated under the same conditions but the concentration was reduced from 0.5 to 0.25 M. The conversion to the chlorinated product improved to 70 % and there was a 30 % conversion to the hydroxylated product. After purification by column chromatography, a 70 % yield of **2.12** was obtained along with a 22 % of the hydroxylated product **4.100**. The enantiomeric ratio of the chlorinated product was 48:52 (Table 4.2, entry 3). The concentration was reduced further to 0.1 M under the same reaction conditions and the crude ^{1}H NMR spectrum showed a similar 69 % conversion to **2.12** (53 % isolated yield) and 31 % conversion to the hydroxylated product (28 % isolated yield). Unfortunately, the enantiomeric ratio of **2.12** remained at 48:52 (Table 4.2, entry 4).

In order to induce enantioselectivity the temperature of the reaction was reduced to -20 °C. The reaction was conducted all at -20 °C and the reagents were added all together, (removing the stirring step before adding the β-ketoester). The crude ^{1}H NMR spectrum showed a 100 % consumption of starting material but only a 19 % conversion to the chlorinated product (16 % isolated yield) and an 81 % conversion to the hydroxylated product (54 % isolated yield). Altering the addition of the reagents and conducting the reaction at – 20 °C increased the amount of hydroxylation significantly and did not affect the enantiomeric ratio of the chlorinated product which remained racemic (Table 4.2, entry 5). The reaction was repeated at – 20 °C using the original method (Table 4.2, entry

6). Dimethyl 2,2-((2-iodo-1,3-phenylene)bis(oxy))(2*R*, 2'*R*)-dipropionate (10 mol %) was reacted with *meta*-chloroperbenzoic acid (1.5 equivalents), hydrochloric acid (5 equivalents) in dichloromethane (0.1 M) and the reaction mixture was stirred at room temperature for 15 minutes. After cooling the reaction mixture to -20 ℃, ethyl 1-oxo-2,3-indanone-2-carboxylate **2.4** was added (Table 4.2, entry 6) and the reaction mixture was stirred at – 20 ℃ for 1 hour. The crude ^{1}H NMR spectrum showed a 100 % conversion was achieved with a 64 % conversion to the chlorinated product **2.12** and a 36 % conversion to the hydroxylated product **4.100**. After purification by column chromatography a 49 % isolated yield of the chlorinated product was obtained as well as 27 % of the hydroxylated product. This result indicated that the addition of reagents and the pre stir at room temperature was important, as the hydroxylation was reduced signficantly. Disappointingly a 48: 52 e.r. was still obtained, following chiral HPLC of the chlorinated product. When the reaction was repeated at -20 ℃ under more concentrated conditions, 0.25 M (Table 4.1, entry 7), a similar result to entry 6 was obtained where the ^{1}H NMR spectrum showed a 65 % conversion to the chlorinated product and a 35 % conversion to the hydroxylated product.

The temperature was then reduced to - 40 ℃ and the reaction was conducted at 0.1 M concentration in entry 8. The crude ^{1}H NMR spectrum showed a 100 % consumption of starting material and a 38 % conversion to **2.12** and a 62 % conversion to the hydroxylated product **4.100**. After purification by column chromatography a 17 % isolated yield of the chlorinated product was achieved as well as a 41 % yield of the hydroxylated product. Chiral HPLC of **2.12** still showed a 51:49 enantiomeric ratio. The low temperature and decreased concentration reduced the amount of **2.12** produced but had no effect on the enantiomeric ratio.

Table 4.3 *Enantioselective chlorination of ethyl 1-oxo-2,3-indanone-2-carboxylate using dimethyl 2,2-((2-iodo-1,3-phenylene)bis(oxy))(2R,2'R)-dipropionate*



2.4 2.12 4.100

Entry[a]	Temp. (°C)	Conc. (M)	Conv[b] (%)	2.12[c] (%)	4.100[c] (%)	e.r. of 2.12[d] (%)
1	-40	0.25	100	68 (42)	32 (28)	49:51
2	-60	0.25	95	61 (60)	39 (36)	50:50
3	-78	0.25	96	68 (54)	28 (27)	50:50
4[e]	-95	0.1	100	33 (26)	67 (50)	51:49
5	-95	0.1	100	65	35	-
6[f]	-95	0.1	100	34 (27)	66 (49)	51:49
7	-95	0.02	90	55 (36)	45 (35)	46:54
8[g]	-95	0.02	100	40 (21)	60 (53)	50:50
9[h]	-95	0.02	100	60	40	-
10[i]	-95	0.02	0	0	0	-

[a] Add iodoarene (20 mol %) **4.86**, *m*CPBA (1.5 equivalents) and HCl (5 equivalents) and stir at room temperature for 15 mins, cool to required temperature for 30 mins before adding **2.4** over 20 min dropwise and stirred for 1 hour at the required temperature; [b] Conversion denoted by the consumption of starting material, determined by ^{1}H NMR spectroscopy; [c] Isolated yields in parenthesis; [d] determined by chiral HPLC; [e] Iodoarene **4.86** (10 mol %); [f] HCl (2.5 equivalents); [g] No iodoarene (control); [h] No iodoarene, *m*CPBA (1.5 equivalents) and HCl (5 equivalents) and **2.4** added at -95 °C; [i] Schlenk flask cooled to – 95 °C before adding HCl (5 equivalents) and **2.4** and the reaction was stirred for 1 hour.

The effect of the reaction temperature and the order of the reagents addition was investigated. The amount of iodoarene **4.86** was increased to 20 mol % to help promote the enantioselective reaction and the chlorination was conducted by stirring the iodoarene **4.86** (20 mol %), *m*CPBA (1.5 equivalents) and HCl (5 equivalents) in dry dichloromethane at room temperature for 15 minutes. After cooling the reaction mixture to -40 ℃ for 30 minutes, ethyl 1-oxo-2,3-indanone-2-carboxylate in dry dichloromethane was added dropwise and the reaction mixture was then stirred at -40 ℃ for 1 hour. The crude ^{1}H NMR spectrum showed a 100 % consumption of starting material with a 68 % conversion to the chlorinated product **2.12** and 32 % conversion to the hydroxylated product **4.100**. Following purification by column chromatography a 42 % isolated yield of the **2.12** was obtained but chiral HPLC of the chlorinated product showed that it was a racemic mixture (Table 4.3, entry 1).

The reaction was repeated at – 60 ℃ and the crude ^{1}H NMR spectrum showed a 95 % consumption of starting material with a 61 % conversion to the conversion to the chlorinated product (Table 4.3, entry 2). After column chromatography **2.12** was isolated in a 60 % yield but chiral HPLC still showed a racemic 50:50 enantiomeric ratio. At -78 ℃ the ^{1}H NMR spectrum of the crude product showed a 96 % consumption of starting material with a 68 % conversion to **2.12** and a 28 % conversion to the hydroxylated product **4.100**. After purification by column chromatography a 54 % isolated yield of the chlorinated product was achieved as well as 27 % yield of the hydroxylated product. Chiral HPLC of the chlorinated product was also racemic.

In entry 4 the reaction temperature was reduced to -95 ℃, the concentration was changed to 0.1 M and 10 mol % of the iodoarene **4.86** was used in order to slow the reaction down. The crude ^{1}H NMR spectrum showed a 100 % consumption of starting material but only a 33 % conversion to the chlorinated product and a 67 % conversion to the hydroxylated product. Following purification by column chromatography a 26 % yield of the chlorinated product was obtained as well as 50 % of the hydroxylated product. These conditions slowed the chlorinated down significantly and increased the amount of hydroxylation occurring but the chiral HPLC showed the chlorinated product was racemic with a 51:49 enantiomeric ratio (Table 4.3, entry 4). In order to determine whether the increased hydroxylation and reduction in chlorination was concentration, temperature or

catalytic loading dependent, the reaction was repeated but using 20 mol % of the iodoarene. The ^{1}H NMR spectrum of the crude product showed a 100 % consumption of starting material with a 65 % conversion to the chlorinated product and a 35 % conversion to the hydroxylated product, which showed that the catalytic loading was important in the reaction (Table 4.3, entry 5).

When the number of equivalents of HCl was reduced to 2.5 equivalents (Table 4.3, entry 6), the crude ^{1}H NMR spectrum showed a 34 % conversion to the chlorinated product **2.12** and a 66 % conversion to the hydroxylated product **4.100**. The reduction in the number of equivalents of HCl reduced the conversion to the ethyl-2-chloro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate and increased the competing background hydroxylation, indicating that 5 equivalents of HCl was required.

The reaction was then repeated under more dilute conditions at 0.02M and the crude ^{1}H NMR spectrum showed a 90 % consumption of starting material with a 55 % conversion to the chlorinated product. After purification by column chromatography a 36 % isolated yield of the ethyl 2-chloro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate **2.12** was obtained and a 35 % yield of the hydroxylated product. Chiral HPLC of the chlorinated product showed the first signs of enantioselectivity with a 46:54 enantiomeric ratio, suggesting that more dilute conditions could help induce enantioselectivity (Table 4.3, entry 7).

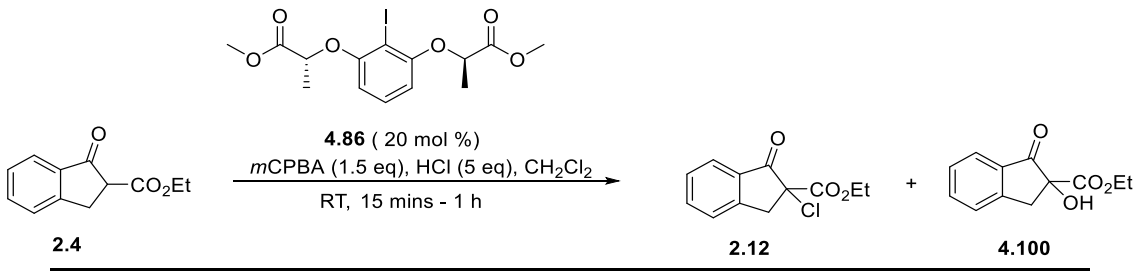
In entry 8 the reaction was conducted in the absence of the iodoarene at – 95 °C at 0.02 M. The crude ^{1}H NMR spectrum showed a 100 % consumption of starting material, with a 40 % conversion to the chlorinated product and a 60 % conversion to the hydroxylated product. Following purification by column chromatography a 21 % isolated yield of the chlorinated product was achieved and a 53 % yield of the hydroxylated product. Chiral HPLC of the chlorinated product showed that it was racemic with a 50:50 % enantiomeric ratio. This result was extremely disappointing and showed that a competing background chlorination was taking place in the absence of the iodoarene.

In order to prevent the background chlorination from occurring, the reaction was repeated in the absence of iodoarene entirely at – 95 °C with no pre stirring before the addition of

the ethyl 1-oxo-2,3-indanone-2-carboxylate **2.4**. The crude ^{1}H NMR spectrum showed a 60 % conversion to the chlorinated product and a 40 % conversion to the hydroxylated product. This method did not prevent the chlorination, and in fact, there was a higher conversion to the chlorinated product.

Finally, in entry 10, the reaction was carried out in the absence of iodoarene and *m*CPBA. Only hydrochloric acid (5 equivalents) was reacted with ethyl 1-oxo-2,3-indanone-2-carboxylate **2.4** at – 95 ℃ and the reaction was stirred for 1 hour. The crude ^{1}H NMR spectrum showed that no reaction had taken place and the starting material was still present. This result shows that the *meta*-chloroperbenzoic acid was reacted with HCl resulted in the background chlorination also hydroxylation.

Table 4.4 *Chlorination of ethyl 1-oxo-2,3-indanone-2-carboxylate*



2.4 **2.12** **4.100**

Entry	Temp. (°C)	Conc. (M)	Conv[a] (%)	2.12[b] (%)	4.100[b] (%)	e.r. of 2.12[c] (%)
1[d]	-95	0.02	59	40 (38)	19 (18)	45:55
2[d, e]	-95	0.02	100	55 (52)	45 (34)	49:51
3[f]	-95	0.02	100	38 (25)	62 (48)	48:52

[a] Conversion denoted by the consumption of starting material, determined by ^{1}H NMR spectroscopy; [b] Isolated yields in parenthesis; [c] determined by chiral HPLC; [d] *m*CPBA (1.5 equivalents) and iodoarene **4.86** was stirred at room temperature for 15 minutes , the reaction was cooled to -95 ℃ for 30 minutes before adding HCl (5 equivalents) and **2.4** in dichloromethane, and then stirring for 1 hour; [e] 2 hours [f] iodoarene **4.86** (20 mol %) and *m*CPBA (1.5 equivalents) was stirred at – 95 ℃ for 15 minutes before adding HCl (5 equivalents) and **2.4** over 20 minutes and the reaction stirred for 1 hour.

The order of addition of the reagents was altered with the aim of eliminating the competing background chlorination and inducing enantioselectivity. The initial method of addition involved reacting iodoarene **4.86**, *m*CPBA (1.5 equivalents) and HCl (5 equivalents) at room temperature for 15 minutes, then the reaction was cooled to the required temperature for 30 minutes before adding the substrate **2.4** in dichloromethane. The reaction was then stirred for 1 hour at the required temperature. The order of addition was altered to react the iodoarene **4.86** (20 mol %), with *m*CPBA (1.5 equivalents) in dry dichloromethane in the first instance and the reaction stirred at room temperature for 15 minutes. The reaction was then cooled to – 95 °C for 30 minutes before adding hydrochloric acid (5 equivalents), followed by the substrate **2.4** in dichloromethane and then the reaction mixture was stirred at – 95 °C for 1 hour. The crude ^{1}H NMR spectrum showed a 59 % consumption of starting material with 40 % conversion to the chlorinated product **2.12** (Table 4.4, entry 1). Following purification by column chromatography a 38 % yield of the chlorinated product was obtained as well as a 18 % yield of the hydroxylated product. The amount of hydroxylation was significantly reduced using this methodology. Chiral HPLC of the chlorinated product showed a 45:55 enantiomeric ratio which was similar to that in entry 7. The reaction was repeated for 2 hours and a 100 % conversion was achieved with a 55 % conversion to the chlorinated product. Surprisingly, however, there was no enantioselectivity and the chlorinated product was obtained in a 52 % yield as a racemic mixture.

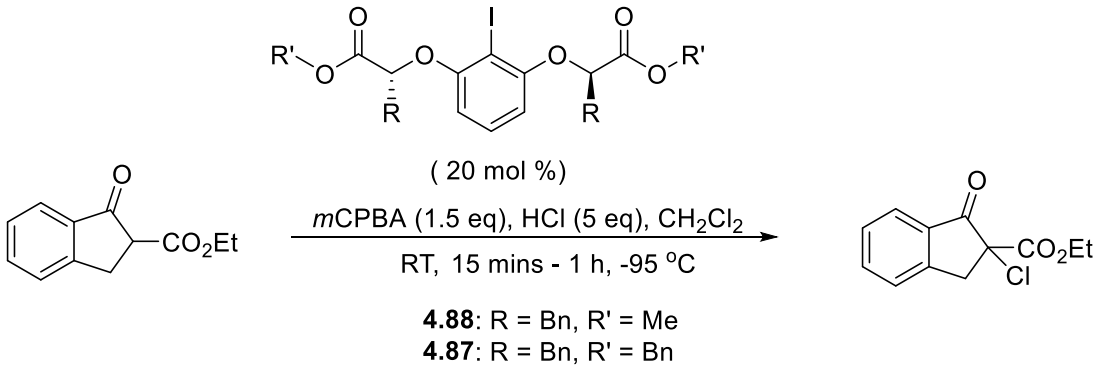
To slow the reaction down further, the reaction was repeated entirely at – 95 °C under the same conditions, rather than stirring *m*CPBA with the iodoarene at room temperature before cooling the reaction down and adding HCl and the ketoester. The crude ^{1}H NMR spectrum showed a 100 % consumption of starting material with a 38 % conversion to **2.12**, and a 62 % conversion to the hydroxylated product (Table 4.4, entry 3) After purification by column chromatography, a 25 % yield of the chlorinated product was achieved and a 48 % yield of the hydroxylated product. Chiral HPLC showed a 48:52 enantiomeric ratio. Interestingly, the hydroxylation increased to 62 % despite the reaction being conducted at low temperature and the large amount of background hydroxylation could have been due to the iodoarene reacting with the *m*CPBA which in turn reacted rapidly and preferentially with the substrate.

The optimum conditions for the chlorination of ethyl 1-oxo-2,3-indanone-2-carboxylate was entry 7 in table 4.3. The reaction was carried out at 0.02 M, using dimethyl 2,2-((2-iodo-1,3-phenylene)bis(oxy))(2*R*, 2'*R*)-dipropionate **4.86** (20 mol %), *m*CPBA (1.5 equivalents), and HCl (5 equivalents) at room temperature, before cooling the reaction mixture to – 95 ℃ for 30 minutes before adding ethyl 1-oxo-2,3-indanone-2-carboxylate in dichloromethane and stirring for 1 hour which gave a 36 % yield of **2.12** and a slight enantiomeric ratio of 46:54.

4.5.3 Enantioselective Chlorination of Ethyl 1-oxo-2,3-indanone-2-carboxylate using Derivatives of Dimethyl 2,2-((2-iodo-1,3-phenylene)bis(oxy))(2*R*, 2'*R*)-dipropionate

The optimum conditions for the chlorination of ethyl 1-oxo-2,3-indanone-2-carboxylate using dimethyl 2,2-((2-iodo-1,3-phenylene)bis(oxy))(2*R*, 2'*R*)-dipropionate **4.86** was then conducted using dimethyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))(2*R*, 2'*R*)-bis(3-phenylpropanoate) **4.88**. Dimethyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))(2*R*, 2'*R*)-bis(3-phenylpropanoate) **4.88** (20 mol %) was reacted with *m*CPBA (1.5 equivalents), HCl (5 equivalents) in dichloromethane and the reaction was stirred at room temperature for 15 minutes. The reaction mixture was then cooled to – 95 ℃ for 30 minutes before adding ethyl 1-oxo-2,3-indanone-2-carboxylate in dry dichloromethane and the reaction was stirred at – 95 ℃ for 1 hour. The crude ^{1}H NMR spectrum showed a 65 % consumption of starting material, with a 29 % conversion to the chlorinated product **2.12** and a 36 % conversion to the hydroxylated product **4.100**. Chiral HPLC of the chlorinated product, gave a 45:55 enantiomeric ratio.

Table 4.5 *Chlorination of ethyl 1-oxo-2,3-indanone-2-carboxylate using dibenzyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))(2R, 2'R)-bis(3-phenylpropanoate)* and *dimethyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))(2R, 2'R)-bis(3-phenylpropanoate)*



4.88: R = Bn, R' = Me
4.87: R = Bn, R' = Bn

Entry	Chiral Iodoarene	Conv[a] (%)	2.17[b] (%)	3.62[b] (%)	e.r of 2.17[c] (%)
1	**4.86** R = Me, R' = Me	90	55 (36)	45 (35)	46:54
2	**4.88** R = Bn, R' = Me	65	29 (16)	36 (36)	45:55
3	**4.87** R = Bn, R' = Bn	74	31 (31)	43 (41)	44:56

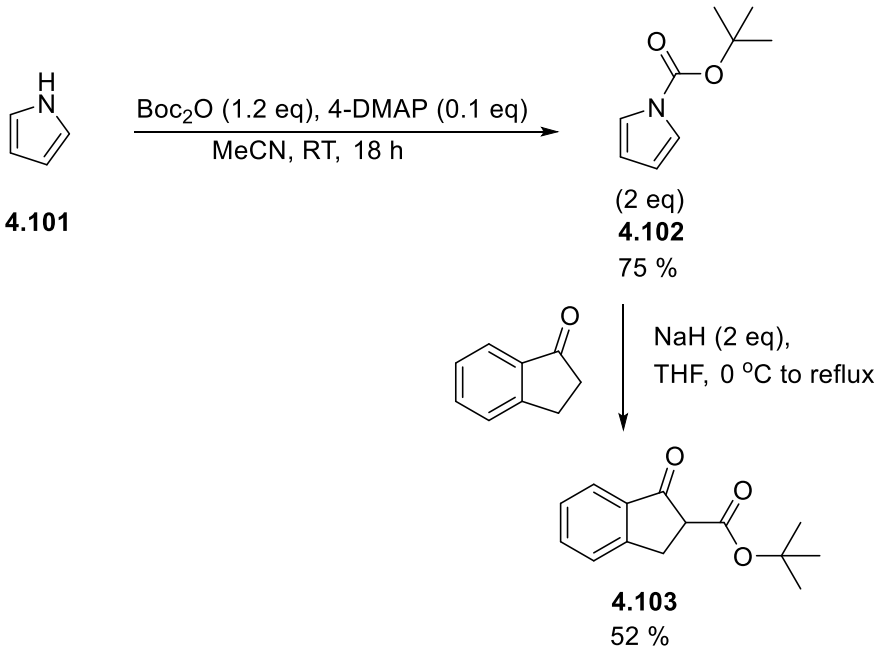
[a] Determined by ^{1}H NMR spectroscopy; [b] Isolated yield in parenthesis; [c] Determined by chiral HPLC.

Dibenzyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))(2*R*, 2'*R*)-bis(3-phenylpropanoate) **4.87** was also used under the same reaction conditions. The crude ^{1}H NMR spectrum showed a 74 % consumption of starting material with a 31 % conversion to the chlorinated product **2.12** and a 43 % conversion to the hydroxylated product **4.100**. Following purification by column chromatography, a 31 % yield of the chlorinated product was achieved and chiral HPLC of the chlorinated product showed a 44:56 enantiomeric ratio.

The dimethyl 2,2-((2-iodo-1,3-phenylene)bis(oxy))(2*R*, 2'*R*)-dipropionate **4.86** iodoarene gave the best conversion (55 %) to the chlorinated product with a 46:54 enantiomeric ratio. All the iodoarenes showed a similar enantiomeric ratio but, the bulkier dibenzyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))(2*R*, 2'*R*)-bis(3-phenylpropanoate) **4.87** was slightly more favourable (44:56 enantiomeric ratio).

4.5.4 Enantioselective Chlorination of *tert*-Butyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate

The enantioselective chlorination of *tert*-butyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate **4.103** was also examined in order to investigate the effect of incorporating a bulkier group onto the substrate. *tert*-Butyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate **4.103** was prepared by the two-step synthesis shown in Scheme 4.40.

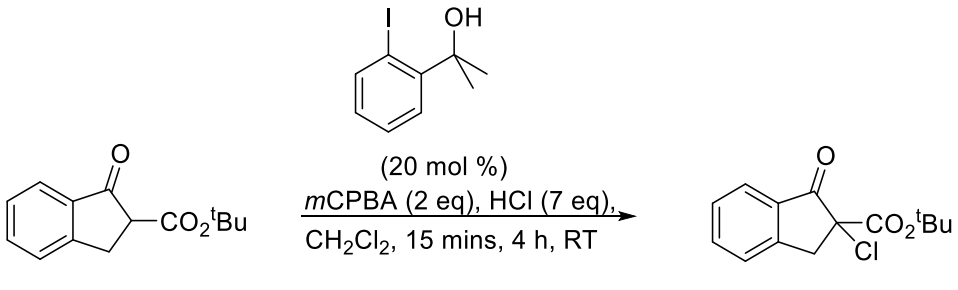


Scheme 4.40 *Synthesis of tert-butyl 1-oxo-2,3-dihydro-1H-indene-2-carboxylate*

Following a procedure by Vesely *et al.*, pyrrole **4.102** was reacted with di-*tert*-butyl dicarbonate and 4-dimethylaminopyridine in acetonitrile at room temperature overnight.[46] After purification by column chromatography a 75 % yield was achieved. The ^{1}H NMR spectrum showed the formation of product by the appearance of a 9H singlet at 1.59 ppm corresponding to the 3 x CH_3 groups as well as the appearance of a 2H singlet at 6.21 ppm and a 2H singlet at 7.23 ppm corresponding to the 4 x CH groups on the pyrrole ring.

N-*tert*-butyloxycarbonyl-pyrrole **4.102** was then reacted with sodium hydride and 1-indanone in dry THF and the reaction was refluxed for 6 hours. After purification by column chromatography, *tert*-butyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate **4.103** was obtained in a 52 % yield. The appearance of a 9H singlet at 1.48 ppm corresponding

to the 3 x CH_3 groups, as well as the appearance of two 1H doublet of doublets at 3.34 ppm and 3.49 ppm corresponding to the CH_2 of the indanone ring confirmed the formation of the product. The product was observed in the mass spectrum where an *m/z* of 255.0991 was observed for the sodiated parent ion.



4.103 **4.104**
83 %

Scheme 4.41 *Chlorination of tert-butyl 1-oxo-2,3-dihydro-1H-indene-2-carboxylate*

tert-Butyl-2-chloro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate **4.104** was prepared by reacting *tert*-butyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate **4.103** with 2-(2-iodophenyl)propan-2-ol **1.59** (20 mol %), *m*CPBA (2 equivalents) and HCl (7 equivalents) in dichloromethane at room temperature for 4 hours (Scheme 4.41). The crude ^{1}H NMR spectrum showed a 100 % consumption of starting material and after purification by column chromatography an 83 % yield of the chlorinated product **4.104** was obtained. The enantiomers of the chlorinated product **4.104** were separated by chiral HPLC using a Chiralcel OJ column. Initially, the flow rate of the mobile phase was set at 0.7 mL/min using hexane : isopropanol (9:1) but unfortunately the enantiomers were not separated fully. The flow rate of the mobile phase was reduced to 0.5 mL/min using the same solvent system hexane : isopropanol (9:1), but again the enantiomers were not separated completely. Finally, the flow rate of the mobile phase was adjusted to 0.7 mL/min and the solvent system was changed to hexane: isopropanol (92:8) and this gave good separation of the enantiomers with retention times of t_1 = 10.17 minutes and t_2 = 13.30 minutes. The optimised conditions were applied to **4.104** and a 50:50 enantiomeric ratio was obtained.

The product was identified by the presence of a 9H singlet at 1.43 ppm in the ^{1}H NMR spectrum corresponding to the *tert*-butyl group, as well as two doublets at 3.55ppm and 4.01 ppm belonging to the CH_2 of the indanone ring. ^{13}C NMR spectroscopy confirmed

the formation of **4.104** by the presence of a singlet at 37.7 ppm corresponding to the 3 x CH_3 of the *tert*-butyl group and the quaternary carbon at 84.4 ppm for the CCl.

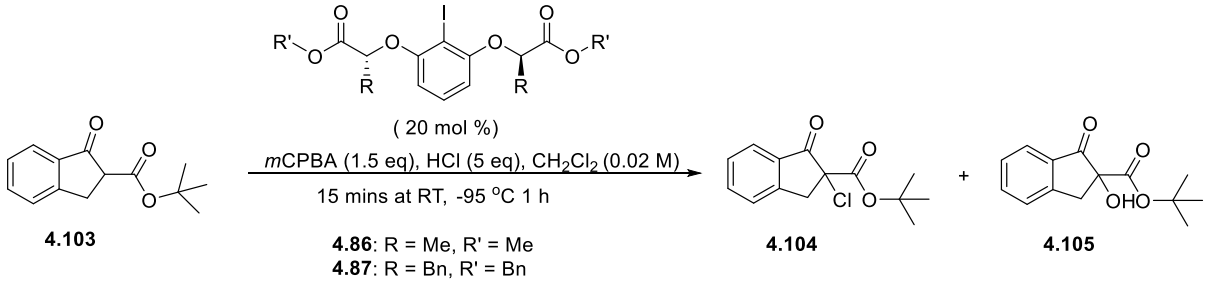
Table 4.6 *Optimisation of the chiral HPLC of tert-butyl 1-oxo-2,3-dihydro-1H-indene-2-carboxylate*

Run	**% IPA**	**Flow rate**	**t_1[a]**	**t_2[b]**
		mL/min	**(minutes)**	**(minutes)**
1	10	0.7	9.8	12.3
2	10	0.5	13.2	17.1
3	8	0.7	10.2	13.3

[a] The retention time of enantiomer 1; [b] the retention time of enantiomer 2; [c] determined by chiral HPLC.

The optimum conditions for the enantioselective chlorination of ethyl 1-oxo-2,3-indanone-2-carboxylate **2.4** were applied to *tert*-butyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate **4.103**. *tert*-Butyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate **4.103** was chlorinated using dimethyl 2,2-((2-iodo-1,3-phenylene)bis(oxy))(2*R*, 2'*R*)-dipropionate **4.86** (20 mol %), *m*CPBA (1.5 equivalents) and HCl (5 equivalents) in dichloromethane (0.02 M) at – 95 °C for 1 hour. The crude ^{1}H NMR spectrum showed a 92 % consumption of starting material and a 36 % conversion to the chlorinated product **4.104** as well as 56 % of the hydroxylated product **4.105**. After purification by column chromatography, a 36 % yield of the chlorinated product was obtained along with a 47 % of the hydroxylated product. Chiral HPLC of the chlorinated product gave a 45:55 enantiomeric ratio. ^{1}H NMR spectroscopy confirmed the formation of the hydroxylated product **4.105** in a 47 % yield by the appearance of a 1H doublet at 3.22 ppm and a 1H doublet at 3.66 ppm corresponding to the CH_2 of the indanone ring and a 1H singlet at 4.01 ppm corresponding to the hydroxyl group.

Table 4.7 *Enantioselective chlorination of tert-butyl 1-oxo-2,3-dihydro-1H-indene-2-carboxylate*



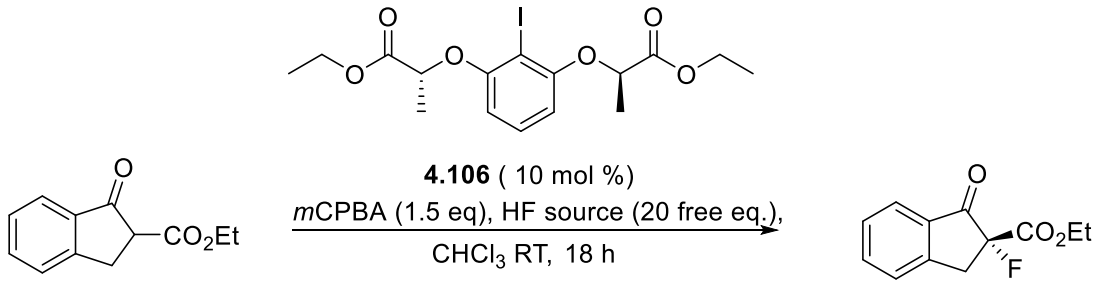
Entry	Iodoarene	Conversion[a] (%)	4.104[b] (%)	4.105[b] (%)	e.r of 4.104[c] (%)
1	**4.86**	92	36 (36)	56 (47)	45:55
2	**4.87**	92	28 (14)	72 (69)	49:51

[a] Conversion denoted by the consumption of starting material, determined by ^{1}H NMR spectroscopy; [b] Isolated yields in parenthesis; [c] Determined by chiral HPLC.

The chlorination of *tert*-butyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate was also carried out using dibenzyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))(2*R*, 2'*R*)-bis(3-phenylpropanoate) **4.87**. The crude ^{1}H NMR spectrum showed a 92 % consumption of starting material, with a 28 % conversion to the chlorinated product **4.104** and a 72 % conversion to the hydroxylated product **4.105**. After purification by column chromatography a 14 % yield of the chlorinated product was obtained followed by a 69 % yield of the hydroxylated product. Chiral HPLC of the chlorinated product **4.104** gave a racemic mixture (49:51 enantiomeric ratio). The optimum iodoarene for this substrate was dimethyl 2,2-((2-iodo-1,3-phenylene)bis(oxy))(2*R*, 2'*R*)-dipropionate **4.86**, which gave a better yield of the chlorinated product and a slight enantiomeric excess (10 %).

Both iodoarenes **4.86** and **4.87** gave only 28-36 % conversion to the chlorinated product and the hydroxylated product was the major product observed in these reactions (56-72 % conversion), in contrast to the reactions using the ethyl 1-oxo-2,3-indanone-2-carboxylate **2.4**. Overall, the chiral iodoarene **4.86** gave a similar 36 % yield of the chlorinated product with a 10 % enantiomeric excess with *tert*-butyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate **4.103** as was observed with ethyl 1-oxo-2,3-indanone-2-carboxylate (36 % yield of the chlorinated product with 8 % enantiomeric excess).

4.5.5 Enantioselective Fluorination of Ethyl 1-oxo-2,3-indanone-2-carboxylate

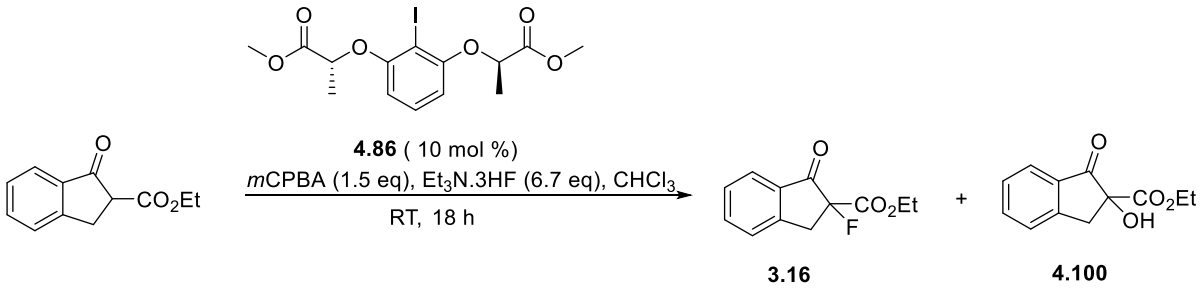


Scheme 4.42 *Rueping's fluorination of ethyl 1-oxo-2,3-indanone-2-carboxylate using* ***4.106***[39]

In order to probe why the chlorination using the chiral iodoarenes resulted in a racemic mixture, Rueping's enantioselective fluorination of ethyl 1-oxo-2,3-indanone-2-carboxylate was conducted. Rueping *et al.* reported the fluorination of ethyl 1-oxo-2,3-indanone-2-carboxylate by reacting iodoarene **4.106** with *m*CPBA and triethylamine trihydrofluoride in chloroform at room temperature for 18 hours. A 25 % yield of the fluorinated product was achieved with a 85:15 enantiomeric ratio (Scheme 4.42).

The separation of the enantiomers of the fluorinated product was developed to determine the enantiomeric ratio. The enantiomers were separated on a chiralcel OJ column and the flow rate of the mobile phase was set at 1.0 mL/min in hexane: isopropanol (9:1). The chiral HPLC of the fluorinated products were run in triplicate and a comparison of the fluorinated product obtained using Rueping's method against the racemic mixture is shown in Table 4.8.

Table 4.8 *Comparison of the retention times of **3.16***



3.16 4.100

Fluorinated Product 3.16	t_1[a] (minutes)	t_2[a] (minutes)	e.r. of 3.16 (%)
Racemic	15.2	22.6	49:51
Rueping's method	15.5	22.9	15:85

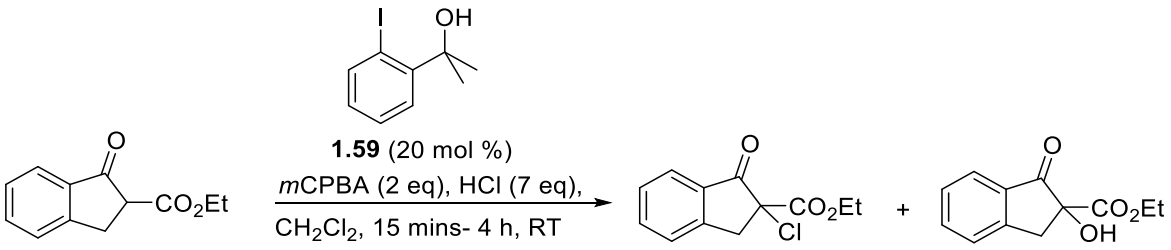
[a] Determined by chiral HPLC.

Following the same procedure, the fluorination was conducted using **4.86** instead of **4.106** and the crude ^{1}H NMR spectrum showed a 61 % consumption of starting material with a 16 % conversion to the fluorinated product **3.16** along with a 23 % conversion to the hydroxylated product **4.100**. Following purification by column chromatography, an 11 % yield of the fluorinated product was achieved. The enantiomers of the fluorinated product were separated on chiral HPLC, using a chiralcel OJ column.

This result was comparable to the literature data where a 25 % conversion to the fluorinated product was obtained with a 85:15 enantiomeric ratio. I obtained a similar 16 % conversion to **3.16** which had a 75:25 e.r. This result confirmed that my chiral iodoarene delivered 50 % enantiomeric excess in the enantioselective fluorination, but only 10 % enantiomeric excess was obtained in the analogous chlorination.

4.5.6 Control Reactions

Table 4.9 *Chlorination of **2.4***



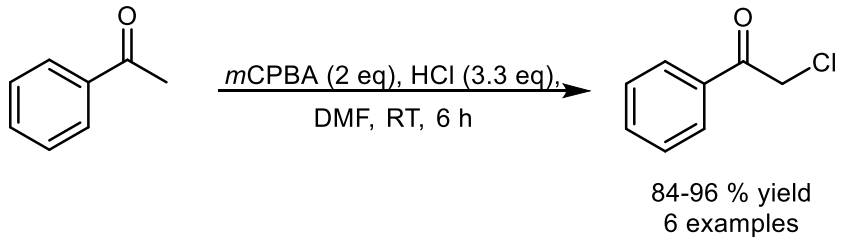
2.12 **4.100**

Entry	Conversion[a] (%)	2.12[b] (%)	4.100[b] (%)
1	100	96 (75)	4 (2)
2[c]	100	76 (72)	24 (18)

[a] Conversion denoted by the consumption of starting material, determined by ^{1}H NMR spectroscopy; [b] Isolated yield in parenthesis; [c] Without iodoalcohol.

To investigate the background reaction in the chlorination of ethyl 1-oxo-2,3-indanone-2-carboxylate **2.4** using iodoalcohol, **1.59**, the reaction was repeated in the absence of iodoalcohol. Ethyl 1-oxo-2,3-indanone-2-carboxylate was reacted with *m*CPBA (2 equivalents) and HCl (7 equivalents) in dichloromethane at room temperature for 4 hours. The crude ^{1}H NMR spectrum showed a 100 % consumption of starting material was achieved with a 76 % conversion to the chlorinated product and a 24 % conversion to the hydroxylated product. A 72 % yield of the chlorinated product and an 18 % yield of the hydroxylated product was obtained after purification by column chromatography, chiral HPLC of the chlorinated product gave a 50:50 e.r. This result compared to entry 1, in the presence of iodoalcohol gave a comparable result. As expected the reaction with iodoalcohol in entry 1 gave a 75 % yield and without iodoalcohol a 72 % yield was obtained. The reaction with iodoalcohol gave 2 % of the hydroxylated product compared to without iodoalcohol which gave an 18 % yield of the hydroxylated product indicating that the iodoalcohol is participating in the reaction.

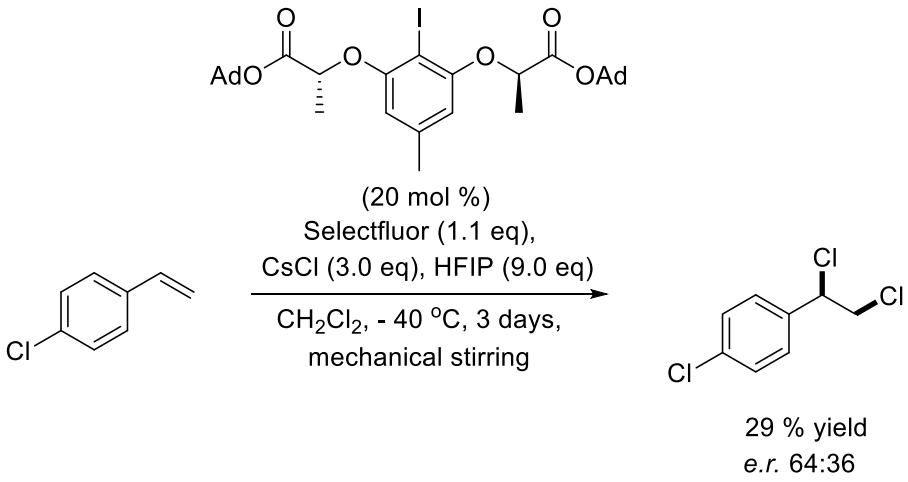
The background chlorination of ethyl 1-oxo-2,3-indanone-2-carboxylate is a result of the *meta*-chloroperbenzoic acid and HCl which promotes the chlorination. The chlorination of carbonyl compounds has been reported in the literature using HCl and *m*CPBA. Ryu and coworkers reported the synthesis of α-chloroketones using *m*CPBA and HCl in DMF to afford α-chloroketones in 84-96 % yields (Scheme 4.43). HCl in combination with hydrogen peroxide has also been used for the synthesis of α-chloroketones. In my system the combination of HCl and a strong oxidant was resulting in the background chlorination, using a different source of chloride could avoid this background reaction.



Scheme 4.43 *Chlorination using mCPBA and HCl*[45]

4.6 Enantioselective Chlorination using Selectfluor and CsCl

In 2019 Gilmour *et al.* reported the first enantioselective, catalytic vicinal dichlorination of unactivated alkenes using C_2 symmetric chiral iodoarenes.[47] This system was a Selectfluor- mediated dichlorination using cesium chloride (Scheme 4.44). Due to the problems of a background chlorination of the ketoesters without an iodoarene present in our system, we became interested in Gilmour's system as he had proved that the reaction did not work without an iodoarene.



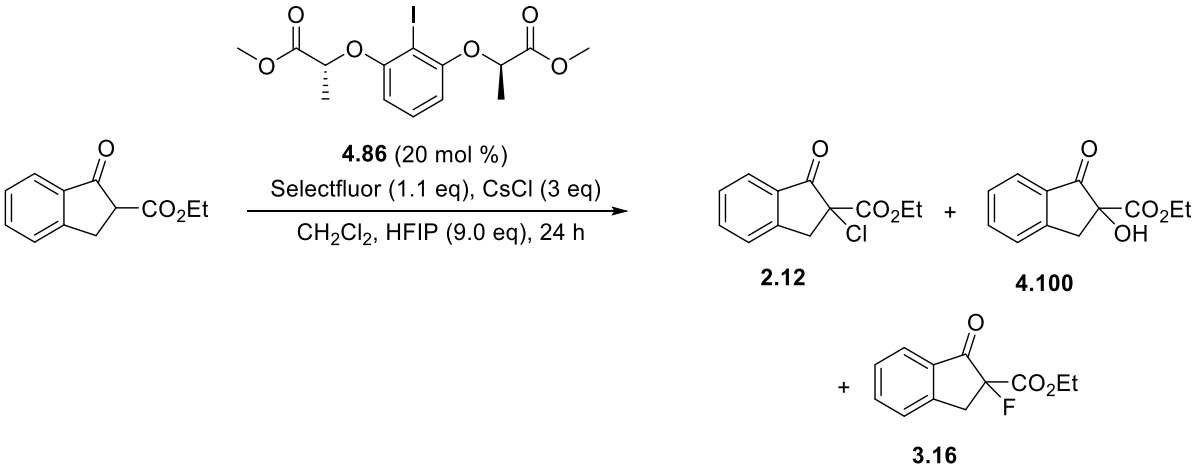
Scheme 4.44 *Gilmour's enantioselective chlorination of unactivated alkenes*[47]

The enantioselective chlorination of ethyl 1-oxo-2,3-indanone-2-carboxylate was investigated using dimethyl 2,2-((2-iodo-1,3-phenylene)bis(oxy))(2*R*, 2'*R*)-dipropionate (20 mol %) **4.86**, Selectfluor (1.1 equivalents), cesium chloride (3 equivalents) and HFIP (0.9 equivalents) in dichloromethane (0.1 M) for 24 hours at – 40 °C (Table 4.10, entry 1). The ^{1}H NMR spectrum of the crude product showed a 41 % consumption of starting material, with a 36 % conversion to the chlorinated product **2.12**, a 4 % conversion to the hydroxylated product **4.100** and a 1 % conversion to the fluorinated product **3.16**. Following purification by column chromatography, a 30 % yield of the chlorinated product was obtained as well as 4 % of the hydroxylated product and 1 % of the fluorinated product. The enantiomers of the chlorinated product **2.12** were separated by chiral HPLC using a chiralcel OJ column to give a 52:48 enantiomeric ratio.

The reaction was then conducted at – 40 °C under more dilute conditions, 0.02 M concentration, for 24 hours. The crude ^{1}H NMR spectrum showed a 27 % consumption of starting material with a 12 % conversion to the chlorinated product, a 15 % conversion to the hydroxylated product and a 1 % conversion to the fluorinated product. Following purification by column chromatography a 4 % isolated yield of the chlorinated product **2.12** was obtained, with a 49:51 enantiomeric ratio. A control reaction was also carried out under the conditions outlined in entry 1; using Selectfluor (1.1 equivalents), cesium chloride (3 equivalents) and HFIP (0.9 equivalents), in dichloromethane (0.1 M) for 24 hours at – 40 °C, in the absence of iodoarene. The ^{1}H NMR spectrum of the crude product showed no conversion to product and only unreacted starting material was recovered. This result showed that the chiral iodoarene is required for the atom-transfer reaction to

take place and that there was no background reaction (Table 4.10, entry 3). Unfortunately, when the reaction was repeated at – 78 °C at the initial concentration, 0.1 M, the crude ^{1}H NMR spectrum showed no conversion to product and only unreacted starting material remained. This result showed that low temperature is preventing the reaction from proceeding under these reaction conditions (entry 4).

Table 4.10 *Enantioselective chlorination using Gilmour's methodology*



2.12 4.100 3.16

Entry	Temp. (°C)	Conv[a] (%)	2.12[b] (%)	4.100[b] (%)	3.16[b] (%)	e.r. of 2.12[c] (%)
1	-40	41	36 (30)	4 (4)	1 (1)	52:48
2[d]	-40	27	12 (4)	15 (10)	1 (1)	49:51
3[e]	-40	0	0	0	0	-
4	-78	0	0	0	0	-

[a] Conversion denoted by the consumption of starting material, determined by ^{1}H NMR spectroscopy; [b] Isolated yields in parenthesis; [c] Determined by chiral HPLC; [d] 0.02 M; [e] No iodoarene (control).

Gilmour's system was better using Selectfluor and cesium chloride rather than *meta*-chloroperbenzoic acid and HCl because there was no background hydroxylation or chlorination. This means that only an enantioselective chlorination could occur, hence enable a true representation of the enantioselectivity observed in this system. Unfortunately, there was no enantioselectivity at - 40 ^{o}C and so more work is required

more work to determine whether the structure of the iodoarene was having a detrimental effect on the reaction or if the reaction is proceeding too quickly. If there was more time available then this system would have been investigated in more depth.

4.7 Conclusions

Three C_2 symmetric iodoarenes were prepared in good yields following a two-step procedure. A new approach for the enantioselective chlorination of 1,3-dicarbonyl compounds using these C_2 symmetric iodoarenes was investigated, but only a small enantiomeric excess was obtained for both substrates explored (8-12 % enantiomeric excesses). Despite conducting the reaction at low temperatures, a competing background hydroxylation was apparent, which was a result of the *m*CPBA. A competing background chlorination was also observed as a consequence of the *m*CPBA in combination with HCl, which could not be eliminated.

The fluorination of ethyl 1-oxo-2,3-indanone-2-carboxylate was investigated using Rueping's conditions, and a comparable yield and enantiomeric ratio was obtained indicating that the chlorination is more challenging because of the background reaction. The Gilmour system was also explored as a potential method to overcome competing background reactions and preliminary work showed that there was no competing reactions. This system could be explored further to develop an enantioselective chlorination of 1,3-dicarbonyl compounds.

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Chapter 5 Conclusions and Future Work

The introduction of nucleophiles into the 2-position of 1,3-dicarbonyl compounds using hypervalent iodine(III) reagents was investigated in this thesis. In chapter 2 a one-pot synthetic method was developed to succesfully introduce nucleophiles into 1,3-dicarbonyl compounds. This work expanded upon previous research within the Stuart group which demonstrated the ability of the fluoroiodane reagent to install a fluoride group using $Et_3N.3HF$ and a tosylate group using para-toluenesulfonic acid as the nucleophile. I reported the introduction of a chloride group into the 2-position of *β*-ketoesters, *β*-ketoamides and a *β*-ketodiketone using fluoroiodane, in good yields (50-69 %) and mild reaction conditions (room temperature for one hour). Methoxylation of a small series of substrates was also successful but required heating to 40 ℃ for 24 hours, to afford the methoxylated products in good yields (32-75 %). The introduction of an ethoxide group was possible but had a limited substrate scope and the reaction was more challenging. Trifluoromethylation and trifluoroethoxylation of ethyl 3-oxo-3-phenylpropanoate was also investigated but was unsucessful. Additionally, nitrogen nucleophiles such as *p*-anisidine and *p*-toluenesulfonamide were explored to observe whether the system was able to tolerate nitrogen nucleophiles. The aminations afforded low yields even when using a Lewis acid catalyst to promote the reaction, this was most likely due to the the low nucleophilcity and bulky nature of the nucleophiles. The fluoroiodane reagent has been shown to introduce a tosyl, fluoride, chloride, methoxy and ethoxy groups into the 2- position of 1,3-dicarbonyl compounds, which is advantageous over many reagents in the literature as it allows for the synthesis of only one reagent to introduce different nucleophiles into 1,3-dicarbonyl compounds. Future investigation into other possible nucleophiles such as bromide or carbon nucleophiles, for example an alkyne would be interesting to test the scope of fluoroiodane.

A catalytic method to introduce different nucleophiles into 1,3-dicarbonyl compounds using the fluoroiodane backbone 2-(2-iodophenyl)propan-2-ol was developed in chapter 3. The chlorination of a small series of *β*-ketoesters was possible using 2-(2-iodophenyl)propan-2-ol (20 mol %) under mild reaction conditions and rapid reactions times (room temperature for 4 hours). This methodology is advantageous as it allows for the *in-situ* generation of the iodine(III) reagent contaning the desired nucleophile, eliminating the need to synthesise fluoroiodane. *p*-Toluenesulfonic acid was explored as a nucleophile and the tosyloxylation of ethyl-3-oxo-3-phenylpropanoate was possible

using 20 mol % 2-(2-iodophenylpropan-2-ol), however problems with hydrolysis of the tosyloxylated product arose, forming α-(tosyloxy)acetophenone, resulting in low isolated yields of the desired product. The corresponding fluorination was explored using $Et_3N.3HF$ but was not possible using sub-stoichiometric quanitities of 2-(2-iodophenyl)propan-2-ol.

1,1,1,3,3,3-hexafluoroisopropanol was investigated as a solvent to promote the fluorination of 1,3-dicarbonyl compounds, by activation of the fluoroiodane reagent through hydrogen bonding. The fluorination of a small series of *β*-ketoesters, *β*-ketoamides and a cylic *β*-ketoester was possible in good to excellent yield using HFIP and fluoroiodane and importantly without the need for $Et_3N.3HF$. This method allows for a very mild fluorination of 1,3-dicarbonyl compounds without the need for harmful sources of HF. ^1H NMR studies revealed the formation of a hydrogen-bonding adduct between fluoroiodane and HFIP providing evidence of activation of fluoroiodane by hydrogen bonding. The hydrogen bonding activation of fluoroiodane by HFIP could be exploited in systems that require a metal catalyst or HF sources, with the aim of developing safer and milder fluorination methodology.

In chapter 4 the enantioselective chlorination of 1,3-dicarbonyl compounds was explored using lactate derived C_2 symmetric chiral iodoarenes, which have been shown to enantioselectively fluorinate 1,3-dicarbonyl compounds in good yields with high enantiomeric excesses. A small series of lactate derived chiral iodoarenes were synthesised in good yields (48-76 %) and subsequently applied to the enantioselective chlorination of ethyl 1-oxo-2,3-indanone-2-carboxylate. The enantioselective chlorination only resulted in small enantiomeric excesses of the two substrates investigated (8-12 %), which was a consequence of a competing background chlorination and hydroxylation due to the *meta*-chloroperbenzoic in combination with hydrochloric acid within this system. An alternative system was explored, the Gilmour system, using cesium chloride and Selectfluor as the oxidant. Preliminary investigations showed no evidence of background reactions. This method would be explored further under more dilute reaction conditions and altering the temperature. The successful system would then be applied to acyclic 1,3-dicarbonyl compounds, as it is currently synthetically challenging to develop enantioselective chlorination methodology capable of chlorinating both cyclic and acyclic substrates in high yields and with high enantiomeric excesses.

Chapter 6 Experimental Section

6.1 General Information

^{1}H, ^{19}F and ^{13}C NMR spectra were recorded on Bruker AV 500, Bruker DRX 400 and Bruker AV 400 spectrometers at ambient temperatures. They were referenced to external $SiMe_4$ (^{1}H) and to external $SiMe_4$ (^{13}C) using the high frequency positive convention. All chemical shifts are quoted in δ (ppm) and coupling constants in Hertz. The specified deuterated solvent was used. The following spectrometer frequencies were used:

Bruker DRX 400 spectrometer: ^{1}H at 400.13 MHz

$^{19}F\{^{1}H\}$ at 376.46 MHz

$^{13}C\{^{1}H\}$ at 100.62 MHz

Bruker AV 500 spectrometer: ^{1}H at 500.13 MHz

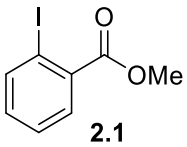
$^{13}C\{^{1}H\}$ at 125.76 MHz

Electron Impact (EI) mass spectra were recorded on a Kratos concept 1 H double focussing, forward geometry mass spectrometer, Atomspheric Solids Analysis Probe (ASAP) mass spectra were recorded on a Xevo QTof mass spectrometer (Waters) coupled to an Acquity LC system (Waters) with an Aquity UPLC BEH C18 column (2.1 x 50 mm) and Electrospray (ESI^{+}) mass spectra were obtained by LC-MS using a Xevo QTof mass spectrometer (Waters) coupled to an Aquity UPLC BEH C18 column (2.1 x 50 mm). Chiral High Pressure Liquid Chromatography (HPLC) was recorded on a PerkinElmer. Inc Series 200 HPLC coupled with a series 200 autosample, series 200 liquid chromatography pump, series 200 peltier column heater and a diode array detector at 25 ℃. The data was analysed using TotalChrom Navigator software version 6.3.4.

Dry solvents were obtained dry from a distillation machine model Puresolve^{TM} and were stored in sealed ampoules over 4Å molecular sieves under an atmosphere of dry nitrogen. Where a reaction was carried out at an elevated temperature, the temperature stated is the dry syn bath temperature. Starting materials were used as received from Sigma-Aldrich, Apollo Scientific, Alfa Aesar, Fluorochem, Acros Organics and Manchester Organic.

6.2 Experimental for Chapter 2

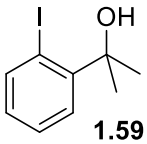
6.2.1 Synthesis of methyl-2-iodobenzoate



2.1

A solution of 2-iodobenzoic acid (25.0 g, 100.8 mmol) in methanol (150 mL) was cooled to 0 °C. Thionyl chloride (11 mL, 151.2 mmol) was added to the solution dropwise over 30 minutes and the reaction mixture was refluxed at 70 °C for 19 hours. The reaction mixture was concentrated *in vacuo,* extracted into ethyl acetate (50 mL) and washed with brine (3 x 50 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* yielding methyl-2-iodobenzoate as a pale yellow oil (25.1 g, 95%). The characterisation data was in agreement with the literature.[1] δ_H (400 MHz, $CDCl_3$) 3.81 (3H, s, OCH_3), 7.01 (1H, td, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.8 Hz, ArH), 7.26 (1H, td, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.3 Hz, ArH), 7.66 (1H, dd, $^3J_{HH}$ = 7.8, $^4J_{HH}$ = 1.6 Hz, ArH), 7.85 (1H, dd, $^3J_{HH}$ = 8.0, $^4J_{HH}$ = 1.2 Hz, ArH). δ_C (100 MHz, $CDCl_3$) 52.5 (CH_3), 94.2 (CI), 127.9 (CH), 130.9 (CH), 132.7 (CH), 135.0 (C), 141.2 (CH), 166.6 (CO). *m/z* (ASAP) 262.9574 (MH^+, $C_8H_8IO_2$ requires 262.9563).

6.2.2 Synthesis of 2-(2-iodophenyl)propan-2-ol

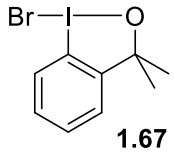


1.59

A dry 3 neck round bottom flask (250 mL) was fitted with a condenser, dropping funnel and a nitrogen supply, then charged with magnesium turnings (4.04 g, 166.0 mmol). Dry diethyl ether (10 mL) was added to the flask and a solution of methyl iodide (7.6 mL, 122.0 mmol) in dry diethyl ether (10 mL) was added to the dropping funnel. The methyl iodide solution was added dropwise to the reaction and upon initiation of the reaction, it was further diluted with diethyl ether (10 mL). The methyl iodide was added at a rate to maintain a gentle reflux. After the addition of methyl iodide was complete, the reaction mixture was cooled to room temperature and allowed to settle. A new three neck round bottom flask (250 mL) was equipped with a dropping funnel, condenser and was evacuated and back-filled with nitrogen. The methylmagnesium iodide solution was transferred by cannula into the new 3-neck round bottom flask. The excess magnesium turnings were rinsed with dry diethyl ether (8.5 mL) which was transferred to the new flask. After cooling the methylmagnesium iodide solution to 0 °C, methyl-2-iodobenzoate (14.5 g, 55.3 mmol) in dry diethyl ether (14 mL) was added dropwise to the Grignard reagent over 10 minutes. The solution was allowed

to warm to room temperature and stirred for a further 18 hours. The reaction mixture was poured gently into an ice cold saturated solution of ammonium chloride (50 mL). Water (60 mL) was added and the mixture was stirred until all the solids had dissolved. Following filtration through celite, the organic layer was separated and the aqueous layer was extracted with diethyl ether (4 x 50 mL). The organic layers were then combined, dried (K_2CO_3) and concentrated under reduced pressure to give 2-(2-iodophenyl)propan-2-ol as a brown oil (9.67 g, 67%). The characterisation data was in agreement with the literature.[2] δ_H (400 MHz, $CDCl_3$) 1.63 (6H, s, CH_3), 2.72 (1H, br s, OH), 6.75 (1H, td, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.7 Hz ArH) 7.18 (1H, td, $^3J_{HH}$ = 8.0, $^4J_{HH}$ = 1.4 Hz, ArH), 7.51 (1H, dd, $^3J_{HH}$ = 8.0, $^4J_{HH}$ = 1.7 Hz, ArH), 7.82 (1H, dd, $^3J_{HH}$ = 7.8, $^4J_{HH}$ = 1.4 Hz, ArH). δ_C (100 MHz, $CDCl_3$) 29.8 (CH_3), 73.6 (C), 93.2 (CI), 124.4 (CH), 128.2 (CH), 128.6 (CH), 142.7 (CH), 148.6 (C). *m/z* (ASAP) 262.9627 (MH^+, $C_9H_{12}IO$ requires 262.9927), 244.9824 (M-OH, $C_9H_{10}I$ requires 244.9822).

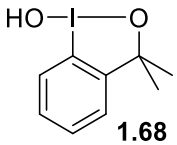
6.2.3 Synthesis of 1-bromo-3,3-dimethyl-1,3-dihydro-λ^3-benzo[*d*][1,2]iodoxole



1.67

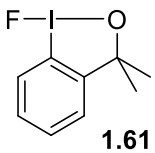
N-Bromosuccinimide (1.71 g, 9.6 mmol) was added, in three portions to a solution of 2-(2-iodophenyl)propan-2-ol (2.29 g, 8.7 mmol) in chloroform (27 mL). The yellow suspension was stirred at room temperature overnight. The reaction mixture was washed with water (3 x 30 mL) and brine (90 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow solid. The yellow solid was recrystallized from ethyl acetate yielding 1-bromo-3,3-dimethyl-1,3-dihydro-λ^3-benzo[*d*][1,2]-iodoxole as yellow crystals (2.80 g, 59%). The characterisation data was in agreement with the literature.[3] δ_H (400 MHz, $CDCl_3$) 1.56 (6H, s, CH_3), 7.14 (1H, m, ArH), 7.53 (2H, m, ArH), 7.99 (1H, m, ArH). δ_C (100 MHz, $CDCl_3$) 29.2 (CH_3), 84.2 (C), 112.0 (CI), 126.0 (CH), 129.3 (CH), 130.4 (CH), 131.1 (CH), 149.8 (C). *m/z* (ESI^+) 340.9037 (MH^+, $C_9H_{11}O^{79}BrI$ requires 340.9032), 342.9023 (MH^+, $C_9H_{11}O^{81}BrI$ requires 342.9012). mp 127-129 °C (lit., 126-128 °C).[3]

6.2.4 Synthesis of 1-hydroxy-3,3-dimethyl-1,3-dihydro-λ^3-benzo[*d*][1,2]iodoxole


1.68

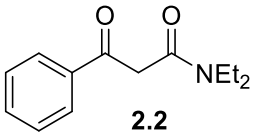
A solution of 1-bromo-3,3-dimethyl-1,3-dihydro-λ^3-benzo[*d*][1,2]iodoxole **4** (6.05 g, 18.8 mmol) in dichloromethane (30 mL) was added to a solution of potassium hydroxide (2.11 g, 37.6 mmol) in water (30 mL) was added to The reaction mixture was stirred at room temperature for 2 hours. After separating the organic layer, the aqueous layer was extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give 1-hydroxy-3,3-dimethyl-1,3-dihydro-λ^3-benzo[*d*][1,2]iodoxole **5** as a pale yellow solid (1.58 g, 78%). The characterisation data was in agreement with the literature.[3] δ_H (400 MHz, $CDCl_3$) 1.48 (6H, s, CH_3), 7.23 (1H, dd, $^3J_{HH}$ = 7.4, $^4J_{HH}$ = 1.4 Hz, ArH), 7.46 (1H, td, $^3J_{HH}$ = 7.2, $^4J_{HH}$ = 1.1 Hz, ArH), 7.51 (1H, td, $^3J_{HH}$ = 7.1, $^4J_{HH}$ = 1.7 Hz, ArH), 7.81 (1H, dd, $^3J_{HH}$ = 8.6, $^4J_{HH}$ = 1.3 Hz, ArH). δ_C (100 MHz, $CDCl_3$) 30.2 (CH_3), 80.3 (C), 115.4 (CI), 126.3 (CH), 126.8 (CH), 129.4 (CH), 130.0 (CH), 149.6 (C). *m/z* (ASAP) 278.9776 (MH^+, $C_9H_{12}IO_2$ requires 278.976). mp 126-129 °C (lit., 126-128 °C).[3]

6.2.5 Synthesis of 1-fluoro-3,3-dimethyl-1,3-dihydro-λ^3-benzo[*d*][1,2]iodoxole


1.61

To a solution of 1-hydroxy-3,3-dimethyl-1,3-dihydro-λ^3-benzo[*d*][1,2]-iodoxole **6** (1.58 g, 5.7 mmol) in dichloromethane (71 mL), $Et_3N.3HF$ (1.11 mL, 6.8 mmol) was added. The reaction mixture was stirred at room temperature for 4 hours. Water (80 mL) was added and the organic layer was separated. After extracting the aqueous layer with dichloromethane (3 x 80 mL), the organic extracts were combined and concentrated *in vacuo* to give a pale yellow solid. The yellow solid was azeotroped with toluene (3 x 100 mL) yielding 1-fluoro-3,3-dimethyl-1,3-dihydro-λ^3-benzo[*d*][1,2]iodoxole, as a pale yellow solid (1.56 g, 98%). The characterisation data was in agreement with the literature. [3] δ_H (400 MHz, $CDCl_3$) 1.46 (6H, s, CH_3), 7.16 (1H, dd, $^3J_{HH}$ = 7.6, $^4J_{HH}$ =1.6 Hz, ArH), 7.40 (1H, td, $^3J_{HH}$ = 7.5, $^4J_{HH}$ = 1.0 Hz, ArH), 7.48 (1H, td, $^3J_{HH}$ = 8.0, $^4J_{HH}$ = 1.4 Hz, ArH), 7.76 (1H, dd, $^3J_{HH}$ = 8.0, $^4J_{HH}$ = 1.0 Hz, ArH). δ_C (400 MHz, $CDCl_3$) 29.1 (CH_3), 85.4 (C), 116.1 (CI), 126.0 (CH), 128.7 (CH), 130.7 (CH), 130.5 (CH), 148.7 (C). δ_F ($CDCl_3$, 376 MHz) -143.1 (s). *m/z* (ASAP) 280.9856 (MH^+, $C_9H_{11}FIO$ requires 280.9839). mp 82-84 °C (lit., 82-84 °C).[3]

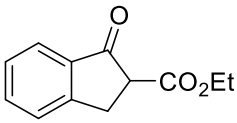
6.2.6 Synthesis of *N,N*-diethyl-3-oxo-3-phenylpropanamide



2.2

A solution of 4-dimethylaminopyridine (1.00 g, 8.20 mmol), diethylamine (8.49 mL, 82.1 mmol) and ethyl 3-oxo-phenylpropanoate (4.74 mL, 27.4 mmol) was prepared in dry toluene (39 mL) under nitrogen. The reaction mixture was stirred at 60 ^{o}C for 26 hours. After concentrating the reaction mixture, the crude product was purified by automated column chromatography (5-20% ethyl acetate in petroleum spirit 40-60^{o}C) to give *N,N*-diethyl-3-oxo-3-phenylpropanamide as a yellow oil (2.27 g, 38%). The characterisation data was in agreement with the literature.[4] δ_H (400 MHz, $CDCl_3$) 1.13 (6H, t, $^3J_{HH}$ = 7.1 Hz, keto, CH_3), 1.18 (6H, t, $^3J_{HH}$ = 7.0 Hz, enol, CH_3), 3.35 (4H, q, $^3J_{HH}$ = 6.6 Hz, keto, CH_2), 3.40 (4H, q, $^3J_{HH}$ = 6.5 Hz, enol, CH_2), 4.04 (2H, s, keto, CH_2), 5.72 (1H, s, enol, CH), 7.34-7.40 (3H, m, enol, ArH), 7.43 (2H, t, $^3J_{HH}$ = 7.4 Hz, keto, ArH), 7.56 (1H, tt, $^3J_{HH}$ = 7.4, $^4J_{HH}$ = 1.3 Hz, keto, ArH), 7.74-7.77 (2H, m, enol, ArH), 8.07 (2H, d, $^3J_{HH}$ = 7.3 Hz, keto, ArH). δ_C (400 MHz, $CDCl_3$) 12.9 (CH_3), 14.2 (CH_3), 40.2 (CH_2), 42.8 (CH_2), 45.8 (CH_2), 84.9 (CH), 125.9 (CH), 128.4 (CH), 128.7 (CH), 130.5 (CH), 133.5 (CH), 135.3 (C), 136.4 (C), 166.1 (C), 171.3 (CO), 171.4 (CO), 194.3 (CO). *m/z* (ASAP) 220.1342 (MH^+, $C_{13}H_{18}NO_2$ requires 220.1338).

6.2.7 Synthesis of ethyl 1-oxo-2,3-indanone-2-carboxylate

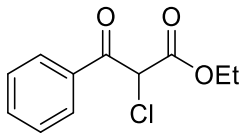


2.4

A solution of 1-indanone (2.01 g, 15.2 mmol) in dry diethyl carbonate (55 mL) was added to a suspension of sodium hydride (1.28 g, 31.9 mmol (60% dispersion in mineral oil)) under nitrogen. After refluxing the reaction mixture at 150 ^{o}C for 3 days, it was cooled to room temperature and HCl (2M, 100 mL) was added. The mixture was extracted into ethyl acetate (4 x 100 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo* to give a brown oil. The crude product was purified by column chromatography (10% ethyl acetate in petroleum spirit 40-60 ^{o}C) affording ethyl-1-indanone-2-carboxylate as a brown oil (2.55 g, 82%). The characterisation data was in agreement with the literature.[5] ^{1}H NMR (400 MHz, $CDCl_3$) 1.30 (3H, t, $^3J_{HH}$ = 7.1 Hz, keto ester CH_3), 1.37 (3H, t, $^3J_{HH}$ = 7.2 Hz, enol CH_3), 3.36 (1H, dd, $^2J_{HH}$ = 17.2, $^3J_{HH}$ = 8.2 Hz, keto CH_2), 3.51 (2H, s, enol CH_2), 3.54 (1H, dd, $^2J_{HH}$ = 17.0, $^3J_{HH}$ = 4.0 Hz, keto CH_2), 3.73 (1H, dd, $^3J_{HH}$ = 8.3, $^4J_{HH}$ = 4.1 Hz, keto CH), 4.24 (2H, m, keto OCH_2), 4.31 (2H, qd, $^3J_{HH}$ = 7.2,

$^3J_{HH}$ = 1.3 Hz, enol OCH_2), 7.36-7.40 (1H keto, 2H enol, m, ArH), 7.42-7.45 (1H, m, enol ArH), 7.49 (1H, d, $^3J_{HH}$ = 7.7 Hz, keto ArH), 7.59-7.60 (1H keto, 1H enol, m, ArH), 7.76 (1H, d, $^3J_{HH}$ = 7.7 Hz, keto, ArH), 10.45 (1H, br s, enol, OH). δ_C (400 MHz, $CDCl_3$) 14.2 (CH_3, keto), 14.5 (CH_3, enol), 30.3 (CH_2, keto), 32.6 (CH_2, enol), 53.3 (CH, keto), 60.1 (CH_2, enol), 61.7 (CH_2, keto), 102.5 (C, enol), 120.7 (CH, enol), 124.7 (CH, keto), 126.3 (C, enol), 126.6 (CH, keto), 126.8 (CH, enol), 127.8 (CH, keto), 129.3 (CH, enol) 135.3 (CH, keto), 135.3 (CH, enol), 143.2 (C, enol), 153.6 (C, keto), 169.1 (C, keto), 200.0 (CO, keto). m/z (ASAP) 205.0864 (MH^+, $C_{12}H_{13}O_3$ requires 205.0865).

6.2.8 General procedure for the chlorination of ethyl 3-oxo-3-phenylpropanoate (Table 2.1)



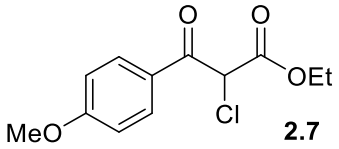
2.5

A 5 mL round bottomed flask was charged with 1-fluoro-3,3-dimethyl-1,3-dihydro-λ^3-benzo[*d*][1,2]iodoxole (0.25 g, 0.90 mmol) in dry acetonitrile (1.2 mL or 2.4 mL) under nitrogen. Ethyl 3-oxo-3-phenylpropanoate (0.13 mL, 0.75 mmol) was then added to the solution, followed by either HCl 37 % (0.06 mL, 1.97 mmol) or TBACl (0.55 g, 1.97 mmol). The Schlenk flask was sealed and stirred at room temperature for 1 hour. After this time the reaction mixture was concentrated *in vacuo*. The crude product was purified by column chromatography using 55% dichloromethane in 45 % petroleum spirit 40-60 ^oC to give ethyl 2-chloro-3-oxo-3-phenylpropanoate as a colourless oil (0.11 g, 63%) in entry 1. The characterisation data was in agreement with the literature.[6] δ_H (400 MHz, $CDCl_3$) 1.21 (3H, t, $^3J_{HH}$ = 7.1 Hz, CH_3), 4.26 (2H, q, $^3J_{HH}$ = 7.0 Hz, OCH_2), 5.62 (1H, s, CHCl), 7.48 (2H, t, $^3J_{HH}$ = 7.6 Hz, ArH), 7.61 (1H, t, $^3J_{HH}$ = 7.4 Hz, ArH), 7.98 (2H, d, $^3J_{HH}$ = 8.4 Hz, ArH). δ_C (400 MHz, $CDCl_3$) 13.9 (CH_3), 60.0 (CH), 63.2 (CH_2), 128.9 (CH), 129.3 (CH), 133.4 (C), 134.4 (CH), 165.3 (CO), 188.2 (CO). *m/z* (ASAP) 227.0489 (MH^+, $C_{11}H_{12}O_3{}^{35}Cl$ requires 227.0475), 229.0460 (MH^+, $C_{11}H_{12}O_3{}^{37}Cl$ requires 229.0449).

6.2.9 General procedure for the chlorination of 1,3-dicarbonyl compounds

A round bottomed flask was charged with 1-fluoro-3,3-dimethyl-1,3-dihydro-λ^{3}-benzo[*d*][1,2]iodoxole (0.25g, 0.90 mmol) in dry acetonitrile (2.4 mL) under nitrogen. The 1,3-dicarbonyl substrate (0.75 mmol) was added to the solution, followed by HCl 37 % (0.06 mL, 1.97 mmol). The reaction flask was sealed and stirred at room temperature for 1 hour. The reaction mixture was then concentrated *in vacuo.*

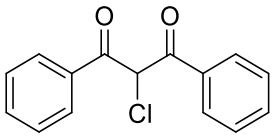
6.2.10 Ethyl 3-(4-methoxyphenyl)-3-oxopropanoate



2.7

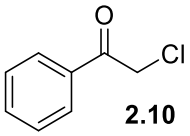
The crude product was purified by column chromatography using 55% dichloromethane in petroleum spirit 40-60 ºC to give ethyl 2-chloro-3-(4-methoxyphenyl)-3-oxopropanoate as a colourless oil (0.94 g, 50%). δ_H (400 MHz, $CDCl_3$) 1.25 (3H, t, $^3J_{HH}$ = 7.1 Hz, CH_3), 3.89 (3H, s, OCH_3), 4.29 (2H, q, $^3J_{HH}$ = 7.2 Hz, OCH_2), 5.57 (1H, s, CHCl), 6.97 (2H, dt, $^3J_{HH}$ = 9.0, $^4J_{HH}$ = 2.0 Hz, ArH), 7.99 (2H, dt, $^3J_{HH}$ = 8.2, $^4J_{HH}$ = 2.0 Hz, ArH). δ_C (400 MHz, $CDCl_3$) 13.9 (CH_3), 55.6 (CH_3), 57.9 (CH), 63.1 (CH_2), 114.2 (CH), 126.2 (C), 131.8 (CH), 164.5 (C), 165.5 (CO), 186.7 (CO). m/z (ASAP) 257.0571 (MH^+, $C_{12}H_{14}O_4{}^{35}Cl$ requires 257.0571), 259.05557 (MH^+, $C_{12}H_{14}O_4{}^{37}Cl$ requires 259.0551).

6.2.11 2-Chloro-1,3-diphenylpropan-1,3-dione



2.8

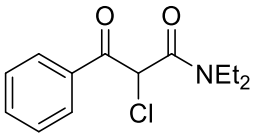
The crude product was purified by precipitating in petroleum spirit (40-60 ºC) and filtering by gravity to give 2-chloro-1,3-diphenylpropane-1,3-dione as a white precipitate (0.11 g, 56 %) and 2-chloro-1,3-phenylethan-1-one as a colourless oil (0.05 g, 25 %). The characterisation data was in agreement with the literature.[6] δ_H (400 MHz, $CDCl_3$) 6.41 (1H, s, CHCl), 7.47 (4H, t, $^3J_{HH}$ = 7.7 Hz, ArH), 7.60 (2H, t, $^3J_{HH}$ = 7.3Hz, ArH), 8.00 (4H, d, $^3J_{HH}$ = 7.7 Hz, ArH). δ_C (400 MHz, $CDCl_3$) 63.0 (CH), 129.0 (CH), 129.3 (CH), 134.0 (C), 134.3 (CH), 189.3 (CO). *m/z* (ASAP) 259.0531 (MH^+, $C_{15}H_{12}{}^{35}ClO_2$ requires 259.0526), 261.0513 (MH^+, $C_{15}H_{12}{}^{37}ClO_2$ requires 261.0501). mp 86-88°C (lit.,[7] 86-87 °C).



2.10

The characterisation data was in agreement with the literature.[8] δ_H (400 MHz, $CDCl_3$) 4.71 (2H, s, CH_2Cl), 7.50 (2H, t, $^3J_{HH}$ = 7.4 Hz, ArH), 7.62 (1H, tt, $^3J_{HH}$ = 7.4 Hz, $^4J_{HH}$ = 1.4 Hz, ArH), 7.96 (2H, dd, $^3J_{HH}$ = 8.2 Hz, $^4J_{HH}$ = 1.4 Hz, ArH). δ_C (400 MHz, $CDCl_3$) 46.0 (CH_2), 128.5 (CH), 128.9 (CH), 134.0 (CH), 134.3 (C), 191.1 (CO). m/z (ASAP) 155.0259 (MH^+, C_8H_8 ^{35}ClO requires 155.0264), 157.0247 (MH^+, $C_8H_8{}^{37}$ClO requires 157.0156).

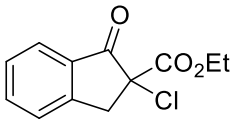
6.2.12 *N,N*-diethyl-3-oxo-3-phenylpropanamide



2.11

The crude product was purified by column chromatography using 20% ethyl acetate in petroleum spirit 40-60 ºC to give *N,N*-diethyl 2-chloro-3-oxo-3-phenylpropanamide as a colourless oil (0.11 g, 69%). δ_H (400 MHz, $CDCl_3$) 1.08 (3H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 1.22 (3H, t, $^3J_{HH}$ = 7.1 Hz, CH_3), 3.37 (2H, qd, $^3J_{HH}$ = 7.0, 2.0 Hz, *N*CH_2), 3.40-3.53 (2H, m, *N*CH_2), 5.84 (1H, s, CHCl), 7.46 (2H, t, $^3J_{HH}$ = 7.7 Hz, ArH), 7.59 (1H, tt, $^3J_{HH}$ = 7.5, $^4J_{HH}$ = 1.2 Hz, ArH), 7.99 (2H, d, $^3J_{HH}$ = 7.2 Hz, ArH). δ_C (400 MHz, $CDCl_3$) 12.2 (CH_3), 14.0 (CH_3), 40.8 (CH_2), 42.5 (CH_2), 60.4 (CH), 128.8 (CH), 128.9 (CH), 133.9 (CH), 134.2 (C), 164.0 (CO), 188.7 (CO). *m/z* (ASAP) 254.0954 (MH^+, $C_{13}H_{17}{}^{35}ClNO_2$ requires 254.0948), 256.0930 (MH^+, $C_{13}H_{17}{}^{37}ClNO_2$ requires 256.0922).

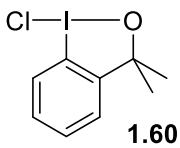
6.2.13 Ethyl 2-chloro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate



2.12

The crude product was purified by column chromatography using 10% ethyl acetate in petroleum spirit 40 – 60 ºC to give ethyl 2-chloro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate as a colourless oil (0.10 g, 57%). The characterisation data was in agreement with the literature.[6] δ_H (500 MHz, $CDCl_3$) 1.27 (3H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 3.56 (1H, d, $^2J_{HH}$ = 17.8 Hz, CH_AH$_B$), 4.10 (1H, d, $^2J_{HH}$ = 17.8 Hz, CH$_A$$H_B$), 4.27 (2H, m, OCH_2), 7.46-7.49 (2H, m, ArH), 7.70 (1H, td, $^3J_{HH}$ = 7.8, $^4J_{HH}$ = 1.1 Hz, ArH), 7.71 (1H, d, $^3J_{HH}$ = 6.8 Hz, ArH). δ_C (500 MHz, $CDCl_3$) 14.0 (CH_3), 43.4 (CH_2), 63.4 (CH_2), 68.0 (C), 126.0 (CH), 126.3 (CH), 128.6 (CH), 132.5 (C), 136.4 (CH), 150.7 (C), 167.1 (CO), 195.1 (CO). m/z (ASAP) 239.0481 (MH^+, $C_{12}H_{12}O_3{}^{35}Cl$ requires 239.0475), 241.0471 (MH^+, $C_{12}H_{12}O_3{}^{37}Cl$ requires 241.0449).

6.2.14 1-Chloro-1,3-dihydro-dimethyl-1,3-benzoiodoxole



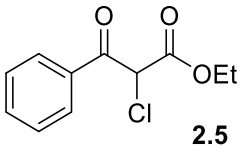
1.60

A 100 mL three necked flask was charged with 2-(2-iodophenyl)propan-2-ol (1.05 g, 4.0 mmol) and acetonitrile (15 mL). Whilst refluxing the solution at 75 ºC, a solution of trichloroisoscyanuric acid (0.32 g, 1.40 mmol) in acetonitrile (5 mL) was added dropwise. The solution was refluxed for a further 5 minutes and the isocyanuric acid precipitated out of solution as a white solid. The solution was filtered through celite (1 cm) in a preheated sintered funnel. The filtrate was concentrated *in vacuo* yielding chloroiodane as a yellow solid (0.98 g, 83 %). The characterisation data was in agreement with the literature.[9] δ_H (500 MHz, $CDCl_3$) 1.56 (6H, s, 2 x CH_3), 7.18 (1H, d, $^3J_{HH}$ = 6.9 Hz, ArH), 7.54 (2H, m, ArH), 8.02 (1H, d, $^3J_{HH}$ = 8.6 Hz, ArH). δ_C (500 MHz, $CDCl_3$) 29.2 (CH_3), 85.1 (C), 114.6 (CI), 126.1 (CH), 128.4 (CH), 130.4 (CH), 140.0 (CH), 149.5 (C). m/z (ASAP) 296.9554 (MH^+, $C_9H_{11}O^{35}ClI$ requires 296.9543), 298.9504 (MH^+, $C_9H_{11}O^{37}ClI$ requires 298.9514). mp 144 – 147 °C (lit.,[9] 145-147 °C).

6.2.15 General procedure for the chlorination of 1,3-dicarbonyl compounds using 1-hydroxy-3,3-dimethyl-1,3-dihydro-λ^3-benzo[*d*][1,2]iodoxole (Scheme 2.19)

A 5 mL round bottomed flask was charged with 1-hydroxy-3,3-dimethyl-1,3-dihydro-λ^3-benzo[*d*][1,2]-iodoxole (0.25 g, 0.90 mmol) in dry acetonitrile (2.4 mL) under nitrogen. The 1,3-dicarbonyl substrate (0.75 mmol) and HCl 37 % (60 µL, 1.97 mmol) were then added to the solution. The flask was sealed and stirred for 2 hours at room temperature. The reaction mixture was concentrated *in vacuo*.

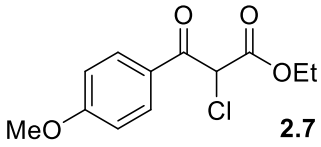
6.2.16 Synthesis of ethyl 2-chloro-3-oxo-3-phenylpropanoate



2.5

The crude product was purified by column chromatography using 5% ethyl acetate in petroleum spirit 40-60 °C to give ethyl 2-chloro-3-oxo-3-phenylpropanoate as a colourless oil (0.10 g, 59%). The characterisation data was in agreement with the literature.[6]

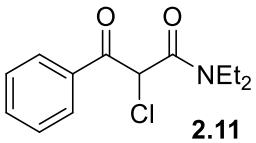
6.2.17 Ethyl 2-chloro-3-(4-methoxyphenyl)-3-oxopropanoate



2.7

The crude product was purified by column chromatography using 55% dichloromethane in petroleum spirit 40-60 °C to give ethyl 2-chloro-3-(4-methoxyphenyl)-3-oxopropanoate as a colourless oil (0.92 mg, 47%).

6.2.18 Synthesis of *N*,*N*-diethyl 2-chloro-3-oxo-3-phenylpropanamide

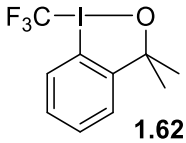


2.11

The crude product was purified by recrystallisation from 20% ethyl acetate in petroleum spirit 40-60°C to give *N*,*N*-diethyl 2-chloro-3-oxo-3-phenylpropanamide as colourless crystals (0.12 g, 64%).

Trifluoromethylation of 1,3-dicarbonyl compounds

6.2.19 Synthesis of 3,3-dimethyl-1-(trifluoromethyl)-1,2-benziodoxole (Togni's reagent)



1.62

A solution of 1-fluoro-3,3-dimethyl-1,3-dihydro-λ^3-benzo[*d*][1,2]iodoxole (0.25 g, 0.90 mmol) in dry acetonitrile (2.4 mL) was prepared under nitrogen. After adding trimethyl(trifluoromethyl)silane (291 µL, 1.97 mmol) to the solution, the reaction flask was sealed and stirred for 2 hours at room temperature. The reaction mixture was concentrated *in vacuo* to give a brown solid. The solid was precipitated in pentane and the filtrate was concentrated to give 3,3-dimethyl-1-(trifluoromethyl)-1,2-benziodoxole as an oily yellow solid (0.28 g, 95%) in a 9:1 mixture with 2-(2-iodophenyl)propan-2-ol. The characterisation data was in agreement with the literature.[9] δ_H (500 MHz, $CDCl_3$) 1.48 (6H, s, 2 x CH_3), 7.23-7.42 (2H, m, ArH), 7.51-7.54 (2H, m, ArH). δ_C (500 MHz, $CDCl_3$) 30.8 (CH_3), 76.5 (C), 109.1 (q, $^1J_{CF}$ 395.5 Hz, CF_3), 110.5 (q, $^3J_{CF}$ = 3.0 Hz, CI), 127.3 (CH), 127.8 (q, $^4J_{CF}$ = 2.0 Hz, CH), 129.8 (CH), 130.6 (CH), 149.2 (C). δ_F (500 MHz, $CDCl_3$) -40.1 (s). m/z (ASAP) 260.9786 ($[M - CF_3]^+$, $C_9H_{10}OI$ requires 260.9776).

Methoxylation of 1,3-dicarbonyl compounds (Scheme 2.24)

6.2.20 General procedure for the methoxylation of ethyl 3-oxo-3-phenylpropanoate (Table 2.4)

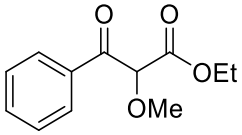
A 5 mL round bottomed flask was charged with 1-fluoro-3,3-dimethyl-1,3-dihydro-λ^3-benzo[*d*][1,2]iodoxole (0.24 g, 0.86 mmol) and the ethyl 3-oxo-3-phenylpropanoate (0.13 mL, 0.72 mmol) in dry dichloromethane (1.2 mL) under nitrogen. After adding methanol (0.087 mL, 2.20 mmol) the flask was sealed and stirred at the required temperature for 24 hours. At the end of the reaction, the reaction mixture was concentrated *in vacuo*.

6.2.21 General procedure for methoxylation of 1,3-dicarbonyl compounds (Scheme 2.25)

A 5 mL round bottomed flask was charged with 1-fluoro-3,3-dimethyl-1,3-dihydro-λ^3-benzo[*d*][1,2]iodoxole (0.24 g, 0.86 mmol) and the 1,3-dicarbonyl compound (0.72 mmol) in dry dichloromethane (1.2 mL) under nitrogen. After adding methanol (0.087

mL, 2.20 mmol) the flask was sealed and refluxed at 40 °C for 24 hours. At the end of the reaction, the reaction mixture was concentrated *in vacuo*.

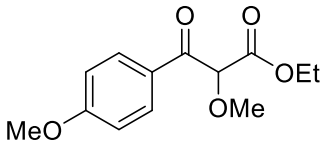
6.2.22 Ethyl 2-methoxy-3-oxo-3-phenylpropanoate



2.16

The crude product was purified using 0.5 % methanol in dichloromethane to give ethyl 2-methoxy-3-oxo-3-phenylpropanoate as a colourless oil (0.116 g, 69%). The characterisation data was in agreement with the literature.[11] δ_H (500 MHz, $CDCl_3$) 1.20 (3H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 3.54 (3H, s, OCH_3), 4.24 (2H, q, $^3J_{HH}$ = 7.1 Hz, OCH_2), 4.93 (1H, s, CH), 7.47 (2H, t, $^3J_{HH}$ = 8.0 Hz, ArH), 7.60 (1H, t, $^3J_{HH}$ = 7.5 Hz, ArH), 8.07 (2H, d, $^3J_{HH}$ = 8.4 Hz, ArH). δ_C (100 MHz, $CDCl_3$) 14.0 (CH_3), 58.7 (CH_3), 61.0 (CH_2), 85.2 (CH), 128.6 (CH), 129.4 (CH), 134.1 (CH), 134.1 (C), 167.5 (CO), 192.5 (CO). m/z (ASAP) 223.0970 (MH^+, $C_{12}H_{15}O_4$ requires 223.0970).

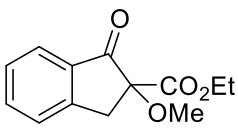
6.2.23 Ethyl 2-methoxy-3-(4-methoxyphenyl)-3-oxopropanoate



2.17

The crude product was purified using 0.5 % methanol in dichloromethane to give ethyl 2-methoxy-3-(4-methoxyphenyl)-3-oxopropanoate as a colourless oil (0.12 g, 68%). The characterisation data was in agreement with the literature.[11] δ_H (400 MHz, $CDCl_3$) 1.20 (3H, t, $^3J_{HH}$ = 7.1 Hz, CH_3), 3.51 (3H, s, OCH_3), 3.86 (3H, s, $ArOCH_3$), 4.22 (2H, q, $^3J_{HH}$ = 7.2 Hz, OCH_2), 4.88 (1H, s, CH), 6.92 (2H, d, $^3J_{HH}$ = 8.9 Hz, ArH), 8.06 (2H, d, $^3J_{HH}$ = 8.9 Hz, ArH). δ_C (400 MHz, $CDCl_3$) 14.0 (CH_3), 55.5 (CH_3), 58.5 (CH_3), 61.9 (CH_2), 85.3 (CH), 113.9 (CH) 127.1 (C), 131.9 (CH), 164.2 (C), 167.7 (CO), 190.9 (CO). m/z (ASAP) 253.1075 (MH^+, $C_{13}H_{17}O_5$ requires 253.1076).

6.2.24 Ethyl 2-methoxy-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate

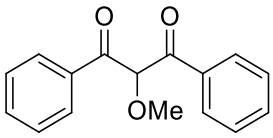


2.18

The crude product was purified using 0.5 % methanol in dichloromethane to give ethyl 2-methoxy-1-oxo-2,3-dihydro-1*H*-2-indene-2-carboxylate as a colourless oil (0.13 g, 76 %). δ_H (400 MHz, $CDCl_3$) 1.24 (3H, t, $^3J_{HH}$ = 7.1 Hz, CH_3), 3.30 (1H, d, $^2J_{HH}$ =

17.2 Hz, CH_AH$_B$), 3.54 (3H, s, OCH_3), 3.66 (1H, d, $^2J_{HH}$ = 17.2 Hz, CH_AH_B), 4.24 (2H, q, $^3J_{HH}$ = 7.2 Hz, OCH_2), 7.42 (1H, t, $^3J_{HH}$ = 7.4 Hz, ArH), 7.47 (1H, d, $^3J_{HH}$ = 7.8 Hz, ArH), 7.65 (1H, td, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.3 Hz, ArH), 7.80 (1H, d, $^3J_{HH}$ = 7.8 Hz, ArH). δ_C (400 MHz, $CDCl_3$) 14.1 (CH_3), 38.1 (CH_2), 54.3 (CH_3), 62.0 (CH_2), 85.6 (C), 125.1 (CH), 126.5 (CH), 128.1 (CH), 134.3 (C), 136.0 (CH), 151.7 (C), 170.0 (CO), 199.0 (CO). m/z (ESI) 235.0968 (MH^+, $C_{13}H_{15}O_4$ requires 235.0970).

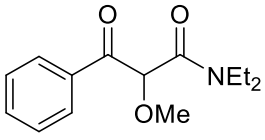
6.2.25 2-Methoxy-1,3-diphenylpropane-1,3-dione



2.19

The crude product was purified using 0-5% ethyl acetate in petroleum spirit 40-60 ºC to give 2-methoxy-1,3-diphenylpropane-1,3-dione as a yellow oil (0.06 g, 32%) aS a mixture of keto: enol (37 %: 63%) tautomers. The characterisation data was in agreement with the literature.[11] δ_H (400 MHz, $CDCl_3$) 3.24 (3H, s, CH_3, enol), 3.54 (3H, s, CH_3, keto), 5.64 (1H, s, CH, keto), 7.42-7.58 (8H enol, 8H keto, m, ArH), 8.10-8.14 (2H enol, 2H keto, m, ArH), 15.80 (1H, br. s, OH). δ_C (400 MHz, $CDCl_3$) 56.9 (CH_3), 61.5 (CH_3), 91.3 (CH), 128.3 (CH), 128.6 (CH), 129.0 (C), 129.1 (CH), 129.7 (CH), 129.9 (C), 131.7 (CH), 132.3 (C), 134.0 (CH), 134.9 (C), 181.9 (CO), 192.5 (CO). m/z (ASAP) 255.1033 (MH^+, $C_{16}H_{15}O_3$ requires 255.1021).

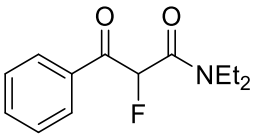
6.2.26 Synthesis of *N*,*N*-diethyl-2-methoxy-1-oxo-3-phenylpropanamide



2.20

A solution of *N*,*N*-diethyl-3-oxo-3-phenylpropanamide (0.16 g, 0.72 mmol) and 1-fluoro-3,3-dimethyl-1,3-dihydro-λ^3-benzo[*d*][1,2]iodoxole (0.24 g, 0.86 mmol) was prepared under nitrogen. After adding methanol (1.2 mL), the flask was sealed and stirred at room temperature for 24 hours. The reaction mixture was then concentrated *in vacuo*. The crude product was purified using 0.5 % methanol in dichloromethane to give *N*,*N*-diethyl-2-methoxy-1-oxo-3-phenylpropanamide as a colourless oil (0.88 g, 49%) and *N*,*N*-diethyl-2-fluoro-3-oxo-3-phenylpropamide as a yellow oil (0.03 g, 17 %). δ_H (500 MHz, $CDCl_3$) 1.06 (3H, t, $^3J_{HH}$ = 7.0 Hz, CH_3), 1.11 (3H, t, $^3J_{HH}$ = 7.0 Hz, CH_3), 3.24-3.39 (2H, m, CH_2), 3.41 – 3.49 (2H, m, CH_2), 3.51 (3H, s, OCH_3), 5.21 (1H, s, CH), 7.45 (2H, t, $^3J_{HH}$ = 7.8 Hz, ArH), 7.57 (1H, t, $^3J_{HH}$ = 7.4 Hz, ArH), 8.15 (2H, d, $^3J_{HH}$ = 7.4

Hz, ArH). δ_C (100 MHz, $CDCl_3$) 12.5 (CH_3), 14.2 (CH_3), 39.2 (CH_2), 42.6 (CH_2), 57.7 (CH_3), 85.3 (CH) 128.5 (CH), 130.2 (CH), 133.7 (CH), 138.2 (C), 176.0 (CO), 194.6 (CO). m/z (ASAP) 250.1444 (MH^+, $C_{14}H_{20}NO_3$ requires 250.1443).



2.22

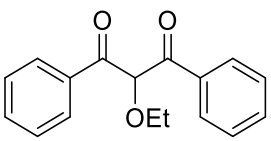
δ_H (500 MHz, $CDCl_3$) 1.11 (3H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 1.19 (3H, t, $^3J_{HH}$ = 7.0 Hz, CH_3), 3.39 (2H, q, $^3J_{HH}$ = 7.0 Hz, CH_2), 3.42-3.48 (1H, m, NCH_AH_B), 3.49-3.56 (1H, m, NCH_AH_B), 6.12 (1H, d, $^2J_{CF}$ = 49.1 Hz, CHF), 7.49 (2H, t, $^3J_{HH}$ = 7.8 Hz, ArH), 7.61 (1H, t, $^3J_{HH}$ = 7.6 Hz, ArH), 8.14 (2H, d, $^3J_{HH}$ = 7.8 Hz, ArH). δ_C ($CDCl_3$, 125 MHz): 12.4 (CH_3), 14.1 (CH_3), 40.9 (CH_2), 41.6 (d, $^4J_{CF}$ = 4.8 Hz, CH_2), 92.5 (d, $^1J_{CF}$ = 197.5 Hz, CHF), 128.6 (CH), 129.6 (d, $^4J_{CF}$ = 2.2 Hz, CH), 133.7 (C), 134.2 (CH), 163.4 (d, $^2J_{CF}$ = 20.6 Hz, CO), 191.9 (d, $^2J_{CF}$ = 20.7 Hz, CO). m/z (ASAP) 238.1245 (MH^+, $C_{13}H_{17}NO_2F$ requires 238.1243).

6.2.27 Methoxylation using 1-hydroxy-3,3-dimethyl-1,3-dihydro-λ³-benzo[*d*][1,2]iodoxole (Scheme 2.27)

A RBF was charged with 1-hydroxy-3,3-dimethyl-1,3-dihydro-λ^3-benzo[*d*][1,2]iodoxole (0.24 g, 0.86 mmol), ethyl 3-(4-methoxyphenyl)-3-oxopropanoate (138 µL, 0.72 mmol) and dry dichloromethane (1.2 mL). After adding methanol (87 µL, 2.2 mmol), the reaction was sealed and heated to 40 ºC for 24 hours. The reaction mixture was then concentrated *in vacuo* but there was no evidence of the desired product by ^{1}H NMR spectroscopy of the crude reaction mixture.

Ethoxylation of 1,3-dicarbonyl compounds

6.2.28 Ethyl-2-ethoxy-1,3-diphenylpropane-1,3-dione (Scheme 2.28)



2.23

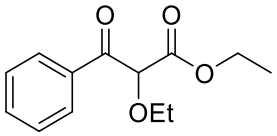
A 5 mL round bottomed flask was charged with 1-fluoro-3,3-dimethyl-1,3-dihydro-λ^3-benzo[*d*][1,2]iodaoxole (0.24 g, 0.86 mmol) and ethanol (1.2 mL) under nitrogen. After adding 1,3-diphenylpropane-1,3-dione (0.16 g, 0.72 mmol), the reaction was sealed and stirred at room temperature for 24 hours. The reaction mixture was

concentrated *in vacuo* and the crude product was purified by column chromatography using 0.5 % methanol in dichloromethane. The product was not isolated due to degradation on silica gel. m/z (ASAP) 269.1176 (MH^+, $C_{17}H_{17}O_3$ requires 269.1178).

6.2.29 General procedure for the ethoxylation of 1,3-dicarbonyl substrates (Scheme 2.29)

A round bottomed flask was charged with 1-fluoro-3,3-dimethyl-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (0.24 g, 0.86 mmol) and dry dichloromethane (1.2 mL). After adding ethyl 3-oxo-3-phenylpropanoate (0.13 mL, 0.72 mmol) and ethanol (126 µL, 2.2 mmol). The reaction was sealed and heated to 40 ^oC for 24 hours. The reaction was then concentrated *in vacuo*.

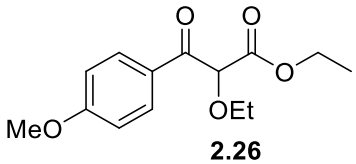
6.2.30 Ethyl 2-ethoxy-3-oxo-3-phenylpropanoate



2.25

The crude product was purified by column chromatography using 100 % dichloromethane to give ethyl 2-ethoxy-3-oxo-3-phenylpropanoate as a colourless oil (0.06 g, 33 %). The characterisation data was in agreement with the literature.[11] δ_H (400 MHz, $CDCl_3$) 1.19 (3H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 1.27 (3H, t, $^3J_{HH}$ = 7.1 Hz, CH_3), 3.65 (1H, m, OCH_AH_B), 3.75 (1H, m, OCH_AH_B), 4.23 (2H, q, $^3J_{HH}$ = 7.2 Hz, OCH_2), 5.01 (1H, s, CH), 7.47 (2H, t, $^3J_{HH}$ = 7.8 Hz, ArH), 7.59 (1H, t, $^3J_{HH}$ = 7.4 Hz, ArH), 8.08 (2H, d, $^3J_{HH}$ = 7.1 Hz, ArH). δ_C (100 MHz, $CDCl_3$) 14.0 (CH_3), 15.1 (CH_3), 61.9 (CH_2), 66.9 (CH_2), 83.8 (CH), 128.6 (CH), 129.4 (CH), 133.9 (CH), 134.2 (C), 167.9 (CO), 192.9 (CO). m/z (ESI^+) 259.0948 (MNa^+, $C_{13}H_{16}O_4Na$ requires 259.0946).

6.2.31 Ethyl-2-ethoxy-3-(4-methoxyphenyl)-3-oxopropanoate

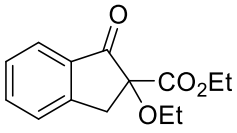


2.26

The crude product was purified by column chromatography using 0.5 % methanol in dichloromethane to give ethyl-2-ethoxy-3-(4-methoxyphenyl)-3-oxopropanoate as a colourless oil (0.17 g, 90 %). δ_H (500 MHz, $CDCl_3$) 1.20 (3H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 1.27 (3H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 3.63 (1H, m, OCH_AH_B)

3.73 (1H, m, OCH_AH_B), 3.87 (3H, s, OCH_3), 4.23 (2H, q, $^3J_{HH}$ = 7.1 Hz, OCH_2CH_3), 4.97 (1H, s, CH), 6.93 (2H, d, $^3J_{HH}$ = 8.6 Hz, ArH), 8.09 (2H, d, $^3J_{HH}$ = 8.6 Hz, ArH). δ_C (100 MHz, $CDCl_3$) 14.0 (CH_3), 15.1 (CH_3), 55.5 (CH_3), 61.7 (CH_2), 66.7 (CH_2), 83.9 (CH), 113.8 (CH), 127.2 (C), 131.9 (CH), 164.1 (C), 168.1 (CO), 191.3 (CO). m/z (ASAP) 267.1232 (MH^+, $C_{14}H_{19}O_5$ requires 267.1232).

6.2.32 Ethyl 2-ethoxy-1-oxo-2,3-dihydro-1*H*-2-indene-2-carboxylate



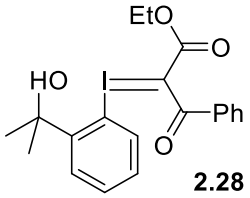
2.27

The crude product was purified by column chromatography using 0.5 % methanol in dichloromethane to give ethyl 2-ethoxy-1-oxo-2,3-dihydro-1*H*-2-indene-2-carboxylate as a pale yellow oil (51 mg, 28 %). δ_H (500 MHz, $CDCl_3$) 1.23 (3H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 1.24 (3H, t, $^3J_{HH}$ = 7.0 Hz, CH_3), 3.30 (1H, d, $^2J_{HH}$ = 17.2 Hz, CH_AH_B), 3.75 (1H, d, $^2J_{HH}$ = 17.2 Hz, CH_AH_B), 3.78 (2H, q, $^3J_{HH}$ = 7.0 Hz, OCH_2), 4.23 (2H, q, $^3J_{HH}$ = 7.1 Hz, OCH_2), 7.41 (1H, t, $^3J_{HH}$ = 7.8 Hz, ArH), 7.46 (1H, d, $^3J_{HH}$ = 7.6 Hz, ArH), 7.64 (1H, td, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.2 Hz, ArH), 7.80 (1H, d, $^3J_{HH}$ = 7.6 Hz). δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 15.6 (CH_3), 39.0 (CH_2), 61.8 (CH_2), 62.5 (CH_2), 85.3 (C), 125.1 (CH), 126.4 (CH), 128.0 (CH), 134.3 (C), 135.9 (CH), 151.7 (C), 170.0 (CO), 198.9 (CO). m/z (ASAP) 271.0782 (MNa^+, $C_{14}H_{16}O_4Na$ requires 271.1314).

6.2.33 General procedure for the trifluoroethoxylation of 1,3-dicarbonyl substrates (Table 2.6)

A round bottomed flask was charged with 1-fluoro-3,3-dimethyl-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (0.24 g, 0.86 mmol) and the required amount of 2,2,2-trifluoroethanol and the required amount of dichloromethane . After adding ethyl 3-oxo-3-phenylpropanoate (0.13 mL, 0.72 mmol) the reaction was sealed and heated to 40 ^oC for 24 hours. After cooling the reaction mixture, it was concentrated *in vacuo*. The crude product was not purified because there was no evidence of trifluoroethoxylation.

6.2.34 Synthesis of ethyl-2-((2-(2-hydroxypropan-2-yl)phenyl-λ^3-iodaneylidene)-3-oxo-3-phenylpropanoate



2.28

A 5 mL round bottomed flask was charged with ethyl 3-oxo-3-phenylpropanoate (0.31 mL, 1.80 mmol) and 1-hydroxy-3,3-dimethyl-1,3-dihydro-λ^3-benzo[*d*][1,2]iodoxole (1.00 g, 3.60 mmol) in dry dichloromethane (3.8 mL) under nitrogen. The flask was sealed and stirred at 40 ^{o}C for 24 hours. The reaction mixture was concentrated *in vacuo* and the crude product was purified by column chromatography using 10 % ethyl acetate in petroleum spirit 40-60 °C followed by 100 % ethyl acetate. The product was washed with diethyl ether to give the iodonium ylide as a white solid (0.40 g, 49 %). The characterisation data was in agreement with the literature.[12] δ_H (500 MHz, $CDCl_3$) 0.85 (3H, t, $^3J_{HH}$ = 7.0 Hz, CH_3), 1.43 (6H, s, CH_3), 3.86 (2H q, $^3J_{HH}$ = 7.1 Hz, OCH_2), 6.72 (1H, br s, OH), 7.19-7.22 (2H, m, ArH), 7.32-7.38 (4H, m, ArH), 7.50 (3H, d, $^3J_{HH}$ = 7.8 Hz, ArH). δ_C (100 MHz, $CDCl_3$) 14.0 (CH_3), 29.8 (CH_3), 60.3 (CH_2), 73.5 (C), 78.4 (CI), 109.6 (ArCI), 127.2 (CH), 127.3 (CH), 127.4 (CH), 127.9 (CH), 129.2 (CH), 129.5 (CH), 129.8 (CH), 140.7 (C), 146.7 (C), 166.3 (CO), 189.2 (CO). m/z (ESI$^+$) 453.0569 (MH^+, $C_{20}H_{22}O_4I$ requires 453.0563). mp 126-129 °C (lit.,[12] 126-127).

6.2.35 Chlorination of ethyl 3-oxo-3-phenylpropanoate using ylide (Scheme 2.32)

A 5mL round bottomed flask was charged with ethyl-2-((2-(2-hydroxypropan-2-yl) phenyl)-λ^3-iodaneylidene)-3-oxo-3-phenylpropanoate (0.120 g, 0.27 mmol) in dry dichloromethane (0.54 mL) under nitrogen. After adding hydrochloric acid 37 % (0.023 mL, 0.72 mmol), the flask was sealed and stirred at 40 ^{o}C for 24 hours. The reaction mixture was cooled to room temperature, dichloromethane (5 mL) was added followed by water (5 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 5 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography using 1 % methanol in dichloromethane to give ethyl 2-chloro-3-oxo-3-phenylpropanoate as a colourless oil (0.050 g, 83 %).

6.2.36 Methoxylation of ethyl 3-oxo-3-phenylpropanoate using ylide (Scheme 2.33)

A 5 mL round bottomed flask was charged with ethyl-2-((2-(2-hydroxypropan-2-yl) phenyl)-λ^3-iodaneylidene)-3-oxo-3-phenylpropanoate (0.137 g, 0.30 mmol) in dry dichloromethane (0.5 mL). After adding methanol (0.037 mL, 0.91 mmol), the flask was sealed and the reaction mixture was stirred either at room temperature or 40 ℃ for 24 hours. The reaction mixture was concentrated *in vacuo*. The reaction was not purified by column chromatography because there was no evidence of methoxylation.

6.2.37 Trifluoroethoxylation of ethyl 3-oxo-3-phenylpropanoate using ylide (Scheme 2.34)

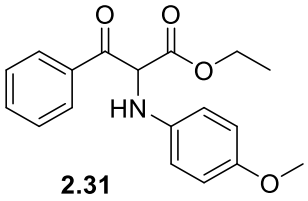
A 5 mL round bottomed flask was charged with ethyl-2-((2-(2-hydroxypropan-2-yl) phenyl)-λ^3-iodaneylidene)-3-oxo-3-phenylpropanoate (0.11 g, 0.24 mmol) and dry dichloromethane (0.48 mL) under nitrogen. After adding trifluoroethanol (0.052 mL, 0.71 mmol), the reaction flask was sealed and heated at 40 ^{o}C for 24 hours. The reaction mixture was cooled to room temperature and dichloromethane (5 mL) was added followed by water (5 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 5 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography using 1 % methanol in dichloromethane but the ^{1}H NMR spectrum of the product showed no evidence of trifluoroethoxylation of ethyl 3-oxo-3-phenylpropanoate.

Amination of ethyl 3-oxo-3-phenylpropanoate

6.2.38 General Procedure for the amination of ethyl 3-oxo-3-phenylpropanoate (Table 2.7)

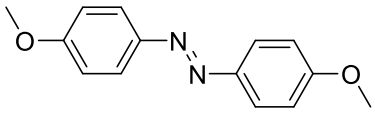
A 5 mL RBF was charged with 1-fluoro-3,3-dimethyl-1,3-dihydro-1l3-benzo[*d*][1,2]iodaoxole (0.24 g, 0.86 mmol) and *p*-anisidine (266 mg, 2.16 mmol) in dry dichloromethane (1.2 mL) under nitrogen. After adding ethyl 3-oxo-3-phenylpropanoate (0.125 mL, 0.72 mmol), the reaction flask was sealed and heated to the required temperature for the required time. The reaction mixture was then cooled to room temperature and concentrated *in vacuo*.

6.2.39 Ethyl 2-((4-methoxyphenyl)amino)-3-oxo-3-phenylpropanoate (Table 2.7, entry 2)



2.31

A 5 mL RBF was charged with 1-fluoro-3,3-dimethyl-1,3-dihydro-1l3-benzo[*d*][1,2]iodaoxole (0.24 g, 0.86 mmol) and *p*-anisidine (266 mg, 2.16 mmol) in dry dichloromethane (1.2 mL) under nitrogen. After adding ethyl 3-oxo-3-phenylpropanoate (0.125 mL, 0.72 mmol), the reaction flask was sealed and heated to 40 °C for 24 hours. The reaction mixture was then cooled to room temperature and concentrated *in vacuo*. The crude product was purified by column chromatography using 10 % ethyl acetate in petroleum spirit 40-60 °C to give ethyl 2-((4-methoxyphenyl)amino)-3-oxo-3-phenylpropanoate as a yellow oil (0.80 g, 40%). (*E*)-1,2-bis(4-methoxyphenyl)diazene was also isolated as a yellow solid (0.01 g, 5 %). The characterisation data did not entirely agree with the literature.[13] δ_H ($CDCl_3$, 400 MHz) 1.32 (3H, t, $^3J_{HH}$ = 7.04 Hz, CH_3), 3.70 (3H, s, OCH_3), 4.20 (2H, q, $^3J_{HH}$ = 7.24 Hz, OCH_2), 4.93 (1H, s, CH), 6.63 (4H, s, ArH), 7.24-7.33 (5H, m, ArH), 10.22 (1H, br s, NH). δ_C ($CDCl_3$, 400 MHz) 14.6 (CH_3), 55.5 (CH_3), 59.2 (CH_2), 89.5 (CH), 113.9 (CH), 124.3 (CH), 128.3 (CH), 128.4 (CH), 129.3 (CH), 133.5 (C), 136.0 (C), 155.8 (C), 159.9 (CO), 170.3 (CO). *m/z* (ESI^+) 314.1391 (MH^+, $C_{18}H_{20}NO_4$ requires 314.1392).



2.32

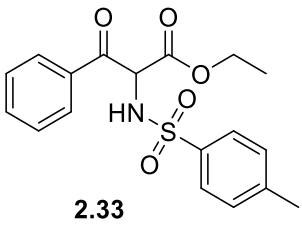
The characterisation data was in agreement with the literature.[14] δ_H ($CDCl_3$, 400 MHz) 3.89 (6H, s, OCH_3), 7.01 (4H, d, $^3J_{HH}$ = 9.0 Hz, ArH), 7.88 (4H, d, $^3J_{HH}$ = 9.0 Hz, ArH). δ_C ($CDCl_3$, 400 MHz) 55.6 (CH_3), 114.2 (CH), 124.3 (CH), 147.1 (C), 161.6 (C). m/z (ESI^+) 243.1138 (MH^+, $C_{14}H_{15}N_2O_2$ requires 243.1134). mp 155-157 °C (lit.,[13] 155-156 °C).

6.2.40 General procedure for aminations using *p*-toluenesulfonamide (Table 2.8)

A Schlenk flask was charged with 1-fluoro-3,3-dimethyl-1,3-dihydro-1l3-benzo[*d*][1,2]iodaoxole (0.30 g, 1.08 mmol) and *p*-toluenesulfamide (185 mg, 1.08 mmol) in dry dichloromethane (1.2 mL). After adding ethyl 3-oxo-3-phenylpropanoate

(0.125 mL, 0.72 mmol), the flask was sealed and heated to the required temperature for the required time.

6.2.41 Ethyl 2-((4-methylphenyl)sulfonamido)-3-oxo-3-phenylpropanoate



2.33

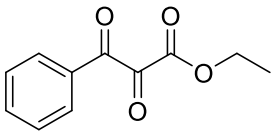
A Schlenk flask was charged with 1-fluoro-3,3-dimethyl-1,3-dihydro-1l3-benzo[*d*][1,2]iodoxole (0.30 g, 1.08 mmol) and *p*-toluenesulfonamide (185 mg, 1.08 mmol) in dry dichloromethane (1.2 mL). After adding ethyl 3-oxo-3-phenylpropanoate (0.125 mL, 0.72 mmol), the flask was sealed and heated to 40 °C for 24 hours. The reaction mixture was then concentrated *in vacuo.* The crude product was purified by column chromatography using dichloromethane to give ethyl 2-((4-methylphenyl)sulfonamido)-3-oxo-3-phenylpropanoate as a white solid (23 mg, 9 %). The characterisation data was in agreement with the literature.[15] δ_H ($CDCl_3$, 400 MHz) 1.05 (3H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 2.38 (3H, s, CH_3), 3.92-4.02 (2H, m, OCH_2), 5.58 (1H, d, $^3J_{HH}$ = 8.9 Hz, CH), 5.94 (1H, d, $^3J_{HH}$ = 8.9 Hz, NH), 7.24 (2H, d, $^3J_{HH}$ = 8.0 Hz, ArH), 7.48 (2H, t, $^3J_{HH}$ = 7.8 Hz, ArH), 7.62 (1H, t, $^3J_{HH}$ = 7.6 Hz, ArH), 7.73 (2H, d, $^3J_{HH}$ = 8.0 Hz, ArH), 7.98 (2H, d, $^3J_{HH}$ = 7.2 Hz, ArH). δ_C ($CDCl_3$, 100 MHz) 13.7 (CH_3), 21.5 (CH_3), 60.9 (CH), 62.6 (CH_2), 127.3 (CH), 128.8 (CH), 129.4 (CH), 129.7 (CH), 133.5 (C), 134.6 (CH), 136.5 (C), 144.0 (C), 166.0 (CO), 190.1 (CO). m/z (ESI^+) 384.0868 (MNa^+, $C_{18}H_{19}NO_5NaS$ requires 384.0882, 100 %), 362.1062 (MH^+, $C_{18}H_{20}NO_5S$ requires 362.1054, 20 %). mp 112-113 °C (lit.,[15] 109-110 °C).

6.3 Experimental for Chapter 3

6.3.1 General procedure for Table 3.1

A 5 mL round bottomed flask was charged with 2-(2-iodophenyl)propan-2-ol (0.038 g, 0.14 mmol), *meta*-chloroperbenzoic acid (0.345 g, 1.44 mmol) and the required amount of hydrochloric acid in dry dichloromethane (0.7 mL). After stirring for 15 minutes, ethyl 3-oxo-3-phenylpropanoate (0.125 mL, 0.72 mmol) in dry dichloromethane (0.7 mL) was added to the reaction. The reaction was stirred for the required time at room temperature and the reaction mixture was concentrated *in vacuo* yielding a white solid which was analysed by ^{1}H NMR spectroscopy.

The crude reaction mixture from entry 2 was purified by column chromatography using 1 % methanol in dichloromethane to afford ethyl 2-chloro-3-oxo-3-phenylpropanoate as a colourless oil (0.06 g, 38 %) and ethyl 2,2-dihydroxy-3-oxo-3-phenylpropanoate as a yellow oil (0.03 g, 18 %). The characterisation data was in agreement with the literature.[16]

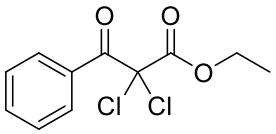


3.7

δ_H (500 MHz, $CDCl_3$) hydrate: 1.08 (3H, t, $^3J_{HH}$ = 7.5 Hz, CH_3), 4.22 (2H, q, $^3J_{HH}$ = 7.2 Hz, OCH_2), 5.30 (2H, br s, OH), 7.48 (2H, t, $^3J_{HH}$ = 8.1 Hz, ArH), 7.63 (1H, t, $^3J_{HH}$ = 7.4 Hz, ArH), 8.07 (2H, d, $^3J_{HH}$ = 8.3 Hz, ArH). δ_C ($CDCl_3$, 126 MHz) 13.7 (CH_3), 63.2 (CH_2), 91.6 (C), 128.8 (CH), 130.0 (CH), 131.4 (C), 134.7 (CH), 169.9 (CO), 191.6 (CO). ketone: 1.39 (3H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 4.43 (2H, q, $^3J_{HH}$ = 7.2 Hz, OCH_2), 7.55 (2H, t, $^3J_{HH}$ = 7.8 Hz, ArH), 7.71 (1H, t, $^3J_{HH}$ = 7.4 Hz, ArH), 8.00 (2H, d, $^3J_{HH}$ = 7.4 Hz, ArH). δ_C ($CDCl_3$, 126 MHz) 13.9 (CH_3), 63.3 (CH_2), 129.2 (CH), 130.2 (CH), 131.6 (C), 135.6 (CH), 160.5 (CO), 183.8 (CO), 190.2 (CO).

6.3.2 Catalytic chlorination of ethyl 3-oxo-3-phenylpropanoate (Table 3.1, entry 4)

A 5 mL round bottomed flask was charged with 2-(2-iodophenyl)propan-2-ol (0.038 g, 0.14 mmol), *meta*-chloroperbenzoic acid (0.345 g, 1.44 mmol) and hydrochloric acid (0.11 mL, 3.6 mmol) in dry dichloromethane (0.7 mL). After stirring for 15 minutes ethyl 3-oxo-3-phenylpropanoate (0.125 mL, 0.72 mmol) in dry dichloromethane (0.7 mL) was added to the reaction. The reaction was stirred for 4 hours at room temperature and the reaction mixture was concentrated *in vacuo* yielding a white solid. The reaction mixture was purified by column chromatography using 1 % methanol in dichloromethane to afford ethyl 2-chloro-3-oxo-3-phenylpropanoate as a colourless oil (0.12 g, 76 %) and ethyl 2,2-dichloro-3-oxo-3-phenylpropanoate as a colourless oil (0.03 g, 15 %).



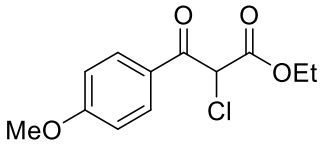
3.9

The characterisation data for ethyl 2,2-dichloro-3-oxo-3-phenylpropanoate was in agreement with the literature.[17] δ_H (500 MHz, $CDCl_3$) 1.20 (3H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 4.33 (2H, q, $^3J_{HH}$ = 7.2 Hz, OCH_2), 7.54 (2H, t, $^3J_{HH}$ = 7.9 Hz, ArH), 7.63 (1H, t, $^3J_{HH}$ = 7.4 Hz, ArH), 8.06 (2H, d, $^3J_{HH}$ = 7.8 Hz, ArH). δ_C (100 MHz, $CDCl_3$) 13.6 (CH_3), 64.7 (CH_2), 81.9 (C), 128.7 (CH), 130.1 (CH), 130.9 (C), 134.2 (CH), 164.1 (CO), 183.3 (CO).

6.3.3 General procedure for the catalytic chlorination of 1,3-dicarbonyl compounds

A 5 mL round bottomed flask was charged with 2-(2-iodophenyl)propan-2-ol (0.038 g, 0.14 mmol), *meta*-chloroperbenzoic acid (0.249 g, 1.44 mmol) and hydrochloric acid (0.15 mL, 5.04 mmol) in dry dichloromethane (0.7 mL). After stirring for 15 minutes the 1,3-dicarbonyl (0.72 mmol) in dry dichloromethane (0.7 mL) was added to the reaction. The reaction was stirred for 4 hours at room temperature and the reaction mixture was concentrated *in vacuo.*

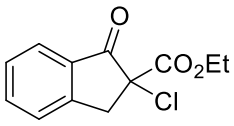
6.3.4 Ethyl 2-chloro-3-(4-methoxyphenyl)-3-oxopropanoate (Scheme 3.8)



2.7

The crude product was purified using 1 % methanol in dichloromethane to give ethyl 2-chloro-3-(4-methoxyphenyl)-3-oxopropanoate as a colourless oil (135 mg, 73 %).

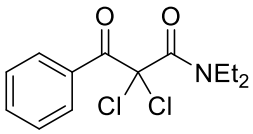
6.3.5 Ethyl-2-chloro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (Scheme 3.9)



2.12

The crude product was purified by column chromatography using 1 % methanol in dichloromethane to give ethyl-2-chloro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate as a colourless oil (0.127 g, 74%). The characterisation data was in agreement with the literature.[6]

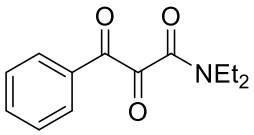
6.3.6 2,2-Dichloro-*N*,*N*-diethyl-3-oxo-3-phenylpropanamide (Scheme 3.10)



3.10

A 5 mL round bottomed flask was charged with 2-(2-iodophenyl)propan-2-ol (38 mg, 0.14 mmol), *meta*-chloroperbenzoic acid (249 mg, 1.44 mmol) and hydrochloric acid (0.078 mL, 2.52 mmol) in dry dichloromethane (0.7 mL). After stirring the reaction for 15 minutes at room temperature, ethyl 3-oxo-3-phenylpropanamide (158 mg, 0.72 mmol) in dry dichloromethane (0.7 mL) was added to the reaction mixture. The reaction was sealed and stirred at room temperature for 4 hours. The reaction was then concentrated *in vacuo* and the crude reaction mixture was purified by column chromatography using 1 % methanol in dichloromethane to give 2,2-dichloro-*N*,*N*-diethyl-3-oxo-3-phenylpropanamide yellow oil (0.011 g, 7 %) and *N*,*N*-diethyl-2,3-

dioxo-3-phenylpropanamide as a yellow oil (0.065 g, 40 %). δ_H (500 MHz, $CDCl_3$) 1.05 (3H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 1.07 (3H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 3.34 (2H, q, $^3J_{HH}$ = 7.0 Hz, NCH_2), 3.38 (2H, q, $^3J_{HH}$ = 7.2 Hz, NCH_2), 7.44 (2H, t, $^3J_{HH}$ = 7.6 Hz, ArH), 7.58 (1H, t, $^3J_{HH}$ = 7.4 Hz, ArH), 8.00 (2H, d, $^3J_{HH}$ = 7.4 Hz, ArH). δ_C (100 MHz, $CDCl_3$) 11.7 (CH_3), 13.0 (CH_3), 41.9 (CH_2), 42.7 (CH_2), 85.9 (CCl_2), 128.5 (CH), 130.5 (CH), 131.6 (C), 140.0 (CH), 162.4 (CO), 184.2 (CO). m/z (ASAP) 288.0552 (MH^+, $C_{13}H_{16}NO_2{}^{35}Cl_2$ requires 288.0558), 290.0539 (MH^+, $C_{13}H_{16}NO_2{}^{35}Cl^{37}Cl$ requires 290.0531), 292.0556 (MH^+, $C_{13}H_{16}NO_2{}^{37}Cl_2$ requires 290.0507).



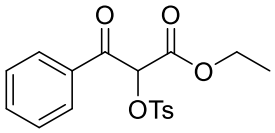
3.11

δ_H (400 MHz, $CDCl_3$) 1.25 (3H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 1.31 (3H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 3.44-3.54 (4H, m, NCH_2), 7.53 (2H, t, $^3J_{HH}$ = 7.8 Hz, ArH), 7.67 (1H, t, $^3J_{HH}$ = 7.4 Hz, ArH), 8.06 (2H, dd, $^3J_{HH}$ = 8.4 Hz, $^4J_{HH}$ = 1.4 Hz, ArH). δ_C (100 MHz, $CDCl_3$) 12.6 (CH_3), 14.4 (CH_3), 39.6 (CH_2), 42.3 (CH_2), 128.9 (CH), 130.4 (CH), 132.1 (C), 135.1 (CH), 165.4 (CO), 185.6 (CO), 192.3 (CO). m/z (ASAP) 234.1121 (MH^+, $C_{13}H_{16}NO_3$ requires 234.1130).

Tosyloxylation of 1,3-dicarbonyl Compounds

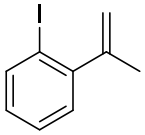
6.3.7 Tosyloxylation of ethyl 3-oxo-3-phenylpropanoate using 1-fluoro-3,3-dimethyl-1,3-dihydro-1l3-benzo[*d*][1,2]iodoxole (Scheme 3.12)

A 5 mL round bottomed flask was charged with 1-fluoro-3,3-dimethyl-1,3-dihydro-1l3-benzo[*d*][1,2]iodoxole (0.24 g, 0.86 mmol) and *p*-toluenesulfonic acid (0.37 g, 1.90 mmol) in dry dichloromethane (1.2 mL) under nitrogen. After adding ethyl 3-oxo-3-phenylpropanoate (0.13 mL, 0.72 mmol), the reaction flask was sealed and stirred at room temperature for 1 hour. The reaction was then concentrated *in vacuo* and the crude product was purified by column chromatography using 15 % ethyl acetate in petroleum spirit 40-60 °C to give ethyl 3-oxo-3-phenyl-2-(tosyloxy)propanoate as a colourless oil (0.21 g, 81 %) and 1-iodo-2-(prop-1-en-2-yl)benzene as a colourless oil (0.085 g, 33 %).



1.15

The characterisation data was in agreement with the literature.[11] δ_H (500 MHz, $CDCl_3$) 1.17 (3H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 2.43 (3H, s, CH_3), 4.13-4.23 (2H, m, OCH_2), 5.98 (1H, s, CH), 7.30 (2H, d, $^3J_{HH}$ = 8.2 Hz, ArH), 7.45 (2H, t, $^3J_{HH}$ = 7.8 Hz, ArH), 7.60 (1H, t, $^3J_{HH}$ = 7.5 Hz, ArH), 7.79 (2H, d, $^3J_{HH}$ = 8.3 Hz, ArH), 7.93 (2H, d, $^3J_{HH}$ = 7.6 Hz, ArH). δ_C (100 MHz, $CDCl_3$) 13.8 (CH_3), 21.7 (CH_3), 62.9 (CH_2), 78.1 (CH), 128.3 (CH), 128.8 (CH), 129.4 (CH), 129.9 (CH), 132.5 (C), 133.4 (C), 134.4 (CH), 145.7 (C), 164.2 (CO), 188.2 (CO). m/z (ASAP) 363.0904 (MH^+, $C_{18}H_{19}O_6S$ requires 363.0902).

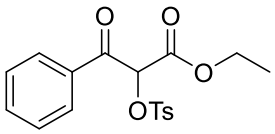


The characterisation data was in agreement with the literature.[17] δ_H (400 MHz, $CDCl_3$) 2.06 (3H, s, CH_3), 4.88 (1H, s, CH), 5.21 (1H, s, CH), 6.92 (1H, td, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.6 Hz, ArH), 7.16 (1H, dd, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.4 Hz, ArH), 7.29 (1H, t, $^3J_{HH}$ = 7.6 Hz, ArH), 7.82 (1H, d, $^3J_{HH}$ = 8.1 Hz, ArH). δ_C (126 MHz, $CDCl_3$) 23.9 (CH_3), 96.9 (CI), 116.0 (CH_2), 128.1 (CH), 128.4 (CH), 128.5 (CH), 139.2 (CH), 148.4 (C), 148.9 (C). m/z (APCI) 244.9838 (MH^+, $C_9H_{10}I$ requires 244.9827).

6.3.8 General procedure for the catalytic tosyloxylation of 1,3-dicarbonyl compounds (Table 3.2)

A 5 mL round bottomed flask was charged with 2-(2-iodophenyl)propan-2-ol (0.038 g, 0.14 mmol), *meta*-chloroperbenzoic acid (0.249 g, 1.44 mmol) and the required amount of *p*-toluenesulfonic acid in dry dichloromethane (1.4 mL). The reaction was stirred for the required temperature for the required amount of time and the reaction mixture was concentrated *in vacuo.* The crude product was analysed by ^{1}H NMR spectroscopy.

6.3.9 Ethyl 3-oxo-3-phenyl-2-(tosyloxy)propanoate (Table 3.2, entry 3)



1.15

The crude product was purified by column chromatography using 1 % methanol in dichloromethane affording ethyl 3-oxo-3-phenyl-2-(tosyloxy)propanoate as a colourless oil (0.074 g, 28 %) and ethyl 2,2,-hydroxy-3-oxo-phenylpropanoate as a yellow oil (0.02 g, 8 %) in a mixture of ketone and hydrate (15:85).

6.3.10 Procedure in Scheme 3.15

A 5 mL round bottomed flask was charged with *meta*-chloroperbenzoic acid (0.249 g, 1.44 mmol) and ethyl 3-oxo-3-phenylpropanoate in dry dichloromethane (1.4 mL). The reaction was stirred at room temperature for 2 hours and the reaction mixture was concentrated *in vacuo*. Ethyl 2,2-dihydroxy-3-oxo-3-phenylpropanoate as a yellow oil (hydrate: 0.02 g, 13 %), (ketone: 0.026 g, 17 %) and ethyl 2-hydroxy-3-oxo-3-phenylpropanoate (0.026 g, 17 %).

6.3.11 General procedure for the catalytic fluorination of ethyl 3-oxo-3-phenylpropanoate (Table 3.3)

A Schlenk flask was charged with 2-(2-iodophenyl)propan-2-ol (0.038 g, 0.14 mmol), *meta*-chloroperbenzoic acid (0.249 g, 1.44 mmol) and the required amount of triethylamine hydrofluoride in the required solvent (1.4 mL) under nitrogen. After stirring at room temperature for 15 minutes, ethyl 3-oxo-3-phenylpropanoate (0.13 mL, 0.72 mmol) was added to the reaction mixture. The reaction flask was sealed and heated to 40 °C for 24 hours. After cooling the reaction mixture to room temperature, it was concentrated *in vacuo* and analysed by ^{1}H NMR and ^{19}F NMR spectroscopy.

6.3.12 General procedure for the catalytic fluorination of ethyl 3-oxo-3-phenylpropanoate (Table 3.4)

A Schlenk flask was charged with 2-(2-iodophenyl)propan-2-ol (0.19 g, 0.72 mmol), *meta*-chloroperbenzoic acid (0.249 g, 1.44 mmol) and triethylamine hydrofluoride (1.18 mL, 7.2 mmol) in the required solvent (0.7 mL) under nitrogen. After stirring at room temperature for the required amount of time, ethyl 3-oxo-3-phenylpropanoate (0.13 mL, 0.72 mmol) was added to the reaction mixture in the required solvent (0.7 mL). The reaction flask was sealed and heated to 40 °C for 24 hours. After cooling the reaction mixture to room temperature, it was concentrated *in vacuo* and analysed by ^{1}H NMR and ^{19}F NMR spectroscopy.

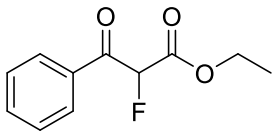
6.3.13 General procedure for the catalytic fluorination of ethyl 3-oxo-3-phenylpropanoate (Table 3.5)

A Schlenk flask was charged with 2-(2-iodophenyl)propan-2-ol (0.19 g, 0.72 mmol), *meta*-chloroperbenzoic acid (0.249 g, 1.44 mmol) and the required amount of triethylamine hydrofluoride in the required amount of hexafluoroisopropanol under nitrogen. After stirring at room temperature for 1 hour, ethyl 3-oxo-3-phenylpropanoate (0.13 mL, 0.72 mmol) was added to the reaction mixture in the required amount of hexafluoroisopropanol. The reaction flask was sealed and heated to 40 °C for 24 hours. After cooling the reaction mixture to room temperature, it was concentrated *in vacuo* and analysed by ^{1}H NMR and ^{19}F NMR spectroscopy.

6.3.14 Procedure of the fluorinations in Table 3.6

A Schlenk flask was charged with 1-fluoro-3,3-dimethyl-1,3-dihydro-1l3-benzo[*d*][1,2]iodoxole (0.30 g, 1.08 mmol) in HFIP (1.2 mL) under nitrogen. After adding the required amount of $Et_3N.3HF$ and ethyl 3-oxo-3-phenylpropanoate (0.13 mL, 0.72 mmol), the flask was sealed and heated to the required temperature for the required amount of time. After cooling the reaction mixture to room temperature, it was concentrated *in vacuo* and the crude product was analysed by ^{1}H NMR and ^{19}F NMR spectroscopy.

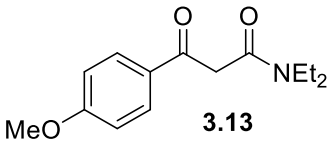
6.3.15 Ethyl 2-fluoro-3-oxo-3-phenylpropanoate (Table 3.6, entry 8)



1.69

The crude product was purified by column chromatography using 1 % methanol in dichloromethane to give ethyl 2-fluoro-3-oxo-3-phenylpropanoate as a yellow oil (117 mg, 73%). The characterisation data was in agreement with the literature.[3] δ_H ($CDCl_3$, 400 MHz) 1.22 (3H, t, $^{3}J_{HH}$ = 7.1 Hz, CH_3), 4.27 (2H, m_{AB}, dq, $^{2}J_{HH}$ = 11.0 Hz, $^{3}J_{HH}$ = 7.2 Hz, OCH_AH_B), 5.87 (1 H, d, $^{2}J_{HF}$ = 50.0 Hz, CHF) 7.48 (2 H, t, $^{3}J_{HH}$ = 8.0 Hz, ArH), 7.61 (1H, t, $^{3}J_{HH}$ = 8.0 Hz, ArH), 8.02 (2H, d, $^{3}J_{HH}$ = 8.0 Hz, ArH). δ_F ($CDCl_3$) -190.4 (s). δ_C ($CDCl_3$) 13.9 (CH_3), 62.7 (CH_2), 90.0 (d, $^{1}J_{CF}$, 197.8 Hz, CH), 128.4 (CH), 129.5 (CH), 133.4 (C), 134.5 (CH), 164.9 (d, $^{2}J_{CF}$ = 24.1 Hz, CO), 189.5 (d, $^{2}J_{CF}$ = 21.1 Hz, CO). *m/z* (ASAP) 211.0779 (MH^+, $C_{11}H_{12}FO_3$ requires 211.0770).

6.3.16 Synthesis of *N,N*-Diethyl-3-4(-methoxyphenyl)-oxopropanamide



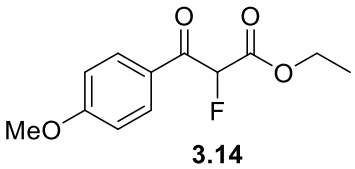
3.13

A solution of 4-(dimethylamino)pyridine (330 mg, 2.7 mmol), diethylamine (4.7 mL, 45.0 mmol) and ethyl-3-(4-methoxy)phenylpropanoate (1.72 mL, 9.0 mmol) in dry toluene (13 mL) was prepared under nitrogen. The reaction was heated to 60 °C for 24 hours. Diethylamine (3 mL, 29 mmol) was added to the reaction mixture and the reaction mixture was heated to 60 °C for 48 hours. The reaction mixture was cooled to room temperature and concentrated *in vacuo.* The crude product was purified by column chromatography using 10 % ethyl acetate in petroleum spirit 40-60 °C to give *N,N*-diethyl-3-4-(methoxyphenyl)-oxopropanamide as a yellow oil (1.5 g, 68 %). The characterisation data was in agreement with the literature.[19] δ_H ($CDCl_3$, 400 MHz) 1.12-1.23 (12H, m, CH_3, keto and enol), 3.36-3.46 (8H, m, CH_2, keto and enol), 3.85 (3H, s, CH_3, enol), 3.87 (3H, s, CH_3, keto), 4.01 (2H, s, CH_2) 5.65 (1H, s, CH, enol), 6.91-6.95 (4H, m, ArH, keto and enol), 7.73 (2H, d, $^3J_{HH}$ = 8.2 Hz, ArH, enol), 8.05 (2H, d, $^3J_{HH}$ = 8.8 Hz, ArH, keto). δ_C ($CDCl_3$, 100 MHz) 12.8 (CH_3), 14.1 (CH_3), 40.1 (CH_2), 42.7 (CH_2), 45.5 (CH_2), 55.3 (CH_3), 55.5 (CH_3), 83.4 (CH), 113.7 (CH), 113.9 (CH), 127.4 (C), 129.4 (CH), 131.0 (CH), 161.5 (C), 163.8 (C), 166.3 (C), 171.1 (CO), 171.5 (CO), 192.7 (CO). *m/z* (ESI^+) 250.1443 (MH^+, $C_{14}H_{20}NO_3$ requires 250.1438).

6.3.17 General Procedure for fluorinations in hexafluoroisopropanol (Scheme 3.17)

A Schlenk flask was charged with 1-fluoro-3,3-dimethyl-1,3-dihydro-λ^3-benzo[*d*][1,2]iodoxole (0.30 g, 1.08 mmol) in 1,1,1,3,3,3-hexafluoropropan-2-ol (1.2 mL) under nitrogen. After adding the 1,3- dicarbonyl compound (0.72 mmol), the flask was sealed and heated to 60 °C for 4 hours. After cooling the reaction mixture to room temperature, it was concentrated *in vacuo.*

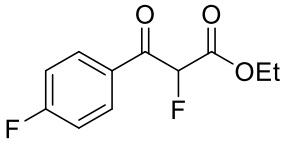
6.3.18 Ethyl 2-fluoro-3-(4-methoxyphenyl)-3-oxo-propanoate



3.14

The crude product was purified by column chromatography using 1 % methanol in dichloromethane to give ethyl 2-fluoro-3-(4-methoxyphenyl)-3-oxo-propanoate as a colourless oil (155 mg, 90 %). The characterisation data was in agreement with the literature.[3] δ_H ($CDCl_3$) 1.23 (3H, t, $^3J_{HH}$ = 7.1 Hz, CH_3), 3.86 (3H, s, CH_3), 4.30 (2H, $m_{AB,}$ dq, $^2J_{HH}$ = 9.8 Hz, $^3J_{HH}$ = 7.1 Hz, OCH_AH_B), 5.82 (1H, d, $^2J_{HF}$ = 48.9 Hz, CH), 6.97 (2H, d, $^3J_{HH}$ = 9.1 Hz, ArH), 8.04 (2H, d, $^3J_{HH}$ = 8.6 Hz, ArH). δ_F ($CDCl_3$) -189.6 (s). δ_C ($CDCl_3$) 14.0 (CH_3), 55.6 (CH_3), 62.6 (CH_2), 90.1 (d, $^1J_{CF}$ = 196.8 Hz, CH), 114.1 (CH), 126.3 (C), 132.1 (d, $^4J_{CF}$ = 3.0 Hz, CH), 164.7 (C), 165.2 (d, $^2J_{CF}$ = 24.1 Hz, CO), 187.8 (d, $^2J_{CF}$ = 20.1 Hz, CO). *m/z* (ASAP) 241.0888 (MH^+, $C_{12}H_{14}FO_4$ requires 241.0876)

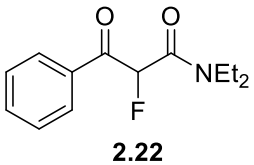
6.3.19 Ethyl 2-fluoro-3-(4-fluorophenyl)-3-oxopropanoate



3.15

The crude product was purified by column chromatography using 1 % methanol in dichloromethane to give ethyl 2-fluoro-3-(4-fluorophenyl)-3-oxopropanoate as a colourless oil (93 %, 153 mg). The characterisation data was in agreement with the literature.[20] δ_H ($CDCl_3$, 400 MHz) 1.27 (3H, t, $^3J_{HH}$ = 7.1 Hz, CH_3), 4.31 (2H, $m_{AB,}$ dq, $^2J_{HH}$ = 14.3 Hz, $^3J_{HH}$ = 7.1 Hz, OCH_AH_B), 5.89 (1H, d, $^2J_{HF}$ = 48.9 Hz, CHF), 7.18 (2H, dd, $^3J_{HH}$ = 8.8 Hz, $^3J_{HF}$ = 7.5 Hz, ArH), 8.08-8.12 (2H, m, ArH). δ_C ($CDCl_3$, 100 MHz) 13.9 (CH_3), 62.8 (CH_2), 90.2 (d, $^1J_{CF}$ = 197.2 Hz, CH), 116.1 (d, $^2J_{CF}$ = 22.1 Hz, CH), 129.8 (C), 132.4 (dd, $^3J_{CF}$ = 10.1 Hz, $^4J_{CF}$ = 3.0 Hz, CH), 164.8 (d, $^2J_{CF}$ = 24.1 Hz, CO), 166.5 (d, $^1J_{CF}$ = 257.6 Hz, C), 188.0 (d, $^2J_{CF}$ = 20.1 Hz, CO). δ_F ($CDCl_3$) -189.6 (1F, s, CHF), -101.8 (1F, s, ArF). *m/z* (ESI^+) 229.0679 (MH^+, $C_{11}H_{11}F_2O_3$ requires 229.0676).

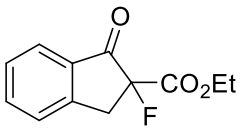
6.3.20 *N,N*-diethyl-2-fluoro-3-oxo-3-phenylpropanamide



2.22

The crude product was purified by column chromatography using 1 % methanol in dichloromethane to give *N,N*-diethyl-2-fluoro-3-oxo-diphenylpropane-1,3-dione as a yellow oil (0.121 mg, 71 %).

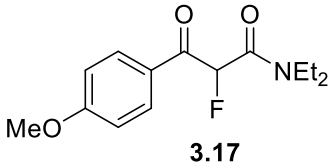
6.3.21 Ethyl 1-indanone-2-fluoro-2-carboxylate



3.16

The crude product was purified by column chromatography using 1 % methanol in dichloromethane to give ethyl 1-indanone-2-fluoro-2-carboxylate as a colourless oil (0.129 g, 81 %). The characterisation data was in agreement with the literature.[3] δ_H ($CDCl_3$, 400 MHz) 1.26 (3H, t, $^3J_{HH}$ = 7.1 Hz, CH_3), 3.44 (1H, dd, $^3J_{HF}$ = 22.6 Hz, $^2J_{HH}$ = 17.6 Hz, ring CH_AH$_B$), 3.80 (1H, dd, $^2J_{HH}$ = 17.6 Hz, $^3J_{HF}$ = 11.7 Hz, ring CH$_A$$H_B$), 4.28 (2H, q, $^3J_{HH}$ = 7.1 Hz, OCH_2), 7.47 (1H, t, $^3J_{HH}$ = 7.9 Hz, ArH), 7.51 (1H, d, $^3J_{HH}$ = 7.9 Hz, ArH), 7.71 (1H, t, $^3J_{HH}$ = 7.9 Hz, ArH), 7.84 (1H, d, $^3J_{HH}$ = 7.9 Hz, ArH). δ_F ($CDCl_3$, 376 MHz) -164.4 (s). δ_C ($CDCl_3$, 100 MHz) 14.0 (CH_3), 38.3 (d, $^2J_{CF}$ = 24.0 Hz, CH_2), 62.6 (CH_2), 94.5 (d, $^1J_{CF}$ = 202.7 Hz, C), 125.6 (CH), 126.6 (CH), 128.6 (CH), 133.3 (C), 136.7 (CH), 150.9 (d, $^3J_{CF}$ = 3.1 Hz, C), 167.3 (d, $^2J_{CF}$ = 27.3 Hz, CO), 195.3 (d, $^2J_{CF}$ = 18.4 Hz, CO). m/z (ESI$^+$) 223.0771 (MH^+, $C_{12}H_{12}FO_3$ requires 223.0770).

6.3.22 *N,N*-Diethyl-2-fluoro-3-(4-methoxyphenyl)-3-oxopropanamide



3.17

The crude product was purified by column chromatography using 1 % methanol in dichloromethane to give *N*,*N*-diethyl-2-fluoro-3-(4-methoxyphenyl)-3-oxopropanamide as a yellow oil (156 mg, 80 %). δ_H ($CDCl_3$, 400 MHz) 1.10 (3H, t, $^3J_{HH}$ = 7.1 Hz, CH_3), 1.17 (3H, t, $^3J_{HH}$ = 7.1 Hz, CH_3), 3.38 (2H, q, $^3J_{HH}$ = 7.1 Hz, NCH_2), 3.43 – 3.57 (2H, m, NCH_2), 3.87 (3H, s, CH_3), 6.08 (1H, d, $^2J_{HF}$ = 49.1 Hz, CHF), 6.95 (2H, d, $^3J_{HH}$ = 9.2 Hz, ArH), 8.15 (2H, d, $^3J_{HH}$ = 9.0 Hz, ArH). δ_C ($CDCl_3$, 100 MHz) 12.5 (CH_3), 14.1 (CH_3), 40.9 (CH_2), 41.5 (CH_2), 55.6 (CH_3), 92.8 (d, $^1J_{CF}$ = 188.4 Hz, CH), 134.0 (CH), 126.6 (C), 132.2 (CH), 163.6 (d, $^2J_{CF}$ = 22.3 Hz, CO), 164.5 (C), 190.1 (d, $^2J_{CF}$ = 17.6 Hz, CO). δ_F ($CDCl_3$, 400 MHz) -186.1 (s). m/z (ASAP) 268.1343 (MH^+, $C_{14}H_{19}FNO_3$ requires 268.1349).

6.3.23 General procedure for fluorination in Table 3.8

A Schlenk flask was charged with 1-fluoro-3,3-dimethyl-1,3-dihydro-λ^3-benzo[*d*][1,2]iodoxole (0.30 g, 1.08 mmol) in solvent (1.2 mL) under nitrogen. After adding the dibenzoylmethane (0.162 g, 0.72 mmol), the flask was sealed and heated to

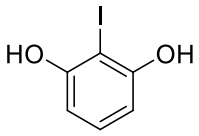
the required temperature for the required amount of time. After cooling the reaction mixture to room temperature, it was concentrated *in vacuo.*

6.3.24 General procedure for Table 3.9

A Schlenk flask was charged with 1-fluoro-3,3-dimethyl-1,3-dihydro-λ^3-benzo[*d*][1,2]iodoxole (0.30 g, 1.08 mmol) in dry HFIP (1.2 mL) under nitrogen. After adding the ethyl 3-oxo-3-phenylpropanoate (0.13 mL, 0.72 mmol) and 2,2,6,6,-tetramethyl-1-piperidinyloxy in the required amount, the flask was sealed and heated to 60 °C for 4 hours. After cooling the reaction mixture to room temperature, it was concentrated *in vacuo* and the crude product was analysed by ^{1}H NMR and ^{19}F NMR spectroscopy.

6.4 Experimental for Chapter 4

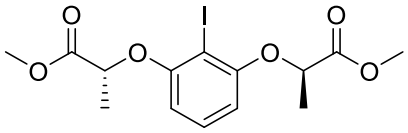
6.4.1 2-Iodoresorcinol



4.92

Following a procedure by Suzuki,[23] resorcinol (4.00 g, 36.3 mmol) and sodium hydrogen carbonate (3.66 g, 43.6 mmol) was dissolved in water (32 mL). The reaction was cooled to 0 °C and iodine (11.1 g, 43.6 mmol) was added under vigorous stirring. The reaction was warmed to room temperature and stirred for 18 hours. The solution was diluted with water (32 mL) and extracted with ethyl acetate (2 x 65 mL). The aqueous layer was acidified with a saturated solution of ammonium chloride and extracted with ethyl acetate (3 x 100 mL). The organic layer combined, dried ($MgSO_4$) and concentrated *in vacuo* to give a brown solid. The brown solid was precipitated in cold chloroform to give 2-iodobenzene-1,3-diol as a white solid (5.45 g, 64 %). The characterisation data was in agreement with the literature.[25] δ_H ($CDCl_3$, 400 MHz) 5.23 (2H, s, OH), 6.56 (2H, d, $^3J_{HH}$ = 8.0 Hz, ArH), 7.11 (1H, t, $^3J_{HH}$ = 8.0 Hz, ArH). δ_C ($CDCl_3$, 100 MHz) 77.7 (CI), 107.3 (CH), 130.4 (CH), 155.6 (C). *m/z* (ESI^+) 236.9417 (MH^+, $C_6H_6IO_2$ requires 236.9412). mp 104-108 °C (lit.,[24] 105-108 °C).

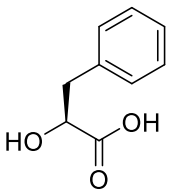
6.4.2 Synthesis of dimethyl 2,2-((2-iodo-1,3-phenylene)bis(oxy))(*2R, 2'R*)-dipropionate



4.86

Following a procedure by Fujita,[25] 2-iodobenzene-1,3-diol (2.36 g, 10.0 mmol), triphenylphosphine (6.56 g, 25.0 mmol) and (-) lactic acid methyl ester (2.4 mL, 25.0 mmol) was prepared in dry THF (38 mL). The solution was cooled to 0 °C and diisopropyl azodicarboxylate (4.9 mL, 25.0 mmol) was added to the solution over 1 hour. The reaction was warmed to room temperature and stirred overnight. Upon completion the reaction mixture was concentrated *in vacuo*. The crude product was purified by column chromatography using 7 % ethyl acetate in petroleum ether 40-60 °C to give dimethyl 2,2-((2-iodo-1,3-phenylene)bis(oxy))(*2R, 2'R*)-dipropionate as a white solid (2.22 g, 55 %). The characterisation data was in agreement with the literature.[24,25] δ_H ($CDCl_3$, 400 MHz) 1.71 (6H, d, $^3J_{HH}$ = 6.8 Hz, 2 x CH_3), 3.75 (6H, s, 2 x OCH_3), 4.77 (2H, q, $^3J_{HH}$ = 6.8 Hz, 2 x CHCO), 6.37 (2H, d, $^3J_{HH}$ = 8.3 Hz, ArH), 7.14 (1H, t, $^3J_{HH}$ = 8.2 Hz, ArH). δ_C ($CDCl_3$, 400 MHz) 18.7 (CH_3), 52.4 (CH_3), 74.2 (CH), 80.6 (CI), 106.9 (CH), 129.7 (CH), 158.3 (C), 172.2 (CO). *m/z* (ESI^+) 409.0150 (MH^+, $C_{14}H_{18}IO_6$ requires 409.0148). $[\alpha]_D^{20}$ = -21.2, c = 1.0, $CHCl_3$ (lit.,[23] $[\alpha]_D^{20}$ = -20.0, c = 1.0, $CHCl_3$). mp 75-76 °C (lit.,[23] 75-76 °C).

6.4.3 (*S*)-2-Hydroxy-3-phenylpropanoic acid

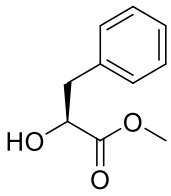


4.95

L-Phenylalanine (10.0 g, 60.5 mmol) was dissolved in sulfuric acid (133 mL, 2 M) and sodium bromide (15.0 g, 14.5 mmol) was added. The mixture was cooled to – 10 °C and sodium nitrite (10.0 g, 145.2 mmol) was added slowly. The reaction was warmed to room temperature and stirred for 3 hours. The crude mixture was extracted with diethyl ether (3 x 140 mL) and the organic layers were combined. After concentrating the reaction mixture *in vacuo*, it was purified by flash column chromatography on silica gel (40 % ethyl acetate in petroleum spirit 40-60 °C) to give the bromide as a brown oil (6.0 g, 43 %). Bromo-3-phenylpropanoic acid was immediately dissolved in water (35 mL) and sodium carbonate (3.04 g, 28.8 mmol) was added slowly to the reaction mixture and the reaction was refluxed for 4 hours. The reaction mixture was cooled to room temperature and was extracted with diethyl ether (35 mL). The aqueous layer was acidified using HCl

(2M) until pH = 2 and extracted with diethyl ether (3 x 50 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The product was recrystallised from diethyl ether and hexane to give (*S*)-2-hydroxy-3-phenylpropanoic acid as a white solid (2.34 g, 37 % over 2 steps). The characterisation data was in agreement with the literature.[26,27] δ_H (MeOD, 400 MHz) 2.91 (1H, dd, $^2J_{HH}$ = 13.8, $^3J_{HH}$ = 8.0 Hz, CH_AH$_B$Ph), 3.12 (1H, dd, $^2J_{HH}$ = 13.8, $^3J_{HH}$ = 4.3 Hz, CH$_A$$H_B$Ph), 4.35 (1H, dd, $^3J_{HH}$ = 8.0, $^3J_{HH}$ = 4.3 Hz, CH), 7.18-7.24 (1H, m, ArH), 7.28 (4H, m, ArH). δ_C (MeOD, 126 MHz) 41.6 (CH_2), 72.8 (CH), 127.5 (CH), 129.2 (CH), 130.6 (CH), 138.9 (C), 175.2 (CO). *m/z* (ESI^+) 165.0552 ($M\text{-}H^-$, $C_9H_9O_3$ requires 165.0552). $[\alpha]_D^{20}$ = - 26.8, *c* = 1.0, acetone, (lit.,[26] $[\alpha]_D^{21}$ = - 26.7, *c* = 0.9, acetone). mp 122-124 °C (lit.,[26] 122-123 °C).

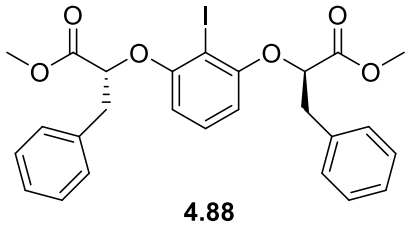
6.4.4 Methyl (*S*)-2-hydroxy-3-phenylpropanoate



4.96

Sulfuric acid 98 % (0.03 mL, 0.49 mmol) was added to a solution of (*S*)-2-hydroxy-3-phenylpropanoic acid (0.81 g, 4.86 mmol) in methanol (6 mL). The reaction was heated at reflux for 4 hours. After cooling the reaction mixture to room temperature, the resultant mixture was concentrated *in vacuo* and diluted with ethyl acetate (20 mL). The organic layer was washed with a saturated sodium hydrogen carbonate solution (20 mL) and brine (20 mL). The organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give methyl (*S*)-2-hydroxy-3-phenylpropanoate as a white solid (0.74 g, 84 %). The characterisation data was in agreement with the literature.[28] δ_H ($CDCl_3$, 500 MHz) 2.70 (1H, d, $^3J_{HH}$ = 6.4 Hz, OH), 2.97 (1H, dd, $^2J_{HH}$ = 13.9, $^3J_{HH}$ = 6.8 Hz, CH_AH$_B$Ph), 3.13 (1H, dd, $^2J_{HH}$ = 13.9, $^3J_{HH}$ = 4.4 Hz, CH$_A$$H_B$Ph), 3.78 (3H, s, OCH_3), 4.44-4.48 (1H, m, CHOH), 7.20-7.32 (5H, m, ArH). δ_C ($CDCl_3$, 126 MHz) 40.6 (CH_2), 52.5 (CH_3), 71.3 (CH), 126.9 (CH), 128.5 (CH), 129.3 (CH), 136.3 (C), 174.6 (CO). $[\alpha]_D^{20}$ = -13.9, *c* = 1.0, CH_2Cl_2 (lit.,[29] $[\alpha]_D^{25}$ = -11.9, *c* = 1.0, CH_2Cl_2). mp 45-46 °C (lit.,[28,29] mp 47 °C).

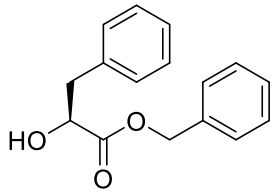
6.4.5 Dimethyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))(2*R*, 2'*R*)-bis(3-phenylpropanoate)



4.88

Following a procedure by Fujita,[25] 2-iodobenzene-1,3-diol (0.77 g, 3.3 mmol), triphenylphosphine (2.57 g, 9.82 mmol) and methyl (*S*)-2-hydroxy-3-phenylpropanoate (1.77 g, 9.82 mmol) was prepared in dry THF (19 mL). The solution was cooled to 0 °C and diisopropyl azodicarbozylate (1.9 mL, 9.82 mmol) was added to the solution over 1 hour. The reaction mixture was warmed to room temperature and stirred overnight. Upon completion the reaction mixture was concentrated *in vacuo*. The crude product was purified by column chromatography using 7 % ethyl acetate in petroleum ether 40-60 °C to give dimethyl 2,2-((2-iodo-1,3-phenylene)bis(oxy))(*2R, 2'R*)-dipropionate as a white solid (1.34 g, 76 %). δ_H ($CDCl_3$, 500 MHz) 3.28 (2H, dd, $^2J_{HH}$ = 14.2 Hz, $^3J_{HH}$ = 4.4 Hz, 2 x CH_AH$_B$), 3.35 (2H, dd, $^2J_{HH}$ = 14.2, $^3J_{HH}$ = 8.2 Hz, 2 x CH$_A$$H_B$), 3.66 (6H, s, 2 x OMe), 4.81 (2H, dd, $^3J_{HH}$ = 8.0, $^4J_{HH}$ = 4.6 Hz, 2 x CH), 6.21 (2H, d, $^3J_{HH}$ = 8.1 Hz, ArH), 7.04 (1H, t, $^3J_{HH}$ = 8.4 Hz, ArH), 7.23-7.25 (2H, m, ArH), 7.30 (4H, t, $^3J_{HH}$ = 7.4 Hz, ArH), 7.42 (4H, d, $^3J_{HH}$ = 7.6 Hz, ArH). δ_C ($CDCl_3$, 126 MHz) 39.1 (CH_2), 52.3 (CH_3), 78.9 (CH), 79.4 (CI), 105.9 (CH), 127.1 (CH), 128.4 (CH), 129.5 (CH), 129.9 (CH), 136.1 (C), 158.1 (C), 171.0 (CO). *m/z* (ESI$^+$) 583.0596 (MNa$^+$, $C_{26}H_{25}O_6NaI$ requires 583.0594, 100 %), 561.0770 (MH$^+$, $C_{26}H_{26}O_6I$ requires 561.0774, 20 %). $[\alpha]_D^{20}$ = 68.5, *c* = 1.0, $CHCl_3$. mp 119-121 °C.

6.4.6 Benzyl (*S*)-2-hydroxy-3-phenylpropanoate

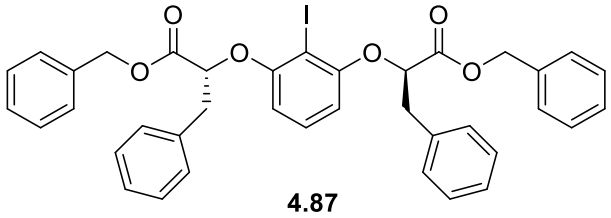


4.97

(*S*)-2-Hydroxy-3-phenylpropanoic acid (2.34 g, 14.1 mmol), benzyl bromide (1.84 mL, 15.5 mmol) and triethylamine (2.4 mL, 16.9 mmol) was dissolved in acetone (20 mL). The reaction was refluxed for 16 hours. The reaction was cooled and the crude mixture was filtered and concentrated *in vacuo*. The crude solid was dissolved in ethyl acetate (50 mL) and washed with water (3 x 50 mL). The aqueous layers were combined and extracted with ethyl acetate (3 x 50 mL). All the organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo* to give benzyl (*S*)-2-hydroxy-3-phenylpropanoate as a colourless oil (2.69 g, 74 %). The characterisation data was in

agreement with the literature.[30] δ_H ($CDCl_3$, 400 MHz) 2.74 (1H, br s, OH), 2.98 (1H, dd, $^2J_{HH}$ = 14.1, $^3J_{HH}$ = 6.5 Hz, CH_AH$_B$Ph), 3.12 (1H, dd, $^2J_{HH}$ = 14.1, $^3J_{HH}$ = 4.7 Hz, CH$_A$$H_B$Ph), 4.49 (1H, dd, $^3J_{HH}$ = 6.5, $^3J_{HH}$ = 4.7 Hz, CHCO), 5.18 (2H, s, OCH_2), 7.13-7.42 (10H, m, ArH). δ_C ($CDCl_3$, 126 MHz) 40.6 (CH_2), 67.4 (CH_2), 71.5 (CH), 126.9, (CH), 128.4 (CH), 128.6 (2 x CH), 128.7 (CH), 129.5 (CH), 135.0 (C), 136.1 (C), 174.0 (CO). *m/z* (ESI$^+$) 279.1003 (MNa^+, $C_{16}H_{16}O_3Na$ requires 279.0997). $[\alpha]_D^{20}$= -45.0, *c* = 3.55, $CHCl_3$ (lit.[30] $[\alpha]_D^{20}$= -45.0, *c* = 3.55, $CHCl_3$).

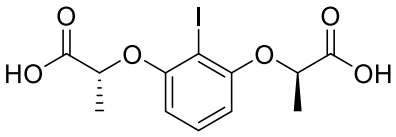
6.4.7 Dibenzyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))(2*R*, 2'*R*)-bis(3-phenylpropanoate)



4.87

Following a procedure by Fujita,[24] 2-iodobenzene-1,3-diol (0.74 g, 3.12 mmol), triphenylphosphine (2.04 g, 7.80 mmol) and benzyl (*S*)-2-hydroxy-3-phenylpropanoate (2.00 g, 7.80 mmol) was prepared in dry THF (12 mL). The solution was cooled to 0 °C and diisopropyl azodicarboxylate (1.54 mL, 7.80 mmol) was added to the solution over 1 hour. The reaction was warmed to room temperature and stirred overnight. Upon completion the reaction mixture was concentrated *in vacuo*. The crude product was purified by column chromatography using 7 % ethyl acetate in petroleum ether 40-60 °C to give dibenzyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))(2*R*, 2'*R*)-bis(3-phenylpropanoate) as a white solid (1.08 g, 48 %). δ_H ($CDCl_3$, 400 MHz) 3.28 (2H, dd, $^2J_{HH}$ = 14.1 Hz, $^3J_{HH}$ = 4.7 Hz, CH_AH$_B$Ph), 3.36 (2H, dd, $^2J_{HH}$ = 14.1 Hz, $^3J_{HH}$ = 7.8 Hz, CH$_A$$H_B$Ph), 4.84 (2H, dd, $^3J_{HH}$ = 7.8 Hz , $^3J_{HH}$ = 3.1 Hz, 2 x CH), 5.07 (4H, s, 2 x OCH_2Ph), 6.16 (2H, d, $^3J_{HH}$ = 8.4 Hz, ArH), 6.89 (1H, t, $^3J_{HH}$ = 8.4 Hz, ArH), 7.13-7.39 (20H, m, ArH). δ_C ($CDCl_3$, 126 MHz) 39.0 (CH_2), 67.0 (CH_2), 78.8 (CH), 79.7 (CI), 106.2 (CH), 127.0 (CH), 128.3 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 129.4 (CH), 130.0 (CH), 135.1 (C), 136.0 (C), 158.1 (C), 170.3 (CO). *m/z* (ESI$^+$) 713.1385 (MH^+, $C_{38}H_{34}IO_6$ requires 713.1400, 100 %). $[\alpha]_D^{20}$= 26.8, *c* = 1.0, $CHCl_3$. mp 89-91 °C.

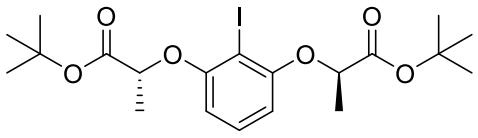
6.4.8 (2*R*, 2'*R*)-2,2'-((2-iodo-1,3-phenylene)bis(oxy))dipropionic acid



4.98

A round bottomed flask was charged with dimethyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))(2*R*, 2'*R*)-dipropionate (1.00 g, 2.45 mmol) in THF (6.5 mL) and methanol (6.5 mL). A 2N solution of sodium hydroxide (6.5 mL) was added to the reaction mixture and the mixture was stirred overnight at room temperature. The reaction mixture was cooled to 0 °C and quenched with 1N HCl (6.5 mL). The aqueous layer was extracted with ethyl acetate (3 x 6.5 mL) and the organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo* to give (2*R*, 2'*R*)-2,2'-((2-iodo-1,3-phenylene)bis(oxy))dipropionic acid as a white solid (0.85 g, 91 %). The characterisation data was in agreement with the literature.[31] δ_H (DMSO, 400 MHz) 1.55 (6H, d, $^3J_{HH}$ = 6.8 Hz, 2 x CH_3), 4.85 (2H, q, $^3J_{HH}$ = 6.9 Hz, 2 x CH), 6.43 (2H, d, $^3J_{HH}$ = 8.4 Hz, ArH), 7.22 (1H, t, $^3J_{HH}$ = 8.2 Hz, ArH), 13.1 (2H, br s, OH). δ_C (DMSO, 126 MHz) 18.3 (CH_3), 72.8 (CH), 79.6 (CI), 105.9 (CH), 129.6 (CH), 157.7 (C), 172.6 (CO). *m/z* (ESI^+) 402.9640 (MNa^+, $C_{12}H_{13}O_6NaI$ requires 402.9655, 100 %). $[\alpha]_D^{20}$ = - 11.7, *c* = 1.0, THF (lit.[32] $[\alpha]_D^{20}$ = - 6.4, *c* = 1.0, THF). mp 100-102 °C.

6.4.9 Di-*tert*-butyl ,2'-((2-iodo-1,3-phenylene)bis(oxy))(2*R*, 2'*R*)-dipropionate



4.99

A round bottomed flask was charged with (2*R*, 2'*R*)-2,2'-((2-iodo-1,3-phenylene)bis(oxy))dipropionic acid (0.40 g, 1.05 mmol), *tert*-butanol (0.252 µL, 2.63 mmol), triethylamine (293 µL, 2.10 mmol) and 4-dimethylaminopyridine (0.32 g, 2.63 mmol) in dry dichloromethane (21 mL). *N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (0.504 g, 2.63 mmol) was added to the reaction and the mixture was stirred at room temperature for 6 hours. 1M HCl (30 mL) was added to the reaction mixture and the product was extracted into dichloromethane (3 x 30 mL). The organic layers were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by column chromatography using 20 % ethyl acetate in petroleum ether 40-60 °C to give di-*tert*-butyl ,2'-((2-iodo-1,3-phenylene)bis(oxy))(2*R*, 2'*R*)-dipropionate as a colourless oil as a mixture of diastereoisomers (7:3) (0.295 g, 57 %). The characterisation

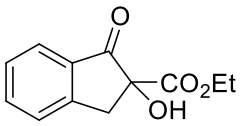
data was in agreement with the literature for the (*R*,*R*) diastereoisomer.[25] δ_H ($CDCl_3$, 500 MHz) 1.43 (18H, s, CH_3, minor), 1.44 (18H, s, CH_3), 1.68 (12H, d, $^3J_{HH}$ = 6.6 Hz, CH_3), 4.67 (4H, q, $^3J_{HH}$ = 8.6 Hz, CH), 6.38 (2H, d, $^3J_{HH}$ = 8.5 Hz, ArH), 6.40 (2H, d, $^3J_{HH}$ = 9.2 Hz, ArH, minor), 7.14 (1H, t, $^3J_{HH}$ = 8.2 Hz ArH), 7.15 (1H, t, $^3J_{HH}$ = 8.5 Hz ArH, minor). δ_C ($CDCl_3$, 126 MHz) 18.4 (CH_3), 27.9 (CH_3, minor), 27.91 (CH_3), 74.5 (CH), 74.7 (CH, minor), 80.4 (CI), 80.6 (CI, minor), 81.9 (C), 106.6 (CH), 106.6 (CH, minor), 129.2 (CH), 158.3 (C), 158.4 (C), 170.8 (CO, minor). 170.81 (CO). $[\alpha]_D^{20}$ = - 20.4, *c* = 1.0, $CHCl_3$ (lit.,[25] $[\alpha]_D^{20}$ = - 31.0, *c* = 1.0, $CHCl_3$). *m/z* (ESI^+) 515.0904 (MNa^+, $C_{20}H_{29}O_6NaI$ requires 515.0907, 100 %).

6.4.10 Procedure for chlorination of ethyl 1-oxo-2,3-indanone-2-carboxylate (Table 4.1)

A Schlenk flask was charged with 4-iodotoluene (0.016 g, 0.072 mmol), *meta*-chloroperbenzoic acid (0.24 g, 1.08 mmol) and hydrochloric acid (0.11 mL, 3.6 mmol) in dry dichloromethane (0.7 mL) under nitrogen. After stirring at the required temperature for the required amount of time, the ethyl 1-oxo-2,3-indanone-2-carboxylate (0.15 g, 0.72 mmol) in dry dichloromethane (0.7 mL) was added to the reaction. The flask was sealed and stirred at the required temperature for 1 hour, the reaction mixture was concentrated *in vacuo* and the crude product was analysed by ^{1}H NMR spectroscopy.

6.4.11 Procedure for chlorination of ethyl 1-oxo-2,3-indanone-2-carboxylate (Table 4.1, entry 4)

A Schlenk flask was charged with 4-iodotoluene (0.016 g, 0.072 mmol), *meta*-chloroperbenzoic acid (0.24 g, 1.08 mmol) and hydrochloric acid (0.11 mL, 3.6 mmol) in dry dichloromethane (0.7 mL) under nitrogen. After stirring at the required temperature for the required amount of time, the ethyl 1-oxo-2,3-indanone-2-carboxylate (0.15 g, 0.72 mmol) in dry dichloromethane (0.7 mL) was added to the reaction. The flask was sealed and stirred at the required temperature for 1 hour, the reaction mixture was concentrated *in vacuo* and the crude product was purified by column chromatography using 1 % methanol in dichloromethane to give ethyl-2-chloro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate as a colourless oil (0.075 g, 44 %) and ethyl 2-hydroxy-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (0.048 g, 28 %).



4.100

The characterisation data was in agreement with the literature.[33] δ_H ($CDCl_3$, 500 MHz) 1.18 (3H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 3.25 (1H, d, $^2J_{HH}$ = 17.4 Hz, C*H*$_A$H$_B$), 3.73 (1H, d, $^2J_{HH}$ = 17.2 Hz, CH$_A$*H*$_B$), 3.99 (1H, br, s, OH), 4.18-4.25 (2H, m, OCH_2), 7.43 (1H, t, $^3J_{HH}$ = 7.2 Hz, ArH), 7.50 (1H, d, $^3J_{HH}$ = 7.6 Hz, ArH), 7.67 (1H, t, $^3J_{HH}$ = 7.4 Hz, ArH), 7.80 (1H, t, $^3J_{HH}$ = 7.8 Hz, ArH). δ_C ($CDCl_3$, 126 MHz) 14.0 (CH_3), 39.3 (CH_2), 62.8 (CH_2), 80.3 (C), 125.3 (CH), 126.5 (CH), 128.1 (CH), 132.8 (C), 136.1 (CH), 152.3 (C), 171.5 (CO), 201.0 (CO). *m/z* (ESI$^+$) 221.0817 (MH^+, $C_{12}H_{13}O_4$ requires 221.0814, 100 %), 221.0817 (MH^+, $C_{12}H_{13}O_4$ requires 221.0814, 100 %), 243.0638 (MNa^+, $C_{12}H_{12}O_4Na$ requires 243.0633, 100%).

6.4.12 General procedure for the enantioselective chlorination of ethyl 1-oxo-2,3-indanone-2-carboxylate (Table 4.2)

A Schlenk flask was charged with dimethyl 2,2-((2-iodo-1,3-phenylene)bis(oxy))(2*R*, 2'*R*)-dipropionate (0.1 mmol), *meta*-chloroperbenzoic acid (0.13 g, 0.75 mmol) and hydrochloric acid (0.077 mL, 2.5 mmol) in dry dichloromethane (12.5 mL) under nitrogen and the reaction mixture was stirred at room temperature for 15 minutes. The reaction mixture was cooled to the required temperatue and stirred for 30 minutes before adding ethyl 1-oxo-2,3-indanone-2-carboxylate (0.102 g, 0.50 mmol) in dry dichloromethane (12.5 mL) dropwise to the reaction over 20 minutes. The flask was sealed and the reaction stirred at the required temperature for 1 hour. The reaction mixture was concentrated *in vacuo* and the crude product was purified by column chromatography using 1 % methanol in dichloromethane and the crude product was analysed by ^{1}H NMR spectroscopy.

6.4.13 General procedure for the enantioselective chlorination of ethyl 1-oxo-2,3-indanone-2-carboxylate (Table 4.3)

A Schlenk flask was charged with dimethyl 2,2-((2-iodo-1,3-phenylene)bis(oxy))(2*R*, 2'*R*)-dipropionate (0.1 mmol), *meta*-chloroperbenzoic acid (0.13 g, 0.75 mmol) and hydrochloric acid (0.077 mL, 2.5 mmol) in the required amount of dry dichloromethane under nitrogen and the reaction mixture was stirred at room temperature for 15 minutes. The reaction mixture was cooled to the required temperature and stirred for 30 minutes

before adding ethyl 1-oxo-2,3-indanone-2-carboxylate (0.102 g, 0.50 mmol) in the required amount of dry dichloromethane dropwise to the reaction over 20 minutes. The flask was sealed and the reaction stirred at the required temperture for 1 hour. After warming the reaction mixture to room temperature, the reaction mixture was concentrated *in vacuo* and the crude product was purified by column chromatography using 1 % methanol in dichloromethane and the crude product was analysed by ^{1}H NMR spectroscopy.

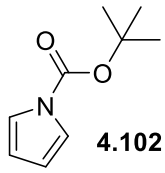
6.4.14 Enantioselective chlorination of ethyl 1-oxo-2,3-indanone-2-carboxylate (Table 4.4, entry 1)

A Schlenk flask was charged with dimethyl 2,2-((2-iodo-1,3-phenylene)bis(oxy))(2*R*, 2'*R*)-dipropionate (0.1 mmol), *meta*-chloroperbenzoic acid (0.13 g, 0.75 mmol) in dry dichloromethane (12.5 mL) and the reaction was stirred at room temperature for 15 minutes. The reaction mixture was cooled to – 95 ℃ and stirred for 30 minutes before adding hydrochloric acid (0.077 mL, 2.5 mmol) and ethyl 1-oxo-2,3-indanone-2-carboxylate (0.102 g, 0.50 mmol) in dry dichloromethane (12.5 mL) dropwise to the reaction over 20 minutes. The flask was sealed and the reaction stirred at - 95 ℃ for 1 hour. After warming the reaction mixture to room temperature, the reaction mixture was concentrated *in vacuo* and the crude product was analysed by ^{1}H NMR spectroscopy.

6.4.15 Enantioselective chlorination of ethyl 1-oxo-2,3-indanone-2-carboxylate (Table 4.5)

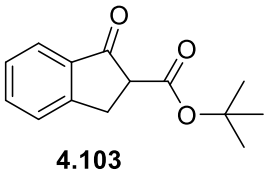
A Schlenk flask was charged with iodoarene (0.1 mmol), *meta*-chloroperbenzoic acid (0.13 g, 0.75 mmol) in dry dichloromethane (12.5 mL) and the reaction was stirred at room temperature for 15 minutes. The reaction mixture was cooled to – 95 ℃ and stirred for 30 minutes before adding hydrochloric acid (0.077 mL, 2.5 mmol) and ethyl 1-oxo-2,3-indanone-2-carboxylate (0.102 g, 0.50 mmol) in dry dichloromethane (12.5 mL) dropwise to the reaction over 20 minutes. The flask was sealed and the reaction stirred at - 95 ℃ for 1 hour. After warming the reaction mixture to room temperature, the reaction mixture was concentrated *in vacuo* and the crude product was analysed by ^{1}H NMR spectroscopy.

6.4.16 Synthesis of *N*-*tert*-butyloxycarbonyl-pyrrole


4.102

A round bottomed flask was charged with pyrrole (3.1 mL, 45 mmol) in acetonitrile (45 mL). After adding di-*tert*-butyl dicarbonate (11.7 g, 54 mmol) and 4-dimethylaminopyridine (0.55 g, 4.5 mmol), the reaction mixture was stirred at room temperature overnight. The reaction mixture was then diluted with diethyl ether (45 mL), washed with a saturated solution of sodium hydrogen carbonate (90 mL) and brine (90 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography using 10 % ethyl acetate in petroleum ether 40-60 ° C to give *N*-tert-butyloxycarbonyl-pyrrole as a brown oil (5.57 g, 75 %). The characterisation data was in agreement with the literature.[34] δ_H ($CDCl_3$, 400 MHz) 1.59 (9H, s, CH_3), 6.21 (2H, s, 2 x CH), 7.23 (2H, s, 2 x CH). δ_C ($CDCl_3$, 126 MHz) 28.0 (CH_3), 83.5 (C), 111.8 (CH), 120.0 (CH), 148.9 (CO). *m/z* (ESI^+) 167.2085 (MNa^+, $C_9H_{13}O_2Na$ requires 167.2080, 100 %).

6.4.17 *tert*-Butyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate

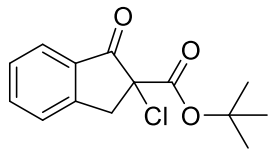

4.103

A round bottomed flask was charged with sodium hydride (2.78 g, 16.6 mmol) in dry THF (32 mL). After adding 1-indanone (1.1 g, 8.3 mmol) in dry THF (8 mL), the reaction mixture was warmed to reflux. *N*-*tert*-butyloxycarbonyl-pyrrole (2.78 g, 16.6 mmol) in dry THF (4 mL) was added dropwise to the solution and the reaction was heated under reflux for 6 hours. The reaction mixture was cooled to 0°C and the solution was acidified with 1M HCl and extracted with ethyl acetate (3 x 50 mL). The organic layers were combined, washed with brine (150 mL), dried ($NaSO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography using 10 % diethyl ether in petroleum ether 40-60 °C to give *tert*-butyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate as a pink oil (1.00 g, 52 %). The characterisation data was in agreement with the literature.[34] δ_H ($CDCl_3$, 500 MHz) 1.48 (9H, s, CH_3), 3.34 (1H, dd, $^2J_{HH}$ = 17.3, $^3J_{HH}$ = 8.2 Hz, ArCH_AH_B), 3.49 (1H, dd, $^2J_{HH}$ = 17.3, $^3J_{HH}$ = 4.1 Hz, ArCH_AH_B), 3.62 (1H, dd, $^3J_{HH}$ = 8.2, $^3J_{HH}$ = 4.1 Hz, CHCO), 7.39 (1H, t, $^3J_{HH}$ = 7.3 Hz, ArH), 7.49 (1H, d, $^3J_{HH}$ = 7.6 Hz, ArH), 7.61 (1H, t, $^3J_{HH}$ = 7.8 Hz, ArH), 7.76 (1H, d, $^3J_{HH}$ = 7.6 Hz, ArH). δ_C ($CDCl_3$, 126 MHz) 28.0 (CH_3), 30.3 (CH_2), 54.4 (CH), 82.1 (C), 124.6 (CH), 126.5 (CH), 127.7

(CH), 135.2 (CH), 135.5 (C), 153.7 (C), 168.4 (CO), 200.0 (CO). *m/z* (ESI^+) 255.0991 (MNa^+, $C_{14}H_{16}O_3Na$ requires 255.0991).

6.4.18 Chlorination of *tert*-Butyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate

A Schlenk flask was charged with 2-(2-iodophenyl)propan-2-ol (0.038 mg, 0.14 mmol), *meta*-chloroperbenzoic acid (0.25 g, 1.44 mmol) and hydrochloric acid (0.16 mL 5.04 mmol) in dry dichloromethane (0.7 mL) and the reaction was stirred at room temperature for 15 minutes. *tert*-Butyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (0.17 g, 0.72 mmol) in dry dichloromethane (0.7 mL) was added to the reaction mixture. The flask was sealed and the reaction stirred at room temperature for 4 hours and the reaction was concentrated *in vacuo*. The crude product was purified by column chromatography using 1 % methanol in dichloromethane to give *tert*-butyl-2-chloro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate as a white solid (0.16 g, 83 %).



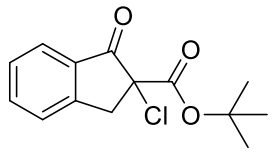
4.104

The characterisation data was in agreement with the literature.[6] δ_H ($CDCl_3$, 400 MHz) 1.43 (9H, s, CH_3), 3.55 (1H, d, $^2J_{HH}$ = 17.7 Hz, C*H*$_A$CH$_B$), 4.02 (1H, d, $^2J_{HH}$ = 17.7 Hz, CH$_A$*H*$_B$), 7.44-7.49 (2H, m, ArH), 7.69 (1H, t, $^3J_{HH}$ = 7.4 Hz, ArH), 7.86 (1H, d, $^3J_{HH}$ = 7.7 Hz, ArH). δ_C ($CDCl_3$, 100 MHz) 27.7 (CH_3), 43.5 (CH_2), 68.8 (C), 84.4 (C), 125.8 (CH), 126.2 (CH), 128.5 (CH), 132.8 (C), 136.2 (CH), 150.7 (C), 165.9 (CO), 195.6 (CO). m/z 289.0610 (MNa^+, $C_{14}H_{15}O_3Na^{35}Cl$ 289.0607) 291.0587 (MNa^+, $C_{14}H_{15}O_3Na^{37}$ requires 291.0578). mp 76-79 °C (lit.,[6] 75-76 °C). The enantiomeric ratio (50:50) was determined by HPLC analysis: Chiralcel OJ column, hexane/i-PrOH: 92/8, 0.7 mL/min, 25 °C, 280 nm, T_R (minor) = 10.2 min, T_R (major) = 13.3 min.

6.4.19 Enantioselective chlorination of *tert*-butyl-2-chloro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (Table 4.7, entry 1)

A Schlenk flask was charged with dimethyl 2,2-((2-iodo-1,3-phenylene)bis(oxy))(*2R, 2'R*)-dipropionate (0.041 g, 0.1 mmol), *meta*-chloroperbenzoic acid (0.129 g, 0.75 mmol) and hydrochloric acid (0.077 mL, 2.5 mmol) in dry dichloromethane (12.5 mL) and the reaction was stirred at room temperature for 15 minutes. The reaction was cooled to – 95 °C for 30 minutes and *tert*-butyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (0.116 g,

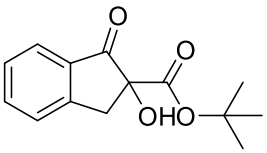
0.5 mmol) in dry dichloromethane (12.5 mL) was added to the reaction mixture dropwise over 20 minutes. The flask was sealed, and the reaction was stirred at – 95 °C for 1 hour. The reaction was concentrated *in vacuo* and the crude product was purified by column chromatography using 1 % methanol in dichloromethane to give *tert*-butyl-2-chloro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate as a white solid (0.057 g, 36 %) and *tert*-butyl-2-hydroxy-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate as a white solid (0.062 g, 47%).



4.104

The enantiomeric ratio (44:55) of *tert*-Butyl-2-chloro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate was determined by HPLC analysis: Chiralcel OJ column, hexane/i-PrOH: 92/8, 0.7 mL/min, 25 °C, 280 nm, T_R (minor) = 9.6 min, T_R (major) = 12.3 min.

6.4.20 *tert*-Butyl-2-hydroxy-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate



4.105

The characterisation data was in agreement with the literature.[34] δ_H ($CDCl_3$, 400 MHz) 1.36 (9H, s, CH_3), 3.22 (1H, d, $^2J_{HH}$ = 17.1 Hz, CH_ACH_B), 3.66 (1H, d, $^2J_{HH}$ = 17.1 Hz, C$H_A H_B$), 4.01 (1H, s, OH), 7.42 (1H, t, $^3J_{HH}$ = 7.5 Hz, ArH), 7.39 (1H, t, $^3J_{HH}$ = 7.8 Hz, ArH), 7.65 (1H, td, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.1 Hz, ArH), 7.79 (1H, dd, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 0.46 Hz, ArH). δ_C ($CDCl_3$, 100 MHz) 27.7 (CH_3), 39.5 (CH_2), 80.6 (C), 84.0 (C), 125.1 (CH), 126.3 (CH), 128.0 (CH), 133.9 (C), 135.4 (CH), 152.4 (C), 170.6 (CO), 201.4 (CO). m/z (ESI$^+$) 271.0944 (MNa^+, $C_{14}H_{16}O_4Na$ requires 271.0946). mp 96-100 °C (lit.,[36] 94-97 °C).

6.4.21 Enantioselective fluorination of ethyl 1-oxo-2,3-indanone-2-carboxylate (Table 4.8)

A Schlenk flask was charged with ethyl-1-indanone-2-carboxylate (0.102 g, 0.5 mmol) and dimethyl 2,2-((2-iodo-1,3-phenylene)bis(oxy))(*2R, 2'R*)-dipropionate (0.02 g, 0.05 mmol) in chloroform (5 mL) under nitrogen. $Et_3N.3HF$ (0.546 mL, 3.35 mmol) and *meta*-chloroperbenzoic (0.13 g, 0.75 mmol) were added and the reaction mixture was stirred at room temperature for 18 hours. 1M K_2CO_3 (25 mL) was added and the product was extracted with chloroform (3 x 25 mL). The combined organic layers were dried

($MgSO_4$), filtered and concentrated *in vacuo.* The crude product was purified by column chromatography using 1 % methanol in dichloromethane to give ethyl 1-indanone-2-fluoro-2-carboxylate as a colourless oil (0.012 g, 11 %). The enantiomeric ratio (25:75) was determined by HPLC analysis: Chiralcel OJ column, hexane/i-PrOH: 90/10, 1.0 mL/min, 25 °C, 280 nm, T_R (minor) = 15.2 min, T_R (major) = 22.6 min.

6.4.22 Chlorination of ethyl 1-oxo-2,3-indanone-2-carboxylate with mCPBA and HCl (Table 4.9, entry 2)

A Schlenk flask was charged with *meta*-chloroperbenzoic acid (0.25 g, 1.44 mmol) and hydrochloric acid (0.156 mL, 5.04 mmol) in dry dichloromethane (0.7 mL) and the reaction was stirred at room temperature for 15 minutes. Ethyl 1-oxo-2,3-indanone-2-carboxylate (0.147 g, 0.72 mmol) was added in dry dichloromethane (0.7 mL), the reaction was stirred at room temperature for 4 hours and the reaction was concentrated *in vacuo*. The crude product was purified by column chromatography using 1 % methanol in dichloromethane to give ethyl 1-indanone-2-fluoro-2-carboxylate as a colourless oil (0.086 g, 72 %) and ethyl 2-hydroxy-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate as a colourless oil (0.031 g, 18 %).

6.4.23 Enantioselective chlorination of ethyl 1-oxo-2,3-indanone-2-carboxylate using cesium chloride and Selectfluor (Table 4.10, entry 1)

A Schlenk flask was charged with ethyl 1-oxo-2,3-indanone-2-carboxylate (0.10 g, 0.5 mmol), dimethyl 2,2-((2-iodo-1,3-phenylene)bis(oxy))(*2R, 2'R*)-dipropionate (0.041 g, 0.1 mmol), cesium chloride (0.28 g, 1.65 mmol) and Selectfluor (0.176 g, 0.55 mmol) in a solution of dry hexafluoroisopropanol (0.47 mL, 4.5 mmol) and dry dichloromethane (5 mL). The flask was sealed, and the reaction mixture was cooled to – 40 °C and stirred for 24 hours. The reaction mixture was quenched with a saturated solution of sodium sulphate (10 mL) and extracted with dichloromethane (3 x 10 mL). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo.* The crude product was purified by column chromatography using 1 % methanol in dichloromethane to give ethyl-2-chloro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate as a colourless oil (0.36 g, 30 %), ethyl 2-hydroxy-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate as a yellow oil (0.004

g, 4 %) and ethyl 1-indanone-2-fluoro-2-carboxylate as a colourless oil (0.001 g, 1 %). The enantiomeric ratio (48:52) was determined by HPLC analysis: Chiralcel OJ column, hexane/i-PrOH: 90/10, 0.7 mL/min, 25 °C, 280 nm, T_R (minor) = 18.1 min, T_R (major) = 27.4 min.

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