Stereoselective Transformations using Chiral Hypervalent Iodine Reagents

A Thesis Submitted to Cardiff University
In Fulfilment of the Requirements for the
Degree of Doctor of Philosophy
by **Florence Malmedy**

PhD Thesis May 2016
Cardiff University

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ACKNOWLEDGEMENTS

This PhD thesis would not have been possible without the help, the support and the encouragement of many people. There are no words that can fully express how thankful and respectful I am for the time that these persons dedicated to me. I will try my best to name all the important ones without whom this journey would not have been the same.

First, I would like to thank Professor Thomas Wirth, my supervisor, for the opportunity he gave me to come to Cardiff and work in his research group. It allowed me to develop and improve my general skills in an organic laboratory as well as exploring the fascinating chemistry of hypervalent iodine(III) reagents. His advices and guidance helped me to overcome issues that came up along the road of this research.

I am also grateful to the Wirth group members as well as to some members of other research groups at Cardiff University. They have been of great support along this PhD thesis but also good friends inside and outside the lab. I always considered them as a second big family: Ale, Ana, Anaïs, Anne, Antoine, Aragorn, Baker, Bénédicte, Célina, Chrissi, Christina, Dan, Daniel, Erika, Fateh, Filipa, Guillaume, Ilaria, James A., James M., James S., Jihan, Joel, Joey, Jon, Kai, Kenta, Kevin, Lou, Marcelo, Maria, Marion, Martin, Matt, Michele, Micol, Mike, Mohamed, Natalia, Nicolas, Nida, Pushpak, Ravi, Rebecca, Rich, Rhino, Rodolfo, Rosaria, Sam, Seb, Simon, Svenia, Tiphaine, Tobi, Tomohiro, Umar, Virginie, Wilke, Xiaoping and Yuri.

I would like to thank more specifically my students Anne, Célina and James T. for all their hard work and contributions to my thesis. I am also very grateful to Mike who introduced me to the field of hypervalent iodine reagent. Mike, Pushpak and Umar have been of great support when I was struggling with my research, helping me to find solutions to these issues. I also want to say a huge thanks to Rich, Ana, Simon and Baker for proof-reading parts or all my thesis. I specially would like to thank Ana, Chrissi and Micol for being such good friends.

I would like to acknowledge all the technical staffs who have been very helpful during this journey: Rob Jenkins, Robin Hicks, Simon Waller, Tom Williams for the MS service and help with the NMR; Benson Kariuki for the X-Ray structures; Sham Ali, Gary Coleman, Jamie Cross, Moira Northam, Heather Amos, Simon James and Owain Harry.

I also thank the EPSRC National Mass Spectrometry Service Centre (Swansea) for the mass spec data.

I am very grateful to Cardiff University who gave me the chance to do my PhD in such a nice environment, and to the EPSRC for their financial support. The RSC also gave me the opportunity to travel to India to present my research, so thank you.

Finally, I would like to thank my family and friends for their support and endless encouragement, specially my parents Cathy and Jean-Pierre, my brothers Vincent and Bernard, my grandparents Marie-Madeleine and Charles and my godfather Jacques.

Dedicated to Cathy and Jean-Pierre

LIST OF ABBREVIATIONS

°C	Degree Celsius
Ø	Diameter
µL	Microlitre
Ac	Acetyl
AcOH	Acetic acid
aq.	Aqueous
APCI	Atmospheric pressure chemical ionisation
Ar	Aryl
BPR	Back-pressure regulator
C	Concentration
Cat.	Catalytic
Conv.	Conversion
CSA	Camphorsulfonic acid
d.r.	Diastereomeric ratio
DBU	1,8-Diazabicycloundec-7-ene
DFT	Density functional theory
DIAD	Di*iso*propyl azodicarboxylate
DIB	(Diacetoxyiodo)benzene
DCE	1,2-Dichloroethane
DME	1,2-Dimethoxyethane
DMP	Dess-Martin periodinane
EDG	Electron donating group
ee	Enantiomeric excess
EI	Electron ionisation
eq.	Equivalent(s)
ESI	Electrospray ionisation
Et	Ethyl
EWG	Electron withdrawing group
g	Gram
GP	General procedure
h	Hour(s)

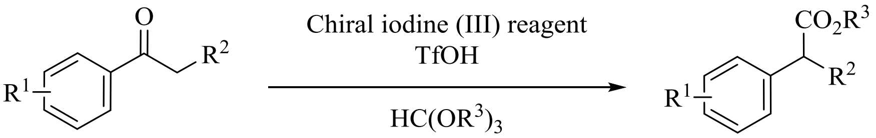
HFIP	Hexafluoro-2-propanol
HOMO	Highest occupied molecular orbital
HPLC	High pressure liquid chromatography
HRMS	High resolution mass spectroscopy
HTIB	Koser’s reagent - [Hydroxy(tosyloxy)iodo]benzene
Hz	Hertz
IBX	2-iodoxybenzoic acid
^{i}Pr	*Iso*-Propyl
IR	Infrared
J	Coupling constant
L	Ligand
LDA	Lithium diisopropylamide
M	Molarity [mol/l]
m.p.	Melting point
m/z	Mass over charge ratio
m-CPBA	*m*-chloroperbenzoic acid
Me	Methyl
Mes	Mesityl
MHz	Megahertz
min	Minute(s)
mL	Millilitre
mmol	Millimole
mol%	Mole percentage
N	Normality
nm	nanometre
NMR	Nuclear magnetic resonance
NSI	Nanospray ionisation
Nu	Nucleophile
OAc	Acetate
o.n.	Overnight
Ph	Phenyl
PIFA	[Bis(trifluoroacetoxy)iodo]benzene
ppm	Part per million

psi	Pounds per square inch
p-TsOH	*p*-Toluenesulfonic acid
R_f	Retention factor (TLC)
r.t.	Room temperature
sat.	Saturated
^{t}Bu	*tert*-butyl
TEMPO	2,2,6,6-Tetramethylpiperidine 1-oxyl
Tf	Trifluoromethanesulfonate
TFA	Trifluoroacetic acid
TFE	2,2,2-Trifluoroethanol
TfOH	Trifluoromethanesulfonic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
t_R	Residence time (Flow system)
T_r	Retention time (HPLC)
Ts	*p*-toluenesulfonyl
vs	versus

ABSTRACT

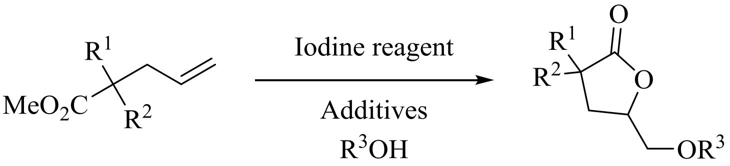
Hypervalent iodine(III) compounds are efficient, selective and environmentally friendly reagents. Due to their electrophilic nature and excellent leaving group ability, they can be used to mediate oxidative transformations; for example, the oxidation of sulfides to sulfoxides, the α-functionalisation of ketones, the dearomatisation of phenols, the functionalisation of alkenes and, more recently, the rearrangement of various substrates.

In this thesis, the stereoselective rearrangement of propiophenone derivatives mediated by chiral hypervalent iodine reagents is described (Scheme i). A chiral lactate-based iodine(III) reagent was used to synthesise 2-arylpropionate derivatives with moderate to good yields and enantioselectivities. These compounds are highly attractive as they are direct precursors to Non-Steroidal Anti-Inflammatory Drugs (NSAIDs).



Scheme i. Rearrangement of propiophenone derivatives to 2-aryl-propionates.

The cyclisation of malonate derivatives, mediated by hypervalent iodine reagents has also been investigated (Scheme ii). Several δ-valerolactone derivatives were synthesised with this method, achieving moderate to good yields.



Scheme ii. Cyclisation of malonate derivatives to synthesise functionalised lactones.

Finally, the design of a new hypervalent iodine reagent is described (Figure i). After its synthesis, the pyridine-based reagent was tested in several model reactions, usually mediated by iodine(III) reagents. Its reactivity was similar to the one of other hypervalent iodine reagents. However, its ability to induce stereoselectivity to different products was quite poor.

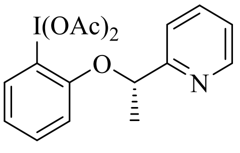


Figure i. Structure of the new hypervalent iodine reagent.

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Chapter 1: Introduction

1.1. General considerations about iodine

Iodine was first isolated in 1811 by the French chemist Bernard Courtois from seaweed's ash as black metallic crystals. With an atomic number of 53, it is the heaviest and most polarisable atom of the halogen group. Its name comes from Greek *ιώδης* meaning violet or purple, due to the characteristic colour of its vapour.

Nowadays, iodine is mainly extracted from brines present in natural gas (Japan, 30% of the world production) and in oil fields (United States) as well as from the caliche deposits (Chile, 60% of the world production). In Chile, calcium iodate [$Ca(IO_3)_2$] is one of the components of caliche deposit extracted from the mines. In contact with an alkaline solution, the iodate ions are liberated in solution and can be reduced to iodide using sulfur dioxide. In Japan, iodine is a by-product resulting from the production of natural gas from brine deposit.[1]

Iodine is a useful tool in analytic chemistry due to its ability to react with alkenes but also starch or sugar to give a blue coloured solution. It can also be oxidised or reduced and therefore, it can be used to determine the amount of reductant or oxidant in a mixture (iodometry). Organoiodides are also well-known reagents for organic synthesis transformations such as oxidative reactions using hypervalent iodine reagents.[2]

Iodine possesses different isotopes but only ^{127}I is stable. However, ^{123}I, with a half-life of 13 h, is often used for the nuclear imaging of thyroid gland where iodine is naturally present. This gland produces a prohormone named thyroxine T_4 which can be deiodinated to the active triiodothyronine T_3, responsible for metabolism regulation (Figure 1.1).

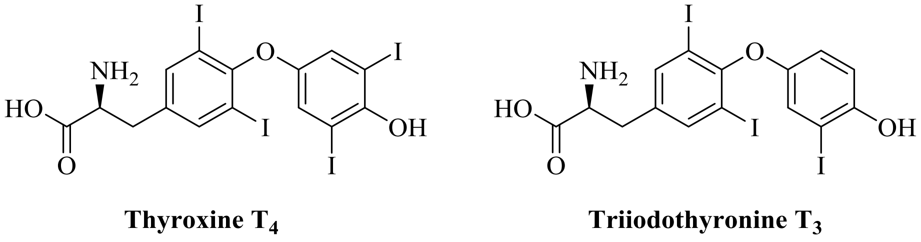


Figure 1.1. Structure of thyroxine T_4 and triiodothyronine T_3.

Iodine is a non-metallic element of the halogen family and can be found in different oxidation states: -1, +1, +3, +5, +7. Due to its high electronegativity, it usually forms iodides with almost all elements with a formal oxidation state of -1.

1.2. Hypervalent iodine

The first hypervalent iodine was discovered in 1886 by the German chemist Conrad Willgerodt.[3] He noticed that by passing chlorine gas through a solution of iodobenzene in chloroform, dichloroiodobenzene [$PhICl_2$] was formed. Since then, the use of these compounds has increased, especially during the last few decades.

1.2.1. Structure of polyvalent iodine

In 1969, J. Musher defined that a hypervalent molecule was a molecule with a least one element from group V-VIII bearing more than eight electrons in its valence shell, therefore not respecting the octet rule. Common examples of this type of molecule are phosphorus pentachloride (PCl_5), sulfur hexafluoride (SF_6) and the triiodide anion (I_3^-).[4]

According to the 1983 IUPAC rules, the term λ^3-iodane and λ^5-iodane are respectively used for iodine(III) and iodine(V) compounds. Trivalent iodine derivatives have 10 electrons at the iodine centre. The most common λ^3-iodane, $ArIL_2$ (L = heteroatom ligand), has a pseudo-trigonal bipyramidal structure (Figure 1.2. a). In this structure, the aryl group (less electronegative group) is in the equatorial position, while the two heteroatom ligands are in the apical positions.

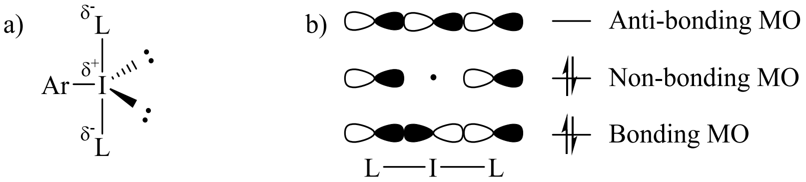


Figure 1.2. a) Pseudo-trigonal bipyramid structure of $ArIL_2$. b) Molecular orbitals of 3c-4e bond in hypervalent iodine(III) compounds.

The hypervalent bond L–I–L can be explained using the three-centre-four-electron (3c-4e) bond model, described independently by G. C. Pimentel[5] and R. E. Rundle[6] in 1951. In this model, three molecular orbitals can be formed from the interaction of the filled 5p orbitals of the central iodine and the partially filled orbitals from the two ligands: bonding, non-bonding and anti-bonding (Figure 1.2. b). As a result of the node in the Highest Occupied Molecular Orbital (HOMO), the hypervalent bond is highly polarised with a strong electrophilic character at the central iodine atom and partial negative charge on the two heteroatom ligands.

Another type of λ^3-iodanes are diaryliodonium salts Ar_2IX, where the most electron-rich aryl group is in the equatorial position. The Ar–I–Ar bond tends to adopt a T-shape and the I–X bond is more ionic in nature than in the case of $ArIL_2$.

In the case of λ^5-iodane ($ArIL_4$), the four ligands tend to be in the equatorial position, forming two orthogonal hypervalent 3c-4e bonds. With regards to the aryl group, it is covalently bound to the iodine centre in the apical position. In other terms, the iodine(V) adopts a square bipyramidal structure as shown in Figure 1.3.

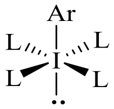


Figure 1.3. Square bipyramidal structure of iodine(V) $ArIL_4$.

1.2.2. Common hypervalent iodine reagents

Hypervalent iodine reagents are now widely used in organic synthesis as mild, selective and efficient reagents. Due to their high interest and their easy synthesis, some have become commercially available. A few examples of hypervalent iodine reagents are shown in Figure 1.4.

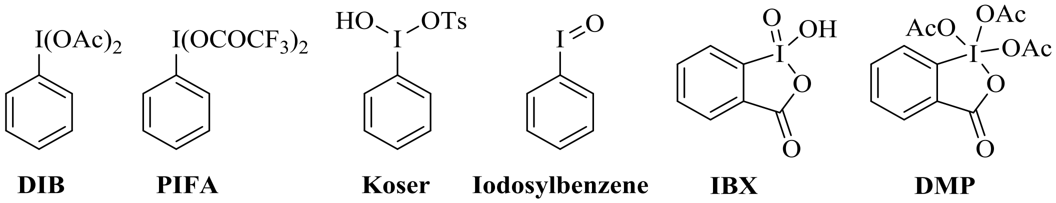


Figure 1.4. Structure of common hypervalent iodine reagents.

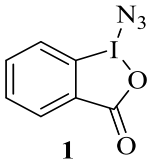
The syntheses of (diacetoxyiodo)benzene (DIB),[7,8] [bis(trifluoroacetoxy)iodo]benzene (PIFA)[9] and [hydroxy(tosyloxy)iodo]benzene (HTIB, also known as Koser's reagent)[10,11] are straightforward with only one step synthesis from iodobenzene in the presence of an oxidant followed by a simple recrystallisation to obtain the pure corresponding iodine(III) compounds. Iodosylbenzene is usually prepared from DIB using an aqueous solution of sodium hydroxide.[12] The resulting yellowish solid can simply be filtered to obtain iodosylbenzene in its polymeric form. This polymeric form can be broken down by addition of water, alcohols or a catalyst (e.g. Lewis or Brønsted acid) to liberate the monomeric reactive iodine(III) reagent. *o*-Iodoxybenzoic acid (IBX) can also easily be synthesised from iodobenzoic acid using Oxone® as the oxidant. Because of its high insolubility, IBX is not largely used in organic syntheses but replaced by the more soluble Dess-Martin periodinane (DMP). These iodine(V) reagents are commonly used for the oxidation of alcohols into their corresponding carbonyl compounds.[13–15]

1.3. General reactivity of hypervalent iodine reagents

Hypervalent iodine reagents have largely been used in organic syntheses due to their low toxicity and their ability to replace heavy metal catalysts in similar reactions. Not only are they mild, selective and efficient reagents for the oxidation of alcohols, but they can also mediate the functionalisation of alkenes and ketones or the dearomatisation of phenols. More recently, they have been used in rearrangement reactions.[2,16–21]

Its electrophilic nature at the iodine centre and the super leaving ability of the phenyliodonio group (10^6 times the triflate's one) when bonded to an sp^3 carbon make this compound an excellent reagent for all the reactions mentioned above.

Different mechanisms are proposed to explain the reactivity of hypervalent iodine reagents. The first one involved a ligand exchange followed by a reductive elimination. However, for iodine(III) with chloro-, oxygen-, nitrogen-ligands, it is also common to propose a radical mechanism due to the small dissociation energy required for the homolytic cleavage in these hypervalent iodine compounds. Typical reactions involving this mechanism are the chlorination of alkanes and alkenes using (dichloroiodo)benzene [$PhICl_2$][22,23] and the azidation[24–26] of C-H bond with iodine(III) reagents of type **1** (Figure 1.5).

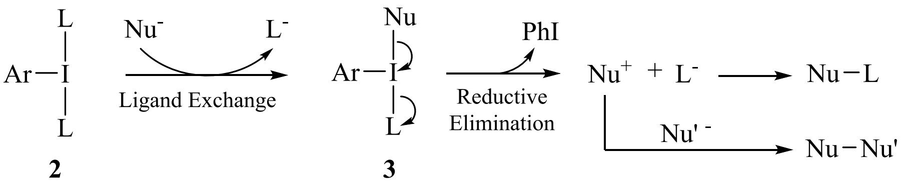


1

Figure 1.5. Structure of hypervalent iodine 1.

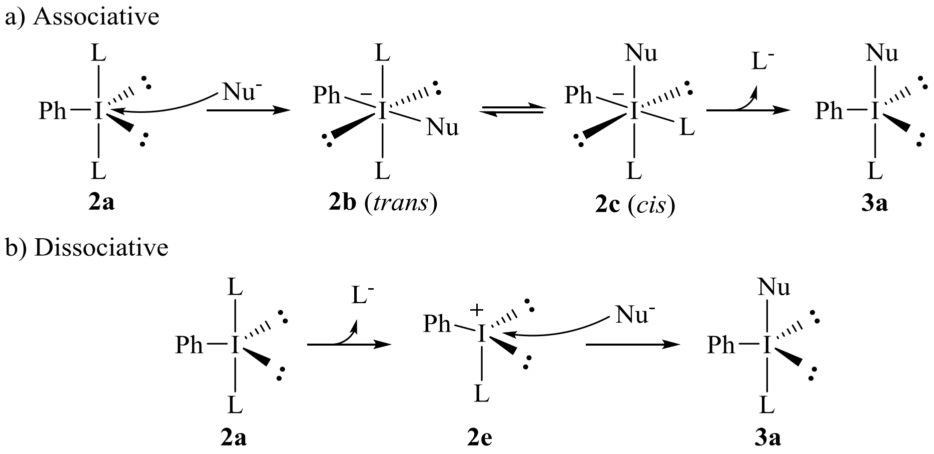
1.3.1. Ligand exchange and reductive elimination mechanism

Most reactions involving a λ^3-iodane $ArIL_2$ proceed *via* the following mechanism. Firstly, the nucleophile exchanges with one of the ligands to obtain intermediate **3**. Secondly, as the iodine is now bonded to an sp^3 carbon and therefore, is an excellent leaving group, a reductive elimination can take place. The nucleophile and the ligand can finally recombine to generate Nu–L type product. However, if a second nucleophile is present, it can react with Nu^+ to afford Nu–Nu' type product (Scheme 1.1).



Scheme 1.1. Schematic mechanism for the ligand exchange and reductive elimination pathway.

The addition of the nucleophile to the hypervalent iodine species can either follow an associative or a dissociative pathway. In the first case, the nucleophile attacks the hypervalent iodine reagent to form a square bipyramidal intermediate **2b** before the elimination of the ligand (Scheme 1.2. a). In the second pathway, the ligand is removed leading to the formation of the iodonium ion ArIL$^+$ **2e** which can react with a nucleophile to obtain the intermediate **3a** (Scheme 1.2. b).



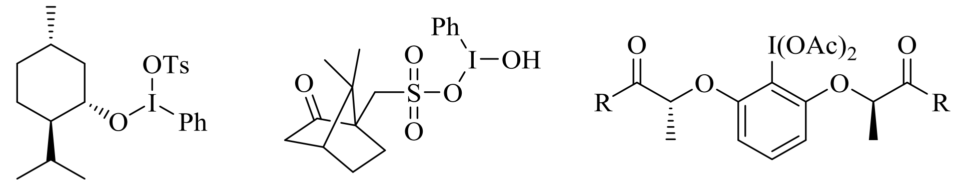
Scheme 1.2. a) Associative and b) dissociative pathway for the ligand exchange step.

In Scheme 1.1, the reactivity of the original nucleophile is changing. In the first step, it reacts as a nucleophile but later on, after the reductive elimination and in the presence of another nucleophile, it has become an electrophile. This Umpolung reactivity is widely harnessed in hypervalent iodine chemistry.

1.4. Introduction to chiral hypervalent iodine reagent

Hypervalent iodine compounds are efficient reagents for a broad range of reactions such as the oxidation of alcohols and sulfides to the corresponding carbonyls or sulfoxides, respectively. They have also been used for the functionalisation of double bonds and carbonyls, the dearomatisation of phenols and more recently, they have been involved in rearrangement transformations. All these reactions can lead to products with one or several new chiral centres. Therefore, it would be interesting to use hypervalent iodine reagents to induce stereoselectivity.

Iodine(III) reagents can have either one aryl/alkyl substituent and two ligands or two aryl/alkyl substituents and one ligand. Each moiety can bear a chiral auxiliary which can induce stereoselective transformations. The first option is to have the chiral auxiliary attached as one ligand of the hypervalent iodine as in iodine(III) reagent **4**[27] or Chen's iodine(III) compound **5**[28] (Figure 1.6).



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5

6a, R = OMe
6b, R = NHMes

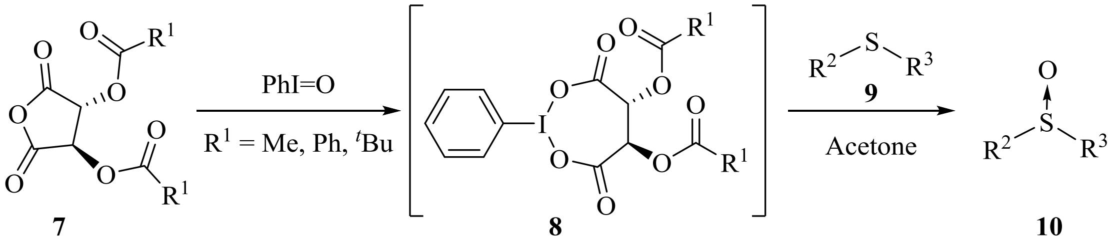
Figure 1.6. Structure of different chiral hypervalent iodine reagents.

The second option is to have the chiral auxiliary on the aryl group like in Ishihara-type reagents **6**.[29] Finally, it would also be possible to use a non-chiral hypervalent iodine reagent in the presence of a chiral ligand in a catalytic amounts.

1.5. Asymmetric syntheses mediated by chiral hypervalent iodine(III) reagents

1.5.1. Oxidation of sulfides to sulfoxides

The first asymmetric oxidation of sulfides to sulfoxides was described by Inamoto *et al.* in 1986. In this work, the authors developed a new chiral iodine(III) reagent combining iodosylbenzene and tartaric anhydride derivatives **7** which they believed to form a C_2-symmetric 7-membered ring **8**. With this reagent, a variety of sulfides **9** were oxidised in good yields and with up to 53% *ee* (Scheme 1.3).[30]



Scheme 1.3. First stereoselective oxidation of sulfides 9 to sulfoxides 10 mediated by hypervalent iodine reagent.

A few years later, Koser demonstrated that the structure of the chiral hypervalent iodine compounds **8** does not actually contain a 7-membered ring but that it is in a polymeric form as shown in Figure 1.7.[31]

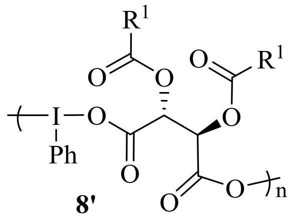


Figure 1.7. Polymeric structure of 8’ proposed by Koser in 1992.

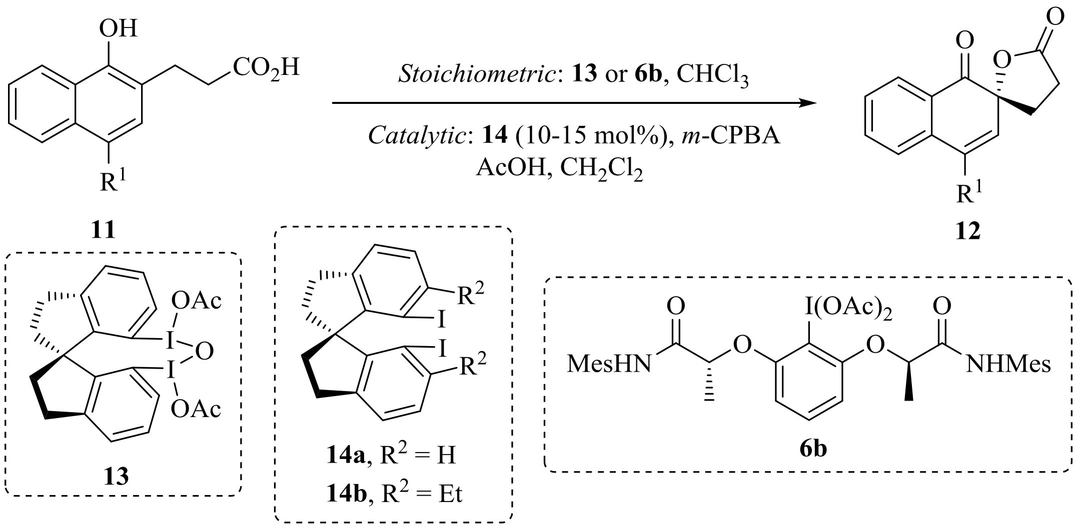
At the same time, Koser *et al.* also designed another chiral hypervalent iodine reagent from menthol. With this reagent **4**, sulfides were oxidised to the corresponding salts in good yields and with low to moderate diastereoselectivity. However, after hydrolysis, the sulfoxides were synthesised with up to 56% *ee* or up to 99% *ee* after recrystallisation.[31]

Kita *et al.* developed a catalytic version of this transformation using 10 mol% of the tartaric acid derivative and iodylbenzene as stoichiometric oxidant in the presence of a catalytic amount of cetyltrimethylammonium bromide.[32] The oxidation occurred with excellent yield and moderate enantioselectivity (up to 72% *ee*). This reaction is highly solvent dependant. The authors used the insolubility of iodylbenzene in most solvents to their advantage. Indeed, the reaction did not work with just the iodine(V) reagent as it was insoluble in the solvent mixture. However, when coordinated to the chiral tartaric acid derivatives, the complex became soluble and could mediate the stereoselective oxidation reaction.

Since then, different new iodine(III) and (V) reagents have been developed and used to mediate this oxidation but none of them gave the corresponding sulfoxides with improved enantioselectivity.[28,33–35]

1.5.2. Dearomatisation of phenols

In 2008, Kita *et al.* published the first enantioselective intramolecular dearomatisation of naphthols **11**. The group developed the reaction both stoichiometrically and catalytically and products **12** were obtained in good yields and with up to 86% *ee* and 69% *ee*, respectively (Scheme 1.4).[36] To achieve this stereoselectivity, chiral hypervalent iodine reagent **13** was used for the stoichiometric transformation. For the catalytic dearomatisation, spiroindane **14a** was oxidised *in situ* using *m*-CPBA in the presence of acetic acid.



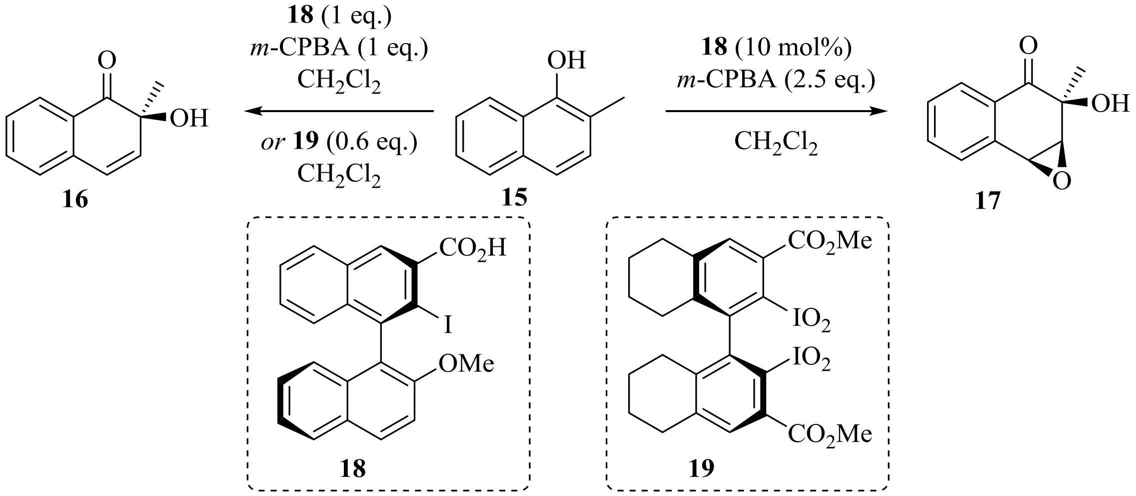
Scheme 1.4. Enantioselective dearomatisation of naphthols by Kita *et al.* and Ishihara *et al.*

In 2013, the same group improved their catalyst **14b** with an extra ethyl group on the aryl group and the corresponding spirolactones were generated in up to 96% yield and with up to 92% *ee*.[37] The ethyl group in the *ortho*-position to the iodine centre allows for a better enantioselectivity because of the steric hindrance of the ethyl group with the ligand (in the apical position) and the substrate. Furthermore, the conformation of the catalyst is maintained due to the rigid backbone of the spirobiindane moiety.

In 2010, Ishihara developed a new series of hypervalent iodine reagent of type **6b** bearing a C_2-symmetry and where there could be possible n-σ^* interactions between the electron-deficient iodine(III) centre and the two carbonyl groups or intramolecular hydrogen bonding. This chiral environment should allow selectivity in the dearomatisation reaction. With their best catalyst, very similar results to the one of Kita's were achieved, with up to 92% *ee*.[29] In 2016, Muñiz and Ishihara demonstrated the hydrogen bonding between the NH group and the acetoxy group of compound **6b** by X-Ray crystallography as well as its derivative bearing a methyl group in the *para*-position to the iodine substituent on the aryl ring. It was also confirmed by ^{1}H NMR that these hydrogen bondings were maintained in solution.[38]

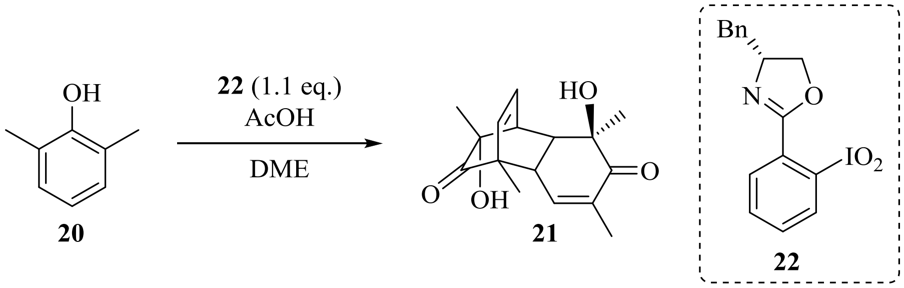
Quideau *et al.* reported in 2009 an enantioselective intermolecular hydroxylative dearomatisation of phenols. Iodoarene **18** was used in catalytic amount with a stoichiometric amount of *m*-CPBA to oxidise the iodine *in situ*. The dearomatisation led to products **16** in good yield (83%) and with 50% *ee*. If an excess of *m*-CPBA (2.5 equivalents) was used, product **16** was not observed as the double bond overreacted to generate the epoxide **17** in 90% yield but with only 29% *ee* (**Scheme 1.5**).[39]

Recently, the same group synthesised a range of biphenylic iodanes **19** and applied them to the enantioselective hydroxylative dearomatisation of phenols to form products **16** in moderate yield but with an improved *ee* of 73%.[40]



Scheme 1.5. Intermolecular hydroxylative phenol dearomatisation.

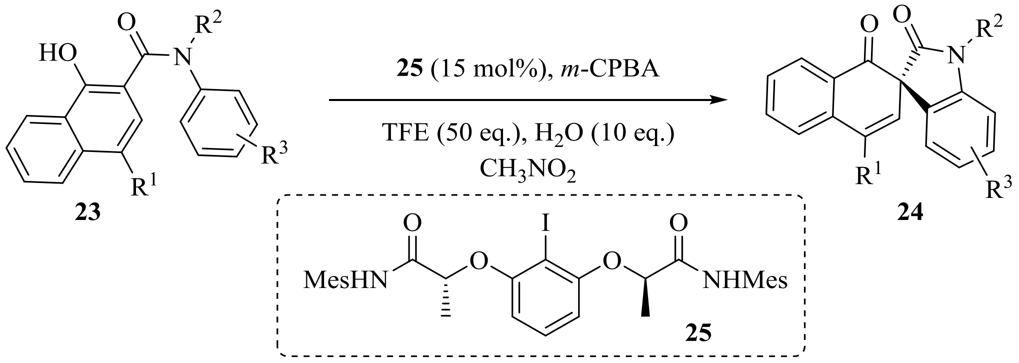
In 2009, Birman and Boppisetti synthesised chiral hypervalent iodine **22** and reacted it with phenols **20**. The generated *o*-quinol derivatives can undergo a [4+2] cycloaddition to generate dimerised products **21** in moderate to good yields and with up to 77% *ee* (Scheme 1.6).[41]



Scheme 1.6. Tandem dearomatisation and [4+2] cycloaddition of phenols.

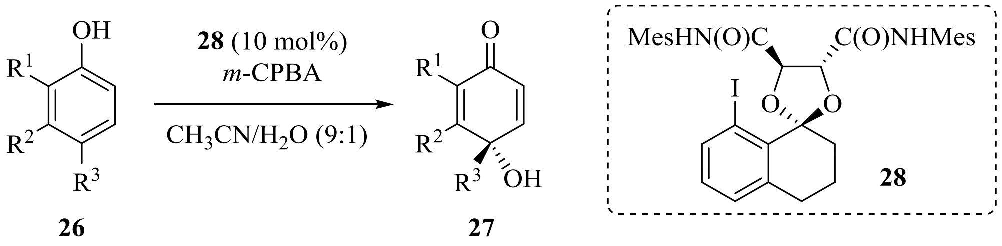
In 2013, Ishihara *et al.* published the same type of tandem dearomatisation and dimerisation reaction of phenols in good to excellent yield and with up to 99% *ee*. The reaction was performed catalytically, using iodoarene **25** and *m*-CPBA as the oxidant.[42]

In 2015, Gong *et al.* developed an enantioselective catalytic spirocyclisation of compounds **23** leading to the formation of products **24** in up to 84% yield and with up to 91% *ee*. Iodoarene **25** was oxidised with *m*-CPBA *in situ* and used to activate the naphthol derivatives. This underwent an intramolecular S_N2'-like Friedel-Craft substitution to yield products **24** (Scheme 1.7).[43]



Scheme 1.7. Enantioselective spirocyclisation of compounds 23.

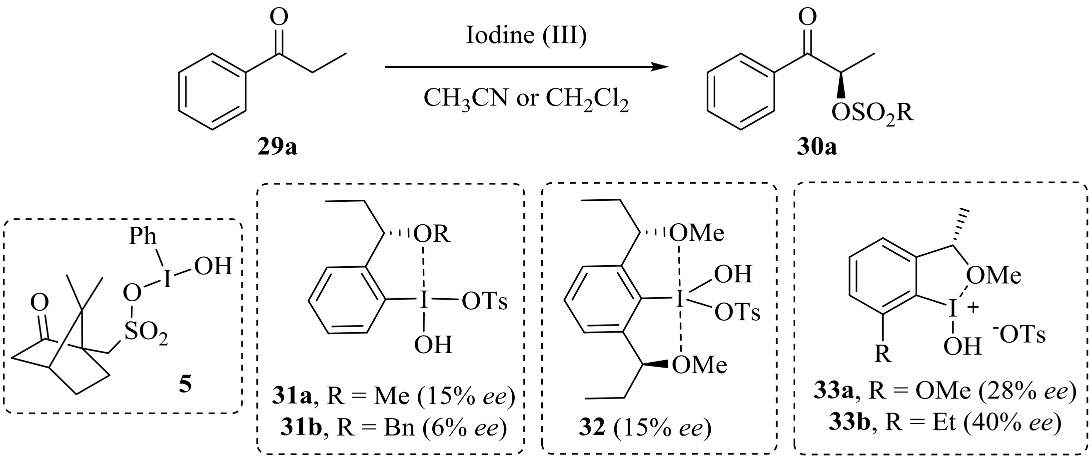
Finally, Harned and Volp developed a *para*-hydroxylative oxidation of phenols **26** using catalyst **28** to yield *p*-quinols **27** in low to good yields and with 6 to 60% *ee* (Scheme 1.8).[44]



Scheme 1.8. Synthesis of *p*-quinols by dearomatisation of phenols 26.

1.5.3. α-Functionalisation of carbonyl compounds

In 1990, Vargolis *et al.* reported an α-oxytosylation using chiral reagent **5** in good yield. However, the reaction suffered from low diastereoselectivity for all substrates investigated.[45] Later on, Wirth *et al.* designed a series of new chiral hypervalent iodine(III) reagents **31-32**. With these new reagents, the corresponding α-oxytosylated products were obtained with enantioselectivities of up to 15% (Scheme 1.9).[46]

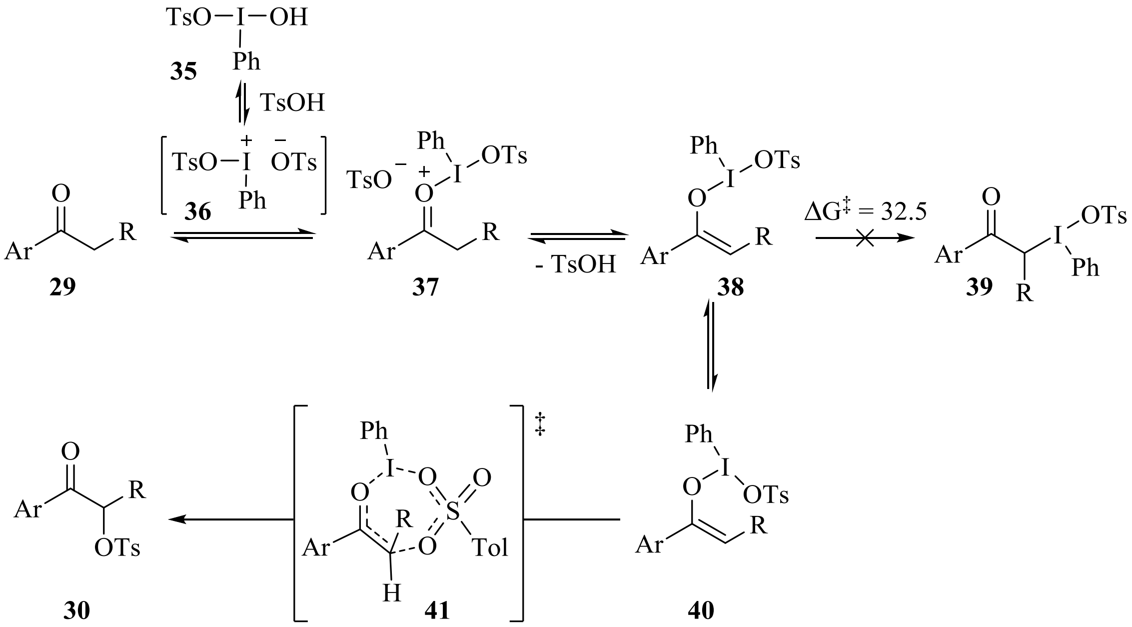


Scheme 1.9. α-Oxytosylation of propiophenone 29a.

A year later, the same group slightly modified the structure of their hypervalent iodine(III) reagent (**33a**) and the desired product was formed with 28% *ee*.[47] In 2001, the effect of the R group on the aryl moiety was investigated and it was found that reagent **33b** gave the best enantioselectivity (40% *ee*).[48]

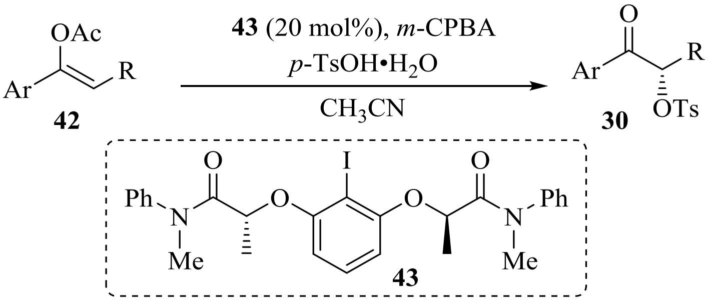
A few years later, the same group developed the first catalytic α-oxytosylation of carbonyls in good yields and moderate enantioselectivities. Catalytic amount of aryliodides (10 mol%) was used in combination with an excess of *m*-CPBA and *p*-TsOH•H_2O.[49] They also designed other iodoarene catalysts but none of them improved the reaction stereoselectivity.[50,51] More recently, Moran,[52] Legault[53], Zhang[54] and Berthiol[55] groups described new iodine catalysts for this transformation and the desired products **30** were obtained with moderate enantioselectivities with 51%, 36%, 58% and up to 34% *ee*, respectively.

In 2015, Legault *et al.* studied the mechanism for this transformation in more detail. The calculations suggest an iodonium enolisation process to form intermediate **38**. This intermediate should not isomerise to the intermediate **39** due to a too high isomerisation barrier ($\Delta G^{\ddagger}$ = 32.5 kcal/mol). The following reductive elimination on the prochiral enolate **40** was found to be the determining step for the stereoselectivity on the final product **30** (Scheme 1.10).[56]



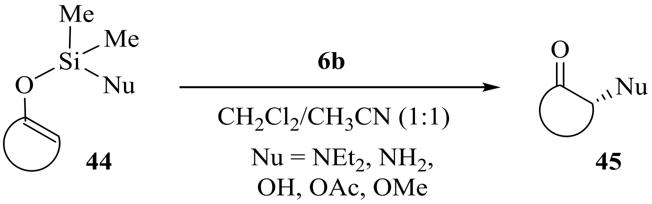
Scheme 1.10. New mechanism for the *α*-oxytosylation of propiophenone derivatives proposed by Legault.

The same year, they applied this method onto enol esters **42** to generate *α*-oxytosylated products **30** in high yields using Koser's reagent (up to 94%).[57] The reaction also proceeded under catalytic conditions (20 mol% of chiral iodoarene **43** and *m*-CPBA as the oxidant) and gave the corresponding products **30** in up to 94% yield and with up to 89% *ee* (Scheme 1.11).[58]



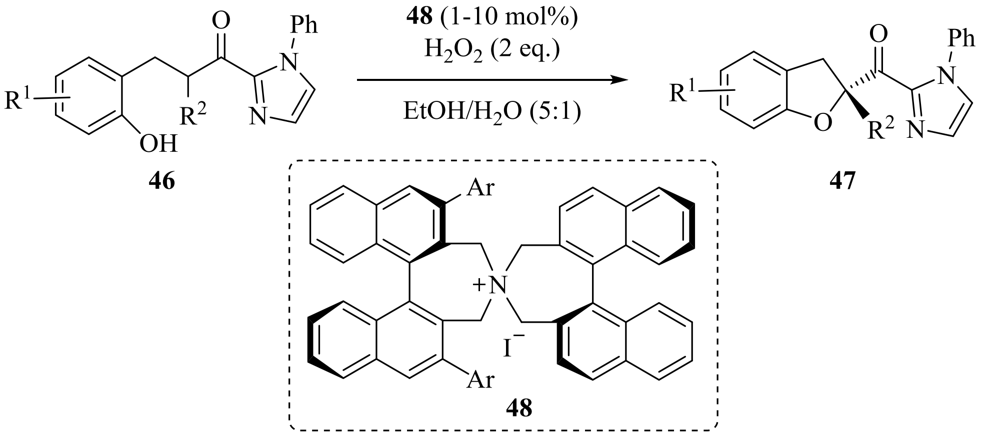
Scheme 1.11. Catalytic enantioselective *α*-oxytosylation of substrates 42.

Finally, Wirth *et al.* applied the concept of "silyl temporary tethers" for the α-functionalisation of carbonyl derivatives. The method allowed the easy generation of nitrogen- and oxygen- α-substituted carbonyl compounds **45** from silyl enol ether **44** in good yields and with up to 94% *ee* (Scheme 1.12).[59]



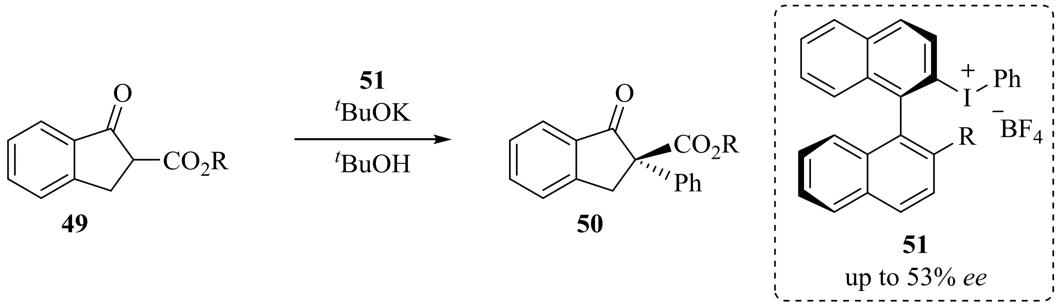
Scheme 1.12. Flexible stereoselective α-functionalisation of ketones through Umpolung reaction with hypervalent iodine reagents.

In 2010, Ishihara reported the enantioselective oxidative cycloetherification of ketophenols **46** using a catalytic amount of the chiral quaternary ammonium (hypo)iodite salt **48** in combination with a stoichiometric amount of hydrogen peroxide. The corresponding dihydrobenzofurans **47** were obtained in low to excellent yields and with up to 96% *ee* (Scheme 1.13).[60]



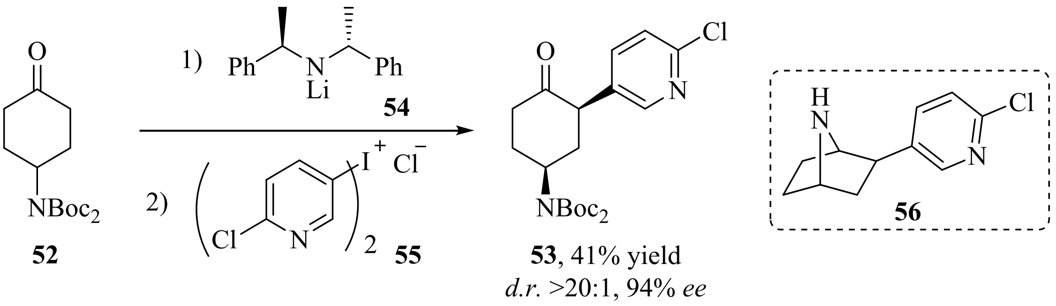
Scheme 1.13. Oxidative cycloetherification of ketophenols 46.

In 1999, Ochiai *et al.* described the asymmetric phenylation of β-ketoesters **49** using chiral diaryliodonium salts **51** in the presence of potassium *tert*-butoxide to give compounds **50** in moderate to good yield and with up to 53% *ee* (Scheme 1.14).[61] Since then, other groups have synthesised chiral diaryliodonium salts but none of them have been reported in an asymmetric phenylation reaction yet.[62,63]



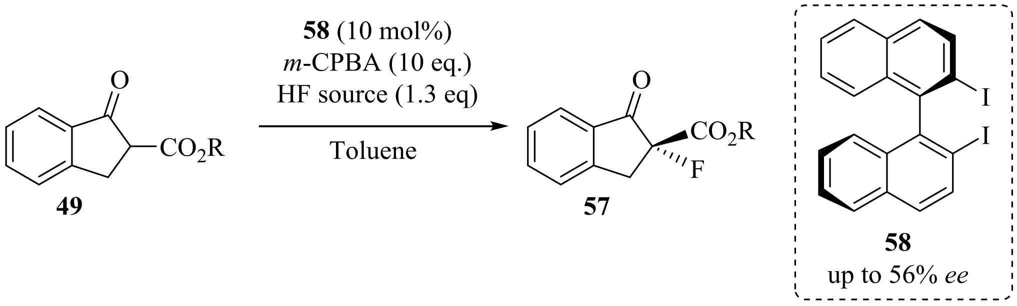
Scheme 1.14. ***α*-Phenylation of *β*-ketoesters 49.**

In 2005, Aggarwal and Olofsson reported another approach for the asymmetric *α*-arylation of ketones **52**. A non-chiral diaryliodonium salt **55** was used in combination with a chiral base (Simpkins' base) **54** to yield products **53** in moderate to good yields and with high enantioselectivities (up to 94%) (Scheme 1.15). This strategy was applied to the asymmetric synthesis of the alkaloid (-)-epibatidine **56**.[64]



Scheme 1.15. ***α*-Arylation of cyclohexanone derivative 52.**

Recently, Shibata *et al.* demonstrated the asymmetric addition of fluorine onto *β*-ketoesters **49** using 10 mol% of catalyst **58** and *m*-CPBA as an internal oxidant in the presence of an HF source (either hydrogen fluoride pyridine or 46% aqueous hydrofluoric acid). With this method, the *α*-fluorinated products **57** were obtained in up to 71% yield and with up to 56% *ee* (Scheme 1.16).[65]



Scheme 1.16. ***α*-Fluorination of *β*-ketoesters 49.**

1.5.4. Rearrangements

Due to the electrophilic nature of hypervalent iodine(III) reagents and their excellent leaving group ability, they are highly suitable species to generate cationic intermediates. Those intermediates can then react with a broad range of nucleophiles or rearrange *via* 1,2-aryl migrations, ring contractions, ring expansions, Hoffmann-type rearrangements or Wagner-Meerwein-type rearrangements. A brief summary of those oxidative rearrangements mediated by hypervalent iodine(III) reagents is described in Chapter 2.

1.5.5. Functionalisation of C-C double bonds

The functionalisation of alkenes is a very important reaction in synthetic chemistry as it allows quick access to more complex molecules. Hypervalent iodine(III) reagents are well known to activate carbon-carbon double bonds to encourage their reaction with a nucleophile. As the iodine reagent is then connected to an sp^3 carbon centre, it is an excellent leaving group and therefore, a second nucleophile can displace the iodine(III), reducing it to iodine(I). A broad variety of nucleophiles can be used and a brief summary can be found in Chapter 4.

1.6. Conclusion

In conclusion, hypervalent iodine reagents are mild, environmentally friendly and selective oxidants for a large number of transformations such as the oxidation of alcohols, the dearomatisation of phenols and the functionalisation of double bonds or ketones. More recently, they have been used in oxidative rearrangement reactions. These reagents are also becoming more and more involved in recent syntheses of natural and biologically active compounds. Their ability to induce stereoselectivity in the final products render hypervalent iodine compounds even more attractive.

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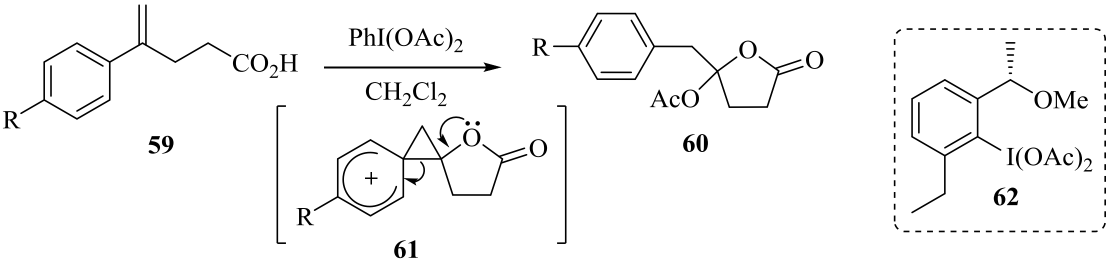
Chapter 2: Introduction of oxidative rearrangements mediated by hypervalent iodine reagents

2.1. Introduction of oxidative rearrangement

In the last few decades, hypervalent iodine(III) reagents have been used in a lot of organic syntheses including oxidative rearrangements.[1–5] Due to their electrophilic nature and their excellent leaving group ability, they are highly suitable species to generate cationic intermediates. Those intermediates can then react with a broad range of nucleophiles or undergo rearrangement *via* 1,2-aryl migrations, ring contractions, ring expansions, Hofmann-type rearrangements or Wagner-Meerwein-type rearrangements. A brief summary of oxidative rearrangements mediated by hypervalent iodine(III) reagents is described below.

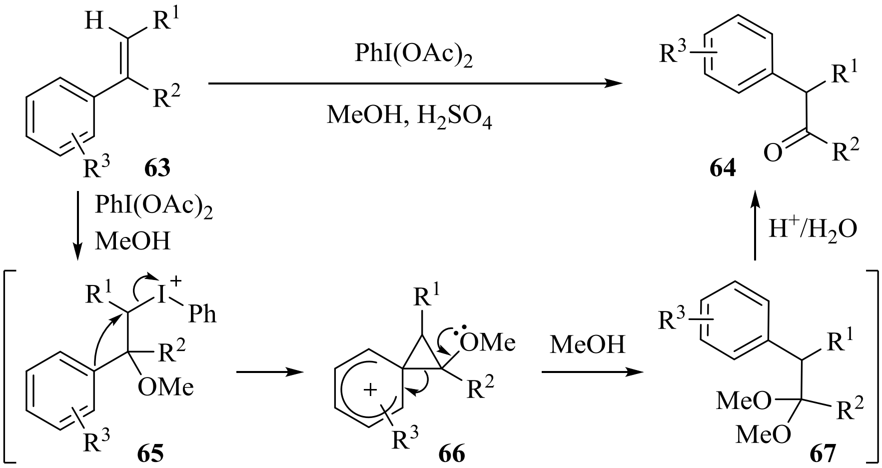
2.2. 1,2-Aryl migrations

The theory that these migration reactions involve an aryl moiety as a cationic species was first proposed by Cram in the late 1940s.[6–11] However it is only quite recently that phenonium ions have been used to explain the rearrangement mediated by hypervalent iodine(III) reagents. In 2003, Wirth *et al.* described the lactonisation of 4-aryl-4-pentenoic acids **59** involving phenonium ion intermediates **61**. The corresponding lactones **60** were obtained in 87% yield when R=H but the yield for the rearranged product dropped drastically when a substituent was in *para* position. Chiral hypervalent iodine reagent **62** also mediated this rearrangement in moderate yield (56%) but with only 4% enantiomeric excess (Scheme 2.1).[12]



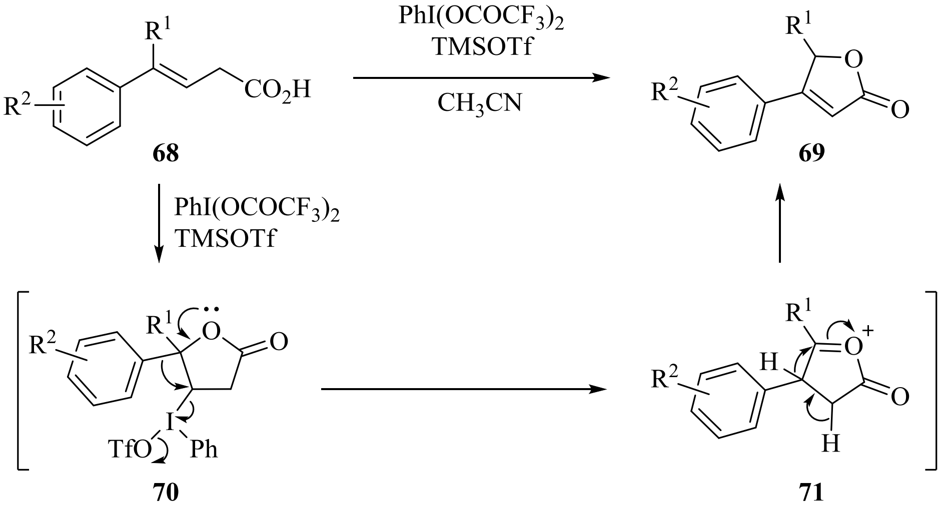
Scheme 2.1. Oxidative 1,2-aryl migration of 4-aryl-4-pentenoic acids 59 mediated by hypervalent iodine reagent.

The next year (2004), Yusobov *et al.* reported the rearrangement of α-substituted styrenes **63** mediated by a hypervalent iodine(III) reagent. They proposed that the reaction started with the activation of the double bond by the iodine reagent in the presence of methanol to generate intermediate **65**. This was followed by the aryl migration to form the phenonium ion **66**. After nucleophilic attack of methanol and hydrolysis, the corresponding arylacetones **64** were obtained in up to 92% yield (Scheme 2.2).[13]



Scheme 2.2. Oxidative 1,2-aryl migration of styrene 63 mediated by hypervalent iodine reagent.

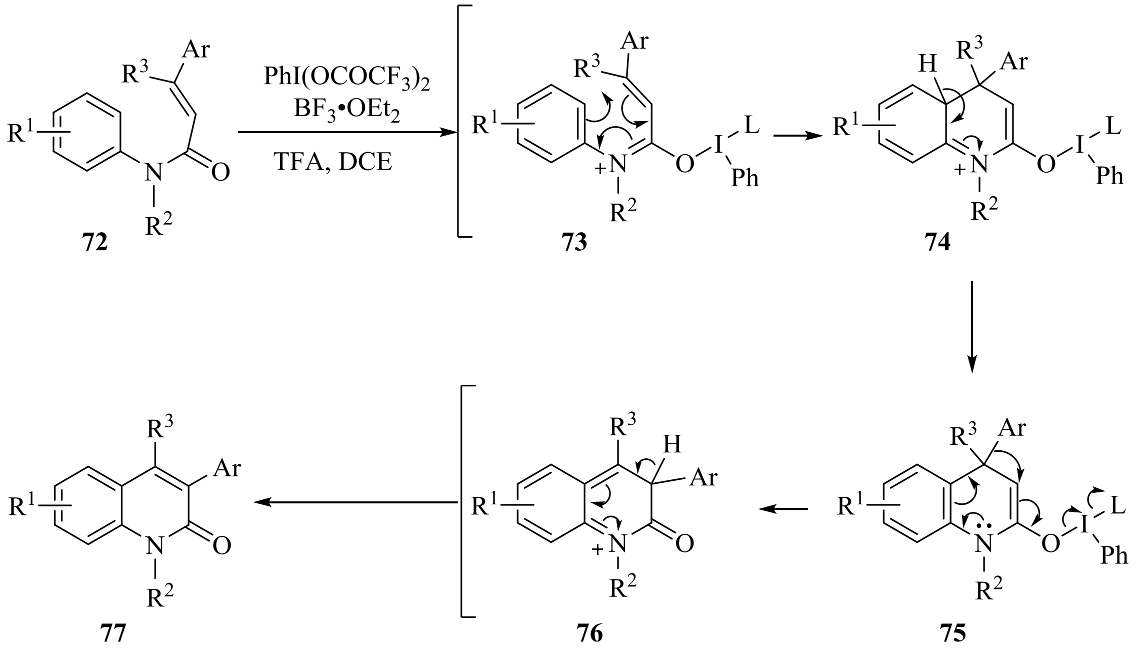
Later on, Wirth *et al.* described the rearrangement of unsaturated carboxylic acids **68** into furanones **69**. It was found that only phenyliodine bistriflate was sufficiently reactive to mediate this reaction. The mechanism was also investigated in detail and DFT calculations confirmed that the 1,2-aryl migration was followed by a 1,2-hydride shift as shown in Scheme 2.3. With this method, different furanones **69** were obtained with up to 95% yield.[14]



Scheme 2.3. Oxidative 1,2-aryl migration of unsaturated carboxylic acids 68 mediated by hypervalent iodine reagent.

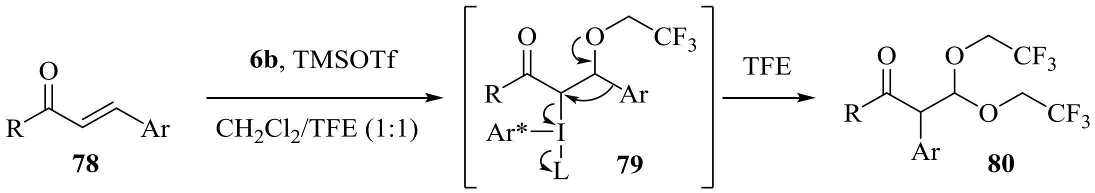
In 2013, Zhao *et al.* reported the oxidative 1,2-aryl migration of *N*-methyl-*N*-phenylcinnamides **72** to generate 3-aryl-quinolin-2ones **77** in up to 90% yield. The rearrangement proceeded in the presence of [bis(trifluoroacetoxy)iodo]benzene (PIFA) and BF_3•OEt_2 as Lewis acid (Scheme 2.4).[15]

The proposed mechanism consists of the attack of the carbonyl oxygen onto the iodine centre to form the 3-azatriene intermediate **73** which can undergo an electrocyclic ring closure and subsequent rearomatisation to yield intermediate **75**. Finally, assisted by the lone-pair of the nitrogen atom, a 1,2-aryl migration proceeds leading to the breakdown of the O–I bond and the desired products **77** are obtained after deprotonation.



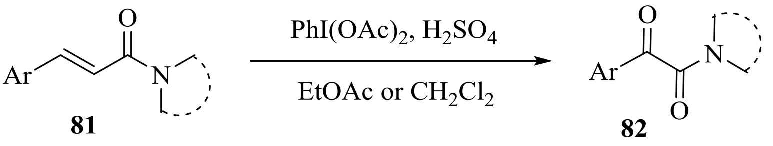
Scheme 2.4. Oxidative 1,2-aryl migration of *N*-methyl-*N*-phenylcinnamides 72 mediated by PIFA.

In 2013, Wirth *et al.* published the first stereoselective rearrangement mediated by hypervalent iodine(III) reagents.[16] This transformation was based on the seminal work of Moriarty *et al.* from 1985 describing the rearrangement of chalcones **78**.[17] Compounds **80** were obtained in good yields (up to 92%) and with high enantioselectivities (up to 97% *ee*). However, the enantioselectivity was directly related to the choice of solvent mixture. Indeed, 2,2,2-trifluoroethanol was essential for the reaction to proceed with high stereoselectivities (Scheme 2.5).



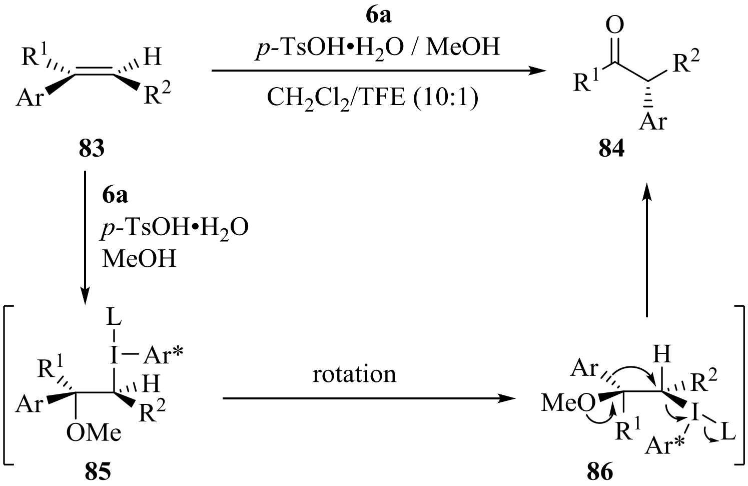
Scheme 2.5. Oxidative 1,2-aryl migration of chalcone derivatives 78 mediated by hypervalent iodine reagent.

Zhao *et al.* reported that acrylic amides **81** were converted into α-ketoamides **82** in the presence of PhI(OAc)$_2$ and concentrated sulfuric acid (Scheme 2.6). The reaction proceeded *via* a tandem aryl migration/ C-C bond cleavage. The same method can be applied for the conversion of acrylates into α-ketoesters (40 to 90% yield).[18]



Scheme 2.6. Tandem aryl migration/ C-C bond cleavage sequence for the synthesis of α-ketoamides 82.

In the 1980s, Koser *et al.* described the oxidative 1,2-aryl migration of 1,1-disubstituted alkenes **83** to obtain *α*-arylated carbonyl compounds **84**.[19,20] Very recently, Wirth *et al.* reported the enantioselective version of this transformation to obtain *α*-arylated carbonyl compounds **84** in up to 90% yield and with up to 94% *ee* (Scheme 2.7).[21] The authors used chiral hypervalent iodine(III) reagent **6a** and generated *in situ* Koser type's reagent.

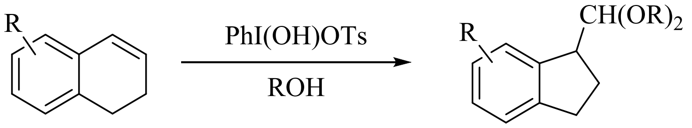


Scheme 2.7. Oxidative 1,2-aryl migration of 1,1-disubstituted alkenes 83 mediated by hypervalent iodine reagent.

2.3. Ring contractions

Ring contractions are important rearrangements in organic synthesis. Over the past 30 years, ring contractions mediated by hypervalent iodine(III) reagents have been used frequently. A detailed discussion on the ring contractions of cycloalkenes and cycloalkanones can be found in a review published by Silva in 2006.[22]

Silva *et al.* also reported the ring contraction of 1,2-dihydronaphthalenes **87** mediated by Koser's reagent to generate indane derivatives **88** in moderate yield.[23] Depending on the solvent used, the indanes generated were bearing different acetals. Dimethyl acetal derivative **88a** was obtained in methanol with a yield of 36% and in 2,2,2-trifluoroethanol, acetal **88b** was synthesised in 73% yield (Scheme 2.8).[24]

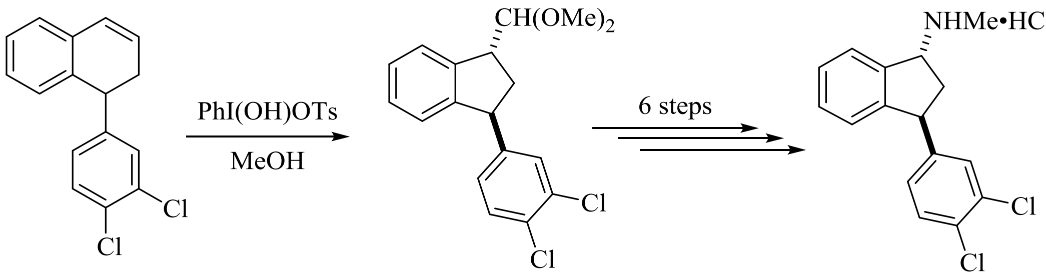


87

88a, R = CH_3 (36%)
88b, R = CH_2CF_3 (73%)

Scheme 2.8. Ring contraction of 1.,2-dihydronaphthalene derivatives 87 mediated by Koser's reagent.

With this method, the precursor **90** for the synthesis of (±)-indatraline **91** was obtained in 62% yield (Scheme 2.9). In 2013, Wirth *et al.* reported the stereoselective ring contraction of tetralone using hypervalent iodine **6b** and triflic acid to activate the iodine reagent. The corresponding indane was obtained with 72% yield and 59% *ee* at -78 °C or 30% yield and 70% *ee* at -100 °C.[16]

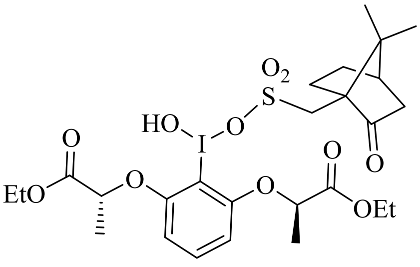


89 **90** **91**, (±)-indatraline

Scheme 2.9. Ring contraction of 1,2-dihydronaphthalene derivative 90 for the synthesis of (±)-indatraline.

Very recently (2016), Silva *et al.* reported the ring contraction of 1,2-dihydronaphthalenes **87** to yield optically active 1-substituted indanes **88**. Chiral hypervalent iodine **92** was prepared *in situ* from the corresponding iodoarene using *m*-CPBA and camphorsulfonic acid [(*R*)-CSA] (Figure 2.1). Different cyclic alkenes were investigated and the corresponding indanes **88** were isolated in moderate to good yields and with up to 78%

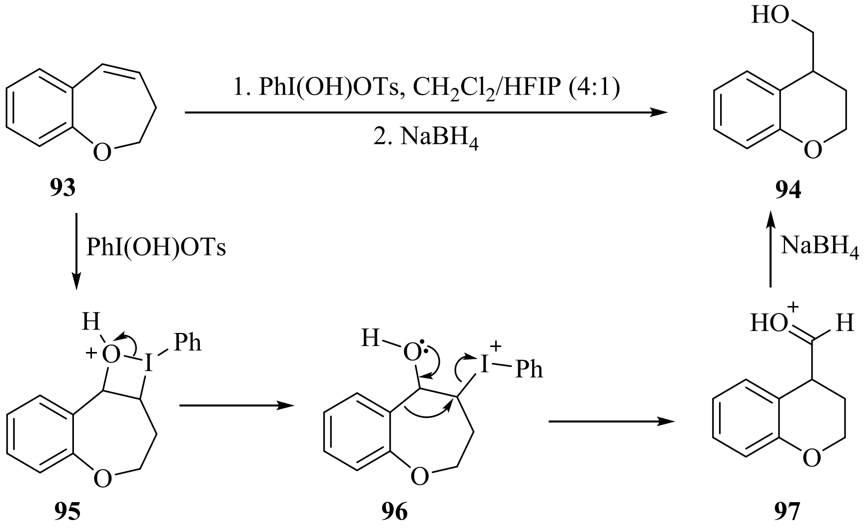
ee. Furthermore, the rearrangement occurred in 5 minutes compared to 14 hours in the previous works which render this method attractive to access indane derivatives.[25]



92

Figure 2.1. Structure of chiral hypervalent iodine 92.

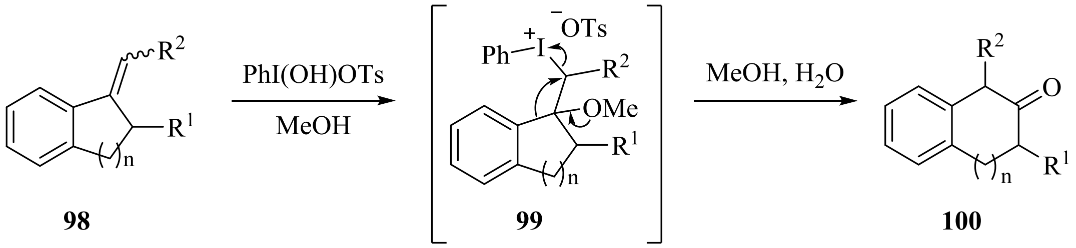
In 2012, Silva *et al.* reported the ring contraction of 2,3-dihydrobenzoxepine **93** using Koser's reagent. The rearrangement proceeded with 58% yield. The proposed mechanism is shown in Scheme 2.10. The reaction was initiated by the activation of the double bond with Koser's reagent, generating a carbocation which can be trapped by the oxygen lone pair to generate intermediate **95**. After ring opening of the four-membered ring, the iodonium species **96** underwent a ring contraction rearrangement leading to the corresponding protonated aldehyde **97**. This aldehyde was easily reduced using sodium borohydride to yield alcohol **94**.[26]



Scheme 2.10. Ring contraction of 2,3-dihydrobenzoxepine 93 mediated by hypervalent iodine reagent.

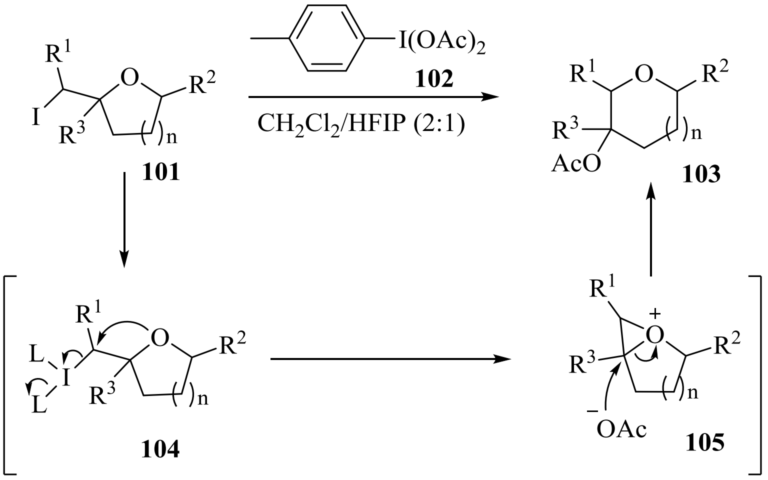
2.4. Ring expansions

In 2005, Koser developed a ring expansion of alkylidenebenzocycloalkenes **98** using Koser's reagent to form β-benzocycloalkenones **100** in up to 99% yield.[27] A possible mechanism involves the formation of cationic intermediates **99** followed by the aryl migration and attack of methanol to provide the corresponding ketal which can be hydrolysed with water to give the desired expanded ring **100** (Scheme 2.11).



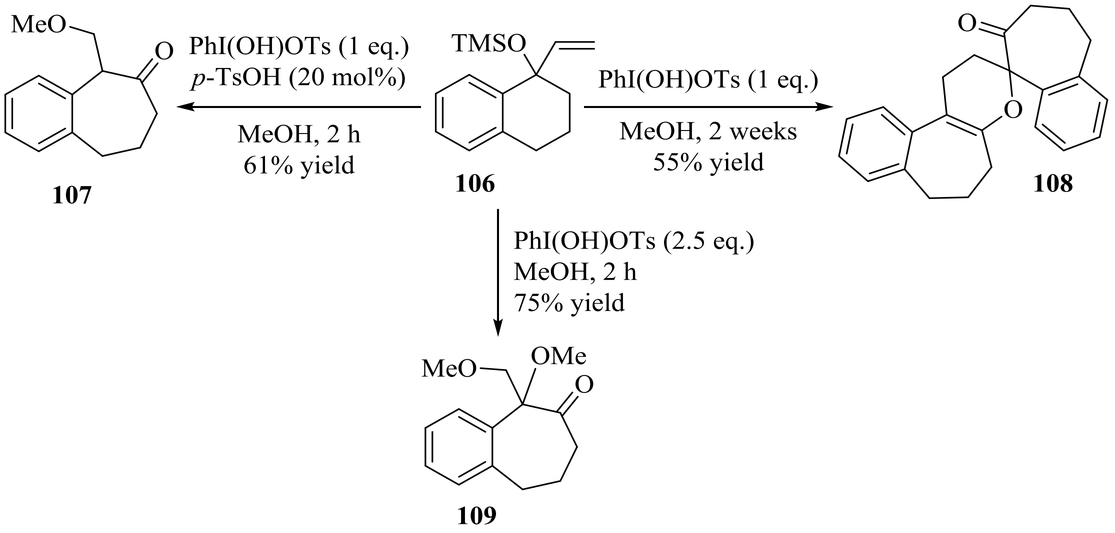
Scheme 2.11. Ring expansion of alkylidenebenzocycloalkenes 98 mediated by Koser's reagent.

The same year, Hara *et al.* reported the ring expansion of iodoalkyl cyclic ethers **101** using (diacetoxyiodo)toluene **102** (Scheme 2.12). A plausible mechanism consists of the *in situ* oxidation of the iodine moiety followed by the attack of the oxygen lone pair to give intermediate **105**. After ring opening by an acetoxy group, the desired expanded cyclic ethers **103** were obtained in good to excellent yields.[28]



Scheme 2.12. Ring expansion of iodoalkyl cyclic ethers 101 mediated by hypervalent iodine reagent.

Silva *et al.* published later on the ring expansion of 1-vinyl cycloalkanols of type **106**. Depending on the reaction conditions, three different compounds **107**, **108** and **109** were generated in moderate to good yields (Scheme 2.13).[29]

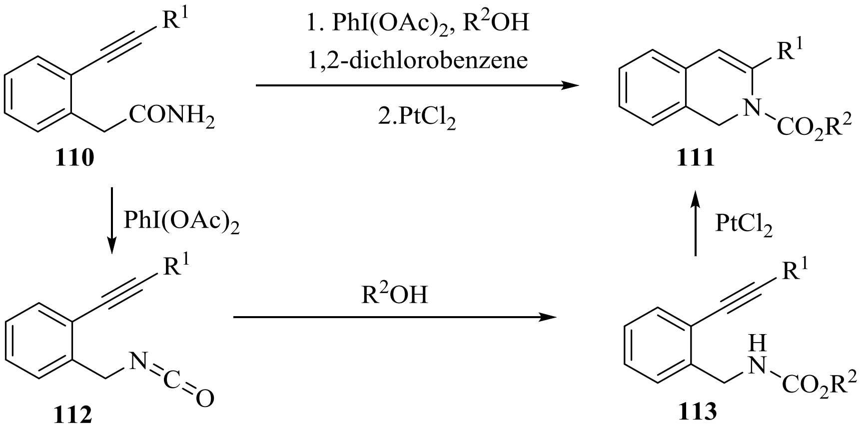


Scheme 2.13. Ring expansion of 1-vinylcycloalkanols derivatives 106 mediated by Koser's reagent.

2.5. Hofmann rearrangement

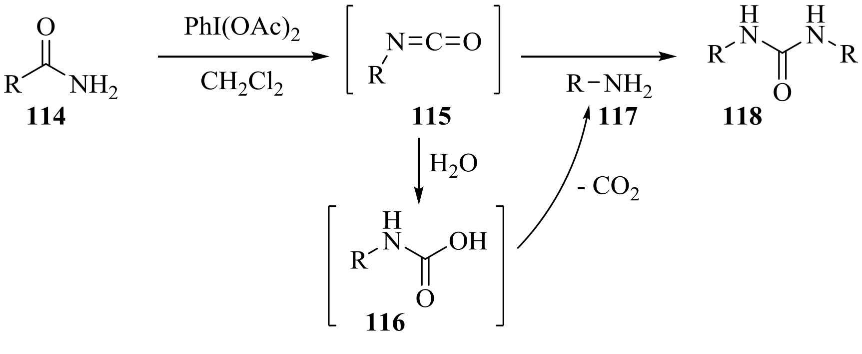
The first Hofmann rearrangement mediated by hypervalent iodine(III) was reported by Loudon *et al.* in 1984. In this paper, the authors described the transformation of aliphatic amides into amines using PIFA with good to excellent yields.[30,31]

Yanada *et al.* published in 2009 the tandem reaction on alkynylbenzylamides **110** to generate benzo-fused nitrogen heteroaromatic systems **111** (Scheme 2.14). This tandem transformation consists of the Hofmann type rearrangement of amides **110** to form the isocyanates **112** which can react with an alcohol to form intermediates **113**. After activation of the triple bond with $PtCl_2$, a ring cyclisation occurred leading to the formation of compounds **111** in up to 92% yield.[32]



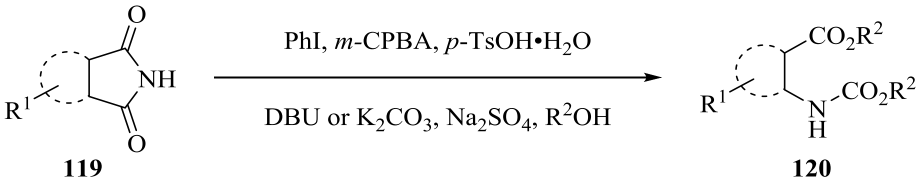
Scheme 2.14. Hofmann rearrangement of alkynylbenzylamides 110 into benzo-fused nitrogen heteroaromatic systems 111 mediated by DIB.

Later on, Kalesse *et al.* synthesised urea **118** using this rearrangement. After generation and hydrolysis of the isocyanates **115**, intermediates **116** were decarboxylated to form the corresponding amines **117** which reacted with the unreacted isocyanates **115** leading to the formation of ureas **118** in up to 60% yield (Scheme 2.15).[33]



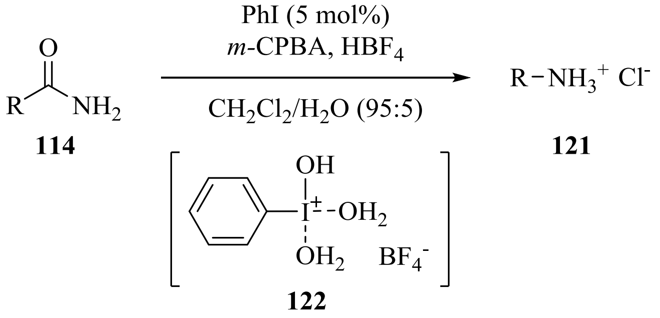
Scheme 2.15. Hofmann rearrangement of amides 104 into ureas 118 mediated by DIB.

Moriyama *et al.* reported the Hofmann rearrangement of imides **119** using an *in situ* oxidation of iodobenzene using *m*-chloroperbenzoic acid (*m*-CPBA). With this method, anthranilic acid derivatives **120** and a number of *β*- and *γ*-amino acids were successfully obtained in good yields (Scheme 2.16).[34]



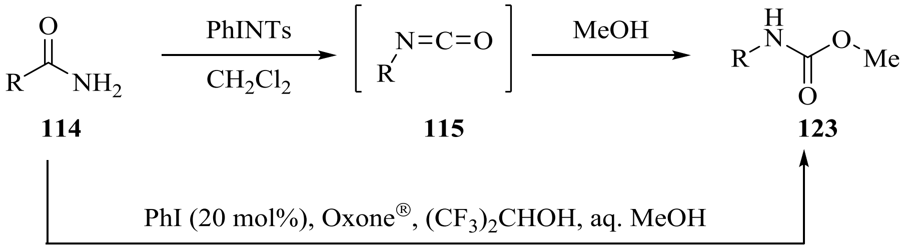
Scheme 2.16. Hofmann rearrangement of aromatic and aliphatic imides 119 mediated by hypervalent iodine reagent.

The same year, Ochiai *et al.* reported the first catalytic Hofmann-type rearrangement on primary amides **114** using iodobenzene with *m*-CPBA as the stoichiometric oxidant, to generate hydrochloride salts **121** in up to 95% yield.[35] The mechanism pathway involves the reaction of the iodine(III) reagent **122** with the nitrogen atom of the amide **114** followed by a 1,2-migration to form the corresponding isocyanate **115**. After hydrolysis with water and decarboxylation, the desired amines were obtained as hydrochloride salts **121** (Scheme 2.17).



Scheme 2.17. Catalytic Hofmann rearrangement of primary carboxamides 114 mediated by hypervalent iodine reagent.

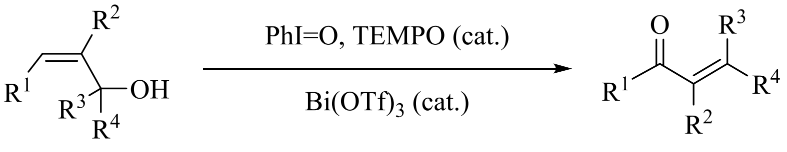
In 2012, Zhdankin also published the rearrangement of amides **114** to generate carbamates **123** using *N*-tosyliminobenzyliodinane [PhINTs] for the stoichiometric transformation.[36] Later on, the same group reported the catalytic version of this rearrangement using Oxone® to oxidise iodobenzene *in situ*.[37] In both methods, the carbamates **123** were formed in 70 to 98% yield (Scheme 2.18).



Scheme 2.18. Hofmann rearrangement of amides 114 into carbamates 123 mediated by hypervalent iodine reagent.

2.6. Other rearrangement reactions

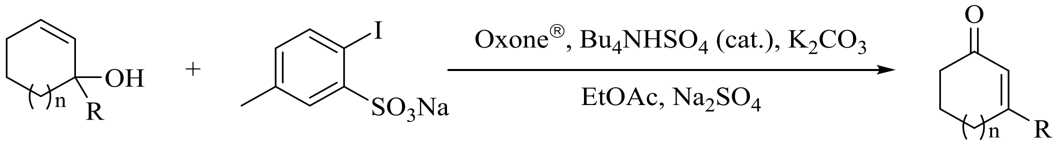
Only a few rearrangements of tertiary alcohols to make *α,β*-unsaturated ketones have been reported to date. Vatèle published in 2008 the rearrangement of cyclic tertiary alcohols **124** mediated by iodosylbenzene with a catalytic amount of TEMPO. Different catalysts were also tried and bismuth triflate was the best one for this specific transformation (Scheme 2.19).[38]



124 **125**

Scheme 2.19. Oxidative rearrangement of tertiary alcohols 124 mediated by hypervalent iodine reagent.

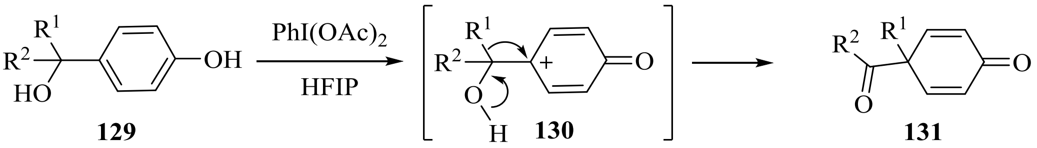
A year later, Ishihara *et al.* described a catalytic rearrangement of cyclic allylic alcohol **126** with only 5 mol% of iodine(I) reagent **127**, using Oxone® as the stoichiometric oxidant in the presence of a catalytic amount of tetrabutylammonium hydrogen sulfate. The corresponding *α,β*-unsaturated ketones **128** were obtained in moderate to good yields (Scheme 2.20).[39]



126 **127** (5 mol%) **128**

Scheme 2.20. Oxidative rearrangement of tertiary alcohols 126 mediated by hypervalent iodine reagent.

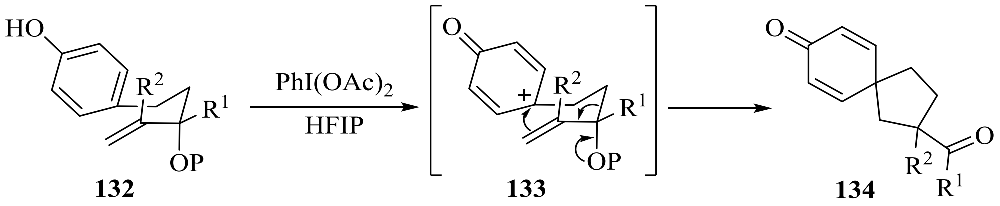
More recently, Canesi *et al.* used hypervalent iodine reagents to mediate a Wagner-Meerwein-type rearrangement. This transformation usually consists of an acid-catalysed conversion of alcohols into olefins involving a 1,2-alkyl or aryl shift. In 2009, the group reported this rearrangement on phenol derivatives **129** (Scheme 2.21). The mechanism involves a dearomatisation of the phenol generating a phenoxenium ion **130** which can then be stabilised by a 1,2-migration to form ketones **131** in moderate yields.[40] The group also extended this method to homoallylic alcohols and the rearrangement proceeded through a 1,3-allyl shift with moderate yields (up to 61%).



Scheme 2.21. Oxidative 1,2-alkyl rearrangement of compounds 129 mediated by DIB.

The same group showed, a few years later, that the chirality from a chiral alcohol could be transferred to generate a quaternary carbon centre with 95% *ee*.[41]

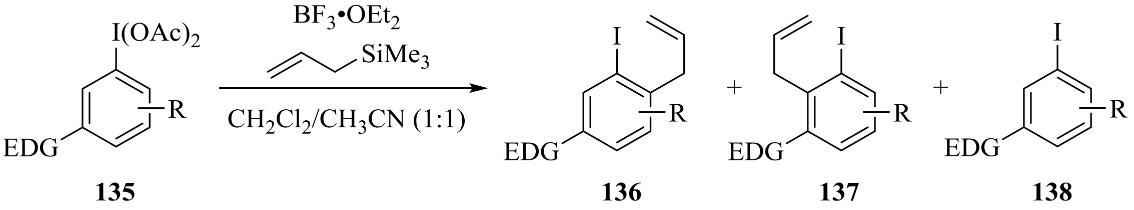
Dearomatisation of phenols can also lead to a Prins–Pinacol type-transformation. Canesi *et al.* reported that phenols **132** were converted into spirodienones **134** when exposed to $PhI(OAc)_2$ (Scheme 2.22). The phenoxonium ion **133** generated can be trapped by the olefin moiety. After ring contraction through migration and loss of the protecting group, the spiro compounds **134** were obtained in good yields (30-84%).[42]



P = protecting group

Scheme 2.22. Prins–Pinacol rearrangement to synthesise spirodienones 134.

Finally, Khatri and Zhu reported the reaction of (diacetoxy)iodoarene **135** with (trimethyl)allylsilane in the presence of BF_3•OEt_2. The reaction proceeded through an iodonio-Claisen rearrangement generating *ortho*-allyliodoarenes **136** as the major products (Scheme 2.23).[43] However, the presence of an electron donating group in the *meta*-position was essential for the reaction to proceed with in good yield (59-93%).



17:0.2:1 to 0.3:0.2:1 ratio

Scheme 2.23. Iodonio-Claisen rearrangement to synthesise *ortho*-allyliodoarenes.

2.7. Summary

Oxidative rearrangements mediated by hypervalent iodine(III) reagents are a versatile way to synthesise precursor for the formation of natural products or more complex molecules. These transformations can proceed *via* a 1,2-aryl migration, ring contraction, ring expansion, Hofmann type rearrangement. However, the number of asymmetric rearrangement transformations available in the literature is currently insufficient and leaves a lot to be accomplished.

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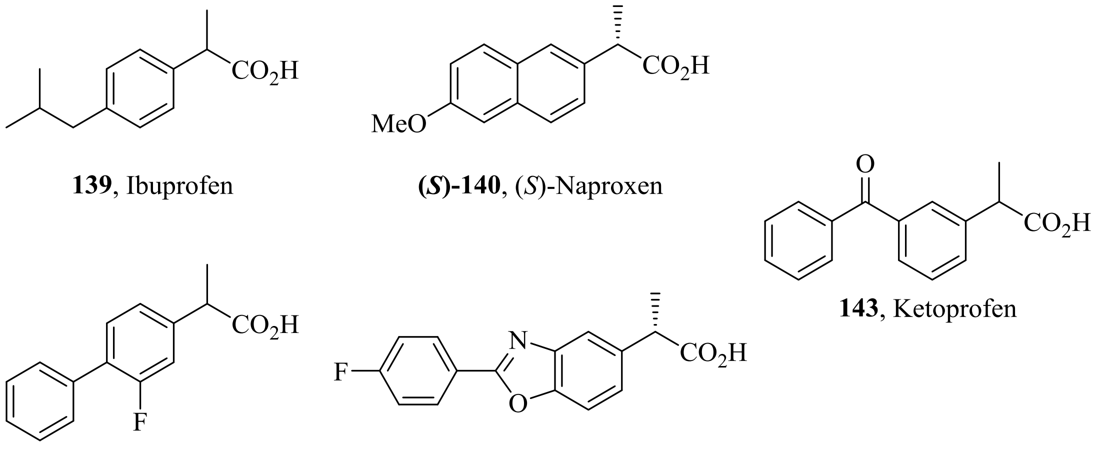
Chapter 3: Rearrangement of propiophenone derivatives into 2-arylpropionates using hypervalent iodine reagents

3.1. Introduction

The synthesis of enantiomerically pure drugs has increased in the recent decades in the chemical industry. However, it is still challenging to obtain these compounds with high stereoselectivity. The role of stereoselectivity in the drug molecules' interaction with the enzyme in the human body is thoroughly considered by drug developers.[1] Indeed, in many cases, one enantiomer is biologically more active than the other one or in extreme cases, the undesirable enantiomer is toxic and can induce some side effects.[2,3] Improving the asymmetric synthesis of those drug molecules would also reduce the total dose given to the patient or avoid the difficult step of separating the two enantiomers at the end of the total synthesis. This separation would also lead to a waste of half of the crude material.[1]

In the 1970s, pharmaceutical industries were mainly focusing their research on the synthesis of racemates. However, with the improvement in chiral technologies in the late 1990s, the percentage of chiral drugs increased from 25% to over 50% of the market in 2000.[3] As a result of this, the concept of chiral-switch has been developed. This term describes drug molecules that have already been approved and marketed as racemates but are re-investigated as single enantiomers. An example of chiral-switch is ibuprofen **139** (Figure 3.1).

Ibuprofen **139**, naproxen **140**, or flurbiprofen **141** are examples of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). Most of those NSAIDs are marketed as racemates with the exception of (*S*)-naproxen **140** and (*S*)-flunoxaprofen **142** (Figure 3.1).



139, Ibuprofen

(*S*)-140, (*S*)-Naproxen

143, Ketoprofen

141, Flurbiprofen

(*S*)-142, (*S*)-Flunoxaprofen

Figure 3.1. Structure of ibuprofen, (*S*)-naproxen, flurbiprofen, (*S*)-flunoxaprofen and ketoprofen.

NSAIDs are used for the treatment of inflammatory diseases such as rheumatoid or arthritis. They are also used as analgesics and anti-pyretics[4]. Their mechanism of action is to non-selectively inhibit the enzymes cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). These enzymes are responsible for the synthesis of prostaglandins from arachidonic acid after an external stimuli (inflammatory or physiological). Prostaglandins contribute to the pain, fever, or swelling resulting from the stimuli (Figure 3.2).[5,6]

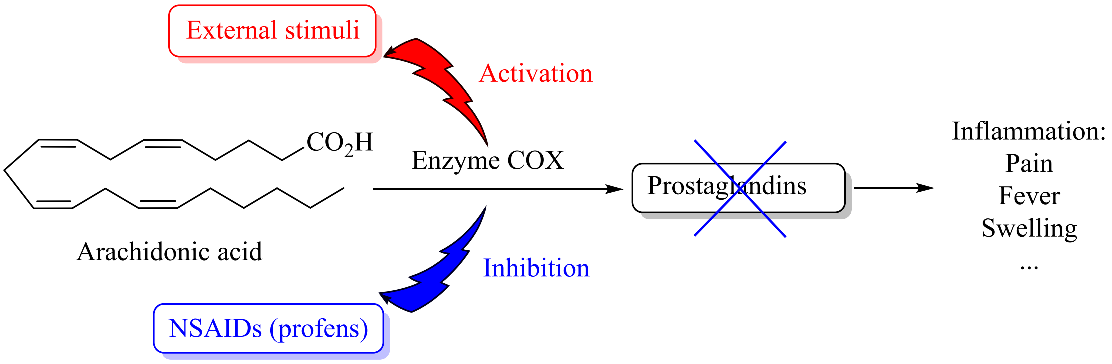


Figure 3.2. Schematic mechanism of inhibition of enzyme COX by profens.

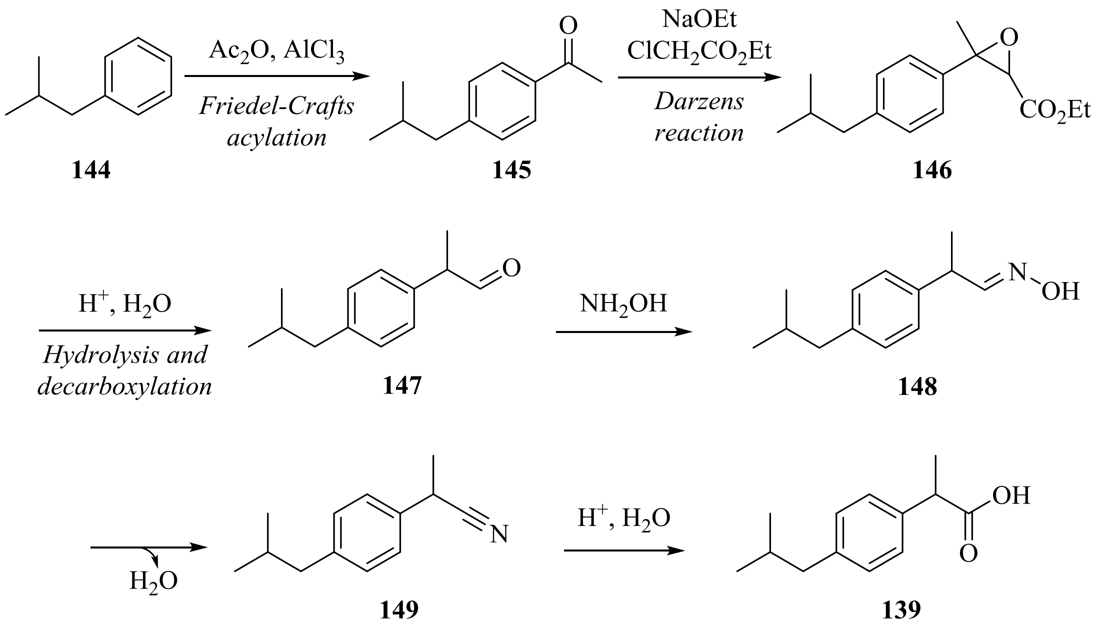
The (*S*)-enantiomer of those profens is usually the only active stereoisomer against the enzymes COX and therefore, the asymmetric synthesis of these drugs would be preferable to the racemic one.[7,8] So far, the chiral-switch protocol has been successfully applied for ibuprofen **139** and ketoprofen **143** in 1994 and 1998, respectively.[3]

In the next section, the synthesis of these profens is described.

3.1.1. Previous synthesis of aryl-propionic acid

3.1.1.1. Brown synthesis of ibuprofen

In the 1960s, Boots Company Pure Drug Company (England) discovered ibuprofen and patented the so called Brown synthesis.[9] Ibuprofen was first introduced on the market as a racemate for the treatment of inflammation related to rheumatic disease in 1969. The Brown synthesis consists of six steps, shown in Scheme 3.1. After acylation of *iso*butylbenzene **144** *via* a Friedel-Craft reaction, the intermediate **146** was generated by addition of ethyl 2-chloroacetate in the presence of sodium ethoxide. The aldehyde **147**, obtained after hydrolysis under acidic condition, was then converted to the corresponding oxime **148**. After loss of water, the nitrile **149** formed was easily hydrolysed under acidic condition leading to the formation of ibuprofen **139**.



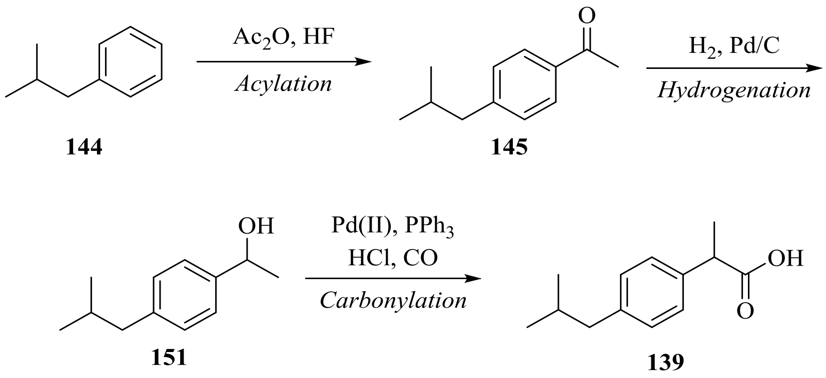
Scheme 3.1. Brown synthesis of ibuprofen 139 (Boots PDC, 1962).[9]

This synthesis uses a very classic methodology but it suffers from a low atom efficiency (40%) and necessitates six reaction steps. Therefore, it is not a very efficient route to produce ibuprofen. Indeed, the hydroxyl amine is introduced in the fourth step to make the oxime **148** which is then converted to the nitrile moiety and finally, to the corresponding carboxylic acid **139**. Therefore, the hydroxylamine is added and then removed which renders this total synthesis inefficient.

3.1.1.2. The Boots-Hoechst-Celanese synthesis of ibuprofen

In 1991, a greener alternative to the brown synthesis was proposed by the Boots-Hoechst-Celanese company. This strategy consists of only three catalytic steps and uses the same precursor, *iso*butylbenzene, as the starting point of this synthesis (Scheme 3.2).[10,11]

In this sequence, *iso*butylbenzene **144** is first acylated using acetic anhydride and in the presence of hydrogen fluoride. After reduction of the ketone **145** to the corresponding alcohol **151** using hydrogen and Pd/C as catalyst, a subsequent carbonylation was performed with Pd(II) catalyst under CO atmosphere in concentrated HCl to yield ibuprofen **139**. This method is considered as the green synthesis of ibuprofen as the aqueous salt waste could be reduced from 60% to just 1%. Furthermore, anhydrous hydrogen fluoride (HF) was used as the solvent in the first step and could be recycled without loss of efficiency. The main waste resulting from this method is acetic acid as by-product. However, the company developed a recycling method and, therefore, reached a total synthesis with almost no waste.



Scheme 3.2. Boots-Hoechst-Celanese synthesis of ibuprofen 139.

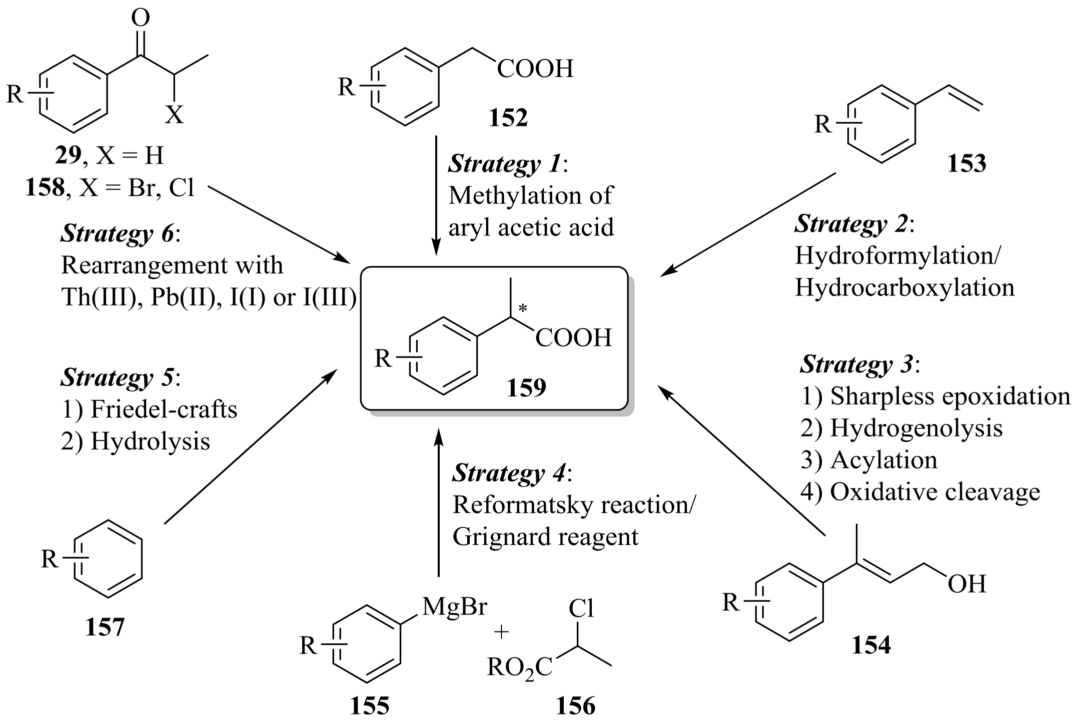
3.1.1.3. General routes for the synthesis of aryl propionic acid

In the last few decades, a number of approaches have been published for the synthesis of aryl-propionic acid **159** with high enantiomeric excess. A selection of strategies are outlined below and summarised in Scheme 3.3.

The first strategy is the direct methylation of the corresponding phenylacetic acid derivatives **152**.[12–14] In 2005, Ramachandran *et al.* reported a new catalytic route for the synthesis of naproxen in a solid–liquid biphasic system using chiral quaternary ammonium salts. With this method, naproxen was obtained with 56% *ee* (93% *ee* after recrystallisation).[15]

Both, the second and third strategies involve the terminal introduction of a carboxylic acid moiety either by functionalisation or by oxidation. Styrene derivatives **153** can react under palladium catalysis with carbon monoxide and BNPPA [(*S*)-(+)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate] as chiral ligand. Alper *et al.* obtained by this method the desired compounds in good yields (85-90%) and with moderate enantioselectivities.[16,17] Stille *et al.* yielded the same target molecules using Hydrogen, carbon monoxide and a complex of Pt(II) containing the chiral ligand (-)-BPPM [(2*S*,4*S*)-*N*-(*tert*-butoxycarbonyl)-4-(diphenylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine] (up to 99% *ee* after recrystallisation).[18]

The third method to synthesise these derivatives was developed by Slobedman *et al.* and consists of a Sharpless epoxidation on allylic alcohols **154** as the key step followed by a hydrogenolysis. However, no data on the enantioselectivity of this process was reported in the manuscript.[19]

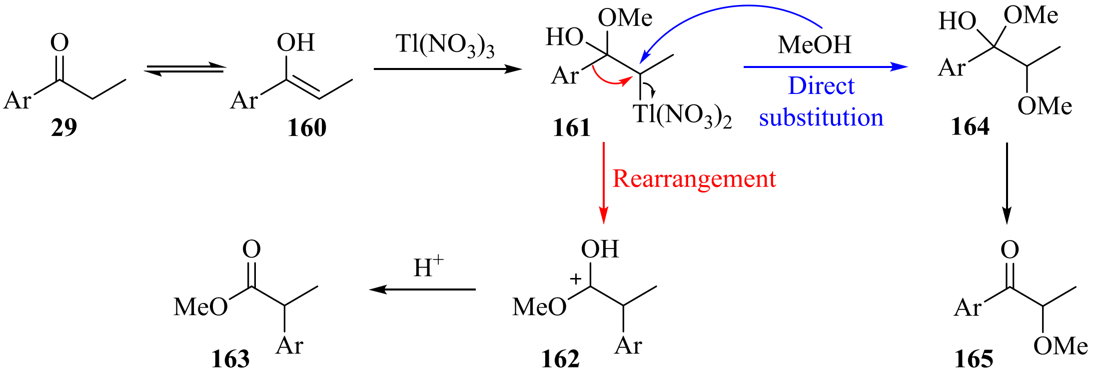


Scheme 3.3. Synthetic approaches for 2-aryl propionic acid 159.

The next possibility to generate the arylpropionic acid is to introduce the entire propionic moiety. This fourth strategy consists of the addition of an activated nucleophilic aryl group onto the Reformatsky reagent **156**. Périchon *et al.* published the α-arylation of aryl halides with α-chloroesters **156** under nickel catalysis to form aryl-propionic esters in moderate to good yields (up to 87% yield).[20] Turner *et al.* reported in 1961 the reaction of 1-phenylethyl chloride with carbon dioxide in presence of magnesium to obtain 2 phenylpropionic acid in 58% yield.[21] In 2015, Nakamura *et al.* described the first iron-catalysed enantioselective cross-coupling reaction between aryl Grignard compounds **155** and α-chloroalkanoates **156** in the presence of a chiral biphosphine ligand and the products were obtained in good yields and with up to 82% *ee*.[22]

The fifth strategy presented by Piccolo *et al.* consists of a Friedel-Craft alkylation of the aryl ring **157**. The aryl-propionate derivatives were obtained in moderate to good yield (40-84%) but the poor regioselectivity of this method renders this reaction less attractive.[23]

The sixth strategy is the rearrangement of propiophenone derivatives. In 1987, Piccolo's group proposed a zinc-catalysed rearrangement of chiral α-haloacetals **158** to obtain 2-arylpropionic acid derivatives **159** with good enantioselectivities (up to 82% *ee*). However, this process is not an asymmetric synthesis as the chiral centre had to be established prior to the reaction when synthesising the haloacetals from enantiomerically pure (*S*)-ethyl lactate and (*S*)-alanine.[24] The preparation of aryl propanoic acid **159** from propiophenone derivatives **29** and thallium(III) nitrate was described by MacKillop *et al.* in 31% yield.[25] They postulated that after the oxythallation of the enol **160**, an oxidative rearrangement occurred through aryl migration and simultaneous reduction of thallium (III) to thallium (I). The authors also observed a competing reaction with the direct substitution of thallium (III) by methanol (Scheme 3.4).



Scheme 3.4. Rearrangement of propiophenone derivatives 29 described by MacKillop *et al.*[25]

Due to the price and toxicity of thallium salts, the industrial applications are limited and other polyvalent reagents were considered. Lead tetraacetate was therefore investigated by Yamauchi *et al.* for the rearrangement of propiophenone **29** in the presence of trimethylorthoformate. The desired rearranged product was obtained in good to excellent yields (73-96%).[26]

Haruta *et al.* described the rearrangement of propiophenone **29** using the less toxic (diacetoxy)iodobenzene [$PhI(OAc)_2$]. This method proceeded most likely through a similar reaction mechanism as with the thallium salt and the authors achieved the synthesis of 2-arylpropionates **163** in up to 88% yield. [27,28] The rearrangement reaction also proceeded with iodine, iodine monochloride and iodine trichloride in moderate to good yields.[29]

3.1.1.4. Flow synthesis of ibuprofen

Another interesting way of synthesising those 2-aryl-propionics acids **159** was demonstrated by McQuade *et al.* in 2009 for the synthesis of ibuprofen.[30] The group developed the first continuous-flow synthesis of ibuprofen using an efficient three-step process which required no purification. The synthetic route consists of a Friedel-Craft acylation on *iso*butylbenzene **144** followed by the rearrangement reaction mediated by

$PhI(OAc)_2$ in $HC(OMe)_3$ and the resulting propionate **163b** was subsequently hydrolysed to yield ibuprofen **139**. With this method, McQuade *et al.* were able to produce 540 mg/h of crude ibuprofen.

In 2015, Jamison *et al.* improved the continuous-flow synthesis of ibuprofen while using quite a harsh reagent for a flow system ($AlCl_3$). Their synthesis was similar to the one of McQuade's group except that the migration reaction was mediated by iodine monochloride instead $PhI(OAc)_2$. An overall yield of 83% was achieved for a three-minute synthesis and the full set up is shown in Figure 3.3. With this method, Jamison *et al.* were able to produce 8.09 g/h of ibuprofen in its salt form **167**.

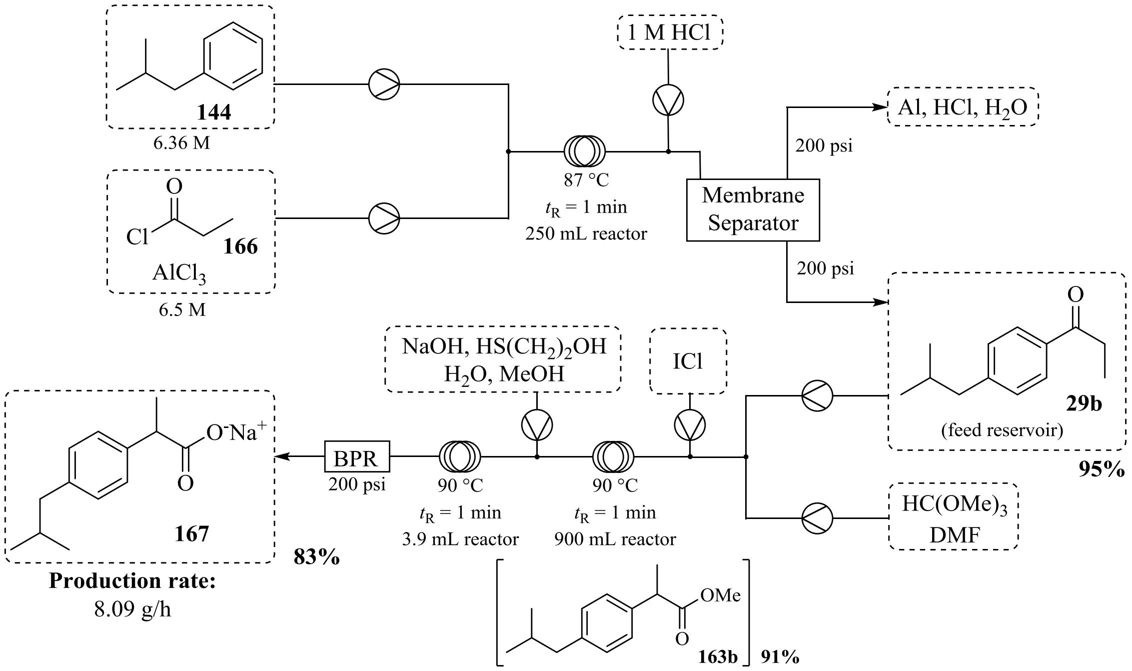
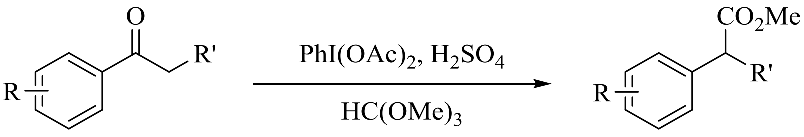


Figure 3.3. Flow synthesis of ibuprofen developed by Jamison *et al.*[31]

3.1.2. Objectives

In this chapter, the rearrangement of propiophenone derivatives **29** into 2-arylpropionates **163** using hypervalent iodine(III) is described. In 1985, Haruta *et al.* explored this rearrangement using (diacetoxy)iodobenzene [$PhI(OAc)_2$] as the oxidant and sulfuric acid as the activator for the reaction. This reaction was performed in trimethyl orthoformate [$HC(OMe)_3$] instead of methanol to avoid the formation of the side product **165** (Scheme 3.5).[27,28]



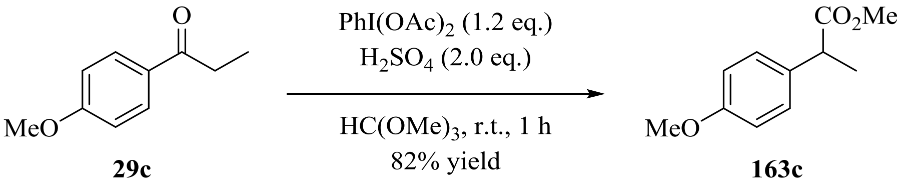
29 **163**

Scheme 3.5. Rearrangement of propiophenone derivatives 29 to 2-arylpropionates 163 by Haruta *et al.*[28]

The aim of this project was to develop an enantioselective method for this particular rearrangement as 2-arylpropionates **163** are direct precursors of non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, naproxen or flurbiprofen. Indeed, (*S*)- or (*R*)-enantiomers have different biological activities and an asymmetric synthesis is desired over kinetic resolutions to separate the two enantiomers.

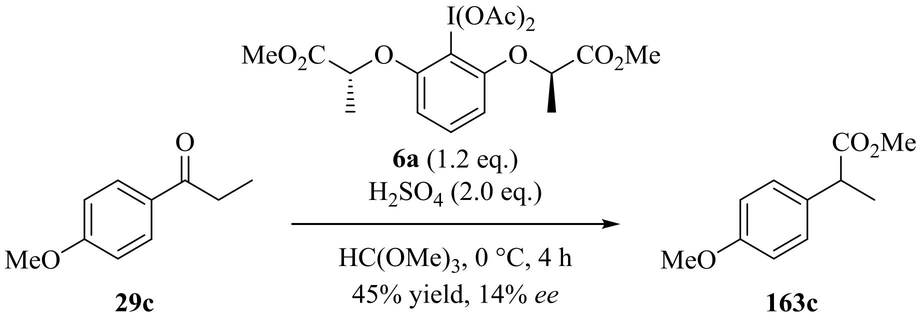
3.2. Optimisation using 4-methoxypropiophenone

In order to become familiar with the reaction, the results presented in Haruta's paper were first reproduced using 4-methoxypropiophenone **29c**. After an hour at room temperature, the desired product **163c** was obtained in 82% yield (Scheme 3.6).



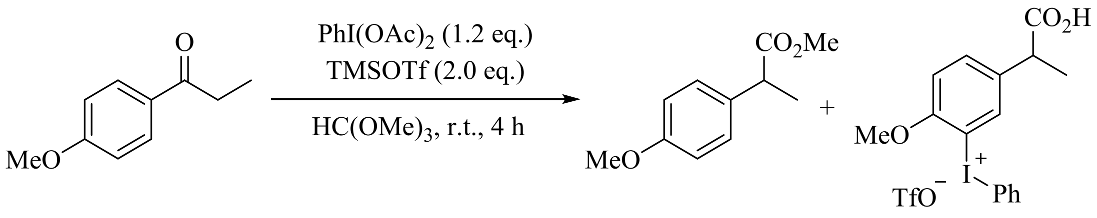
Scheme 3.6. Rearrangement of 4-methoxypropiophenone into molecule 163c following Haruta's method.

The asymmetric transformation was then performed using Ishihara ester **6a** as the chiral iodine(III) reagent and sulfuric acid as the activator at 0 °C. The desired product was obtained in 45% yield and with 14% *ee* (Scheme 3.7).



Scheme 3.7. First attempt of stereoselective rearrangement of 4-methoxypropiophenone 29c using Ishihara ester 6a.

In order to increase the enantioselectivity, trimethylsilyl trifluoromethanesulfonate [TMSOTf] was used to perform the reaction under milder conditions. The reaction was initially done using (diacetoxy)iodobenzene [PhI(OAc)$_2$], producing the racemic product. The desired product **163c** was formed in 82% yield but it also further reacted with the excess amount of PhI(OAc)$_2$ to produce the diaryliodonium salt **168** in 11% yield (Scheme 3.8). The ester moiety was also cleaved during the work up to lead to the formation of the carboxylic acid derivative **168**. Interestingly, only the rearranged product further reacted with DIB to give diaryliodonium salt **168**. No diaryliodonium salt generated from propiophenone **29c** was observed. A plausible explanation is the deactivation of the aryl ring by the acyl moiety on the aryl ring of propiophenone **29c**.



29c **163c,** 82% **168,** 11%

Scheme 3.8. Rearrangement of 4-methoxypropiophenone 29c into molecule 163c and diaryliodonium salt 168.

A crystal structure was obtained to confirm the structure of the diaryliodonium salt **168**. (Figure 3.4).

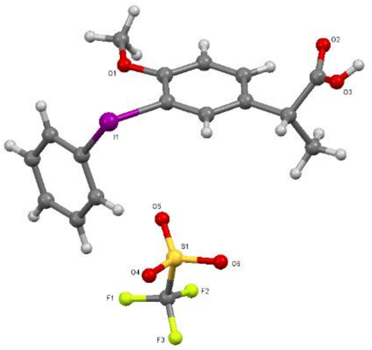
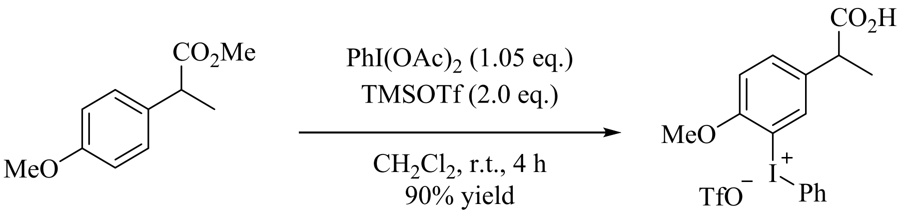


Figure 3.4. Crystals structure of iodonium salt 168.

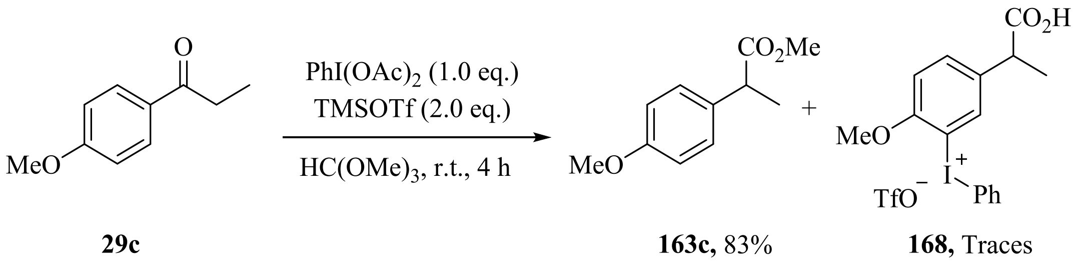
To prove that methyl 2-(4-methoxyphenyl)propionate **163c** was an intermediate of the diaryliodonium salt **168**, molecule **163c** was reacted under the same reaction conditions except for the solvent that was replaced by dichloromethane (usual solvent used for the formation of diaryliodonium salts). The diaryliodonium salt **168** was obtained in 90% yield after 4 h at room temperature (Scheme 3.9).



163c **168**

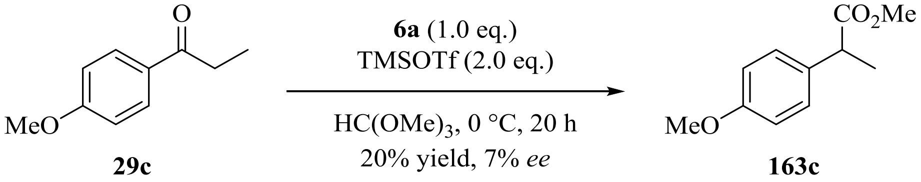
Scheme 3.9. Formation of diaryliodonium salt 168 from methyl 2-(4-methoxyphenyl)propionate 163c.

To suppress the formation of the diaryliodonium salt **168**, $PhI(OAc)_2$ was used in a strictly stoichiometric amount and this salt **168** was only found in traces amount in the reaction mixture while the yield for the desired compound **163c** remained the same (Scheme 3.10).



Scheme 3.10. Rearrangement of 4-methoxypropiophenone 29c into molecule 163c using TMSOTf.

The asymmetric transformation was then carried out and the desired rearranged product **163c** was obtained in low yield with no improvement of enantioselectivity compared to the reaction with sulfuric acid (Scheme 3.11).



Scheme 3.11. Asymmetric rearrangement of 4-methoxypropiophenone 29c using TMSOTf.

Considering the fairly acidic property of the proton in the α-position of the ester, it was envisioned that the product **163c** might racemise leading to lower enantioselectivity. To check this, a sample was taken after 1, 3, 5, and 20 h, worked up and the enantiomeric excess (*ee*) was measured by HPLC. No change of *ee* was observed overtime and therefore this hypothesis of racemisation was abandoned.

The optimisation was not continued with 4-methoxypropiophenone **29c** but instead with propiophenone **29a**. In the case of propiophenone **29a**, the addition of a slight excess of the iodine(III) reagent would not lead to the formation of diaryliodonium salt **168**. Indeed, the phenyl ring of propiophenone is not activated anymore by the methoxy group and therefore, it is much less likely to react a second time with the iodine(III) reagent.

3.3. Optimisation using propiophenone

The rearrangement of propiophenone **29a** was first performed using $PhI(OAc)_2$ and two acids were compared. These acids were used to activate the iodine(III) reagent to make it more reactive. Both Lewis acid and Brønsted acid gave full conversion into methyl-2-phenylpropionate **163a** and the product was isolated in 62% and 40% yield, respectively (Table 3.1).

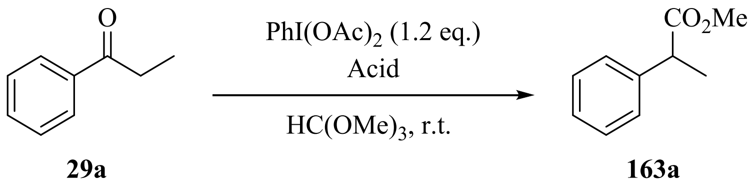


Table 3.1. Racemic rearrangement of propiophenone 29a into methyl-2-phenylpropionate163a.

Entry	Time [h]	Acid (eq.)	Yield[a] [%]
1	4	TMSOTf (2)	62 (99)
2	3	*p*-TsOH•H_2O (2)	40 (99)

[a] The yield reported are the isolated yields; the consumptions of starting material (called conversion in the text) are shown in brackets.

With moderate results of the racemic version of this reaction and no trace of the corresponding diaryliodonium salt, the asymmetric transformation was performed using different conditions as shown in Table 3.2. The reaction was first investigated using Ishihara ester **6a** as the iodine(III) reagent and two Lewis acids were compared. Surprisingly, the reaction did not lead to the formation of the desired product **163a** under dry reaction conditions but resulted in complete degradation of starting material (Table 3.2, Entries 1 and 2). When the reaction was performed with normal grade $HC(OMe)_3$ and without inert atmosphere, the desired product was observed with very good conversion and acceptable isolated yield considering the volatility of product **163a**. However, the enantioselectivity remained low with 25% and 10% respectively (Table 3.2, Entries 3 and 4).

To prove that water was involved in the reaction, dry $HC(OMe)_3$ was used in combination with ten equivalents of water under nitrogen atmosphere. The desired product **163a** was obtained with slightly lower conversion than in just normal grade $HC(OMe)_3$ but the enantioselectivity increased to 33% (Table 3.2, Entries 4 and 5).

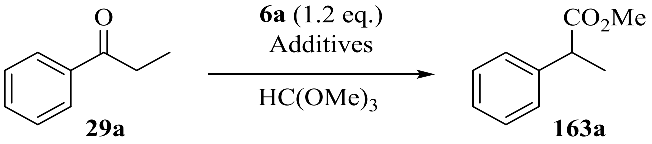


Table 3.2. Effect of the additives on the asymmetric rearrangement of propiophenone 29a into methyl-2-phenylpropionate 163a.

Entry	Temperature [°C]	Time [h]	Additives (eq.)	Yield[a] [%]	*ee*[b] [%]
1[c]	0	24	TMSOTf (2)	n.p.	-
2[c]	0	24	TfOH (2)	n.p.	-
3	0	22	TMSOTf (2)	22 (84)	25
4	0	16	TfOH (2)	36 (89)	10
5[c]	r.t.	24	TfOH (2), H_2O (10)	34 (61)	33
6	r.t.	24	H_2SO_4 (2)	44 (77)	23
7	r.t.	24	*p*-TsOH•H_2O (2)	48 (75)	13
8[c]	r.t.	24	TfOH (2), MeOH (3)	(66)	33

n.p. = no desired product; [a] The consumptions of starting material (called conversion in the text) are shown in brackets; [b] The major isomer was the (*R*)-isomer; [c] Dry HC(OMe)$_3$ was used.

For the simplicity of the reaction setup, normal grade HC(OMe)$_3$ was used instead of the addition of water into dry HC(OMe)$_3$. Two Brønsted acids were also used to see their effect on the reaction's conversion and selectivity. Sulfuric acid and *p*-TsOH•H_2O worked similarly well with conversions of 77% and 75%, respectively. However, the *ee* remained very low with 23% and 13%, respectively (Table 3.2, Entries 6 and 7).

The water present in the reaction could activate trimethylorthoformate in the presence of an acid to generate methyl formate and methanol. Therefore, if the water was directly replaced by dry methanol in dry HC(OMe)$_3$, it should lead to similar result. Indeed, both reactions gave the desired product with roughly the same conversion and exactly the same enantioselectivity (Table 3.2, Entries 5 and 8).

The effect of the solvent was then tested and the results are shown in Table 3.3. The reaction worked quite well in dichloromethane with 56% yield and 33% *ee* (Table 3.3, Entry 1). 2,2,2-Trifluoroethanol (TFE) is known to increase the enantioselectivity in the presence of hypervalent iodine(III).[32] Therefore, the reaction was also performed in a mixture of dichloromethane and 2,2,2-trifluoroethanol (1:1). The conversion of the reaction was increased from 60% to 88% but the *ee* dropped to 22% (Table 3.3, Entries 1 and 2).

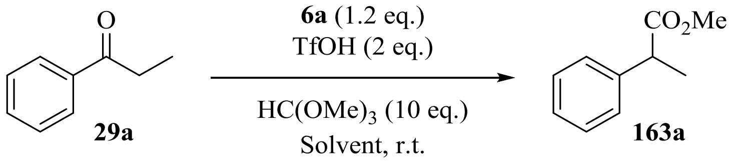
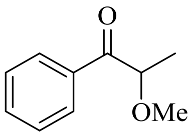


Table 3.3. Effect of the solvent on the asymmetric rearrangement of propiophenone into methyl-2-phenylpropionate.

Entry	Solvent (eq.)	Time [h]	Yield[a] [%]	*ee*[b] [%]
1	CH_2Cl_2	4	56 (60)	33
2	CH_2Cl_2 / TFE (1:1)	5	64 (88)	22
3	CH_3CN	22	n.r.	-
4[c, d]	CH_2Cl_2 / MeOH (3)	24	(17)	-
5[d]	CH_2Cl_2 / MeOH (3)	24	n.r.	-
6[c]	CH_2Cl_2 / MeOH (3)	24	54 (100)	-
7	CH_2Cl_2 / MeOH (10)	24	35[e]	

n.r. = no reaction; [a] The consumptions of starting material (called conversion in the text) are shown in brackets; [b] The major isomer was the (*R*)-isomer; [c] $PhI(OAc)_2$ was used instead of Ishihara ester 6a; [d] No $HC(OMe)_3$ was used; [e] α-OMe addition product 165a was obtained as the only product.

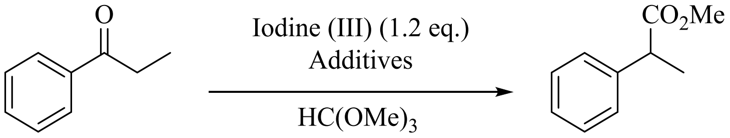
Acetonitrile was also used as the solvent for this transformation but no product was observed and starting material was recovered. The reaction was also carried out using only three equivalents of methanol instead of trimethylorthoformate. With $PhI(OAc)_2$, the desired product was only observed in 17% conversion while with the Ishihara ester **6a**, no product **163a** was formed and the starting material was fully recovered (Table 3.3, Entries 4 and 5). Finally, both methanol and trimethylorthoformate were used in combination and the product was obtained with full conversion using $PhI(OAc)_2$. Unfortunately, with Ishihara ester **6a**, no rearranged product **163a** was observed and only the α-methoxy addition product (2-methoxy-1-phenylpropan-1-one **165a**, (Figure 3.5)) was observed in 35% yield (Table 3.3, Entry 7).



165a

Figure 3.5. Structure of the side product 2-methoxy-1-phenylpropan-1-one 165a.

Different temperatures were then compared as shown in Table 3.4. When the reaction was performed at -20 °C using Ishihara ester **6a**, the enantioselectivity increased to 40% (Table 3.4, Entry 3). The temperature was further lowered down to -48 °C, but this led only to the formation of (1,1-dimethoxypropyl)benzene with some starting material recovered (Table 3.4, Entry 4).



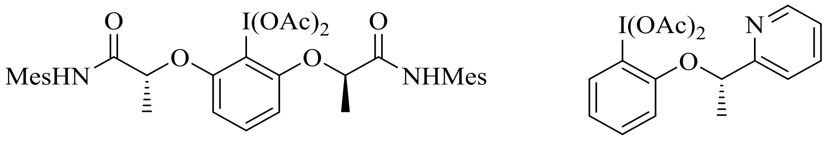
29a **163a**

Table 3.4. Effect of the temperature and the iodine(III) reagent on the asymmetric rearrangement of propiophenone into methyl-2-phenylpropionate 163a.

Entry	Iodine (III)	Temperature [°C]	Time [h]	Additives (eq.)	Yield[a] [%]	*ee*[b] [%]
1	**6a**	0	22	TMSOTf (2)	22 (84)	25
2	**6a**	0	16	TfOH (2)	36 (89)	10
3	**6a**	-20	24	TfOH (2)	(96)	40
4	**6a**	-48	10	TfOH (2)	n.p.[c]	-
5	**6b**	-20	24	TfOH (2)	49 (91)	53
6	**6b**	-20	24	TMSOTf (2)	18 (39)	51
7	**6b**	-20	24	BF_3•OEt_2 (2)	n.r.	-
8	**169**	0	23	TfOH (2)	69 (93)	15

n.p. = no desired product; n.r. = no reaction; [a] The yields reported are the isolated yields and the consumptions of starting materials (called conversion in the text) are shown in brackets; [b] The major isomer was the (*R*)-isomer except for Entry 8 where the (*S*)-isomer was formed as the major isomer; [c] (1,1-Dimethoxypropyl)benzene was isolated as well as some starting material.

Two other hypervalent iodine reagents were also investigated for this reaction in order to improve the enantioselectivity (Figure 3.6).



6b **169**

Figure 3.6. Structure of Ishihara amide 6b and (*S*)-(2-(1-(pyridin-2-yl)ethoxy)phenyl)-l3-iodanediyl diacetate 169.

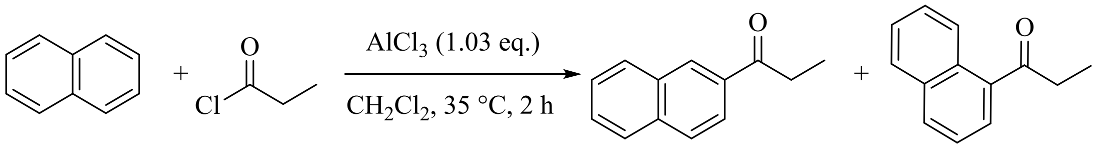
The reaction was initially performed with Ishihara amide **6b** using the same reaction conditions as previously with the Ishihara ester **6a**. The desired product was obtained with very good conversion and a higher enantioselectivity of 53% (Table 3.4, Entry 5). The effect of the Lewis acid in combination with the Ishihara amide **6b** was also investigated. The enantioselectivity was as good using TMSOTf (51% *ee*) but the conversion dropped to 39% (Table 3.4, Entry 6). When BF_3•OEt_2 was used, no reaction occurred and starting material was recovered (Table 3.4, Entry 7).

During this research, the synthesis of a new chiral hypervalent iodine(III) reagent **169** was achieved and will be described in Chapter 6. This new reagent is believed to induce more enantioselectivity because of the pyridine ring that could coordinate with the iodine centre and therefore block one side of the reagent. In this reaction, this positive effect was not significantly observed as the enantioselectivity remained very low (15% *ee*) while the conversion stayed as high as with the other iodine(III) reagents (Table 3.4, Entry 8).

The volatility of methyl-2-phenylpropionate **163a** rendered the analysis of this reaction difficult. Indeed, the isolated yield depended on how long the reaction mixture was left on the rotary evaporator before the yield was calculated. Therefore, those results have a great standard deviation. To overcome this problem, a substrate with a larger aryl ring system was used to form a product with a much lower volatility. Propionylnaphthalenes were chosen as they are easily accessible using Friedel-Craft reaction.

3.4. Optimisation using propionylnaphthalene

Propionylnaphthalene was synthesised using standard Friedel-Craft methodology.[33] Naphthalene was stirred together with aluminium chloride and propionyl chloride for 2 h at 35 °C. A mixture of 1-propionylnaphthalene **172** and 2-propionylnaphthalene **171** was obtained with a conversion determined by ^{1}H NMR of 91% and 9%, respectively (Scheme 3.12). However, the two compounds could not be fully separated by column chromatography but some pure fractions could be isolated.

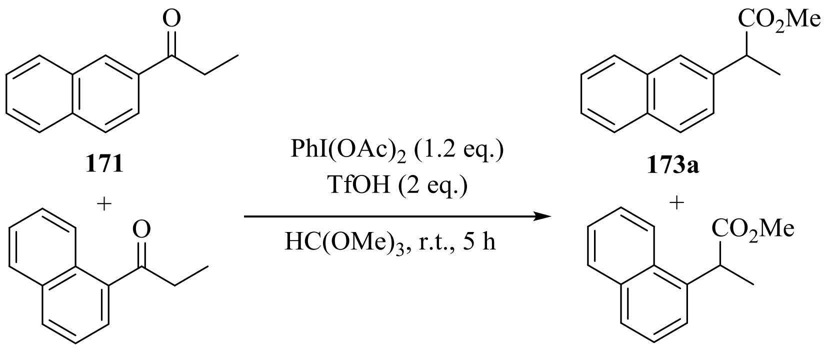


170, 1.1 eq. **166**, 1.0 eq. **171** **172**

9:91 ratio

Scheme 3.12. Synthesis of 1-propionylnaphthalene and 2-propionylnaphthalene using Friedel-Craft method.

Nevertheless, the rearrangement transformation was performed on the mixture of both 1- and 2-propionylnaphthalenes (91:9 ratio by ^{1}H NMR) and it resulted in complete conversion into their corresponding rearranged products **174a** and **173a** (Scheme 3.13).



172 **174a**

171:**172** = 9:91 ratio **173a**:**174a** = 9:91 ratio

Scheme 3.13. Rearrangement of a mixture of 1-propionylnaphthalene and 2-propionylnaphthalene into their corresponding methyl (*R*)-2-(naphthalen-1-yl)propionate 174a and methyl (*R*)-2-(naphthalen-2-yl)propionate 173a.

The rearrangement transformation was then performed on both pure 1- or 2-propionylnaphthalene and the results are showed in Table 3.5. Both substrates gave the rearranged product in very good yields (87% and 83%) (Table 3.5, Entries 1 and 2). The reaction was then carried out using Ishihara ester **6a** as the chiral iodine(III) reagent. Again, both transformations occurred with moderate yields and the same enantioselectivity (Table 3.5, Entries 3 and 4).

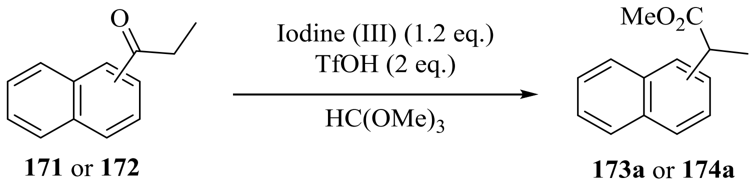


Table 3.5. Rearrangement of 1- or 2-propionylnaphthalene.

Entry	Substrate	Iodine (III)	Temperature [°C]	Time [h]	Yield[a] [%]	*ee*[b] [%]
1	**171**	PhI(OAc)$_2$	r.t.	5	83	-
2	**172**	PhI(OAc)$_2$	r.t.	5	87	-
3	**171**	**6a**	-20	24	48	24
4	**172**	**6a**	-20	24	62	22

[a] The yields reported are the isolated yields; [b] The major isomer was the (*R*)-isomer.

As both substrates showed very similar reactivity and 1-propionylnaphthalene was synthesised in larger amount than 2-propionylnaphthalene, the optimisation was carried out using 1-propionylnaphthalene and results are shown in Table 3.6.

First, the reaction was performed with Ishihara amide **6b** to confirm that it was still the preeminent chiral iodine(III) reagent among the one used in this thesis to induce stereoselectivity. The reaction worked well and the desired product **174a** was isolated in 91% yield while the enantioselectivity increased to 46% *ee* (Table 3.5, Entry 4 and Table 3.6, Entry 1).

To elucidate if the reaction could be performed with a catalytic amount of Lewis acid, the reaction was carried out using the same reaction conditions with the amount of Lewis acid that was reduced to 0.2 equivalents. Unfortunately, this resulted in no reaction and the starting material was recovered (Table 3.6, Entry 2). This indicates that the Lewis acid is there to activate the iodine(III) species and not only to form an equilibrium between the ketone and the enol form. In the second case, a catalytic amount of acid should be sufficient. Another Lewis acid, BF_3•OEt_2, was also tested in this transformation but only starting materials were observed in the crude mixture (Table 3.6, Entry 3).

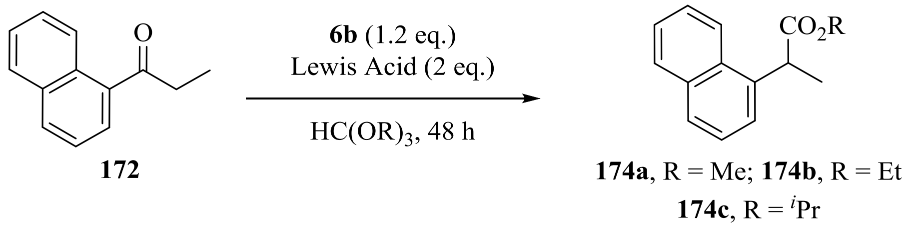


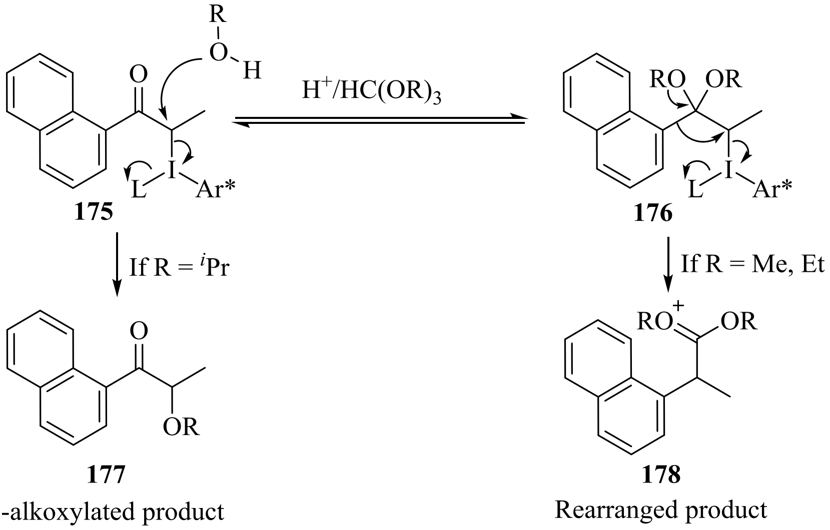
Table 3.6. Optimisation of rearrangement of 1-propionylnaphthalene.

Entry	Lewis Acid (eq.)	R	Temperature [°C]	Yield[a] [%]	*ee*[b] [%]
1	TfOH (2)	Me	-20	91	46
2	TfOH (0.2)	Me	-20	n.r.	-
3	BF_3•OEt_2 (2)	Me	-20	n.r.	-
4	TfOH (2)	Et	-20	70	62
5	TfOH (2)	^{i}Pr	-20	22[c]	-
6	TfOH (2)	Me	r.t.	81	44
7	TfOH (2)	Me	40	40	40

n.r. = no reaction; [a] The yields reported are the isolated yields; [b] The major isomer was the (*R*)-isomer; [c] No desired product formed and the yield reported is the yield for 2-isopropoxy-1-(naphthalen-1-yl)propan-1-one.

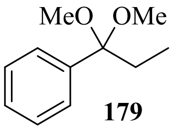
The influence of the orthoformate's alkyl chain was then investigated. Triethyl orthoformate allowed the reaction to be more selective with 62% *ee* while maintaining a high yield (Table 3.6, Entry 4). This higher enantioselectivity can be explained by the greater steric bulk around the migrating aryl group. To test this hypothesis, an even bulkier orthoformate was tested. However, the reaction with the tri-*iso*-propyl orthoformate did not lead to the desired rearranged product **174c**. The *iso*-propyl group was added at the α-position of the ketone in 22% yield (Table 3.6, Entry 5). This might be due to the very large steric bulk of the *iso*-propyl moiety (Scheme 3.14). Indeed, the formation of the ketal **176** should be much more favoured in the case of the less bulky trimethyl or triethyl orthoformate than for the bulkier tri-*iso*-propyl orthoformate. If the equilibrium is shifted to the ketal form **176** (R = Me, Et), the presence of two oxygens will favour the rearranged transformation as they can stabilise the positive charge resulting from the aryl group's migration. On the other hand, if the equilibrium is shifted towards the ketone form **175** (R = ^{i}Pr), the free alcohol is more likely to attack the carbon in α-position in an S_N2 manner to generate the α-alkoxylated product **177**.

To verify this hypothesis, the *iso*-propyl ketal could be isolated prior to the rearrangement reaction. If the reaction occurs, this would imply that the ketal is a key intermediate in this transformation. However, if no rearranged product is observed, it does not disprove this theory as under the reaction conditions, the ketal **176** is in equilibrium with the ketone form **175**. If the equilibrium is completely shifted to the left, no ketal **176** would remain in the reaction mixture and therefore no rearranged product **178** would be observed.



Scheme 3.14. Equilibrium between ketone and ketal form to explain the selectivity for either the *α*-alkoxylated product or the rearranged product.

When exposed to the reaction conditions, the dimethyl ketal derivative **179** equilibrated rapidly to the corresponding ketone **29a**. Therefore, it was assumed that it would be the same for the *iso*-propyl ketal moiety. As the equilibrium is more shifted to the ketone form, no rearranged product would then be observed if this experiment was performed.



179

Figure 3.7. Structure of dimethyl ketal derivative 179.

Finally, the effect of the temperature on the selectivity was also investigated. At room temperature, the reaction worked similarly well than at -20 °C with 81% yield and 44% *ee* (Table 3.6, Entry 6). When the reaction was heated at 40 °C, the isolated yield for the desired product **174a** dropped to 40% and many side products were observed in the crude ^{1}H NMR. However, the product **174a** was still obtained with 40% *ee*. Therefore, the best reaction conditions are with Ishihara amide **6b**, triethyl orthoformate and two equivalents of triflic acid at room temperature. However, trimethyl orthoformate was chosen to be used for the reaction scope to ensure good conversion and chemical yield into the 2-arylpropionate derivatives **163**.

3.5. Scope of the reaction

3.5.1. Influence of the alkyl chain

The influence of the alkyl chain was investigated. The results are presented in Table 3.7. When butyrophenone **29d** was used, the selectivity increased, to reach 63% *ee* (Table 3.7, Entry 2). This might be due to the slightly higher bulkiness of the ethyl group compared to the methyl. Therefore, if an *iso*-propyl group is used, the selectivity should also increase. Indeed, when the reaction was performed with isovalerophenone **29e**, the selectivity increased to 73% *ee* (Table 3.7, Entry 3). Unfortunately, as the selectivity increased with the bulkiness of the alkyl chain, the reactivity and hence, the conversion dropped significantly.

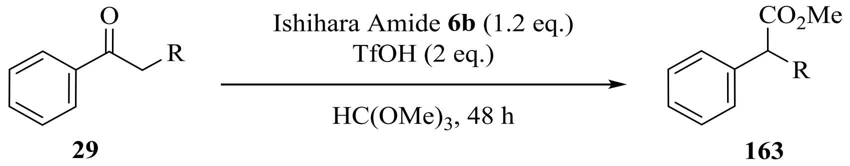
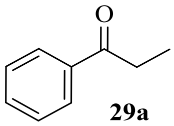
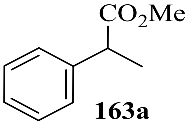
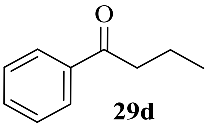
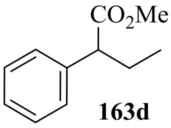
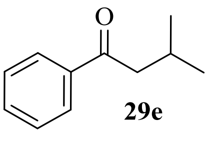
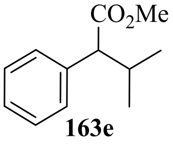
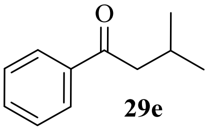
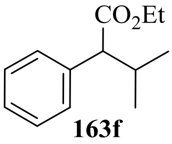


Table 3.7. Effect of the alkyl chain on the enantioselectivity of the rearrangement reaction.

Entry	Substrate	Product	Temperature [°C]	Yield[a] [%]	*ee*[b] [%]
1	 **29a**	 **163a**	-20	49 (91)	53
2	 **29d**	 **163d**	-20	56	63
3	 **29e**	 **163e**	-20	31	73
4			r.t.	31	68
5[c]	 **29e**	 **163f**	r.t.	31	35

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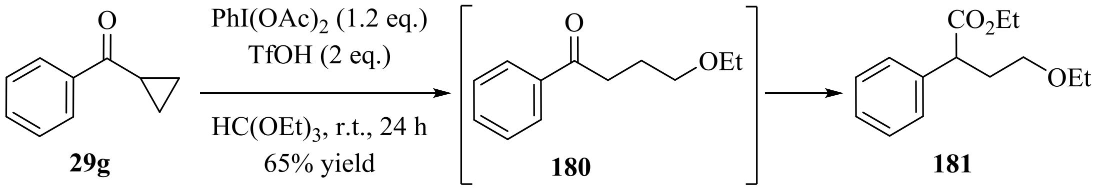
[a] The yields reported are the isolated yields and the consumptions of starting material (called conversion in the text) is shown in brackets; [b] The major isomer was the (*R*)-isomer; [c] $HC(OEt)_3$ was used instead of $HC(OMe)_3$.

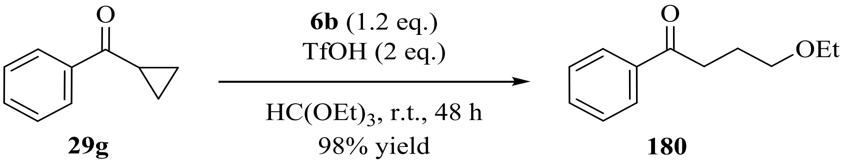
The reaction with isovalerophenone **29e** was also performed at room temperature to check on another substrate that the temperature did not have a big impact on the selectivity. The enantioselectivity dropped only by 5% and confirmed the relatively small impact of temperature on the rearrangement (Table 3.7, Entry 4). The reaction was also carried out with triethyl orthoformate as it was beneficial for the rearrangement of 1-propionylnaphthalene (Table 3.6, Entry 4). However, with isovalerophenone as substrate, the enantioselectivity dropped to 35% *ee* (Table 3.7, Entry 5).

The reaction was also carried out with cyclopropyl(phenyl)methanone **29g**. In the racemic reaction, the substrate rearranged after ring opening of the cyclopropane moiety to give molecule **181** in 65% yield (Scheme 3.15).



Scheme 3.15. Racemic rearrangement of cyclopropyl(phenyl)methanone 29g.

Unfortunately, the asymmetric rearrangement did not occur and stopped at the ring opening stage with almost quantitative yield (Scheme 3.16).

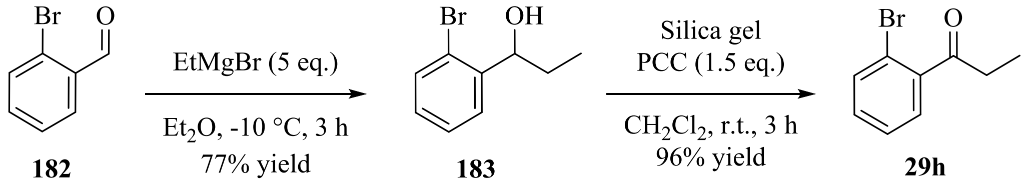


Scheme 3.16. Attempt of asymmetric rearrangement of cyclopropyl(phenyl)methanone 29g.

3.5.2. Influence of the substituent on the aryl group

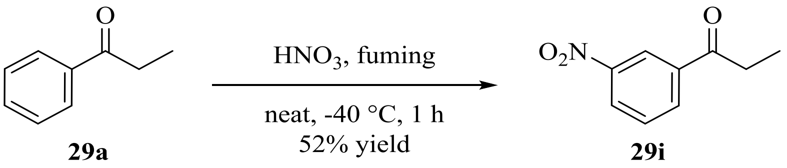
The influence of the electron density of the aromatic ring was then studied and the results are listed in Table 3.8 and Table 3.9. Most substrates were commercially available but a number of them were quite expensive. Therefore, prior to the rearrangement transformation, a few of them were synthesised following known procedures.

2-Bromopropiophenone was synthesised from the corresponding benzaldehyde **182** *via* addition of ethyl magnesium bromide to give the alcohol **183** in 77% yield. The alcohol was subsequently oxidised with pyridinium chlorochromate (PCC) to the ketone **29h** in 96% yield (Scheme 3.17)[34].



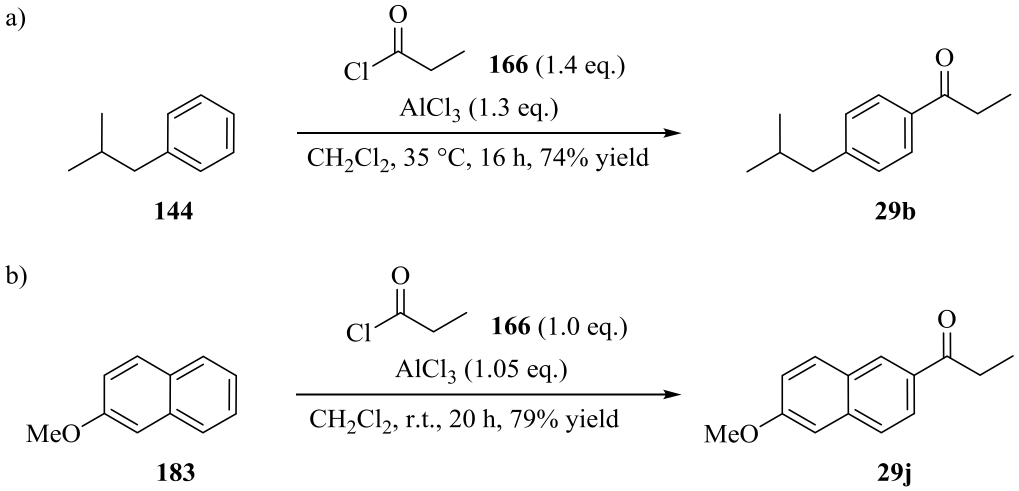
Scheme 3.17. Synthesis of 2-bromopropiophenone 29h from 2-bromobenzaldehyde 182.

3-Nitropropiophenone **29i** was easily prepared by nitration of commercially available propiophenone **29a** using fuming nitric acid (Scheme 3.18).[35]



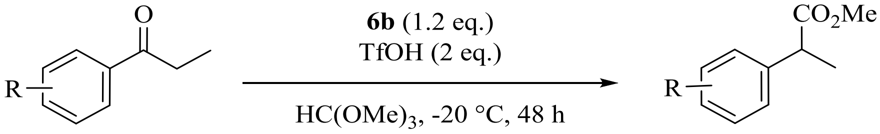
Scheme 3.18. Nitration of propiophenone to synthesise 3-nitropropiophenone 29i.

Finally, 4-*iso*-butylpropiophenone **29b** and 6-methoxy-2-propionylnaphthalene **29j** were synthesised *via* a Friedel-Craft reaction between propionyl chloride **166** and *iso*-butylbenzene **144** or 2-methoxynaphthalene **184**, respectively. Both reactions gave the desired products in good yields (Scheme 3.19).



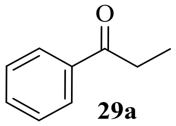
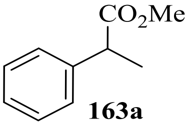
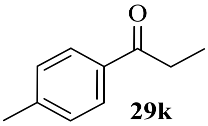
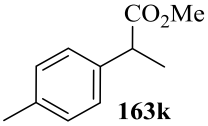
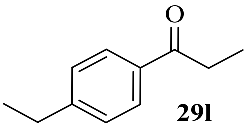
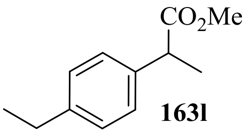
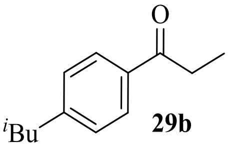
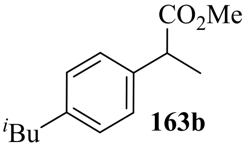
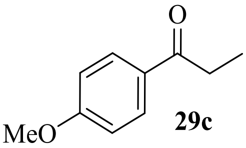
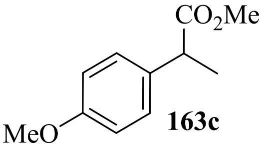
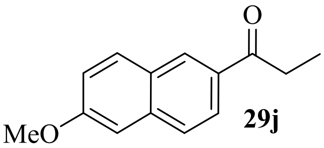
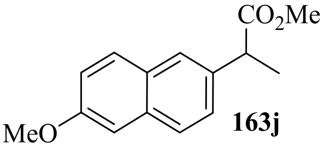
Scheme 3.19. Friedel-Craft reaction to prepare a) 4-*iso*-butylpropiophenone 29b and b) 6-methoxy-2-propionylnaphthalene 29j.

The effect of the electron density of the aryl group was first shown on propiophenone derivatives with an electron-rich aryl moiety and the results are listed in Table 3.8. The rearranged products are obtained in very good yield with all the alkyl chain substituted aromatic compounds (Table 3.8, Entries 2-4). The reaction worked similarly well with 4-methoxypropiophenone **29c** with 80% yield but surprisingly did not work with 6-methoxy-2-propionylnaphthalene **29j** (Table 3.8, Entries 5 and 6). Only trace amount of the desired product could be observed in the crude ^{1}H NMR for the racemic reaction and no product was formed in the asymmetric transformation.



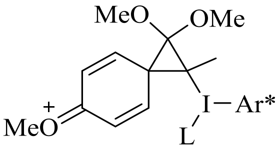
29 **163**

Table 3.8. Rearrangement of propiophenone derivatives with electron-rich aryl group.

Entry	**Substrate**	**Product**	**T [°C]**	**Yield[a] [%]**	***ee*[b] [%]**
1	 **29a**	 **163a**	-20	49 (62)	53
2	 **29k**	 **163k**	r.t.	79 (86)	46
3	 **29l**	 **163l**	r.t.	87 (91)	44
4	 **29b**	 **163b**	r.t.	72 (94)	35
5[c]	 **29c**	 **163c**	r.t.	80 (82)	27
6[c]	 **29j**	 **163j**	r.t.	(Traces)	-

[a] The yields reported are the isolated yields for the asymmetric transformation and the yields for the racemic reaction are shown in brackets; [b] The major isomer was the (*R*)-isomer; [c] Only one equivalent of iodine(III) reagent was used.

The trend for the yield can be explained by the fact that the more electron-rich the aryl ring is, the faster the migration of the aryl group is. Indeed, the positive charge of the phenonium ion **185** generated is more stabilised than with electron-poor aromatic moieties (Figure 3.8).



185

Figure 3.8. Stabilisation of the phenonium ion 185 by the methoxy group on the aromatic ring.

The slightly lower yield for the 4-methoxypropiophenone **29c** could be due to the lower amount of Ishihara amide **6b** used in this reaction (1.0 equivalent instead of 1.2 equivalents) to avoid as much as possible the formation of the diaryliodonium salt (see Scheme 3.8). However, this substrate might still overreact to form the corresponding diaryliodonium salt, therefore lowering the isolated yield of the desired product.

The enantioselectivity seems to follow the opposite trend. This may be due to the fact that the reaction rate is faster for the more electron-rich aromatic ring and therefore, the interaction with the chiral auxiliary is not strong enough to induce high selectivity.

The results for the rearrangement of propiophenone derivatives **29** with an electron-deficient aromatic moiety are shown in Table 3.9. The enantioselectivity does not seem to be affected by the substituent. Indeed, for all the compounds for which enantioselectivity could be measured, the enantiomeric excess was very similar with 44 to 46% *ee* (Table 3.9, Entries 1, 3 and 4). However the yield of this reaction is highly dependent on the electron withdrawing group. The yield decreased when a bromine was in the *para* position compared to a fluorine (28% and 50%, repectively; Table 3.9, Entries 1 and 2). The position on the aromatic ring is also important. While the *para* and *meta* substituents gave poor yields (28% and 14%), the *ortho* substituted product **163h** was obtained in moderate yield (46%) (Table 3.9, Entries 2-4). When a trifluoromethyl substituent was in the *meta* position of the aryl ring, the desired rearranged product **163p** could only be obtained in trace amounts and the α-ethoxylated product **186** was isolated as the major product in 13% yield. Finally, the rearrangement of *meta*-nitro-propiophenone **29i** mediated with the Ishihara amide **6b** did not occur and the starting material was fully recovered from the reaction mixture. However, in its racemic version, substrate **29i** reacted with PhI(OAc)$_2$ to give the desired rearranged product **163i** in 75% yield.

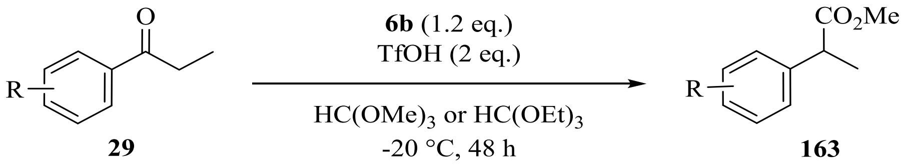
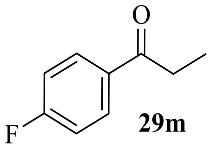
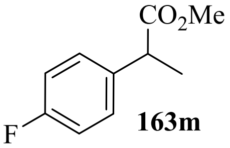
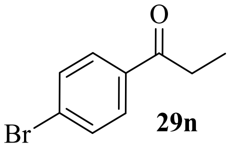
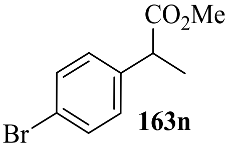
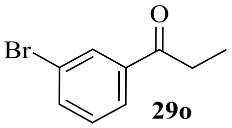
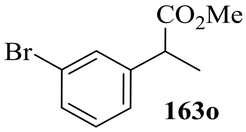
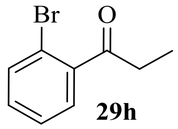
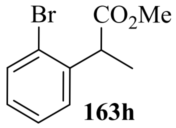
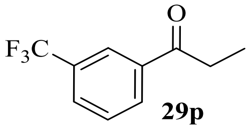
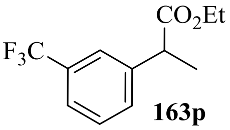
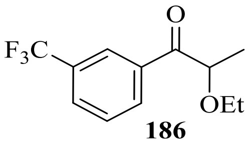
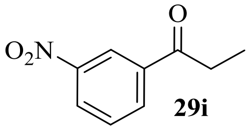
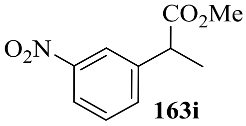
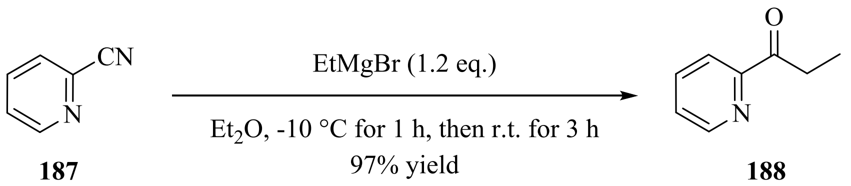


Table 3.9. Rearrangement of propiophenone derivatives with electron-poor aryl group.

Entry	Substrate	Product	T [°C]	Yield[a] [%]	*ee*[b] [%]
1	 **29m**	 **163m**	-20	50 (92)	45
2	 **29n**	 **163n**	r.t.	28 (76)	-[d]
3	 **29o**	 **163o**	r.t.	14 (98)	46
4	 **29h**	 **163h**	r.t.	46 (79)	44
5[c]	 **29p**	 **163p** +  **186**	r.t.	Traces (73) 13 (23)	- -[d]
6	 **29i**	 **163i**	r.t.	n.r. (75)	-

[a] The yields reported are the isolated yields for the asymmetric transformation and the yield for the racemic reaction are shown in brackets; [b] The major isomer was the (*R*)-isomer; [c] HC(OEt)$_3$ was used instead of HC(OMe)$_3$; [d] The enantiomeric excess could not be determined as the enantiomers could not be separated by HPLC but all products showed some negative optical rotation values.

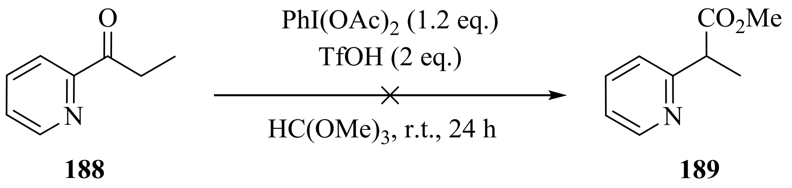
The rearrangement reaction was also performed with compound **188**, which contains a heteroaromatic ring. The substrate was synthesised from picolinonitrile **187** and ethyl magnesium bromide in 97% yield *via* a standard Grignard addition (Scheme 3.20).



Scheme 3.20. Synthesis of 1-(pyridin-2-yl)propan-1-one 188 from picolinonitrile.

The propionyl group was placed in the *ortho*-position to determine if there could be a coordination of the nitrogen atom of the pyridine ring with the hypervalent iodine reagent to induce a greater stereoselectivity.

During the rearrangement reaction, no desired product **189** was formed but the starting material was fully converted into another product (Scheme 3.21). After purification by column chromatography, only a small amount of starting material could be isolated back. This is surprising as no starting material was observed in crude ^{1}H NMR. This suggested that the product was not stable on silica.

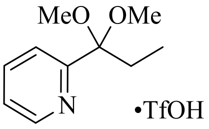


Scheme 3.21. Attempt of rearrangement of 1-(pyridin-2-yl)propan-1-one 188.

The reaction was repeated and a number of experiments were done to determine the structure. A shift downfield of the aromatic protons was observed in the ^{1}H NMR and the signals for the ethyl group were shifted upfield. The shift downfield of the four aromatic protons suggested that the nitrogen atom of the pyridine ring was either protonated or coordinated to iodine or a triflate ion. If the pyridine's nitrogen was coordinating to PhI(OAc)$_2$, the ratio between the protons from the pyridine ring and the proton from the phenyl ring of PhI(OAc)$_2$ should be the same. This was not the case as the ratio was of 1:1.8. Therefore it is believed that the phenyl signals are those from iodobenzene and have nothing to do with this main unknown product. To prove further this theory, a third of the sample was subjected to vacuum. Under these conditions, iodobenzene should evaporate and the main product would remain. A ^{1}H NMR of that sample showed the disappearance of iodobenzene as expected.

The second option was a possible coordination to the triflate ion. To verify this hypothesis, a basic work up was performed using an aqueous sodium bicarbonate solution and the organic compound was extracted with dichloromethane. If the triflate ion is present, a ^{19}F NMR should show a peak for the crude fraction but not for the fraction with the basic work up as the triflate ion would then be trapped in the aqueous layer. Indeed, for the fraction from the high vacuum, a peak at -78.3 ppm could be observed, indicating the presence of a triflate ion. On the other hand, only traces of the triflate ion peak was observed by ^{19}F NMR after basic work up. This suggested that the triflate ion was coordinating to the pyridine's nitrogen in the original mixture.

The other point to discuss on the structure is the shift upfield of the ethyl group peaks. This means that the ketone is probably not present and it was confirmed by ^{13}C NMR that no carbonyl peak is part of the molecule. The other peak that is seen in the crude ^{1}H NMR is a peak at 3.15 ppm integrating for 6 protons. This suggests that the ketone is protected as a dimethyl ketal moiety. The chemical shifts were compared with similar compounds and matched those found in the literature.[36] The proposed structure of this product is shown in Figure 3.9.



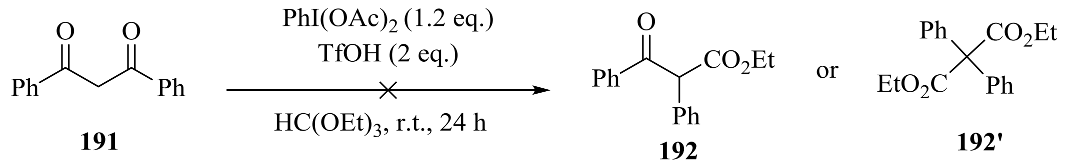
190

Figure 3.9. Proposed structure from the rearrangement reaction of 1-(pyridin-2-yl)propan-1-one 188.

To check if this transformation needed the presence of hypervalent iodine to occur, the reaction was repeated again but in the absence of $PhI(OAc)_2$. In the crude ^{1}H NMR, the same product was observed as the major product. This suggests that the hypervalent iodine did not interact at all with substrate **188** under these conditions.

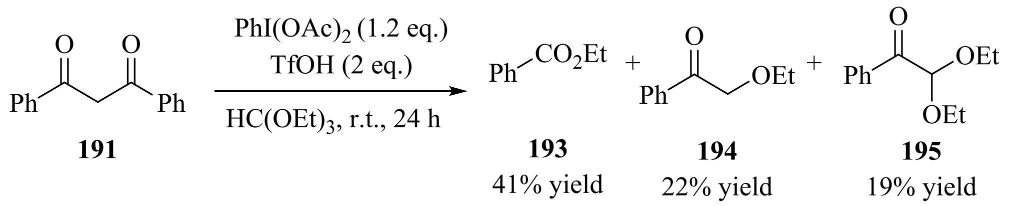
3.5.3. Substrates with other functional groups

The rearrangement was also performed on other substrates to verify if other functional groups in the molecule were tolerated. The reaction was first carried out on dibenzoylmethane **191**. The expected products were either the mono-rearranged product **192** or the double rearranged product **192'** (Scheme 3.22).



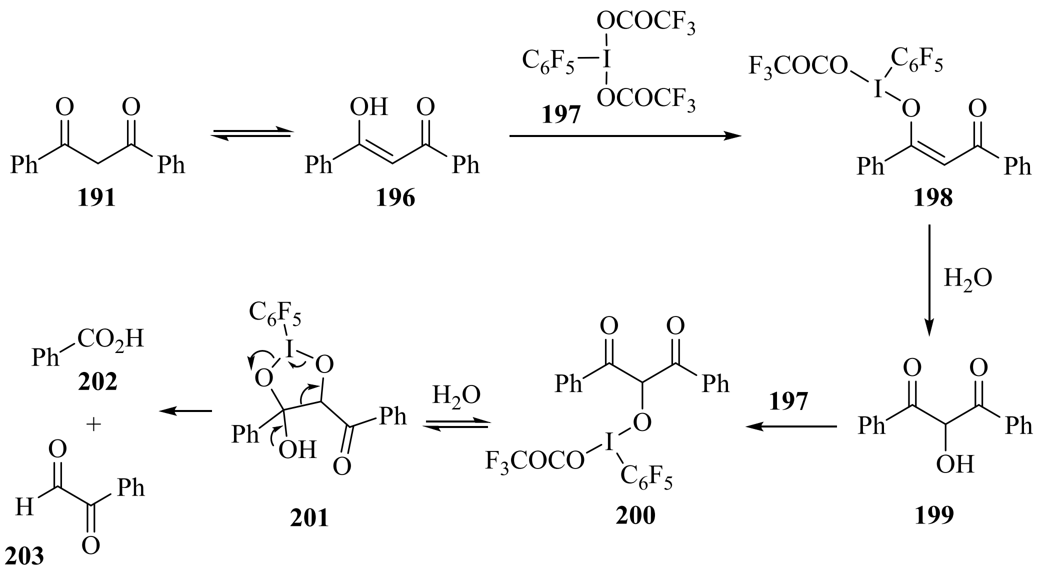
Scheme 3.22. Expected products from the rearrangement of dibenzoylmethane 190.

However, the reaction did not work as expected and no rearranged product was observed. Instead, the cleavage of the molecule was noted as ethylbenzoate **193** was formed in 81% yield as well as 2-ethoxy-1-phenylethan-1-one **194** (43% yield) and 2,2-diethoxy-1-phenylethan-1-one **195** (39% yield) (Scheme 3.23).



Scheme 3.23. Attempt of rearrangement on dibenzoylmethane 190.

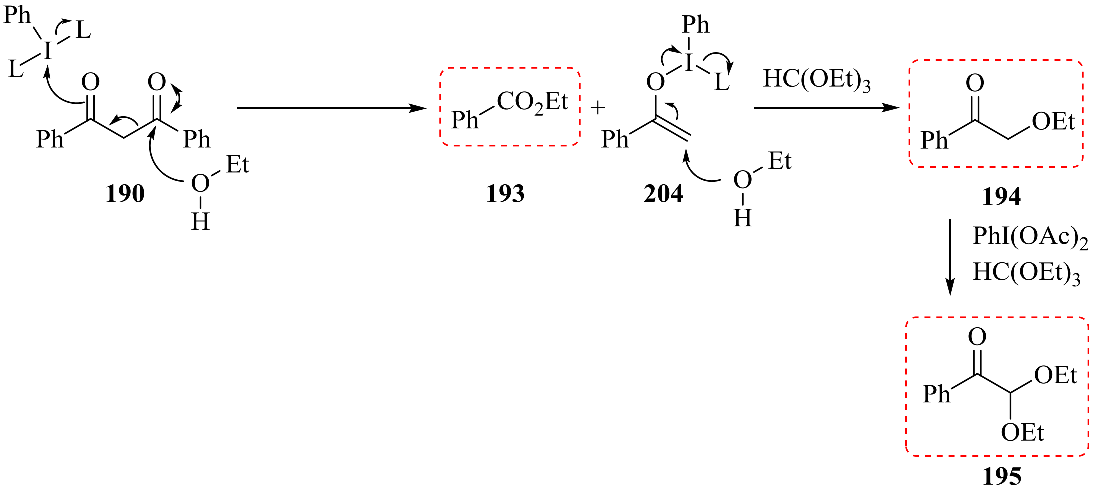
The mechanism for this cleavage is not obvious. In 1987, Moriarty *et al.* proposed a plausible mechanism for the transformation of dibenzoylmethane **190** into phenylglyoxal **203** and benzoic acid **202** using pentafluoroiodobenzene bis(trifluoroacetate) **197**[37] (Scheme 3.24).



Scheme 3.24. Mechanism for the cleavage of dibenzoylmethane 191 proposed by Moriarty *et al.* using pentafluoroiodobenzene bis(trifluoroacetate) 197[37].

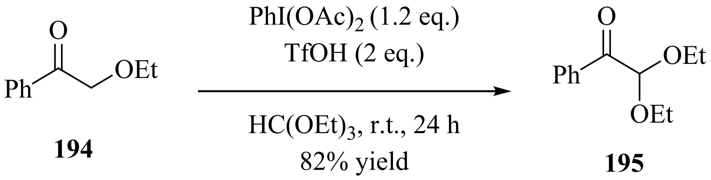
After the formation of the enol **196**, the substrate reacted with the hypervalent iodine **197** reagent to form the intermediate **198**. Water was added to the molecule leading to the reduction of **197** to its corresponding iodine(I). Intermediate **199** reacted with a second equivalent of iodine(III) reagent **197** and intermediate **200** was generated. In the presence of water, an equilibrium between **200** and **201** was proposed to finally produce benzoic acid **202** and phenylglyoxal **203**.

A similar activation of the ketone by the iodine(III) reagent could be used in this specific case. However, if the mechanism was exactly the same, no mono ethoxy product **194** would be observed and only the protected aldehyde **195** would be isolated with ethylbenzoate. Therefore, a slightly different mechanism is proposed. As suggested by Moriarty, the iodine(III) can activate one of the ketones while ethanol (generated from triethyl orthoformate) attacked the other carbonyl group. As shown in Scheme 3.25, ethyl benzoate and intermediate **204** are the products of this addition. A second molecule of ethanol can react with compound **204** to generate the mono-*α*-ethoxylated product **194**. Then, with the excess amount of iodine(III) reagent, this mono-*α*-ethoxylated product **194** was further oxidised using another equivalent of iodine(III) reagent to yield **195**.



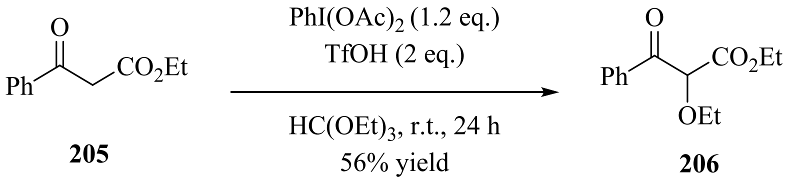
Scheme 3.25. Plausible mechanism for the formation of products 193, 194 and 195.

To prove that compound **194** was the precursor for molecule **195**, the reaction was performed with the isolated molecule **194** under the same reaction condition (Scheme 3.26). The expected product **195** was obtained in 82% yield supporting the second part of the mechanism showed in Scheme 3.25.



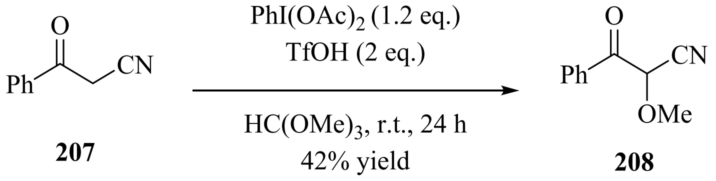
Scheme 3.26. *α*-Ethoxylation of 2-ethoxy-1-phenylethan-1-one 194.

The reaction was then carried out with ethyl benzoylacetate **205** to evaluate if the ester would survive under the reaction conditions. The ester remained in the final product however, no rearrangement product was observed and only product **206** was isolated in 56% yield (Scheme 3.27).



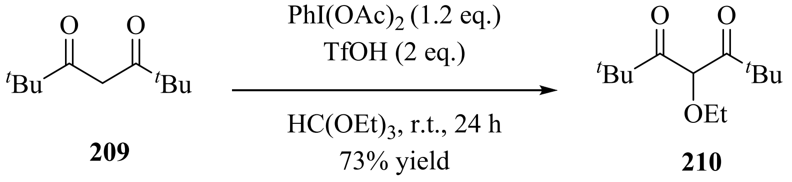
Scheme 3.27. Attempt of rearrangement on ethyl benzoylacetate 205.

The same outcome was observed in the reaction of benzoylacetonitrile **207** and the *α*-ethoxylated product **208** was isolated in 42% yield (Scheme 3.28).



Scheme 3.28. Attempt of rearrangement on benzoylacetonitrile 207.

tert-Butyl group is usually quite good in migration reactions as it can stabilise the positive charge formed. However, in this particular migration reaction, no desired product was observed and only the product **210** was isolated in 73% yield (Scheme 3.29).

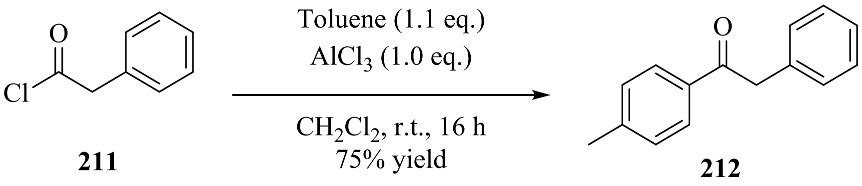


Scheme 3.29. Attempt of rearrangement on 2,2,6,6-tetramethyl-3,5-heptanedione 209.

The results above show that this reaction only works when an aryl group is present next to the ketone. Also, if an electron withdrawing group is present in *α*-position of the ketone, no rearranged product is formed and only the *α*-ethoxylated product can be isolated.

Another aryl group in the *α*-position of the carbonyl may induce better stereoselectivity due to the higher bulkiness of the phenyl group compare to a methyl group.

Substrate **212** was synthesised *via* a Friedel-Craft reaction from toluene and phenylacetyl chloride **211** in 75% yield.



Scheme 3.30. Synthesis of 2-phenyl-1-(p-tolyl)ethan-1-one 212 *via* Friedel-Craft reaction.

The rearrangement transformation was then carried out using PhI(OAc)$_2$ under the general reaction conditions (Table 3.10, Entry 1). The desired product **213a** was isolated as the major product in 70% yield. However, this was not the only compound isolated as compound **214a** and compound **215a** were also obtained in 10% yield each.

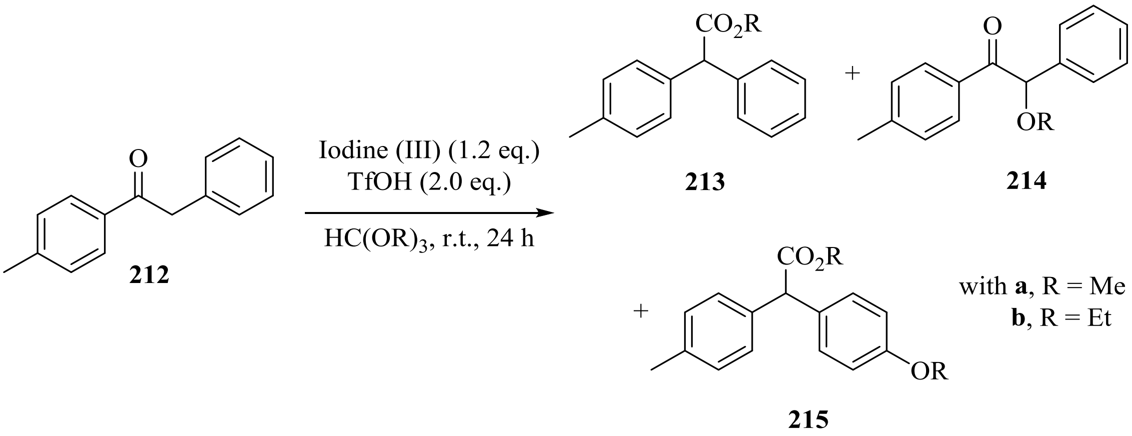
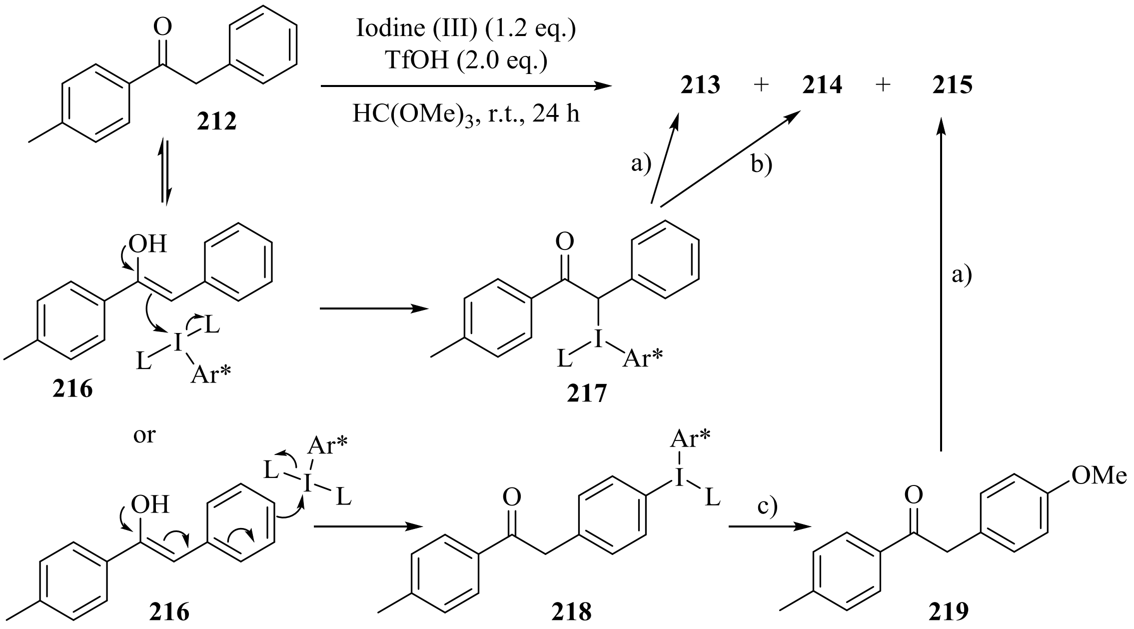


Table 3.10. Rearrangement of 2-phenyl-1-(p-tolyl)ethan-1-one 212.

Entry	Iodine(III) reagent	R	213		214		215	
			Yield[a] [%]	*ee* [%]	Yield[a] [%]	*ee* [%]	Yield[a] [%]	*ee* [%]
1	PhI(OAc)$_2$	Me	70	-	10	-	10	-
2	**6b**	Me	62	25	11	7	4	5
3	PhI(OAc)$_2$	Et	54	-	-	-	-	-

[a] The yields reported are the isolated yields.

A plausible mechanism for the formation of these two products is provided in Scheme 3.31. The ketone **212** is in equilibrium with the enol intermediate **216** under the acidic condition of the reaction. This enol **216** can then react with the iodine(III) reagent to obtain intermediate **217** with the iodine in α-position of the ketone. The *p*-tolyl group can then migrate to generate the product **213**. However, the intermediate **217** can also react with methanol in a nucleophilic substitution to obtain compound **214**. Enol **216** can react slightly differently as the mesomeric form suggests also a partially negative charge in the *para*-position of the phenyl ring. After addition of the hypervalent iodine reagent, intermediate **218** would then be generated. After a reductive elimination process, the methoxy group is added in *para*-position on the phenyl ring. Then this intermediate **219** can undergo the rearrangement reaction in the same way as compound **213** to generate product **215**.



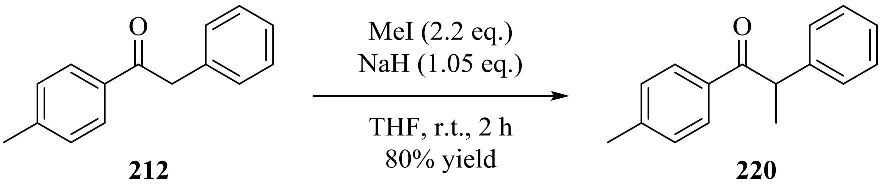
Scheme 3.31. Possible mechanism for the formation of product 213, 214, 215 with a) rearrangement reaction; b) direct addition; c) reductive elimination.

The asymmetric reaction was then performed with the Ishihara amide **6b** as the iodine(III) reagent. The reaction worked in similar manner as for the racemic version with isolated yield of 62%, 11% and 4% for product **213a**, **214a** and **215a**, respectively. Despite the relatively good overall yield, the enantioselectivities obtained for the different compounds were quite low with 25%, 7% and 5% *ee*, respectively. Two explanations can be proposed for these low stereoselectivities. The orientation of the phenyl moiety was unable to sterically inhibit one side of the molecule when the iodine(III) was added onto the molecule. The second possibility is the acidic character of the proton in α-position of the carbonyl group. The products were maybe racemising during the purification and the analyses. Therefore, the enantioselectivities showed in Table 3.10 (Entry 2) would be erroneous.

The same reaction was also performed with triethyl orthoformate to see if the *p*-ethoxy product **215b** would also be formed in this case. Only the product **213b** was isolated in a slightly lower yield (54%). However, this reaction was not very clean and the formation of the two other products cannot be excluded.

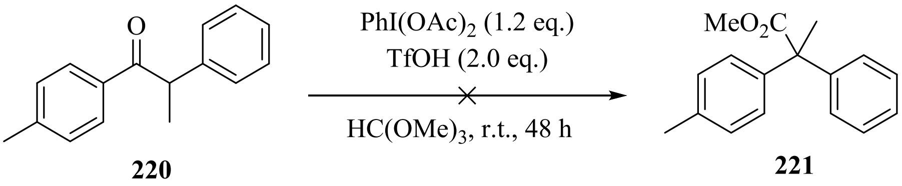
3.5.4. Formation of quaternary carbon centre

The asymmetric synthesis of quaternary centres still remains challenging. Therefore, substrate **220** was synthesised in order to check if these reaction conditions would allow the easy synthesis of molecules containing a chiral quaternary carbon. Substrate **220** was prepared by the methylation of compound **212** using methyl iodide as the methylating agent and sodium hydride as the base. Compound **220** was obtained in 80% yield (Scheme 3.32).



Scheme 3.32. Synthesis of 2-phenyl-1-(p-tolyl)propan-1-one 220.

The reaction was then carried out under the general racemic conditions but unfortunately, after two days of reaction, no product **221** was observed by ^{1}H NMR and the starting material **220** was fully recovered (Scheme 3.33).

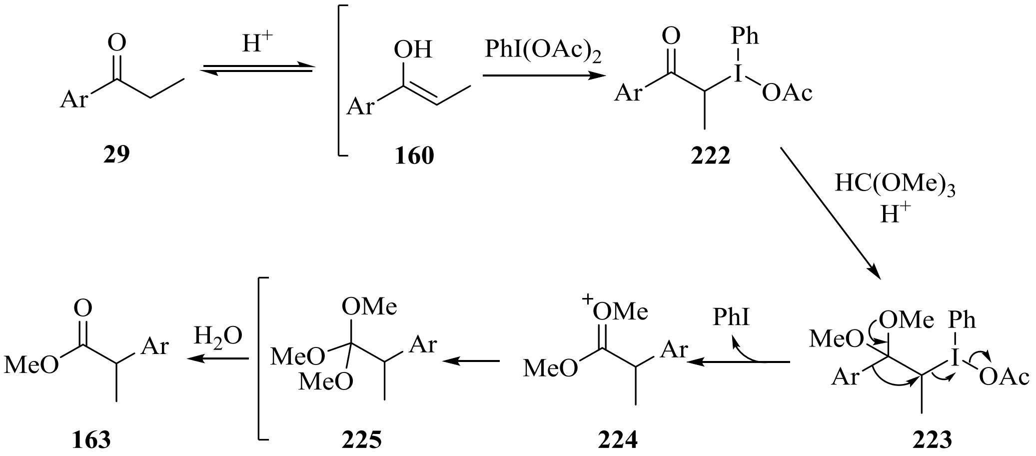


Scheme 3.33. Attempt of rearrangement reaction on 2-phenyl-1-(p-tolyl)propan-1-one 220.

In conclusion, the rearrangement transformation was shown to work quite well in the presence of relatively electron rich systems while the yields dropped quite drastically with electron withdrawing substituents. The reaction also has some limitations. If an electron withdrawing group is present in α-position of the carbonyl, the migration reaction does not occur. Instead, the product from the nucleophilic substitution is always observed. The migration does not work with an alkyl chain such as a *tert*-butyl group. Finally, the reaction conditions do not allow the formation of a quaternary centre.

3.6. Mechanistic studies

When Haruta *et al.* investigated this reaction in the racemic manner, they also proposed the mechanism shown in Scheme 3.34.[28] Under acidic conditions, the propiophenone derivative is in equilibrium with its enol form **160**. It can then react with $PhI(OAc)_2$ to give intermediate **222**. After the formation of the ketal on the ketone, the aryl group can migrate. As the iodine is connected to an *sp*^{3} carbon, it is an excellent leaving group and therefore the intermediate **224** is obtained. The positive charge is then trapped by another methoxy group and after hydrolysis, the final methyl ester product **163** is formed.



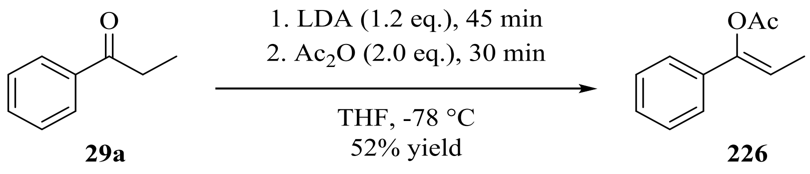
Scheme 3.34. Mechanism proposed by Haruta *et al.* in 1985.[28]

In order to improve the enantioselectivity, it would be interesting to know at which stage of the mechanism the stereochemistry is induced and if the stereoselectivity is changing over the reaction time. The first possibility is that the formation of the enol is selective. The second possibility would be the addition of the iodine onto the enol and the third option is the migration of the aryl group. Each point will be discussed in the section below.

3.6.1. Origin of the stereoselectivity

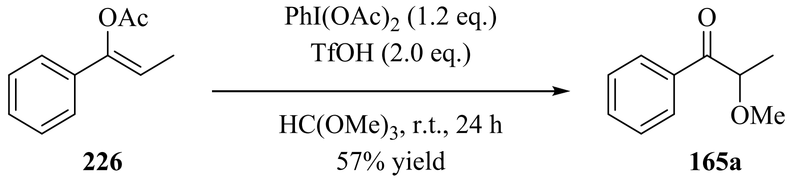
If the formation of the enol is at the origin of the selectivity, each enol ((*E*) and (*Z*)) might give the opposite enantiomer **222** in the presence of a chiral iodine(III) reagent. However both enol might not behave in a similar way towards the iodine(III) reagent and therefore the other two possibilities to induce the stereoselectivity were first explored.

Recently, Legault *et al.* obtained much higher enantioselectivities using enol ether as precursor for the α-oxytosylation of propiophenone.[38–40] The authors believed that the enol ether prevents the formation of the O-bonded intermediate after addition of the hypervalent iodine reagent, and that only the C-bonded intermediate is generated, leading to higher enantioselectivities. This approach was investigated for this rearrangement reaction. Acetylated propiophenone **226** was easily synthesised using lithium diisopropylamide (LDA) and acetic anhydride in 52% yield (Scheme 3.35).



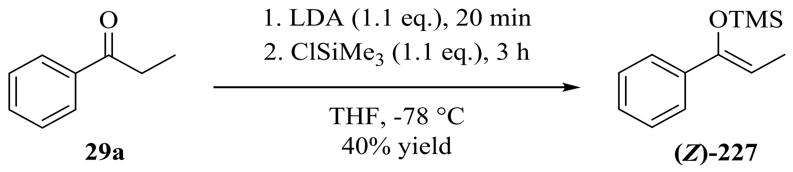
Scheme 3.35. Acetylation of propiophenone 29a.

The rearrangement reaction was performed using the optimised conditions and with PhI(OAc)$_2$. No rearranged product was observed and only the α-methoxylated product **165a** was isolated in 57% yield. The remaining starting material was recovered. This result suggested that the rearrangement did not occur as the formation of the ketal moiety was not possible (see section 3.6.2 below).



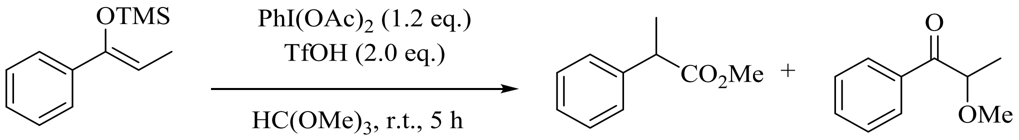
Scheme 3.36. Attempt of rearrangement on substrate 226.

A more labile protecting group (TMS) was therefore used to render possible the formation of the hemiketal/ketal and therefore favoured the migration pathway. The protected (*Z*)-enolate **227** was synthesised (Scheme 3.37).



Scheme 3.37. Synthesis of vinyl silyl ether (*Z*)-227 from propiophenone.

Vinyl silyl ether **(*Z*)-227** was then used for the rearrangement reaction (Scheme 3.38). Under the best reaction conditions found in section 3.4, the rearranged product **163a** was only observed in trace amount while the main product synthesised was again the addition of the methoxy at the α-position of the ketone.

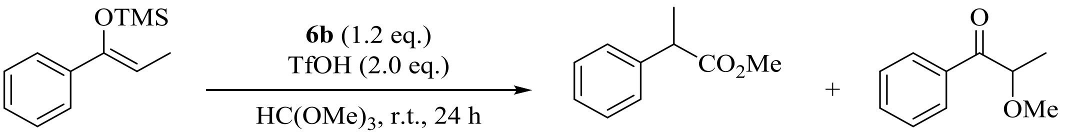


(*Z*)-227 **163a** Traces **165a** 88% yield

Scheme 3.38. Attempt of rearrangement transformation on vinyl silyl ether (*Z*)-227.

The main product of the reaction shown in Scheme 3.38 was the α-methoxylated propiophenone **165a**. This compound is the result of the direct nucleophilic substitution of the iodine by a methoxy group. As this process is an S$_N$2 reaction, it would involve complete inversion of configuration and therefore, the enantioselectivity observed should be the opposite of the one due to the addition of the iodine(III) reagent onto the double bond. In other words, if some enantiomeric excess is observed in the molecule **165a** in the presence of a chiral iodine(III) reagent, the reaction of hypervalent iodine and the enol would be the determining step for the stereochemistry in the final product.

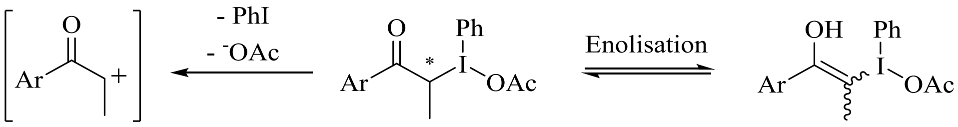
The reaction was carried out with vinyl silyl ether compound **(*Z*)-227** and Ishihara amide **6b** using the optimised conditions (Scheme 3.39). Again, the rearranged product **163a** was isolated only in very small amount (4%) and the main product of the reaction remained **165a** with 80% yield. Surprisingly, the enantiomeric excess of compound **165a** was of 78% *ee* which is much higher than the rearranged product **163a** (47% *ee*).



(*Z*)-227 **163a** 4% yield, 47% *ee* (*R*) **165a** 80% yield, 78% *ee* (*S*)

Scheme 3.39. Asymmetric transformation of vinyl silyl ether (*Z*)-227.

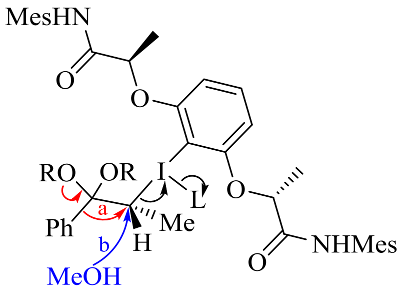
This means that the addition of the iodine on the double bond of the enol is rather selective but unfortunately, this selectivity is much smaller in the final product of the rearrangement reaction. One explanation would be the racemisation of the final product between its formation and the analyses by HPLC. However, it was shown with 4-methoxypropiophenone **29c** that the product was not racemising over time as the enantiomeric excess was the same after 1, 3, 5 and 20 h. Therefore, the intermediate might be racemising before the migration occurs. The enolisation of intermediate **222** would lead to enol **222a**. However, this process is not so favoured and might be difficult. On the other hand, hypervalent iodine reagent are excellent leaving group when bonded to an *sp*^{3} carbon. Therefore, it is plausible to generate the cationic species **222b**. As the carbon centre is now *sp*^{2}-hybridised, it is planar and the stereochemistry induced during the addition of the iodine reagent is lost, leading to racemisation. Depending on the rate of this cleavage compare to the migration reaction, a partial racemisation could be observed.



222b **222** **222a**

Scheme 3.40. Possible mechanism leading to racemisation of intermediate 222.

Both products **163a** and **165a** are believed to be synthesised from the same precursor **(*R*)-223**. The rearranged product would be obtained after an antiperiplanar migration of the phenyl group to generate the (*R*)-isomer (pathway a). On the other hand, the methoxylated product would yield the (*S*)-isomer (pathway b). Both pathways proceed with inversion of configuration at the stereogenic centre. However, due to the Cahn–Ingold–Prelog priority rules, the final absolute configuration is opposite.

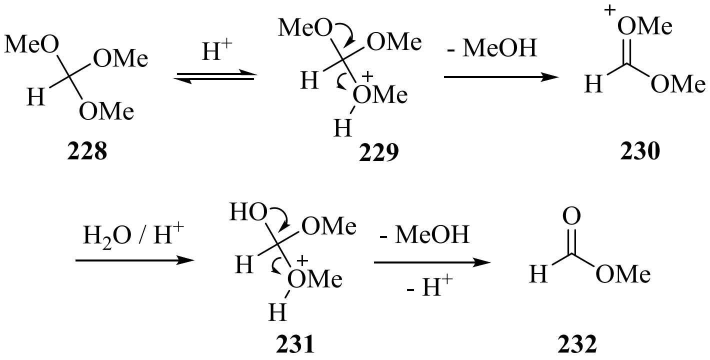


223a

Figure 3.10. Structure of intermediate 223a and possible mechanism to explain the stereochemistry of the products.

3.6.2. Trimethyl orthoformate *vs* methanol

Trimethyl orthoformate under acidic conditions and with traces of water forms methanol and methyl formate **232** (Scheme 3.41). Therefore, is it necessary to use trimethyl orthoformate as the solvent of the reaction or could methanol be used instead?



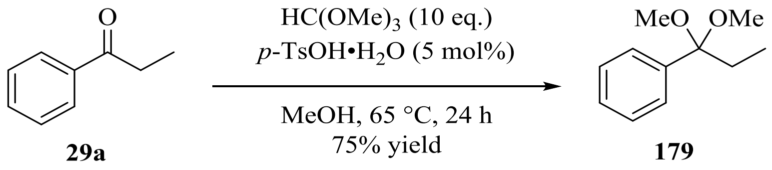
Scheme 3.41. Reaction of trimethyl orthoformate with water under acidic conditions.

When the rearrangement reaction of propiophenone was performed with methanol (3 equivalents) and in absence of orthoformate, no conversion into desired rearranged product was observed. The same reaction was also carried out with a mixture of methanol (3 equivalents) and trimethyl orthoformate (3 equivalents) and the rearranged product was obtained in 54% yield. However, if the amount of methanol was increased to 10 equivalents, the α-methoxylated product **165a** was observed in 35% yield (Table 3.3, Entries 4, 6 and 7).

The first experiment shows the importance of the trimethyl orthoformate in this reaction as it seems to be necessary for the formation of the ketal intermediate. This key molecule is probably essential for the migration step to occur. Indeed, when no trimethyl orthoformate is present and therefore no ketal intermediate is formed, no rearranged product is observed and only the α-methoxylated product was present in the crude ^{1}H NMR. The formation of the hemiketal instead of the ketal cannot be excluded from the mechanism pathway as the ketal formation is quite slow compared to the excellent leaving ability of the iodine moiety. However, the hemiketal would still help for the migration step to occur.

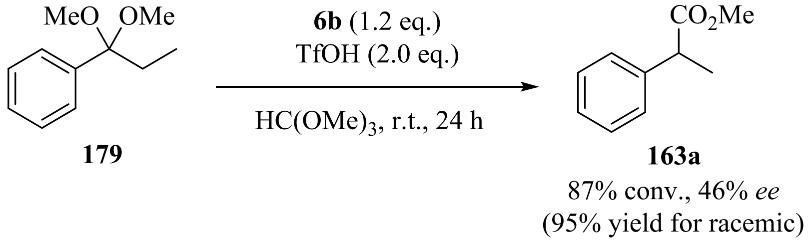
The second and the third experiments show the importance of the amount of methanol present in the reaction mixture compared to trimethyl orthoformate. When only three equivalents of methanol were used, the rearranged product was the only isolated product of the reaction. However, with ten equivalents of methanol, no rearrangement occurred and only the α-methoxylated product was formed.

The reaction was also performed using the isolated dimethyl ketal propiophenone **179** (Scheme 3.43). This substrate was synthesised from propiophenone using a published method in 75% yield (Scheme 3.42).[36]



Scheme 3.42. Synthesis of (1,1-dimethoxypropyl)benzene 179.

The rearrangement proceeded similarly well than with propiophenone and the conversion (87%) and the enantioselectivity (46% *ee*) were similar (Scheme 3.43). This result would then suggest a rapid interconversion of the ketone **29a** with the ketal/hemiketal under the reaction conditions. Indeed, the enol form is needed for the addition of the hypervalent iodine reagent but the ketal/hemiketal intermediate is also required for the migration step to occur.



Scheme 3.43. Rearrangement reaction of (1,1-dimethoxypropyl)benzene 179.

To verify if the ketone and the ketal forms interchange in solution, the same reaction was performed on the isolated ketal **179** but in absence of the iodine(III) reagent. Crude ^{1}H NMR data were measured NMR data showed a mixture of the ketone **29a**, a small amount of the ketal **179** as well as the hemiketal form.

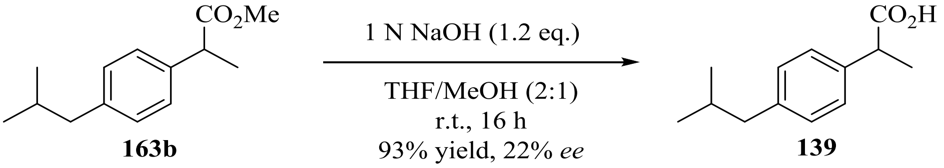
In conclusion, the mechanism proposed by Haruta *et al.* in 1985 is relatively in agreement with the experiments done in this section. However, the equilibrium of every intermediate with the corresponding ketone/ketal/hemiketal forms has to be taken into account. The stereoselective step of the mechanism is the addition of the iodine(III) reagent onto the substrate but unfortunately the migration pathway does not seem as stereoselective as the methoxylation by direct substitution of the iodine(III) moiety by methanol.

3.7. Hydrolysis

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are present on the market either in their carboxylic acid form or as their corresponding salts. Therefore, the methyl ester of molecule **163b** needs to be hydrolysed to the corresponding carboxylic acid **139**.

To avoid racemisation during the hydrolysis, the reaction was first performed under acidic conditions with trifluoroacetic acid in dichloromethane in the presence of water. Unfortunately, no reaction occurred and the methyl ester was recovered after the reaction.

The use of a week base (Na_2CO_3) was also not sufficient to hydrolyse the ester. Therefore, a stronger base was employed (NaOH) in tetrahydrofuran and methanol. Ibuprofen **139** was isolated in excellent yield and with 22% *ee* (Scheme 3.44).

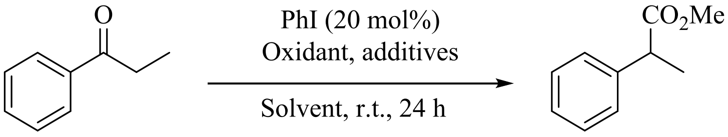


Scheme 3.44. Hydrolysis of compound 163b to generate ibuprofen.

3.8. Towards catalytic transformations

Finally, it would be really interesting to perform this reaction catalytically to increase the atom efficiency. The catalytic transformation was investigated using $PhI(OAc)_2$ as the *in situ* synthesised hypervalent iodine reagent. The results are showed in Table 3.11. A well-known oxidant for the formation of $PhI(OAc)_2$ from iodobenzene is sodium perborate tetrahydrate ($NaBO_3•4H_2O$). However, this oxidant requires the presence of small quantities of acetic acid to work. Therefore, ten equivalents of acetic acid were added to the reaction mixture.

The reaction was carried out with sodium perborate tetrahydrate, trimethyl orthoformate, acetic acid in dichloromethane but no product formation was observed and the starting material was recovered (Table 3.11, Entry 1). The same reaction was also performed using trimethyl orthoformate as the solvent of the reaction instead of dichloromethane but again no reaction occurred (Table 3.11, Entry 2).



29a **163a**

Table 3.11. Attempts of catalytic rearrangement of propiophenone.

Entry	Oxidant (eq.)	Additives (eq.)	Solvent	Results
1	$NaBO_3•4H_2O$ (10)	AcOH (10) $HC(OMe)_3$ (10)	CH_2Cl_2	n.r.
2	$NaBO_3•4H_2O$ (10)	AcOH (10)	$HC(OMe)_3$	n.r.
2	*m*-CPBA (2)	MeOH (8)	CH_3CN	n.r.
3	*m*-CPBA (2)	$HC(OMe)_3$ (10)	CH_3CN	n.r.
4	*m*-CPBA (2)	$HC(OMe)_3$ (10)	CH_2Cl_2	n.r.
5	*m*-CPBA (2)	$HC(OMe)_3$ (10) TMSOTf (1)	CH_3CN	100% conv.[a]

n.r. = no reaction; [a] propiophenone dimethyl acetal 179 was the main product of the reaction.

Another oxidant used in catalytic transformations involving iodine reagents is *m*-chloroperbenzoic acid (*m*-CPBA). The reaction was carried out using two different solvents (dichloromethane and acetonitrile) and in presence of either trimethyl orthoformate or methanol but in all cases, only starting material was observed in the crude ^{1}H NMR. Only in the case when some TMSOTf was added, the reaction went to completion. However, the crude mixture showed many unwanted products and the main product was not the desired rearranged product **163a**. Instead, propiophenone dimethyl acetal **179** was the major product.

3.9. Conclusions and outlook

The stereoselective rearrangement of propiophenone derivatives mediated by hypervalent iodine(III) reagent was described in this chapter. 2-Arylpropionate derivatives **163** were synthesised in moderate to good yields with moderate enantioselectivities using Ishihara amide **6b** in the presence of TfOH in trimethyl orthoformate. The hydrolysis of compound **163b** into ibuprofen **139** was successfully achieved using sodium hydroxide. Further investigations to improve the enantioselectivity or to develop a catalytic method are still necessary to make this route attractive to synthesise NSAIDs in a larger scale.

3.10. References

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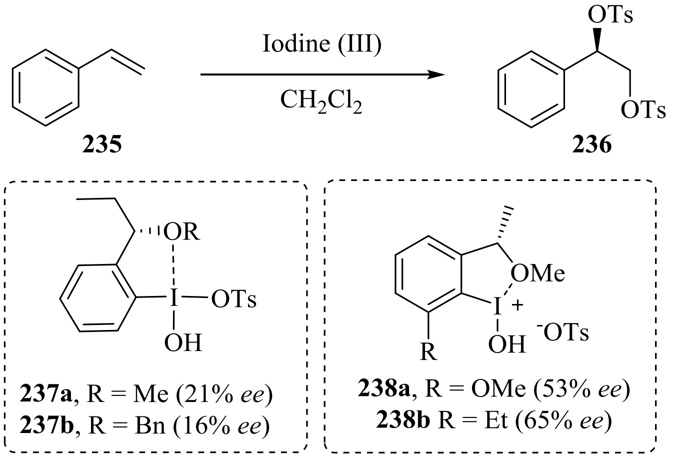
Chapter 4: Introduction on the functionalisation of carbon-carbon double bonds

4.1. Introduction about the functionalisation of carbon-carbon double bonds

The functionalisation of alkenes is a very important reaction in synthetic chemistry as it allows quick access to more complex molecules. Hypervalent iodine(III) reagents are well known to activate carbon-carbon double bonds to promote their reaction with a nucleophile. As the iodine reagent is then connected to an sp^3 carbon centre, it is an excellent leaving group and therefore, a second nucleophile can displace the iodine(III), reducing it to iodine(I). A broad variety of nucleophiles can be used and a brief summary of enantioselective functionalisation is presented below.

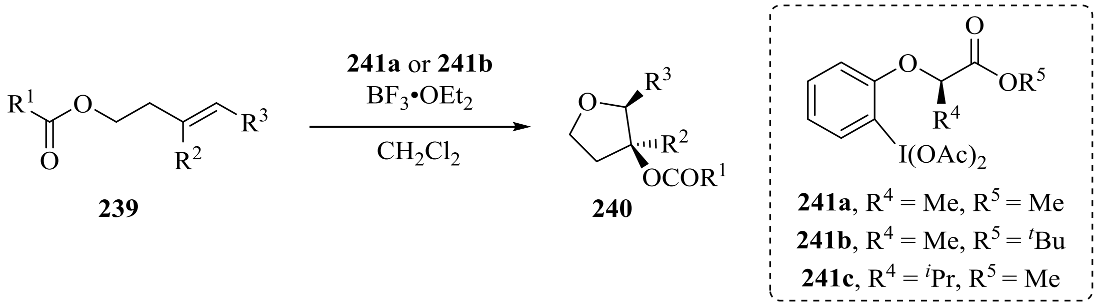
4.2. Dioxygenation

In 1997, Wirth *et al.* developed the first enantioselective oxidation of styrene **235** mediated by a hypervalent iodine reagent. Different reagents **237** were investigated and the bisoxytosylated product **236** was obtained in moderate to good yield and with up to 21% *ee*.[1] A year later, their chiral iodine(III) reagent **238a** was further functionalised to yield product **236** with an improved enantioselectivity of 53%.[2] This stereoselectivity was further enhanced by changing the substituent on the aryl ring of the reagent **238b** (65% *ee*) (Scheme 4.1).[3]



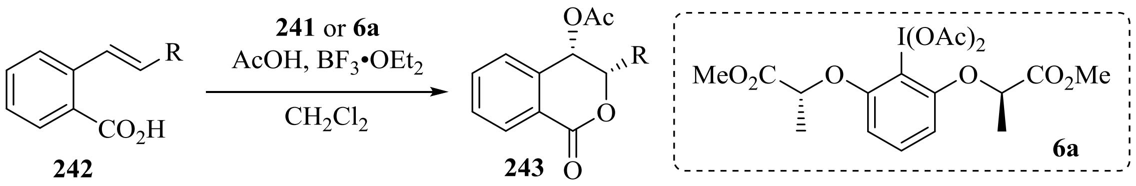
Scheme 4.1. Bisoxytosylation of styrene 235.

Fujita *et al.* reported in 2007 an enantioselective intramolecular oxygenation of but-3-enyl carboxylates **239** mediated by chiral hypervalent iodine(III) reagents **241a** and **241b**. The corresponding tetrahydrofuran derivatives were obtained in up to 73% yield and with up to 64% *ee* (Scheme 4.2).[4]



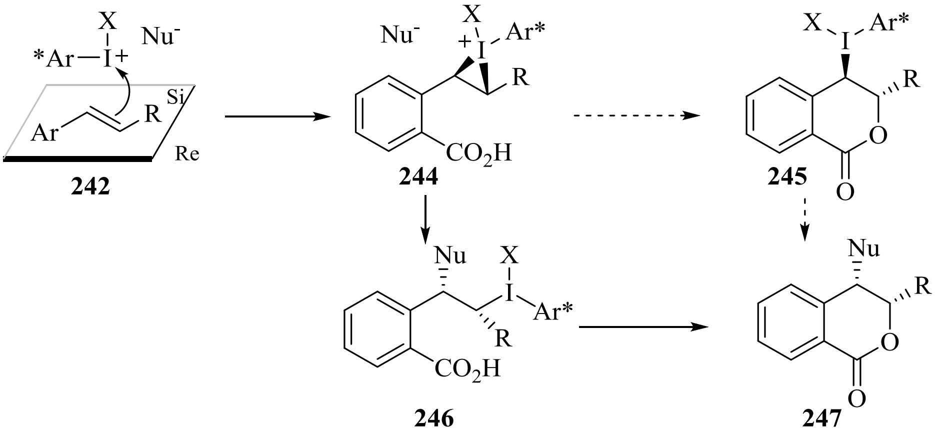
Scheme 4.2. Enantioselective intramolecular oxygenation of but-3-enyl carboxylates 239.

In 2010, the same group developed the first *endo*-selective oxylactonisation, generating an unexpected 6-membered ring with high regioselectivities and high enantioselectivities (up to 97% *ee*) (Scheme 4.3).[5]



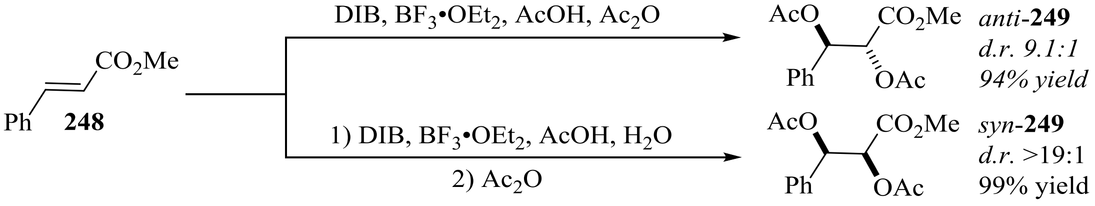
Scheme 4.3. *Endo*-selective oxylactonisation of *ortho*-alk-1-enylbenzoate 242.

The proposed mechanism for this transformation is shown in Scheme 4.4. The activation of the (diacetoxyiodo)arene by BF_3•OEt_2 and electrophilic addition onto the double bond leads to intermediate **244**. This intermediate **244** can react in two different ways to give intermediates **245** or **246**, followed by a second nucleophilic substitution to obtain the desired product **247**. As both nucleophilic additions proceed with inversion of configuration, only the *syn*-product is formed. Furthermore, the first nucleophilic addition is proposed to take place at the benzylic position where a positive charge can be delocalised, leading to the preferred intermediate **246**. After the addition of the internal carboxylic acid, the iodine moiety is displaced, leading to the desired product **247**.



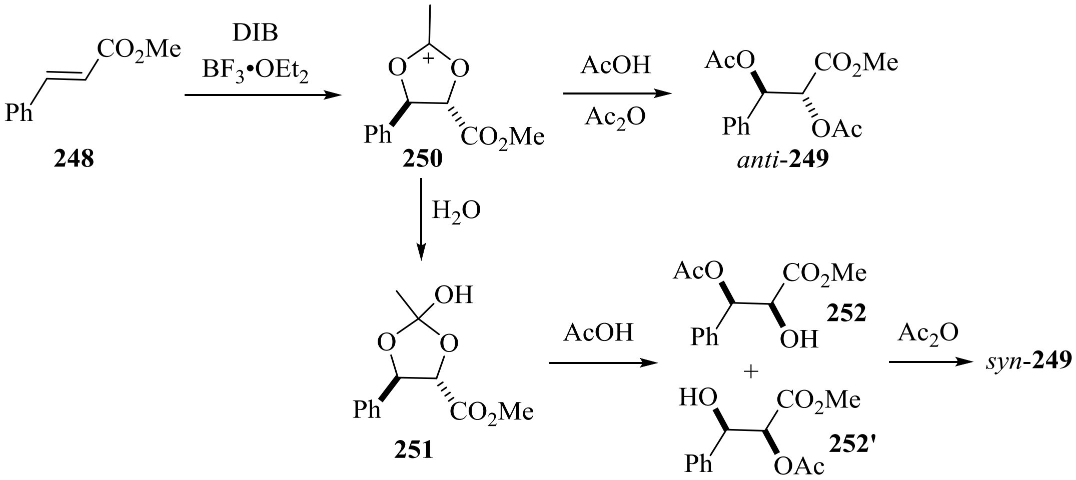
Scheme 4.4. Plausible mechanism for the *endo*-selective oxylactonisation.

Li *et al.* reported the diastereoselective acetoxylation of alkenes **248** using PhI(OAc)$_2$ and BF_3•OEt_2 to activate the iodine reagent. They demonstrated that the *syn*- or *anti*-products **249** were obtained selectively depending on the presence of water. This reaction was also performed on a larger scale (5 g) without loss of yield or selectivity (Scheme 4.5).[6]



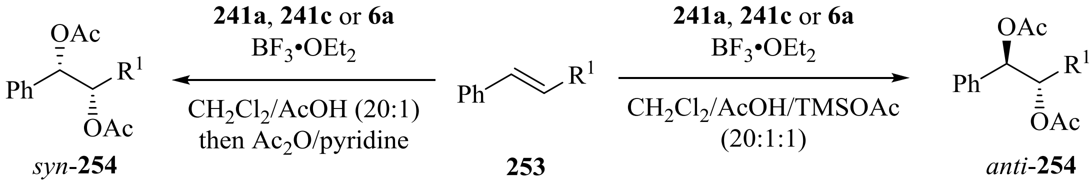
Scheme 4.5. Diastereoselective diacetoxylation of alkenes 248.

A plausible mechanism to explain the selectivity is shown in Scheme 4.6. After activation of $PhI(OAc)_2$ by BF_3•OEt_2, electrophilic attack onto the alkene **248** occurred and intermediate **250** was generated. In the absence of water, acetic acid can act as the nucleophile and yield the *anti*-**249** in the presence of acetic anhydride. However, when water was added to the reaction mixture, it reacted with the carbocation to form intermediate **251**. The intermediate was then ring-opened with the addition of an acetate to yield hydroxylated compounds **252** and **252'**. After acetylation using acetic anhydride, the desired *syn*-**249** was obtained.



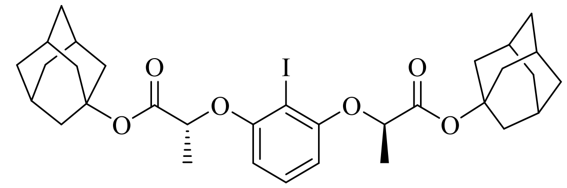
Scheme 4.6. Plausible mechanism for the diastereoselective diacetoxylation of alkenes 248.

In 2011, Fujita *et al.* published the enantioselective Prevost and Woodward reaction on styrene derivatives **253** (Scheme 4.7). It was found that by changing the solvent mixture and therefore the nature of the nucleophile, either the *syn*- or the *anti*-product **254** was obtained in moderate to good yields and with up to 96% *ee*. This is a nice example of switchover of stereochemistry in a reaction.[7]



Scheme 4.7. Enantioselective Prevost and Woodward reaction.

Very recently, Muñiz *et al.* reported the enantioselective diacetoxylation of styrene derivatives using iodine reagent **255** (Figure 4.1). The catalyst (20 mol%) was oxidised *in situ* with Selectfluor® and activated with TMSOTf. The hydroxyacetates obtained were then fully acetylated using acetic anhydride. The corresponding diacetoxylated products were obtained in good yields (55 to 92%) and with up to 96% *ee*.[8]

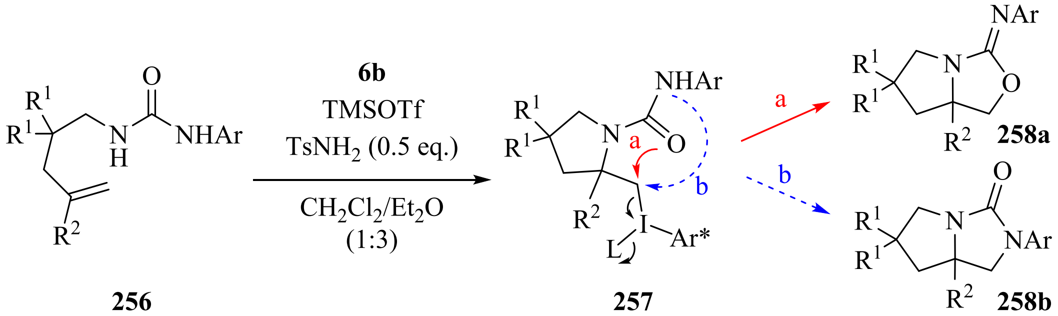


255

Figure 4.1. Structure of iodoarene 255.

4.3. Oxyamination

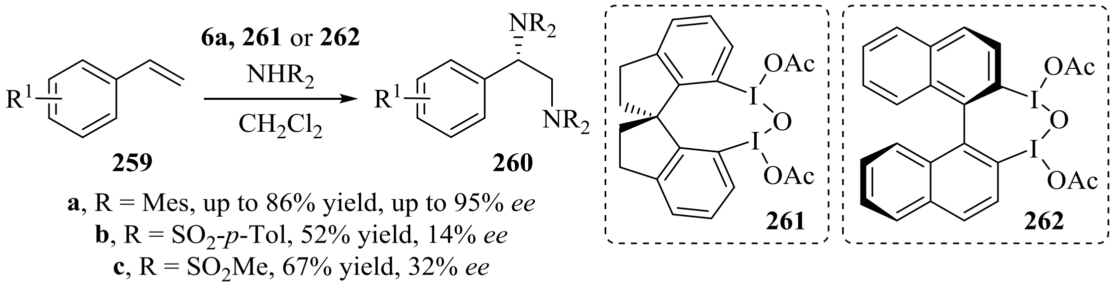
In 2012, Farid and Wirth developed the first highly enantioselective oxyamination of alkenes **256** mediated by a hypervalent iodine(III) reagent. The corresponding isoureas **258a** were synthesised in good yields (60-71%) and with up to 99% *ee* (Scheme 4.8).[9] Michael *et al*. studied in 2008 the effect of the Lewis acid and the urea substituents on the formation of either the oxyamination product **258a** or the diamination compound **258b**.[10] They showed that under strong acidic conditions, product **258a** was formed as the major product due to the better nucleophilicity of the oxygen. These oxyaminated products are direct precursors to unnatural amino acids.



Scheme 4.8. Enantioselective oxyamination mediated by hypervalent iodine reagents.

4.4. Diamination

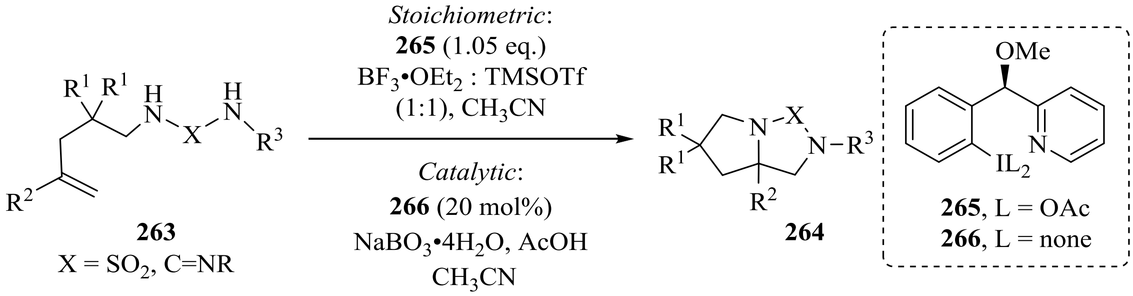
Muñiz *et al*. reported the first enantioselective intermolecular diamination on styrene derivatives **259** using hypervalent iodine(III) reagent in 2011. Chiral Ishihara ester **6a** or reagent **261** were used together with mesitylamine to yield diaminated products **260a** in up to 86% yield and with up to 95% *ee* (Scheme 4.9).[11] In 2013, they developed dinuclear iodine(III) reagents and used them for the diamination of a variety of alkenes. It was found that using a binaphthyl dinuclear iodine(III) reagent **262** was leading to the formation of optically active diamine products **260b** (14% *ee*) and **260c** (32% *ee*).[12]



a, R = Mes, up to 86% yield, up to 95% *ee*
b, R = SO_2-*p*-Tol, 52% yield, 14% *ee*
c, R = SO_2Me, 67% yield, 32% *ee*

Scheme 4.9. Diamination of styrene derivatives 259.

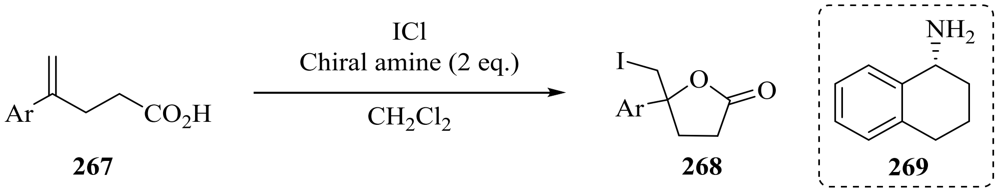
A year later (2014), Wirth *et al.* published the intramolecular enantioselective diamination of alkenes, leading to bicyclic products **264** in moderate to good yields and with up to 94% *ee*.[13] The synthesis of a novel hypervalent iodine(III) reagent **265** bearing a pyridine moiety was developed. Pyridine is known to coordinate with hypervalent iodine reagents and its proximity with the stereogenic centre should allow good stereoselectivity.[14,15] This reaction was also performed catalytically using catalyst **266** sodium perborate tetrahydrate as the internal oxidant. The reaction worked similarly well with up to 72% yield and with up to 86% *ee* (Scheme 4.10).



Scheme 4.10. Intramolecular enantioselective diamination of alkenes 263.

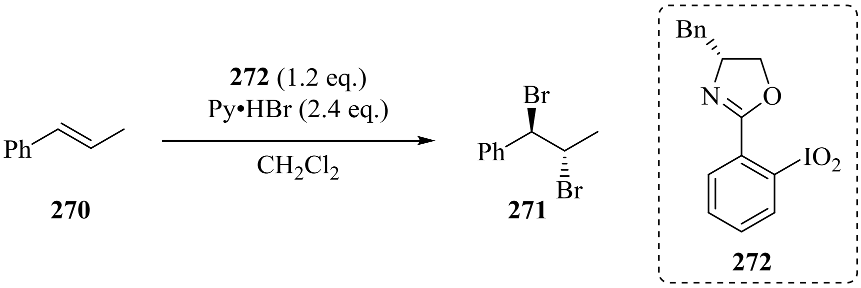
4.5. Halogenation

In 2002, Wirth *et al.* reported the asymmetric iodolactonisation of unsaturated carboxylic acid **267** using iodine monochloride in the presence of a chiral amine. Amine **269** gave the best enantioselectivity with up to 49% *ee*. With this method, the iodolactates **268** were isolated in around 80% yield (Scheme 4.11).[16]



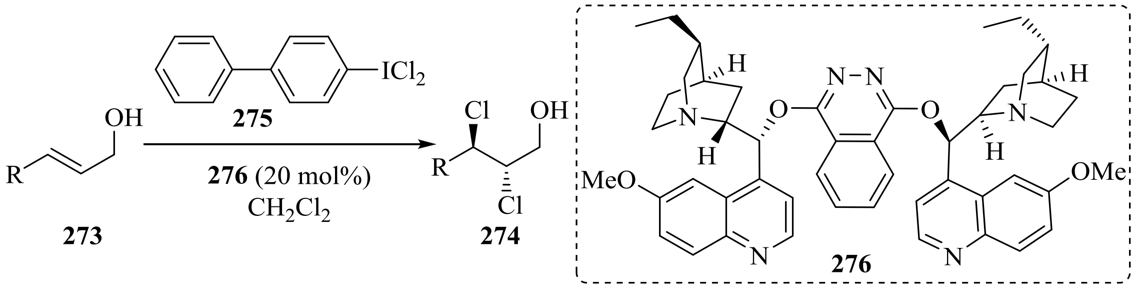
Scheme 4.11. Asymmetric iodolactonisation of 267 mediated by ICl.

A few years later, Lupton performed the dibromination of styrene derivatives **270** using chiral hypervalent iodine reagent **272** in the presence of pyridine hydrobromide. The desired product **271** was obtained in 82% yield but poor enantioselectivity was observed (3% *ee*). Changing the temperature or the solvent did not improved the selectivity of this transformation (Scheme 4.12).[17]



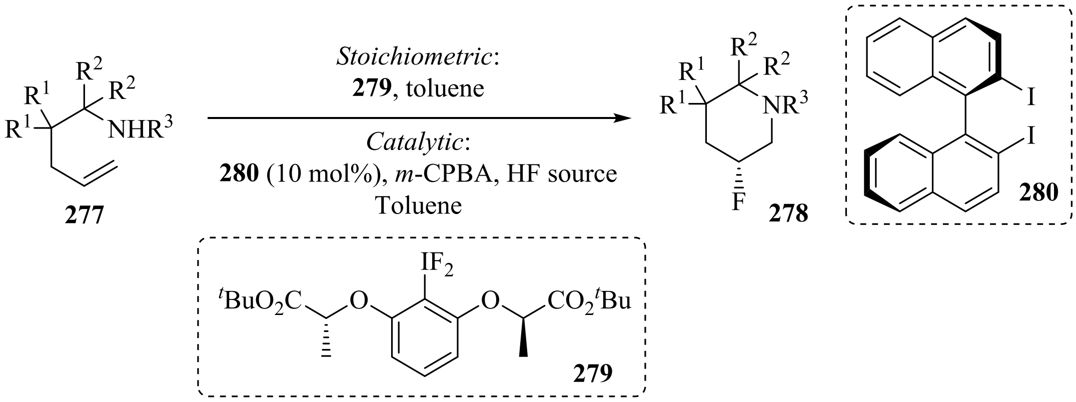
Scheme 4.12. Attempt of asymmetric dibromination of styrene derivatives 270.

In 2011, Nicolaou described the first enantioselective dichlorination of allylic alcohols **273** using dichloroiodoarene **275** in the presence of (DHQ)2PHAL **276** as a chiral catalyst. Various *trans*-cinnamyl alcohols were successfully dichlorinated in moderate to good yield (35-90%) and with up to 85% *ee* (Scheme 4.13).[18]



Scheme 4.13. Dichlorination of allylic alcohols 273.

In 2013, Nevado *et al.* reported the first intramolecular, regio- and enantioselective aminofluorination of alkenes **277** induced by chiral hypervalent iodine **279**. Products **278** were obtained in good to excellent yields and with up to 88% *ee* (Scheme 4.14). It was also found that *p*-xylene difluoride could be employed for the racemic aminofluorination of a range of styrene derivatives.[19]



Scheme 4.14. Enantioselective aminofluorination of alkenes 277.

Kita *et al.* published a year later the first catalytic aminofluorination of alkenes **277** using iodoarene **280** as a catalyst with a stoichiometric amount of *m*-CPBA in the presence of a fluorine source (hydrogen fluoride pyridine or 46% aqueous hydrofluoric acid).[20] Aminofluorinated compounds **278** were obtained in moderate yields (60-65%) and with up to 70% *ee*.

4.6. Conclusion

In conclusion, hypervalent iodine reagents are powerful tools for the asymmetric difunctionalisation of carbon-carbon double bonds. They can be used either as chiral reagents or as racemates in the presence of a chiral auxiliary. More recently, a few groups have developed enantioselective catalytic functionalisation of alkenes. These are quite promising tools for the organic synthesis of natural products and drugs.

4.7. References

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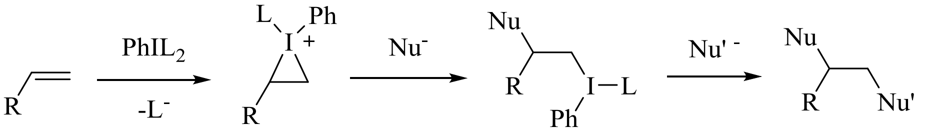
Chapter 5: Cyclisation of malonate derivatives mediated by hypervalent iodine reagents

5.1. Introduction

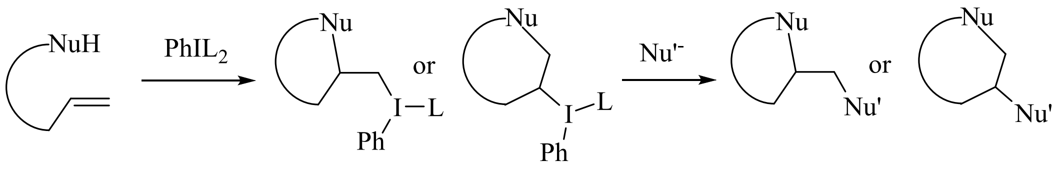
Functionalisation of alkenes is usually a key step in the synthesis of more complex molecules such as natural products.[1–5] Electrophilic iodine(III) species can activate unsaturated compounds to functionalise them. After the first attack of the iodine(III) onto the double bond, a first nucleophile can add from the opposite side of the double bond to form the intermediate **283**. Due to the high leaving group ability of the iodine(III) species when bonded to an *sp*^{3} carbon, the reaction proceeds with the addition of a second nucleophile (the same or different to the first one) to afford the difunctionalised product **284** (Scheme 5.1).



281 **282** **283** **284**

Scheme 5.1. Schematic interaction of hypervalent iodine with alkene 281.

Furthermore, if the alkene such as **285** contains a nucleophile (e.g. alcohol, amine, thiol, carboxylic acid…), an intramolecular nucleophilic attack can occur, leading to the products as shown in Scheme 5.2. Two products can be formed during this reaction, the *exo*- and the *endo*-cyclised products **286** and **287**. This selectivity will depend on the substrate and usually the Baldwin's rules can be applied to predict it (Scheme 5.2).[6]



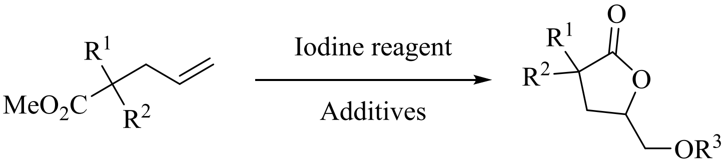
285 *exo*-**286** *endo*-**287** *exo*-**288** *endo*-**289**

Scheme 5.2. *Exo*- and *endo*-selectivity for the intramolecular nucleophilic attack onto the activated alkene 285.

The double addition of nucleophiles onto the double bond can generate two new stereocentres. It is therefore of great interest to use chiral iodine(III) reagents to generate the desired products stereoselectively.

5.2. Objectives

The aim of this project is to synthesise lactone derivatives **291** using hypervalent iodine(III) reagents, as shown in Scheme 5.3. These molecules are highly functionalised and can be used as precursor for further transformations, such as intramolecular cascade reactions, to generate natural products or drugs.



290 **291**

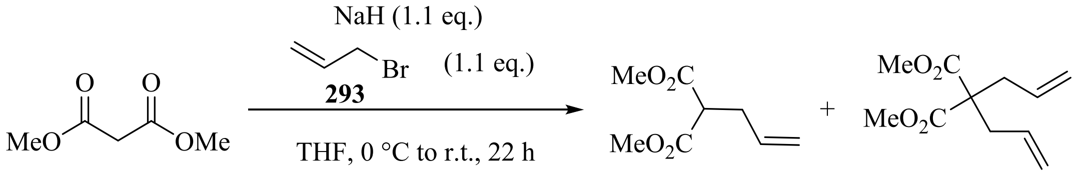
Scheme 5.3. General scheme for the cyclisation of compounds 290 using hypervalent iodine(III) reagent.

These lactone derivatives **291** with two chiral centres will be prepared *via* an intramolecular cyclisation using hypervalent iodine reagents to activate the double bond. Furthermore, the use of chiral hypervalent iodine could induce some stereoselectivity in the resulting lactones.

5.3. Results and discussion

5.3.1. Optimisation of the reaction conditions on dimethyl malonate derivative 297

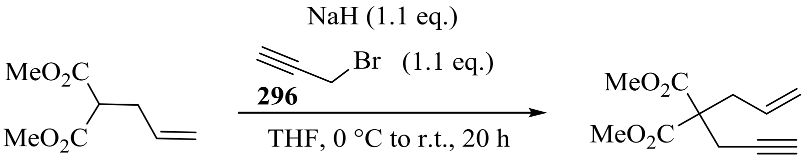
Substrate **297** was chosen for the optimisation of the reaction conditions. It contains an alkene and an alkyne functionality and two ester moieties that can act as the internal nucleophiles for the cyclisation. Compound **297** was easily prepared from dimethyl malonate **292** by two alkylation steps. The first one was performed using sodium hydride and allyl bromide **293** to install the allyl moiety. Both mono- and bis-alkylated products **294** and **295** were generated in 50% and 20% yield, respectively (Scheme 5.4).



292 **294**, 50% **295**, 20%

Scheme 5.4. Synthesis of mono- and di-alkylated compounds 294 and 295.

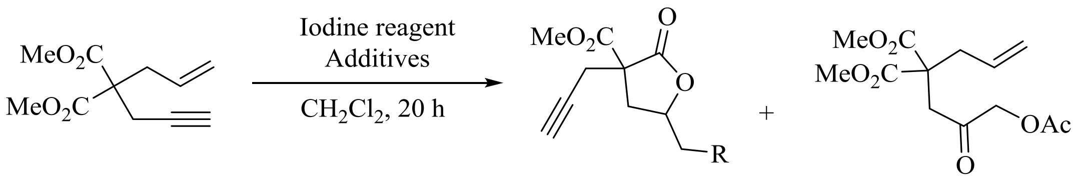
Mono-alkylated malonate **294** was then treated again with sodium hydride but in the presence of propargyl bromide **296**. The desired propargylated product **297** was obtained in 64% yield (Scheme 5.5).



294 **297**

Scheme 5.5. Addition of propargyl bromide onto malonate derivative 294.

Different conditions were investigated to optimise the cyclisation reaction of malonate derivative **297** as shown in Table 5.1. The reaction was initially performed using only the iodine reagent at -20 °C. Both $PhI(OAc)_2$ and $I(OAc)_3$ did not mediate any cyclisation after 3 days of reaction and the starting material was fully recovered (Table 5.1, Entries 1 and 2).



297 **298a**, R = OAc **298b**, R = OH **299**

Table 5.1. Effect of the additives on the cyclisation of malonate derivative 297.

Entry	Iodine(III)	Additives	T	Yield[a] [%]		*d.r.*
	(eq.)	(eq.)	[°C]	298x	299	298
1	DIB (1)	-	-20 to r.t.	n.r.[b]	-	-
2	$I(OAc)_3$ (1)	-	-20	n.r.	-	-
3	DIB (1)	$BF_3\bullet OEt_2$ (2)	-20	**a**: 16 (54)	Traces	10:1[d]
4	DIB (1.2)	$BF_3\bullet OEt_2$ (2)	-20	**a**: (60)	Traces	10:1[d]
5	DIB (1.2)	$BF_3\bullet OEt_2$ (2)	-20	**a**: 15 (61)[b]	Traces	10:1[d]
6	DIB (1.2)	$BF_3\bullet OEt_2$ (2)	0	**a**: 48	45	6:1[d]
7	DIB (1.2)	$BF_3\bullet OEt_2$ (2)	r.t.	**a**: (100)[c]	n.d.	2:3[d]
8	Koser (1.2)	$BF_3\bullet OEt_2$ (2)	-20	**b**: 20 (49)	-	-
9	PIFA (1.5)	$BF_3\bullet OEt_2$ (2)	-20	n.p.	-	-
10	DIB (1.2)	$BF_3\bullet OEt_2$ (3)	-20	**a**: (83)	-	5:1[d]
11	DIB (1.2)	$BF_3\bullet OEt_2$ (3) AcOH (12.5)	-20	**a**: 58 (85)	6	11:1[d]
12	DIB (1.2)	$BF_3\bullet OEt_2$ (2) AcOH (12.5)	-20	**a**: 24 (100)	32	8:1[d]
13	DIB (1.2)	$BF_3\bullet OEt_2$ (2) H_2O (0.01)	-20	**b**: 39 (57)	-	5:1

n.r. = no reaction; starting material could be recovered. n.p. = no product could be isolated due to complete degradation. [a] Yields reported are the isolated yields. The consumptions of starting materials measured by ^{1}H NMR (called conversion in the text) are shown in brackets. [b] The reaction was stirred for 3 days. [c] Full consumptions of the starting material was observed but much more degradation was observed.[d] d.r. is given as trans:cis ratio.

It was suspected that the iodine reagent alone was not reactive enough, therefore, a Lewis acid was added to activate it. $BF_3\bullet OEt_2$ was chosen and a cyclised product could be observed and isolated in 16% yield (Table 5.1, Entry 3). A ratio of 10:1 between the two diastereomers was measured in the crude ^{1}H NMR. In order to determine whether the

5-*exo* or the 6-*endo* cyclised product was formed (Figure 5.1), 2D NMR spectra were recorded.

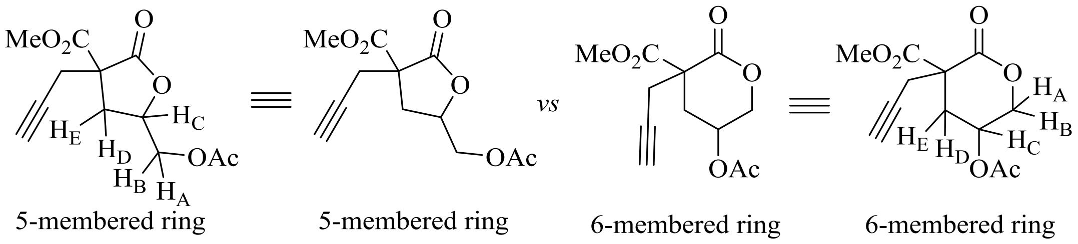


Figure 5.1. 5- and 6-membered ring structure of product 298a.

On the spectrum (Figure 5.2), H_C is interacting in the space with H_A, H_B, H_D and H_E which indicates that H_C is attached to the carbon bearing the OAc moiety or CH_2OAc group. Furthermore, on the zoom picture of this experiment (Figure 5.3), only H_A is interacting with H_E. This suggests that there could be a 1,3-diaxial interaction between these two protons and therefore, a six membered-ring lactone would fit better the NOESY results. Indeed, if it was the 5-membered lactone that was obtained, protons H_A and H_B should interact the same way towards H_D and H_E as the carbon bearing H_A and H_B should freely rotate. As only H_A and H_E are interacting in the space (1,3-diaxial interaction), this also means that those two protons are in axial position and H_B and H_D are in equatorial position of the chair-like conformation.

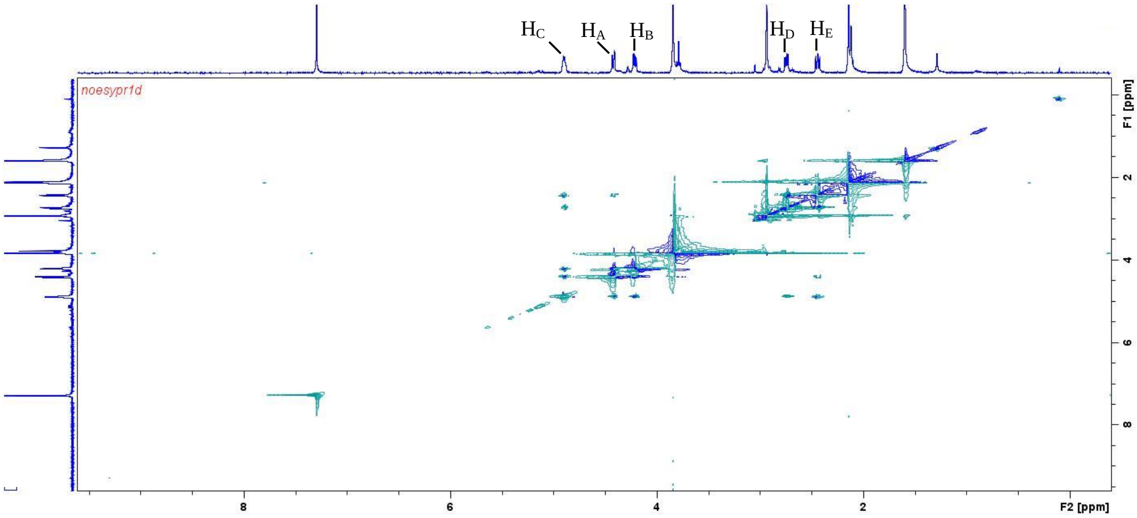


Figure 5.2. NOESY spectra of molecule 298a.

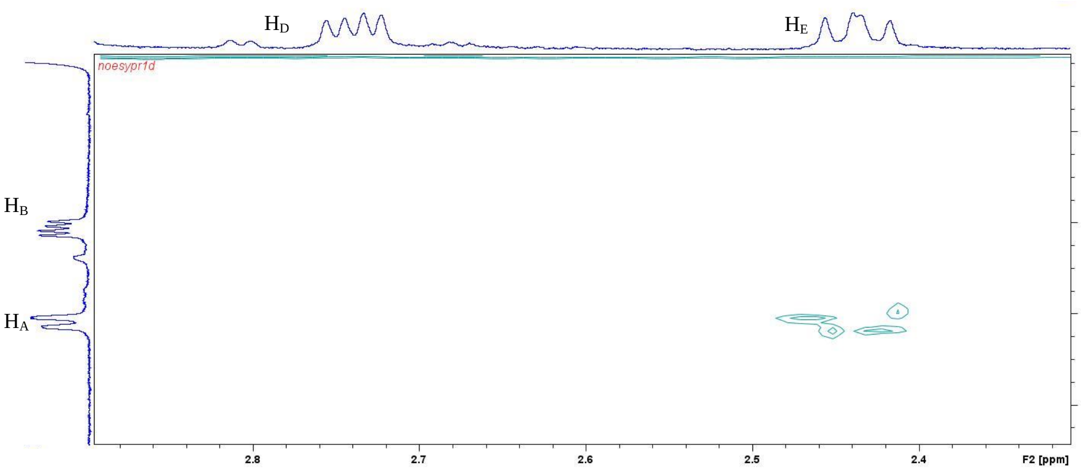


Figure 5.3. Zoom of the NOESY spectra of molecule 298a.

However, the infrared spectra show two absorption peaks at 1776 and 1736 cm^{-1}. The peak at 1736 cm^{-1} is most likely the C=O stretch of the methyl ester and the acetate. On the other hand, the peak at 1776 cm^{-1} is very characteristic of a 5-membered ring lactone which usually appears around 1770 cm^{-1} while the absorbance band for a 6-membered ring lactone is in the region of 1735 cm^{-1}[7]. This result is in disagreement with the NOESY experiment. It is also unclear why H$_C$ is interacting with all the four other protons around it.

In order to unambiguously determine the exact structure of the lactone, a crystal structure would be ideal. Fortunately, the oily product slowly crystallised over two years' time at room temperature on the bench and the X-Ray crystal structure (Figure 5.4) finally established that it was the 5-membered ring lactone that was formed during the reaction. The crystal structure also revealed the relative stereochemistry of the major diastereomer, with the methyl ester and the CH$_2$-acetate trans to each other.

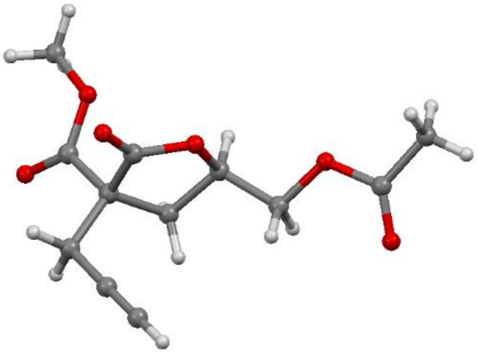


Figure 5.4. Crystal structure of lactone 298a.

A possible explanation for the interaction, in the NOESY spectrum, only between H_E and H_A (and not H_B) might be due to a blocked conformation of the CH_2-acetate moiety.

An excess of the iodine reagent was then used to try to improve the conversion. However, this did not make a big difference with only an increase of 4% conversion and the diastereomeric ratio remained unchanged (Table 5.1, Entry 4). The yield was not improved by stirring the reaction for three days at room temperature and also the selectivity remained the same (Table 5.1, Entry 5).

The effect of the temperature on the conversion and the selectivity was then studied. Increasing the temperature to 0 °C improved the conversion to 100% and the cyclised product **298a** was isolated in 48% yield. However, the formation of a major side product was observed. After isolation and characterisation, it was found that a competing oxidation of the triple bond was occurring and in addition, the oxidised compound **299** was isolated in 45% yield (Table 5.1, Entry 6). The selectivity also started to drop with a diastereomeric ratio of 6:1 being observed. When the reaction was warmed up to room temperature, considerable degradation was observed and products could not be isolated. The selectivity decreased even further with a diastereomeric ratio of approximately 2:3 (Table 5.1, Entry 7).

Two other iodine reagents were then compared with $PhI(OAc)_2$. Koser's reagent gave the cyclised product **298b** (R = OH) in 20% yield. The selectivity could not be determined by ^1H NMR as the peaks were overlapping (Table 5.1, Entry 8). Using PIFA together with $BF_3{\bullet}OEt_2$ led to complete degradation to unidentifiable products (Table 5.1, Entry 9).

Increasing the amount of $BF_3{\bullet}OEt_2$ to 3 equivalents led to a better conversion (83%), but the selectivity dropped to a diastereomeric ratio of 5:1 (Table 5.1, Entry 10). The addition of an excess of nucleophile could also help to improve conversion of the starting material into the cyclised product **298a**. Therefore, additional acetic acid was added to the reaction mixture and the cyclised product was isolated in 58% yield with slightly improved diastereomeric ratio of 11:1 (Table 5.1, Entry 11). As the increased amount of Lewis acid was detrimental for the selectivity, the reaction was also performed with only two equivalents of $BF_3{\bullet}OEt_2$. The starting material was fully converted but surprisingly, it also led to much more formation of side product **299** as well as one other uncharacterised side product. Furthermore, the selectivity decreased to a ratio of 8:1 (Table 5.1, Entry 12). Finally, it has to be noted than in the presence of water (1 mol%), the cyclisation still proceeded but with a lower conversion. Only product **298b** was isolated in 39% yield and with a diastereomeric ratio of 5:1 (Table 5.1, Entry 13).

The effect of the solvent was also studied and the results are shown in Table 5.2. When the reaction was performed in acetonitrile, no product was isolated due to complete degradation of the reaction mixture into uncharacterised products. The addition of acetic acid did not lead to a cleaner reaction (Table 5.2, Entries 2 and 3).

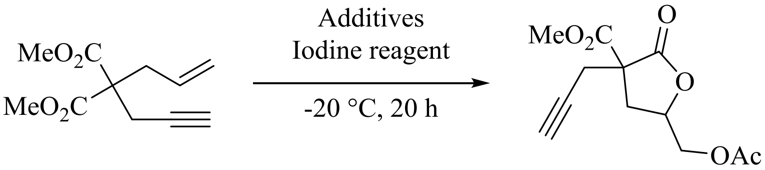


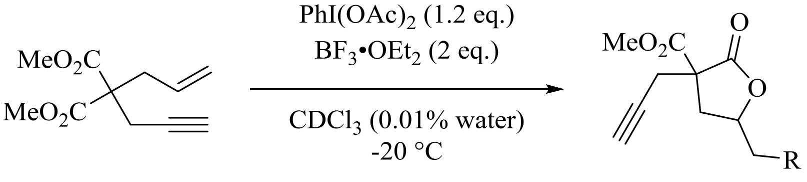
Table 5.2. Effect of the solvent on the cyclisation of malonate derivative 297.

Entry	Solvent	Additives (eq.)	Yield[a] [%]	*d.r.*
1	CH_2Cl_2	BF_3•OEt_2 (2)	16 (54)	10:1[b]
2	CH_3CN	BF_3•OEt_2 (2)	n.p.	-
3	CH_3CN	BF_3•OEt_2 (2) AcOH (12.5)	n.p.	-
4	CH_2Cl_2 /TFE (5:1)	BF_3•OEt_2 (2)	n.p.	-

n.p. = no product could be isolated due to complete degradation. [a] Yields reported are the isolated yields. The consumptions of starting material measured by ^{1}H NMR (called conversion in the text) is shown in brackets. [b] Trans:Cis ratio

2,2,2-Trifluorethanol (TFE) is known to coordinate to the iodine reagent and in several cases, has led to increased selectivity.[8] However, when a mixture of dichloromethane and TFE (5:1) was used as the solvent, complete degradation of the starting material was observed (Table 5.2, Entry 4).

In order to further optimise the reaction time of the cyclisation, the reaction was monitored by ^{1}H NMR analysis. The cyclisation was directly performed in deuterated chloroform to allow for a direct measurement. The sample was taken from the reaction mixture and the results over time are shown in Table 5.3. The conversion kept increasing with the reaction time to reach 83% conversion.



297

298a, R = OAc
298b, R = OH

Table 5.3. Evolution of the ratio between 298a and 298b over time.

Entry	Time [h]	Conversion[a] [%]	298a/298b ratio
1	0.5	30	1:4
2	1	35	1:1.7
3	2	37.5	1:1.7
4	3	48	2:1
5	24	59	2.3:1
6	48	61	1.3:1
7	53	83	1:1

[a] Consumptions of starting material (called conversion in the text) was measured by ^{1}H NMR.

Surprisingly, the product **298b** was observed in large quantities in every fraction collected. This means that even trace amounts of water present in the bottle of deuterated chloroform (brand new) was enough to induce the addition of a hydroxyl group instead of the acetoxy moiety. The ratio between **298a** and **298b** was changing with the reaction time and no trend can be clearly observed. Therefore, depending on the time the reaction was stopped, product **298a** or product **298b** would be the major product of the reaction.

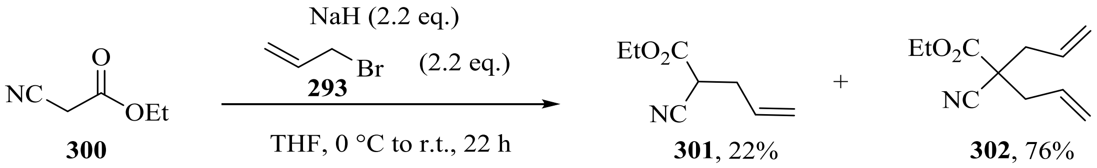
The isolated yield and the conversion measured in the crude ^{1}H NMR were quite different and therefore, different hypotheses have been considered. The first one is the decomposition of the product when exposed to silica during the purification by column chromatography. This hypothesis was rapidly rejected. Indeed, the crude mixture and silica were stirred in a mixture of hexane and ethyl acetate for an hour, then filtered and analysed by ^{1}H NMR. The same proportion of product was found as previously observed and no loss of material was measured. The same experiment was also performed but using basic alumina and the same outcome confirmed that the product was completely stable under the purification conditions.

It was then considered that the lower yield would be due to a loss of product during the work up. Again, different methods were compared with basic, neutral or acidic work up. All methods led to an acceptable crude mass and similar crude ^{1}H NMR spectra were measured with no significant changes for the diastereomeric ratio. Therefore, it can be stated that the problem was not coming from the work up itself.

The last possibility for the lower yield is the potential volatility of the products formed. This was confirmed by exposing the samples to high vacuum and measuring the mass before and after the process. Therefore, after the discovery, no sample was dried under high vacuum to avoid evaporation of the product mixture.

5.3.2. Optimisation on ethyl 2-cyanoacetate derivatives

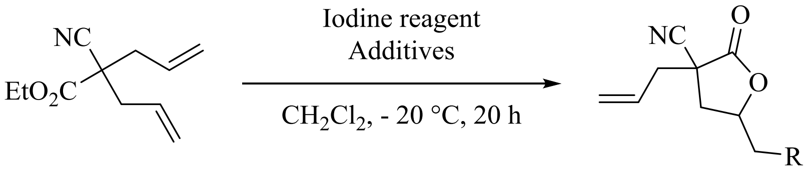
The cyclisation reaction was also performed on ethyl 2-cyanoacetate derivative **302** and different iodine reagents were again used to confirm that DIB was still the reagent of choice. First, the substrate was synthesised from ethyl 2-cyanoacetate in the presence of sodium hydride and 2.2 equivalents of allyl bromide. The mono- and di-alkylated products **301** and **302** were obtained in 22% and 76% yield, respectively (Scheme 5.6).



Scheme 5.6. Synthesis of mono- and di-alkylated ethyl 2-cyanoacetate 301 and 302.

The cyclisation reaction was then performed using di-alkylated substrate **302** in the presence of DIB and BF_3•OEt_2. The expected cyclised product **303a** with the acetoxy group addition was isolated in 43% yield but the diastereomeric ratio was only 3:1 (Table 5.4, Entry 1). Another Lewis acid (TMSOTf) was used for direct comparison. The cyclisation occurred with lower yield but no acetoxy group was added onto the double bond. Instead, the triflate anion from the Lewis acid reacted as the nucleophile to lead to product **303c** (Table 5.4, Entry 2). The addition of TFE resulted again in complete degradation of the starting material to unknown compounds (Table 5.4, Entry 3).

Changing the iodine(III) reagent did not improve the isolated yield of the cyclised product **303** or the selectivity. Iodosylbenzene and Koser's reagent both mediated the addition of a hydroxyl group onto the double bond in 37% and 21% yield, respectively (Table 5.4, Entries 4 and 5). Finally, the use of PIFA resulted in complete degradation into unknown products.



302

303a, R = OAc
303b, R = OH
303c, R = OTf

Table 5.4. Optimisation of the cyclisation of 302.

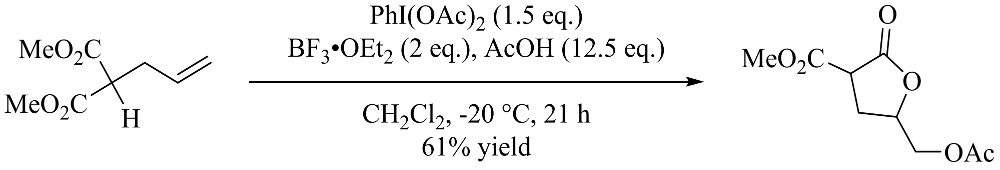
Entry	Iodine(III) (eq.)	Additives (eq.)	Yield[a] (303x) [%]	*d.r.*
1	DIB (1.2)	BF_3•OEt_2 (2)	**a**: 43	3:1
2	DIB (1.2)	TMSOTf (2)	**c**: 28	n.d.
3	DIB (1.2)	TMSOTf (2) TFE	n.p.	-
4	PhI=O (1)	BF_3•OEt_2 (2)	**b**: 37	n.d.
5	Koser (1.5)	BF_3•OEt_2 (2)	**b:** 21	2:1
6	PIFA (1.5)	BF_3•OEt_2 (2)	n.p.	-

n.d. = not determined due to the overlapping of the peaks in ^{1}H NMR. n.p. = no desired product and degradation into unknown products was observed. [a] The yields reported are the isolated yields.

From both substrate optimisations, the best reaction conditions were using $PhI(OAc)_2$ in the presence of BF_3•OEt_2 and acetic acid. The resulting mixture was stirred in dichloromethane for 20 hours at -20 °C. These conditions were used for the scope of the reaction presented in the next section.

5.3.3. Scope of the reaction

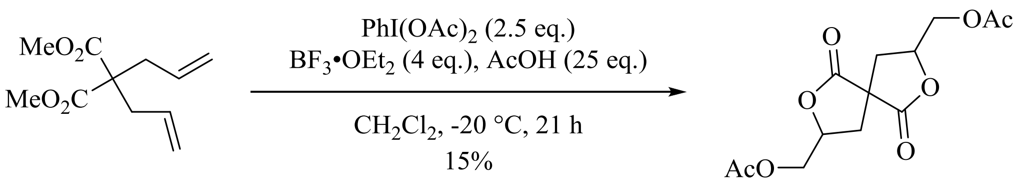
The cyclisation of malonate derivatives was performed using the best reaction conditions found above. The mono-allylated dimethyl malonate **294** was reacted with DIB to give compound **304** in 61% yield (Scheme 5.7). The diastereomeric ratio determined in the crude ^{1}H NMR was very low with 1.3:1.



294 **304**

Scheme 5.7. Cyclisation of mono-allyl dimethyl malonate 294.

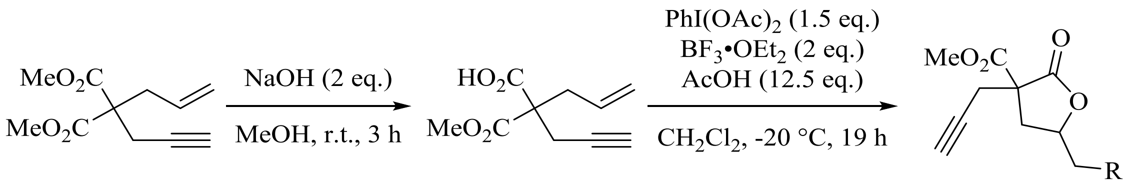
The cyclisation also worked for the di-allylated substrate **295**. As two carbon-carbon double bonds and two esters were present in the molecule, it was in principle possible to obtain the double cyclised spiro compound **305** by increasing the amount of iodine(III) reagent. Product **305** was isolated in 15% yield as the major product (Scheme 5.8).



295 **305**

Scheme 5.8. Double cyclisation of substrate 305.

If there is an addition of a carboxylic acid through the double bond, the cyclisation reaction should occur more easily if it is synthesised and isolated prior to the reaction. For this, malonate derivative **297** was treated with sodium hydroxide in methanol and the mono-hydrolysed malonate **306** was isolated in 96% yield. The cyclisation was then performed using the best conditions found during the optimisation. Two different cyclised product were formed during the reaction, one with the addition of a hydroxyl group onto the double bond (**298b**, 13%) and the other one with an acetoxy moiety (**298a**, 28% yield) (Scheme 5.9).



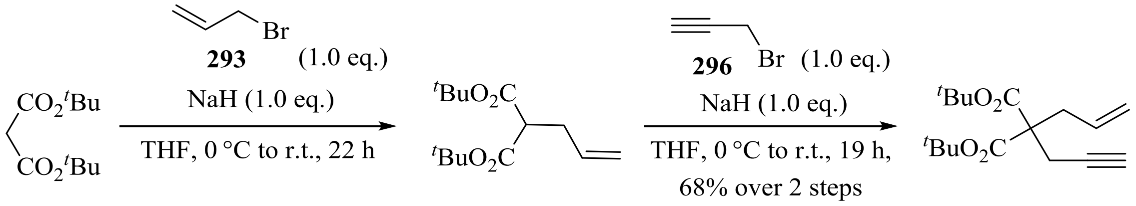
297

306, 96%

298a, R = OAc, 28%
298b, R = OH, 13%

Scheme 5.9. Selective hydrolysis followed by cyclisation mediated by DIB.

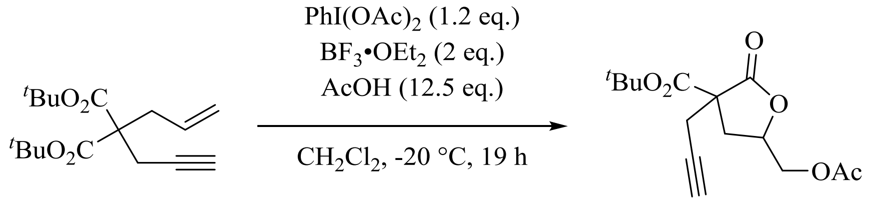
If a loss of methyl cation from the ester is assumed in the mechanism, di-*tert*-butyl malonate derivatives should provide better yields as the *tert*-butyl cation is a better leaving group. Indeed, it is more stabilised and also generates isobutene, by loss of a proton, which can be liberated as a gas. The synthesis of the compounds **308** and **309** was the same as for the previous substrates. The first alkylation was performed on di-*tert*-butyl malonate **307** with allyl bromide to form compound **308**. This crude mixture was used directly after a work up for the second alkylation using propargyl bromide. The resulting product **309** was obtained in 68% yield over the two steps (Scheme 5.10).



307 **308** **309**

Scheme 5.10. Synthesis of malonate derivatives 308 and 309.

Substrate **309** gave the desired cyclised product **310** in moderate conversion (58%) and with moderate selectivity (*d.r.* = 4:1) (Scheme 5.11). The yield of the reaction remained the same as the one for the methyl ester substrate. However, the selectivity dropped drastically from 11:1 to 4:1 (*d.r.*).

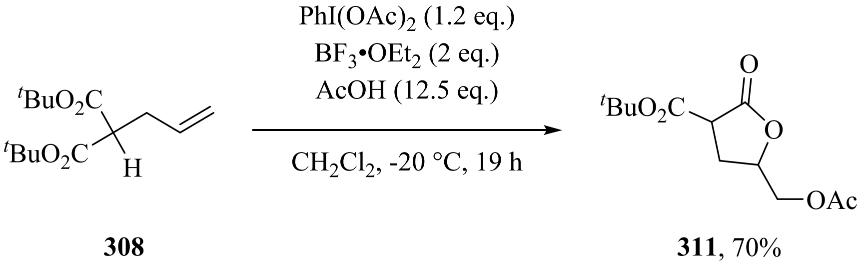


309

310, 58% conversion
d.r. = 4:1

Scheme 5.11. Cyclisation of malonate derivative 309.

Finally, the mono-allylated di-*tert*-butyl malonate **308** was also submitted to the same reaction conditions and led to the cyclised product **311** in good yield (70%) but with moderate selectivity of 4:1 (Scheme 5.12). The stereochemistry of the major isomer (*cis*) was determined by NOESY experiment on the isolated mixture (*d.r.* = 1.2:1) (see experimental section).



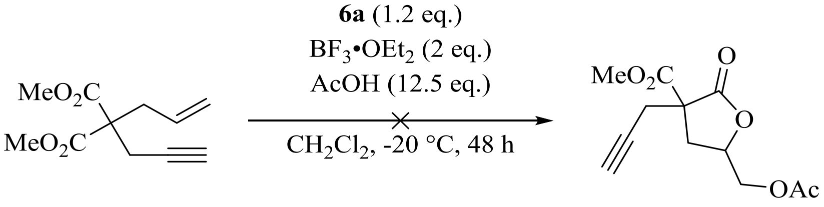
308

311, 70%
d.r. = 4:1 (*cis*:*trans*)

Scheme 5.12. Cyclisation of malonate derivative 308.

5.3.4. Asymmetric cyclisation

As mentioned in the introduction, there are two chiral centres in this highly functionalised product **298a**. Therefore, it would be of great interest to use a chiral hypervalent iodine reagent to mediate the cyclisation through a stereoselective addition across the double bond. The reaction was performed under the best reaction conditions, simply replacing PhI(OAc)$_2$ with the Ishihara ester **6a** (Scheme 5.13). Unfortunately this reaction did not lead to the desired product. No further investigation was performed on the asymmetric version of the cyclisation.



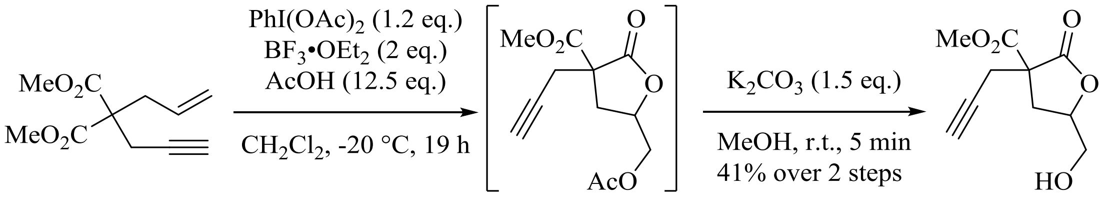
297

298a

Scheme 5.13. Attempt of asymmetric cyclisation of malonate derivative 297.

5.3.5. Hydrolysis of the acetate moiety

In order to further functionalise the molecule, it would also be interesting to selectively hydrolyse the acetate group as the liberated alcohol could then be used as a nucleophile. This was easily done using potassium carbonate (1.5 equivalents) in methanol in only 5 minutes reaction time. The hydrolysis was directly combined with the cyclisation reaction and the alcohol **312** was obtained in 41% yield over the two steps. However, the diastereoselectivity dropped drastically during the hydrolysis step to a diastereomeric ratio of 2:1 (Scheme 5.14). This decrease in the diastereomeric ratio might be due to the presence of the base which can potentially deprotonate in α-position of the acetate moiety, leading to a possible epimerisation.

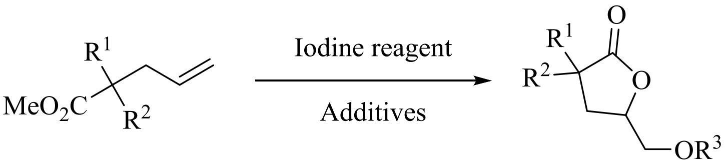


297 **298a**, *d.r.* = 11:1 **312**, *d.r.* = 2:1

Scheme 5.14. Cyclisation of malonate derivative 297, followed by the hydrolysis of the acetate moiety.

5.4. Conclusion and outlook

Malonate derivatives were successfully cyclised into their corresponding highly functionalised lactones with moderate to good diastereoselectivities. Furthermore, the 5-membered ring structure was confirmed by X-Ray crystallography. Using other functional groups for R^1 and R^2 would also lead to a bigger library of valuable compounds for further functionalisation.



290 **291**

Scheme 5.15. General scheme for the cyclisation of compounds 290 using hypervalent iodine(III) reagent.

It would also be of great interest to further investigate the asymmetric version of this cyclisation to produce chiral precursors for many transformations. Finally, the use of a catalytic amount of iodine reagent would render this reaction more atom efficient and therefore more attractive.

5.5. References

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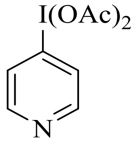
Chapter 6: Synthesis of new hypervalent iodine(III) reagents

6.1. Introduction and objectives

Hypervalent iodine reagents are largely used to replace transition-state metals in similar transformations. As mentioned in the introduction, they are highly electrophilic at the iodine centre and excellent leaving groups when bonded to an *sp*^{3} carbon. In order to enhance this electrophilicity further, an electron deficient iodoarene can be used.

Use of a pyridine ring rather than a benzene ring, should improve the electrophilicity at the iodine centre. Indeed, the lone pair of the nitrogen is not able to increase the electron density of the π-electron system on the aromatic ring due to its geometry. Furthermore, the electron withdrawing ability of the electronegative nitrogen atom renders the aromatic ring more electron deficient. Therefore, the iodine atom would be more electrophilic.

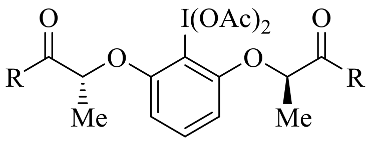
The first type of new iodine reagent that will be discussed in this chapter is represented in Figure 6.1. The reactivity of this non-chiral iodine(III) reagent **315** can be directly compared with $PhI(OAc)_2$ to determine whether it is beneficial for the reactivity to have an electron poor aromatic system bonded to the iodine centre.



315

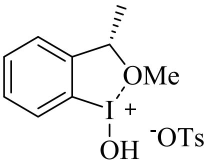
Figure 6.1. Structure of new hypervalent iodine(III) 315.

Lactate-based iodine(III) reagents such as **6** are well known reagents for stereoselective transformations. The conformational flexibility of these reagents can render the interaction of the oxygen or nitrogen atom with the iodine centre weaker. In the case of iodine(III) **33c**, a strong interaction between the iodine atom and the methoxy group was observed (Figure 6.2).[1]

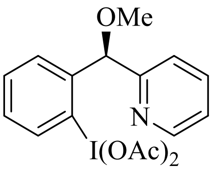


6a, R = OMe

6b, R = NHMes



33c

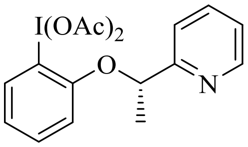


265

Figure 6.2. Structure of different chiral hypervalent iodine(III) reagents.

Pyridine has the advantage that the lone pair of the nitrogen atom can coordinate with the iodine centre and this interaction has been reported in various publications.[2–4] If a chiral centre was present in the iodine(III) reagent, it would be possible to induce some stereoselectivity, which should be enhanced by the coordination of the pyridine ring with the iodine atom. In 2014, Wirth *et al*. designed a new iodine(III) reagent **265** with a similar backbone to compound **33c** but bearing a pyridine moiety. With this reagent, diamination cyclised products could be obtained with up to 94% *ee*.[5]

In this section, another pyridine-based iodine(III) reagent **316** is described and its reactivity and ability to induce stereoselectivity is determined. The most notable difference between reagent **265** and **316** is the number of atoms between the iodine centre and the nitrogen atom of the pyridine moiety. Comparison of these two hypervalent iodine reagents would reveal if the number of atoms between the iodine and the coordinating nitrogen is important with regards to the induction of stereoselectivity (Figure 6.3).



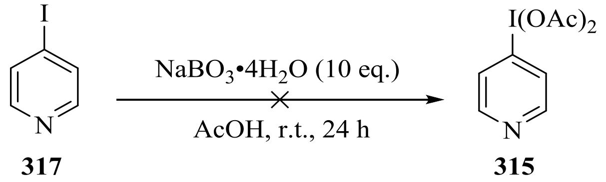
(*S*)-316

Figure 6.3. Structure of iodine(III) reagent (*S*)-316.

6.2. Oxidation of iodopyridine

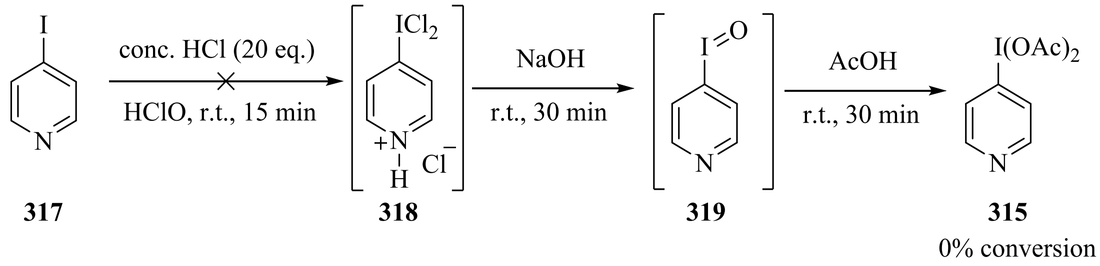
6.2.1. 4-Iodopyridine

In order to oxidise 4-iodopyridine **317**, a classical method with sodium perborate tetrahydrate was used. However, no oxidation occurred and the starting material was fully recovered (Scheme 6.1).



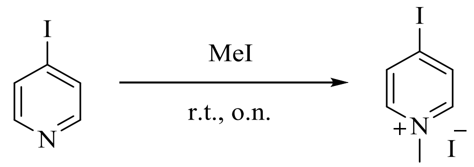
Scheme 6.1. Attempt for the oxidation of 4-iodopyridine using $NaBO_3•4H_2O$.

Another approach was then investigated to yield the (diacetoxy)iodopyridine compound **315**. First, it was proposed that the (dichloro)iodoarene **318** could be generated *in situ* from 4-iodopyridine in the presence of hypochlorous acid and hydrochloric acid. Under these acidic conditions, it was assumed that the pyridine moiety would then be protonated with chloride as plausible counter ion. Compound **318** would then be hydrolysed under basic condition using sodium hydroxide to obtain intermediate **319** which would be acetylated with acetic acid. However, no traces of oxidised iodine reagent **315** was observed in the crude mixture. Therefore, the first step of this sequence maybe did not give the (dichloro)iodopyridine derivative **318** making this route inefficient for the synthesis of (diacetoxy)iodopyridine **315** (Scheme 6.2).



Scheme 6.2. Attempt for the oxidation of 4-iodopyridine using HClO.

It was suspected that an oxidant may also react with the nitrogen atom. Therefore, the pyridine moiety was methylated prior to the oxidation. The *N*-methylated product **320** was synthesised following a known procedure.[6] After reaction with iodomethane in tetrahydrofuran, the desired product was observed with 53% conversion.



317 **320**

Table 6.1. Methylation of 4-iodopyridine.

Entry	MeI (eq.)	Solvent	Yield[a] [%]
1	2	THF	(53)
2	31	-	95 (100)

[a] **The yield reported is the isolated yield, the consumptions of starting materials (called conversion in the text) are shown in brackets.**

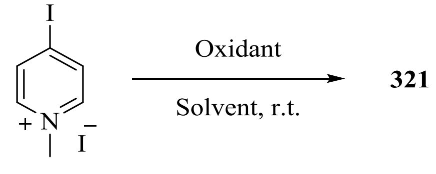
In order to improve the conversion of this transformation, iodomethane was used in a larger amount and the reaction was stirred in neat iodomethane overnight. Product **320** was isolated in 95% yield.

The oxidation of compound **320** was first attempted using *m*-CPBA and acetic acid in a mixture of dichloromethane and 2,2,2-trifluoroethanol (TFE). After evaporation of the solvent, which was red coloured, a new compound **321** was formed with 28% conversion (Table 6.2, Entry 1). However, this product was not the desired oxidised hypervalent iodine reagent. Elucidation of this unknown species is described below.

Other oxidants were also investigated for the oxidation of 4-iodopyridinium derivative **320**. Oxone®, Selectfluor®, peracetic acid and fuming nitric acid in trifluoroacetic anhydride did not yield any new product as judged by the crude ^{1}H NMR (Table 6.2, Entries 2-5). However, a similar red-coloured solvent was evaporated after the reaction. Xenon difluoride is known to oxidise iodoarenes to their corresponding difluoroiodoarene. However, in this case, the reaction with xenon difluoride did not lead to any oxidised product (Table 6.2, Entry 6). Due to the possible instability of the generated hypervalent iodine reagent, the *in situ* generation of the hypervalent iodine moiety and its direct use for the α-fluorination of a ketone (propiophenone) was also investigated. However, no fluorination reaction occurred and the starting materials were recovered, suggesting no formation of the desired oxidised species.

The same unknown product **321** was observed in 86% conversion when compound **320** was treated with sodium perborate tetrahydrate at room temperature (Table 6.2, Entry 7).

Finally, an iodine(V) reagent, $NaIO_4$ was used to oxidise molecule **320**. However, no product was observed with this method (Table 6.2, Entry 8).



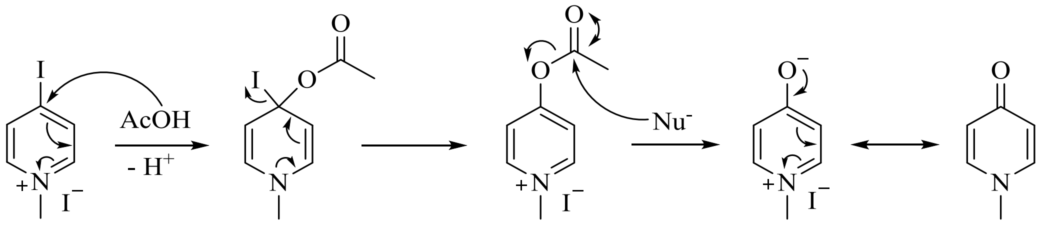
320

Table 6.2. Optimisation of the oxidant for the oxidation of compound 320.

Entry	Oxidant (eq.)	Solvent	Time [h]	Conversion[a] [%]
1	*m*-CPBA (1)	CH_2Cl_2/TFE (1:1) + AcOH (12 eq.)	5	28
2	Oxone® (1)	$CHCl_3$/AcOH (1:1)	5	n.r.
3	Selectfluor® (5)	CH_3CN/AcOH (3.2:1)	5	n.r.
4	Peracetic acid	-	24	n.r.
5	TFAA (6), HNO_3 (2)	-	96	n.r.
6	XeF_2 (1)	CH_2Cl_2	24	n.r.
7	$NaBO_3 \cdot 4H_2O$ (10)	AcOH	5	86
8[b]	$NaIO_4$ (1), $AcONa \cdot H_2O$ (2.2)	AcOH/Ac_2O (10:1)	2	n.r.

n.r. = no reaction; [a] Consumptions of starting materials (called conversion in the text) were measured in the crude ^1H NMR. [b] The reaction was stirred at reflux instead of room temperature.

The red colour of the evaporated solution in each reaction could be due to some iodine I_2 in solution. In the crude ^1H NMR, a high field shift of the two doublets of the aromatic protons (7.62 and 6.11 ppm) indicates a possible bond with an electron donating group such as an oxygen- or nitrogen- containing moiety instead of the iodine. The pyridine was still methylated as indicated by a peak at 3.62 ppm. This signal was also shifted high field compared to that of the starting material **320**. The tendency to have a lower chemical shift compared to the iodopyridinium species **320** is not the right one for a hypervalent iodine compound. Usually, these reagents are shifted downfield when they are oxidised. ^{13}C NMR data also confirmed the presence of a carbonyl peak in the structure and only two aromatic carbon shifts were observed. The proposed structure for this compound is 1-methylpyridin-4(1*H*)-one **321**. A plausible mechanism for the formation of this compound is shown in Scheme 6.3. First, an acetate moiety is added onto the pyridinium ring *via* an S_NAr pathway. Indeed, the *para* position of the nitrogen atom is now much more electrophilic as the pyridine is methylated and therefore, positively charged. After the cleavage of the iodide anion, assisted by the nitrogen lone pair, the acetate moiety **323** can be deprotected by a nucleophile (water, acetic acid…) to liberate the intermediate **321'** which is a mesomeric form of compound **321**.

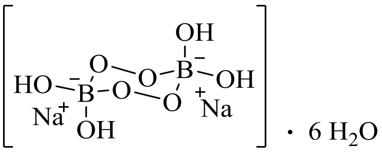


320 **322** **323** **321'** **321**

Scheme 6.3. Plausible mechanism for the formation of 1-methylpyridin-4(1*H*)-one 321 from compound 320.

However, some parts of the mechanism are still not very clear and not in accordance with the experimental observation. First, there is the question of which is the first nucleophile for the S_NAr reaction. It can be either the oxidant or the acetic acid. However, if only the acetic acid acts as the nucleophile, the reaction should proceed for all the reactions where acetic acid was present. Second, the red colour of the distillate suggested the formation of iodine I_2. This suggests that the iodide I^- has been oxidised during the reaction.

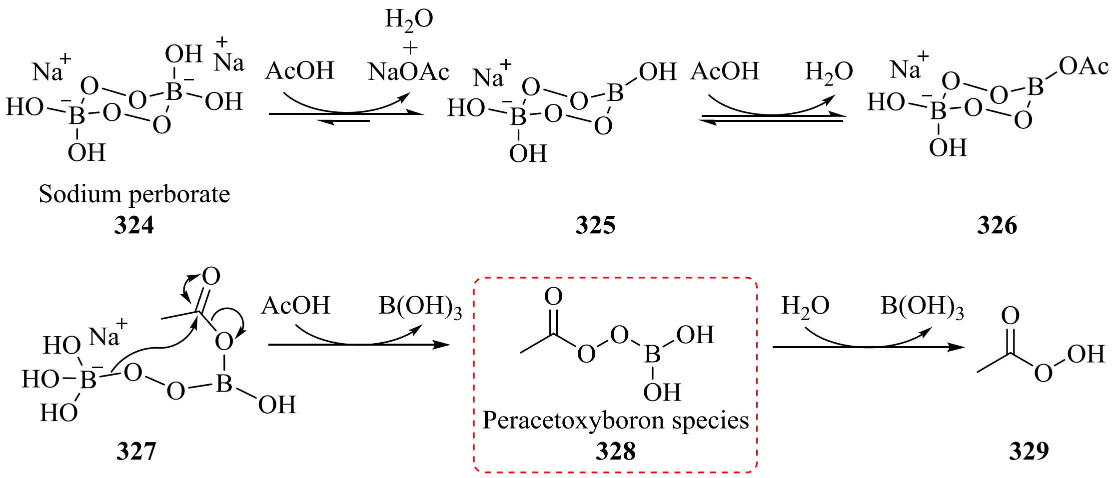
In order to better understand the mechanism of this reaction and especially why sodium perborate tetrahydrate is much more reactive than other oxidants, the reactivity of this reagent was investigated. Sodium perborate tetrahydrate is actually a disodium salt of a 1,4-diboratetroxane dianion **324** surrounded by 6 molecules of water as shown in 1961 by Hansson (Figure 6.4).[7]



324

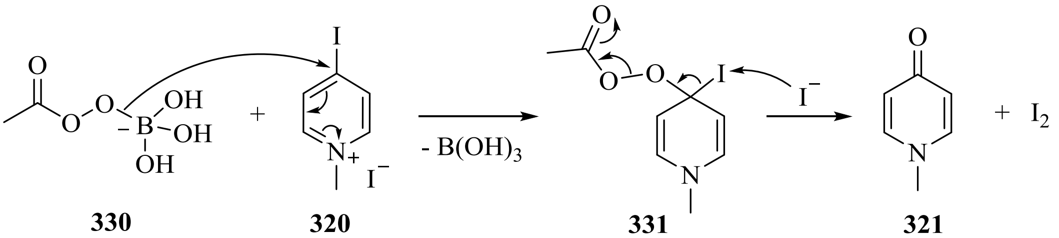
Figure 6.4. Structure of sodium perborate tetrahydrate as disodium salt of a 1,4.-diboratetroxane dianion 324.

In the presence of acetic acid, sodium perborate reacts slightly differently to generate the more reactive peracetoxyboron species, by a sequence of equilibria and reactions as shown in Scheme 6.4.[8] McKillop and Sanderson reported that this species was probably more reactive than peracetic acid.



Scheme 6.4. Mechanism for the formation of peracetoxyboron species from the reaction of sodium perborate and acetic acid.

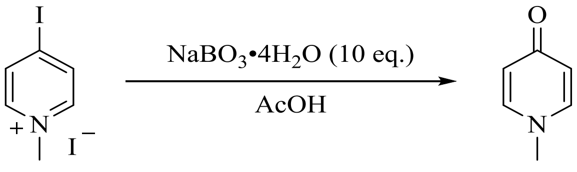
The peracetoxyboron species can probably be present in solution as intermediate **330** which is a good nucleophile. Therefore, it can add onto the aryl ring of molecule **320** *via* an S_NAr to yield intermediate **331**. The free iodide I^- can then cleave off the iodine attached to the ring, generating iodine I_2. The formation of iodine would explain the red coloured distillate observed after the reaction. Then, the cleavage of iodine leads to the desired product **321** after elimination of the acetate moiety (Scheme 6.5).



Scheme 6.5. Second plausible mechanism for the formation of product 321 using sodium perborate.

This mechanism still does not explain why the reaction works with *m*-CPBA but not with peracetic acid. However, it is maybe a first step in the understanding of the reaction mechanism, especially concerning sodium perborate.

The best results for the formation of compound **321** were obtained with sodium perborate tetrahydrate. In order to see if the formation of this product **321** can be avoided, different temperatures and reaction times were investigated. The results are combined in Table 6.3. Increasing the temperature to 55 °C led to a very low conversion of 24% to product **321** (Table 6.3, Entry 2). The reaction time was then modified to show the evolution of the conversion into product **321** and to check if other products were formed, depending on the reaction time. The conversion increased over time to get to its maximum after 5 hours (86%) before decreasing drastically to 17% after 65 hours of reaction.



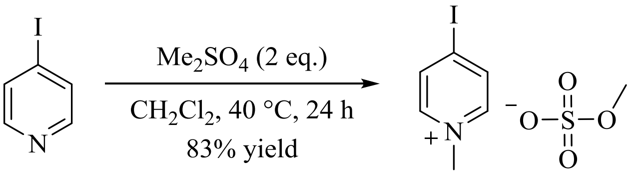
320 **321**

Table 6.3. Effect of the temperature and the reaction time on the formation of product 321.

Entry	T [°C]	Time [h]	Conversion[a] [%]
1	r.t.	5	86
2	55	5	24
3	r.t.	1	56
4	r.t.	3	51
5	r.t.	65	17

[a] Consumptions of starting materials (called conversion in the text) were measured by ^{1}H NMR.

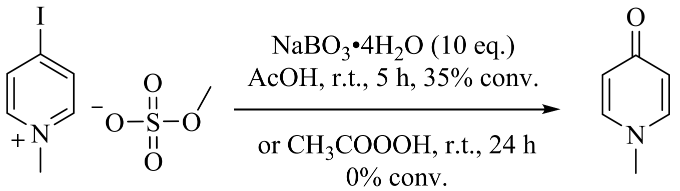
The effect of the counter ion was also investigated. Therefore, 4-iodopyridine was methylated using dimethylsulfate to obtain the iodopyridinium derivative **332** in 83% yield (Scheme 6.6).



317 **332**

Scheme 6.6. *N*-methylation of 4-iodopyridine with dimethylsulfate.

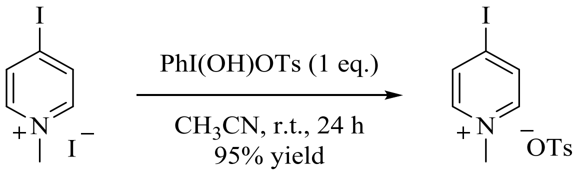
Compound **332** was then treated with two different oxidants, sodium perborate tetrahydrate and peracetic acid. Again, no hypervalent iodine reagent was observed but the same product **321** was obtained in 35% conversion with sodium perborate. A similar red-coloured solution was again evaporated, which suggests the formation of iodine. However, no product was formed with peracetic acid and the starting material was completely recovered (Scheme 6.7).



332 **321**

Scheme 6.7. Oxidation of compound 332.

Finally, hypervalent iodine reagent can also be synthesised by ligand exchange of an iodoarene with another hypervalent iodine reagent such as Koser's reagent [PhI(OH)OTs]. The reaction of compound **320** with one equivalent of Koser's reagent led to a simple counter ion exchange to yield molecule **333** in 95% yield (Scheme 6.8). The addition of a second equivalent of Koser's reagent did not change the course of the reaction.



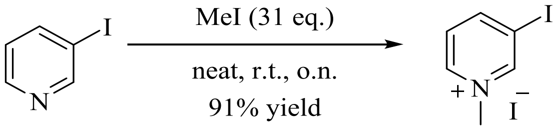
320 **333**

Scheme 6.8. Reaction of compound 320 with Koser's reagent.

The fact that the pyridine was methylated completely changed the electronic properties of the iodoarene substrate and this was detrimental for the oxidation of the iodoarene to a hypervalent iodine reagent.

6.2.2. 3-Iodopyridine

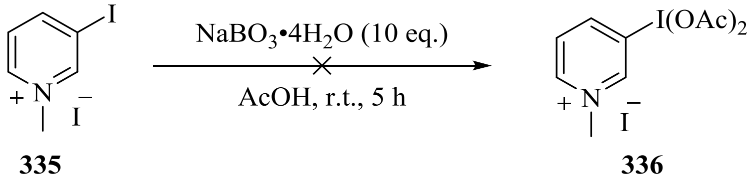
In order to understand slightly better the mechanism for the formation of compound **321** and the role that the nitrogen atom plays in this reaction, molecule **335** was synthesised. The same procedure was used to methylate 3-iodopyridine and the corresponding product **335** was obtained in 91% yield (Scheme 6.9).



334 **335**

Scheme 6.9. *N*-methylation of 3-iodopyridine.

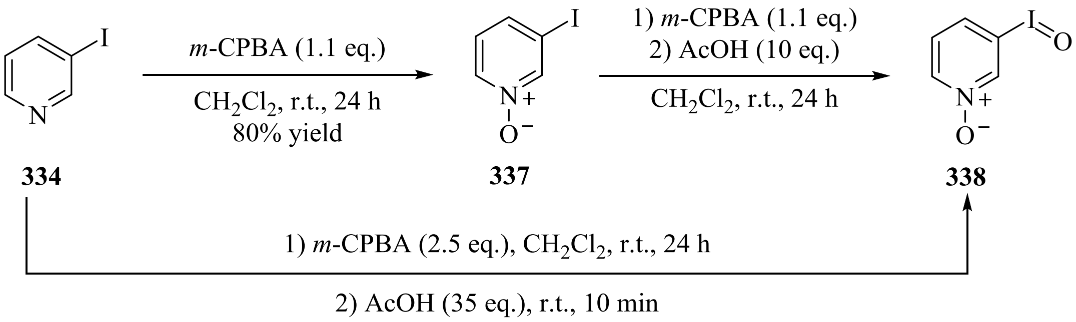
The oxidation reaction was then performed using the best conditions used for the 4-iodopyridinium derivative **320**. However, no reaction occurred and the starting material **335** was recovered. Fuming nitric acid in trifluoroacetic anhydride also did not mediate the oxidation of the iodine to the desired hypervalent iodine compound **336** (Scheme 6.10).



Scheme 6.10. Attempt for the oxidation of molecule 335 with sodium perborate.

The product of an S_NAr was not observed which was expected. Indeed, the *ipso*-substitution cannot occur in this case as the carbon centre is in the *meta*-position to the positively charged nitrogen atom. Furthermore, by methylating the nitrogen atom of the pyridine, the electron properties of the iodoarene are changed. Therefore, the oxidation reaction was performed directly with 3-iodopyridine using *m*-CPBA. Only the pyridine *N*-oxide **337** was observed in the crude mixture and was isolated in 80% yield (Scheme 6.11).

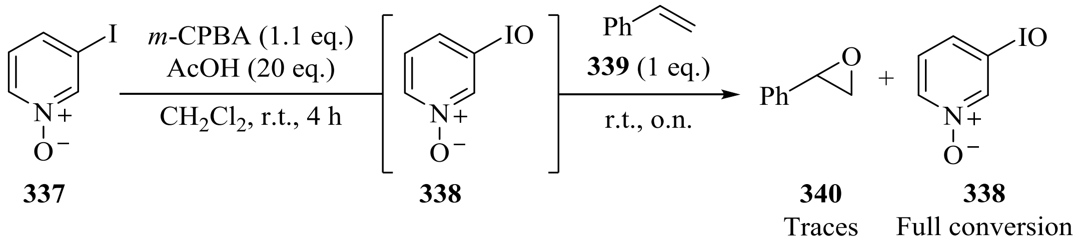
A second equivalent of *m*-CPBA was then added to further oxidise the pyridine *N*-oxide derivative **337** to the corresponding hypervalent iodine reagent. Acetic acid was also added after stirring the reaction overnight in order to yield (diacetoxy)iodoarene derivative. However, the desired product was not observed in the crude mixture as no acetate peak was present in the ^{1}H NMR data. Nonetheless, the *m*-CPBA was reduced to its corresponding carboxylic acid (confirmed by mass spectrometry, and NMR data). This means that something else was oxidised and therefore, the iodosoarene derivative **338** was proposed as the product of the oxidation reaction. In the mass spectra, the molecular peak of compound **338** was not found but the hypervalent bond is usually cleaved under the ionisation conditions and therefore, it is not surprising that only an m/z value corresponding to the iodine(I) derivative **337** was observed in the MS data.



Scheme 6.11. Oxidation of 3-iodopyridine with *m*-CPBA.

It was also possible to yield the same product **338** directly from 3-iodopyridine **334** by adding 2.5 equivalents of *m*-CPBA. However, this reaction led to much more degradation and formation of other unidentified products.

The easiest way to confirm that compound **338** was an iodine(III) reagent was to use this reagent in a reaction where hypervalent is commonly employed to mediate the transformation. The diacetoxylation of styrene was chosen. Pyridine *N*-oxide **337** was oxidised *in situ* using *m*-CPBA, prior to the addition of styrene (Scheme 6.12). No desired mono- or diacetoxylated product was observed in the crude mixture. However, compound **338** was fully recovered and traces amount of the epoxide **340** was generated. This is probably due to the slight excess of *m*-CPBA which reacted directly with styrene. Therefore, there is no clear evidence for the formation of any hypervalent iodine reagent.



Scheme 6.12. Attempt of diacetoxylation of styrene 339 mediated by reagent 338.

6.2.3. Conclusion

The electronic properties of the iodoarene were completely changed when a pyridine ring was used compared to a phenyl group. In the case of the 4-iodopyridine, no oxidation occurred in the presence of a classical oxidant ($NaBO_3 \bullet 4H_2O$) to generate hypervalent iodine reagents. However, 3-iodopyridine was selectively oxidised to the pyridine *N*-oxide derivative **337** using 1.1 equivalent of *m*-CPBA and was further oxidised using another 1.1 equivalent of the same oxidant.

This change in reactivity compared to iodobenzene was even stronger with the methylated pyridine derivatives. While the 3-iodopyridinium compound **335** did not lead to any products in the presence of sodium perborate tetrahydrate, the 4-iodopyridinium derivatives showed the formation of product **321** after cleavage of the iodide, which was oxidised to I_2.

Due to the change of electron density induced by methylation, the iodine centre would no longer be electrophilic and therefore, this type of reagent would probably not be more efficient that the parent iodobenzene and other hypervalent iodine derivatives.

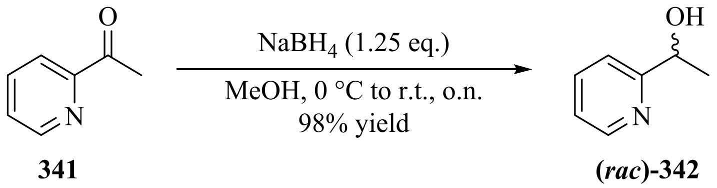
Another strategy was then considered. As the pyridine cannot be the centre core of the reagent, it might be interesting to install this aryl system on the side chain of an iodoarene, which would lead to a possible coordination with the iodine centre and therefore, to some selectivity. This strategy is explained in the next section.

6.3. Synthesis of a new chiral hypervalent iodine(III) reagent

6.3.1. Synthesis

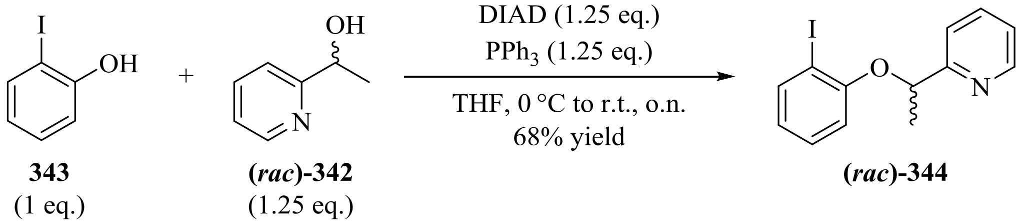
The proposed synthesis of the new iodine(III) reagent **316** looked straightforward with a Mitsunobu reaction between 2-iodophenol and the corresponding alcohol **342**, followed by the oxidation of the iodoarene **344** to the iodine(III) reagent **316**.

Prior to the Mitsunobu reaction, the alcohol **(*rac*)-342** was synthesised by reduction of 2-acetylpyridine **341** using sodium borohydride. The desired product was obtained in 98% yield (Scheme 6.13).



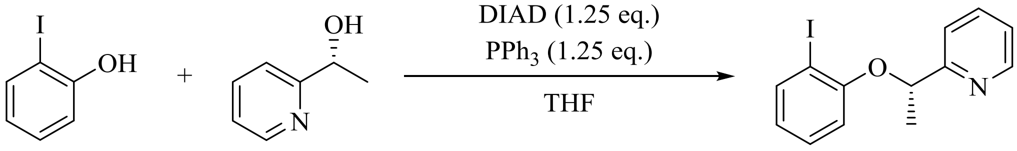
Scheme 6.13. Reduction of 2-acetylpyridine 341.

The Mitsunobu was then performed with **(*rac*)-342** and 2-iodophenol **343** using standard conditions and the corresponding product **(*rac*)-344** was synthesised in 68% yield (Scheme 6.14). An excess of the pyridine derivatives was used to increase the conversion and to avoid that any 2-iodophenol remained in the reaction mixture. Indeed, 2-iodophenol had the same R_f in the TLC (thin layer chromatography) as **344** and any leftover would render the purification difficult.



Scheme 6.14. Mitsunobu reaction on iodophenol with (*rac*)-342 for the synthesis of compound (*rac*)-344.

With this encouraging result, the chiral iodoarene reagent **(*S*)-344** was synthesised using the same methodology. The (*R*)-**342** substrate, which is commercially available, was used together with 2-iodophenol in the Mitsunobu reaction and the desired product **(*S*)-344** was obtained in 86% yield and with 91% *ee* (Table 6.4, Entry 1). As the Mitsunobu reaction proceeds with an inversion of configuration, the (*S*)-isomer was assumed to be the major product of the reaction. However, the enantioselectivity in the final product was not very high. Therefore, the reaction was performed at lower temperature (0 °C) to see if there would be an improvement in the enantioselectivity. The reaction proceeded similarly well with 85% yield but the enantioselectivity remained unchanged with 91% *ee* (Table 6.4, Entry 2).



343 (1 eq.) **(*R*)-342** (1.25 eq.) **(*S*)-344**

Table 6.4. Effect of the temperature on the enantioselectivity of the Mitsunobu reaction.

Entry	Temperature [°C]	Time [h]	Yield[a] [%]	*ee* [%]
1	r.t.	18	86	91
2	0	46	85	91

[a] **The yields reported are the isolated yields.**

In order to understand the reason of this low selectivity, a few experiment were undertaken. The first one was to check if the product **(*S*)-344** was racemising over time. The enantiomeric excess of the iodoarene was measured again after two weeks of storage at room temperature and under air but no change in the *ee* was observed (still 91% *ee*).

The second option was that the starting material was not as pure as stated on the bottle of the commercially available **(*R*)-342**. Therefore, the enantioselectivity was checked by HPLC and it was only of 85% *ee* (97% written on the bottle). The higher enantioselectivity of the product compared to the one of the starting material was not obvious to understand. A kinetic study was performed to see if one of the enantiomers **(*S*)-342** or **(*R*)-342** was reacting faster than the other one, therefore explaining the slightly higher selectivity of the product. The Mitsunobu reaction was performed with 1.1 equivalents of the pyridine moiety **342** and different samples were taken at several stages of the reaction. Each time, the sample was passed through a silica plug to remove any triphenylphosphine oxide and the solvent was evaporated. The enantioselectivity was then measured by HPLC for each sample and the consumptions of starting material was also measured by ^{1}H NMR. All the results are summarised in the graph below (Figure 6.5).

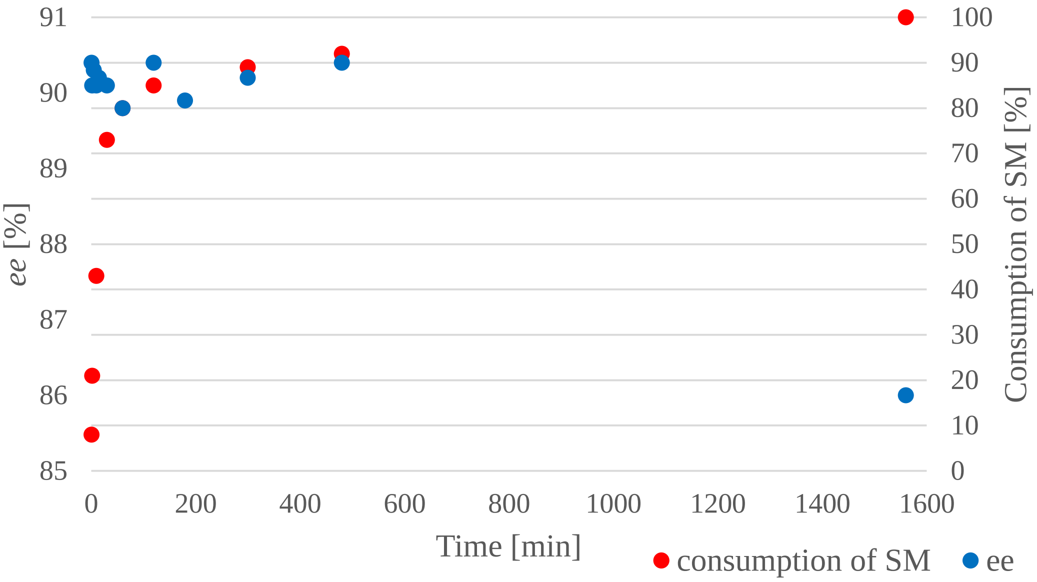
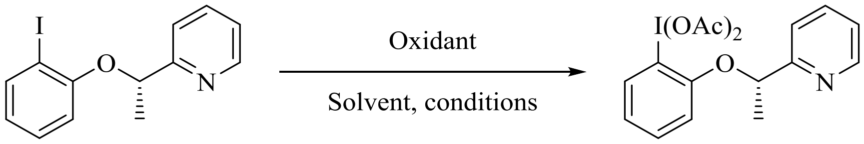


Figure 6.5. Evolution of the consumptions of starting material (called conversion in the text) and the enantioselectivity during the Mitsunobu reaction.

In this graph, the enantioselectivity is pretty constant at around 90% *ee* until 8 hours of reactions. However, the selectivity dropped to 86% *ee* after 26 h of reaction. However, this decrease in selectivity could be attributed to the experimental error of the measurement by HPLC. Concerning the conversion, the reaction was quite fast as after only 2 hours, the desired product was observed with 85% conversion. Full conversion into the desired product was measured in the crude NMR. The pyridine reagent **342** was used in slight excess (1.1 equivalents) which mean that a maximum of 90% conversion can be due to the (*R*)-isomer. The slightly higher enantioselectivity observed in the product **344** compared to the one of the starting material **342** can maybe be due to an asymmetric amplification[9] but an experimental error of the instrument cannot be excluded.

The next step to synthesise this novel iodine(III) reagent was to oxidise the iodoarene **(*S*)-344**. A well-known oxidant for this transformation is sodium perborate tetrahydrate. However, for this iodoarene substrate, the desired product **316** was only formed in 40% conversion (Table 6.5, Entry 1). Selectfluor® was used instead in a mixture of acetonitrile and acetic acid and the desired product was obtained in 92% yield (Table 6.5, Entry 2).



(*S*)-344 **(*S*)-316**

Table 6.5. Oxidation of iodoarene (*S*)-344.

Entry	Oxidant (eq.)	Solvent	Temperature [°C]	Time [h]	Yield[a] [%]
1	$NaBO_3•4H_2O$	AcOH	45	7	(40)
2	Selectfluor®	CH_3CN/AcOH (3.2:1)	r.t.	24	92 (100)

[a] The yields reported are the isolated yields; the consumptions of starting materials measured by ^1H NMR (called conversion in the text) are shown in brackets.

The enantiopurity of the iodine(III) reagent was assumed to be of 91% (the same as the iodoarene **(*S*)-344**). This induces some limitations for enantioselective transformations, however, the reagent could still be tested in different known reactions to verify its efficiency. If the reagent shows promising results, the enantiopurity of the reagent could be improved by using a starting material with a higher enantiomeric excess. This alcohol can be synthesised by the selective reduction of 2-acetylpyridine using, for example, a chiral rhodium[10] or iron[11] catalyst.

As iodine(III) reagent **316** is a solid compound, recrystallisation was attempted in order to see if there was any interaction in the solid state between the nitrogen atom of the pyridine moiety and the iodine centre. This was successfully performed on **(*rac*)-316** by dissolving it in dichloromethane and overlaying it with hexane for a slow evaporation. The crystal structure is shown in Figure 6.6. In each elementary cell, two molecules of **(*R*)-316** and two molecules of **(*S*)-316** were crystallised together.

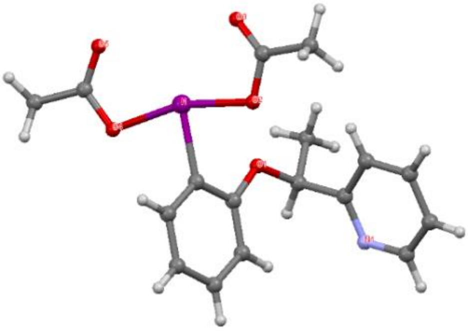
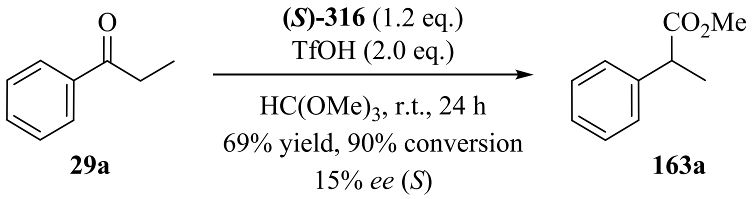


Figure 6.6. Crystal structure of (*rac*)-316.

In this crystal structure, the nitrogen atom of the pyridine moiety is not interacting with the iodine centre. This observation in the solid state suggested that the reagent may not be efficient for inducing an enantioselective reaction. However, compound **316** may behave differently in solution than in its crystal form. The reactivity and the selectivity of this new reagent **(*S*)-316** was investigated in different typical reactions, usually mediated by hypervalent iodine reagents. The results are described in the section below.

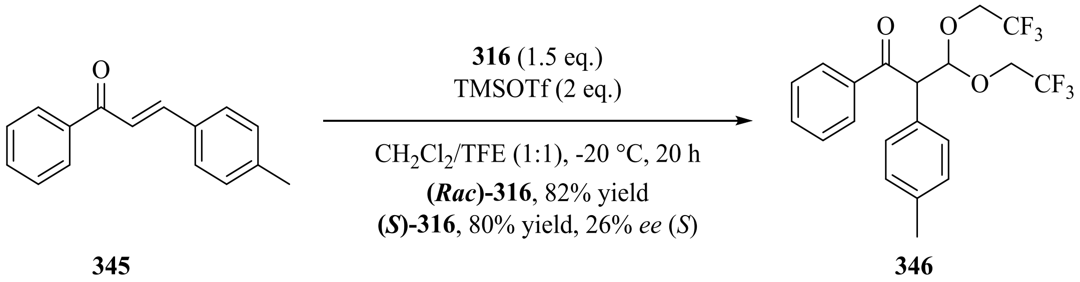
6.3.2. Evaluation of the reactivity and the selectivity of reagent (*S*)-316

The first transformation investigated with hypervalent iodine **(*S*)-316** was the rearrangement of propiophenone **29a** described in chapter 3. As mentioned in this chapter, the 1,2-aryl migration proceeded well with 90% conversion and 69% isolated yield. However, the selectivity was low with only 15% *ee* (Scheme 6.15). Furthermore, this iodine(III) reagent mediated the reaction with a much lower selectivity than the Ishihara amide **6b**. The same reaction was also performed at 0 °C to improve the enantioselectivity. However, product **163a** was obtained in similar yield (87% conversion, 65% yield) and with 14% *ee*. This demonstrates the low impact of the temperature on the selectivity of this migration reaction.



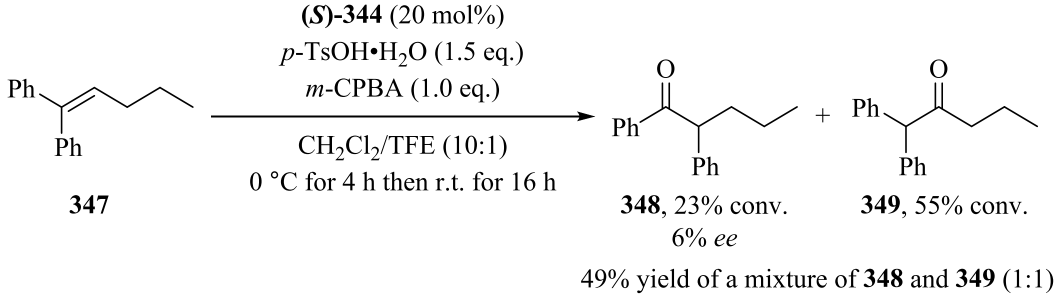
Scheme 6.15. Rearrangement of propiophenone 29a using iodine(III) reagent (*S*)-316.

Wirth *et al.* described the rearrangement of chalcone derivatives **345** into compounds **346**.[12] With the Ishihara amide **6b** as the iodine(III) reagent and TMSOTf as the activating agent, the rearranged product **346** was obtained in 80% yield and with 86% *ee*. With reagent **(*S*)-316**, the same product **346** was isolated in the same yield (80%). However, the selectivity induced by the reagent **(*S*)-316** was much lower with 26% *ee* (Scheme 6.16).



Scheme 6.16. Rearrangement of chalcone 345 using iodine(III) reagent (*S*)-316.

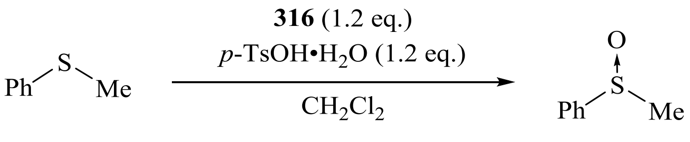
Very recently, the enantioselective rearrangement of 1,1-disubstituted alkenes was described by Wirth *et al.*[13] Substrate **347** was investigated and the corresponding *α*-arylated ketones **348** was obtained in 87% yield and with 94% *ee*. The catalytic transformation is currently under optimisation and catalyst **(*S*)-344** was considered for the mediation of the migration. With *m*-CPBA as the internal oxidant and *p*-TsOH•H_2O to activate the iodine(III) compound generated *in situ*, the *α*-arylated ketone **348** was obtained in 23% conversion and with 6% *ee*. However, ketone **348** was not the major product but instead, product **349** was observed in 55% conversion. Nevertheless, the selectivity induced by catalyst **(*S*)-344** was very poor compared to other iodine catalysts which could mediate the rearrangement with up to 75% *ee* (Scheme 6.17).



Scheme 6.17. Catalytic rearrangement mediated by iodoarene (*S*)-344.

The oxidation of thioanisole was also studied using iodine(III) reagent **(*S*)-316**. Following Koser's method,[14] (methylsulfinyl)benzene **351** was successfully synthesised in 90% yield using chiral reagent **(*S*)-316** (Table 6.6, Entry 2). However, product **351** was obtained as a racemate.

In order to improve the selectivity, the temperature was lowered down to -78 °C. At this temperature, the reaction should be slower and therefore, chiral reagent **(*S*)-316** would have more time to interact with the substrate and induce some chirality in the product generated. The reaction proceeded similarly well and the desired oxidised product **351** was obtained in 94% yield but the selectivity was almost none (2% *ee*) (Table 6.6, Entry 3).



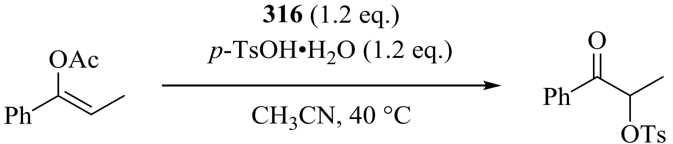
350 **351**

Table 6.6. Oxidation of thioanisole 350 using iodine(III) reagent 316.

Entry	Iodine(III)	Temperature [°C]	Time [h]	Yield[a] [%]	*ee* [%]
1	**(*rac*)-316**	r.t.	2	93	-
2	**(*S*)-316**	r.t.	2	90	0
3	**(*S*)-316**	-78	1	94	2 (*R*)

[a] The yields reported are the isolated yields.

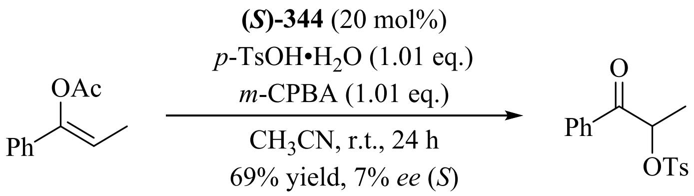
The *α*-oxytosylation of propiophenone was also performed using iodine(III) reagent **(*S*)-316**. Substrate **227** was used instead of propiophenone as it had previously shown better enantioselectivity.[15] Following the procedure published by Legault *et al.*, the reaction of the vinyl acetate derivative **227** with reagent **(*S*)-316** in the presence of *p*-TsOH•H$_2$O proceeded with moderate yield (63% yield). However, the enantioselectivity induced by the chiral reagent was low (6% *ee*) (Scheme 6.18).



227 (**(*Rac*)-316**, 24 h, 36% yield; **(*S*)-316**, 48 h, 63% yield, 6% *ee* (*S*)) **30a**

Scheme 6.18. *α*-Oxytosylation of compound 227 using iodine(III) reagent (*S*)-316.

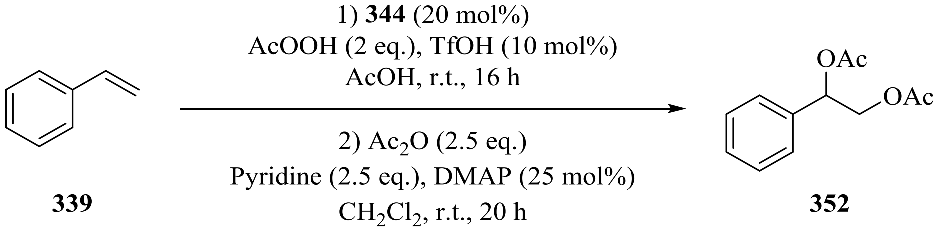
Legault *et al.* also described the catalytic oxytosylation of substrate **227** using a lactate-based iodoarene, *m*-CPBA as the internal oxidant and *p*-TsOH•H$_2$O to activate the *in situ* generated iodine(III) reagent.[16,17] Under these conditions, the *α*-oxytosylated ketone **30a** was obtained in 49% yield and with 83% *ee*.[17] The reaction was directly compared with the novel iodine(III) reagent using iodoarene **(*S*)-344** and the same reaction conditions described by Legault *et al.* The corresponding *α*-oxytosylated ketone **30a** was isolated in higher yield (69%) but with low enantioselectivity (7% *ee*) (Scheme 6.19).



227 **30a**

Scheme 6.19. Catalytic *α*-oxytosylation of 227 using iodoarene (*S*)-344.

Finally, the diacetoxylation of styrene was investigated using reagent **(*S*)-344** and following the method described by Muñiz *et al.* in 2016.[18] The iodoarene **(*S*)-344** was first oxidised *in situ* using peracetic acid in acetic acid to generate the iodine(III) reagent which was activated with triflic acid. This was then followed by the addition of styrene to obtain a dioxygenated intermediate which was then fully acetoxylated with acetic anhydride to yield diacetoxylated product **352** in 37% yield. However, the iodine reagent **316** did not induce any stereoselectivity for this transformation (Scheme 6.20).



339 **352**

(***Rac***)**-344**, 37% yield
(***S***)**-344**, 44% yield, 0% *ee*

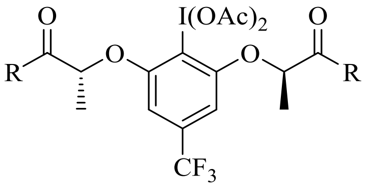
Scheme 6.20. Diacetoxylation of styrene 339 using iodoarene 344.

6.4. Conclusion and future work

The oxidation of 3- and 4-iodopyridine to hypervalent iodine reagent was attempted. However, no desired product was observed in the crude mixture. The oxidation of 3-iodopyridine led to the formation of 3-iodopyridine *N*-oxide **337**, while the 4-iodopyridinium derivative **320** yielded product **321** after cleavage of the carbon-iodine bond.

Another approach was then considered and the synthesis of a novel chiral iodine(III) reagent **(*S*)-316** was described. Its reactivity and selectivity was investigated. The reagent mediated transformations in similar yield to those described in the literature. However, the enantioselectivity remained low. This trend might be explained by the lack of interaction between the nitrogen atom of the pyridine moiety and the hypervalent iodine centre, as observed in the crystal structure. Indeed, without this interaction, the chain can freely rotate which means that no high enantioselectivity can be obtained.

Modifications to the chain such as its length, the nature of the heteroatoms and their position in the chain, and also production of a *C*$_2$-symmetric reagent could improve the selectivity of this pyridine-based reagent whilst maintaining a good reactivity. Another possibility is to install a CF$_3$ moiety in the para position of the iodine centre such as in compound **353**. The hypervalent iodine reagent generated should be more electrophilic and therefore, more reactive (Figure 6.7).



353

Figure 6.7. Structure of hypervalent iodine reagent 353.

6.5. References

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Chapter 7: Experimental Part

7.1. General considerations

The reactions were performed using standard laboratory equipment. All air sensitive reactions were carried out under argon or nitrogen atmosphere using oven dried glassware. All reaction were stirred using a stirrer plate and a magnetic stirrer bar and heating if necessary over a hotplate with a temperature probe control and an adapted heating block.

Lower temperatures were obtained using ice/water bath (0 °C), liquid nitrogen/acetonitrile bath (-40 °C), dry ice/acetone bath (-78 °C) or using a chiller (0 to -20 °C).

Büchi B-461, B-481 or B-490 were used for solvent evaporations (reduced pressure up to 15 mbar) and a high vacuum instruments was used to further dry the products except when the compounds were volatile.

A Büchi GKR-50 Kugelrohr distillation instrument was employed for Kugelrohr distillations.

Dry diethyl ether, tetrahydrofuran, toluene and acetonitrile were collected from a solvent purification system (SPS) from the company M BRAUN (MB SPS-800). Dry dichloromethane was distilled over calcium hydride under nitrogen atmosphere. Other dry solvents and chemicals were purchased from Sigma Aldrich, Alfa Aesar, Acros Organic, FluoroChem or TCI UK and were used without further purification.

7.2. Chromatographic Methods

7.2.1. Thin-layer chromatography (TLC)

All reactions were monitored by thin-layer chromatography (TLC) which was performed on precoated aluminium sheets of Merck silica gel 60 F254 (0.20 m) and visualised by UV radiation (254 nm) or/and by staining with ceric ammonium molybdate solution (235 mL distilled H_2O, 12 g ammonium molybdate, 0.5 g ceric ammonium molybdate, 15 mL concentrated sulfuric acid), potassium permanganate solution (1.5 g $KMnO_4$, 10 g K_2CO_3, 1.25 mL 10% NaOH, 200 mL distilled H_2O) or iodine.

7.2.2. Column Chromatography

7.2.2.1. Manual column chromatography

Manual column chromatography was performed using silica gel 60 (Merck, 230-400 mesh) under increased pressure (Flash Chromatography) or as gravitational column chromatography. The solvents used for the purification are indicated in the text and were purchased from Fisher Scientific as laboratory grade.

7.2.2.2. Automated column chromatography (Biotage)

Automated column chromatography was performed on a Biotage® Isolera Four using some Biotage® cartridges SNAP Ultra 10 g, SNAP Ultra 25 g, SNAP Ultra 50 g, SNAP Ultra 100 g, Telos® 12 g and Telos® 20 g. The solvents used for the purification are indicated in the text and were purchased from Fisher Scientific as laboratory grade.

7.2.3. High Pressure Liquid Chromatography (HPLC)

The HPLC measurements were carried out on a Shimadzu instrument. The different modules were SIL-10ADVP (auto injector), LC-10ATVP (liquid chromatograph), FCV-10ALVP (pump), DGU-14A (degasser), CTO-10ASVP (column oven), SCL-10AVP (system controller) and SPD-M10A (diode array detector). The solvents used were hexane and 2-propanol and were bought from Fischer scientific as HPLC grade. The chiral columns used for the separation of the enantiomers were Daicel Chiralcel *OD-H* (0.46 cm Ø x 25 cm), Daicel Chiralcel *OJ* (0.46 cm Ø x 25 cm), Daicel

Chiralcel *OB-H* (0.46 cm Ø x 25 cm), *YMC* Chiral Amylose-C S-5µm (0.46 cm Ø x 25 cm) and Regis® Pirkle Covalent (*R*,*R*) Whelk-O 1 (0.46 cm Ø x 25 cm).

7.3. Physical Data

7.3.1. ^{1}H NMR Spectroscopy

^{1}H NMR spectra were measured on Bruker DPX 500 (500 MHz), Bruker DPX 400 (400 MHz), Bruker DPX 300 (300 MHz) and Bruker DPX 250 (250 MHz) instruments. The chemical shifts δ are given in ppm downfield of tetramethylsilane (δ = 0 ppm). Compounds and crude reaction mixtures were dissolved in either deuterated chloroform, deuterated methanol or deuterated dimethylsulfoxide. Coupling constants (*J*) are given in Hertz. The multiplicity of signals is designated: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sept = septet, dt = doublet of triplet, td = triplet of doublet, bs = broad singlet, m = multiplet. Residual solvent peaks are 7.26 ppm for chloroform, 3.31 ppm for methanol and 2.54 ppm for dimethylsulfoxide.

7.3.2. ^{13}C NMR Spectroscopy

^{13}C NMR spectra were measured on Bruker DPX 500 (125 MHz), Bruker DPX 400 (100 MHz) and Bruker DPX 300 (75 MHz) instruments. The chemical shifts δ are given in ppm downfield of tetramethylsilane (δ = 0 ppm). Compounds and crude reaction mixtures were dissolved in either deuterated chloroform, deuterated methanol or deuterated dimethylsulfoxide. Coupling constants (*J*) with fluorine are given in Hertz. The multiplicity of signals is designated: d = doublet, q = quartet. Residual solvent peaks are 77.16 ppm for chloroform, 49.00 ppm for methanol, 39.52 ppm for dimethylsulfoxide.

7.3.3. ^{19}F NMR Spectroscopy

^{19}F NMR spectra were measured on Jeol Eclipse 300 (283 MHz) instrument. The chemical shifts δ are given in ppm.

7.3.4. Mass Spectrometry

Mass spectrometric measurements were performed by the EPSRC Mass Spectrometry Service Centre, Swansea University or by R. Jenkins/R. Hick/S. Waller at Cardiff University. Ions were generated by the atmospheric pressure chemical ionisation (APCI), Electrospray (ES) or Electron Ionisation (EI). Mass fragments usually are in atomic mass units per elementary charges (m/z) with relative abundance of ion in percentage (%). The high resolution mass spectrometry (HRMS) for most of the compounds was carried out at EPSRC Mass Spectrometry Service Centre, Swansea University. The molecular ion peak values quoted for either molecular ion $[M]^+$, molecular ion plus hydrogen $[M+H]^+$, molecular ion plus ammonium ion $[M+NH_4]^+$ or molecular ion plus sodium $[M+Na]^+$.

7.3.5. IR Spectroscopy

IR spectra were recorded on a Shimadzu IR Affinity-1S instrument. Wavenumbers are quoted in cm^{-1}. All compounds were measured neat directly on the crystal of the IR machine.

7.3.6. Melting Points

Melting points were measured using a Gallenkamp variable heater with samples in open capillary tubes.

7.3.7. Optical Rotation

Optical rotation were measured with a SCHMIDT and HAENSCH UniPol L polarimeter at 20 °C in a cuvette of 50 mm length with a sodium light (589.30 nm). HPLC grade chloroform was used to prepare the solution and the concentration is indicated in the data section.

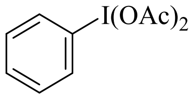
7.3.8. X-Ray Crystallography

Single-crystal XRD data were collected on an Agilent SuperNova Dual Atlas diffractometer with a mirror monochromator (using either Cu (λ= 1.5418 Å) or Mo (λ = 0.7107 Å) radiation), equipped with an Oxford cryosystems cooling instrument. Crystal structures were solved and refined using SHELX. Non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were inserted in idealised positions, and a riding model was used with Uiso set at 1.2 or 1.5 times the value of Ueq for the atom to which they are bonded.

7.4. Experimental data

7.4.1. Synthesis of common iodine(III) reagents

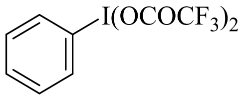
(Diacetoxyiodo)benzene DIB



To a solution of iodobenzene (2.75 mL, 25.4 mmol) in acetic acid (250 mL), sodium perborate tetrahydrate (37.7 g, 254 mmol) was added over 15 minutes. The resulting mixture was then heated at 50 °C for 3 h. After removing the acetic acid under vacuum, water (100 mL) was added. The organic phase was extracted with $CHCl_3$ (3 x 100 mL), dried over $MgSO_4$ and concentrated under vacuum. Hexane (30 mL) was added to precipitate the pure product as a white powder (90% yield, 7.09 g, 24.5 mmol).

The spectroscopic data are in agreement with literature.[1] **m.p.** = 161 - 164 °C (lit.[1] 162 - 163 °C) **^{1}H NMR (300 MHz, $CDCl_3$)**: δ = 8.10 – 8.08 (m, 2H, H-Ar), 7.61 – 7.58 (m, 1H, H-Ar), 7.54 – 7.47 (m, 2H, H-Ar), 2.01 (s, 6H, 2 CH_3) ppm.

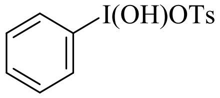
[Bis(trifluoroacetoxy)iodo]benzene PIFA



To a solution of iodobenzene (2.0 mL, 17.9 mmol) in trifluoroacetic acid (20 mL), Oxone® (11.0 g, 17.9 mmol) was added. The resulting mixture was stirred at room temperature for 3 h. The solvent was then evaporated and chloroform (20 mL) was added. The resulting precipitate was filtered and the filtrate was concentrated under vacuum. After recrystallisation (5 mL TFA + 50 mL petroleum ether), the desired product was obtained as a yellow crystalline compound (21% yield, 1.61 g, 3.72 mmol).

The spectroscopic data are in agreement with literature.[2] **m.p.** = 115 - 118 °C (lit.[2] 118 - 120 °C) **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 7.18 (dd, J = 8.5, 1.0 Hz, 2H, H-Ar), 6.62 (tt, J = 7.5, 1.1 Hz, 1H, H-Ar), 7.18 (tt, J = 8.0, 1.5 Hz, 2H, H-Ar) ppm.

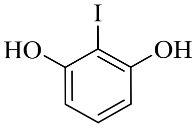
Koser's reagent



To a stirred solution of iodobenzene (1.1 mL, 9.8 mmol) in CH_2Cl_2 (9 mL) and 2,2,2-trifluoroethanol (9 mL), *m*-CPBA (2.2 g, 9.8 mmol) and *p*-TsOH•H_2O (1.9 g, 9.8 mmol) were successively added. The resulting solution was stirred at room temperature for 40 minutes and concentrated under a stream of air. Then, Et_2O (15 mL) was added to the remaining residue and the precipitate was filtered off and dried under vacuum to give the desired product as a colourless solid (90% yield, 3.47 g, 8.8 mmol).

The spectroscopic data are in agreement with literature.[3] **m.p.** = 126 - 128 °C (lit.[3] 132 - 135 °C); **^{1}H NMR (400 MHz, CD_3OD)**: δ = 8.38 (d, *J* = 7.7 Hz, 2H, H-Ar), 7.86 (t, *J* = 7.5 Hz, 1H, H-Ar), 7.74 – 7.69 (m, 4H, H-Ar), 7.25 (d, *J* = 8.0 Hz, 2H, H-Ar), 2.39 (s, 3H, CH_3) ppm.

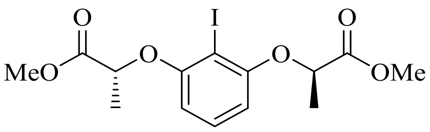
2-Iodoresorcinol



Resorcinol (5.0 g, 45.4 mmol) and iodine (12.3 g, 48.4 mmol) were dissolved in H_2O (32 mL) and cooled down to 0 °C. Sodium bicarbonate (4.23 g, 50.3 mmol) was added slowly with vigorous stirring. After 30 minutes, the brown slurry mixture was extracted with EtOAc (3 x 40 mL). The combined organic layers were washed with sat. aq. sodium thiosulfate solution (100 mL) and brine (100 mL), dried over $MgSO_4$ and concentrated under vacuum. The resulting solid was triturated with cold $CHCl_3$ (20 mL, -10 °C) and left to crystallise at -10 °C. The pale brown crystals were filtered, washed with cold $CHCl_3$ and dried under vacuum (53% yield, 5.63 g, 23.8 mmol).

The spectroscopic data are in agreement with literature.[4] **m.p.** = 106 - 107 °C (lit.[5] 105 - 108 °C); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 7.18 (t, *J* = 8.1 Hz, 1H, H-Ar), 6.62 (d, *J* = 8.1 Hz, 2H, H-Ar), 5.27 (s, 2H, OH) ppm.

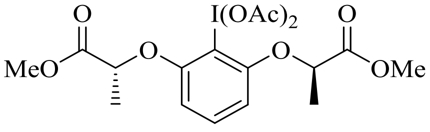
Dimethyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))(2*R*,2'*R*)-dipropionate 354



2-iodoresorcinol (4.79 g, 20.3 mmol), triphenylphosphine (13.3 g, 50.8 mmol) and methyl (*S*)-(-)-lactate (4.85 mL, 50.8 mmol) were dissolved in dry THF (100 mL) under N_2 and wrapped in aluminium foil. The reaction was cooled at 0 °C and DIAD (10.0 mL, 50.8 mmol) was added dropwise. After 1 h at 0 °C, the mixture was warmed up to room temperature and stirred overnight. The solvent was removed under vacuum and Et_2O (100 mL) was added. The triphenylphosphine oxide, which precipitated, was removed by filtration and the filtrate was evaporated under vacuum. The product was obtained after column chromatography (0 to 20% EtOAc in hexane) as a white solid (84% yield, 6.96 g, 17.1 mmol).

The spectroscopic data are in agreement with literature.[6] **m.p.** = 75 - 76 °C; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 7.14 (t, *J* = 8.3 Hz, 1H, H-Ar), 6.37 (d, *J* = 8.3 Hz, 2H, H-Ar), 4.76 (q, *J* = 6.8 Hz, 2H, 2 C**H**CH_3), 3.75 (s, 6H, 2 OCH_3), 1.70 (d, *J* = 6.8 Hz, 6H, 2 CHC**H**$_3$) ppm; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -20.0 (c = 1.0, $CHCl_3$) (lit.[7] $[\alpha]_D^{20}$ = -21.0 (c = 1.2, $CHCl_3$)).

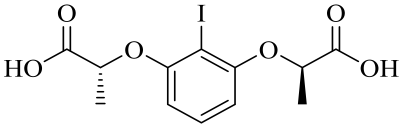
Dimethyl-2,2'-((2-(diacetoxy-λ^3-iodanyl)-1,3-phenylene)bis(oxy))(2*R*,2'*R*)-dipropionate 6a



Dimethyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))(2*R*,2'*R*)-dipropionate **354** (408 mg, 1.00 mmol) and Selectfluor® (1.77 g, 5.00 mmol) were dissolved in CH_3CN (32 mL) and glacial acetic acid (10 mL) under N_2. After 5 h, the solvents were removed under vacuum and the resulting oil was diluted with CH_2Cl_2 (50 mL) and H_2O (50 mL). The aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The resulting yellow oil was used without further purification. (94% yield, 505 mg, 0.963 mmol).

The spectroscopic data are in agreement with literature.[6] **^{1}H NMR (400 MHz, CDCl$_3$)**: δ = 7.40 (t, *J* = 8.4 Hz, 1H, H-Ar), 6.57 (d, *J* = 8.4 Hz, 2H, H-Ar), 4.87 (q, *J* = 6.8 Hz, 2H, 2 C**H**CH$_3$), 3.76 (s, 6H, 2 OCH$_3$), 1.98 (s, 6H, 2 OC(O)CH$_3$), 1.68 (d, *J* = 6.8 Hz, 6H, 2 CHC**H$_3$**).

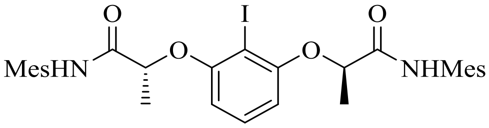
(2*R*,2'*R*)-2,2'-((2-Iodo-1,3-phenylene)bis(oxy))dipropionic acid 355



Dimethyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))(2*R*,2'*R*)-dipropionate **354** (4.0 g, 9.8 mmol) was dissolved in a mixture of THF (50 mL) and MeOH (50 mL). After cooling at 0 °C, 2 N NaOH (50 mL) was added slowly and the resulting solution was stirred at room temperature overnight. The reaction was quenched with 1 N HCl (120 mL) at 0 °C, extracted with EtOAc (3 x 100 mL), dried over MgSO$_4$ and concentrated under vacuum. The resulting white solid was used without further purification (99% yield, 3.7 g, 9.7 mmol).

The spectroscopic data are in agreement with literature.[6] **^{1}H NMR (400 MHz, DMSO-d$_6$)**: δ = 7.21 (t, *J* = 8.3 Hz, 1H, H-Ar), 6.42 (d, *J* = 8.4 Hz, 2H, H-Ar), 4.85 (q, *J* = 6.7 Hz, 2H, 2 C**H**CH$_3$), 1.54 (d, *J* = 6.8 Hz, 6H, 2 CHC**H$_3$**) ppm.

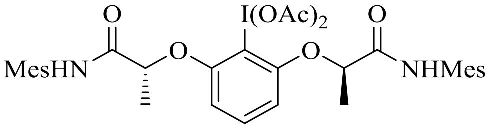
(2*R*,2'*R*)-2,2'-((2-Iodo-1,3-phenylene)bis(oxy))bis(*N*-mesitylpropanamide) 25



(2*R*,2'*R*)-2,2'-((2-iodo-1,3-phenylene)bis(oxy))dipropionic acid **355** (3.57 g, 9.39 mmol) and SOCl$_2$ (10.2 mL, 141 mmol) were refluxed for 1.5 h. The solvent was co-evaporated with benzene (3 x 5 mL) and the resulting brown oil was placed under N$_2$ atmosphere and then dissolved in dry CH$_2$Cl$_2$ (50 mL). The reaction was cooled at 0 °C, 2,4,6-trimethylaniline (3.96 mL, 28.2 mmol) was added dropwise and the reaction was stirred at room temperature overnight. The solution was cooled to 0 °C, quenched with 1 N HCl (20 mL), extracted with CH$_2$Cl$_2$ (3 x 50 mL), dried over MgSO$_4$ and concentrated under vacuum. The pure product **25** was obtained after column chromatography (0 to 10% EtOAc in $CHCl_3$) as a pale yellow solid (81% yield, 4.67 g, 7.61 mmol).

The spectroscopic data are in agreement with literature.[6] **m.p.** = 230 - 232 °C; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 8.01 (s, 2H, 2 NH), 7.35 (t, *J* = 8.3 Hz, 1H, H-Ar), 6.91 (s, 4H, H-Ar), 6.64 (d, *J* = 8.4 Hz, 2H, H-Ar), 5.01 (q, *J* = 6.7 Hz, 2H, 2 C**H**CH_3), 2.27 (s, 6H, 2 CH_3), 2.15 (s, 12H, 4 CH_3), 1.78 (d, *J* = 6.7 Hz, 6H, 2 CHC**H_3**) ppm; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -121.0 (c = 1.01, $CHCl_3$).

(2,6-bis(((*R*)-1-(mesitylamino)-1-oxopropan-2-yl)oxy)phenyl)-λ^3-iodanediyl diacetate 6b



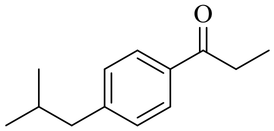
(2*R*,2'*R*)-2,2'-((2-Iodo-1,3-phenylene)bis(oxy))bis(*N*-mesitylpropanamide) **25** (618 mg, 1.00 mmol) and Selectfluor® (1.77 g, 5.00 mmol) were dissolved in CH_3CN (32 mL) and glacial acetic acid (10 mL) under N_2. After 5 h, the solvents were removed under vacuum and the resulting solid was diluted with CH_2Cl_2 (50 mL) and H_2O (50 mL). The aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The resulting yellow solid was used without further purification. (90% yield, 657 mg, 0.897 mmol).

The spectroscopic data are in agreement with literature.[6] **m.p.** = 117 - 120 °C (lit.[8] 118 - 120 °C); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 8.35 (s, 2H, 2 N**H**), 7.57 (t, *J* = 8.4 Hz, 1H, H-Ar), 6.93 (d, *J* = 8.5 Hz, 2H, H-Ar), 6.79 (s, 4 H, H-Ar), 5.15 (q, *J* = 6.7 Hz, 2H, 2 C**H**CH_3), 2.21 (s, 6H, 2 CH_3), 2.10 (bs, 12H, 4 CH_3), 1.88 (d, *J* = 6.7 Hz, 6H, 2 CHC**H_3**), 1.49 (s, 6H, 2 OC(O)C**H_3**) ppm; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -80.0 (c = 1.0, $CHCl_3$).

7.4.2. Rearrangement of propiophenone derivatives

7.4.2.1. Synthesis of substrates

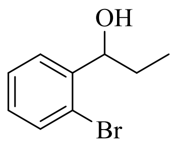
1-(4-Isobutylphenyl)propan-1-one 29b



The product **29b** was synthesised using a known procedure.[9] To a suspension of $AlCl_3$ (1.29 g, 9.68 mmol) in dry CH_2Cl_2 under N_2, propionyl chloride (910 µL, 10.4 mmol) was slowly added at 0 °C. After stirring for 20 minutes, *iso*-butylbenzene (1.17 mL, 7.45 mmol) was added dropwise and the resulting solution was stirred at room temperature for 2 h. The mixture was poured into a solution of crunched ice and concentrated HCl (2.5 mL) and left to warm up to room temperature. The reaction mixture was extracted with CH_2Cl_2 (2 x 30 mL), washed with sat. aq. $NaHCO_3$ solution (20 mL), water (30 mL), dried over $MgSO_4$ and concentrated under vacuum. The pure product was obtained after purification by column chromatography (0 to 10% EtOAc in hexane) as a colourless oil (74% yield, 1.05 g, 5.52 mmol).

The spectroscopic data are in agreement with literature.[9] Colourless oil; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 7.89 – 7.87 (m, 2H, H-Ar), 7.23 – 7.21 (m, 2H, H-Ar), 2.99 (q, J = 7.3 Hz, 2H, $C\mathbf{H_2}CH_3$), 2.52 (d, J = 7.2 Hz, 2H, $C\mathbf{H_2}CH(CH_3)_2$), 1.93 – 1.84 (m, 1H, $CH_2C\mathbf{H}(CH_3)_2$), 1.22 (t, J = 7.3 Hz, 3H, $CH_2C\mathbf{H_3}$), 0.90 (d, J = 6.6 Hz, 6H, $CH_2CH(C\mathbf{H_3})_2$) ppm; **^{13}C NMR (125 MHz, $CDCl_3$)**: δ = 200.7 (C=O), 147.4 (C_{Ar}), 134.9 (C_{Ar}), 129.4 (2 $C_{Ar}H$), 128.1 (2 $C_{Ar}H$), 45.5 ($\mathbf{C}H_2CH(CH_3)_2$), 31.8 ($\mathbf{C}H_2CH_3$), 30.2 ($CH_2\mathbf{C}H(CH_3)_2$), 22.5 ($CH_2CH(\mathbf{C}H_3)_2$), 8.5 ($CH_2\mathbf{C}H_3$) ppm; **IR (neat)**: 2955, 1682, 1607, 1460, 1225, 1180, 951, 783 cm^{-1}; **HRMS (NSI)**: $[M+H]^+$ calc. 191.1430, found 191.1426 $[C_{13}H_{19}O]^+$.

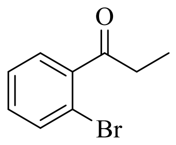
1-(2-Bromophenyl)propan-1-ol 183



The product **183** was synthesised using a known procedure.[10] To a solution of 2-bromobenzaldehyde **182** (234 µL, 2.00 mmol) in dry Et_2O (10 mL) at -10 °C, a solution of ethyl magnesium bromide in Et_2O (3.34 mL, 3 M, 10.0 mmol) was added. The resulting solution was stirred at -10 °C for 3 h, then quenched with sat. aq. NH_4Cl solution (20 mL) and the organic phase was extracted with EtOAc (3 x 30 mL), dried over $MgSO_4$ and concentrated under vacuum. 1-(2-Bromophenyl)propan-1-ol **183** was obtained as a colourless oil and used without further purification (77% yield, 332 mg, 1.54 mmol).

The spectroscopic data are in agreement with literature.[11] **^{1}H NMR (300 MHz, $CDCl_3$)**: δ = 7.56 – 7.50 (m, 2H, H-Ar), 7.33 (td, *J* = 7.6, 0.9 Hz, 1H, H-Ar), 7.12 (td, *J* = 7.7, 1.7 Hz, 1H, H-Ar), 5.03 – 5.00 (m, 1H, C**H**OH), 2.01 (bs, 1H, OH), 1.88 – 1.66 (m, 2H, $CHC\mathbf{H_2}CH_3$), 1.01 (t, *J* = 7.4 Hz, 3H, $CHCH_2C\mathbf{H_3}$) ppm.

1-(2-Bromophenyl)propan-1-one 29h

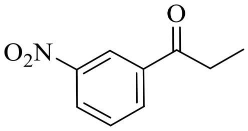


The product **29h** was synthesised using a known procedure.[10] To a suspension of pyridinium chlorochromate (PCC; 500 mg, 2.32 mmol) and silica gel (500 mg) in dry CH_2Cl_2 (2 mL), a solution of 1-(2-bromophenyl)propan-1-ol **183** (332 mg, 1.54 mmol) in dry CH_2Cl_2 (3 mL) was added dropwise. After 3 h at room temperature, the reaction mixture was filtered through a silica plug, washing the silica with CH_2Cl_2 (200 mL). The solvent was removed under vacuum and the desired product was obtained as a pale yellow oil which was used without further purification (96% yield, 316 mg, 1.48 mmol).

The ^{1}H NMR spectrum is in agreement with literature.[12] **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 7.61 – 7.59 (m, 1H, H-Ar), 7.37 – 7.35 (m, 2H, H-Ar), 7.30 – 7.27 (m, 1H, H-Ar), 2.93 (q, *J* = 7.3 Hz, 2H, CH_2), 1.21 (t, *J* = 7.2 Hz, 3H, CH_3) ppm; **^{13}C NMR (125 MHz,**

$CDCl_3$): δ = 205.1 (C=O), 142.2 (C_{Ar}), 133.7 (C_{Ar}H), 131.4 (C_{Ar}H), 128.3 (C_{Ar}H), 127.5 (C_{Ar}H), 118.7 (C_{Ar}), 36.2 (CH_2), 8.2 (CH_3) ppm; **IR (neat)**: 2978, 1699, 1587, 1427, 1213, 748 cm^{-1}; **HRMS (NSI)**: $[M+H]^+$ calc. 212.9910, found 212.9912 $[C_9H_{10}OBr]^+$.

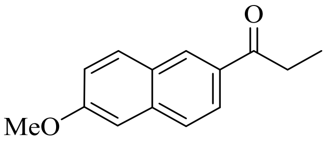
1-(3-Nitrophenyl)propan-1-one 29i



The product **29i** was synthesised using a known procedure.[13] Fuming nitric acid (9.7 mL) was added at -45 °C to propiophenone (1.00 mL, 7.45 mmol) and the resulting solution was stirred for 1 h at -45 °C. Crunched ice was added and the resulting green mixture was left to warm up to room temperature. The organic phase was extracted with Et_2O (2 x 30 mL), washed with water (20 mL), aq. 2 N NaOH solution (30 mL), brine, dried over $MgSO_4$ and concentrated under vacuum. EtOH (4 mL) was added to the crude solid and the solution was kept at -15 °C for 1 h. The pure product was obtained, after filtration, as pale yellow crystals (52% yield, 700 mg, 3.91 mmol).

m.p. = 95 - 97 °C; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 8.77 (t, *J* = 1.9 Hz, 1H, H-Ar), 8.41 (ddd, *J* = 8.2, 2.2, 1.0 Hz, 1H, H-Ar), 8.32 – 8.27 (m, 1H, H-Ar), 7.68 (t, *J* = 8.0 Hz, 1H, H-Ar), 3.07 (q, *J* = 7.2 Hz, 2H, CH_2), 1.26 (t, *J* = 7.2 Hz, 3H, CH_3) ppm; **^{13}C NMR (125 MHz, $CDCl_3$)**: δ = 198.5 (C=O), 148.7 (C_{Ar}), 138.3 (C_{Ar}), 133.6 (C_{Ar}H), 130.0 (C_{Ar}H), 127.3 (C_{Ar}H), 123.0 (C_{Ar}H), 32.3 (CH_2), 8.1 (CH_3) ppm; **IR (neat)**: 2988, 1687, 1526, 1346, 1213, 1096, 732, 675 cm^{-1}; **HRMS (NSI)**: $[M+H]^+$ calc. 180.0655, found 180.0655 $[C_9H_{10}O_3N]^+$.

1-(6-Methoxynaphthalen-2-yl)propan-1-one 29j



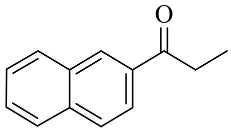
To a solution of propionyl chloride (1.20 mL, 13.6 mmol) and $AlCl_3$ (1.88 g, 14.0 mmol) in dry CH_2Cl_2 (4 mL), a solution of 2-methoxynaphthalene (2.37 g, 15.0 mmol) in dry CH_2Cl_2 (6 mL) was added *via* syringe pump (6 mL/h) at room temperature. The resulting mixture was stirred for 20 h, then quenched with crunched ice. The organic phase was extracted with CH_2Cl_2 (3 x 25 mL), dried over $MgSO_4$ and concentrated under vacuum. After column chromatography (0 to 10% EtOAc in hexane), the desired product was obtained as a white solid (79% yield, 2.55 g, 11.9 mmol).

The spectroscopic data are in agreement with literature.[9] **m.p.** = 105 - 107 °C (lit.[9] 109 °C); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 8.40 (s, 1H, H-Ar), 8.01 (dd, *J* = 8.6, 1.7 Hz, 1H, H-Ar), 7.84 (d, *J* = 9.0 Hz, 1H, H-Ar), 7.76 (d, *J* = 8.7 Hz, 1H, H-Ar), 7.20 (dd, *J* = 8.9, 2.5 Hz, 1H, H-Ar), 7.14 (d, *J* = 2.4 Hz, 1H, H-Ar), 3.94 (s, 3H, OCH_3), 3.11 (q, *J* = 7.3 Hz, 2H, CH_2), 1.27 (t, *J* = 7.3 Hz, 3H, CH_3) ppm; **^{13}C NMR (125 MHz, $CDCl_3$)**: δ = 200.6 (C=O), 159.8 (C_{Ar} – OMe), 137.3 (C_{Ar}), 132.5 (C_{Ar}), 131.2 (C_{Ar}H), 129.5 (C_{Ar}H), 128.0 (C_{Ar}), 127.2 (C_{Ar}H), 124.8 (C_{Ar}H), 119.8 (C_{Ar}H), 105.9 (C_{Ar}H), 55.5 (OCH_3), 31.8 (CH), 8.6 (CH_3) ppm; **IR (neat)**: 1678, 1620, 1481, 1350, 1265, 1022, 821 cm^{-1}; **HRMS (ESI)**: $[M+H]^+$ calc. 215.1067, found 215.1065 $[C_{14}H_{15}O]^+$.

Synthesis of 1-Propionylnaphthalene and 2-Propionylnaphthalene

To a solution of propionyl chloride (2.46 mL, 28.1 mmol) and $AlCl_3$ (3.85 g, 28.9 mmol) in dry CH_2Cl_2 (8 mL), a solution of naphthalene (3.95 g, 30.8 mmol) in dry CH_2Cl_2 (8 mL) was added *via* syringe pump (0.2 mL/min) at 35 °C. The resulting mixture was stirred for an additional hour. The reaction was quenched at 0 °C with 3 N HCl (30 mL). The organic phase was extracted with CH_2Cl_2 (3 x 50 mL), dried over $MgSO_4$ and concentrated under vacuum. Crude ^{1}H NMR showed full conversion into the two products with a ratio of 91:9 (1-naphthyl: 2-naphthyl). After column chromatography (100% hexane), the two propionylnaphthalenes could not be fully separated but some pure fractions were isolated.

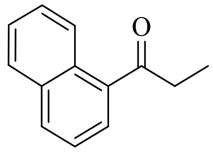
2-Propionylnaphthalene 171



The spectroscopic data are in agreement with literature.[14] White solid; **m.p**. = 62 - 64 °C (Lit.[15] 64 - 65 °C); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 8.48 (s, 1H, H-Ar), 8.05 (dd, *J* = 8.2, 1.7 Hz, 1H, H-Ar), 7.97 (d, *J* = 8.0 Hz, 1H, H-Ar), 7.89 (t, *J* = 8.4 Hz, 2H, H-Ar), 7.62-7.53 (m, 2H, H-Ar), 3.15 (q, *J* = 7.2 Hz, 2H, CH_2), 1.29 (t, *J* = 7.2 Hz, 3H, CH_3)

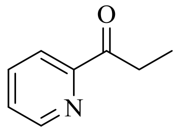
ppm; **^{13}C NMR (125 MHz, $CDCl_3$)**: δ = 200.9 (C=O), 135.7 (C_{Ar}), 134.5 (C_{Ar}), 132.8 (C_{Ar}H), 129.7 (C_{Ar}H), 129.6 (C_{Ar}H), 128.5 (C_{Ar}H), 128.4 (C_{Ar}H), 127.9 (C_{Ar}H), 126.9 (C_{Ar}H), 124.1 (C_{Ar}H), 32.0 (CH_2), 8.6 (CH_3) ppm; **IR (neat)**: 2974, 1678, 1373, 1276, 1188, 1126, 798 cm^{-1}; **HRMS (ESI)**: $[M+H]^+$ calc. 185.0961, found 185.0961 $[C_{13}H_{13}O]^+$.

1-Propionylnaphthalene 172



The spectroscopic data are in agreement with literature.[16] Pale yellow oil; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 8.56 (d, *J* = 8.5 Hz, 1H, H-Ar), 7.98 (d, *J* = 8.2 Hz, 1H, H-Ar), 7.87 – 7.84 (m, 2H, H-Ar), 7.61 – 7.48 (m, 3H, H-Ar), 3.09 (q, *J* = 7.3 Hz, 2H, CH_2), 1.29 (t, *J* = 7.3 Hz, 3H, CH_3) ppm; **^{13}C NMR (125 MHz, $CDCl_3$)**: δ = 205.4 (C=O), 136.5 (C_{Ar}), 134.1 (C_{Ar}), 132.4 (C_{Ar}H), 130.3 (C_{Ar}), 128.5 (C_{Ar}H), 127.9 (C_{Ar}H), 127.2 (C_{Ar}H), 126.5 (C_{Ar}H), 126.0 (C_{Ar}H), 124.5 (C_{Ar}H), 35.6 (CH_2), 8.8 (CH_3) ppm; **IR (neat)**: 2974, 2934, 1678, 1508, 1230, 1176, 1111, 794 cm^{-1}; **HRMS (ESI)**: $[M+H]^+$ calc. 185.0961, found 185.0958 $[C_{13}H_{13}O]^+$.

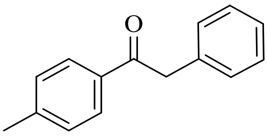
1-(Pyridin-2-yl)propan-1-one 189



The product **189** was synthesised using a known procedure.[17] To a solution of 2-cyanopyridine (0.92 mL, 9.6 mmol) in dry Et_2O (15 mL) at -20 °C, a solution of ethyl magnesium bromide (3.84 mL, 3 M, 11.5 mmol) was slowly added. After the addition, the reaction mixture was stirred at that temperature for 1 h and then gradually warmed up to room temperature over 3 h. The reaction was quenched with 2 N HCl (5 mL) and stirred for additional 15 minutes. The two layers were separated, the aqueous phase was neutralised to pH = 8 using 2 N NaOH. The organic phase was extracted with CH_2Cl_2 (3 x 10 mL), washed with water, brine, dried over $MgSO_4$ and concentrated under vacuum. The pure product was obtained after distillation (0.1 mbar, 80 °C) as a colourless oil (97% yield, 1.25 g, 9.26 mmol).

The spectroscopic data are in agreement with literature.[17] **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 8.69 – 8.63 (m, 1H, H-Ar), 8.03 (d, J = 7.9 Hz, 1H, H-Ar), 7.82 (t, J = 7.7 Hz, 1H, H-Ar), 7.48 – 7.41 (m, 1H, H-Ar), 3.23 (q, J = 7.3 Hz, 2H, CH_2), 1.21 (t, J = 7.3 Hz, 3H, CH_3) ppm; **^{13}C NMR (125 MHz, $CDCl_3$)**: δ = 202.7 (C=O), 153.6 (C_{Ar}), 149.0 (C_{Ar}H), 136.9 (C_{Ar}H), 127.1 (C_{Ar}H), 121.8 (C_{Ar}H), 31.2 (CH_2), 8.1 (CH_3) ppm; **IR (neat)**: 2976, 1697, 1584, 4356, 1223, 995, 760 cm^{-1}; **HRMS (EI)**: $[M]^+$ calc. 135.0684, found 135.0681 $[C_8H_9NO]^+$.

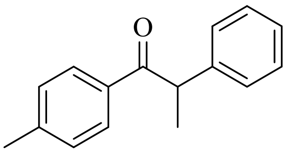
2-Phenyl-1-(p-tolyl)ethan-1-one 212



To a solution of phenyl acetyl chloride (0.86 mL, 6.5 mmol) and $AlCl_3$ (0.86 g, 6.5 mmol) in dry CH_2Cl_2 (10 mL), toluene (0.76 mL, 7.1 mmol) was added dropwise at 0 °C. The resulting mixture was stirred at room temperature for 16 h. The reaction was quenched with crunched ice and the organic phase was extracted with CH_2Cl_2 (3 x 25 mL), dried over $MgSO_4$ and concentrated under vacuum. After column chromatography (0 to 10% EtOAc in hexane), the pure product **212** was obtained as white crystals (75% yield, 1.02 g, 4.78 mmol).

The spectroscopic data are in agreement with literature.[18] **m.p.** = 102 - 105 °C (lit.[18] 104 - 105 °C); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 7.92 (d, J = 8.2 Hz, 2H, H-Ar), 7.34 – 7.30 (m, 2H, H-Ar), 7.27 – 7.24 (m, 5H, H-Ar), 4.26 (s, 2H, CH_2), 2.40 (s, 3H, CH_3) ppm; **^{13}C NMR (125 MHz, $CDCl_3$)**: δ = 197.4 (C=O), 144.1 (C_{Ar}), 135.0 (C_{Ar}), 134.4 (C_{Ar}), 129.6 (2 C_{Ar}H), 129.5 (2 C_{Ar}H), 128.9 (2 C_{Ar}H), 128.8 (2 C_{Ar}H), 127.0 (C_{Ar}H), 45.6 (CH_2), 21.8 (CH_3) ppm; **IR (neat)**: 2982, 2904, 1678, 1604, 1334, 1168 cm^{-1}; **HRMS (NSI)**: $[M+H]^+$ calc. 211.1117, found 211.1114 $[C_{15}H_{15}O]^+$.

2-Phenyl-1-(*p*-tolyl)propan-1-one 220



To a suspension of NaH (18 mg, 0.77 mmol) in dry THF (30 mL) at 0 °C, a solution of 2-phenyl-1-(*p*-tolyl)ethan-1-one **212** (154 mg, 0.734 mmol) in dry THF (30 mL) was added over 30 minutes using a dropping funnel. The reaction was warmed up to room temperature, iodomethane (100 µL, 1.60 mmol) was added and the resulting mixture was stirred for 2 h. After quenching the reaction with water (50 mL), the organic phase was extracted with Et_2O (3 x 50 mL), dried over $MgSO_4$ and concentrated under vacuum. After purification by column chromatography (0 to 10% EtOAc in hexane) the pure product **220** was obtained as a colourless oil (80% yield, 132 mg, 0.587 mmol).

The spectroscopic data are in agreement with literature.[19] **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 7.47 – 7.44 (m, 2H, H-Ar), 7.37 – 7.33 (m, 2H, H-Ar), 7.30 – 7.28 (m, 1H, H-Ar), 3.16 (s, 6H, 2 OCH_3), 1.91 (q, J = 7.5 Hz, 2H, CH_2), 0.59 (t, J = 7.5 Hz, 3H, CH_3) ppm; **^{13}C NMR (125 MHz, $CDCl_3$)**: δ = 200.1 (C=O), 143.6 (C_{Ar}), 141.9 (C_{Ar}), 134.2 (C_{Ar}), 129.3 (2 C_{Ar}H), 129.1 (2 C_{Ar}H), 129.0 (2 C_{Ar}H), 127.9 (2 C_{Ar}H), 126.9 (C_{Ar}H), 47.9 (CH), 21.7 (CH_3), 19.6 (CH_3) ppm; **HRMS (APCI)**: $[M+H]^+$ calc. 225.1274, found 225.1269 $[C_{16}H_{17}O]^+$.

7.4.2.2. Rearrangement reaction

General procedure GP1 for the racemic synthesis of compounds 163

To a solution of propiophenone derivative **29** (0.609 mmol) and $PhI(OAc)_2$ (235 mg, 0.731 mmol) in $HC(OMe)_3$ (1.5 mL), TfOH (220 µL, 1.22 mmol) was added dropwise. The resulting mixture was stirred at room temperature for 5 h, quenched with water (1 mL), extracted with Et_2O (3 x 2 mL), dried over a Telos® phase separator and the solvent was removed under reduced pressure. After column chromatography (0 to 10% EtOAc in hexane), the corresponding pure product **163** was obtained.

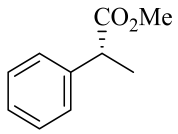
General procedure GP2 for the asymmetric synthesis of compounds 163 using Ishihara ester reagent

To a solution of propiophenone derivative **29** (0.609 mmol) and Ishihara ester **6a** (385 mg, 0.731 mmol) in $HC(OMe)_3$ (1.5 mL), TMSOTf or TfOH (1.22 mmol) was added dropwise at the desired temperature. The resulting mixture was stirred at the temperature and for the time mentioned in Chapter 3, quenched with water (1 mL), extracted with Et_2O (3 x 2 mL), dried over a Telos® phase separator and the solvent was removed under reduced pressure. After column chromatography (0 to 10% Et_2O in hexane), the corresponding pure product **163** was obtained.

General procedure GP3 for the asymmetric synthesis of compounds 163 using Ishihara amide reagent.

To a solution of propiophenone derivative **29** (0.305 mmol) and Ishihara amide (267 mg, 0.365 mmol) in $HC(OMe)_3$ (1.5 mL), TfOH (0.609 mmol) was added dropwise at the temperature mentioned in Chapter 3. The resulting mixture was stirred at that temperature for 24-48 h, quenched with water (1 mL), extracted with CH_2Cl_2 (3 x 2 mL), dried over a Telos® phase separator and the solvent was removed under reduced pressure. After column chromatography (0 to 10% Et_2O in hexane), the corresponding pure product **163** was obtained.

Methyl (*R*)-2-phenylpropionate 163a



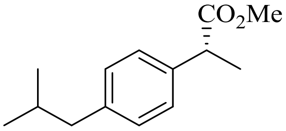
Racemate: The product **163a** was synthesised using general procedure **GP1** at r.t. for 5 h (0.609 mmol scale) (62% yield, 62 mg, 0.378 mmol).

Asymmetric: The product **163a** was synthesised using general procedure **GP3** at -20 °C for 24 h (0.186 mmol scale) (49% yield, 15 mg, 0.091 mmol).

The spectroscopic data are in agreement with literature.[20] Colourless oil; **^{1}H NMR (300 MHz, $CDCl_3$)**: δ = 7.33 – 7.29 (m, 5H, H-Ar), 3.77 – 3.66 (overlapped q and s, J_q = 7.2 Hz, 1H+3H, CH and OCH_3), 1.51 (d, J = 7.2 Hz, 3H, CH_3). **^{13}C NMR (125 MHz,**

$CDCl_3$): δ = 175.2 (C=O), 140.7 (C_{Ar}), 128.8 (2 $C_{Ar}H$), 127.6 (2 $C_{Ar}H$), 127.3 ($C_{Ar}H$), 52.2 (OCH_3), 45.5 (CH), 18.7 (CH_3) ppm; **HRMS (EI)**: $[M]^+$ calc. 164.0837, found 164.0837 $[C_{10}H_{12}O_2]^+$; **IR (neat)**: 2921, 1732, 1454, 1435, 1207, 1165, 698 cm^{-1}; ***ee***: 53%, determined by HPLC analysis: Daicel Chiralcel *OJ* column (25 cm), hexane/*i*-PrOH: 99/1, 0.7 mL/min, 20 °C, 226 nm, T_r (minor, (*S*)-isomer) = 23.7 min, T_r (major, (*R*)-isomer) = 32.2 min; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -53.8 (c = 0.53, $CHCl_3$) (lit.[21] for the (*R*)-isomer $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -71.3 (c = 1.03, EtOH)).

Methyl (*R*)-2-(4-isobutylphenyl)propionate 163b



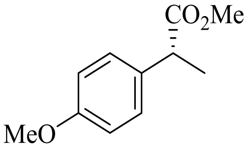
Racemate: The product **163b** was synthesised using general procedure **GP1** at r.t. for 24 h (0.394 mmol scale) (94% yield, 82 mg, 0.371 mmol).

Asymmetric: The product **163b** was synthesised using general procedure **GP3** at r.t. for 48 h (0.247 mmol scale) (72% yield, 39 mg, 0.177 mmol).

The spectroscopic data are in agreement with literature.[22] Colourless oil; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 7.21 – 7.19 (m, 2H, H-Ar), 7.10 – 7.08 (m, 2H, H-Ar), 3.70 (q, *J* = 7.2 Hz, 1H, C**H**CH_3), 3.66 (s, 3H, OCH_3), 2.44 (d, *J* = 7.2 Hz, 2H, C$\mathbf{H_2}$$CH(CH_3)_2$), 1.89 – 1.79 (m, 1H, CH_2C**H**$(CH_3)_2$), 1.49 (d, *J* = 7.2 Hz, 3H, CHC$\mathbf{H_3}$), 0.90 (d, *J* = 6.6 Hz, 6H, CH_2CH(C$\mathbf{H_3}$)$_2$) ppm; **^{13}C NMR (125 MHz, $CDCl_3$)**: δ = 175.4 (C=O), 140.7 (C_{Ar}), 137.9 (C_{Ar}), 129.5 (2 $C_{Ar}H$), 127.3 (2 $C_{Ar}H$), 52.1 (OCH_3), 45.2 (**C**$H_2CH(CH_3)_2$), 45.2 (**C**HCH_3), 30.3 (CH_2**C**$H(CH_3)_2$), 22.5 (CH_2CH(**C**H_3)$_2$), 18.8 (CH**C**H_3) ppm; **IR (neat)**: 2953, 1736, 1513, 1433, 1204, 1161 cm^{-1}; **HRMS (NSI)**: $[M+H]^+$ calc. 221.1536, found 221.1535 $[C_{14}H_{21}O_2]^+$; **MS (EI)**: m/z 238 (55%), 221 ($[M+H]^+$, 74%), 161 (100%); ***ee***: 35%, determined by HPLC analysis: Daicel Chiralcel *OJ* column (25 cm), hexane/*i*-PrOH: 99/1, 1.0 mL/min, 20 °C, 226 nm, T_r (minor, (*S*)-isomer) = 8.0 min, T_r (major, (*R*)-isomer) = 9.2 min; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -18.9 (c = 0.74, $CHCl_3$) (lit.[23] for the (*S*)-isomer $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = +55.7 (c = 1.0, $CHCl_3$)).

The absolute configuration was established by comparison with the literature optical rotation. In 1987, Piccolo *et al.* synthesised methyl (*S*)-2-(4-isobutylphenyl)propionate from (*R*)-2-chloropropionic acid which was itself prepared from (*S*)-lactic acid. The optical rotation measured for methyl (*S*)-2-(4-isobutylphenyl)propionate was +55.7 (c = 1, $CHCl_3$).[23]

Methyl (*R*)-2-(4-methoxyphenyl)propionate 163c



a) **Racemic synthesis using H_2SO_4:** To a solution of 4-methoxy-propiophenone (100 mg, 0.609 mmol) and $PhI(OAc)_2$ (235 mg, 0.731 mmol) in $HC(OMe)_3$ (1.5 mL), H_2SO_4 (68 µL, 1.22 mmol) was added dropwise. The resulting mixture was stirred at room temperature for 1 h, quenched with water (1 mL), extracted with Et_2O (3 x 2 mL), dried over a Telos® phase separator and the solvent was removed under reduced pressure. After column chromatography (0 to 10% EtOAc in hexane), the pure product **163c** was obtained as a yellow oil (82% yield, 97 mg, 0.499 mmol).

b) **Asymmetric synthesis using H_2SO_4:** To a solution of 4-methoxy-propiophenone (84 mg, 0.510 mmol) and Ishihara ester **6a** (250 mg, 0.602 mmol) in $HC(OMe)_3$ (1.5 mL), H_2SO_4 (57 µL, 1.02 mmol) was added dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 4 h, quenched with water (1 mL), extracted with Et_2O (3 x 2 mL), dried over a Telos® phase separator and the solvent was removed under reduced pressure. After column chromatography (0 to 10% EtOAc in hexane), the pure product **163c** was obtained as a yellow oil (45% yield, 45 mg, 0.232 mmol, 14% *ee* of (*R*)-isomer).

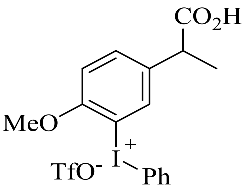
c) **Racemic synthesis using TMSOTf:** To a solution of 4-methoxy-propiophenone (100 mg, 0.609 mmol) and $PhI(OAc)_2$ (235 mg, 0.731 mmol) in $HC(OMe)_3$ (1.5 mL), TMSOTf (220 µL, 1.22 mmol) was added dropwise. The resulting mixture was stirred at room temperature for 4 h, quenched with water (1 mL), extracted with Et_2O (3 x 2 mL), dried over a Telos® phase separator and the solvent was removed under reduced pressure. After column chromatography (0 to 10% EtOAc in hexane), the pure product **163c** was obtained as a yellow oil (82% yield, 97 mg, 0.499 mmol). The aqueous phase was kept and left to crystallise for two days showing the formation of diaryliodonium salt **168** as pale yellow crystals (11% yield, 34 mg, 0.066 mmol).

d) **Asymmetric synthesis using TMSOTf:** To a solution of 4-methoxy-propiophenone (100 mg, 0.609 mmol) and Ishihara ester **6a** (250 mg, 0.609 mmol) in $HC(OMe)_3$ (1.5 mL), TMSOTf (220 µL, 1.22 mmol) was added dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 4 h, quenched with water (1 mL), extracted with Et_2O (3 x 2 mL), dried over a Telos® phase separator and the solvent was removed under reduced pressure. After column chromatography (0 to 10% EtOAc in hexane), the pure product **163c** was obtained as a yellow oil (20% yield, 24 mg, 0.124 mmol, 7% *ee* of (*R*)-isomer).

e) **Asymmetric synthesis using TfOH:** To a solution of 4-methoxy-propiophenone (34 mg, 0.205 mmol) and Ishihara amide **6b** (150 mg, 0.205 mmol) in $HC(OMe)_3$ (1.0 mL), TfOH (36 µL, 0.41 mmol) was added dropwise at room temperature. The resulting mixture was stirred at room temperature for 24 h, quenched with water (1 mL), extracted with CH_2Cl_2 (3 x 2 mL), dried over a Telos® phase separator and the solvent was removed under reduced pressure. After column chromatography (0 to 10% Et_2O in hexane), the pure product **163c** was obtained as a pale yellow oil (80% yield, 32 mg, 0.165 mmol, 27% *ee* of (*R*)-isomer, $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -23.8 (c = 0.589, $CHCl_3$)) (lit.[24] for the (*R*)-isomer $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -69.7 (c = 0.32, $CHCl_3$)).

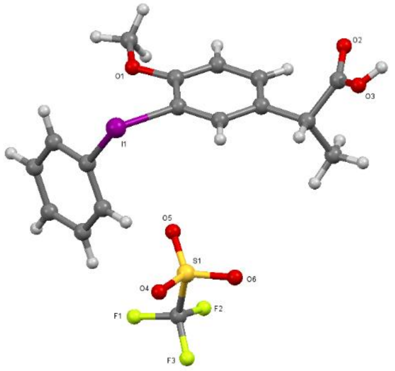
The spectroscopic data are in agreement with literature.[20] Pale yellow oil; **^{1}H NMR (300 MHz, $CDCl_3$)**: δ = 7.22 (d, *J* = 8.0 Hz, 2H, H-Ar), 6.86 (d, *J* = 8.0 Hz, 2H, H-Ar), 3.79 (s, 3H, OCH_3), 3.68 (q, *J* = 7.2 Hz, 1H, CH), 3.65 (s, 3H, OCH_3), 1.46 (d, *J* = 7.2 Hz, 3H, CH_3) ppm; **^{13}C NMR (75 MHz, $CDCl_3$)**: δ = 175.4 (C=O), 158.8 (**C**$_{Ar}$-OMe), 132.8 (C_{Ar}), 128.6 (2 C_{Ar}H), 114.1 (2 C_{Ar}H), 55.4 (OCH_3), 52.1 (OCH_3), 44.7 (CH), 18.8 (CH_3) ppm; **IR (neat)**: 2951, 1732, 1612, 1512, 1435, 1207, 1033, 968 cm^{-1}; **HRMS (EI)**: $[M]^+$ calc. 194.0943, found 194.043 $[C_{11}H_{14}O_3]^+$; ***ee*** were determined by HPLC analysis: Daicel Chiralcel *OD-H* column (25 cm), hexane/*i*-PrOH: 99/1, 0.5 mL/min, 10 °C, 277 nm, T_r (minor, (*S*)-isomer) = 16.7 min, T_r (major, (*R*)-isomer) = 18.0 min.

(5-(1-Carboxyethyl)-2-methoxyphenyl)(phenyl)iodonium trifluoromethanesulfonate 168



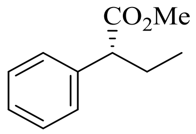
Yellow oil; **^{1}H NMR (300 MHz, CD$_3$OD)**: δ = 8.15 (d, J = 2.1 Hz, 1H, H-Ar), 8.11 (dd, J = 8.0, 1.2 Hz, 2H, H-Ar), 7.67 (overlapped t and dd, J_t = 8.1 Hz, J_{dd} = 7.1, 2.0 Hz, 2H, H-Ar), 7.52 (t, J = 8.0 Hz, 2H, H-Ar), 7.26 (d, J = 9.0 Hz, 2H, H-Ar), 3.90 (s, 3H, OCH$_3$), 3.77 (q, J = 7.2 Hz, 1H, CH), 1.48 (d, J = 7.2 Hz, 3H, CH$_3$) ppm; **^{13}C NMR (75 MHz, CDCl$_3$)**: δ = 179.9 (C=O), 157.5 (C$_{Ar}$ - OMe), 137.8 (C$_{Ar}$), 137.1 (C$_{Ar}$H), 136.5 (2 C$_{Ar}$H), 135.6 (C$_{Ar}$H), 133.5 (C$_{Ar}$H), 133.0 (2 C$_{Ar}$H), 121.8 (q, J = 319 Hz, CF$_3$), 115.1 (C$_{Ar}$), 114.0 (C$_{Ar}$H), 105.6 (C$_{Ar}$), 57.8 (OCH$_3$), 45.2 (CH), 18.7 (CH$_3$) ppm; **IR (neat)**: 3402, 1636, 1225, 1175, 1026 cm^{-1};

X-Ray Crystallographic structure: **CCDC-1487362**



No mass data could be obtained for this compound.

Methyl (*R*)-2-phenylbutanoate 163d

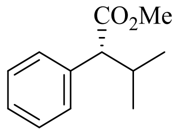


Racemate: The product **163d** was synthesised using general procedure **GP1** at r.t. for 5 h (0.337 mmol scale) (58% yield, 35 mg, 0.196 mmol).

Asymmetric: The product **163d** was synthesised using general procedure **GP3** at -20 °C for 48 h (0.289 mmol scale) (56% yield, 26 mg, 0.146 mmol).

The spectroscopic data are in agreement with literature.[25] Colourless oil; **^{1}H NMR (400 MHz, CDCl$_3$)**: δ = 7.35 – 7.23 (m, 5H, H-Ar), 3.66 (s, 3H, OCH$_3$), 3.46 (t, *J* = 7.75 Hz, 1H, CH), 2.12 (dquint, *J* = 13.6, 7.4 Hz, 1H, C**H$_A$**H$_B$), 1.80 (dquint, *J* = 13.6, 7.4 Hz, 1H, CH$_A$**H$_B$**), 0.89 (t, *J* = 7.4 Hz, 3H, CH$_3$) ppm; **^{13}C NMR (125 MHz, CDCl$_3$)**: δ = 174.6 (C=O), 139.3 (C$_{Ar}$), 128.7 (2 C$_{Ar}$H), 128.1 (2C$_{Ar}$H), 127.3 (C$_{Ar}$), 53.6 (OCH$_3$), 52.0 (CH), 26.9 (CH$_2$), 12.3 (CH$_3$) ppm; **IR (neat)**: 2966, 1732, 1454, 1435, 1203, 1165, 698 cm^{-1}; **HRMS (ESI)**: [M+H]$^+$ calc. 179.1067, found 179.1064 [C$_{11}$H$_{15}$O$_2$]$^+$; ***ee***: 63%, determined by HPLC analysis: *YMC* Chiral Amylose-C S-5µm (25 cm), hexane/*i*-PrOH: 99.7/0.3, 1.0 mL/min, 20 °C, 254 nm, T$_r$ (minor, (*S*)-isomer) = 5.7 min, T$_r$ (major, (*R*)-isomer) = 6.1 min; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -28.6 (c = 0.21, CHCl$_3$) (it is assumed to be the (*R*)-isomer by analogy with the other rearranged product).

Methyl (*R*)-3-methyl-2-phenylbutanoate 163e

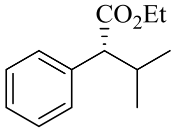


Racemate: The product **163e** was synthesised using general procedure **GP1** at r.t. for 5 h (0.337 mmol scale) (93% yield, 62 mg, 0.322 mmol).

Asymmetric: The product **163e** was synthesised using general procedure **GP3** at -20 °C for 48 h (0.119 mmol scale) (31% conversion, ~7 mg, 0.036 mmol).

The spectroscopic data are in agreement with literature.[26] Pale yellow oil; **^{1}H NMR (400 MHz, CDCl$_3$)**: δ = 7.36 – 7.23 (m, 5H, H-Ar), 3.65 (s, 3H, OCH$_3$), 3.15 (d, *J* = 10.6 Hz, 1H, C**H**CO$_2$Me), 2.34 (dsept, *J* = 10.6, 6.6 Hz, 1H, C**H**(CH$_3$)$_2$), 1.03 (d, *J* = 6.5 Hz, 3H, CH(C**H$_3$**)$_2$), 0.89 (d, *J* = 6.7 Hz, 3H, CH(C**H$_3$**)$_2$) ppm; **^{13}C NMR (125 MHz, CDCl$_3$)**: δ = 174.6 (C=O), 138.5 (C$_{Ar}$), 128.7 (2 C$_{Ar}$H), 128.6 (2 C$_{Ar}$H), 127.4 (C$_{Ar}$H), 60.2 (OCH$_3$), 51.8 (**C**HCO$_2$Me), 32.0 (CH), 21.6 (CH$_3$), 20.3 (CH$_3$) ppm; **IR (neat)**: 2959, 1732, 1454, 1435, 1203, 1153, 702 cm^{-1}; **HRMS (NSI)**: [M+H]$^+$ calc. 193.1223, found 193.1221 [C$_{12}$H$_{17}$O$_2$]$^+$; ***ee***: 73%, determined by HPLC analysis: Daicel Chiralcel *OD-H* column (25 cm), hexane/*i*-PrOH: 99.5/0.5, 1.0 mL/min, 20 °C, 225 nm, T$_r$ (minor, (*S*)-isomer) = 4.4 min, T$_r$ (major, (*R*)-isomer) = 5.1 min; $[\alpha]_D^{20}$ = -52.2 (c = 0.23, CHCl$_3$) (it is assumed to be the (*R*)-isomer by analogy with the other rearranged product).

Ethyl (*R*)-3-methyl-2-phenylbutanoate 163f



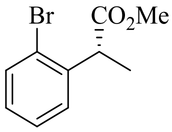
Racemate: The product **163f** was synthesised using general procedure **GP1** (HC(OEt)$_3$ was used instead of HC(OMe)$_3$) at r.t. for 5 h (0.337 mmol scale) (80% yield, 52 mg, 0.267 mmol).

Asymmetric: The product **163f** was synthesised using general procedure **GP3** (HC(OEt)$_3$ was used instead of HC(OMe)$_3$) at -20 °C for 48 h (0.283 mmol scale) (31% yield, 18 mg, 0.088 mmol).

Colourless oil; **^{1}H NMR (400 MHz, CDCl$_3$)**: δ = 7.35 – 7.25 (m, 5H, H-Ar), 4.16 – 4.02 (m, 2H, OCH$_2$), 3.12 (d, *J* = 10.6 Hz, 1H, C**H**CO$_2$Et), 2.33 (dsept, *J* = 10.6, 6.6 Hz, 1H, C**H**(CH$_3$)$_2$), 1.22 (t, *J* = 7.1 Hz, 3H, OCH$_2$C**H$_3$**), 1.04 (d, *J* = 6.5 Hz, 3H, CH$_3$), 0.70 (d, *J* = 6.7 Hz, 3H, CH$_3$) ppm; **^{13}C NMR (125 MHz, CDCl$_3$)**: δ = 174.1 (C=O), 138.7 (C$_{Ar}$), 128.7 (2C$_{Ar}$H), 128.5 (2C$_{Ar}$H), 127.3 (C$_{Ar}$H), 60.6 (OCH$_2$), 60.4 (**C**HCO$_2$Et), 32.1(**C**H(CH$_3$)$_2$), 21.6 (CH$_3$), 20.4 (CH$_3$), 14.3 (CH$_2$**C**H$_3$) ppm; **IR (neat)**: 2962, 1732, 1454, 1369, 1288, 1153, 1030 cm^{-1}; **HRMS (ESI)**: [M+H]$^+$ calc. 207.1380, found 207.1379 [C$_{13}$H$_{19}$O$_2$]$^+$; ***ee***: 35%, determined by HPLC analysis: Daicel Chiralcel *OJ* column (25 cm), hexane/*i*-PrOH: 99/1, 1.0 mL/min, 20 °C, 254 nm, T$_r$ (major, (*R*)-isomer)

= 5.0 min, T_r (minor, (*S*)-isomer) = 6.5 min; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -18.3 (c = 0.58, $CHCl_3$) (it is assumed to be the (*R*)-isomer by analogy with the other rearranged product).

Methyl (*R*)-2-(2-bromophenyl)propionate 163h

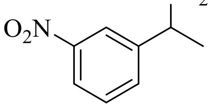


Racemate: The product **163h** was synthesised using general procedure **GP1** at r.t. for 24 h (0.394 mmol scale) (79% yield, 76 mg, 0.313 mmol).

Asymmetric: The product **163h** was synthesised using general procedure **GP3** at r.t. for 48 h (0.211 mmol scale) (46% yield, 19 mg, 0.078 mmol).

Colourless oil; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 7.57 (d, *J* = 8.0 Hz, 1H, H-Ar), 7.31 – 7.27 (m, 2H, H-Ar), 7.14 – 7.10 (m, 1H, H-Ar), 4.23 (q, *J* = 7.1 Hz, 1H, CH), 3.69 (s, 3H, OCH_3), 1.49 (d, *J* = 7.2 Hz, 3H, CH_3) ppm; **^{13}C NMR (125 MHz, $CDCl_3$)**: δ = 174.6 (C=O), 140.3 (C_{Ar}), 133.2 (C_{Ar}H), 128.7 (C_{Ar}H), 128.5 (C_{Ar}H), 128.0 (C_{Ar}H), 124.5 (C_{Ar}), 52.3 (OCH_3), 44.8 (CH), 18.0 (CH_3) ppm; **IR (neat)**: 2938, 1736, 1472, 1433, 1207, 1169, 1022, 750 cm^{-1}; **HRMS (NSI)**: $[M+H]^+$ calc. 243.0015, found 243.0019 $[C_{10}H_{12}O_2Br]^+$; **MS (EI)**: m/z 262 (49%), 260 (48%), 245 (96%), 243 ($[M]^+$, 100%), 182 (52%); ***ee***: 44%, determined by HPLC analysis: Regis® Pirkle Covalent (*R*,*R*) Whelk-O 1 (25 cm), hexane/*i*-PrOH: 99/1, 1.0 mL/min, 20 °C, 227 nm, T_r (major, (*R*)-isomer) = 7.5 min, T_r (minor, (*S*)-isomer) = 8.5 min; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -46.7 (c = 0.129, $CHCl_3$) (it is assumed to be the (*R*)-isomer by analogy with the other rearranged product).

Methyl 2-(3-nitrophenyl)propionate 163i

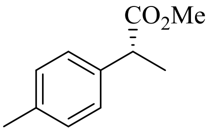


Racemate: The product **163i** was synthesised using general procedure **GP1** at r.t. for 24 h (0.394 mmol scale) (75% yield, 62 mg, 0.296 mmol).

Asymmetric: The product **163i** was not obtained using general procedure **GP3** at r.t. for 48 h (0.171 mmol scale).

Colourless oil; **^{1}H NMR (400 MHz, CDCl$_3$)**: δ = 8.10 (t, *J* = 2.0 Hz, 1H, H-Ar), 8.05 (ddd, *J* = 8.2, 2.3, 1.0 Hz, 1H, H-Ar), 7.58 – 7.56 (m, 1H, H-Ar), 7.43 (t, *J* = 7.9 Hz, 1H, H-Ar), 3.77 (q, *J* = 7.2 Hz, 1H, CH), 3.61 (s, 3H, OCH$_3$), 1.49 (d, *J* = 7.2 Hz, 3H, CH$_3$) ppm; **^{13}C NMR (125 MHz, CDCl$_3$)**: δ = 173.9 (C=O), 148.6 (C$_{Ar}$), 142.5 (C$_{Ar}$), 133.9 (C$_{Ar}$H), 129.7 (C$_{Ar}$H), 122.9 (C$_{Ar}$H), 122.4 (C$_{Ar}$H), 52.5 (OCH$_3$), 45.2 (CH), 18.5 (CH$_3$) ppm; **IR (neat)**: 2953, 1732, 1528, 1348, 1211, 1165, 735 cm^{-1}.

Methyl (*R*)-2-(*p*-tolyl)propionate 163k

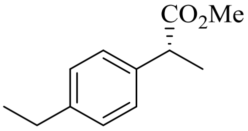


Racemate: The product **163k** was synthesised using general procedure **GP1** at r.t. for 24 h (0.394 mmol scale) (86% yield, 60 mg, 0.339 mmol).

Asymmetric: The product **163k** was synthesised using general procedure **GP3** at r.t. for 48 h (0.211 mmol scale) (79% yield, 29 mg, 0.165 mmol).

The spectroscopic data are in agreement with literature.[27] Colourless oil; **^{1}H NMR (500 MHz, CDCl$_3$)**: δ = 7.19 (d, *J* = 8.0 Hz, 2H, H-Ar), 7.14 (d, *J* = 7.9 Hz, 2H, H-Ar), 3.70 (q, *J* = 7.2 Hz, 1H, CH), 3.65 (s, 3H, OCH$_3$), 2.33 (s, 3H, CH$_3$), 1.49 (d, *J* = 7.2 Hz, 3H, CHC**H$_3$**) ppm; **^{13}C NMR (125 MHz, CDCl$_3$)**: δ = 175.3 (C=O), 137.7 (C$_{Ar}$), 136.9 (C$_{Ar}$), 129.5 (2 C$_{Ar}$H), 127.5 (2 C$_{Ar}$H), 52.1 (OCH$_3$), 45.1 (CH), 21.2 (CH$_3$), 18.6 (CH**C**H$_3$) ppm; **IR (neat)**: 2951, 1734, 1514, 1433, 1204, 1163 cm^{-1}; **HRMS (NSI)**: $[M+H]^+$ calc. 179.1067, found 179.1064 $[C_{11}H_{15}O_2]^+$; ***ee***: 46%, determined by HPLC analysis: Daicel Chiralcel *OJ* column (25 cm), hexane/*i*-PrOH: 99/1, 1.0 mL/min, 20 °C, 234 nm, T$_r$ (major, (*R*)-isomer) = 16.2 min, T$_r$ (minor, (*S*)-isomer) = 19.9 min; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -69.9 (c = 0.0286, CHCl$_3$) (lit.[24] for the (*R*)-isomer $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -73.6 (c = 0.23, CHCl$_3$)).

Methyl (*R*)-2-(4-ethylphenyl)propionate 163l

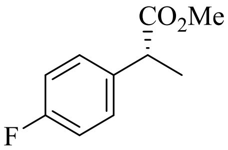


<u>Racemate</u>: The product **163l** was synthesised using general procedure **GP1** at r.t. for 24 h (0.394 mmol scale) (91% yield, 69 mg, 0.358 mmol).

<u>Asymmetric</u>: The product **163l** was synthesised using general procedure **GP3** at r.t. for 48 h (0.211 mmol scale) (87% yield, 35 mg, 0.185 mmol).

Colourless oil; **^{1}H NMR (300 MHz, CDCl$_3$)**: δ = 7.22 (d, *J* = 8.3 Hz, 2H, H-Ar), 7.16 (d, *J* = 8.2 Hz, 2H, H-Ar), 3.70 (q, *J* = 7.2 Hz, 1H, CH), 3.66 (s, 3H, OCH$_3$), 2.63 (q, *J* = 7.6 Hz, 2H, C**H$_2$**CH$_3$), 1.49 (d, *J* = 7.2 Hz, 3H, CHC**H$_3$**), 1.23 (t, *J* = 7.6 Hz, 3H, CH$_2$C**H$_3$**) ppm; **^{13}C NMR (125 MHz, CDCl$_3$)**: δ = 175.3 (C=O), 143.2 (C$_{Ar}$), 137.9 (C$_{Ar}$), 128.3 (2 C$_{Ar}$H), 127.5 (2 C$_{Ar}$H), 52.1 (OCH$_3$), 45.2 (CH), 28.6 (**C**H$_2$CH$_3$), 18.6 (CH**C**H$_3$), 15.6 (CH$_2$**C**H$_3$) ppm; **IR (neat)**: 2965, 1736, 1514, 1433, 1203, 1163 cm^{-1}; **HRMS (NSI)**: [M+H]$^+$ calc. 193.1223, found 193.1221 [C$_{12}$H$_{17}$O$_2$]$^+$; ***ee***: 44%, determined by HPLC analysis: Daicel Chiralcel *OJ* column (25 cm), hexane/*i*-PrOH: 99/1, 1.0 mL/min, 20 °C, 234 nm, T$_r$ (major, (*R*)-isomer) = 14.8 min, T$_r$ (minor, (*S*)-isomer) = 16.9 min; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -22.8 (c =0.351, CHCl$_3$) (it is assumed to be the (*R*)-isomer by analogy with the other rearranged product).

Methyl (*R*)-2-(4-fluorophenyl)propionate 163m

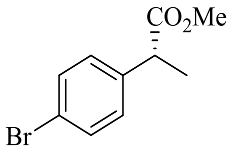


<u>Racemate</u>: The product **163m** was synthesised using general procedure **GP1** at r.t. for 48 h (0.657 mmol scale) (92% yield, 110 mg, 0.604 mmol).

<u>Asymmetric</u>: The product **163m** was synthesised using general procedure **GP3** at -20 °C for 48 h (0.146 mmol scale) (50% conversion, ~13 mg, 0.073 mmol).

The spectroscopic data are in agreement with literature.[28] Colourless oil; **^{1}H NMR (400 MHz, CDCl$_3$)**: δ = 7.28 (dt, *J* = 8.6, 3.3 Hz, 2H, H-Ar), 7.02 (tt, *J* = 8.7, 2.2 Hz, 2H, H-Ar), 3.72 (q, *J* = 7.2 Hz, 1H, CH), 3.68 (s, 3H, OCH$_3$), 1.50 (d, *J* = 7.2 Hz, 3H, CH$_3$) ppm; **^{13}C NMR (125 MHz, CDCl$_3$)**: δ = 175.0 (C=O), 162.1 (d, *J* = 245 Hz, C-F), 136.4 (d, *J* = 3 Hz, 2 C$_{Ar}$), 129.1 (d, *J* = 8 Hz, C$_{Ar}$), 115.6 (d, *J* = 21 Hz, 2 C$_{Ar}$), 52.2 (OCH$_3$), 44.8 (CH), 18.8 (CH$_3$) ppm; **^{19}F NMR (283 MHz, CDCl$_3$)**: δ = -115.5 (d, *J* = 14 Hz) ppm; **IR (neat)**: 2955, 1732, 1508, 1435, 1222, 1157, 837 cm^{-1}; **HRMS (APCI)**: [M+H]$^+$ calc. 183.0816, found 183.0812 [C$_{10}$H$_{12}$FO$_2$]$^+$; **MS (EI)**: m/z 183 ([M+H]$^+$, 85%), 125 (10%), 123 (100%), 103 (10%); ***ee***: 45%, determined by HPLC analysis: Daicel Chiralcel *OJ* column (25 cm), hexane/*i*-PrOH: 90/10, 0.5 mL/min, 20 °C, 254 nm, T$_r$ (major, (*R*)-isomer) = 13.3 min, T$_r$ (minor, (*S*)-isomer) = 14.2 min; $[\alpha]_D^{20}$ = -42.9 (c = 0.14, CHCl$_3$) (lit.[21] for the (*R*)-isomer $[\alpha]_D^{20}$ = -5.6 (c = 1.0, EtOH)).

Methyl (*R*)-2-(4-bromophenyl)propionate 163n

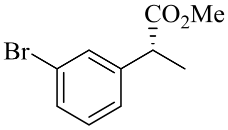


<u>Racemate</u>: The product **163n** was synthesised using general procedure **GP1** at r.t. for 24 h (0.394 mmol scale) (76% yield, 69 mg, 0283 mmol).

<u>Asymmetric</u>: The product **163n** was synthesised using general procedure **GP3** at r.t. for 48 h (0.211 mmol scale) (28% yield, ~14 mg, 0.0576 mmol).

The ^{1}H NMR spectrum is in agreement with literature.[29] Colourless oil; **^{1}H NMR (300 MHz, CDCl$_3$)**: δ = 7.45 (d, *J* = 8.5 Hz, 2H, H-Ar), 7.18 (d, *J* = 8.4 Hz, 2H, H-Ar), 3.70 (q, *J* = 7.2 Hz, 1H, CH), 3.66 (s, 3H, OCH$_3$), 1.48 (d, *J* = 7.2 Hz, 3H, CH$_3$) ppm; **^{13}C NMR (125 MHz, CDCl$_3$)**: δ = 174.6 (C=O), 139.6 (C$_{Ar}$), 131.9 (2 C$_{Ar}$H), 129.4 (2 C$_{Ar}$H), 121.2 (C$_{Ar}$), 52.3 (OCH$_3$), 45.0 (CH), 18.6 (CH$_3$) ppm; **IR (neat)**: 2949, 1734, 1487, 1163, 1011 cm^{-1}; **HRMS (NSI)**: [M+NH$_4$]$^+$ calc. 260.0281, found 260.0284 [C$_{10}$H$_{15}$O$_2$NBr]$^+$; ***ee***: could not be determined by HPLC analysis as the two enantiomers were not separable; $[\alpha]_D^{20}$ = -24.1 (c = 0.249, CHCl$_3$) (it is assumed to be the (*R*)-isomer by analogy with the other rearranged product).

Methyl (*R*)-2-(3-bromophenyl)propionate 163o

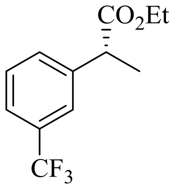


Racemate: The product **163o** was synthesised using general procedure **GP1** at r.t. for 24 h (0.394 mmol scale) (98% yield, 94 mg, 0.385 mmol).

Asymmetric: The product **163o** was synthesised using general procedure **GP3** at r.t. for 48 h (0.211 mmol scale) (14% yield, ~7 mg, 0.0288 mmol).

Colourless oil; **^{1}H NMR (300 MHz, $CDCl_3$)**: δ = 7.45 (t, *J* = 1.6 Hz, 1H, H-Ar), 7.39 (dt, *J* = 7.2, 1.8 Hz, 1H, H-Ar), 7.22 – 7.19 (m, 2H, H-Ar), 3.68 (q, *J* = 7.2 Hz, 1H, CH), 3.67 (s, 3H, OCH_3), 1.49 (d, *J* = 7.2 Hz, 3H, CH_3) ppm; **^{13}C NMR (125 MHz, $CDCl_3$)**: δ = 174.5 (C=O), 142.8 (C_{Ar}), 130.8 (C_{Ar}H), 130.5 (C_{Ar}H), 130.3 (C_{Ar}H), 126.3 (C_{Ar}H), 122.8 (C_{Ar}), 52.4 (OCH_3), 45.2 (CH), 18.6 (CH_3) ppm; **IR (neat)**: 2949, 1734, 1568, 1427, 1203, 1163, 692 cm^{-1}; **HRMS (NSI)**: $[M+NH_4]^+$ calc. 260.0281, found 260.0284 $[C_{10}H_{15}O_2NBr]^+$; ***ee***: 46%, determined by HPLC analysis: Daicel Chiralcel *OJ* column (25 cm), hexane/*i*-PrOH: 99/1, 0.5 mL/min, 20 °C, 230 nm, T_r (minor, (*S*)-isomer) = 22.6 min, T_r (major, (*R*)-isomer) = 24.3 min; $[\alpha]_D^{20}$ = -61.5 (c = 0.065, $CHCl_3$) (it is assumed to be the (*R*)-isomer by analogy with the other rearranged product).

Ethyl (*R*)-2-(3-(trifluoromethyl)phenyl)propionate 163p

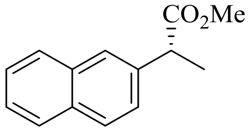


Racemate: The product **163p** was synthesised using general procedure **GP1** ($HC(OEt)_3$ was used instead of $HC(OMe)_3$) at r.t. for 20 h (0.394 mmol scale) (73% yield, 71 mg, 0.288 mmol).

Asymmetric: The product **163p** was synthesised using general procedure **GP3** ($HC(OEt)_3$ was used instead of $HC(OMe)_3$) at -20 °C for 48 h (0.247 mmol scale) (Traces).

Colourless oil; **^{1}H NMR (500 MHz, $CDCl_3$)**: δ = 7.56 (s, 1H, H-Ar), 7.53 – 7.50 (m, 2H, H-Ar), 7.45 (d, *J* = 7.7 Hz, 1H, H-Ar), 4.17 – 4.10 (m, 2H, $OC\mathbf{H_2}CH_3$), 3.76 (q, *J* = 7.2 Hz, 1H, CH), 1.52 (d, *J* = 7.2 Hz, 3H, CH_3), 1.21 (t, *J* = 7.1 Hz, 3H, $OCH_2C\mathbf{H_3}$) ppm; **^{13}C NMR (125 MHz, $CDCl_3$)**: δ = 173.9 (C=O), 141.7 (C_{Ar}), 131.2 (q, *J* = 32 Hz, $\mathbf{C}_{Ar}$-CF_3), 131.1 (C_{Ar}), 129.2 (C_{Ar}), 124.6 (q, *J* = 4 Hz, $\mathbf{C}H_{Ar}$-C_{Ar}-CF_3), 124.2 (q, *J* = 272 Hz, CF_3), 124.1 (q, *J* = 4 Hz, $\mathbf{C}_{Ar}H$ – C_{Ar} – CF_3), 61.1 (OCH_2), 45.6 (CH), 18.6 (CH_3), 14.2 (CH_3) ppm; **^{19}F NMR (283 MHz, $CDCl_3$)**: δ = -62.5 ppm; **IR (neat)**: 2984, 1732, 1450, 1327, 1161, 1072, 702 cm^{-1}; **HRMS (APCI)**: $[M+H]^+$ calc. 247.0940, found 247.0940 $[C_{12}H_{14}O_2F_3]^+$; ***ee***: 44%, determined by HPLC analysis: Regis® Pirkle Covalent (*R*,*R*) Whelk-O 1 (25 cm), hexane/*i*-PrOH: 99/1, 0.5 mL/min, 20 °C, 254 nm, T_r (minor, (*S*)-isomer) = 11.6 min, T_r (major, (*R*)-isomer) = 12.9 min. $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -38.8 (c = 0.11, $CHCl_3$) (it is assumed to be the (*R*)-isomer by analogy with the other rearranged product).

Methyl (*R*)-2-(naphthalen-2-yl)propionate 173a



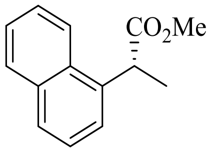
Racemate: The product **173a** was synthesised using general procedure **GP1** at r.t. for 5 h (0.271 mmol scale) (83% yield, 48 mg, 0.223 mmol).

Asymmetric: The product **173a** was synthesised using general procedure **GP2** at -20 °C for 48 h (0.271 mmol scale) (52% yield, 30 mg, 0.140 mmol).

The spectroscopic data are in agreement with literature.[30] Colourless oil; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 7.83 – 7.81 (m, 3H, H-Ar), 7.75 (s, 1H, H-Ar), 7.48 – 7.43 (m, 3H, H-Ar), 3.90 (q, *J* = 7.2 Hz, 1H, CH), 3.67 (s, 3H, OCH_3), 1.60 (d, *J* = 7.2 Hz, 3H, CH_3) ppm; **^{13}C NMR (125 MHz, $CDCl_3$)**: δ = 175.1 (C=O), 138.2 (C_{Ar}), 133.7 (C_{Ar}), 132.8 (C_{Ar}), 128.5 ($C_{Ar}H$), 127.9 ($C_{Ar}H$), 127.8 ($C_{Ar}H$), 126.31 ($C_{Ar}H$), 126.28 ($C_{Ar}H$), 126.0 ($C_{Ar}H$), 125.9 ($C_{Ar}H$), 52.2 (OCH_3), 45.7 (CH), 18.7 (CH_3) ppm; **IR (neat)**: 2936, 1732, 1454, 1330, 1195 cm^{-1}; **HRMS (ESI)**: $[M+H]^+$ calc. 215.1067, found 215.1067 $[C_{14}H_{15}O_2]^+$; ***ee***: 24%, determined by HPLC analysis: Daicel Chiralcel *OD-H* column (25 cm), hexane/*i*-PrOH: 99.5/0.5, 0.7 mL/min, 10 °C, 254 nm, T_r (major, (*R*)-isomer) =

15.7 min, T$_r$ (minor, (*S*)-isomer) = 17.8 min; $[\alpha]_D^{20}$ = -12.6 (c = 0.63, $CHCl_3$) (lit.[24] for the (*R*)-isomer $[\alpha]_D^{20}$ = -65.3 (c = 0.42, $CHCl_3$)).

Methyl (*R*)-2-(naphthalen-1-yl)propionate 174a

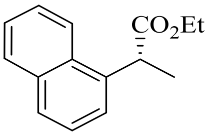


<u>Racemate</u>: The product **174a** was synthesised using general procedure **GP1** at r.t. for 5 h (0.271 mmol scale) (87% yield, 50 mg, 0.233 mmol).

<u>Asymmetric</u>: The product **174a** was synthesised using general procedure **GP3** at -20 °C for 48 h (0.271 mmol scale) (91% yield, 53 mg, 0.247 mmol).

The spectroscopic data are in agreement with literature.[31] Colourless oil; **^{1}H NMR (400 MHz, CDCl$_3$)**: δ = 8.08 (d, *J* = 8.5 Hz, 1H, H-Ar), 7.88 (dd, *J* = 7.9, 1.3 Hz, 1H, H-Ar), 7.80 – 7.76 (m, 1H, H-Ar), 7.57 – 7.45 (m, 4H, H-Ar), 4.52 (q, *J* = 7.1 Hz, 1H, CH), 3.66 (s, 3H, OCH_3), 1.66 (t, *J* = 7.1 Hz, 3H, CH_3) ppm; **^{13}C NMR (125 MHz, CDCl$_3$)**: δ = 175.5 (C=O), 137.0 (C_{Ar}), 134.2 (C_{Ar}), 131.5 (C_{Ar}), 129.2 ($C_{Ar}H$), 127.9 ($C_{Ar}H$), 126.5 ($C_{Ar}H$), 125.8 ($C_{Ar}H$), 125.7 ($C_{Ar}H$), 124.7 ($C_{Ar}H$), 123.2 ($C_{Ar}H$), 52.2 (OCH_3), 41.5 (CH), 18.4 (CH_3) ppm; **IR (neat)**: 2951, 1732, 1454, 1199, 1095, 779 cm^{-1}; **HRMS (ESI)**: $[M+H]^+$ calc. 215.1067, found 215.1067 $[C_{14}H_{15}O_2]^+$; ***ee***: 46%, determined by HPLC analysis: Daicel Chiralcel *OJ* column (25 cm), hexane/*i*-PrOH: 99/1, 0.7 mL/min, 20 °C, 254 nm, T$_r$ (minor, (*S*)-isomer) = 34.3 min, T$_r$ (major, (*R*)-isomer) = 38.1 min; $[\alpha]_D^{20}$ = -60.7 (c = 0.89, $CHCl_3$) (lit.[24] for the (*R*)-isomer $[\alpha]_D^{20}$ = -89.5 (c = 0.34, $CHCl_3$)).

Ethyl (*R*)-2-(naphthalen-1-yl)propionate 174b

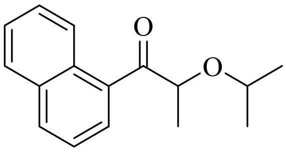


Racemate: The product **174b** was synthesised using general procedure **GP1** ($HC(OEt)_3$ was used instead of $HC(OMe)_3$) at r.t. for 5 h (0.271 mmol scale) (53% yield, 33 mg, 0.145 mmol).

Asymmetric: The product **174b** was synthesised using general procedure **GP3** ($HC(OEt)_3$ was used instead of $HC(OMe)_3$) at -20 °C for 48 h (0.119 mmol scale) (70% yield, 19 mg, 0.083 mmol).

The spectroscopic data are in agreement with literature.[32] Yellow oil; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 7.89 (d, *J* = 8.5 Hz, 1H, H-Ar), 7.68 – 7.65 (m, 1H, H-Ar), 7.58 – 7.56 (m, 1H, H-Ar), 7.36 – 7.25 (m, 4H, H-Ar), 4.29 (q, *J* = 7.1 Hz, 1H, CH), 3.97 – 3.89 (m, 2H, $OC\mathbf{H_2}CH_3$), 1.44 (d, *J* = 7.1 Hz, 3H, CH_3), 0.96 (t, *J* = 7.1 Hz, 3H, $OCH_2C\mathbf{H_3}$) ppm; **^{13}C NMR (100 MHz, $CDCl_3$)**: δ = 175.1 (C=O), 137.1 (C_{Ar}), 134.1 (C_{Ar}), 131.4 (C_{Ar}), 129.1 ($C_{Ar}H$), 127.8 ($C_{Ar}H$), 126.4 ($C_{Ar}H$), 125.7 (2 $C_{Ar}H$), 124.5 ($C_{Ar}H$), 123.3 ($C_{Ar}H$), 61.0 (OCH_2), 41.5 (CH), 18.3 (CH_3), 14.2 (CH_3) ppm; **IR (neat)**: 2978, 1732, 1454, 1377, 1192, 1099, 779 cm^{-1}; **HRMS (ESI)**: $[M+H]^+$ calc. 229.1223, found 229.1222 $[C_{15}H_{17}O_2]^+$; ***ee***: 62%, determined by HPLC analysis: Daicel Chiralcel *OJ* column (25 cm), hexane/*i*-PrOH: 98/2, 1.0 mL/min, 20 °C, 219 nm, T_r (minor, (*S*)-isomer) = 19.3 min, T_r (major, (*R*)-isomer) = 24.9 min; $[\alpha]_D^{20}$ = -77.4 (c = 0.31, $CHCl_3$)) (it is assumed to be the (*R*)-isomer by analogy with the other rearranged product).

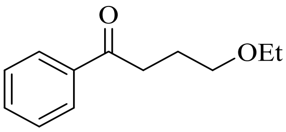
2-Isopropoxy-1-(naphthalen-1-yl)propan-1-one 177c



The product **177c** was synthesised using general procedure **GP1** ($HC(O^iPr)_3$ was used instead of $HC(OMe)_3$) at r.t. for 5 h (0.271 mmol scale) (22% yield, 12 mg, 0.048 mmol).

Colourless oil; **^{1}H NMR (400 MHz, CDCl$_3$)**: δ = 8.39 (d, *J* = 8.4 Hz, 1H, H-Ar), 7.99 (d, *J* = 8.3 Hz, 1H, H-Ar), 7.91 – 7.87 (m, 2H, H-Ar), 7.61 – 7.49 (m, 3H, H-Ar), 4.83 (q, *J* = 7.0 Hz, 1H, C**H**CH$_3$), 3.69 (sept, *J* = 6.1 Hz, 1H, C**H**(CH$_3$)$_2$), 1.44 (d, *J* = 7.0 Hz, 3H, CHC**H$_3$**), 1.22 (d, *J* = 6.0 Hz, 3H, CH(C**H$_3$**)$_2$), 1.15 (d, *J* = 6.1 Hz, 3H, CH(C**H$_3$**)$_2$) ppm; **^{13}C NMR (125 MHz, CDCl$_3$)**: δ = 205.7 (C=O), 134.8 (C$_{Ar}$), 134.1 (C$_{Ar}$), 132.5 (C$_{Ar}$H), 130.7 (C$_{Ar}$), 128.6 (C$_{Ar}$H), 128.0 (C$_{Ar}$H), 127.1 (C$_{Ar}$H), 126.6 (C$_{Ar}$H), 125.7 (C$_{Ar}$H), 124.3 (C$_{Ar}$H), 78.0 (OCH), 71.6 (OCH), 23.0 (CH$_3$), 21.9 (CH$_3$), 19.3 (CH$_3$) ppm; **IR (neat)**: 2970, 2341, 1693, 1508, 1084, 779 cm^{-1}; **HRMS (ESI)**: [M+H]$^+$ calc. 243.1380, found 243.1380 [C$_{16}$H$_{19}$O$_2$]$^+$; **MS (EI)**: m/z 243 ([M+H]$^+$, 100%), 233 (13%), 183 (57%), 155 (4%).

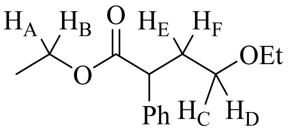
4-Ethoxy-1-phenylbutan-1-one 180



The product **180** was the undesired product from the rearrangement reaction of cyclopropyl(phenyl)methanone **29g** using general procedure **GP3** at r.t. for 24 h (0.247 mmol scale) (98% yield, 46 mg, 0.239 mmol).

The ^{1}H NMR spectra is in agreement with literature.[12] Colourless oil; **^{1}H NMR (400 MHz, CDCl$_3$)**: δ = 7.99 – 7.97 (m, 2H, H-Ar), 7.57 – 7.53 (m, 1H, H-Ar), 7.48 – 7.44 (m, 2H, H-Ar), 3.51 and 3.47 (overlapped t and q, J_t = 6.1 Hz, J_q = 7.0 Hz, 2H + 2H, OCH$_2$ and OC**H$_2$**CH$_3$), 3.09 (t, *J* = 7.2 Hz, 2H, PhC(O)C**H**$_2$), 2.06 – 1.99 (m, 2H, CH$_2$C**H$_2$**CH$_2$), 1.19 (t, *J* = 7.2 Hz, 3H, OCH$_2$C**H$_3$**) ppm; **^{13}C NMR (125 MHz, CDCl$_3$)**: δ = 200.2 (C=O), 137.3 (C$_{Ar}$), 133.0 (C$_{Ar}$H), 128.7 (2 C$_{Ar}$H), 128.2 (2 C$_{Ar}$H), 69.7 (OCH$_2$), 66.2 (OCH$_2$), 35.4 (CH$_2$), 24.6 (CH$_2$), 15.3 (CH$_3$) ppm; **IR (neat)**: 2860, 2361, 1684, 1448, 1107, 690 cm^{-1}; **HRMS (NSI)**: [M+H]$^+$ calc. 193.1223, found 193.1222 [C$_{12}$H$_{17}$O$_2$]$^+$; **MS (EI)**: m/z 244 (10%), 193 ([M+H]$^+$, 40%), 147 (100%).

Ethyl 4-ethoxy-2-phenylbutanoate 181

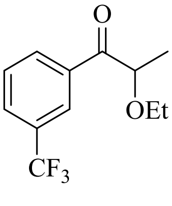


Racemate: The product **181** was synthesised from cyclopropyl(phenyl)methanone **29g** using general procedure **GP1** at r.t. for 20 h (0.394 mmol scale) (65% yield, 60 mg, 0.255 mmol).

Asymmetric: Cyclopropyl(phenyl)methanone **29g** did not rearrange but only gave 4-ethoxy-1-phenylbutan-1-one **180** as the single product.

Colourless oil; **^{1}H NMR (500 MHz, CDCl$_3$)**: δ = 7.34 – 7.23 (m, 5H, H-Ar), 4.15 (dq, *J* = 10.8, 7.1 Hz, 1H, H_A), 4.08 (dq, *J* = 10.8, 7.1 Hz, 1H, H_B), 3.77 (t, *J* = 7.7 Hz, 1H, CH), 3.50 – 3.36 (m, 3H, OCH_2 (OEt) and H_C), 3.29 (ddd, *J* = 9.6, 7.6, 5.5 Hz, 1H, H_D), 2.37 (dtd, *J* = 13.5, 7.7, 5.7 Hz, 1H, H_E), 1.99 (ddd, *J* = 13.5, 7.6, 5.7 Hz, 1H, H_F), 1.20 (t, *J* = 7.1 Hz, 3H, CH_3), 1.18 (t, *J* = 7.0 Hz, 3H, CH_3) ppm; **^{13}C NMR (125 MHz, CDCl$_3$)**: δ = 174.0 (C=O), 139.0 (C_{Ar}), 128.7 (2 C_{Ar}H), 128.1 (2 C_{Ar}H), 127.3 (C_{Ar}H), 67.9 (CH), 66.3 (OCH_2), 60.8 (OCH_2), 48.3 (OCH_2), 33.5 (CH_2), 15.3 (CH_3), 14.2 (CH_3) ppm; **HRMS (NSI)**: $[M+H]^+$ calc. 237.1485, found 237.1485 $[C_{14}H_{21}O_3]^+$; **MS (EI)**: m/z 237 ($[M+H]^+$, 100%), 191 (55%), 163 (11%).

2-Ethoxy-1-(3-(trifluoromethyl)phenyl)propan-1-one 186

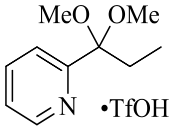


Racemate: The product **186** was synthesised using general procedure **GP1** ($HC(OEt)_3$ was used instead of $HC(OMe)_3$) at r.t. for 24 h (0.394 mmol scale) (23% yield, 23 mg, 0.091 mmol).

Asymmetric: The product **186** was synthesised using general procedure **GP3** ($HC(OEt)_3$ was used instead of $HC(OMe)_3$) at -20 °C for 48 h (0.247 mmol scale) (13% yield, 8 mg, 0.033 mmol).

Colourless oil; **^{1}H NMR (500 MHz, CDCl$_3$)**: δ = 8.39 (s, 1H, H-Ar), 8.30 (d, *J* = 7.8 Hz, 1H, H-Ar), 7.83 (d, *J* = 7.8 Hz, 1H, H-Ar), 7.61 (t, *J* = 7.8 Hz, 1H, H-Ar), 4.59 (q, *J* = 6.9 Hz, 1H, CH), 3.53 (qd, *J* = 7.0, 1.8 Hz, 2H, OC**H$_2$**CH$_3$), 1.52 (d, *J* = 6.9 Hz, 3H, CH$_3$), 1.21 (t, *J* = 7.0 Hz, 3H, OCH$_2$C**H$_3$**) ppm; **^{13}C NMR (125 MHz, CDCl$_3$)**: δ = 199.9 (C=O), 135.3 (C$_{Ar}$), 132.1 (C$_{Ar}$), 131.2 (q, *J* = 33 Hz, **C**$_{Ar}$ – CF$_3$), 129.6 (q, *J* = 4 Hz, **C**$_{Ar}$H – C$_{Ar}$ – CF$_3$), 129.1 (C$_{Ar}$), 126.0 (q, *J* = 4 Hz, **C**$_{Ar}$H – C$_{Ar}$ – CF$_3$), 123.7 (q, *J* = 273 Hz, CF$_3$), 79.9 (OCH), 65.4 (OCH$_2$), 18.5 (CH$_3$), 18.3 (CH$_3$) ppm; **^{19}F NMR (283 MHz, CDCl$_3$)**: δ = -62.7 ppm; **IR (neat)**: 2922, 2361, 1732, 1629, 1460, 1325, 1128, 696 cm^{-1}; **HRMS (NSI)**: [M+H]$^+$ calc. 247.0940, found 247.0943 [C$_{12}$H$_{14}$O$_2$F$_3$]$^+$; **MS (EI)**: m/z 304 (100%), 287 (72%), 263 (28%), 247 ([M+H]$^+$, 83%), 199 (81%); ***ee***: could not be determined by HPLC analysis as the two enantiomers were not separable; $[\alpha]_D^{20}$ = -38.3 (c = 0.18, CHCl$_3$).

2-(1,1-Dimethoxypropyl)pyridine trifluoromethanesulfonate 190



The product **190** was synthesised using general procedure **GP1** at room temperature for 24 h (0.394 mmol scale) (99% conversion). This product could not be isolated as it decomposed over column chromatography but the crude NMRs were clear enough to do some characterisation.

Pale yellow oil; **^{1}H NMR (400 MHz, CDCl$_3$)**: δ = 9.13 (d, *J* = 5.8 Hz, 1H, H-Ar), 8.54 (td, *J* = 7.9, 1.5 Hz, 1H, H-Ar), 8.08 – 7.96 (m, 2H, H-Ar), 3.28 (s, 6H, 2 OCH$_3$), 2.10 (q, *J* = 7.6 Hz, 2H, CH$_2$), 0.64 (t, *J* = 7.6, 3H, CH$_3$) ppm; **^{13}C NMR (125 MHz, CDCl$_3$)**: δ = 155.0 (C$_{Ar}$), 146.8 (C$_{Ar}$H), 142.5 (C$_{Ar}$H), 126.8 (C$_{Ar}$H), 125.3 (C$_{Ar}$H), 122.3 (**C**(OMe)$_2$), 49.8 (2 OCH$_3$), 29.4 (CH$_2$), 7.2 (CH$_3$) ppm; **^{19}F NMR (283 MHz, CDCl$_3$)**: δ = -78.3 ppm.

Stacked ^{1}H NMR of the experiments performed on the crude sample is showed below and was discussed in the main text (see Page 69).

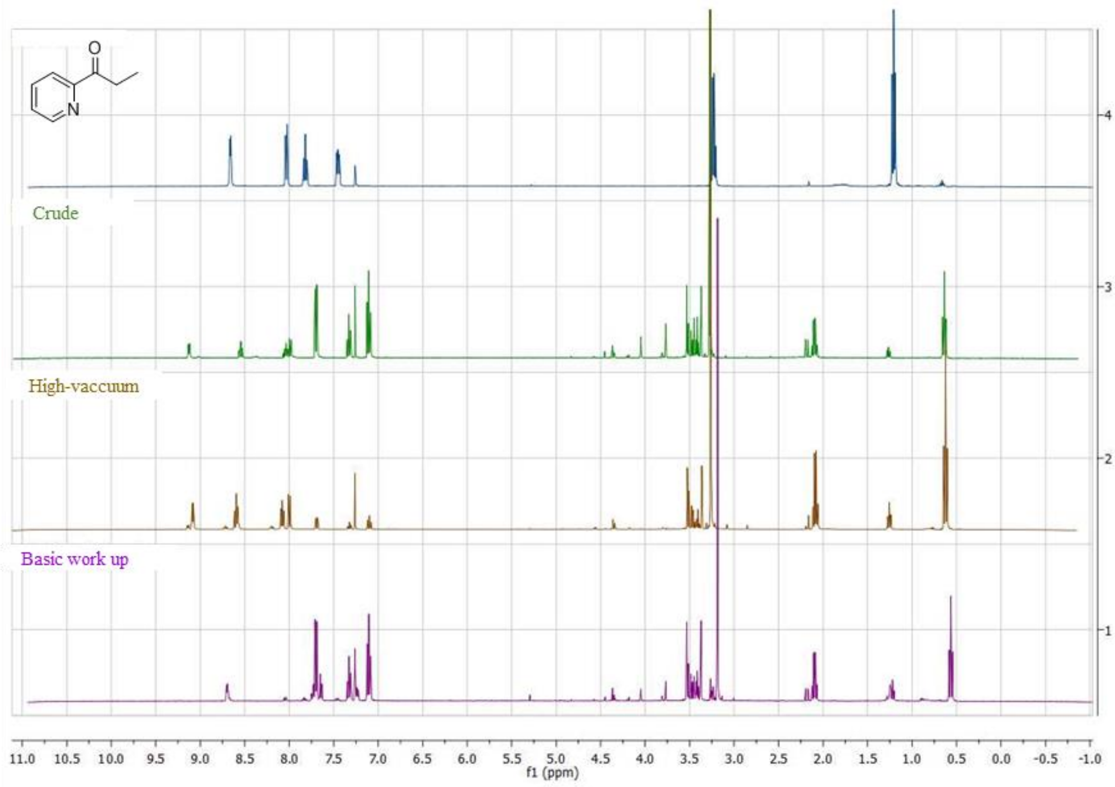
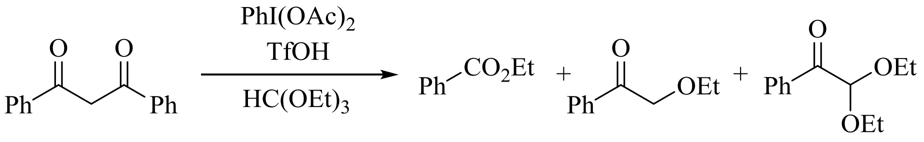


Figure 7.1. Stacked spectra for the formation of 2-(1,1-Dimethoxypropyl)pyridine trifluoromethanesulfonate.

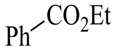
Reaction with dibenzoylmethane



191 **193** **194** **195**

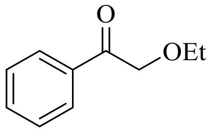
The products **193**, **194** and **195** were synthesised using general procedure **GP1** at r.t. for 20 h (0.394 mmol scale).

Ethyl benzoate 193



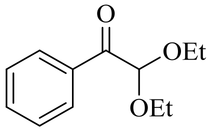
41% yield (48 mg, 0.319 mmol); The spectroscopic data are in agreement with literature.[33] Colourless oil; **^{1}H NMR (500 MHz, CDCl$_3$)**: δ = 8.06 (dd, *J* = 8.3, 1.3 Hz, 2H, H-Ar), 7.54 (tt, *J* = 7.4, 1.3 Hz, 1H, H-Ar), 7.44 (tt, *J* = 7.7, 1.6 Hz, 2H, H-Ar), 4.38 (q, *J* = 7.1 Hz, 2H, OCH$_2$), 1.40 (t, *J* = 7.1 Hz, 3H, CH$_3$) ppm; **^{13}C NMR (125 MHz, CDCl$_3$)**: δ = 166.8 (C=O), 132.9 (C$_{Ar}$H), 130.7 (C$_{Ar}$), 129.7 (2 C$_{Ar}$H), 128.4 (2 C$_{Ar}$H), 61.1 (OCH$_2$), 14.5 (CH$_3$) ppm.

2-Ethoxy-1-phenylethan-1-one 194



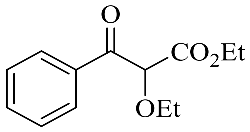
22% yield (28 mg, 0.170 mmol); The ^{1}H NMR spectra is in agreement with literature.[34] Colourless oil; **^{1}H NMR (500 MHz, CDCl$_3$)**: δ = 7.94 (dd, *J* = 8.2, 1.2 Hz, 2H, H-Ar), 7.58 (tt, *J* = 7.4, 1.2 Hz, 1H, H-Ar), 7.47 (t, *J* = 7.8 Hz, 2H, H-Ar), 4.75 (s, 2H, OCH$_2$), 3.65 (q, *J* = 7.0 Hz, 2H, OC**H$_2$**CH$_3$), 1.29 (t, *J* = 7.0 Hz, 3H, CH$_3$) ppm; **^{13}C NMR (125 MHz, CDCl$_3$)**: δ = 196.7 (C=O), 135.2 (C$_{Ar}$), 133.6 (C$_{Ar}$H), 128.8 (2 C$_{Ar}$H), 128.1 (2 C$_{Ar}$H), 73.7 (OCH$_2$), 67.4 (O**C**H$_2$CH$_3$), 15.2 (CH$_3$) ppm; **HRMS (APCI)**: [M+H]$^+$ calc. 165.0910, found 165.0906 [C$_{10}$H$_{13}$O$_2$]$^+$.

2,2-Diethoxy-1-phenylethan-1-one 195



19% yield (32 mg, 0.154 mmol); The spectroscopic data are in agreement with literature.[35] Colourless oil; **^{1}H NMR (500 MHz, CDCl$_3$)**: δ = 8.16 (dd, *J* = 8.5, 1.4 Hz, 2H, H-Ar), 7.57 (tt, *J* = 7.4, 1.2 Hz, 1H, H-Ar), 7.45 (t, *J* = 7.9 Hz, 2H, H-Ar), 5.27 (s, 1H, CH), 3.77 (dq, *J* = 9.6, 7.1 Hz, 2H, OC**H$_A$**H$_B$CH$_3$), 3.66 (dq, *J* = 9.5, 7.0 Hz, 2H, OCH$_A$**H$_B$**CH$_3$), 1.25 (t, *J* = 7.1 Hz, 6H, CH$_3$) ppm; **^{13}C NMR (125 MHz, CDCl$_3$)**: δ = 194.2 (C=O), 134.0 (C$_{Ar}$), 133.5 (C$_{Ar}$H), 129.9 (2 C$_{Ar}$H), 128.5 (2 C$_{Ar}$H), 102.8 (OCH), 63.4 (2 OCH$_2$), 15.3 (2 CH$_3$) ppm; **HRMS (NSI)**: [M+H]$^+$ calc. 209.1172, found 209.1172 [C$_{12}$H$_{17}$O$_3$]$^+$.

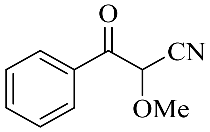
Ethyl 2-ethoxy-3-oxo-3-phenylpropionate 206



The product **206** was synthesised from ethyl 3-oxo-3-phenylpropionate **205** using general procedure **GP1** at r.t. for 20 h (0.394 mmol scale) (56% yield, 52 mg, 0.220 mmol).

The spectroscopic data are in agreement with literature.[36] Colourless oil; **^{1}H NMR (500 MHz, CDCl$_3$)**: δ = 8.08 (dd, *J* = 8.5, 1.2 Hz, 2H, H-Ar), 7.59 (tt, *J* = 7.4, 1.7 Hz, 1H, H-Ar), 7.46 (t, *J* = 7.6 Hz, 2H, H-Ar), 5.00 (s, 1H, CH), 4.23 (q, *J* = 7.1 Hz, 2H, OC**H$_2$**CH$_3$), 3.75 (dq, *J* = 9.1, 7.0 Hz, 1H, OC(O)C**H$_A$**H$_B$CH$_3$), 3.64 (dq, *J* = 9.1, 7.0 Hz, 1H, OC(O)CH$_A$**H$_B$**CH$_3$), 1.27 (t, *J* = 7.0 Hz, 3H, OC(O)CH$_A$H$_B$C**H$_3$**), 1.19 (t, *J* = 7.1 Hz, 3H, OCH$_2$C**H$_3$**) ppm; **^{13}C NMR (125 MHz, CDCl$_3$)**: δ = 193.0 (C=O, ketone), 168.0 (C=O, ester), 134.3 (C$_{Ar}$), 134.0 (C$_{Ar}$H), 129.6 (2 C$_{Ar}$H), 128.7 (2 C$_{Ar}$H), 83.9 (CH), 67.0 (O**C**H$_2$), 62.0 (O**C**H$_2$), 15.2 (CH$_3$), 14.1 (CH$_3$) ppm; **HRMS (NSI)**: [M+H]$^+$ calc. 237.1121, found 237.1121 [C$_{13}$H$_{17}$O$_4$]$^+$; **MS (EI)**: m/z 254 (53%), 237 ([M+H]$^+$, 100%), 163 (15%).

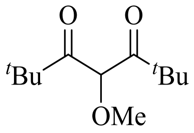
2-Methoxy-3-oxo-3-phenylpropanenitrile 208



The product **208** was synthesised from 3-oxo-3-phenylpropanenitrile **207** using general procedure **GP1** at r.t. for 20 h (0.394 mmol scale) (42% yield, 31 mg, 0.165 mmol).

Pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.07 (d, *J* = 8.4 Hz, 2H), 7.72 (t, *J* = 6.9 Hz, 1H), 7.57 (t, *J* = 7.7 Hz, 2H), 4.03 (s, 3H), 3.64 (s, 1H) ppm; ^{13}C NMR (126 MHz, CDCl$_3$): δ = 186.0 (C=O), 134.9 (C$_{Ar}$), 130.1 (2 C$_{Ar}$), 128.9 (2 C$_{Ar}$), 128.7 (C$_{Ar}$), 126.1 (CN), 53.6 (OMe), 52.7 (OMe) ppm.

4-Methoxy-2,2,6,6-tetramethylheptane-3,5-dione 210

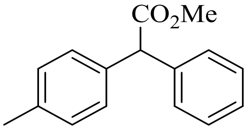


The product **210** was synthesised from di-*tert*-butylmalonate **209** using general procedure **GP1** (0.394 mmol scale) (73% yield, 62 mg, 0.289 mmol).

Crystalline colourless solid; **m.p.** = 35 - 36 °C; **^{1}H NMR (300 MHz, CDCl$_3$)**: δ = 4.90 (s, 1H, CH), 3.37 (s, 3H, OCH$_3$), 1.19 (s, 18H, 6 CH$_3$) ppm; **^{13}C NMR (125 MHz, CDCl$_3$)**: δ = 210.6 (2 C=O), 85.6 (CH), 59.0 (OCH$_3$), 44.5 (2 C), 26.8 (6 CH$_3$) ppm;

IR (neat): 2972, 1695, 1479, 1365, 1124, 1059, 948 cm^{-1}; **HRMS (NSI)**: $[M+NH_4]^+$ calc. 232.1907, found 232.1908 $[C_{12}H_{26}O_3N]^+$.

Methyl 2-phenyl-2-(*p*-tolyl)acetate 213a

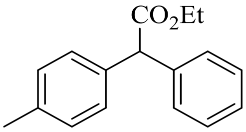


<u>Racemate</u>: The product **213a** was synthesised using general procedure **GP1** at r.t. for 24 h (0.657 mmol scale) (70% yield, 110 mg, 0.460 mmol).

<u>Asymmetric</u>: The product **213a** was synthesised using general procedure **GP3** at -20 °C for 48 h (0.328 mmol scale) (62% yield, 48 mg, 0.200 mmol).

The spectroscopic data are in agreement with literature.[37] Colourless oil; **^{1}H NMR (400 MHz, CDCl$_3$)**: δ = 7.28 – 7.19 (m, 5H, H-Ar), 7.16 (d, J = 7.1 Hz, 2H, H-Ar), 7.09 (d, J = 7.1 Hz, 2H, H-Ar), 4.96 (s, 1H, CH), 3.69 (s, 3H, OCH_3), 2.28 (s, 3H, CH_3) ppm; **^{13}C NMR (125 MHz, CDCl$_3$)**: δ = 173.2 (C=O), 139.0 (C_{Ar}), 137.1 (C_{Ar}), 135.8 (C_{Ar}), 129.5 (2 $C_{Ar}H$), 128.71 (2 $C_{Ar}H$), 128.70 (2 $C_{Ar}H$), 128.6 (2 $C_{Ar}H$), 127.3 ($C_{Ar}H$), 56.8 (CH or OCH_3), 52.4 (CH or OCH_3), 21.2 (CH_3) ppm; **IR (neat)**: 3028, 2951, 1732, 1512, 1435, 1195, 1149, 729 cm^{-1}; **HRMS (ESI)**: $[M+H]^+$ calc. 241.1223, found 241.1224 $[C_{16}H_{17}O_2]^+$; **MS (EI)**: m/z 263 (38%), 241 ($[M+H]^+$, 98%), 209 (100%), 181 (14%); ***ee***: 25%, determined by HPLC analysis: Daicel Chiralcel *OJ* column (25 cm), hexane/*i*-PrOH: 99/1, 1.0 mL/min, 20 °C, 254 nm, T_r (major) = 44.0 min, T_r (minor) = 53.3 min; $[\alpha]_D^{20}$ = +4.6 (c = 0.863, $CHCl_3$).

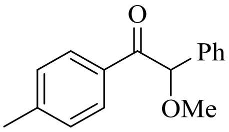
Ethyl 2-phenyl-2-(*p*-tolyl)acetate 213b



<u>Racemate</u>: The product **213b** was synthesised using general procedure **GP1** ($HC(OEt)_3$ was used instead of $HC(OMe)_3$) at r.t. for 24 h (0.657 mmol scale) (54% yield, 90 mg, 0.354 mmol).

Colourless oil; **^{1}H NMR (400 MHz, CDCl$_3$)**: δ = 7.37 – 7.34 (m, 4H, H-Ar), 7.31 – 7.29 (m, 1H, H-Ar), 7.25 (d, *J* = 8.1 Hz, 2H, H-Ar), 7.17 (d, *J* = 8.1 Hz, 2H, H-Ar), 5.02 (s, 1H, CH) 4.25 (q, *J* = 7.1 Hz, 2H, $OC\mathbf{H_2}CH_3$), 2.37 (s, 3H, CH_3), 1.30 (t, *J* = 7.1 Hz, 3H, $OCH_2C\mathbf{H_3}$) ppm; **^{13}C NMR (125 MHz, CDCl$_3$)**: δ = 172.8 (C=O), 139.2 (C_{Ar}), 137.0 (C_{Ar}), 136.0 (C_{Ar}), 129.4 (2 C_{Ar}H), 128.71 (2 C_{Ar}H), 128.67 (2 C_{Ar}H), 128.6 (2 C_{Ar}H), 127.3 (C_{Ar}), 61.2 ($O\mathbf{C}H_2CH_3$), 57.0 (CH), 21.2 (CH_3), 14.3 ($OCH_2\mathbf{C}H_3$) ppm; **IR (neat)**: 2978, 1732, 1512, 1305, 1147, 1026 cm^{-1}; **HRMS (APCI)**: $[M+H]^+$ calc. 255.1380, found 255.1378 $[C_{17}H_{19}O_2]^+$.

2-Methoxy-2-phenyl-1-(*p*-tolyl)ethan-1-one 214a

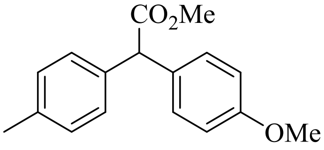


Racemate: The product **214a** was synthesised using general procedure **GP1** at r.t. for 24 h (0.657 mmol scale) (10% yield, 15 mg, 0.064 mmol).

Asymmetric: The product **214a** was synthesised using general procedure **GP3** at -20 °C for 48 h (0.328 mmol scale) (11% yield, 9 mg, 0.375 mmol).

Colourless oil; **^{1}H NMR (400 MHz, CDCl$_3$)**: δ = 7.90 (d, *J* = 8.2 Hz, 2H, H-Ar), 7.45 (d, *J* = 7.0 Hz, 2H, H-Ar), 7.36 – 7.28 (m, 3H, H-Ar), 7.18 (d, *J* = 8.0 Hz, 2H, H-Ar), 5.50 (s, 1H, CH), 3.45 (s, 3H, OCH_3), 2.35 (s, 3H, CH_3) ppm; **^{13}C NMR (125 MHz, CDCl$_3$)**: δ = 196.9 (C=O), 144.2 (C_{Ar}), 136.5 (C_{Ar}), 132.7 (C_{Ar}), 129.35 (2 C_{Ar}H), 129.32 (2 C_{Ar}H), 128.9 (2 C_{Ar}H), 128.6 (C_{Ar}H), 127.7 (2 C_{Ar}H), 86.6 (CH), 57.6 (OCH_3), 21.8 (CH_3) ppm; **IR (neat)**: 2985, 1685, 1604, 4281, 1180, 1103 cm^{-1}; **HRMS (ESI)**: $[M+H]^+$ calc. 241.1223, found 241.1221 $[C_{16}H_{17}O_2]^+$; **MS (EI)**: m/z 263 (26%), 241 ($[M+H]^+$, 100%), 209 (91%), 181 (12%); ***ee***: 7%, determined by HPLC analysis: YMC Chiral Amylose-C S-5µm (25 cm), hexane/*i*-PrOH: 99/1, 0.7 mL/min, 20 °C, 254 nm, T_r (major) = 39.5 min, T_r (minor) = 53.2 min; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -14.0 (c = 0.143, CHCl$_3$).

Methyl 2-(4-methoxyphenyl)-2-(*p*-tolyl)acetate 215a



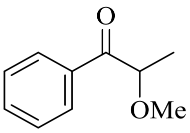
Racemate: The product **215a** was synthesised using general procedure **GP1** at r.t. for 24 h (0.657 mmol scale) (10% yield, 18 mg, 0.065 mmol).

Asymmetric: The product **215a** was synthesised using general procedure **GP3** at -20 °C for 48 h (0.328 mmol scale) (4% yield, 3 mg, 0.011 mmol).

The spectroscopic data are in agreement with literature.[26] Colourless oil; **^{1}H NMR (400 MHz, CDCl$_3$)**: δ = 7.22 (d, *J* = 8.8 Hz, 2H, H-Ar), 7.18 (d, *J* = 8.1 Hz, 2H, H-Ar), 7.13 (d, *J* = 8.1 Hz, 2H, H-Ar), 6.85 (d, *J* = 8.8 Hz, 2H, H-Ar), 4.95 (s, 1H, CH), 3.78 (s, 3H, OCH$_3$), 3.73 (s, 3H, OCH$_3$), 2.32 (s, 3H, CH$_3$) ppm; **^{13}C NMR (125 MHz, CDCl$_3$)**: δ = 173.5 (C=O), 158.9 (C$_{Ar}$ – OMe), 137.0 (C$_{Ar}$), 136.0 (C$_{Ar}$), 131.2 (C$_{Ar}$), 129.8 (2 C$_{Ar}$H), 129.4 (2 C$_{Ar}$H), 128.5 (2 C$_{Ar}$H), 114.1 (2 C$_{Ar}$H), 56.0 (CH or OCH$_3$), 55.4 (CH or OCH$_3$), 52.3 (CH or OCH$_3$), 21.2 (CH$_3$) ppm; **IR (neat)**: 2951, 1732, 1508, 1249, 1149 cm^{-1}; **HRMS (ESI)**: [M+NH$_4$]$^+$ calc. 288.1594, found 288.1592 [C$_{17}$H$_{22}$O$_3$N]$^+$; **MS (EI)**: m/z 288 ([M+NH$_4$]$^+$, 100%), 271 (M$^+$, 30%), 211 (30%), 179 (20%), 163 (10%); ***ee***: 5%, determined by HPLC analysis: Regis® Pirkle Covalent (*R*,*R*) Whelk-O 1 (25 cm) hexane/*i*-PrOH: 99/1, 1.0 mL/min, 20 °C, 232 nm, T$_r$ (major) = 34.7 min, T$_r$ (minor) = 43.6 min.

7.4.2.3. Mechanistic studies

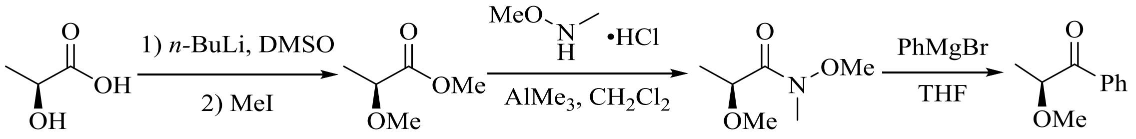
2-Methoxy-1-phenylpropan-1-one 165a



To a solution of (*Z*)-trimethyl((1-phenylprop-1-en-1-yl)oxy)silane **(*Z*)-226** (64 mg, 0.309 mmol) and Ishihara amide **6b** (271 mg, 0.371 mmol) in HC(OMe)$_3$ (1.5 mL), TfOH (55 µL, 0.618 mmol) was added at -20 °C. The resulting solution was stirred at that temperature for 24 h, quenched with water (1 mL), left to warm up to room temperature and extracted with CH_2Cl_2 (3 x 2 mL). The organic phase was dried over a Telos® phase separator and concentrated under vacuum. After column chromatography, 2-methoxy-1-phenylpropan-1-one **165a** was obtained as the major product (80% yield, 41 mg, 0.247 mmol, 78% *ee*) as well as the rearranged product **163a** (~4% yield, ~2 mg, 0.0124 mmol, 47% *ee*).

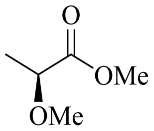
The spectroscopic data for **165a** are in agreement with literature.[38] Pale yellow oil; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 8.05 (dd, *J* = 8.5, 1.2 Hz, 2H, H-Ar), 7.59 (tt, *J* = 7.4, 1.3 Hz, 1H, H-Ar), 7.48 (t, *J* = 7.9 Hz, 2H, H-Ar), 4.64 (q, *J* = 6.9 Hz, 1H, CH), 3.39 (s, 3H, OCH_3), 1.49 (d, *J* = 6.9 Hz, 3H, CH_3) ppm; **^{13}C NMR (125 MHz, $CDCl_3$)**: δ = 200.7 (C=O), 135.1 (C_{Ar}), 133.5 (C_{Ar}H), 128.9 (2 C_{Ar}H), 128.8 (2 C_{Ar}H), 80.5 (CH), 57.4 (OCH_3), 18.6 (CH_3) ppm; ***ee***: 78%, determined by HPLC analysis: *YMC* Chiral Amylose-C S-5µm (25 cm), hexane/*i*-PrOH: 99/1, 1.0 mL/min, 20 °C, 254 nm, T_r (major) = 7.6 min, T_r (minor) = 8.9 min; $[\alpha]_D^{20}$ = -35.1 (c = 0.057, $CHCl_3$).

The absolute stereochemistry of molecule **165a** was determined by its synthesis *via* another route, starting with *L*-lactic acid [(*S*)-lactic acid].



***L*-lactic acid** **(*S*)-165a**

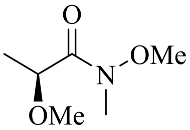
Methyl (*S*)-2-methoxypropanoate



n-BuLi (2.5 M in hexane, 4.60 mL, 11.6 mmol) was added dropwise to anhydrous DMSO (10 mL) at r.t. under inert atmosphere. (*S*)-lactic acid (460 µL, 5.11 mmol) was then added dropwise and the resulting solution was stirred for 15 minutes. Iodomethane (800 µL, 12.7 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 20 h. The mixture was poured in cold water (50 mL) and extracted with ether, dried over $MgSO_4$ and concentrated under vacuum. The resulting yellow oil product was unstable and was used without further purification (47% yield, 286 mg, 2.42 mmol).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.88 (q, *J* = 6.6 Hz, 1H, CH), 3.75 (s, 3H, OMe), 3.38 (s, 3H, OMe), 1.39 (d, *J* = 6.7 Hz, 3H, CH_3) ppm; **^{13}C NMR (125 MHz, $CDCl_3$)**: δ = 173.7 (C=O), 76.5 (CH), 57.8 (OMe), 52.0 (OMe), 18.5 (CH_3) ppm; $[\alpha]_D^{20}$ = -57.1 (c = 0.7, $CHCl_3$).

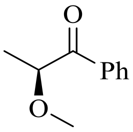
(*S*)-*N*,2-Dimethoxy-*N*-methylpropanamide



N,O-Dimethylhydroxylamine hydrochloride (545 mg, 5.59 mmol) was dissolved in dry CH_2Cl_2 (7 mL) and cooled down to -15 °C. $AlMe_3$ (2 M in toluene, 2.8 mL, 5.59 mmol) was added dropwise and the reaction was warmed to r.t. After 1 h, the reaction was cooled down to -15 °C and a solution of methyl (*S*)-2-methoxypropanoate (220 mg, 1.86 mmol) in dry CH_2Cl_2 (7 mL) was added. The resulting mixture was warmed up to r.t. and stirred for 24 h. A 15% aqueous solution of potassium, sodium tartrate (20 mL) was added very slowly at 0 °C and the resulting mixture was stirred for 1 h and then filtered through celite. The filtrate was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. After purification by column chromatography (0 to 100% EtOAc in hexane) the product was obtained as a pale yellow oil (51% yield, 140 mg, 0.951 mmol).

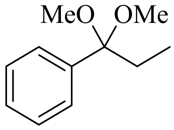
^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.23 (q, *J* = 6.1 Hz, 1H, CH), 3.71 (s, 3H, Me), 3.35 (s, 3H, Me), 3.22 (s, 3H, Me), 1.36 (d, *J* = 6.6 Hz, 3H, $CHCH_3$) ppm; **^{13}C NMR (125 MHz, $CDCl_3$)**: δ = 173.9, 77.4, 74.3, 61.5, 57.2, 17.8 ppm; **$[\alpha]_D^{20}$** = –95.0 (c = 0.8, $CHCl_3$).

(*S*)-2-Methoxy-1-phenylpropan-1-one (*S*)-165a



(*S*)-*N*,2-Dimethoxy-*N*-methylpropanamide (25 mg, 0.17 mmol) was dissolved in dry THF (2 mL) and cooled down to 0 °C. A solution of phenyl magnesium bromide in ether (3 M, 85 µL, 0.25 mmol) was added dropwise and the resulting solution was stirred for 15 minutes at 0 °C. The mixture was quenched with sat. aq. NH_4Cl (1 mL) and extracted with Et_2O (3 x 3 mL). The combined organic layers were washed with brine, dried through a Telos® phase separator and concentrated under vacuum. After purification by preparative TLC (20% Ether in hexane) the pure product was obtained as a colourless oil (82% yield, 23 mg, 0.14 mmol). **$[\alpha]_D^{20}$** = –76.9 (c = 0.676, $CHCl_3$). This established a negative rotation for the (*S*)-enantiomer.

(1,1-Dimethoxypropyl)benzene 179

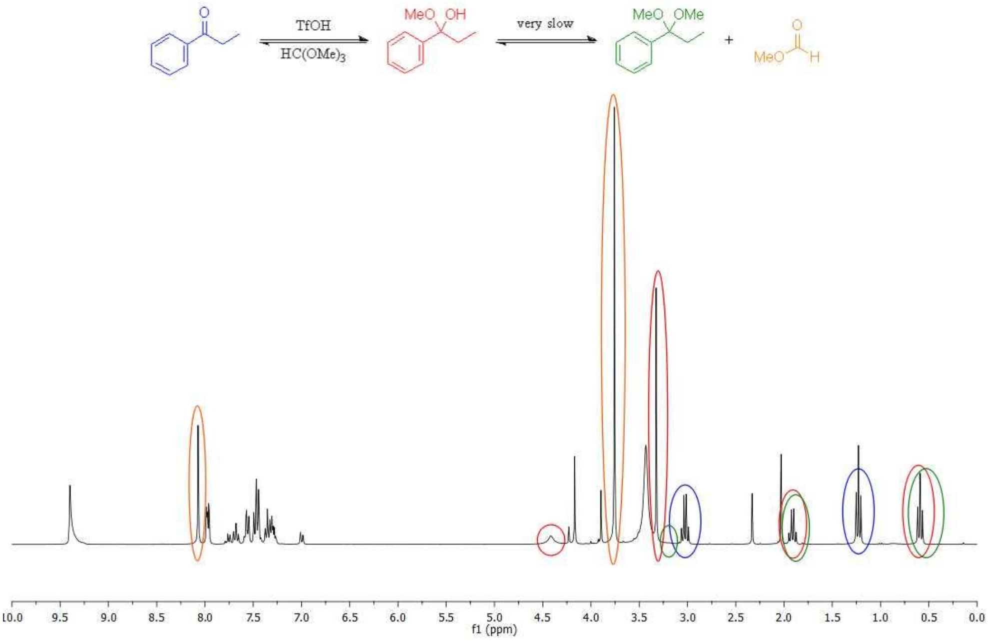


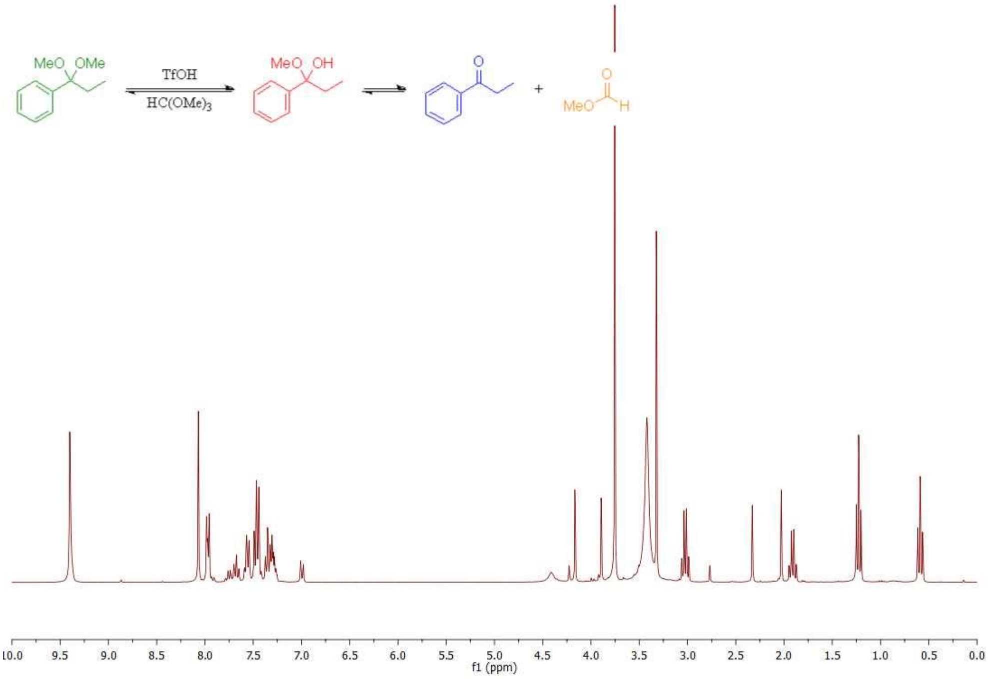
Propiophenone (665 µL, 5.00 mmol), *p*-TsOH•H_2O (47.6 mg, 0.250 mmol) and trimethyl orthoformate (5.47 mL, 50.0 mmol) were dissolved in methanol (15 mL) and the resulting solution was stirred at reflux for 24 h. The solvent was remove using a rotary evaporator. Et_2O (10 mL) was added and the organic phase was washed with sat. aq. $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated under vacuum. After purification by column chromatography (0 to 5% EtOAc in hexane) the pure product **179** was obtained as a colourless oil (75% yield, 676 mg, 3.75 mmol).

The spectroscopic data are in agreement with literature.[39] **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 7.47 – 7.44 (m, 2H, H-Ar), 7.37 – 7.33 (m, 2H, H-Ar), 7.30 – 7.28 (m, 1H, H-Ar), 3.16 (s, 6H, 2 OCH_3), 1.91 (q, *J* = 7.5 Hz, 2H, CH_2), 0.59 (t, *J* = 7.5 Hz, 3H, CH_3) ppm; **^{13}C NMR (125 MHz, $CDCl_3$)**: δ = 140.8 (C_{Ar}), 128.0 (2 $C_{Ar}H$), 127.6 ($C_{Ar}H$), 127.2 (2 $C_{Ar}H$), 48.7 (2 OCH_3), 30.1 (CH_2), 7.9 (CH_3) ppm.

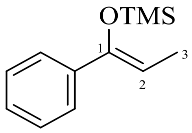
Interconversion between 29a and 179 *via* the hemiketal

In a NMR tube, propiophenone **29a** or ketal **179** (10 mg or 13 mg, 0.075 mmol) were dissolved in $CDCl_3$ (0.6 mL) and $HC(OMe)_3$ (41 µL, 0.37 mmol) was added, followed by TfOH (14 µL, 0.15 mmol). The ^{1}H NMR were measured and are shown below.





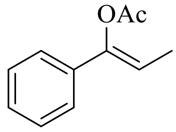
(*Z*)-Trimethyl((1-phenylprop-1-en-1-yl)oxy)silane (*Z*)-226



To a solution of lithium diisopropylamide (4.1 mL, 2 M, 8.2 mmol) in THF (50 mL) at -78 °C under N_2, propiophenone (1.00 mL, 7.45 mmol) was added dropwise. The resulting mixture was stirred at -78 °C for 20 minutes and then, TMSCl (1.04 mL, 8.19 mmol) was added. After 3 h at -78 °C, the reaction was quenched with sat. aq. NH_4Cl solution (50 mL), extracted with Et_2O (3 x 50 mL), dried over $MgSO_4$ and concentrated under vacuum. After purification by column chromatography (0 to 10% EtOAc in hexane) the pure product (*Z*)-226 was obtained as a colourless oil (40% yield, 610 mg, 2.96 mmol).

The spectroscopic data are in agreement with literature.[40] **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 7.47 – 7.44 (m, 2H, H-Ar), 7.31 – 7.21 (m, 3H, H-Ar), 5.34 (q, *J* = 6.9 Hz, 1H, CH), 1.74 (d, *J* = 6.9 Hz, 3H, CH_3), 0.14 (s, 9H, TMS) ppm; **^{13}C NMR (125 MHz, $CDCl_3$)**: δ = 150.1 (C^1), 139.4 (C_{Ar}), 128.2 (2 C_{Ar}H), 127.4 (C_{Ar}H), 125.4 (2 C_{Ar}H), 105.4 (C^2), 11.8 (C^3), 0.7 (3 CH_3 (TMS)) ppm; **IR (neat)**: 2959, 1651, 1493, 1323, 1249, 1060, 879 cm^{-1}; **HRMS (APCI)**: $[M+H]^+$ calc. 207.1200, found 207.1196 $[C_{12}H_{19}OSi]^+$.

(*Z*)-1-phenylprop-1-en-1-yl acetate 227



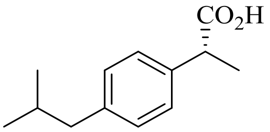
To a solution of lithium diisopropylamide (4.8 mL, 2 M, 9.6 mmol) in dry THF (35 mL) under N_2, propiophenone (1.06 mL, 8.00 mmol) was added at -78 °C. The resulting orange solution was stirred at that temperature for 45 minutes before adding acetic anhydride (1.5 mL, 16 mmol). After 30 minutes, the mixture was poured into sat. aq. $NaHCO_3$ solution (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The pure product **227** was obtained after purification by column chromatography (0 to 20% EtOAc in hexane) (52% yield, 0.735 g, 4.2 mmol).

The spectroscopic data are in agreement with literature.[41] Colourless oil; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 7.41 – 7.39 (m, 2H, H-Ar), 7.34 – 7.31 (m, 2H, H-Ar), 7.28 – 7.24 (m, 1H, H-Ar), 5.91 (q, *J* = 7.0 Hz, 1H, CH), 2.31 (s, 3H, $OC(O)CH_3$), 1.72

(d, *J* = 7.0 Hz, 3H, CH_3) ppm; **HRMS (APCI)**: $[M+H]^+$ calc. 177.0910, found 177.0907 $[C_{11}H_{18}O_2]^+$.

7.4.2.4. Hydrolysis of the ester 163b to obtain ibuprofen

(*R*)-Ibuprofen (*R*)-139



To a solution of ester **(*R*)-163b** (30 mg, 0.136 mmol, 35% *ee*) in THF (1 mL) and MeOH (0.5 mL), NaOH (82 µL, 2 N, 0.163 mmol) was added and the resulting mixture was stirred at r.t. for 16 h. The basic solution was washed with $CHCl_3$ (2 mL). The aqueous layer was then acidified to pH = 1 with 1 N HCl and extracted with CH_2Cl_2 (3 x 2 mL). The combined organic layers were then dried over a Telos® phase separator and concentrated under vacuum to yield pure product as a white solid (93% yield, 26 mg, 0.126 mmol).

The spectroscopic data are in agreement with literature.[42] **m.p.** = 74 - 75 °C (lit.[43] 76 - 77 °C); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 11.35 (s, 1H, COOH), 7.23 (d, *J* = 7.2 Hz, 2H, H-Ar), 7.11 (d, *J* = 7.4 Hz, 2H, H-Ar), 3.71 (q, *J* = 7.1 Hz, 1H, C***H**CH_3), 2.45 (d, *J* = 7.1 Hz, 2H, CH_2), 1.91 – 1.76 (m, 1H, C**H**$(CH_3)_2$), 1.50 (d, *J* = 7.1 Hz, 3H, C*HC**H**$_3$), 0.90 (d, *J* = 6.6 Hz, 6H, CH(C**H**$_3$)$_2$) ppm; **^{13}C NMR (125 MHz, $CDCl_3$)**: δ = 180.9 (C=O), 141.0 (C_{Ar}), 137.1 (C_{Ar}), 129.5 (2 $C_{Ar}H$), 127.4 (2 $C_{Ar}H$), 45.2 (**C**$H_2CH(CH_3)_2$), 45.1 (**C***HCH_3), 30.3 (CH_2**C**$H(CH_3)_2$), 22.5 (CH_2CH(**C**H_3)$_2$), 18.3 (CH**C**H_3) ppm; **HRMS (EI)**: $[M]^+$ calc. 206.1307, found 206.1311 $[C_{13}H_{18}O_2]^+$; **MS (EI)**: m/z 206 ($[M]^+$, 64%), 163 (86%), 161 (100%), 119 (31%), 117 (42%), 91 (30%), 83 (40%); ***ee***: 22%, determined by HPLC analysis: Regis® Pirkle Covalent (*R*,*R*) Whelk-O 1 (25 cm), hexane/*i*-PrOH: 99/1 + 0.05% AcOH, 0.9 mL/min, 20 °C, 267 nm, T_r (minor, (*S*)-isomer) = 15.0 min, T_r (major, (*R*)-isomer) = 17.4 min; $[\alpha]_D^{20}$ = -9.5 (c = 0.42, $CHCl_3$). (lit.[44] for the (*R*)-isomer $[\alpha]_D^{20}$ = -54.3 (c = 2.0, EtOH)).

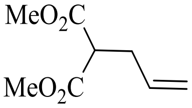
7.4.3. Cyclisation of malonate derivatives

7.4.3.1. Synthesis of substrates

Alkylation of dimethyl malonate

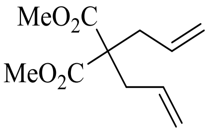
Sodium hydride (0.800 g, 33.3 mmol) was added portionwise to a solution of dimethyl malonate (4.00 g, 30.3 mmol) in dry THF (50 mL) at 0 °C. After 10 minutes, allyl bromide (2.90 mL, 33.3 mmol) was added dropwise. The resulting mixture was stirred for 18 h at room temperature, cooled down to 0 °C and quenched with water (20 mL). The organic phase was extracted with Et_2O (3 x 50 mL), washed with brine (30 mL), dried over $MgSO_4$ and concentrated under vacuum. The resulting crude dimethyl 2-allylmalonate was purified by column chromatography (0 to 10% EtOAc in hexane) to afford the mono- and di-alkylated malonate derivatives **294** and **295** as colourless oils.

Dimethyl 2-allylmalonate 294



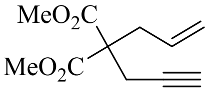
50% yield (2.61 g, 15.2 mmol); The spectroscopic data are in agreement with literature.[45] **^{1}H NMR (400 MHz, CDCl$_3$)**: δ = 5.76 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H, $CH_2C\mathbf{H}=CH_2$), 5.16 – 5.02 (m, 2H, $CH_2CH=C\mathbf{H_2}$), 3.73 (s, 6H, 2 OCH_3), 3.46 (t, *J* = 7.6 Hz, 1H, CH), 2.65 (t, *J* = 7.2 Hz, 2H, $C\mathbf{H_2}CH=CH_2$) ppm.

Dimethyl 2,2-diallylmalonate 295



20% yield (1.29 g, 6.06 mmol); The spectroscopic data are in agreement with literature.[45] **^{1}H NMR (400 MHz, CDCl$_3$)**: δ = 5.67 – 5.50 (m, 2H, 2 $CH_2C\mathbf{H}=CH_2$), 5.08 – 4.99 (m, 4H, 2 $CH_2CH=C\mathbf{H_2}$), 3.65 (s, 6H, 2 OCH_3), 2.57 (d, J = 7.4 Hz, 4H, 2 $C\mathbf{H_2}CH=CH_2$) ppm; **^{13}C NMR (125 MHz, CDCl$_3$)**: δ = 171.3 (2 C=O), 132.4 (2 **C**=CH), 119.4 (2 C=**C**H), 57.8 (C), 52.5 (2 OCH_3), 37.1 (2 CH_2) ppm.

Dimethyl 2-allyl-2-(prop-2-yn-1-yl)malonate 297



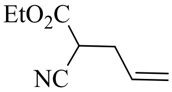
Sodium hydride (0.510 g, 12.8 mmol) was added portionwise to a solution of dimethyl 2-allylmalonate **294** (2.08 g, 11.6 mmol) in dry THF (40 mL) at 0 °C. After 10 minutes, propargyl bromide (solution, 80 wt.% in toluene, 4.35 mL, 17.5 mmol) was added dropwise. The resulting mixture was stirred for 18 h at room temperature, cooled down to 0 °C and quenched with water (20 mL). The organic phase was extracted with Et_2O (3 x 50 mL), washed with brine (30 mL), dried over $MgSO_4$ and concentrated under vacuum. The resulting crude was purified by column chromatography (pure hexane) to afford the pure product **297** (64% yield, 1.72 g, 8.19 mmol).

The spectroscopic data are in agreement with literature.[46] Colourless oil; **^{1}H NMR (300 MHz, $CDCl_3$)**: δ = 5.69 – 5.55 (m, 1H, C**H**=CH_2), 5.22 – 5.11 (m, 2H, CH=C**H_2**), 3.74 (s, 6H, 2 OCH_3), 2.82 – 2.80 (m, 4H, 2 CH_2), 2.02 (t, J = 5.0 Hz, 1H, C≡C**H**) ppm; **^{13}C NMR (125 MHz, $CDCl_3$)**: δ = 170.3 (2 C=O), 131.8 (**C**=CH_2), 120.1 (C=**C**H_2), 78.9 (**C**≡CH), 71.6 (C≡**C**H), 57.0 (C), 52.9 (2 OCH_3), 36.6 (**C**H_2CH=CH_2), 22.8 (**C**H_2C≡CH) ppm.

Mono- and di-alkylation of ethyl 2-cyanoacetate

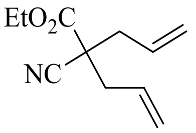
To a solution of ethyl 2-cyanoacetate (2.28 g, 20.2 mmol) in dry THF (100 mL), sodium hydride (2.13 g, 44.4 mmol) was added portionwise at 0 °C. The resulting mixture was stirred for 15 minutes. Allyl bromide (7.68 mL, 44.4 mmol) was then added *via* syringe pump (0.1 mL/min). The reaction was warmed up to room temperature and stirred for 22 h. The reaction was cooled to 0 °C, quenched with water and extracted with diethyl ether (3 x 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under vacuum. After column chromatography, both mono- and di-alkylated products **301** and **302** were isolated as colourless oils.

Ethyl 2-cyanopent-4-enoate 301



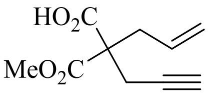
22% yield (895 mg, 5.85 mmol); The spectroscopic data are in agreement with literature.[47] **^{1}H NMR (400 MHz, CDCl$_3$)**: δ = 5.91 – 5.77 (m, 1H, $CH_2C\mathbf{H}=CH_2$), 5.36 – 5.21 (m, 2H, $CH_2CH=C\mathbf{H_2}$), 4.29 (q, *J* = 7.1 Hz, 2H, $OC\mathbf{H_2}CH_3$), 3.58 (t, *J* = 6.8 Hz, 1H, CH), 2.73 – 2.69 (m, 2H, $C\mathbf{H_2}CH=CH_2$), 1.34 (t, *J* = 7.1 Hz, 3H, $OCH_2C\mathbf{H_3}$) ppm; **^{13}C NMR (125 MHz, CDCl$_3$)**: δ = 165.6 (C=O), 131.5 ($\mathbf{C}H=CH_2$), 120.2 ($CH=\mathbf{C}H_2$), 116.2 (C≡N), 63.0 ($O\mathbf{C}H_2CH_3$), 37.6 (CH_2), 34.0 (CH), 14.1 ($OCH_2\mathbf{C}H_3$) ppm.

Ethyl 2-allyl-2-cyanopent-4-enoate 302



76% yield (2.98 g, 15.4 mmol); The spectroscopic data are in agreement with literature.[48] **^{1}H NMR (400 MHz, CDCl$_3$)**: δ = 5.96 – 5.67 (m, 2H, 2 $CH_2C\mathbf{H}=CH_2$), 5.25 – 5.22 (m, 4H, 2 $CH_2CH=C\mathbf{H_2}$), 4.25 (q, *J* = 7.1 Hz, 2H, $OC\mathbf{H_2}CH_3$), 2.64 (dd, *J* = 13.8, 7.4 Hz, 2H, 2 $C\mathbf{H_A}H_BCH=CH_2$), 2.54 (dd, *J* = 13.8, 7.2 Hz, 2H, 2 $CH_A\mathbf{H_B}CH=CH_2$), 1.30 (t, *J* = 7.1 Hz, 3H, $OCH_2C\mathbf{H_3}$) ppm; **^{13}C NMR (125 MHz, CDCl$_3$)**: δ = 168.1 (C=O), 130.6 (2 $\mathbf{C}H=CH_2$), 121.1 (2 $CH=\mathbf{C}H_2$), 118.6 (C≡N), 62.8 ($O\mathbf{C}H_2CH_3$), 49.4 (C), 40.8 (2 CH_2), 14.3 ($OCH_2\mathbf{C}H_3$) ppm.

2-(Methoxycarbonyl)-2-(prop-2-yn-1-yl)pent-4-enoic acid 306



Dimethyl 2-allyl-2-(prop-2-yn-1-yl)malonate **297** (294 mg, 1.40 mmol) was dissolved in methanol (5 mL). Sodium hydroxide (1.4 mL, 2 N, 2.8 mmol) was added and the resulting solution was stirred at room temperature for 3 h. The reaction was cooled to 0 °C, quenched with HCl (5 mL, 1 N) and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ to yield the pure product as a colourless oil (96% yield, 263 mg, 1.34 mmol).

The spectroscopic data are in agreement with literature.[49] **^{1}H NMR (400 MHz, CDCl$_3$)**: δ = 5.65 (ddt, *J* = 17.5, 10.1, 7.5 Hz, 1H, $C\mathbf{H}=CH_2$), 5.24 – 5.15 (m, 2H, $CH=C\mathbf{H_2}$), 3.79

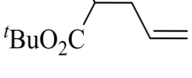
(s, 3H, OCH_3), 2.88 – 2.77 (m, 4H, 2 CH_2), 2.06 (t, *J* = 2.7 Hz, 1H, C≡C**H**) ppm; **^{13}C NMR (125 MHz, $CDCl_3$)**: δ = 173.4 (COOH), 170. (**C**OOMe), 131.4 (**C**=CH_2), 120.4 (C=**C**H_2), 78.6 (**C**≡CH), 71.9 (C≡**C**H), 57.1 (C), 53.2 (OCH_3), 37.4 (**C**H_2CH=CH_2), 23.4 (**C**H_2C≡CH) ppm.

Mono- and di-alkylation of di-*tert*-butyl malonate

To a solution of di-*tert*-butyl malonate (1.93 g, 8.93 mmol) in dry THF (20 mL), sodium hydride (0.357 g, 60% in mineral oil, 8.93 mmol) was added portionwise at 0 °C. The resulting mixture was stirred for 30 minutes. Allyl bromide (0.77 mL, 8.93 mmol) was added dropwise, the reaction was warmed up to room temperature and stirred for 20 h. The reaction was then cooled to 0 °C, quenched with water and extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with brine (25 mL), dried over $MgSO_4$ and concentrated under vacuum. The resulting pale yellow oil was used without further purification for the second alkylation (70% conversion to the desired product).

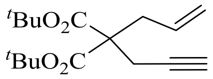
To a solution of di-*tert*-butyl 2-allylmalonate (1.5 g, 70% purity, 5.85 mmol) in dry THF (20 mL), sodium hydride (0.234 g, 60% in mineral oil, 5.85 mmol) was added portionwise at 0 °C. The resulting mixture was stirred for 30 minutes. Propargyl bromide (solution, 80 wt.% in toluene, 0.87 mL, 5.85 mmol) was added dropwise, the reaction was warmed up to room temperature and stirred for 20 h. It was then cooled to 0 °C, quenched with water and extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with brine (25 mL), dried over $MgSO_4$ and concentrated under vacuum. After purification by column chromatography, the pure product was obtained as colourless solid (68% yield, 820 mg, 2.79 mmol).

Di-tert-butyl 2-allylmalonate 308



^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.78 (ddt, *J* = 17.0, 10.1, 6.8 Hz, 1H, CH_2C**H**=CH_2), 5.18 – 4.97 (m, 2H, CH_2CH=C**H₂**), 3.21 (t, *J* = 7.6 Hz, 1H, CH), 2.55 (t, *J* = 7.2 Hz, 2H, C**H₂**CH=CH_2), 1.45 (s, 18H, 6 CH_3) ppm.

Di-tert-butyl 2,2-diallylmalonate 309



^{1}H NMR (300 MHz, CDCl$_3$): δ = 5.63 (ddt, *J* = 17.4, 10.0, 7.5 Hz, 1H, C**H**=CH$_2$), 5.24 – 5.08 (m, 2H, CH=C**H$_2$**), 2.75 – 2.66 (m, 4H, 2 CH$_2$), 2.00 (t, J = 2.7 Hz, 1H, C≡CH), 1.45 (s, 18H, 6 CH$_3$) ppm; **^{13}C NMR (125 MHz, CDCl$_3$):** δ = 169.1 (2 C=O), 132.3 (**C**H=CH$_2$), 119.6 (CH=**C**H$_2$), 81.9 (**C**≡CH), 71.2 (C≡**C**H), 57.4 (C), 36.3 (**C**H$_2$CH=CH$_2$), 28.0 (6 CH$_3$), 22.5 (**C**H$_2$C≡CH) ppm.

7.4.3.2. Cyclisation reaction

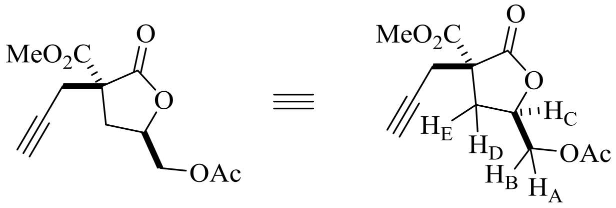
General procedure for the cyclisation reaction GP4

Iodine(III) reagent (1 to 1.5 eq.) was dissolved in dry dichloromethane (2 mL) under argon and cooled down to -20 °C. Lewis acid (2 or 3 eq.) was then added and the resulting mixture was stirred for 5 minutes. A solution of starting material (0.28 mmol) in dry dichloromethane (2 mL) was then added and the resulting mixture was stirred for 20 h at the temperature mentioned in Table 5.1. The reaction was quenched with sat. aq. solution of sodium bicarbonate (0. 5 mL) and the organic phase was extracted with dichloromethane (3 x 5 mL). The combined organic layers were dried through a Telos® phase separator and concentrated under vacuum. The pure product was obtained after purification by column chromatography (0 to 30% EtOAc in hexane).

General procedure with the optimised conditions for the cyclisation reaction GP5.

PhI(OAc)$_2$ (108 mg, 0.340 mmol) was dissolved in dry dichloromethane (2 mL) under argon and the reaction was cooled down to -20 °C. BF$_3$•OEt$_2$ (70 µL, 0.56 mmol) and AcOH (200 µL, 3.5 mmol) was then added and the resulting mixture was stirred for 5 minutes. A solution of starting material (0.28 mmol) in dry dichloromethane (2 mL) was then added and the resulting mixture was stirred for 19 h at -20 °C. The reaction was quenched with sat. aq. solution of sodium bicarbonate (0.5 mL) and the organic phase was extracted with dichloromethane (3 x 5 mL). The combined organic layers were dried through a Telos® phase separator and concentrated under vacuum. The pure product was obtained after purification by column chromatography (0 to 30% EtOAc in hexane).

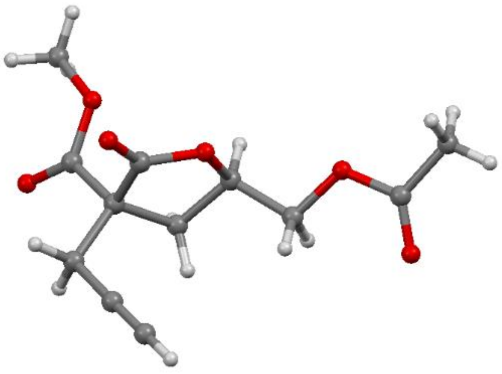
Methyl 5-(acetoxymethyl)-2-oxo-3-(prop-2-yn-1-yl)tetrahydrofuran-3-carboxylate 298a



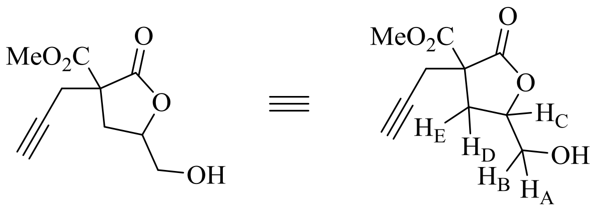
The product **298a** was synthesised using general procedure **GP5** at -20 °C for 20 h (0.28 mmol scale) (58% yield, 42 mg, 0.162 mmol).

Colourless oil; **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 4.87 (dtd, *J* = 9.7, 6.3, 3.1 Hz, 1H, H_C), 4.39 (dd, *J* = 12.4, 3.1 Hz, 1H, H_A), 4.18 (dd, *J* = 12.4, 6.1 Hz, 1H, H_B), 3.81 (s, 3H, OCH_3), 2.90 (t, *J* = 2.4 Hz, 2H, C**H_2**C≡CH), 2.71 (dd, *J* = 13.4, 6.6 Hz, 1H, H_D), 2.41 (dd, *J* = 13.4, 10.0 Hz, 1H, H_E), 2.11 (s, 3H, CH_3 (OAc)), 2.09 (t, *J* = 2.6 Hz, 1H, CH_2C≡C**H**) ppm; **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 172.2 (C=O), 170.6 (C=O), 168.7 (C=O), 78.4 (**C**≡CH), 75.8 (**C**HOAc), 72.2 (C≡**C**H), 64.4 (OCH_2), 54.7 (C), 53.7 (OCH_3), 32.2 (CH_2), 23.9 (**C**H_2C≡CH), 20.8 (CH_3 (OAc)) ppm; **IR (neat)**: 3281, 2916, 2387, 1776, 1736, 1537, 1435, 1232, 1178, 1038 cm^{-1}; **HRMS (AP+)**: $[M+H]^+$ calc. 255.0869, found 255.0869 $[C_{12}H_{15}O_6]^+$.

After 2 years at r.t. the colourless oil crystallised and the resulting crystal structure established the ring size of the lactone to be a 5-membered ring.



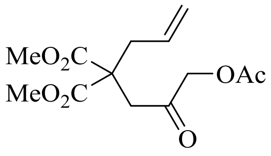
Methyl 5-(hydroxymethyl)-2-oxo-3-(prop-2-yn-1-yl)tetrahydrofuran-3-carboxylate 298b



The product **298b** was synthesised using general procedure **GP4** at -20 °C for 20 h (0.28 mmol scale) (39% yield of a mixture 2:1 of both enantiomers, 20 mg, 0.094 mmol).

Colourless oil; **^{1}H NMR (400 MHz, CDCl$_3$):** δ = 4.73 – 4.68 (m, 1.5H, H$_C$ (major) + H$_C$ (minor)), 3.91 (dd, *J* = 12.8, 2.7 Hz, 1H, H$_A$ (major)), 3.83 (dd, *J* = 12.6, 3.1 Hz, 0.5H, H$_A$ (minor)), 3.74 (s, 3H , OCH$_3$ (major)), 3.73 (s, 1.5H , OCH$_3$ (minor)), 3.67 (dd, *J* = 12.8, 4.3 Hz, 0.5H, H$_B$ (minor)), 3.63 (dd, *J* = 12.8, 4.3 Hz, 1H, H$_B$ (major)), 2.84 – 2.82 (m, 3H, CH$_2$ (major) + CH$_2$ (minor)), 2.67 (dd, *J* = 13.7, 7.0 Hz, 0.5H, H$_D$ (minor)), 2.58 (dd, *J* = 13.3, 6.6 Hz, 1H, H$_D$ (major)), 2.53 (dd, *J* = 13.7, 8.1 Hz, 0.5H, H$_E$ (minor)), 2.53 (dd, *J* = 13.3, 9.7 Hz, 1H, H$_E$ (major)), 2.03 (t, *J* = 2.7 Hz, 0.5H, C≡C**H** (minor)), 2.02 (t, *J* = 2.6 Hz, 1H, C≡C**H** (major)) ppm; **IR (neat)**: 3476, 3277, 1769, 1732, 1435, 1248, 1180, 1030 cm^{-1}; **HRMS (ES-)**: [M-H]$^-$ calc. 211.0606, found 211.0605 [C$_{10}$H$_{11}$O]$^-$.

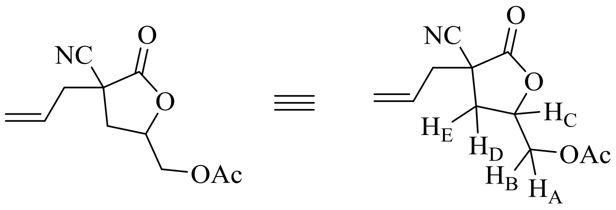
Dimethyl 2-(3-acetoxy-2-oxopropyl)-2-allylmalonate 299



The product **299** was a side-product synthesised using general procedure **GP4** at -20 °C for 20 h (0.28 mmol scale).

Colourless oil; **^{1}H NMR (400 MHz, CDCl$_3$)**: δ = 5.66 – 5.56 (m, 1H, CH$_2$C**H**=CH$_2$), 5.14 – 5.09 (m, 2H, CH$_2$CH=C**H$_2$**), 4.65 (s, 2H, C**H$_2$**OAc), 3.74 (s, 6H, 2 OCH$_3$), 3.05 (s, 2H, C**H$_2$**C=O), 2.77 (d, *J* = 7.0 Hz, 2H, C**H$_2$**CH=CH$_2$), 2.15 (s, 3H, CH$_3$ (OAc)) ppm; **^{13}C NMR (125 MHz, CDCl$_3$)**: δ = 200.8 (C=O), 170.6 (2 **C**(O)OCH$_3$), 170.2 (C=O (OAc)), 132.4 (**C**H=CH$_2$), 120.2 (CH=**C**H$_2$), 68.0 (**C**H$_2$OAc), 55.2 (C), 53.0 (2 OCH$_3$), 41.2 (CH_2), 38.0 (CH_2), 20.5 (CH_3) ppm; **IR (neat)**: 2957, 1732, 1435, 1221, 1040 cm^{-1}; **HRMS (ES+)**: $[M+Na]^+$ calc. 309.0950, found 309.0936 $[C_{13}H_{18}NO_7Na]^+$.

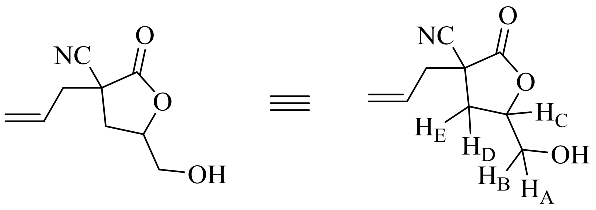
(4-Allyl-4-cyano-5-oxotetrahydrofuran-2-yl)methyl acetate 303a



The product **303a** was synthesised from molecule **302** using general procedure **GP5** at -20 °C for 20 h (0.24 mmol scale) (43% yield, 24 mg, 0.103 mmol).

Pale yellow oil; **^{1}H NMR (500 MHz, CDCl$_3$)**: δ = 5.84 – 5.76 (m, 1H, $CH_2C\mathbf{H}=CH_2$), 5.36 – 5.31 (m, 2H, $CH_2CH=C\mathbf{H_2}$), 4.91 – 4.86 (m, 1H, H_C), 4.39 (dd, *J* = 12.6, 3.2 Hz, 1H, H_A), 4.17 (dd, *J* = 12.6, 5.4 Hz, 1H, H_B), 2.87 (dd, *J* = 14.1, 7.2 Hz, 1H, H_F), 2.69 (dd, *J* = 13.5, 6.2 Hz, 1H, H_D), 2.60 (dd, *J* = 15.0, 8.2 Hz, 1H, H_G), 2.17 (dd, *J* = 13.5, 10.1 Hz, 1H, H_E), 2.11 (s, 3H, CH_3 (OAc)) ppm; **^{13}C NMR (125 MHz, CDCl$_3$)**: δ = 170.3 (C=O), 169.0 (C=O), 129.7 ($\mathbf{C}H=CH_2$), 122.4 ($CH=\mathbf{C}H_2$), 116.8 ($\mathbf{C}\equiv N$), 75.6 ($\mathbf{C}$HOAc), 63.6 ($O\mathbf{C}H_2$), 43.5 (C), 39.3 (CH_2), 34.9 (CH_2), 20.7 (CH_3 (OAc)) ppm; **IR (neat)**: 2959, 2320, 1778, 1742, 1443, 1370, 1236, 1182, 1011, 933 cm^{-1}; **HRMS (ES+)**: $[M+H]^+$ calc. 224.0923, found 224.0925 $[C_{11}H_{14}NO_4]^+$.

3-Allyl-5-(hydroxymethyl)-2-oxotetrahydrofuran-3-carbonitrile 303b

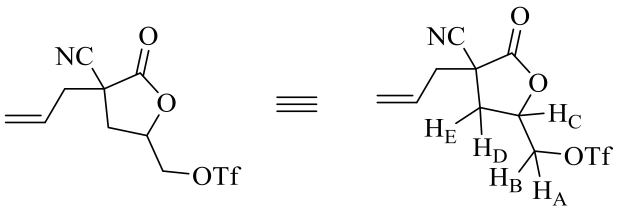


The product **303b** was synthesised from molecule **302** and iodosylbenzene using general procedure **GP4** at -20 °C for 20 h (0.24 mmol scale) (37% yield for both diastereomers, 44 mg, 0.089 mmol; 28% yield for major isomer, 12 mg, 0.066 mmol; 9% yield for minor isomer, 4 mg, 0.022 mmol).

<u>*Major diastereoisomer*</u>: Pale yellow oil; **^{1}H NMR (400 MHz, CDCl$_3$)**: δ = 5.88 – 5.76 (m, 1H, $CH_2C\mathbf{H}{=}CH_2$), 5.37 – 5.29 (m, 2H, $CH_2CH{=}C\mathbf{H_2}$), 4.78 (ddd, *J* = 12.5, 6.2, 3.1 Hz, 1H, H_C), 4.05 (dd, *J* = 12.9, 2.6 Hz, 1H, H_A), 3.65 (dd, *J* = 12.9, 3.3 Hz, 1H, H_B), 2.87 (ddt, *J* = 14.1, 6.9, 1.1 Hz, 1H, H_F), 2.64 – 2.54 (m, 2H, H_D + H_G), 2.41 (dd, *J* = 13.5, 9.7 Hz, 1H, H_E) ppm; **^{13}C NMR (125 MHz, CDCl$_3$)**: δ = 169.7 (C=O), 131.5 ($\mathbf{C}H{=}CH_2$), 121.9 ($CH{=}\mathbf{C}H_2$), 117.1 (C≡N), 78.4 (CHOH), 61.9 (OCH_2), 43.7 (C), 39.1 ($\mathbf{C}H_2CH{=}CH_2$), 33.6 (CH_2) ppm; **IR (neat)**: 3424, 2936, 2981, 1771, 1439, 1350, 1184, 1094, 995, 931 cm^{-1}; **HRMS (EI+)**: $[M]^+$ calc. 181.0739, found 181.0737 $[C_9H_{11}NO_3]^+$.

<u>*Minor diastereoisomer*</u>: Pale yellow oil; **^{1}H NMR (400 MHz, CDCl$_3$)**: δ = 5.84 – 5.72 (m, 1H, $CH_2C\mathbf{H}{=}CH_2$), 5.35 – 5.24 (m, 2H, $CH_2CH{=}C\mathbf{H_2}$), 4.56 (tdd, *J* = 7.3, 4.1, 2.9 Hz, 1H, H_C), 3.92 (dd, *J* = 12.6, 2.9 Hz, 1H, H_A), 3.65 (dd, *J* = 12.6, 4.1 Hz, 1H, H_B), 2.73 (dd, *J* = 13.9, 6.8 Hz, 1H, H_F), 2.63 (dd, *J* = 13.6, 7.6 Hz, 1H, H_D), 2.54 (dd, *J* = 13.9, 7.7 Hz, 1H, H_G), 2.41 (dd, *J* = 13.6, 7.3 Hz, 1H, H_E) ppm; **^{13}C NMR (125 MHz, CDCl$_3$)**: δ = 169.8 (C=O), 129.7 ($\mathbf{C}H{=}CH_2$), 122.5 ($CH{=}\mathbf{C}H_2$), 120.7 (C≡N), 78.4 (CHOH), 62.1 (OCH_2), 43.6 (C), 40.0 ($\mathbf{C}H_2CH{=}CH_2$), 32.8 (CH_2) ppm; **IR (neat)**: 3420, 2934, 2289, 1769, 1441, 1366, 1188, 1020, 932 cm^{-1}.

(4-Allyl-4-cyano-5-oxotetrahydrofuran-2-yl)methyl trifluoromethanesulfonate 303c

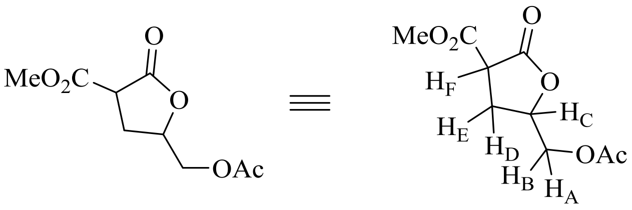


The product **303c** was synthesised using general procedure **GP5** (TMSOTf was used instead of $BF_3{\bullet}OEt_2$) at -20 °C for 20 h (0.24 mmol scale) (28% yield, 21 mg, 0.067 mmol).

Colourless oil; **^{1}H NMR (300 MHz, CDCl$_3$):** δ = 5.72 (ddt, *J* = 17.5, 10.3, 7.3 Hz, 1H, $CH_2C\mathbf{H}{=}CH_2$), 5.36 – 5.23 (m, 2H, $CH_2CH{=}C\mathbf{H_2}$), 4.89 (dddd, *J* = 10.2, 6.5, 4.1, 2.7 Hz, 1H, H_C), 4.75 (dd, *J* = 11.8, 2.7 Hz, 1H, H_A), 4.49 (dd, *J* = 11.8, 4.1 Hz, 1H, H_B), 2.82 (dd, *J* = 14.1, 7.1 Hz, 1H, H_F), 2.70 (dd, *J* = 13.7, 6.4 Hz, 1H, H_D), 2.56 (dd, *J* = 14.1, 7.4 Hz, 1H, H_G), 2.23 (dd, *J* = 13.7, 10.0 Hz, 1H, H_E) ppm; **^{13}C NMR (125 MHz, CDCl$_3$):** δ = 168.1 (C=O), 129.1 ($CH{=}\mathbf{C}H_2$), 123.0 ($\mathbf{C}H{=}CH_2$), 116.4 (C≡N), 74.0 (CHOTf), 73.1

(OCH$_2$), 43.3 (C), 39.2 (CH$_2$), 33.6 (CH$_2$) ppm; **IR (neat)**: 3437, 2920, 1765, 1641, 1441, 1246, 1182, 1028, 930 cm^{-1}.

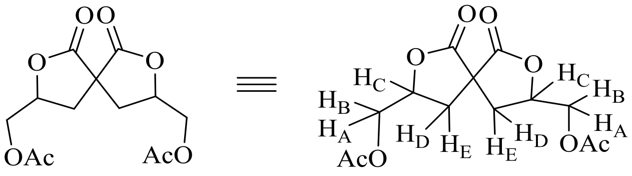
Methyl 5-(acetoxymethyl)-2-oxotetrahydrofuran-3-carboxylate 304



The product **304** was synthesised from molecule **294** using general procedure **GP5** at -20 °C for 20 h (0.28 mmol scale) (61% conversion, could not be fully isolated).

Pale yellow oil; **^{1}H NMR (400 MHz, CDCl$_3$)**: δ = 4.78 (tdd, *J* = 6.6, 4.1, 2.6 Hz, 1H, C**H**OAc), 3.97 (dd, *J* = 13.0, 2.6 Hz, 1H, H$_A$), 3.78 (s, 2H, OCH$_3$), 3.75 (dd, *J* = 4.5, 2.7 Hz, 2H, H$_F$), 3.63 (dd, *J* = 13.0, 4.2 Hz, 1H, H$_B$), 3.08 (dd, *J* = 13.6, 6.5 Hz, 1H, H$_D$), 2.44 (dd, *J* = 13.6, 9.5 Hz, 1H, H$_E$), 2.14 (s, 2H, CH$_3$ (OAc)) ppm; **HRMS (ES+)**: [M+Na]$^+$ calc. 239.0532, found 239.0530 [C$_9$H$_{12}$O$_6$Na]$^+$.

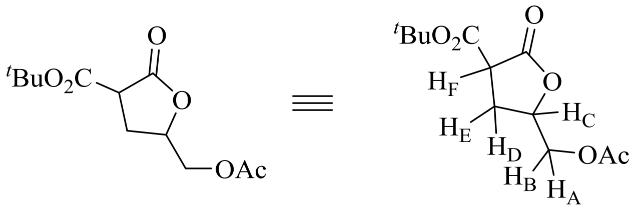
(1,6-Dioxo-2,7-dioxaspiro[4.4]nonane-3,8-diyl)bis(methylene) diacetate 305



The product **305** was synthesised from molecule **295** using general procedure **GP5** at -20 °C for 20 h (0.28 mmol scale) (15% yield, 13 mg, 0.042 mmol).

Light yellow oil; **^{1}H NMR (400 MHz, CDCl$_3$)**: δ = 5.16 – 5.06 (m, 2H, H$_C$), 4.39 (dd, *J* = 12.6, 3.0 Hz, 2H, H$_A$), 4.18 (dd, *J* = 12.6, 5.3 Hz, 2H, H$_B$), 2.86 (dd, *J* = 13.2, 6.8 Hz, 2H, H$_D$), 2.15 (dd, *J* = 11.9, 7.6 Hz, 2H, H$_E$), 2.12 (s, 6H, 2 CH$_3$ (OAc)) ppm; **^{13}C NMR (125 MHz, CDCl$_3$)**: δ = 172.7 (2 C=O), 170.4 (2 C=O), 76.2 (2 **C**HOAc), 64.0 (2 OCH$_2$), 52.6 (C), 34.6 (2 CH$_2$), 20.8 (2 OAc) ppm; **IR (neat)**: 2963, 1740, 1370, 1258, 1229, 1018, 795 cm^{-1}; **HRMS (ES-)**: [M+Cl]$^-$ calc. 335.0534, found 335.0536 [C$_{13}$H$_{16}$NO$_8$Cl]$^-$

***tert*-Butyl 5-(acetoxymethyl)-2-oxotetrahydrofuran-3-carboxylate 311**



The product **311** was synthesised using general procedure **GP5** at -20 °C for 20 h (0.098 mmol scale) (70% yield for the mixture of both diastereomers (1.2:1 ratio *cis*:*trans*), 18 mg, 0.068 mmol).

Pale yellow oil; **^{1}H NMR (300 MHz, $CDCl_3$)**: δ = 4.91 – 4.81 (m, 1H, H_C (*Cis*-isomer)), 4.72 – 4.62 (m, 1H, H_C (*Trans*-isomer)), 4.36 (dd, *J* = 7.1, 3.1 Hz, 1H, H_A (*Trans*-isomer)), 4.32 (dd, *J* = 7.1, 3.1 Hz, 1H, H_A (*Cis*-isomer)), 4.20 (dd, *J* = 12.3, 6.6 Hz, 1H, H_B (*Trans*-isomer)), 4.13 (dd, *J* = 12.4, 4.9 Hz, 1H, H_B (*Cis*-isomer)), 3.60 – 3.51 (m, 2H, H_F (Both isomers)), 2.71 (ddd, *J* = 13.3, 7.9, 6.0 Hz, 1H, H_D (*Cis*-isomer)), 2.58 – 2.36 (m, 2H, H_D and H_E (*Trans*-isomer)), 2.25 (ddd, 1H, H_E (*Cis*-isomer)), 2.11 (s, 3H, OAc (*Trans*-isomer)), 2.11 (s, 3H, OAc (*Cis*-isomer)), 1.50 (s, 9H, 3 CH_3 (*Cis*-isomer)), 1.50 (s, 9H, 3 CH_3 (*Trans*-isomer)) ppm; **^{13}C NMR (125 MHz, $CDCl_3$)**: *Cis*-isomer: δ = 171.7 (C=O), 170.6 (C=O), 166.7 (C=O), 83.5 (**C**(CH_3)$_3$), 76.5 (**C**H_COAc), 65.2 (OCH_2), 47.6 (CH_F), 28.3 (CH_2), 28.0 (3 CH_3 (^{t}Bu)), 20.9 (CH_3 (OAc)) ppm; *Trans*-isomer: δ = 171.5 (C=O), 170.8 (C=O), 166.5 (C=O), 83.4 (**C**(CH_3)$_3$), 76.0 (**C**H_COAc), 65.0 (OCH_2), 47.6 (CH_F), 27.9 (CH_2), 28.0 (3 CH_3 (^{t}Bu)), 20.8 (CH_3 (OAc)) ppm; **IR (neat)**: 2963, 1774, 1736, 1369, 1258, 1231, 1080, 1013, 793 cm^{-1}; **HRMS (ES+)**: [M+Na]$^+$ calc. 281.1001, found 2813.0999 [$C_{12}H_{18}O_6Na$]$^+$.

NOESY NMR data:

To determine which isomers were *cis* and *trans*, a NOESY experiment was recorded. In one of the two stereoisomers, an interaction through the space can be obserbed between H_C and H_F. This suggests that those two protons are *cis* to each other and that the major isomer was therefore the *cis* cyclised lactone **311**. In the NOESY spectrum below (Figure 7.2), the *cis*-isomer is shown in red while the *trans*-isomer is represented in green.

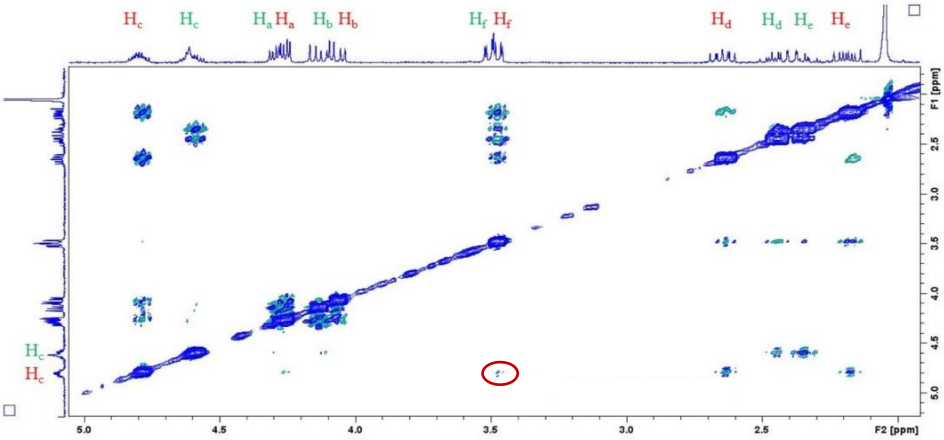
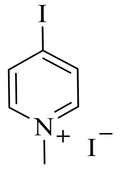


Figure 7.2. NOESY experiment of molecule 311.

7.4.4. Synthesis of new iodine reagents and their application

7.4.4.1. Iodopyridine

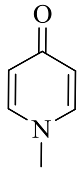
4-Iodo-1-methylpyridin-1-ium iodide 320



A solution of 4-iodopyridine (212 mg, 1.03 mmol) in methyl iodide (2.0 mL) was stirred at room temperature for 14 h under argon atmosphere and in the dark. After evaporation of the solvent under vacuum, the pure product was obtained as a pale yellow solid (95% yield, 340 mg, 0.978 mmol).

m.p. = 65 - 68 °C; **^{1}H NMR (300 MHz, DMSO-d$_6$)**: δ = 8.64 (d, *J* = 6.8 Hz, 2H, H-Ar), 8.59 (d, *J* = 6.9 Hz, 2H, H-Ar), 4.20 (s, 1H, CH_3) ppm; **^{13}C NMR (125 MHz, DMSO-d$_6$)**: δ = 144.8 (2 C_{Ar}H), 119.4 (C_{Ar}H), 106.4 (C_{Ar}), 47.6 (CH_3) ppm.

1-Methylpyridin-4(1H)-one 321

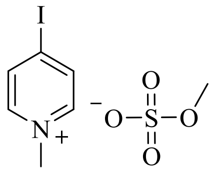


4-Iodo-1-methylpyridin-1-ium iodide **320** (50 mg, 0.14 mmol) was dissolved in glacial acetic acid. $NaBO_3•4H_2O$ (222 mg, 1.44 mmol) was slowly added and the resulting mixture was stirred at 55 °C for 5 h and became progressively red coloured. The solvent was evaporated to yield an off-white solid. The resulting solid was diluted with $CHCl_3$ (4 mL) and the solid was discarded by filtration. The pure product was isolated as a pale yellow oil after evaporation of the solvent under vacuum (70% yield, 11 mg, 0.101 mmol).

The spectroscopic data are in agreement with literature.[50] **^{1}H NMR (400 MHz, CDCl$_3$)**: δ = 7.34 – 7.30 (m, 2H, H-Ar), 6.58 – 6.54 (m, 2H, H-Ar), 3.70 (s, 3H, CH_3) ppm;

^{13}C NMR (125 MHz, CDCl$_3$): δ = 179.0 (C=O), 144.1 (2 CH), 117.1 (2 CH), 44.0 (CH$_3$) ppm; **MS (ES+)**: m/z 110 ([M+H]$^+$.

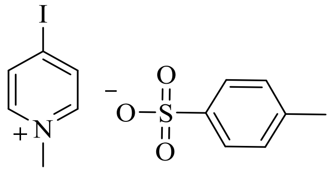
4-Iodo-1-methylpyridin-1-ium methyl sulfate 322



To a solution of 4-iodopyridine (150 mg, 0.732 mmol) in CH$_2$Cl$_2$ (2 mL), methyl sulfate (139 µL, 1.46 mmol) was added under nitrogen. The resulting mixture was heated at reflux and stirred for 24 h. The solvent was evaporated under vacuum and the desired product was obtained as colourless solid (83% yield, 200 mg, 0.607 mmol).

m.p. = 58 - 61 °C; **^{1}H NMR (400 MHz, DMSO-d$_6$)**: δ = 8.64 (d, *J* = 6.4 Hz, 2H, H-Ar), 8.60 (d, *J* = 6.2 Hz, 2H, H-Ar), 4.20 (s, 3H, N-CH$_3$), 3.36 (s, 3H, OCH$_3$) ppm; **^{13}C NMR (125 MHz, DMSO-d$_6$)**: δ = 144.9 (2 C$_{Ar}$H), 136.8 (2 C$_{Ar}$H), 118.8 (C$_{Ar}$), 52.8 (OCH$_3$), 47.6 (N-**C**H$_3$) ppm.

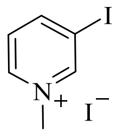
4-Iodo-1-methylpyridin-1-ium 4-methylbenzenesulfonate 333



A solution of Koser's reagent (226 mg, 0.576 mmol) and 4-iodo-1-methylpyridin-1-ium iodide **320** (200 mg , 0.576 mmol) in acetonitrile (10 mL) was stirred at room temperature for 24 h. The resulting solid was filtered to yield pure 4-iodo-1-methylpyridin-1-ium 4-methylbenzenesulfonate **333** as a pale yellow solid (95% yield, 214 mg, 0.547 mmol).

^{1}H NMR (300 MHz, DMSO-d$_6$): δ = 8.63 (d, *J* = 6.8 Hz, 2H, H-Ar), 8.59 (d, *J* = 7.0 Hz, 2H, H-Ar), 7.50 – 7.43 (m, 2H, H-Ar (Ts)), 7.11 (dd, *J* = 8.4, 0.6 Hz, 2H, H-Ar (Ts)), 4.20 (s, 3H, N-CH$_3$), 2.28 (s, 3H, CH$_3$).

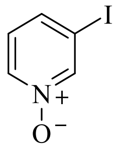
3-Iodo-1-methylpyridin-1-ium iodide 335



A solution of 3-iodopyridine (424 mg, 2.06 mmol) in methyl iodide (4.0 mL) was stirred at room temperature for 14 h under argon atmosphere and in the dark. After evaporation of the solvent under vacuum, the pure product was obtained as a pale yellow solid (91% yield, 663 mg, 1.91 mmol).

m.p. = 172 - 174 °C; **^{1}H NMR (400 MHz, DMSO-d$_6$)**: δ = 9.39 (s, 1H, H-Ar), 9.00 (d, *J* = 6.0 Hz, 1H, H-Ar), 8.92 (d, *J* = 8.2 Hz, 1H, H-Ar), 7.95 – 7.86 (m, 1H, H-Ar), 4.28 (s, 3H, CH_3) ppm; **^{13}C NMR (125 MHz, DMSO-d$_6$)**: δ = 152.4 (C_{Ar}H), 150.7 (C_{Ar}H), 144.5 (C_{Ar}H), 128.2 (C_{Ar}H), 96.0 (C_{Ar}), 47.7 (CH_3) ppm.

3-Iodopyridine 1-oxide 337

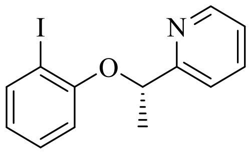


To a solution of 3-iodopyridine (200 mg, 0.976 mmol) in CH_2Cl_2 (20 mL), *m*-CPBA (240 mg, 1.073 mmol) was added. The resulting mixture was stirred at r.t. for 20 h. The solvent was evaporated. After addition of diethyl ether (5 mL), the product precipitate as a yellow crystalline compound (80% yield, 173 mg, 0.781 mmol).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.52 (t, *J* = 1.4 Hz, 1H, H-Ar), 8.17 (ddd, *J* = 6.5, 1.7, 0.9 Hz, 1H, H-Ar), 7.59 (ddd, *J* = 8.1, 1.4, 0.9 Hz, 1H, H-Ar), 7.03 (dd, *J* = 8.0, 6.6 Hz, 1H, H-Ar) ppm; **^{13}C NMR (75 MHz, $CDCl_3$)**: δ = 145.5 (C_{Ar}H), 138.7 (C_{Ar}H), 134.3 (C_{Ar}H), 126.4 (C_{Ar}H), 91.1 (C_{Ar}) ppm; **MS (AP+)**: m/z 222 ($[M+H]^+$).

7.4.4.2. Synthesis of (*S*)-316

(*S*)-2-(1-(2-iodophenoxy)ethyl)pyridine (*S*)-344

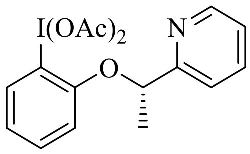


To a solution of 2-iodophenol **343** (357 mg, 1.62 mmol), (*R*)-2-(1-Hydroxyethyl)pyridine **342** (250 mg, 2.03 mmol) and triphenylphosphine (532 mg, 2.03 mmol) in dry THF (25 mL), DIAD (400 µL, 2.03 mmol) was added at 0 °C under dark conditions. The resulting mixture was warmed up to room temperature and stirred for 20 h. The solvent was removed under vacuum and the pure product **(*S*)-344** was obtained after column chromatography (0 to 20% EtOAc in hexane) as a colourless oil (92% yield, 486 mg, 1.49 mmol).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.56 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H, H-Ar), 7.77 (dd, *J* = 7.8, 1.6 Hz, 1H, H-Ar), 7.68 (td, *J* = 7.7, 1.8 Hz, 1H, H-Ar), 7.56 – 7.49 (m, 1H, H-Ar), 7.23 – 7.10 (m, 2H, H-Ar), 6.72 – 6.61 (m, 2H, H-Ar), 5.47 (q, *J* = 6.5 Hz, 1H, CH), 1.73 (d, *J* = 6.5 Hz, 3H, CH$_3$) ppm; **^{13}C NMR (75 MHz, CDCl$_3$)**: δ = 162.0 (C$_{Ar}$), 156.3 (C$_{Ar}$), 149.0 (C$_{Ar}$), 139.6 (C$_{Ar}$), 137.4 (C$_{Ar}$), 129.4 (C$_{Ar}$), 122.7 (C$_{Ar}$), 122.6 (C$_{Ar}$), 120.0 (C$_{Ar}$), 114.0 (C$_{Ar}$), 87.2 (C$_{Ar}$-I), 78.3 (O-CH), 22.7 (CH$_3$) ppm; **IR (neat)**: 3059, 2978, 2360, 1582, 1470, 1435, 1273, 1238, 1072, 1018, 748 cm^{-1}; **HRMS (EI)**: [M]$^+$ calc. 324.9964, found 324.9963 [C$_{13}$H$_{12}$NOI]$^+$; **MS (EI)**: m/z 325 (M$^+$, 10%), 220 (97%), 198 (100%), 106 (99%), 78 (58%); ***ee***: 92%, determined by HPLC analysis: *YMC* Chiral Amylose-C S-5µm (25 cm), hexane/*i*-PrOH: 99/1, 0.7 mL/min, 10 °C, 289 nm, T$_r$ (major, (*S*)-isomer) = 16.0 min, T$_r$ (minor, (*R*)-isomer) = 18.3 min; $[\alpha]_D^{20}$ = +122.2 (c = 1.10, CHCl$_3$).

The absolute configuration of the major enantiomer was assumed to be the (*S*)-isomer as the Mitsunobu reaction proceeds with inversion of configuration and (*R*)-2-(1-hydroxyethyl)pyridine was used as reagent.

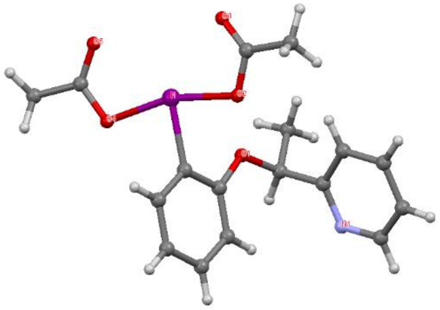
(*S*)-(2-(1-(Pyridin-2-yl)ethoxy)phenyl)-l3-iodanediyl diacetate (*S*)-316



(*S*)-2-(1-(2-iodophenoxy)ethyl)pyridine **(*S*)-344** (100 mg, 0.308 mmol) and Selectfluor® (545 mg, 1.54 mmol) were flushed under a flow of N_2 for 30 minutes. After addition of CH_3CN (9.8 mL) and glacial acetic acid (3 mL), the mixture was stirred at room temperature for 20 h. The solvents were evaporated, water (30 mL) was added and the organic phase was extracted with CH_2Cl_2 (3 x 25 mL), dried over $MgSO_4$ and concentrated under vacuum. The resulting oil slowly solidified to obtain a pale yellow solid that was used without further purification (92% yield, 126 mg, 0.284 mmol). For the analysis, a recrystallisation from CH_2Cl_2/hexane led to the formation of colourless crystals.

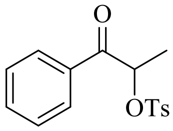
m.p. = 128 - 131 °C; **^{1}H NMR (400 MHz, CDCl$_3$)**: δ = 8.59 (ddd, *J* = 5.0, 1.8, 0.9 Hz, 1H, H-Ar), 8.13 (dd, *J* = 8.2, 1.6 Hz, 1H, H-Ar), 7.74 (td, *J* = 7.7, 1.7 Hz, 1H, H-Ar), 7.59 (d, *J* = 7.9 Hz, 1H, H-Ar), 7.47 – 7.39 (m, 1H, H-Ar), 7.31 – 7.27 (m, 1H, H-Ar), 7.03 – 6.96 (m, 2H, H-Ar), 5.68 (q, *J* = 6.5 Hz, 1H, CH), 2.01 (s, 3H, CH_3 (OAc)), 1.93 (s, 3H, CH_3 (OAc)), 1.70 (d, *J* = 6.5 Hz, 3H, CH_3) ppm; **^{13}C NMR (125 MHz, CDCl$_3$)**: δ = 176.8 (C=O), 175.8 (C=O), 160.8 (C_{Ar}), 154.3 (C_{Ar}), 148.3 (C_{Ar}), 138.5 (C_{Ar}), 137.8 (C_{Ar}), 134.5 (C_{Ar}), 123.4 (C_{Ar}), 123.1 (C_{Ar}), 120.6 (C_{Ar}), 120.4 (C_{Ar}), 114.2 (C_{Ar}-I), 78.2 (CH), 22.6 (CH_3 (OAc)), 20.9 (CH_3 (OAc)), 20.4 (CH_3) ppm; **IR (neat)**: 2935, 1645, 1471, 1273, 748, 665 cm^{-1}; **HRMS (ESI)**: $[M+H-2OAc]^+$ calc. 326.0036, found 326.0040 $[C_{13}H_{13}ONI]^+$; $[\alpha]_D^{20}$ = +76.0 (c = 1.0, $CHCl_3$).

X-Ray Crystallographic structure: **CCDC-1487361**



7.4.4.3. Evaluation of the reactivity and selectivity of (*S*)-316

1-Oxo-1-phenylpropan-2-yl 4-methylbenzenesulfonate 30a



a) **Stoichiometric reaction at 40 °C**: A solution of iodine(III) **(*S*)-316** (150 mg, 0.338 mmol) and *p*-TsOH•H_2O (70 mg, 0.37 mmol) in dry CH_3CN (1 mL) was stirred for 30 minutes at room temperature. A solution of (*Z*)-1-phenylprop-1-en-1-yl acetate **227** (54 mg, 0.31 mmol) in dry CH_3CN (1 mL) was then added to the first reaction mixture and the resulting solution was stirred at 40 °C for 40 h. The reaction was quenched with sat. aq. $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 3 mL). After purification by column chromatography (0 to 5% EtOAc in hexane), the pure compound **30a** was obtained as a white solid (63% yield, 59 mg, 0.19 mmol, 6% *ee*).

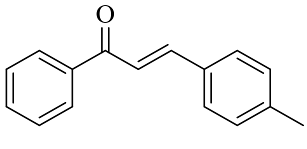
b) **Catalytic reaction at room temperature**: To a solution of iodine(I) **(*S*)-344** (15 mg, 0.046 mmol), *m*-CPBA (9.3 mg, 77% pure, 0.042 mmol) and *p*-TsOH•H_2O (8 mg, 0.042 mmol) in dry CH_3CN (1 mL), a solution of (*Z*)-1-phenylprop-1-en-1-yl acetate **227** (40 mg, 0.23 mmol) in dry CH_3CN (1 mL) and a solution of *m*-CPBA (51 mg, 77% pure, 0.23 mmol) and *p*-TsOH•H_2O (44 mg, 0.23 mmol) in dry CH_3CN (1 mL) was added *via* syringe pump (0.01 mL/min). The resulting mixture was stirred at room temperature for 24 h, quenched with sat. aq. $Na_2S_2O_3$ (1 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (5 mL) and brine (5 mL), dried over $MgSO_4$ and concentrated under vacuum. After purification by column chromatography (0 to 5% EtOAc in hexane), the pure compound **30a** was obtained as a white solid (69% yield, 48 mg, 0.16 mmol, 7% *ee*).

The racemate was synthesised following the stoichiometric procedure but using the racemate of the iodine(III) reagent **(*S*)-316**.

The spectroscopic data are in agreement with literature.[51] **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 7.79 (d, *J* = 7.9 Hz, 2H, H-Ar), 7.67 (d, *J* = 7.3 Hz, 2H, H-Ar), 7.51 (t, *J* = 7.0 Hz, 1H, H-Ar), 7.37 (t, *J* = 7.3 Hz, 2H, H-Ar), 7.18 (d, *J* = 7.7 Hz, 2H, H-Ar), 5.71 (q, *J* = 6.9 Hz, 1H, C**H**CH_3), 2.33 (s, 3H, CH_3 (OTs)), 1.51 (d, *J* = 6.9 Hz, 3H, CHC**H$_3$**) ppm; **^{13}C NMR (125 MHz, $CDCl_3$)**: δ = 194.9 (C=O), 145.2 (C_{Ar}), 134.0 (C_{Ar}H), 133.5 (C_{Ar}), 129.9 (2 C_{Ar}H), 128.9 (2 C_{Ar}H), 128.8 (2 C_{Ar}H), 128.6 (C_{Ar}), 128.0 (2 C_{Ar}H), 77.5 (**C**HCH_3), 21.7 (CH_3), 18.9 (CH_3) ppm; **HRMS (NSI)**: $[M+NH_4]^+$ calc. 322.1108, found 322.1105 $[C_{16}H_{20}O_4NS]^+$; ***ee***: determined by HPLC analysis: Daicel Chiralcel *OB-H* column (25 cm), hexane/*i*-PrOH: 60/40, 0.5 mL/min, 40 °C, 232 nm, T_r ((*R*)-isomer) = 16.2 min, T_r ((*S*)-isomer) = 19.2 min;[52] $[\alpha]_D^{20}$ = +8.0 (c = 0.50, $CHCl_3$).

The absolute configuration was determined by comparison with the literature value.[53] The absolute configuration was determined by its independent synthesis from (S)-(-)-lactic acid.[54]

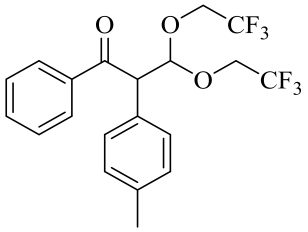
(*E*)-1-Phenyl-3-(*p*-tolyl)prop-2-en-1-one 345



To a solution of acetophenone (1.20 g, 10.0 mmol) and 4-methylbenzaldehyde (1.20 g, 10.0 mmol) in MeOH (25 mL), an aqueous solution of NaOH (1 mL, 50% *w/v*) was added dropwise. The resulting mixture was stirred at room temperature for 24 h. The reaction was quenched with 1 N HCl (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The pure product **345** was obtained after column chromatography (0% to 10% EtOAc in hexane) as a yellow solid (82% yield, 1.83 g, 8.21 mmol).

The spectroscopic data are in agreement with literature.[55] Pale yellow solid; **m.p.** = 79 - 81 °C (lit.[55] 80 – 84 °C); **^{1}H NMR (400 MHz, CDCl$_3$)**: δ = 8.02 (d, *J* = 7.7 Hz, 2H, H-Ar), 7.80 (d, *J* = 15.7 Hz, 1H, C**H**=CH), 7.62 – 7.46 (m, 6H, 5 H-Ar and CH=C**H**), 7.23 (d, *J* = 7.7 Hz, 2H, H-Ar), 2.40 (s, 3H, CH$_3$) ppm.

1-Phenyl-2-(*p*-tolyl)-3,3-bis(2,2,2-trifluoroethoxy)propan-1-one 346



To a solution of iodine(III) **(*S*)-316** (180 mg, 0.393 mmol) in dry CH$_2$Cl$_2$ (2.4 mL) and 2,2,2-trifluoroethanol (2.4 mL), TMSOTf (97 µL, 0.523 mmol) was added dropwise at -20 °C. The resulting mixture was stirred for 30 minutes before the addition of (*E*)-1-phenyl-3-(p-tolyl)prop-2-en-1-one **345** (60 mg, 0.262 mmol). The reaction was stirred at -20 °C for 20 h, quenched with sat. aq. NaHCO$_3$ (1 mL) and extracted with CH$_2$Cl$_2$. The combined organic layers were passed through a Telos® phase separator and concentrated under vacuum. After column chromatography (0 to 5% EtOAc in hexane), the pure product **346** could be obtained as a pale yellow oil (80% yield, 88 mg, 0.21 mmol).

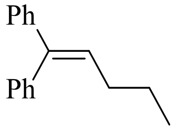
The racemate product was obtained following the same procedure using racemate iodine(III) reagent **(*rac*)-316** (82% yield).

The spectroscopic data are in agreement with literature.[55] **^{1}H NMR (400 MHz, CDCl$_3$)**: δ = 7.85 (d, *J* = 7.6 Hz, 2H, H-Ar), 7.44 (t, *J* = 7.2 Hz, 1H, H-Ar), 7.33 (t, *J* = 7.4 Hz, 2H, H-Ar), 7.19 (d, *J* = 7.6 Hz, 2H, H-Ar), 7.06 (d, *J* = 7.5 Hz, 2H, H-Ar), 5.39 (d, *J* = 8.4 Hz, 1H, CH), 4.78 (d, *J* = 8.4 Hz, 1H, CH), 4.10 – 3.81 (m, 2H, CH$_2$CF$_3$), 3.61 (q, *J* = 8.4 Hz, 2H, CH$_2$CF$_3$), 2.22 (s, 1H, CH$_3$) ppm; **^{13}C NMR (125 MHz, CDCl$_3$)**: δ = 196.6 (C=O), 138.3 (C$_{Ar}$), 136.3 (C$_{Ar}$), 133.6 (C$_{Ar}$H), 130.14 (C$_{Ar}$), 130.07 (2 C$_{Ar}$H), 128.9 (2 C$_{Ar}$H), 128.81 (2 C$_{Ar}$H), 128.79 (2 C$_{Ar}$H), 123.5 (q, *J* = 278 Hz, CF$_3$), 123.4 (q, *J* = 278 Hz, CF$_3$), 105.8 (CH), 65.7 (q, *J* = 66 Hz, CH$_2$CF$_3$), 63.8 (q, *J* = 64 Hz, CH$_2$CF$_3$), 57.1 (CH), 21.2 (CH$_3$) ppm; **HRMS (NSI)**: [M+NH$_4$]$^+$ calc. 438.1498, found 438.1495 [C$_{13}$H$_{12}$NOI]$^+$; ***ee***: 26%, determined by HPLC analysis: Daicel Chiralcel *OD-H* column (25 cm), hexane/*i*-PrOH: 99.7/0.3, 0.5 mL/min, 20 °C, 254 nm, T$_r$ (minor, (*R*)) = 15.0 min,

T_r (major, (*S*)) = 19.1 min; $[\alpha]_D^{20}$ = -14.3 (c = 1.82, $CHCl_3$) (lit. for the (*R*) isomer: $[\alpha]_D^{20}$ = +48.6 (c = 1.64, $CHCl_3$)).

The absolute configuration was determined by comparison with the literature data. The authors confirmed the stereochemistry of the chiral centre to be (*R*) by recrystallizing 2-(4-bromophenyl)-1-phenyl-3,3-bis(2,2,2-trifluoroethoxy)propan-1-one and it was assumed that the absolute configuration would be the same for every substrates.

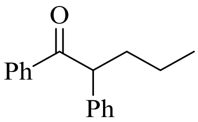
Pent-1-ene-1,1-diyldibenzene 347



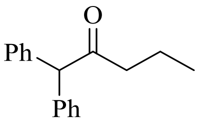
To a solution of butyltriphenylphosphonium bromide (1.32 g, 3.29 mmol) in dry THF (10 mL), *n*-BuLi (1.57 mL, 2.1 M in hexane, 3.29 mmol) was added at 0 °C. The resulting mixture was stirred at 0 °C until complete dissolution of the salt. A solution of benzophenone (500 mg, 2.74 mmol) in dry THF (5 mL) was then added to the reaction mixture. It was warmed up to room temperature and stirred for 20 h. The resulting mixture was quenched with sat. aq. NH_4Cl and extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$ and dried under vacuum. After purification by column chromatography, the pure product **347** was obtained a pale yellow oil (82% yield, 500 mg, 2.25 mmol).

The spectroscopic data are in agreement with literature.[8] **^{1}H NMR (400 MHz, CDCl$_3$)**: δ = 7.43 – 7.18 (m, 10H, H-Ar), 6.12 (t, *J* = 7.4 Hz, 1H, CHPh), 2.12 (q, *J* = 7.3 Hz, 2H, C**H$_2$**CH$_2$CH$_3$), 1.49 (sext, *J* = 7.4 Hz, 2H, CH$_2$C**H$_2$**CH$_3$), 0.93 (t, *J* = 7.3 Hz, 3H, CH$_2$CH$_2$C**H$_3$**) ppm; **^{13}C NMR (125 MHz, CDCl$_3$)**: δ = 142.9 (C), 141.6 (C), 140.4 (C), 130.2 (CH), 130.0 (2 C$_{Ar}$H), 128.1 (2 C$_{Ar}$H), 128.1 (2 C$_{Ar}$H), 127.2 (2 C$_{Ar}$H), 126.8 (CH), 126.8 (CH), 31.8 (**C**H$_2$CH$_2$CH$_3$), 23.2 (CH$_2$**C**H$_2$CH$_3$), 13.9 (CH$_2$CH$_2$**C**H$_3$) ppm.

1,2-Diphenylpentan-1-one 348 and 1,1-diphenylpentan-2-one 349



348



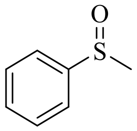
349

Pent-1-ene-1,1-diyldibenzene **347** (67 mg, 0.30 mmol) was dissolved in a mixture of CH_2Cl_2/TFE (10:1, 3.5 mL) at 0 °C. Iodoarene **(*S*)-344** (20 mg, 0.060 mmol), *m*-CPBA (52 mg, 0.30 mmol), MeOH (97 µL, 2.4 mmol) and *p*-TsOH•H_2O (85 mg, 0.451 mmol) were successively added to the reaction mixture. The resulting solution was stirred at 0 °C for 4 h, then warmed up to room temperature and stirred for additional 16 h. The reaction mixture was quenched with sat. aq. $NaHCO_3$ solution (1.5 mL), diluted with water (10 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over a Telos® phase separator and concentrated under vacuum. In the crude mixture, product **348** was observed in 23% conversion whilst product **349** was obtained with 55% conversion. After purification by preparative TLC (10% EtOAc in hexane), a mixture of both compounds **348** and **349** (1:1 ratio) was isolated as a colourless oil (49% total yield, 35 mg, 0.15 mmol).

The spectroscopic data for are in agreement with literature.[8] **^{1}H NMR (300 MHz, $CDCl_3$)**: δ = 7.90 – 7.88 (m, 2H, H-Ar, **348**), 7.43 – 7.10 (m, 18H, H-Ar, **348** and **349**), 5.05 (s, 1H, CH, **349**), 4.49 (t, *J* = 7.3 Hz, 1H, CH, **348**), 2.45 (t, *J* = 7.4 Hz, 1H, C$\mathbf{H_2}$$CH_2CH_3$, **349**), 2.14 – 2.02 (m, 1H, C$\mathbf{H_A}$$H_BCH_2CH_3$, **348**), 1.78 – 1.70 (m, 1H, $CH_A$$\mathbf{H_B}$$CH_2CH_3$, **348**), 1.58 – 1.50 (m, 2H, $CH_2C$$\mathbf{H_2}$$CH_3$, **349**), 1.27 – 1.16 (m, 2H, $CH_2C$$\mathbf{H_2}$$CH_3$, **348**), 0.84 (t, *J* = 7.4 Hz, 3H, CH_3, **348**), 0.79 (t, *J* = 7.4 Hz, 3H, CH_3, **349**) ppm; **^{13}C NMR (125 MHz, $CDCl_3$, 348)**: δ = 200.3 (C=O), 139.9 (C_{Ar}), 137.1 (C_{Ar}), 132.9 ($C_{Ar}H$), 129.0 (2 $C_{Ar}H$), 128.8 (2 $C_{Ar}H$), 128.6 (2 $C_{Ar}H$), 128.4 (2 $C_{Ar}H$), 127.1 ($C_{Ar}H$), 53.6 (CH), 36.3 ($\mathbf{C}H_2CH_2CH_3$), 21.0 ($CH_2CH_2CH_3$), 14.2 (CH_3) ppm; **^{13}C NMR (125 MHz, $CDCl_3$, 349)**: δ = 208.7 (C=O), 138.6 (2 C_{Ar}), 129.1 (4 $C_{Ar}H$), 128.8 (4 $C_{Ar}H$), 127.3 (2 $C_{Ar}H$), 64.3 (CH), 45.0 ($\mathbf{C}H_2CH_2CH_3$), 17.6 ($CH_2\mathbf{C}H_2CH_3$), 13.8 (CH_3) ppm; ***ee* (348)**: 6%, determined by HPLC analysis: *YMC* Chiral Amylose-C S-5µm (25 cm), hexane/*i*-PrOH: 99.5/0.5, 1.0 mL/min, 10 °C, 243 nm, T_r ((*S*)-isomer) = 9.3 min, T_r ((*R*)-isomer) = 12.3 min.

The absolute configuration of **348** was determined by comparison using the HPLC data available in the literature.[8] The authors established the absolute configuration by comparison of the optical rotation. In this paper, the independent synthesis of (*S*)-1,2-diphenylpropan-1-one from (*S*)-ethyl lactate is described.[56]

(Methylsulfinyl)benzene 351



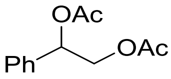
A solution of iodine(III) **(*S*)-316** (200 mg, 0.450 mmol) and *p*-TsOH•H_2O (85 mg, 0.45 mmol) in dry CH_2Cl_2 (4 mL) was stirred at -78 °C for 1 h. Thioanisole **350** (44 µL, 0.38 mmol) was added dropwise and the reaction mixture was then stirred at -78 °C for an additional hour. The resulting mixture was quenched with sat. aq. $NaHCO_3$ (1 mL) and extracted with CH_2Cl_2. The combined organic layers were passed through a Telos® phase separator and concentrated under vacuum. After purification by column chromatography, the pure product **351** was obtained as a pale yellow oil (94% yield, 50 mg, 0.36 mmol).

The racemate was synthesised following the same procedure but using the racemate of the iodine(III) reagent **(*rac*)-316** and at room temperature.

The spectroscopic data are in agreement with literature.[57] **^{1}H NMR (400 MHz, CDCl$_3$)**: δ = 7.66 – 7.64 (m, 2H, H-Ar), 7.53 – 7.51 (m, 3H, H-Ar), 2.73 (s, 3H, CH_3) ppm; **^{13}C NMR (125 MHz, CDCl$_3$)**: δ = 145.7 (C_{Ar}), 131.2 (C_{Ar}H), 129.5 (2 C_{Ar}H), 123.6 (2 C_{Ar}H), 44.0 (CH_3) ppm; **HRMS (EI+)**: $[M]^+$ calc. 140.0296, found 140.0302 $[C_7H_8OS]^+$; ***ee***: 2%, determined by HPLC analysis: Daicel Chiralcel *OB-H* column (25 cm), hexane/*i*-PrOH: 80/20, 1.0 mL/min, 20 °C, 254 nm, T_r ((*S*)-isomer) = 11.2 min, T_r ((*R*)-isomer) = 18.9 min;[57] $[\alpha]_D^{20}$ = -2.1 (c = 0.93, $CHCl_3$).

The absolute configuration was determined by comparison with the optical rotation in the literature. They established it by the reduction of the corresponding (*S*)-sulfinate ester to the sulfoxide.[58]

1-Phenylethane-1,2-diyl diacetate 352



To a solution of iodoarene **(*S*)-344** (65 mg, 0.20 mmol) and triflic acid (9 µL, 0.1 mmol) in acetic acid (10 mL), peracetic acid (135 µL, 32 wt.% in AcOH, 2 mmol) was added and the resulting mixture was stirred at r.t. for 1 h. A solution of freshly distilled styrene (115 µL, 1 mmol) in acetic acid (7.5 mL) was then added *via* a syringe pump

(0.03 mL/min) and the reaction was stirred at r.t. for additional 16 h. Water (10 mL) and brine (20 mL) were added and the organic phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum to obtain a yellow oil which was used without further purification in the next step.

The crude mixture was dissolved in dry CH_2Cl_2 (3 mL) and acetic anhydride (236 µL, 2.5 mmol), pyridine (201 µL, 2.5 mmol) and DMAP (30 mg, 0.25 mmol) were added successively. The resulting mixture was stirred at r.t. for 18 h. The reaction was quenched with 2 N HCl and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were passed through a Telos® phase separator and dried under vacuum. After purification by column chromatography (0 to 10% EtOAc in hexane), the pure product was obtained as a colourless oil (44% yield, 98 mg, 0.441 mmol).

The racemate was synthesised following the same procedure but using the racemate of the iodine(III) reagent (37% yield, 81 mg, 0.365 mmol).

The spectroscopic data are in agreement with literature.[59] **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 7.43 – 7.28 (m, 5H, H-Ar), 6.06 – 5.96 (m, 1H, C**H**OAc), 4.40 – 4.22 (m, 2H, C**H_2**OAc), 2.12 (s, 3H, CH_3 (OAc)), 2.06 (s, 3H, CH_3 (OAc)) ppm; **^{13}C NMR (125 MHz, $CDCl_3$)**: δ = 170.8 (C=O), 170.2 (C=O), 136.6 (C_{Ar}), 128.8 (2 C_{Ar}H), 128.6 (C_{Ar}H), 126.8 (2 C_{Ar}H), 73.4 (**C**HOAc), 66.2 (**C**H_2OAc), 21.2 (CH_3 (OAc)), 20.9 (CH_3 (OAc)) ppm; **HRMS (NSI)**: $[M+NH_4]^+$ calc. 240.1230, found 240.1229 $[C_{12}H_{18}O_4N]^+$; ***ee***: 0%, determined by HPLC analysis: Daicel Chiralcel *OD-H* (25 cm), hexane/*i*-PrOH: 99.7/0.3, 1.0 mL/min, 20 °C, 218 nm, T_r = 32.9 min, T_r = 38.1 min; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = 0.0 (c = 0.81, $CHCl_3$).

7.5. References

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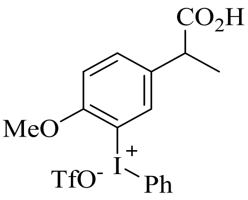
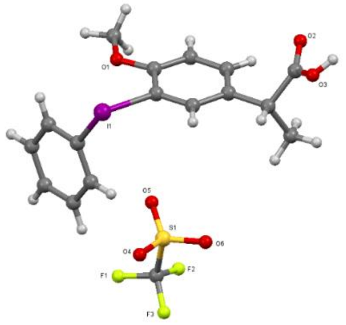
Chapter 8: Appendix

8.1. Crystallographic data

(5-(1-Carboxyethyl)-2-methoxyphenyl)(phenyl)iodonium trifluoromethanesulfonate 168





Audit creation method: SHELXL-2013

Chemical formula sum: 'C17 H16 F3 I O6 S'

Chemical formula weight: 532.26

'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4': 'C' 'C' 0.0181 0.0091

'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4': 'H' 'H' 0.0000 0.0000

'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4': 'F' 'F' 0.0727 0.0534

'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4': 'O' 'O' 0.0492 0.0322

'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4': 'S' 'S' 0.3331 0.5567

'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4': 'I' 'I' -0.3257 6.8362

Space group crystal system: triclinic

Space group IT number: 2

Space group name H-M alt: 'P -1'

Space group name Hall: '-P 1'

Shelx space group comment: The symmetry employed for this shelxl refinement is uniquely defined by the following loop, which should always be used as a source of symmetry information in preference to the above space-group names.

Cell length a: 9.7588(5)

Cell length b: 10.9245(6)

Cell length c: 11.1613(8)

Cell angle alpha: 69.878(6)

Cell angle beta: 68.181(6)

Cell angle gamma: 68.636(5)

Cell volume: 998.36(12)

Cell formula units Z: 2

Cell measurement temperature: 200(2)

Exptl crystal density diffrn: 1.771

Exptl crystal F 000: 524

Exptl crystal size max: 0.202

Exptl crystal size mid: 0.149

Exptl crystal size min: 0.081

Exptl absorpt coefficient mu: 14.129

Shelx estimated absorpt T min: 0.163

Shelx estimated absorpt T max: 0.394

Diffrn ambient temperature: 200(2)

Diffrn radiation wavelength: 1.54184

Diffrn radiation type: CuK\a

Diffrn reflns number: 6818

Diffrn reflns av unetI/netI: 0.0310

Diffrn reflns av R equivalents: 0.0260

Diffrn reflns limit h min: -11

Diffrn reflns limit h max: 12

Diffrn reflns limit k min: -13

Diffrn reflns limit k max: 11

Diffrn reflns limit l min: -13

Diffrn reflns limit l max: 13

Diffrn reflns theta min: 4.397

Diffrn reflns theta max: 74.056

Diffrn reflns theta full: 67.684

Diffrn measured fraction theta max: 0.960

Diffrn measured fraction theta full: 0.995

Diffrn reflns Laue measured fraction max: 0.960

Diffrn reflns Laue measured fraction full: 0.995

Diffrn reflns point group measured fraction max: 0.960

Diffrn reflns point group measured fraction full: 0.995

Reflns number total: 3898

Reflns number gt: 3717

Reflns threshold expression: 'I > 2\s(I)'

Reflns Friedel coverage: 0.000

Reflns special details: Reflections were merged by SHELXL according to the crystal class for the calculation of statistics and refinement. Reflns Friedel fraction is defined as the number of unique Friedel pairs measured divided by the number that would be possible theoretically, ignoring centric projections and systematic absences.

Computing structure refinement 'SHELXL-2013 (Sheldrick, 2013)'

Refine ls structure factor coef: Fsqd

Refine ls matrix type: full

Refine ls weighting scheme: calc

Refine ls weighting details: 'w=1/[\s^2^(Fo^2^)+(0.0511P)^2^+1.3498P]
where P=(Fo^2^+2Fc^2^)/3'

Atom sites solution hydrogens: geom

Refine ls hydrogen treatment: constr

Refine ls extinction method: none

Refine ls number reflns: 3898

Refine ls number parameters: 256

Refine ls number restraints: 0

Refine ls R factor all: 0.0375

Refine ls R factor gt: 0.0359

Refine ls wR factor ref: 0.0930

Refine ls wR factor gt: 0.0916

Refine ls goodness of fit ref: 1.068

Refine ls restrained S all: 1.068

Refine ls shift/su max: 0.001

Refine ls shift/su mean: 0.000

Atomic coordinates and equivalent isotropic displacement parameters

C1 C -0.0234(4) 0.5381(4) 0.7584(4) 0.0307(7) Uani 1 1 d

C2 C -0.0355(5) 0.4108(5) 0.7802(5) 0.0429(10) Uani 1 1 d

```
H2 H 0.0165 0.3609 0.7137 0.052 Uiso 1 1 calc R U
C3 C -0.1264(6) 0.3568(5) 0.9030(5) 0.0534(12) Uani 1 1 d
H3 H -0.1377 0.2689 0.9209 0.064 Uiso 1 1 calc R U
C4 C -0.2000(7) 0.4302(6) 0.9987(5) 0.0594(14) Uani 1 1 d
H4 H -0.2610 0.3923 1.0828 0.071 Uiso 1 1 calc R U
C5 C -0.1857(8) 0.5568(6) 0.9730(6) 0.0646(16) Uani 1 1 d
H5 H -0.2378 0.6067 1.0396 0.078 Uiso 1 1 calc R U
C6 C -0.0967(6) 0.6144(5) 0.8522(5) 0.0468(11) Uani 1 1 d
H6 H -0.0865 0.7026 0.8343 0.056 Uiso 1 1 calc R U
C7 C 0.3052(4) 0.5890(4) 0.6268(4) 0.0308(8) Uani 1 1 d
C8 C 0.3824(4) 0.4556(4) 0.6740(4) 0.0329(8) Uani 1 1 d
C9 C 0.5139(5) 0.4343(4) 0.7082(4) 0.0373(9) Uani 1 1 d
H9 H 0.5690 0.3449 0.7425 0.045 Uiso 1 1 calc R U
C10 C 0.5647(5) 0.5437(5) 0.6924(4) 0.0408(9) Uani 1 1 d
H10 H 0.6543 0.5273 0.7170 0.049 Uiso 1 1 calc R U
C11 C 0.4893(5) 0.6758(4) 0.6421(4) 0.0381(9) Uani 1 1 d
C12 C 0.3564(4) 0.6989(4) 0.6098(4) 0.0348(8) Uani 1 1 d
H12 H 0.3010 0.7885 0.5766 0.042 Uiso 1 1 calc R U
C13 C 0.3930(6) 0.2203(5) 0.7407(6) 0.0539(12) Uani 1 1 d
H13A H 0.4967 0.1924 0.6827 0.081 Uiso 1 1 calc R U
H13B H 0.3327 0.1616 0.7488 0.081 Uiso 1 1 calc R U
H13C H 0.3987 0.2128 0.8289 0.081 Uiso 1 1 calc R U
C14 C 0.5439(6) 0.7988(5) 0.6211(6) 0.0515(12) Uani 1 1 d
H14 H 0.4775 0.8806 0.5743 0.062 Uiso 1 1 calc R U
C15 C 0.7083(5) 0.7851(5) 0.5359(5) 0.0451(10) Uani 1 1 d
C16 C 0.5291(9) 0.8220(8) 0.7511(8) 0.081(2) Uani 1 1 d
H16A H 0.5878 0.7405 0.8015 0.121 Uiso 1 1 calc R U
H16B H 0.4209 0.8419 0.8026 0.121 Uiso 1 1 calc R U
H16C H 0.5689 0.8986 0.7339 0.121 Uiso 1 1 calc R U
C17 C -0.2153(7) 1.0091(6) 0.8926(6) 0.0613(14) Uani 1 1 d
O1 O 0.3207(3) 0.3584(3) 0.6847(3) 0.0419(7) Uani 1 1 d
O2 O 0.8124(3) 0.6836(3) 0.5378(3) 0.0446(7) Uani 1 1 d
O3 O 0.7259(5) 0.9012(4) 0.4503(6) 0.0786(14) Uani 1 1 d
H3A H 0.8192 0.8990 0.4225 0.118 Uiso 1 1 calc R U
```

O4 O -0.2269(6) 1.1212(7) 0.6546(5) 0.114(2) Uani 1 1 d

O5 O -0.0307(8) 0.9150(5) 0.6940(6) 0.106(2) Uani 1 1 d

O6 O -0.0171(6) 1.1231(5) 0.7070(5) 0.0887(15) Uani 1 1 d

S1 S -0.11063(14) 1.04254(11) 0.71590(12) 0.0459(3) Uani 1 1 d

I1 I 0.10698(2) 0.62744(2) 0.57237(2) 0.03271(10) Uani 1 1 d

F1 F -0.3089(6) 0.9358(5) 0.9172(4) 0.1024(16) Uani 1 1 d

F2 F -0.1292(7) 0.9502(9) 0.9678(5) 0.160(3) Uani 1 1 d

F3 F -0.3049(6) 1.1213(5) 0.9287(5) 0.1058(17) Uani 1 1 d

Anisotropic displacement parameters

C1 0.0244(17) 0.0363(19) 0.0277(18) -0.0043(15) -0.0023(14) -0.0126(15)

C2 0.043(2) 0.043(2) 0.045(2) -0.0131(19) -0.0049(19) -0.0176(19)

C3 0.061(3) 0.045(3) 0.055(3) -0.002(2) -0.009(2) -0.032(2)

C4 0.060(3) 0.066(3) 0.039(3) -0.001(2) 0.003(2) -0.031(3)

C5 0.078(4) 0.058(3) 0.041(3) -0.019(2) 0.012(3) -0.023(3)

C6 0.057(3) 0.035(2) 0.039(2) -0.0116(18) 0.001(2) -0.014(2)

C7 0.0243(17) 0.037(2) 0.0279(18) -0.0063(15) -0.0039(14) -0.0098(15)

C8 0.0270(18) 0.0358(19) 0.0287(18) -0.0065(15) 0.0013(14) -0.0110(15)

C9 0.0294(19) 0.041(2) 0.034(2) -0.0037(16) -0.0069(16) -0.0071(16)

C10 0.0271(19) 0.057(3) 0.038(2) -0.0119(19) -0.0072(16) -0.0123(18)

C11 0.0281(19) 0.043(2) 0.041(2) -0.0140(18) -0.0011(16) -0.0128(17)

C12 0.0266(18) 0.038(2) 0.036(2) -0.0089(16) -0.0023(15) -0.0117(15)

C13 0.059(3) 0.035(2) 0.059(3) -0.004(2) -0.012(2) -0.015(2)

C14 0.040(2) 0.048(3) 0.074(3) -0.018(2) -0.018(2) -0.015(2)

C15 0.034(2) 0.043(2) 0.064(3) -0.007(2) -0.019(2) -0.0168(19)

C16 0.081(5) 0.092(5) 0.088(5) -0.048(4) -0.010(4) -0.034(4)

C17 0.074(4) 0.054(3) 0.051(3) -0.008(2) -0.009(3) -0.025(3)

O1 0.0373(15) 0.0337(14) 0.0513(18) -0.0070(13) -0.0097(13) -0.0117(12)

O2 0.0338(15) 0.0453(17) 0.057(2) -0.0075(14) -0.0132(14) -0.0169(14)

O3 0.050(2) 0.049(2) 0.118(4) 0.004(2) -0.023(2) -0.0141(17)

O4 0.059(3) 0.166(6) 0.055(3) 0.010(3) -0.009(2) -0.003(3)

O5 0.130(5) 0.050(2) 0.096(4) -0.024(2) 0.026(3) -0.031(3)

O6 0.094(3) 0.095(3) 0.083(3) -0.028(3) 0.010(3) -0.062(3)

S1 0.0482(6) 0.0363(5) 0.0435(6) -0.0043(4) -0.0049(5) -0.0138(4)
I1 0.02662(14) 0.04001(15) 0.02842(14) -0.00446(10) -0.00523(9) -0.01176(10)
F1 0.121(4) 0.116(3) 0.074(3) -0.025(2) 0.021(2) -0.084(3)
F2 0.109(4) 0.269(8) 0.064(3) 0.030(4) -0.044(3) -0.051(5)
F3 0.126(4) 0.104(3) 0.080(3) -0.051(3) 0.026(3) -0.052(3)

geom special details: All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Geom bond atom site label 1
Geom bond atom site label 2
Geom bond distance
Geom bond site symmetry 2
Geom bond publ flag

C1 C2 1.369(6)
C1 C6 1.383(6)
C1 I1 2.105(4)

C2 C3 1.390(7)
C3 C4 1.378(8)
C4 C5 1.362(8)
C5 C6 1.383(7)
C7 C8 1.391(6)
C7 C12 1.392(6)
C7 I1 2.096(4)
C8 O1 1.351(5)
C8 C9 1.391(6)
C9 C10 1.388(6)
C10 C11 1.384(6)
C11 C12 1.386(6)
C11 C14 1.534(6)
C13 O1 1.438(6)
C14 C16 1.504(9)
C14 C15 1.513(7)
C15 O2 1.201(6)
C15 O3 1.324(6)
C17 F2 1.258(8)
C17 F3 1.313(7)
C17 F1 1.322(7)
C17 S1 1.829(6)
O4 S1 1.399(5)
O5 S1 1.382(5)
O6 S1 1.440(5)

Geom angle atom site label 1
Geom angle atom site label 2

Geom angle atom site label 3

Geom angle

Geom angle site symmetry 1

Geom angle site symmetry 3

Geom angle publ flag

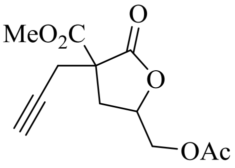
C2 C1 C6 123.2(4)
C2 C1 I1 119.5(3)
C6 C1 I1 117.3(3)
C1 C2 C3 117.8(4)
C4 C3 C2 120.3(5)
C5 C4 C3 120.1(5)
C4 C5 C6 121.4(5)
C1 C6 C5 117.2(4)
C8 C7 C12 122.9(4)
C8 C7 I1 119.0(3)
C12 C7 I1 118.0(3)
O1 C8 C9 125.9(4)
O1 C8 C7 116.8(4)
C9 C8 C7 117.2(4)
C10 C9 C8 120.0(4)
C11 C10 C9 122.3(4)
C10 C11 C12 118.3(4)
C10 C11 C14 123.6(4)
C12 C11 C14 118.0(4)
C11 C12 C7 119.1(4)
C16 C14 C15 108.8(5)
C16 C14 C11 111.7(5)
C15 C14 C11 112.2(4)
O2 C15 O3 121.8(5)
O2 C15 C14 126.7(4)
O3 C15 C14 111.4(4)
F2 C17 F3 107.2(7)
F2 C17 F1 109.1(6)
F3 C17 F1 104.9(6)
F2 C17 S1 113.4(5)
F3 C17 S1 111.6(4)
F1 C17 S1 110.2(4)
C8 O1 C13 118.0(4)
O5 S1 O4 118.9(5)
O5 S1 O6 115.0(4)
O4 S1 O6 110.8(4)
O5 S1 C17 103.8(3)
O4 S1 C17 103.0(3)
O6 S1 C17 102.8(3)
C7 I1 C1 97.58(15)

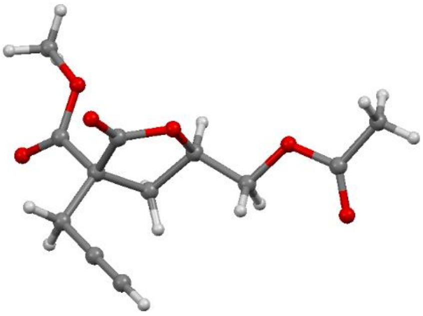
Refine diff density max: 0.995

Refine diff density min: -1.010

Refine diff density rms: 0.100

Methyl 5-(acetoxymethyl)-2-oxo-3-(prop-2-yn-1-yl)tetrahydrofuran-3-carboxylate





Audit creation method: SHELXL-2013

Chemical name systematic

Chemical formula sum: $C_{12}H_{14}O_6$

Chemical formula weight: 254.23

International Tables Vol C Tables 4.2.6.8 and 6.1.1.4: 'C' 'C' 0.0181 0.0091

International Tables Vol C Tables 4.2.6.8 and 6.1.1.4: 'H' 'H' 0.0000 0.0000

International Tables Vol C Tables 4.2.6.8 and 6.1.1.4: 'O' 'O' 0.0492 0.0322

Space group crystal system: orthorhombic

Space group IT number: 33

Space group name H-M alt: 'P n a 21'

Space group name Hall: 'P 2c -2n'

Shelx space group comment:

The symmetry employed for this shelxl refinement is uniquely defined by the following loop, which should always be used as a source of symmetry information in preference to the above space-group names.

They are only intended as comments.

Space group symop operation xyz

'x, y, z'

'-x, -y, z+1/2'

'x+1/2, -y+1/2, z'

'-x+1/2, y+1/2, z+1/2'

Cell length a: 7.0545(3)

Cell length b: 16.5628(5)

Cell length c: 10.7323(4)

Cell angle alpha: 90

Cell angle beta: 90

Cell angle gamma: 90

Cell volume: 1253.99(8)

Cell formula units Z: 4

Cell measurement temperature: 293(2)

Exptl crystal density diffrn: 1.347

Exptl crystal F 000: 536

Exptl crystal size max: 0.176

Exptl crystal size mid: 0.157

Exptl crystal size min: 0.049

Exptl absorpt coefficient mu: 0.929

Shelx estimated absorpt T min: 0.854

Shelx estimated absorpt T max: 0.956

Diffrn ambient temperature: 293(2)

Diffrn radiation wavelength: 1.54184

Diffrn radiation type: CuK\a

Diffrn reflns number: 20059

Diffrn reflns av unetI/netI: 0.0251

Diffrn reflns av R equivalents: 0.0597

Diffrn reflns limit h min: -8

Diffrn reflns limit h max: 8

Diffrn reflns limit k min: -20

Diffrn reflns limit k max: 20

Diffrn reflns limit l min: -13

Diffrn reflns limit l max: 13

Diffrn reflns theta min: 4.910

Diffrn reflns theta max: 74.123

Diffrn reflns theta full: 67.684

Diffrn measured fraction theta max: 0.996

Diffrn measured fraction theta full: 1.000

Diffrn reflns Laue measured fraction max: 0.996

Diffrn reflns Laue measured fraction full: 1.000

Diffrn reflns point group measured fraction max: 0.993

Diffrn reflns point group measured fraction full: 1.000

Reflns number total: 2532

Reflns number gt: 2350

Reflns threshold expression: 'I > 2\s(I)'

Reflns Friedel coverage: 0.887

Reflns Friedel fraction max: 0.988

Reflns Friedel fraction full: 1.000

Reflns special details:

Reflections were merged by SHELXL according to the crystal class for the calculation of statistics and refinement.

Reflns Friedel fraction is defined as the number of unique Friedel pairs measured divided by the number that would be possible theoretically, ignoring centric projections and systematic absences.

Computing structure refinement: 'SHELXL-2013 (Sheldrick, 2013)'

Refine ls structure factor coef: Fsqd

Refine ls matrix type: full

Refine ls weighting scheme: calc

Refine ls weighting details: 'w=1/[\s^2^(Fo^2^)+(0.0563P)^2^+0.2518P]
where P=(Fo^2^+2Fc^2^)/3'

Atom sites solution hydrogens: geom

Refine ls hydrogen treatment: constr

Refine ls extinction method: none

Refine ls abs structure details: Flack x determined using 1050 quotients [(I+)-(I-)]/[(I+)+(I-)]

(Parsons and Flack (2004), Acta Cryst. A60, s61).

Refine ls abs structure Flack: -0.14(12)

Refine ls number reflns: 2532

Refine ls number parameters: 165

Refine ls number restraints: 1

Refine ls R factor all: 0.0398

Refine ls R factor gt: 0.0359

Refine ls wR factor ref: 0.0968

Refine ls wR factor gt: 0.0925

Refine ls goodness of fit ref: 1.036

Refine ls restrained S all: 1.035

Refine ls shift/su max: 0.000

Refine ls shift/su mean: 0.000

loop

Atom site label

Atom site type symbol

Atom site fract x

Atom site fract y

Atom site fract z

Atom site U iso or equiv

Atom site adp type

Atom site occupancy

Atom site site symmetry order

Atom site calcflag

Atom site refinement flags posn

Atom site refinement flags adp

Atom site refinement flags occupancy

Atom site disorder assembly

Atom site disorder group

Atomic coordinates and equivalent isotropic displacement parameters

C1 C 1.0956(5) 0.81923(18) 0.0820(3) 0.0423(7) Uani 1 1 d

H1A H 1.0759 0.8750 0.1027 0.063 Uiso 1 1 calc R U

H1B H 1.0078 0.8035 0.0181 0.063 Uiso 1 1 calc R U

H1C H 1.2229 0.8119 0.0525 0.063 Uiso 1 1 calc R U

C2 C 1.0648(4) 0.76849(16) 0.1949(3) 0.0332(6) Uani 1 1 d

C3 C 1.0690(4) 0.63505(15) 0.2731(2) 0.0315(6) Uani 1 1 d

H3A H 0.9422 0.6402 0.3071 0.038 Uiso 1 1 calc R U

H3B H 1.1595 0.6477 0.3384 0.038 Uiso 1 1 calc R U

C4 C 1.1006(4) 0.55056(15) 0.2267(2) 0.0268(5) Uani 1 1 d

H4 H 1.2235 0.5467 0.1845 0.032 Uiso 1 1 calc R U

C5 C 0.8793(4) 0.45552(14) 0.1643(2) 0.0259(5) Uani 1 1 d

C6 C 0.9718(3) 0.41922(14) 0.2795(2) 0.0247(5) Uani 1 1 d

C7 C 1.0897(4) 0.48929(15) 0.3322(2) 0.0291(5) Uani 1 1 d

H7A H 1.0284 0.5126 0.4048 0.035 Uiso 1 1 calc R U

H7B H 1.2153 0.4710 0.3557 0.035 Uiso 1 1 calc R U

C8 C 1.1014(4) 0.34952(15) 0.2431(2) 0.0288(5) Uani 1 1 d

C9 C 1.3141(5) 0.30175(19) 0.0899(3) 0.0500(8) Uani 1 1 d

H9A H 1.2600 0.2488 0.0972 0.075 Uiso 1 1 calc R U

H9B H 1.4258 0.3051 0.1407 0.075 Uiso 1 1 calc R U

H9C H 1.3471 0.3119 0.0045 0.075 Uiso 1 1 calc R U

C10 C 0.8193(4) 0.38841(15) 0.3696(2) 0.0287(5) Uani 1 1 d

H10A H 0.7493 0.3448 0.3305 0.034 Uiso 1 1 calc R U

H10B H 0.8795 0.3672 0.4440 0.034 Uiso 1 1 calc R U

C11 C 0.6878(4) 0.45294(17) 0.4046(3) 0.0339(6) Uani 1 1 d

C12 C 0.5868(4) 0.5064(2) 0.4332(3) 0.0453(7) Uani 1 1 d

H12 H 0.5070 0.5487 0.4558 0.054 Uiso 1 1 calc R U

O1 O 1.0190(4) 0.79169(12) 0.2966(2) 0.0486(6) Uani 1 1 d

O2 O 1.0930(3) 0.68971(11) 0.16960(17) 0.0330(4) Uani 1 1 d

O3 O 0.9482(3) 0.52952(10) 0.14075(17) 0.0286(4) Uani 1 1 d

O4 O 0.7593(3) 0.42453(11) 0.10045(18) 0.0350(4) Uani 1 1 d

O5 O 1.1339(3) 0.29260(12) 0.3086(2) 0.0436(5) Uani 1 1 d

O6 O 1.1767(3) 0.36170(12) 0.13125(19) 0.0404(5) Uani 1 1 d

Anisotropic displacement parameters

C1 0.0446(16) 0.0322(14) 0.0500(18) 0.0097(12) -0.0078(14) -0.0028(12)

C2 0.0312(13) 0.0291(12) 0.0393(15) -0.0022(10) -0.0084(12) -0.0015(10)

C3 0.0413(15) 0.0279(11) 0.0253(12) 0.0021(10) -0.0005(10) -0.0037(10)

C4 0.0271(12) 0.0278(11) 0.0254(11) 0.0019(9) -0.0020(10) -0.0022(9)

C5 0.0282(12) 0.0270(11) 0.0226(12) -0.0012(9) -0.0023(10) 0.0025(9)

C6 0.0270(12) 0.0261(10) 0.0210(11) 0.0015(9) -0.0026(9) 0.0009(9)

C7 0.0304(13) 0.0308(12) 0.0261(12) 0.0038(9) -0.0070(10) -0.0033(10)

C8 0.0283(12) 0.0297(12) 0.0284(12) 0.0020(10) -0.0016(10) 0.0013(10)

C9 0.0483(18) 0.0474(17) 0.0544(19) 0.0025(14) 0.0221(17) 0.0132(14)

C10 0.0320(14) 0.0275(11) 0.0265(11) 0.0027(9) 0.0026(10) -0.0025(9)

C11 0.0298(14) 0.0382(14) 0.0337(13) -0.0016(10) 0.0035(11) -0.0070(11)

C12 0.0335(15) 0.0472(16) 0.0553(19) -0.0143(15) 0.0014(13) 0.0025(12)
O1 0.0650(15) 0.0373(10) 0.0434(13) -0.0078(10) -0.0068(11) 0.0076(10)
O2 0.0454(11) 0.0244(8) 0.0292(9) 0.0024(7) 0.0016(8) -0.0021(7)
O3 0.0363(9) 0.0266(8) 0.0230(8) 0.0026(7) -0.0058(7) -0.0005(7)
O4 0.0356(10) 0.0383(9) 0.0309(9) 0.0004(8) -0.0097(8) -0.0034(8)
O5 0.0536(13) 0.0372(10) 0.0402(12) 0.0103(9) 0.0043(10) 0.0145(9)
O6 0.0435(11) 0.0411(10) 0.0366(11) 0.0053(9) 0.0133(9) 0.0122(9)

Geom special details:

All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

loop
Geom bond atom site label 1
Geom bond atom site label 2
Geom bond distance
Geom bond site symmetry 2
Geom bond publ flag

C1 C2 1.490(4)
C1 H1A 0.9600
C1 H1B 0.9600
C1 H1C 0.9600
C2 O1 1.202(4)
C2 O2 1.347(3)
C3 O2 1.443(3)
C3 C4 1.502(3)
C3 H3A 0.9700
C3 H3B 0.9700
C4 O3 1.459(3)
C4 C7 1.523(3)
C4 H4 0.9800
C5 O4 1.204(3)
C5 O3 1.343(3)
C5 C6 1.522(3)
C6 C8 1.524(3)
C6 C10 1.534(3)
C6 C7 1.536(3)
C7 H7A 0.9700
C7 H7B 0.9700
C8 O5 1.198(3)
C8 O6 1.328(3)
C9 O6 1.457(3)
C9 H9A 0.9600
C9 H9B 0.9600
C9 H9C 0.9600
C10 C11 1.464(4)
C10 H10A 0.9700
C10 H10B 0.9700
C11 C12 1.178(4)
C12 H12 0.9300

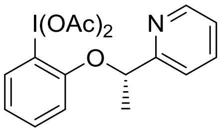
loop
Geom angle atom site label 1
Geom angle atom site label 2
Geom angle atom site label 3
Geom angle
Geom angle site symmetry 1
Geom angle site symmetry 3
Geom angle publ flag

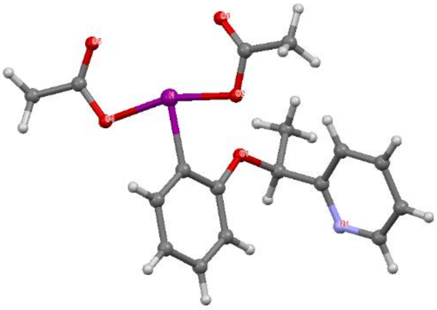
C2 C1 H1A 109.5
C2 C1 H1B 109.5
H1A C1 H1B 109.5
C2 C1 H1C 109.5
H1A C1 H1C 109.5
H1B C1 H1C 109.5
O1 C2 O2 122.2(3)
O1 C2 C1 126.7(3)
O2 C2 C1 111.2(3)
O2 C3 C4 108.2(2)
O2 C3 H3A 110.1
C4 C3 H3A 110.1
O2 C3 H3B 110.1
C4 C3 H3B 110.1
H3A C3 H3B 108.4
O3 C4 C3 108.8(2)
O3 C4 C7 105.89(19)
C3 C4 C7 111.5(2)
O3 C4 H4 110.2
C3 C4 H4 110.2
C7 C4 H4 110.2
O4 C5 O3 122.4(2)
O4 C5 C6 126.6(2)
O3 C5 C6 111.0(2)
C5 C6 C8 110.4(2)
C5 C6 C10 110.1(2)
C8 C6 C10 109.33(19)
C5 C6 C7 103.46(18)
C8 C6 C7 110.0(2)
C10 C6 C7 113.5(2)
C4 C7 C6 104.89(19)
C4 C7 H7A 110.8
C6 C7 H7A 110.8
C4 C7 H7B 110.8
C6 C7 H7B 110.8
H7A C7 H7B 108.8
O5 C8 O6 125.0(2)
O5 C8 C6 124.0(2)
O6 C8 C6 110.9(2)
O6 C9 H9A 109.5
O6 C9 H9B 109.5
H9A C9 H9B 109.5
O6 C9 H9C 109.5
H9A C9 H9C 109.5
H9B C9 H9C 109.5
C11 C10 C6 111.3(2)
C11 C10 H10A 109.4
C6 C10 H10A 109.4
C11 C10 H10B 109.4
C6 C10 H10B 109.4
H10A C10 H10B 108.0

C12 C11 C10 177.9(3)
C11 C12 H12 180.0
C2 O2 C3 115.8(2)
C5 O3 C4 111.44(18)
C8 O6 C9 116.0(2)

Refine diff density max: 0.136
Refine diff density min: -0.145
Refine diff density rms: 0.038

(S)-(2-(1-(Pyridin-2-yl)ethoxy)phenyl)-l3-iodanediyl diacetate





Audit creation method: SHELXL-2013

Chemical name systematic

Chemical formula sum: $C_{17}H_{18}INO_5$

Chemical formula weight: 443.22

'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4': 'C' 'C' 0.0181 0.0091

'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4': 'H' 'H' 0.0000 0.0000

'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4': 'O' 'O' 0.0492 0.0322

'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4': 'I' 'I' -0.3257 6.8362

'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4': 'N' 'N' 0.0311 0.0180

Space group crystal system: monoclinic

Space group IT number: 14

Space group name H-M alt: 'P 21/n'

Space group name Hall: '-P 2yn'

Cell length a: 8.9340(2)

Cell length b: 11.6335(3)

Cell length c: 17.3231(4)

Cell angle alpha: 90

Cell angle beta: 96.746(2)

Cell angle gamma: 90

Cell volume: 1787.99(7)

Cell formula units Z: 4

Cell measurement temperature: 150(2)

Exptl crystal density diffrn: 1.647

Exptl crystal F 000: 880

Exptl crystal size max: 0.490

Exptl crystal size mid: 0.304

Exptl crystal size min: 0.230

Exptl absorpt coefficient mu: 14.303

Shelx estimated absorpt T min: 0.054

Shelx estimated absorpt T max: 0.137

Diffrn ambient temperature: 150(2)

Diffrn radiation wavelength: 1.54184

Diffrn radiation type: CuK\a

Diffrn reflns number: 6790

Diffrn reflns av unetI/netI: 0.0356

Diffrn reflns av R equivalents: 0.0391

Diffrn reflns limit h min: -10

Diffrn reflns limit h max: 10

Diffrn reflns limit k min: -14

Diffrn reflns limit k max: 10

Diffrn reflns limit l min: -21

Diffrn reflns limit l max: 17

Diffrn reflns theta min: 4.588

Diffrn reflns theta max: 74.101

Diffrn reflns theta full: 67.684

Diffrn measured fraction theta max: 0.962

Diffrn measured fraction theta full: 0.996

Diffrn reflns Laue measured fraction max: 0.962

Diffrn reflns Laue measured fraction full: 0.996

Diffrn reflns point group measured fraction max: 0.962

Diffrn reflns point group measured fraction full: 0.996

Reflns number total: 3503

Reflns number gt: 3400

Reflns threshold expression: 'I > 2\s(I)'

Reflns Friedel coverage: 0.000

Reflections were merged by SHELXL according to the crystal class for the calculation of statistics and refinement.

Reflns Friedel fraction is defined as the number of unique Friedel pairs measured divided by the number that would be possible theoretically, ignoring centric projections and systematic absences.

Computing structure refinement: 'SHELXL-2013 (Sheldrick, 2013)'
Refine ls structure factor coef: Fsqd
Refine ls matrix type: full
Refine ls weighting scheme: calc
Refine ls weighting details: 'w=1/[\s^2^(Fo^2^)+(0.0886P)^2^+0.1459P]
where P=(Fo^2^+2Fc^2^)/3'

Atom sites solution hydrogens: geom
Refine ls hydrogen treatment: constr
Refine ls extinction method: none
Refine ls number reflns: 3503
Refine ls number parameters: 220
Refine ls number restraints: 0
Refine ls R factor all: 0.0446
Refine ls R factor gt: 0.0439
Refine ls wR factor ref: 0.1140
Refine ls wR factor gt: 0.1128
Refine ls goodness of fit ref: 1.074
Refine ls restrained S all: 1.074
Refine ls shift/su max: 0.001
Refine ls shift/su mean: 0.000

Atomic coordinates and equivalent isotropic displacement parameters

C1 C 0.6666(4) 0.1650(3) 0.1013(2) 0.0191(7) Uani 1 1 d
C2 C 0.5789(5) 0.0802(4) 0.1302(3) 0.0294(8) Uani 1 1 d
H2 H 0.5089 0.0995 0.1654 0.035 Uiso 1 1 calc R U
C3 C 0.5947(6) -0.0329(4) 0.1073(3) 0.0386(10) Uani 1 1 d
H3 H 0.5369 -0.0925 0.1267 0.046 Uiso 1 1 calc R U
C4 C 0.6968(5) -0.0563(4) 0.0554(3) 0.0359(10) Uani 1 1 d
H4 H 0.7100 -0.1326 0.0379 0.043 Uiso 1 1 calc R U

```
C5 C 0.7786(5) 0.0322(4) 0.0297(2) 0.0328(10) Uani 1 1 d
H5 H 0.8479 0.0148 -0.0062 0.039 Uiso 1 1 calc R U
C6 C 0.6561(4) 0.2888(4) 0.12692(18) 0.0175(7) Uani 1 1 d
H6 H 0.7211 0.3381 0.0973 0.021 Uiso 1 1 calc R U
C7 C 0.7000(4) 0.3056(4) 0.2135(2) 0.0274(8) Uani 1 1 d
H7A H 0.6911 0.3871 0.2265 0.041 Uiso 1 1 calc R U
H7B H 0.8044 0.2804 0.2275 0.041 Uiso 1 1 calc R U
H7C H 0.6330 0.2601 0.2425 0.041 Uiso 1 1 calc R U
C8 C 0.4382(3) 0.3472(3) 0.03915(18) 0.0116(6) Uani 1 1 d
C9 C 0.2861(4) 0.3782(3) 0.02921(19) 0.0102(6) Uani 1 1 d
C10 C 0.2098(4) 0.4031(3) -0.0436(2) 0.0168(7) Uani 1 1 d
H10 H 0.1070 0.4257 -0.0484 0.020 Uiso 1 1 calc R U
C11 C 0.2849(5) 0.3945(3) -0.1091(2) 0.0203(8) Uani 1 1 d
H11 H 0.2341 0.4102 -0.1593 0.024 Uiso 1 1 calc R U
C12 C 0.4365(4) 0.3625(3) -0.0999(2) 0.0196(7) Uani 1 1 d
H12 H 0.4889 0.3568 -0.1444 0.023 Uiso 1 1 calc R U
C13 C 0.5124(4) 0.3387(3) -0.0269(2) 0.0164(6) Uani 1 1 d
H13 H 0.6154 0.3165 -0.0220 0.020 Uiso 1 1 calc R U
C14 C 0.1166(4) 0.1718(3) 0.1831(2) 0.0176(7) Uani 1 1 d
C15 C 0.1018(5) 0.0426(3) 0.1859(2) 0.0278(8) Uani 1 1 d
H15A H 0.0772 0.0193 0.2373 0.042 Uiso 1 1 calc R U
H15B H 0.1972 0.0071 0.1761 0.042 Uiso 1 1 calc R U
H15C H 0.0213 0.0176 0.1461 0.042 Uiso 1 1 calc R U
C16 C 0.1271(4) 0.6345(3) 0.1510(2) 0.0168(7) Uani 1 1 d
C17 C 0.1244(5) 0.7601(3) 0.1358(2) 0.0277(8) Uani 1 1 d
H17A H 0.0330 0.7935 0.1527 0.042 Uiso 1 1 calc R U
H17B H 0.1252 0.7738 0.0800 0.042 Uiso 1 1 calc R U
H17C H 0.2133 0.7960 0.1646 0.042 Uiso 1 1 calc R U
O1 O 0.5010(3) 0.3286(2) 0.11333(13) 0.0162(5) Uani 1 1 d
O2 O 0.1781(3) 0.2083(3) 0.12238(13) 0.0201(6) Uani 1 1 d
O3 O 0.0751(3) 0.2351(2) 0.23194(15) 0.0239(5) Uani 1 1 d
O4 O 0.1908(3) 0.5742(2) 0.09967(14) 0.0169(5) Uani 1 1 d
O5 O 0.0738(3) 0.5888(2) 0.20544(17) 0.0237(6) Uani 1 1 d
I1 I 0.17266(2) 0.39308(2) 0.12663(2) 0.01054(13) Uani 1 1 d
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N1 N 0.7671(4) 0.1425(3) 0.0521(2) 0.0264(7) Uani 1 1 d

Anisotropic displacement parameters

C1 0.0145(16) 0.0237(19) 0.0189(16) 0.0034(14) 0.0008(12) 0.0096(14)

C2 0.027(2) 0.028(2) 0.036(2) 0.0028(18) 0.0123(16) 0.0038(18)

C3 0.043(2) 0.021(2) 0.052(3) 0.0024(19) 0.006(2) 0.0003(18)

C4 0.038(2) 0.023(2) 0.044(2) -0.0080(18) -0.0041(18) 0.0137(18)

C5 0.029(2) 0.036(2) 0.0348(19) -0.0041(18) 0.0079(16) 0.0205(18)

C6 0.0072(14) 0.0236(19) 0.0217(17) 0.0023(12) 0.0019(12) 0.0049(12)

C7 0.0179(17) 0.034(2) 0.0285(18) -0.0066(16) -0.0053(14) 0.0080(15)

C8 0.0128(15) 0.0049(14) 0.0177(14) 0.0028(11) 0.0036(11) 0.0029(11)

C9 0.0105(15) 0.0067(13) 0.0146(14) -0.0014(10) 0.0062(12) 0.0002(11)

C10 0.0166(17) 0.0146(17) 0.0189(17) -0.0025(12) 0.0009(13) 0.0052(12)

C11 0.026(2) 0.0175(19) 0.0174(17) -0.0014(12) 0.0012(17) 0.0027(13)

C12 0.0276(19) 0.0141(16) 0.0195(16) -0.0001(14) 0.0132(14) 0.0014(15)

C13 0.0138(15) 0.0133(15) 0.0236(15) 0.0009(12) 0.0091(12) 0.0030(12)

C14 0.0144(16) 0.0127(17) 0.0259(17) 0.0024(14) 0.0024(13) -0.0012(13)

C15 0.034(2) 0.0135(19) 0.0347(19) 0.0069(15) -0.0018(16) -0.0057(15)

C16 0.0116(15) 0.0147(16) 0.0249(17) -0.0056(15) 0.0058(13) 0.0032(14)

C17 0.036(2) 0.0073(17) 0.0411(19) -0.0070(15) 0.0104(17) 0.0021(15)

O1 0.0095(11) 0.0218(12) 0.0179(11) 0.0017(9) 0.0041(8) 0.0104(9)

O2 0.0282(16) 0.0060(12) 0.0278(14) -0.0014(8) 0.0106(12) 0.0021(8)

O3 0.0245(13) 0.0183(13) 0.0311(13) 0.0035(11) 0.0121(10) 0.0006(10)

O4 0.0242(13) 0.0066(11) 0.0229(12) 0.0000(10) 0.0147(10) 0.0012(10)

O5 0.0300(16) 0.0164(12) 0.0275(13) -0.0014(10) 0.0149(12) 0.0033(11)

I1 0.00806(17) 0.00721(18) 0.01717(17) -0.00083(5) 0.00492(10) 0.00235(5)

N1 0.0237(17) 0.0269(18) 0.0304(16) 0.0027(14) 0.0108(13) 0.0133(15)

Geom special details:

All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Geom bond atom site label 1
Geom bond atom site label 2
Geom bond distance
Geom bond site symmetry 2
Geom bond publ flag

C1 N1 1.334(5)
C1 C2 1.390(6)
C1 C6 1.513(6)
C2 C3 1.386(6)
C2 H2 0.9500
C3 C4 1.381(7)
C3 H3 0.9500
C4 C5 1.366(7)
C4 H4 0.9500
C5 N1 1.349(6)
C5 H5 0.9500
C6 O1 1.453(4)
C6 C7 1.518(4)
C6 H6 1.0000
C7 H7A 0.9800
C7 H7B 0.9800
C7 H7C 0.9800
C8 O1 1.358(4)
C8 C13 1.391(4)
C8 C9 1.398(4)
C9 C10 1.391(5)
C9 I1 2.075(3)
C10 C11 1.388(6)
C10 H10 0.9500
C11 C12 1.395(6)
C11 H11 0.9500
C12 C13 1.392(5)
C12 H12 0.9500
C13 H13 0.9500
C14 O3 1.212(5)
C14 O2 1.314(4)
C14 C15 1.510(5)
C15 H15A 0.9800
C15 H15B 0.9800
C15 H15C 0.9800
C16 O5 1.226(5)
C16 O4 1.315(5)
C16 C17 1.484(5)
C17 H17A 0.9800
C17 H17B 0.9800
C17 H17C 0.9800
O2 I1 2.151(3)
O4 I1 2.168(3)

Geom angle atom site label 1
Geom angle atom site label 2
Geom angle atom site label 3
Geom angle
Geom angle site symmetry 1
Geom angle site symmetry 3
Geom angle publ flag

N1 C1 C2 122.8(4)
N1 C1 C6 116.3(4)
C2 C1 C6 120.8(3)

C3 C2 C1 119.3(4)	C3 C2 H2 120.3	C1 C2 H2 120.3
C4 C3 C2 118.1(4)	C4 C3 H3 121.0	C2 C3 H3 121.0
C5 C4 C3 118.9(4)	C5 C4 H4 120.5	C3 C4 H4 120.5
N1 C5 C4 124.1(4)	N1 C5 H5 117.9	C4 C5 H5 117.9
O1 C6 C1 110.3(3)	O1 C6 C7 104.5(3)	C1 C6 C7 113.3(3)
O1 C6 H6 109.6	C1 C6 H6 109.6	C7 C6 H6 109.6
C6 C7 H7A 109.5	C6 C7 H7B 109.5	H7A C7 H7B 109.5
C6 C7 H7C 109.5	H7A C7 H7C 109.5	H7B C7 H7C 109.5
O1 C8 C13 125.7(3)	O1 C8 C9 116.5(3)	C13 C8 C9 117.9(3)
C10 C9 C8 122.1(3)	C10 C9 I1 119.1(2)	C8 C9 I1 118.8(2)
C11 C10 C9 119.6(3)	C11 C10 H10 120.2	C9 C10 H10 120.2
C10 C11 C12 118.8(3)	C10 C11 H11 120.6	C12 C11 H11 120.6
C13 C12 C11 121.3(3)	C13 C12 H12 119.3	C11 C12 H12 119.3
C8 C13 C12 120.3(3)	C8 C13 H13 119.8	C12 C13 H13 119.8
O3 C14 O2 123.6(3)	O3 C14 C15 123.2(3)	O2 C14 C15 113.2(3)
C14 C15 H15A 109.5	C14 C15 H15B 109.5	H15A C15 H15B 109.5
C14 C15 H15C 109.5	H15A C15 H15C 109.5	H15B C15 H15C 109.5
O5 C16 O4 121.8(4)	O5 C16 C17 124.3(3)	O4 C16 C17 113.9(3)
C16 C17 H17A 109.5	C16 C17 H17B 109.5	H17A C17 H17B 109.5
C16 C17 H17C 109.5	H17A C17 H17C 109.5	H17B C17 H17C 109.5
C8 O1 C6 118.9(2)	C14 O2 I1 106.4(2)	C16 O4 I1 108.9(2)
C9 I1 O2 82.75(11)	C9 I1 O4 81.36(11)	O2 I1 O4 163.91(9)
C1 N1 C5 116.7(4)		

Refine diff density max: 1.603

Refine diff density min: -2.411

Refine diff density rms: 0.208