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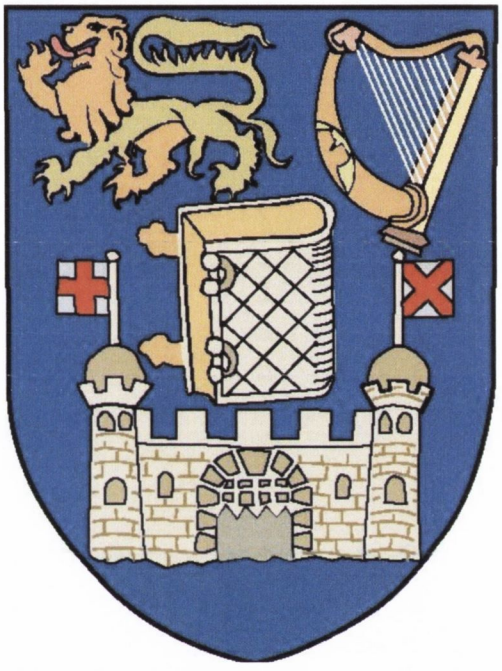
THE DEVELOPMENT OF NOVEL METHODOLOGIES FOR THE SELECTIVE TISHCHENKO REACTION AND THE USE OF ACYLPYRAZOLES AS DIRECTING GROUPS IN ORGANOCATALYTIC 1,4-CONJUGATE ADDITION REACTIONS



A thesis submitted to the University of Dublin for the degree of Doctor of Philosophy

By

Simon Curran B.A. (Mod.)

March 2014

Trinity College Dublin

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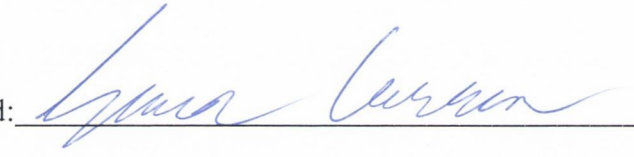
Signed: 

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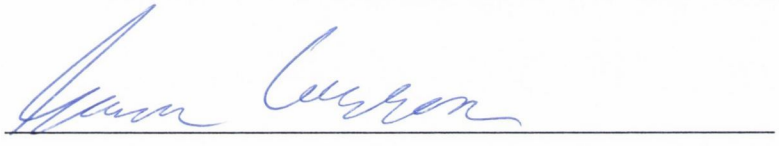
I hereby declare that the work described in this thesis was performed by me unless otherwise stated



Simon Curran

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Deserving of special mention are the dedicated PhD students of the Connon group who proof-read this thesis: Claudio, Claire-Louise, Emiliano, Eoghan, Lauren and Michelle. I'd like to extend my personal thanks to the Lab B guys: Sean, Lauren, Emiliano and Claudio for the constant banter, ridiculous music and for not killing me during my smelly selenium phase.

Abbreviations

Ac	-	Acetyl
Ali	-	Aliphatic
Alk	-	Alkyl
Ar	-	Aryl
BINOL	-	2,2'-binaphthol
Bn	-	Benzyl
br	-	Broad
Bu	-	Butyl
Cat.	-	Catalyst
COD	-	Cyclooctadiene
Conv.	-	Conversion
CPME	-	Cyclopentyl methyl ether
CSP	-	Chiral stationary phase
Cy	-	Cyclohexyl
d	-	Doublet
DA	-	Diels Alder
DABCO	-	1,4-diazabicyclo[2.2.2]octane
DBU	-	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	-	*N,N*-dicyclohexylcarbodiimine
DMAP	-	*N,N*-dimethylaminopyridine
DMF	-	*N,N*-dimethylformamide
DMS	-	Dimethylsulfide
DMSO	-	Dimethylsulfoxide
d.r.	-	Diastereomeric ratio
EDG	-	Electron donating group
ee	-	Enantiomeric excess
Et	-	Ethyl
EWG	-	Electron withdrawing group
HPLC	-	High pressure liquid chromatography
MBH	-	Morita Baylis Hillman
Me	-	Methyl
MTBE	-	Methyl-tert-butylether
MW	-	Microwave

NHC	-	*N*-heterocyclic carbene
NMR	-	Nuclear magnetic resonance
Nu	-	Nucleophile
PCC	-	Pyridinium chlorochromate
Ph	-	Phenyl
Pr	-	Propyl
PTSA	-	Paratoluenesulfonic acid
q	-	Quartet
rt	-	Room temperature
s	-	Singlet
TBDPS	-	Tert-butyldiphenylsilyl
TBS	-	Tributylsilyl
Tf	-	Triflyl
THF	-	Tetrahydrofuran
TMP	-	Tetramethylpiperidine
TMS	-	Trimethylsilyl
Ts	-	Tosyl

Chapter 1: Introduction

1.1 The Tishchenko reaction

1.1.1 A historical perspective

Originally discovered in 1887 by L. Claisen,[1] the Tishchenko reaction involves the disproportionation of two aldehyde molecules to yield an ester. He noted the formation of benzyl benzoate from benzaldehyde in the presence of sodium ethoxide. In 1906 W. E. Tischtschenko, a Russian chemist for whom the reaction is named, reported that the same reaction was also catalysed by aluminium and magnesium alkoxides.[2] He also disclosed that the substrate scope was not limited to benzaldehyde, but that the esterification of aliphatic aldehydes could be promoted while limiting the formation of aldol products. For recent reviews on the subject please see the references provided.[3]

1.1.2 Industrial application of the Tishchenko reaction

The production of ethyl acetate is the most prevalent industrial application of the Tishchenko reaction.[4] The dimerisation of acetaldehyde is performed at 0 – 5 °C in the presence of a $Al(OEt)_3$ catalyst and a $ZnCl_2$ co-catalyst. Synthetic applications of the Tishchenko reaction are very limited due to the lack of chemoselectivity in reactions involving two different aldehydes. As such, it has long been considered more of a mechanistic curiosity than a tool in organic synthesis.

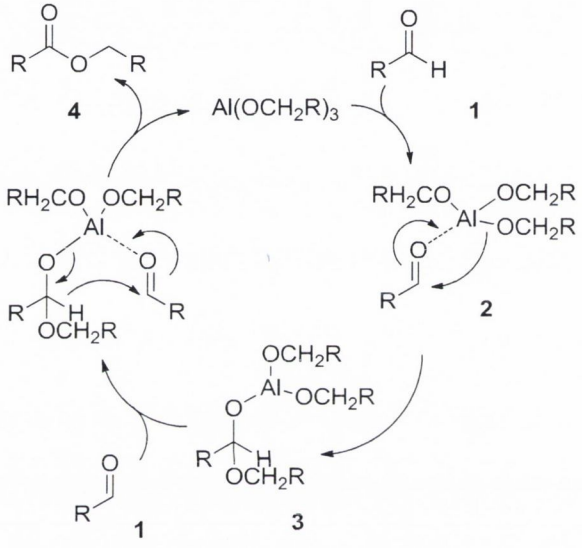
1.1.3 The aluminium alkoxide mediated Tishchenko reaction

It was found that the aluminium alkoxide catalyst needed to be tailored to the substrate used in the reaction. For example, a mixture of ethyl and methyl formates resulted from the reaction of paraformaldehyde with $Al(OEt)_3$. The process is also subject to side reactions, such as the aldol condensation in the case of enolisable aliphatic substrates. Though the reaction was discovered in the late part of the nineteenth century, it was much later that the reaction mechanism and the role of the aluminium alkoxide were fully elucidated.

1.1.3.1 The Tishchenko reaction mediated by $Al(OR)_3$: mechanism

Ogata *et al.* proposed two mechanistic rationales for the Tishchenko reaction, of which the mechanism that best supported that experimental data is outlined in Scheme 1.1.[5] It consists of the initial chelation of the aldehyde substrate **1** to the metal alkoxide to form complex **2**. An alkoxide molecule migrates from the metal centre to the carbonyl carbon to form **3**.

Scheme 1.1 Proposed mechanism of aluminium alkoxide mediated Tishchenko reaction



A second aldehyde molecule then coordinates to the aluminium ion allowing intermolecular hydride transfer to occur. This is followed by the dissociation of the ester product **4**, and reformation of the metal alkoxide catalyst. Ogata *et al.* proved that this is the correct catalytic pathway by first showing that the formation of isopropylacetate occurred faster than ethyl acetate when $Al(O\textit{i}Pr)_3$ is used as the catalyst, suggesting that initial alkoxide transfer occurs from the catalyst. This was further confirmed by the absence of isopropyl acetate from the addition of $Al(O\textit{i}Pr)_3$ to a solution of ethyl acetate, *i.e.* no transesterification was observed.

1.1.3.2 Additives effecting rates of reaction

Adkins *et al.* noted that the presence of water had a detrimental effect on the rate of the reaction.[6] They hypothesised that water may have two effects: degrading the catalyst by substituting in place of the ethoxide; and further, forming a layer of protective alumina around the alkoxide. It was also noted that the addition of Lewis acidic metal salts as co-

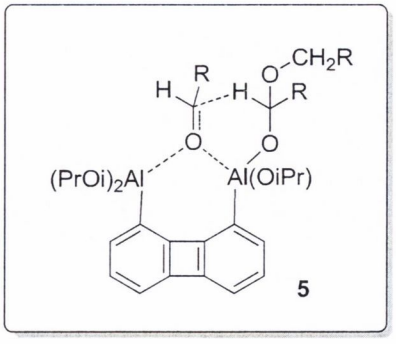
catalysts augmented the yield of ester obtained. The best salts for the promotion of the reaction were found to be chlorides of aluminium, zinc and mercury.

Ogata *et al.* reported that the reaction of impure benzaldehyde and $Al(OBn)_3$ catalyst proceeded at a higher rate than that of pure benzaldehyde. [7] This effect was attributed to the presence of benzoic acid in the reaction. On analysis of other acids they found that those with a pK_a similar to that of benzoic acid (4.19, H_2O),[8] such as acetic acid, were also capable of acting as promoters for the reaction. They also noted that anhydrides of these acids also acted as promoters, in particular acetic anhydride which gave the highest conversion. This effect was attributed to the formation of $CH_3CO_2Al(OBn)_2$, which they claim is a more Lewis-acidic compound than the corresponding trialkoxide.

1.1.3.3 A bidentate aluminium alkoxide catalyst

In more recent years, Marouka *et al.* have reported the use of highly active bidentate aluminium complexes that are capable of promoting the formation of ester dimers in high yields with catalyst loadings as low as 0.2 mol%.[9] It was noted that aliphatic substrates were more amenable to reaction using this catalyst than aromatic substrates and that competing reactions, such as the aldol reaction were completely suppressed. The elevated catalyst activity is attributed to the presence of the second aluminium atom which increases the rate of hydride transfer by chelating a molecule of aldehyde in the transition state (Figure 1.1).

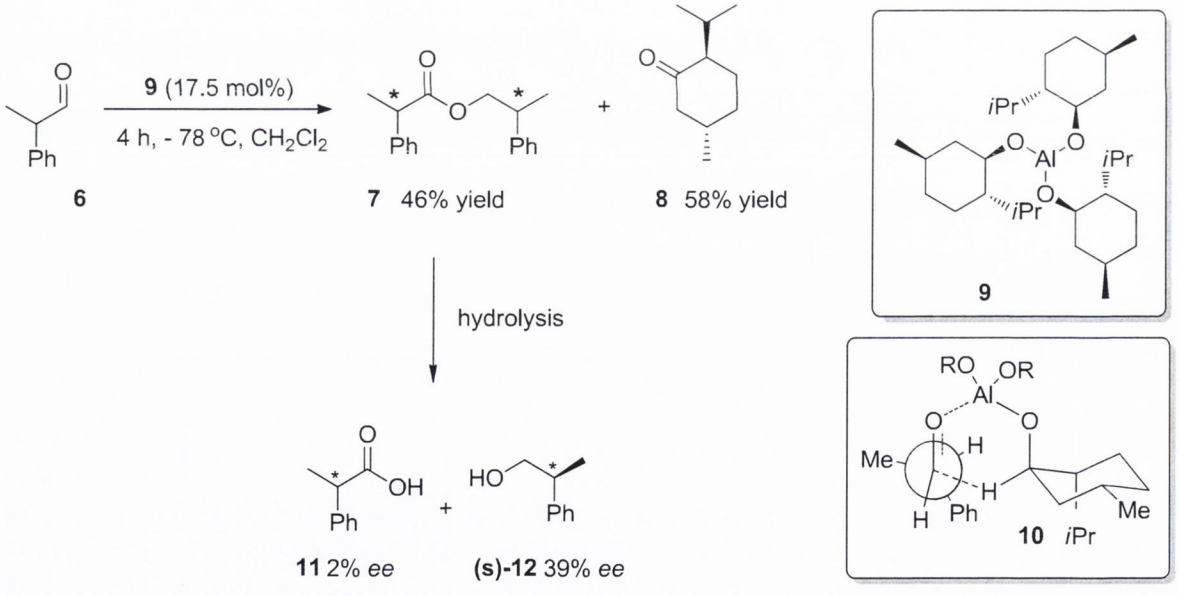
Figure 1.1 Proposed mode of action of the bidentate aluminium catalyst



1.1.3.4 The asymmetric aluminium alkoxide catalysed Tishchenko reaction

The use of an optically pure aluminium alkoxide, derived from (-)-menthol **9**, has been shown to confer a degree of enantioselectivity in the dimerisation of α-phenylpropionaldehyde, (**6**, Scheme 1.2).[10] The alcohol **12** was obtained in 39% *ee* from the hydrolysis of ester **7**, but the acid **11** was shown to have negligible enantiopurity. It is also interesting to note that only 58% of (-)-menthone **8** was isolated from the reaction. This demonstrates that the hydride is transferred from the alkoxide of the aluminium catalyst to a molecule of aldehyde, *via* a Meerwein-Ponndorf-Verley (MPV) reaction **10**, thereby conferring enantiocontrol. It also may indicate why only a small amount of enantioselectivity was observed, *i.e.* the enantiopure aluminium alkoxide involved in hydride transfer step is decreasing in concentration as (-)-menthone **8** is being produced.

Scheme 1.2 The aluminium (-)-trimenthyloxide catalysed dimerization of α-phenylpropionaldehyde



1.1.4 Other catalytic systems that have been applied to the Tishchenko reaction

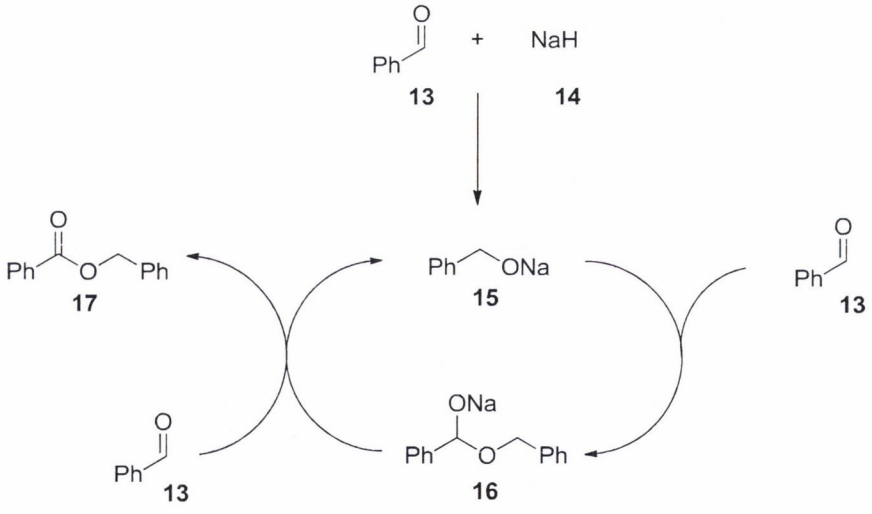
Since the initial report of the disproportionation of aldehydes to esters, aluminium alkoxide-based catalysts have been the most prevalent promoters of the Tishchenko reaction. The major drawbacks of the aluminium alkoxide-based catalysts include: low yields; competing side reactions (MPV and aldol); catalyst must match substrate; and poor substrate scope.

There has been a renewed interest in the subject in recent years, with more active catalysts being designed to give higher yields of product and a larger substrate scope than those observed in the aluminium alkoxide catalysed Tishchenko reaction.[3b]

1.1.4.1 Alkali metal-based catalysts

Sodium hydride has been reported as a catalyst for the Tishchenko reaction of aromatic aldehydes.[11] Werner *et al.* posited that sodium hydride (**14**) is acting as a precatalyst to generate sodium alkoxide **15** from **13** (Scheme 1.3). Once the sodium alkoxide **15** is generated the reaction proceeds analogously to Claisen's original discovery with sodium ethoxide; *i.e.*, intermediate **16** is formed by the addition of **15** to another molecule of aldehyde, subsequent hydride transfer from **16** to a molecule of aldehyde, yields benzyl benzoate (**17**). They reported that high yields were attainable using both electron-rich and electron–deficient aromatic systems.

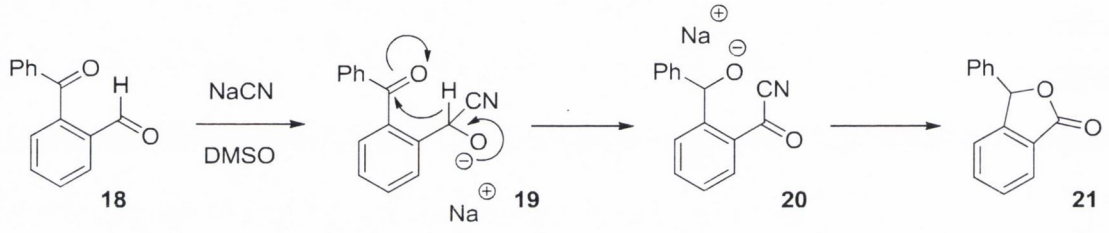
Scheme 1.3 Reaction mechanism of sodium hydride catalysed Tishchenko reaction



Waddell *et al.* have also reported that sodium hydride promotes the Tishchenko reaction in a solvent free, high speed ball milling system.[12] They noted that this methodology is not only more environmentally friendly, but also is of increased substrate scope including often challenging heteroaromatic substrates.

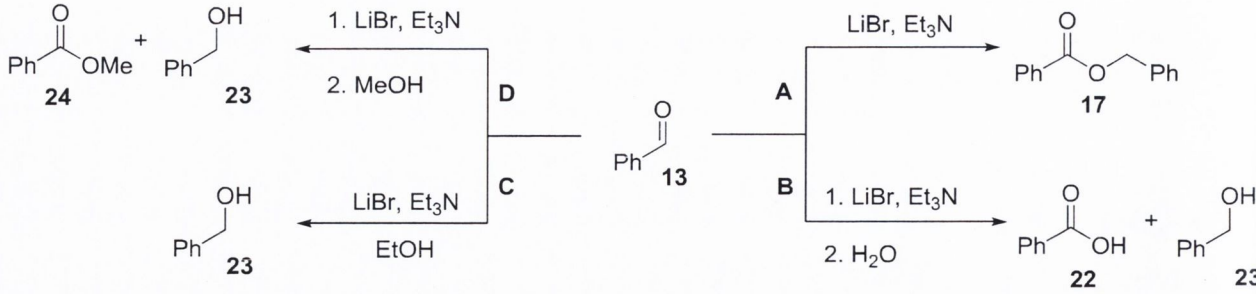
It was reported by Schmalz *et al.* that sodium cyanide was capable of promoting the intramolecular Tishchenko reaction of 2-formyl benzophenones **18** in DMSO (Scheme 1.4).[13] They theorised that the lactone **21** was formed by *via* the hydride transfer from the conjugate base of the cyanohydrin (*i.e.* **19**) to produce alkoxide **20**. A large range of 2-formylbenzophenones are amenable to this methodology, including electron-rich, electron-deficient and hetero-aromatic benzophenones. It is interesting to note at this juncture that the authors were capable of catalysing same reaction using lithium ethanethiolate.

Scheme 1.4 The sodium cyanide catalysed intramolecular Tishchenko reaction



Abaee *et al.* described the lithium bromide-catalysed Tishchenko reaction of aromatic aldehydes using triethylamine as the solvent, (**A**, Scheme 1.5).[14] They demonstrated that the products from this reaction could be easily manipulated, in one pot, to yield the Cannizarro products **22** and **23** *via* hydrolysis, (**B**, Scheme 1.5), the MPV product **23** formed *via* the oxidation of ethanol, (**C**, Scheme 1.5) and the mixed ester **24** *via* methanolysis, (**D**, Scheme 1.5). Due to the diverse product range available, this methodology has greatly expanded the synthetic utility of the Tishchenko reaction.

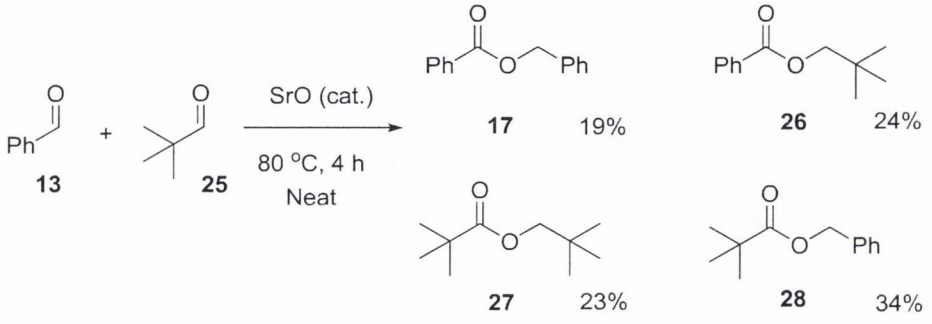
Scheme 1.5 The lithium bromide catalysed Tishchenko reaction



1.1.4.2 Alkali earth metal-based catalysts

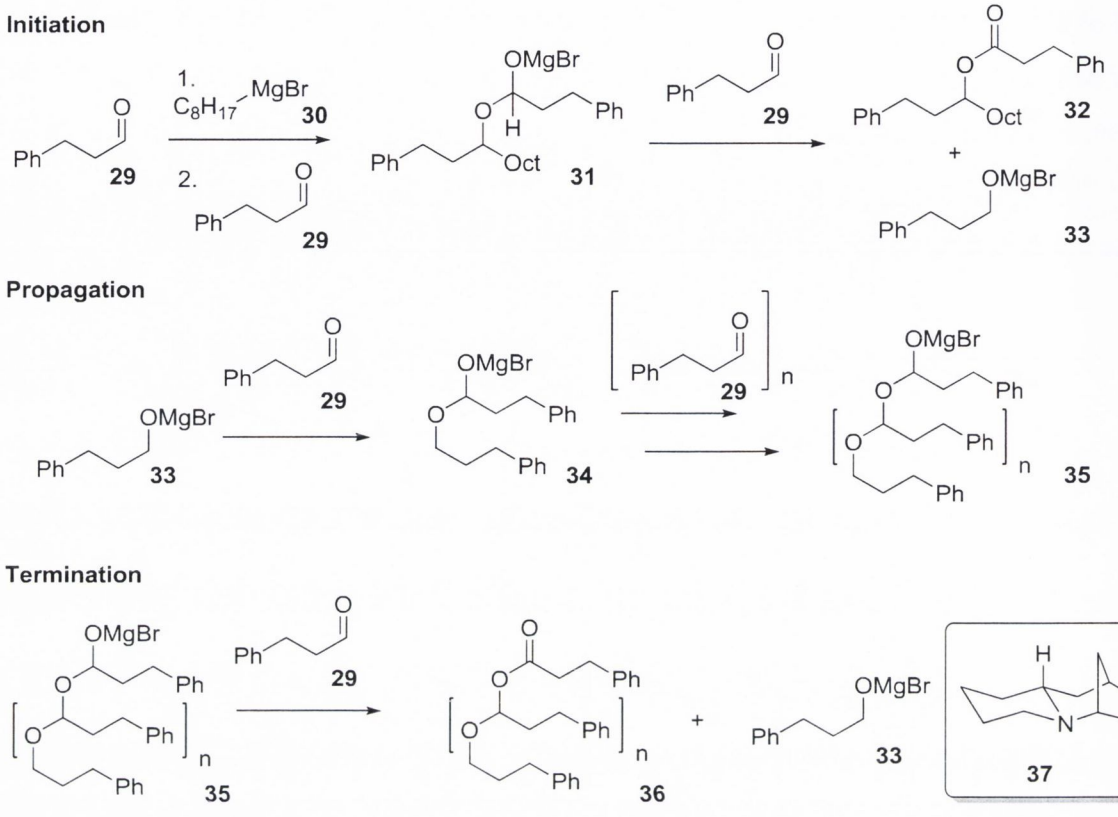
Oxides of alkali earth metals have been used by Hattori *et al.* to generate phthalide from *o*-phthalaldehyde.[15] They found that oxides of magnesium, calcium, strontium and barium were all active, of which strontium was found to be superior.

Scheme 1.6 Alkali earth metal oxide-catalysed mixed aldehyde Tishchenko reaction



They were later able to show that alkali earth metal oxides were capable of generating classical Tishchenko esters from aliphatic aldehydes.[16] It was also noted that the alkoxides are further capable of differentiating (to a small degree) between two different aldehydes in a reaction system, furnishing mixed ester **28** in a slightly elevated yield. This topic will be covered further in Section 1.2. Alkali earth amides have also been shown to be active catalysts for the Tishchenko reaction of a diverse range of aldehydes.[17]

Scheme 1.7 Polymerisation of 3-phenylpropanal using octyl magnesium bromide as an initiator



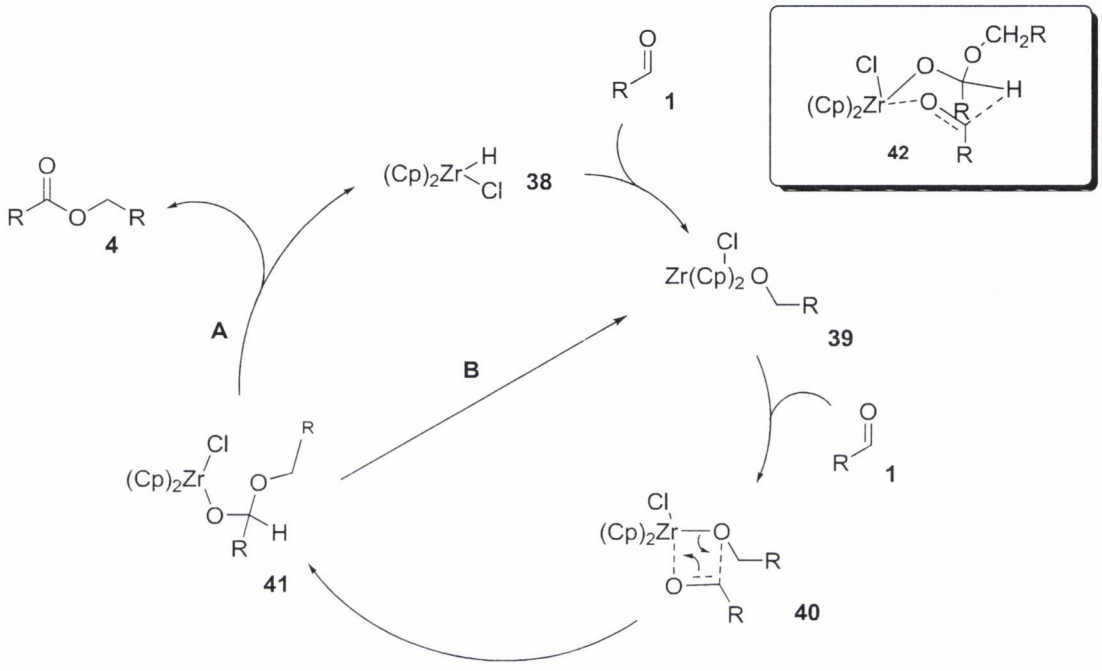
Okamoto *et al.* were able to demonstrate the polymerisation of 3-phenylpropanal **29** initiated by the Grignard reagent **30** (Scheme 1.7).[18] Hydride transfer from the magnesium bromide hemiacetal conjugate base **31** to a molecule of aldehyde **29**, yields the alkoxide **33** which self-polymerises to form the oligomer **35**. The termination step is accomplished by another Tishchenko reaction yielding the ester-terminating oligomer **36**. The use of enantiopure (-)-sparteine **37** allowed the generation of chiral oligomers of **36** in up to 70% *ee*. Sparteine **37** has been widely used in asymmetric organic synthesis, and has been shown to chelate alkali metal ions.[19]

1.1.4.3 Transition metal-based catalysts

Transition metal-based catalysts for the Tishchenko reaction largely come in the form of transition metal hydrides; the first of such catalysts to be reported was by Yamamoto *et al.*[20] Their $RuH_2(PPh_3)_4$ catalyst was capable of producing Tishchenko ester products in moderate yields from various unbranched aliphatic aldehydes. They were later able to demonstrate a

possible mechanism for the reaction, which was amended by Morita *et al.* using $ZrH(Cp)_2Cl$ (Scheme 1.8). [21 22]

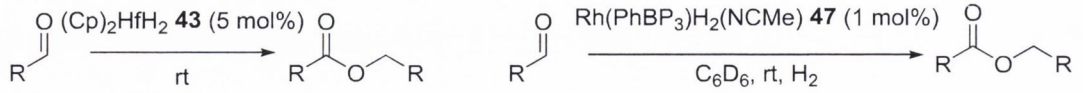
Scheme 1.8 The zirconocene hydride-catalysed Tishchenko reaction: proposed mechanism



The mechanism Morita *et al.* published differs in that the initial hydride transferred is from the Zr complex **38** to form the zirconocene alkoxide **39**, and not from the aldehyde. The reaction then proceeds *via* the four membered transition state **40** producing the zirconocene hemiacetal conjugate base **41**. However, they were unable to determine whether the pathway continued through route **A** (β-hydride elimination to reform the original complex) or *via* the six membered transition state **42**, route **B**.

Morita *et al.* were able to demonstrate that hydrides of hafnium and titanium were also capable of promoting the Tishchenko reaction of aliphatic aldehydes in moderate to high yields, of which they found that hafnium-based catalysts **43** were superior (Scheme 1.9).

Scheme 1.9 The substrate scope of the transition metal hydride-based catalysts **43** and **47**



Ester	R	Yield (%)
44		78
45		57
25		84
46		80
17		9

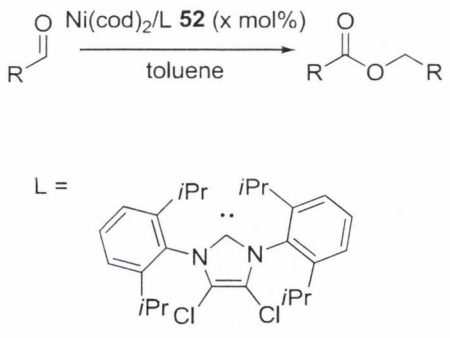
Ester	R	Yield (%)
17		81
48	F_3C	92
49	MeO	0
50		91
46		88

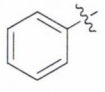
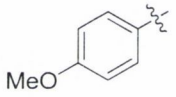
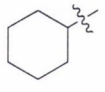
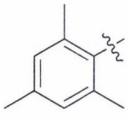
Tejel *et al.* later reported a rhodium (III) hydride catalysed Tishchenko reaction which extended the scope of this class of catalyst, furnishing high yields of ester-dimer products from electron-deficient aromatics and even the previously recalcitrant furfural.[23]

1.1.4.3.1 The Ni (0) catalysed Tishchenko reaction

Very recently (after the work described in this thesis had begun), Ogoshi *et al.* reported that Ni (0) complexes of **52** were capable of promoting the rapid Tishchenko reaction of both aliphatic and aromatic aldehydes with a relatively broad substrate scope; primary, secondary and tertiary aliphatic aldehydes along with electron-rich and sterically constrained aromatics are reported to proceed with catalysts loadings of 3 mol% or lower (Scheme 1.10).[24] They note that electron-deficient aldehydes are amenable to the methodology with increased catalyst loadings or at high temperatures.

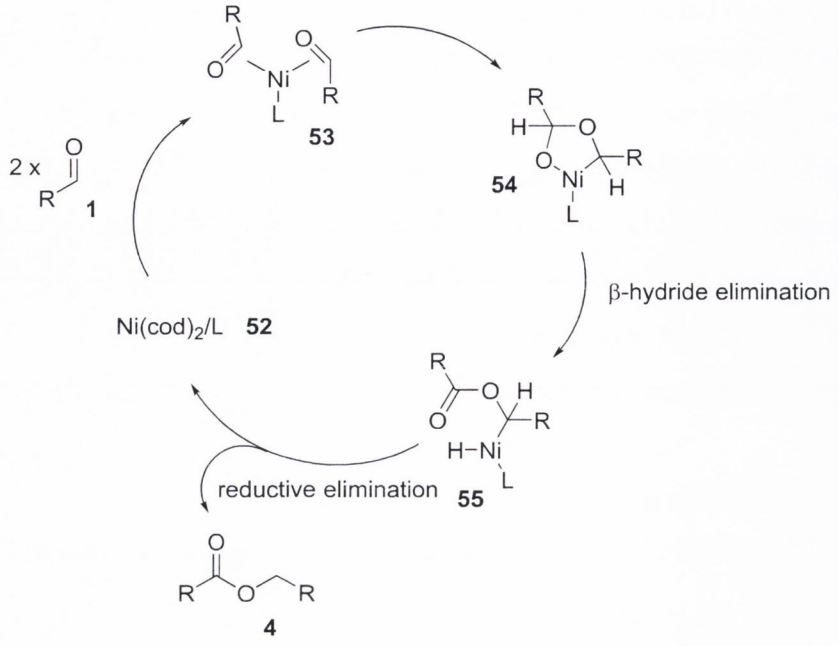
Scheme 1.10 The Ni (0) catalysed Tishchenko reaction



Ester	R	x mol%	Yield (%)
17		1	99
49		2	95
50		2	62
46		1	99
51		3	84

The proposed reaction mechanism is illustrated in Scheme 1.11: Ni (0) complexes with two molecules of aldehyde **1** to yield complex **53**, which was identified by ^{1}H NMR spectroscopy at -60 °C. This complex undergoes an oxidative cyclisation to form the "oxa-nickelacyl" intermediate **54**, and β-hydride elimination furnishes complex **55**. Reductive elimination yields the ester product **4** and reforms the Ni (0) catalyst **52**.

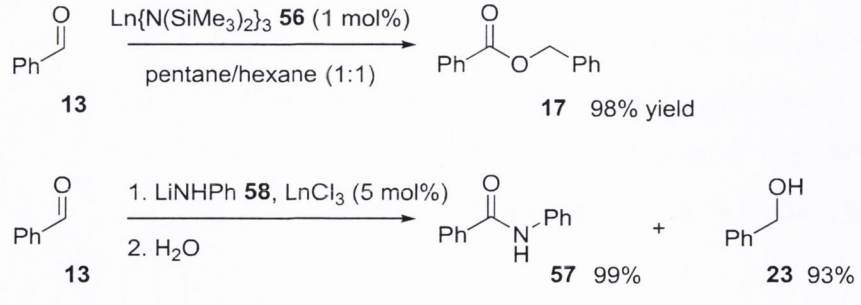
Scheme 1.11 Proposed reaction mechanism of the Ni (0) catalysed Tishchenko reaction



1.1.4.4 Lanthanide ion-based catalysts

Lanthanum amides have been shown to catalyse the Tishchenko reaction of benzaldehyde **13** in high yield (Scheme 1.12). [25] A wide substrate scope was demonstrated, encompassing electron-rich and electron-deficient aromatic systems, however, only low to moderate yields of such products were isolated (35 – 86% yield). In addition to this $LnCl_3$ has been demonstrated to catalyse the Cannizzaro-type reaction of aromatic aldehydes in the presence of lithium amides (*i.e.* **58**) to afford alcohol **23** and amide product **57** in high yields.[26]

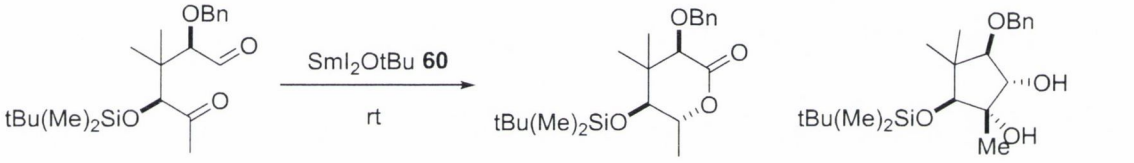
Scheme 1.12 Lanthanide ion catalysed hydride transfer reactions



1.1.4.4.1 Diastereoselective and enantioselective catalysis of the samarium iodide catalysed intramolecular Tishchenko reaction

Uenishi *et al.* reported that the reaction of impure SmI_2 with a δ-keto-aldehyde **59** not only gave the pinocol product **62** they desired, but also a δ-lactone (*i.e.* **61**, Scheme 1.13).[27] They hypothesised that the formation of this lactone was catalysed by Sm^{3+} ions in the solution. On carrying out the same reaction catalysed by SmI_2OtBu they found that the δ-lactone **61** was formed exclusively. They noted that on repeating the reaction with a catalytic amount of Sm^{2+} and methanol (forming SmI_2OMe *in situ*), δ-lactone **61** was the only observed product. Arguably the most interesting part of this reaction is that the lactone is formed in the *anti*-configuration selectively.

Scheme 1.13 Lactonisation of δ keto-aldehydes mediated by Sm^{3+} ions

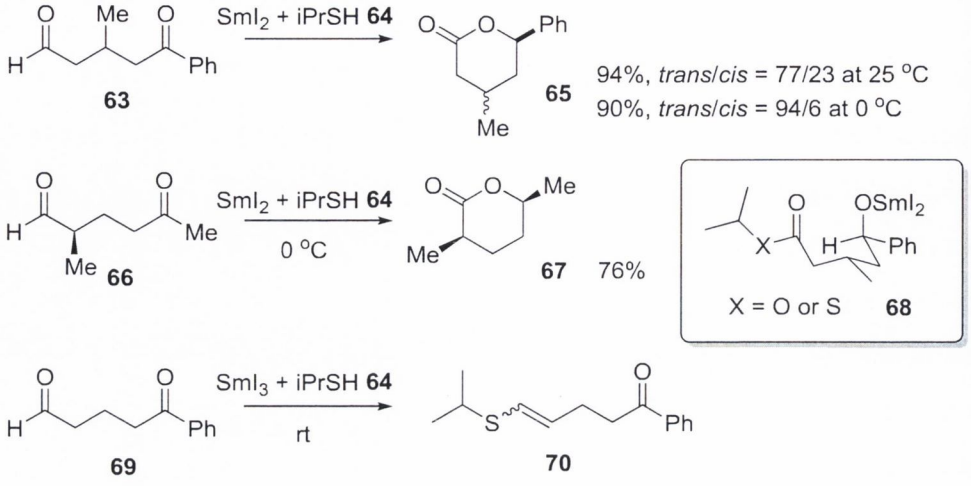


59 **61** 86% **62** 0%

Fang *et al.* reported that a similar reaction could be carried out using a thiol (*e.g.* *i*PrSH **64**) promoter instead of methanol to produce higher yields of δ-lactone **65** and much cleaner reaction mixtures.[28] They attributed this increase in activity of thiols over alcohols to the formation of intermediate **68**, the lactonisation of which would be faster in the case of the thioester (Scheme 1.14).

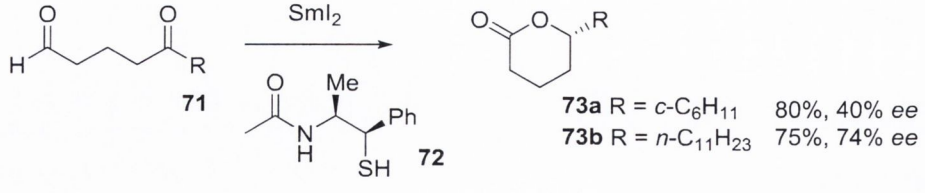
Fang *et al.* were able to show that the δ-lactone **65** could be formed with varying degrees of diastereoselectivity, depending on the temperature used. They also demonstrated that the existing chirality in the substrate can influence the stereochemistry of the final molecule, *i.e.* the formation of **67** from **66**. Like Uenishi *et al.*, they too hypothesised that Sm^{3+} is formed *in situ* but they were also unable to prove it. On mixing SmI_3 and thiol **64** with compound **69**, it was found that only thioenol ether **70** was formed, which was attributed to the formation of HI.

Scheme 1.14 Stereoselective Tishchenko reaction mediated by samarium thiolates



Using various chiral aliphatic thiols Fang *et al.* sought to develop a method of producing enantioenriched δ-lactones *via* the samarium ion-mediated intramolecular Tishchenko reaction (Scheme 1.15). They found that thiols capable of hydrogen bonding were superior to thiols that contained bulky groups. As such, they found that the ephedrine-derived thiol **72**, performed best in this reaction: allowing the formation of δ-lactone **73** in 74% *ee* where R is *n*-undecyl; and 40% where it is *c*-hexyl. This represents the literature benchmark for the asymmetric intramolecular Tishchenko reaction.

Scheme 1.15 Enantioselective intramolecular Tishchenko reaction mediated by samarium thiolates



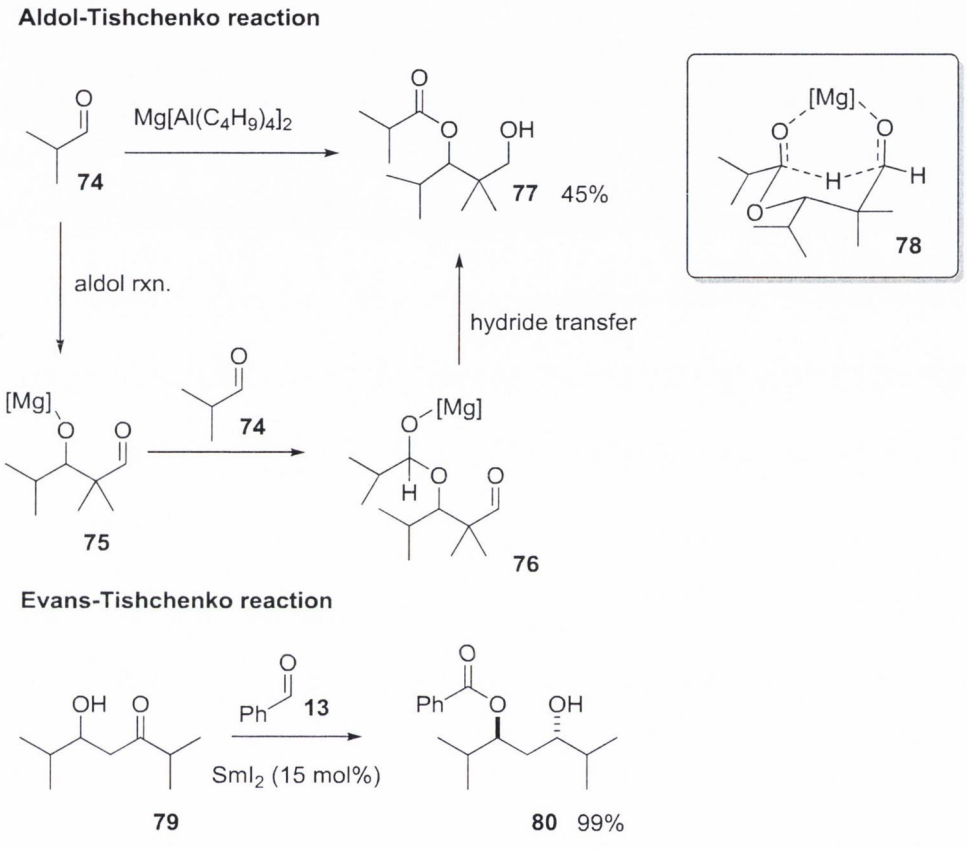
1.1.5 The Tishchenko-aldol reaction

1.1.5.1 Reaction mechanism

The Tishchenko-aldol reaction was originally discovered by Villani *et al.* and is an extension of the aldol reaction of simple enolisable aldehydes.[29] The reaction proceeds *via* the

enolisation and subsequent aldol reaction of isobutyraldehyde **74** to give the β-hydroxy aldehyde **75** (Scheme 1.16).

Scheme 1.16 The aldol-Tishchenko reaction of isobutyraldehyde

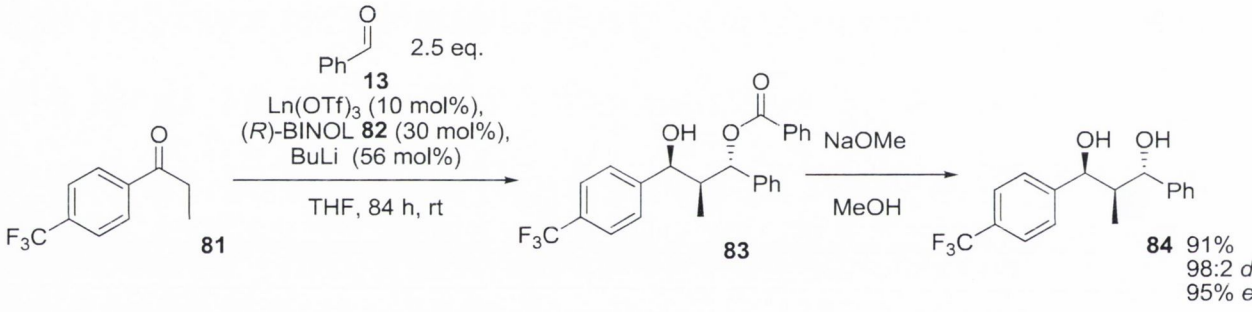


The β-hydroxy aldehyde **75** then reacts with another molecule of aldehyde to produce the hemiacetal anion **76**, which undergoes an intramolecular hydride transfer *via* the postulated six-membered transition state **78**, to yield the product **77**. Villani *et al.* were able to extend the substrate scope to include longer chain aldehydes and mixed systems of aliphatic and aromatic aldehydes to give mixed glycol ester products.[30] A variant on this reaction is the Evans-Tishchenko reaction, which is the conversion of a β-hydroxy ketone into a glycol ester.[31] This reaction is thought to occur through the same type of intermediate as the aldol-Tishchenko reaction furnishing product **80** from β-hydroxy ketone **79** in exclusive *anti*-configuration and quantitative yield. Many other examples of these reactions exist but for the purposes of this thesis only relevant examples will be discussed.

1.1.5.2 Asymmetric variants

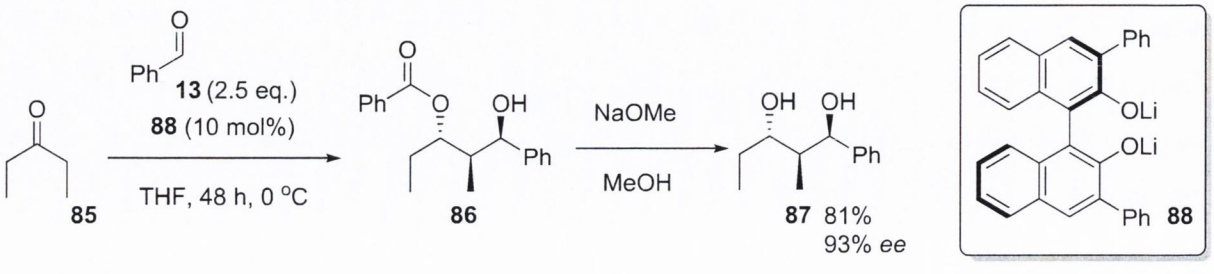
Shibasaki *et al.* reported the direct catalytic asymmetric aldol-Tishchenko reaction of aryl ketones and aldehydes to furnish 1,3-diols in high enantiomeric excess.[32] Using a lanthanum triflate-based catalyst and the *bis*-lithium conjugate base of (*R*)-BINOL **82** as a ligand, they were able to selectively generate the Tishchenko-aldol product **83** from ketone **81** and benzaldehyde (**13**). Compound **83** was subjected to methanolysis to yield the 1,3-diol **84**, in high *dr* and *ee* (Scheme 1.17). The authors were able to demonstrate that this methodology allows the use of other halogen-substituted aromatic ketones and aldehydes, as well as electron-rich and heteroaromatic aldehydes.

Scheme 1.17 The $Ln(OTf)_3$ catalysed asymmetric aldol-Tishchenko reaction



Later, Nakajima *et al.* were able to demonstrate that the *bis*-lithium conjugate base of 2,2'-diphenyl-substituted (*R*)-BINOL derivative **88** catalysed the asymmetric aldol-Tishchenko reaction of aliphatic ketones and aromatic aldehydes (Scheme 1.18).[33] They were able to demonstrate that a variety of cyclic and acyclic ketones were amenable to the methodology, as well as electron-rich aromatics.

Scheme 1.18 The *bis*-lithium conjugate base of 2,2'-diphenyl-substituted BINOL catalysed asymmetric aldol-Tishchenko reaction



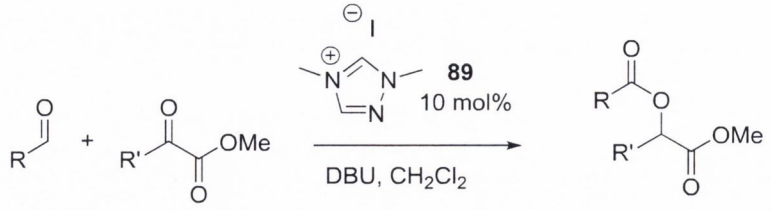
1.2 The catalytic crossed Tishchenko reaction: the study of a selective hydride transfer from an aldehyde to another carbonyl species in the reaction

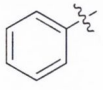
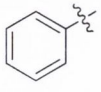
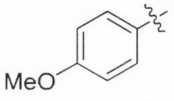
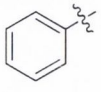
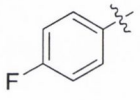
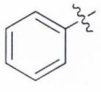
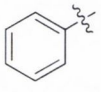
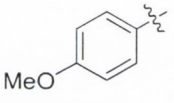
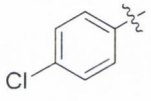
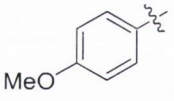
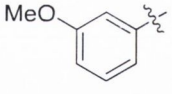
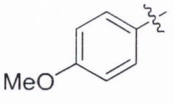
Until now, the topic of the crossed Tishchenko reaction between two different carbonyl species has not been largely discussed. The aim of this Section is to outline, firstly the difficulties involved in such an endeavour, and secondly methodologies that have been employed to date, to partially circumvent these difficulties.

1.2.1 The *N*-heterocyclic carbene (NHC)-catalysed hydroacylation of pyruvates

Scheidt *et al.* disclosed the first Tishchenko-type reaction of aromatic aldehydes and non-enolisable pyruvates, using a simple NHC catalyst.[34] Initially, they showed that the formation of ester **90** could be achieved in 78% yield (entry 1, Scheme 1.19). After the optimisation of this reaction, the authors demonstrated that electron-rich and halogen-substituted crossed esters **91** and **92** could be synthesised selectively in moderate yields (entries 2 and 3). They showed that the substrate scope could be extended to the heterocyclic furan-derived aldehyde, furnishing product **93** in 71% yield (entry 4). The authors demonstrated that electron-rich and halogen-substituted pyruvates could efficiently form ester products **94** and **95** on reaction with 4-methoxybenzaldehyde in moderate to high yields (entries 5 – 6). Finally, the crossed ester product **96** was demonstrated to form in 73% yield from the corresponding heterocyclic pyruvate derivative (entry 7)

Scheme 1.19 The NHC catalysed hydroacylation of pyruvates with various aldehydes

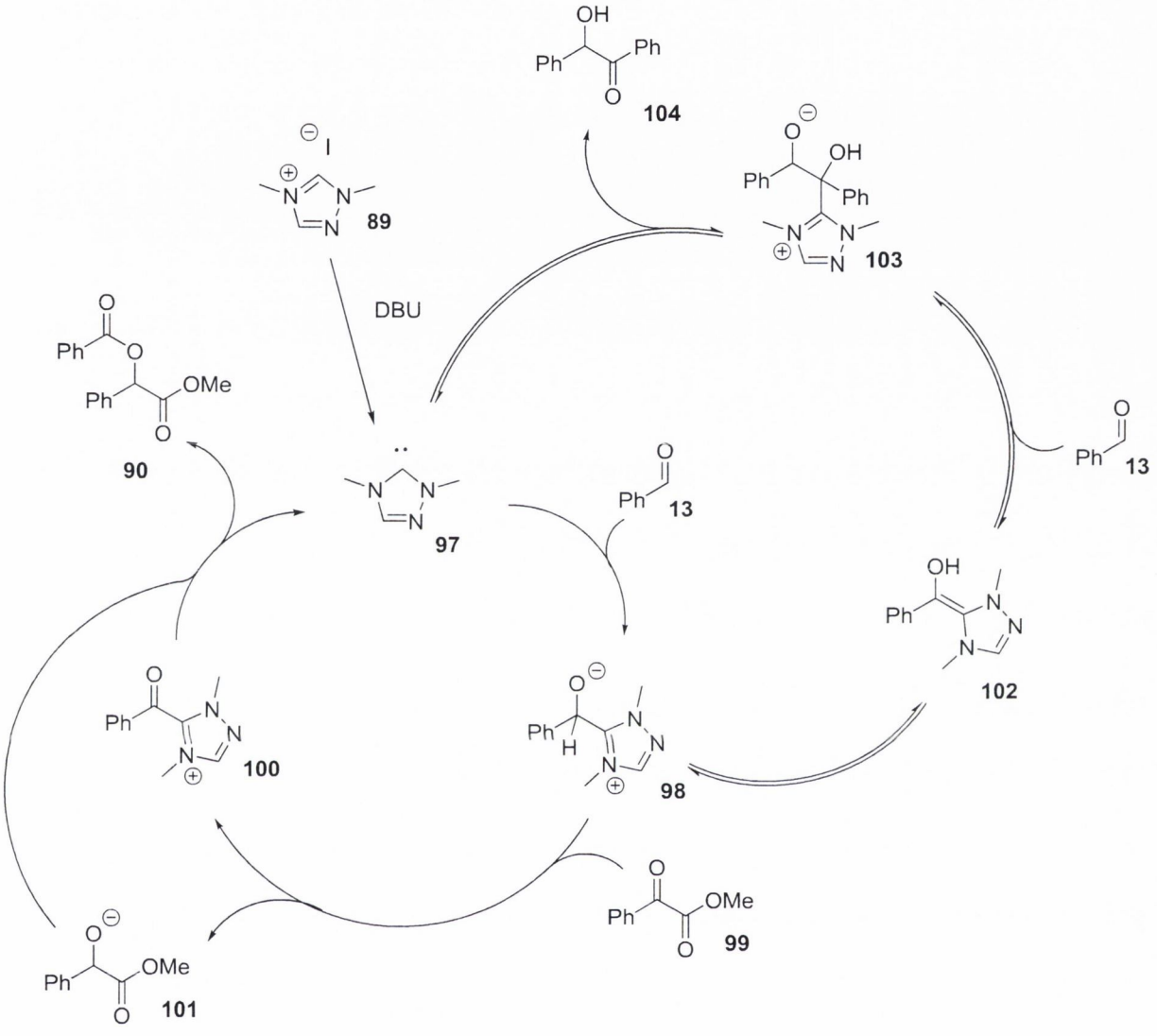


Entry	Ester Product	R	R'	Yield (%)
1	**90**			78
2	**91**			77
3	**92**			71
4	**93**			73
5	**94**			81
6	**95**			72
7	**96**			73

1.2.1.1 Reaction mechanism

Scheidt *et al.* hypothesised that the reaction occurs *via* a similar pathway to that associated with the benzoin condensation (Scheme 1.20). The carbene **97** is formed by the deprotonation of the triazolium **89**, which then attacks the aldehyde **13**, forming the adduct **98**. Intermediate **98** can either undergo proton transfer to form the Breslow intermediate **102** and eventually, benzoin (**104**), or it can transfer a hydride to the pyruvate ester **99**, forming the acyltriazolium **100** and the alkoxide **101**.

Scheme 1.20 Proposed mechanism of NHC-catalysed Tishchenko-type reaction of aldehydes and pyruvates



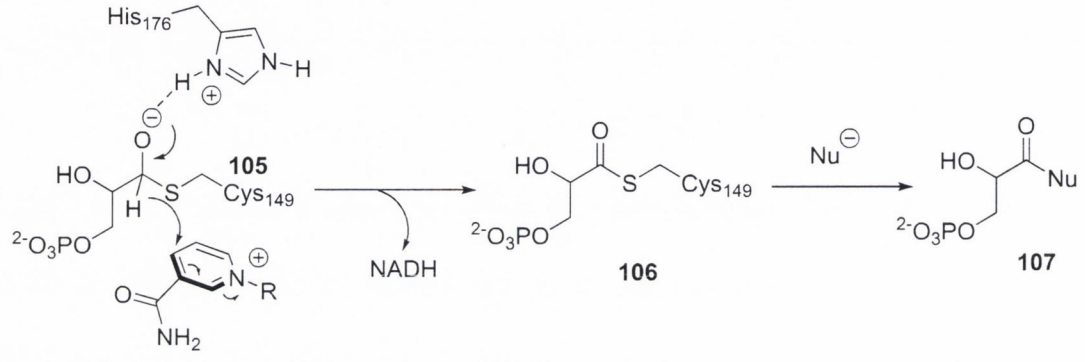
Finally, acyl transfer furnishes the hydroacylated pyruvate product **90**. The formation of **104** can be either suppressed or favoured depending on the catalyst structure, *i.e.* if the 1,2,4-triazolium precatalyst is more electron-deficient, proton transfer of **98** to form the Breslow intermediate **102** is favoured.[35]

1.2.2 The magnesium thiolate-catalysed Tishchenko reaction

In 2010, Connon *et al.* reported a bromomagnesium thiolate-catalysed Tishchenko reaction, inspired by the proposed mode of action of the glyceraldehyde-3-phosphate dehydrogenase

enzyme (GAPDH).[36] This enzyme has a specific substrate, glyceraldehyde-3-phosphate, of which it catalyses the oxidation *via* the base mediated addition of the cysteine-149 residue to the aldehyde moiety to form the stabilised complex **105** (Scheme 1.21). An intermolecular hydride transfer occurs to an enzyme-bound NAD^+ molecule, forming the thioester **106**, which is then either hydrolysed or phosphorylated to give **107**.[37]

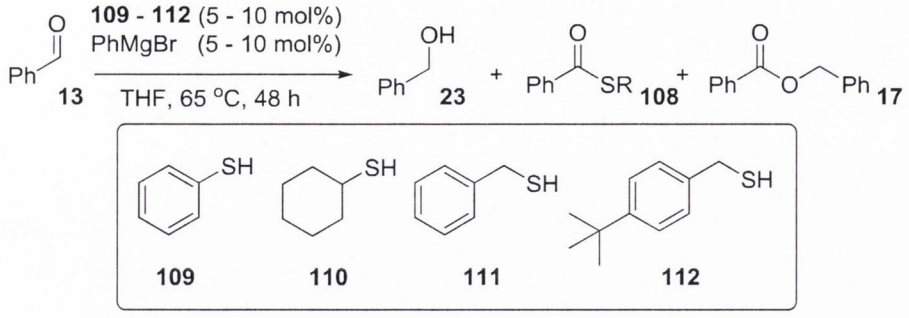
Scheme 1.21 The mechanism of oxidation by GAPDH of glyceraldehyde-3-phosphate



1.2.1.1 Catalyst properties influencing activity

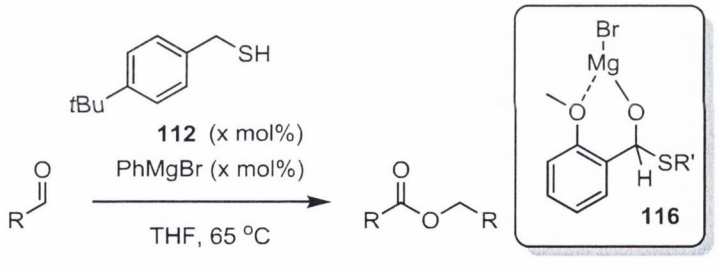
Connon *et al.* evaluated the performance of four catalyst types in the disproportionation of benzaldehyde (**13**), of which they found that the benzylic thiolates performed best (Scheme 1.22). The phenolic thiol **109** and the aliphatic thiol **110** both catalysed the formation of the ester **17** in 48% yield in 24 hours with catalytic loadings of 5 mol%. The benzylic thiolate of **111** catalysed the formation of **17** in 100% yield with thiol **112** performing with slightly less efficiency to produce **17** in 97% yield with catalyst loadings of 10 mol%. As the difference in yield of ester **17** obtained between **111** and **112** was very low and thiol **111** has a strong stench (a factor that may hinder its synthetic application), it was deemed that benzylic thiol **112** was the preferred catalyst for the reaction.

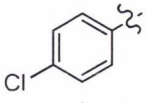
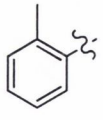
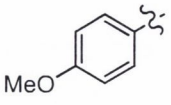
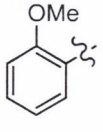
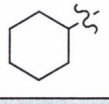
Scheme 1.22 Catalyst screening in the Tishchenko reaction of benzaldehyde



It was demonstrated that the magnesium thiolate-catalysed Tishchenko chemistry could be performed on a range of different substrates, *i.e.* electron-rich, electron-poor and halogen-substituted aromatic aldehydes (Scheme 1.23).

Scheme 1.23 Selected substrate scope of magnesium bromide thiolate catalysed Tishchenko reaction



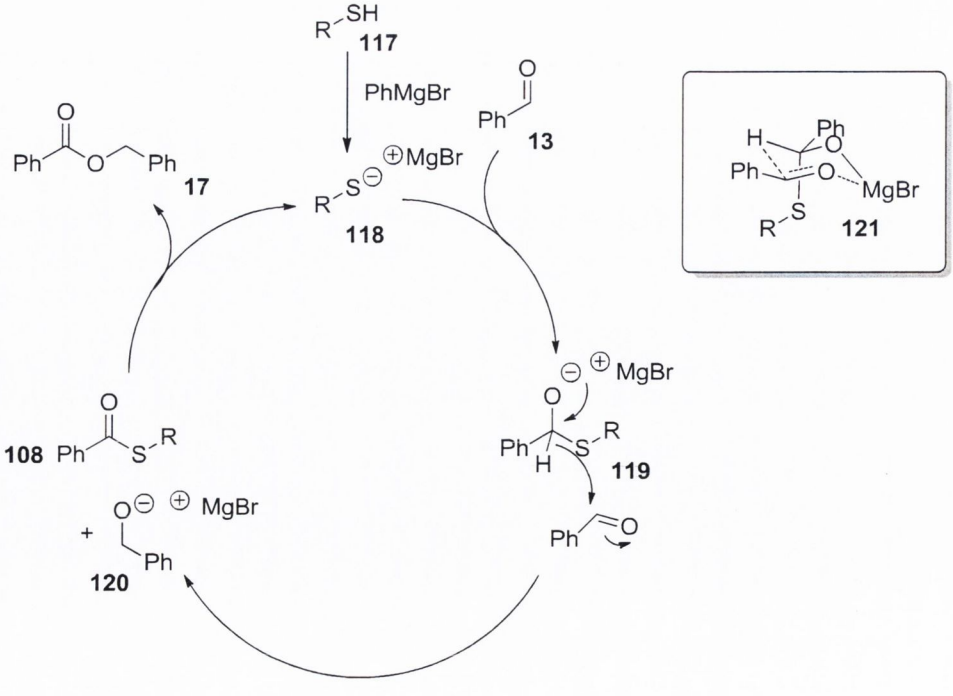
Entry	Ester product	R	x (mol%)	Time (h)	Yield (%)
1	**113**		10	12	92
2	**114**		20	96	87
3	**49**		20	48	92
4	**115**		20	96	56
5	**46**		20	48	63

Two substrates of note proved difficult: firstly, *o*-methoxybenzaldehyde dimerised in 56% yield and it was proposed that this reaction was hindered by chelation of the hemiacetal conjugate base to the magnesium ion **116**; and secondly cyclohexanecarboxaldehyde, the dimerisation of which to form ester **51**, could only be achieved in 63% yield due to a competing aldol reaction. In general, long reaction times and high catalyst loadings were required for the dimerisation of aldehydes compared with those observed in other catalytic systems.

1.2.1.2 Proposed reaction mechanism

Connon *et al.* proposed the reaction mechanism illustrated in Scheme 1.24. The hemithioacetal conjugate base **119**, which is generated from the bromomagnesium thiolate **118** and benzaldehyde **13**, transfers a hydride to a chelated benzaldehyde *via* the postulated six membered transition state **121**. The resulting thioester **108** is then converted to benzyl benzoate **17** by reaction with the magnesium bromide benzyl alkoxide **120**. It was noted that this acyl transfer step was the rate determining step for the reaction, indicating that hydride transfer is rapid, and likely irreversible.

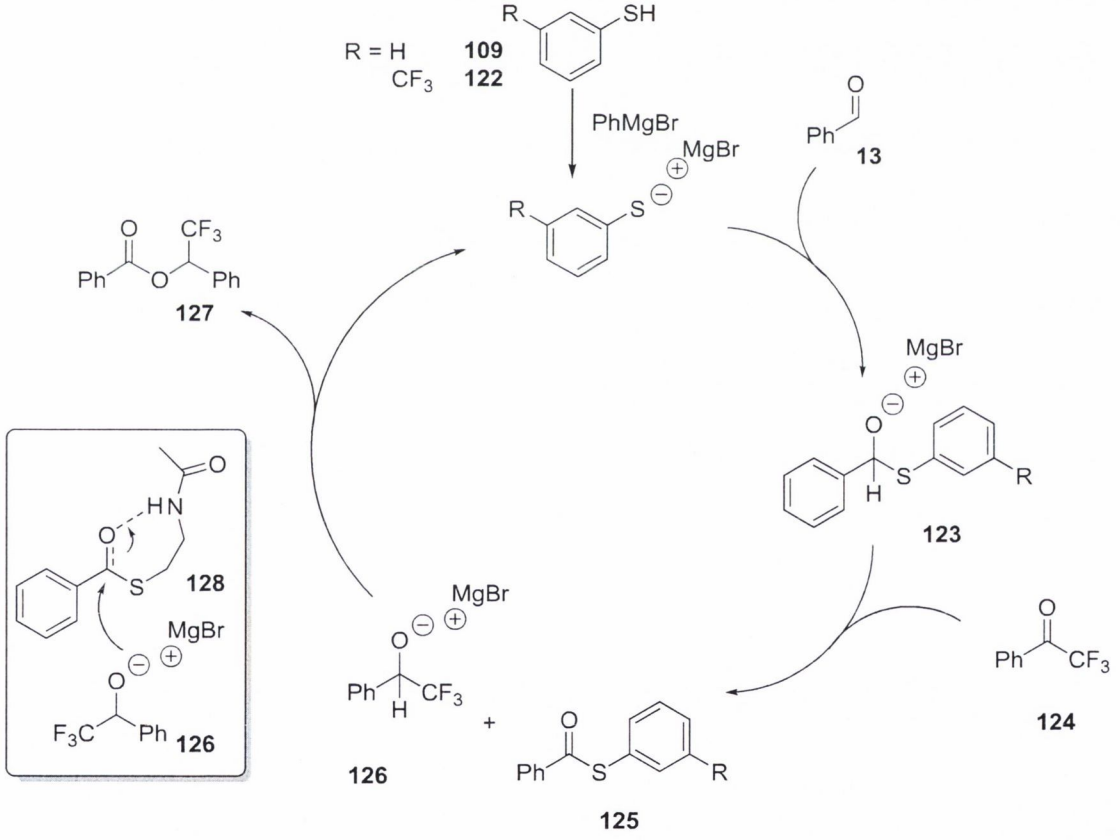
Scheme 1.24 Proposed reaction mechanism of the thiolate-catalysed disproportionation of aldehydes



1.2.2.3 Catalysis of the crossed intermolecular Tishchenko reaction

Connon *et al.* noted that there were no reports in the literature of a crossed-intermolecular Tishchenko reaction between aldehydes and ketones. They attributed this to the enolisability of ketones (*i.e.* favouring aldol chemistry) and to the higher electophilicity of aldehydes relative to ketones (*i.e.* favouring aldehyde dimerisation). To counteract both of these effects they employed 2,2,2-trifluoroacetophenone (**124**), which is a commercially available, non-enolisable and highly electrophilic ketone (Scheme 1.25).

Scheme 1.25 Proposed reaction mechanism of bromomagnesium thiolate catalysed Tishchenko reaction of 2,2,2-trifluoroacetophenone and benzaldehyde

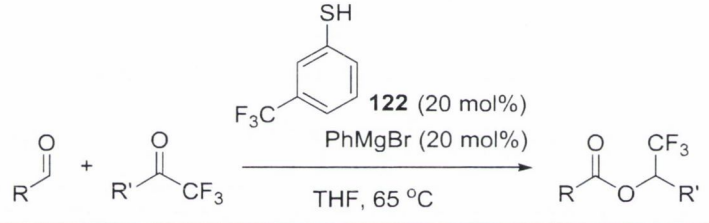


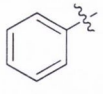
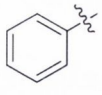
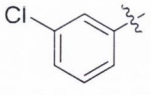
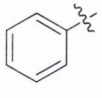
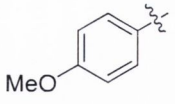
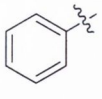
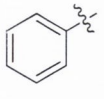
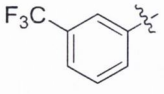
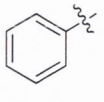
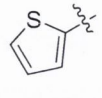
On evaluation of this reaction with the best catalyst for the dimerisation of two aldehydes (*i.e.* **112**) it was noted that the crossed ester product **127** only formed in 37% yield. They attributed this to the reduced nucleophilicity of the α-trifluoromethyl benzylalkoxide **126**, and therefore sought to overcome this by making the resulting thioester **125** more electrophilic (*i.e.* by making the thiol precatalyst more acidic). This was achieved by using aromatic thiols which have a much lower pK_a than benzylic thiols (pK_a 15.4, DMSO).[38] On

using thiophenol (**109**, pK_a 10.3, DMSO),[38] they formed the crossed product **127** in 90% yield after 24 hours and were able to increase this yield to 96% by using the magnesium bromide conjugate base of *m*-trifluorothiophenol (**122**, conjugate acid pK_a 8.09, DMSO).[38]

Connon *et al.* also employed a biomimetic approach in this reaction by using a molecule that would generate at thioester capable of hydrogen bonding (**128**, Scheme 1.25). On application of the bromomagnesium thiolate of *N*-acetyl cystamine to this reaction it was found, remarkably, that the crossed ester product **127** was formed in 65% yield after 24 hours. This was very interesting as it shows that hydrogen bonding has the potential to play an important role in this reaction.

Scheme 1.26 Selected examples of the crossed-intermolecular Tishchenko reaction of aldehydes and trifluoroketones



Entry	Ester Product	R	R'	Time (h)	Yield (%)
1	**127**			24	96
2	**129**			24	87
3	**130**			67	92
4	**131**			40	80
5	**132**			40	78

A moderate substrate scope was found to be amenable to this magnesium thiolate-catalysed methodology (Scheme 1.26). The halogen-substituted crossed ester product **129** was found to

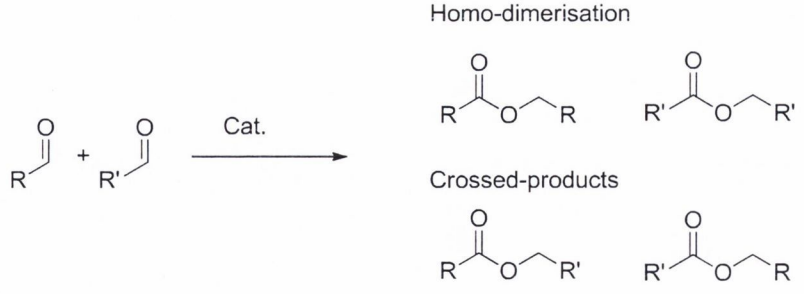
form in the high yield of 87% in 24 hours (entry 2). The electron-rich, previously recalcitrant 4-methoxybenzaldehyde, was found to form ester **130** in 92% yield on reaction with 2,2,2-trifluoroacetophenone (entry 3). The ester **131**, derived from the reaction of benzaldehyde and 3'-trifluoromethyl-2,2,2- trifluoroacetophenone, was formed in 80% yield in 40 hours (entry 4). Finally, the heterocyclic thiophene-derived ester **132** was formed in 78% yield in 40 hours, representing the only heterocyclic product capable of being furnished by this methodology (entry 5).

As with the dimerisation reaction, the crossed-intermolecular Tishchenko reaction requires long reaction times and high catalyst loadings to achieve the yields specified.

1.2.3 Recent advances in selective crossed Tishchenko reactions between two different aldehydes

Due to the high electrophilicity of the carbonyl functionality in aldehydes it is difficult to differentiate between two different aldehydes, and as such a non-selective catalytic Tishchenko reaction would be expected to give four possible products (Scheme 1.27).[3b] This observation was discussed briefly in Section 1.1.4.2, where the SrO-catalysed Tishchenko reaction of benzaldehyde and pivaldehyde generate one mixed ester in slightly elevated yield.

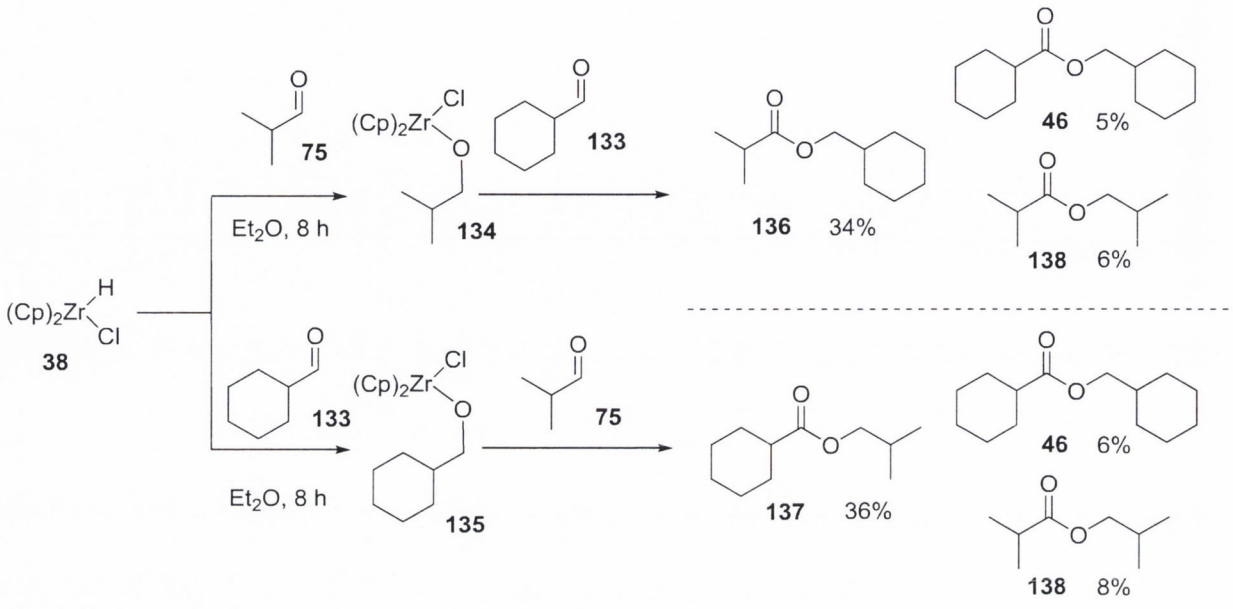
Scheme 1.27 Products formed by a non-selective Tishchenko reaction of two different aldehydes



1.2.3.1 The zirconocene-mediated selective Tishchenko reaction

Morita *et al.* demonstrated their understanding of the mechanism of the zirconocene-catalysed Tishchenko reaction, discussed in Section 1.1.4.3, by executing the selective formation of a single mixed ester from stoichiometric quantities of catalyst (Scheme 1.28).[20]

Scheme 1.28 The synthesis of mixed esters using zirconocene hydride in stoichiometric quantities

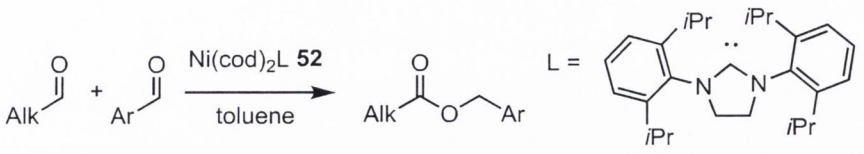


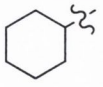
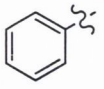
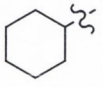
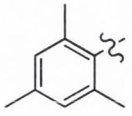
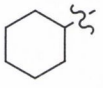
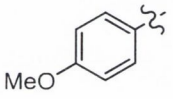
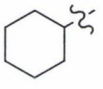
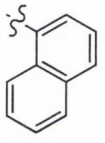
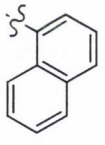
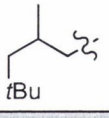
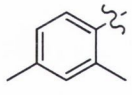
This was accomplished by the formation of the zirconocene alkoxide complex with one aldehyde exclusively (*i.e.* **134** and **135**), at which point a second aldehyde is added to allow the formation of the mixed esters **136** and **137**. It is interesting to note the formation of both ester dimers **46** and **138**; this implies that the formation of the zirconocene complexes is reversible. They were unable to conduct this reaction with catalytic loadings of the zirconocene hydride **38**.

1.2.3.2 The Ni(0)-catalysed selective crossed Tishchenko reaction

In 2011, after outset of the research described in this thesis, Ogoshi *et al.* reported the first selective crossed Tishchenko reaction between two different aldehydes.[39] Using a modified version of the Ni(0) catalysed methodology described in Section 1.1.4.3, they were able to demonstrate the formation of a single ester from the Tishchenko reaction of aliphatic and aromatic aldehydes (Scheme 1.26). They found that aliphatic aldehydes exclusively underwent oxidative coupling, while the aromatic aldehydes underwent reduction.

Scheme 1.29 Selected products from the Ni(0)-catalysed selective crossed Tishchenko reaction between aliphatic and aromatic aldehydes



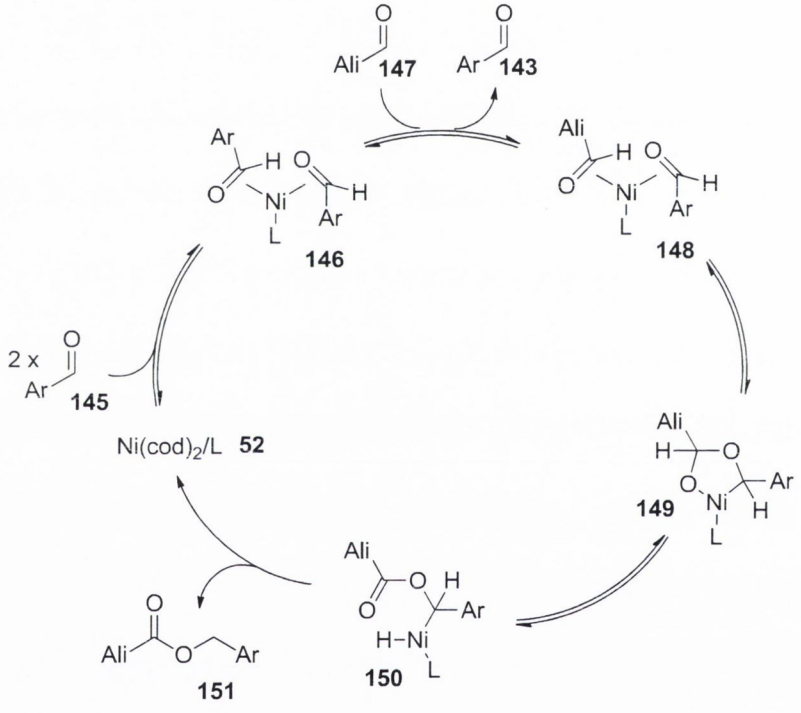
Entry	Ester Product	Alk	Ar	Loading (mol%)	Yield (%)
1	**139**			2	84
2	**140**			3	57
3	**141**			2	82
4	**142**			2	47
5	**143**			2	65
6	**144**			1	83

A substrate scope encompassing primary, secondary and tertiary aliphatic aldehydes as well as electron-rich and hydrocarbon-substituted aromatics was charted in the presence of this Ni(0) catalyst, furnishing products in low (47%) to high yields (84%) (entries 1 - 6, Scheme 1.29). It is noteworthy that electron-deficient and halogen-substituted aromatics are not amenable to this methodology.

The selectivity observed was attributed to two major effects: the rate of the Ni(0)-catalysed dimerisation of aromatic aldehydes being slower than that of aliphatic aldehydes; and the relatively high stability of complex **146**, derived from coordination of two aromatic aldehydes **145** to the nickel catalyst (Scheme 1.30). The stability of this complex is thought to originate from the ability of electron-deficient π systems to participate in strong back-bonding

interaction with the metal.[40] In a reaction mixture of nickel catalyst and both aromatic, and aliphatic aldehydes at -60 °C, the authors were able to identify complex **146** as the major intermediate. It was then theorised that complex **148** is formed by the substitution of the more electron-rich aliphatic aldehyde, at which point oxidative cyclisation occurs forming the metallacycle **149** exclusively. Subsequent β-hydride elimination and reductive elimination furnishes the mixed ester **151** and regenerates the catalyst **52**.

Scheme 1.30 Postulated reaction mechanism of Ni (0) catalysed selective crossed Tishchenko reaction between aliphatic and aromatic aldehydes



1.2.4 Summary

In conclusion, prior to the work described in this thesis had begun the Tishchenko reaction had little synthetic application, with the focus of most synthetic methodologies on achieving broader substrate scopes for the disproportionation reaction of aldehydes. The magnesium thiolate-catalysed methodology, though bearing some disadvantages including low substrate scope, long reaction times and high catalyst loadings, is a step towards the previously impossible selective Tishchenko reaction between two different aldehydes.

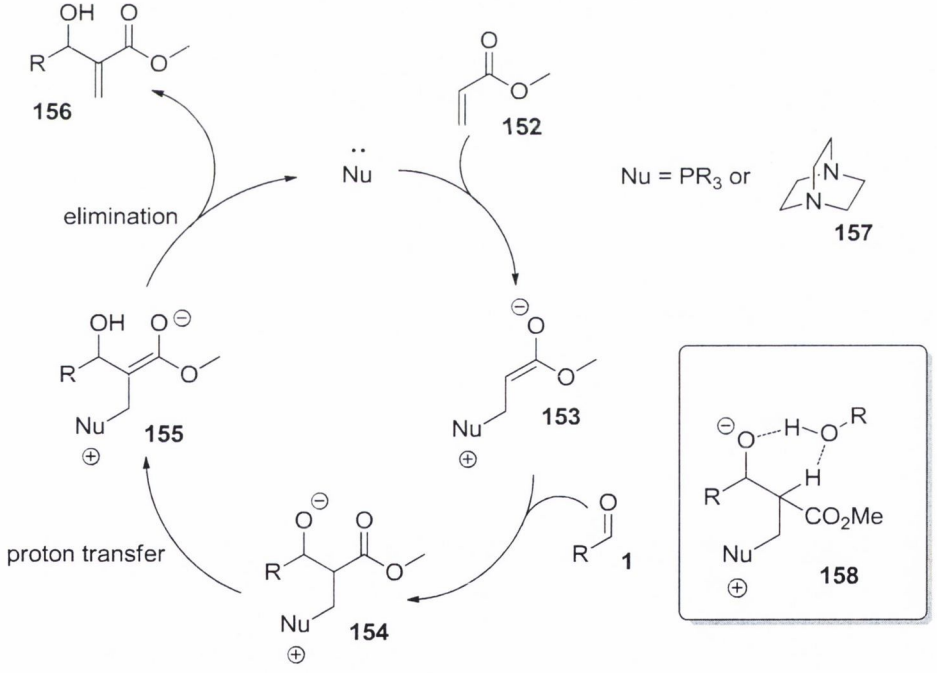
1.3 The Morita-Baylis-Hillman reaction

Originally reported by Morita *et al.*, the Morita-Baylis-Hillman (MBH) reaction is a carbon-carbon bond forming reaction between an acrylate or acrylonitrile and an aldehyde catalysed by a tertiary phosphine or amine.[41,42]

1.3.1 Reaction mechanism

The reaction proceeds *via* the 1,4-conjugate addition of the nucleophile catalyst to, for instance methyl acrylate **152**, forming the adduct **153**, which attacks a molecule of aldehyde **1** to generate the MBH adduct **154** (Scheme 1.31). Proton transfer and successive elimination yields the MBH product **156** and regenerates the catalyst.

Scheme 1.31 General reaction mechanism of the Morita-Baylis-Hillman reaction

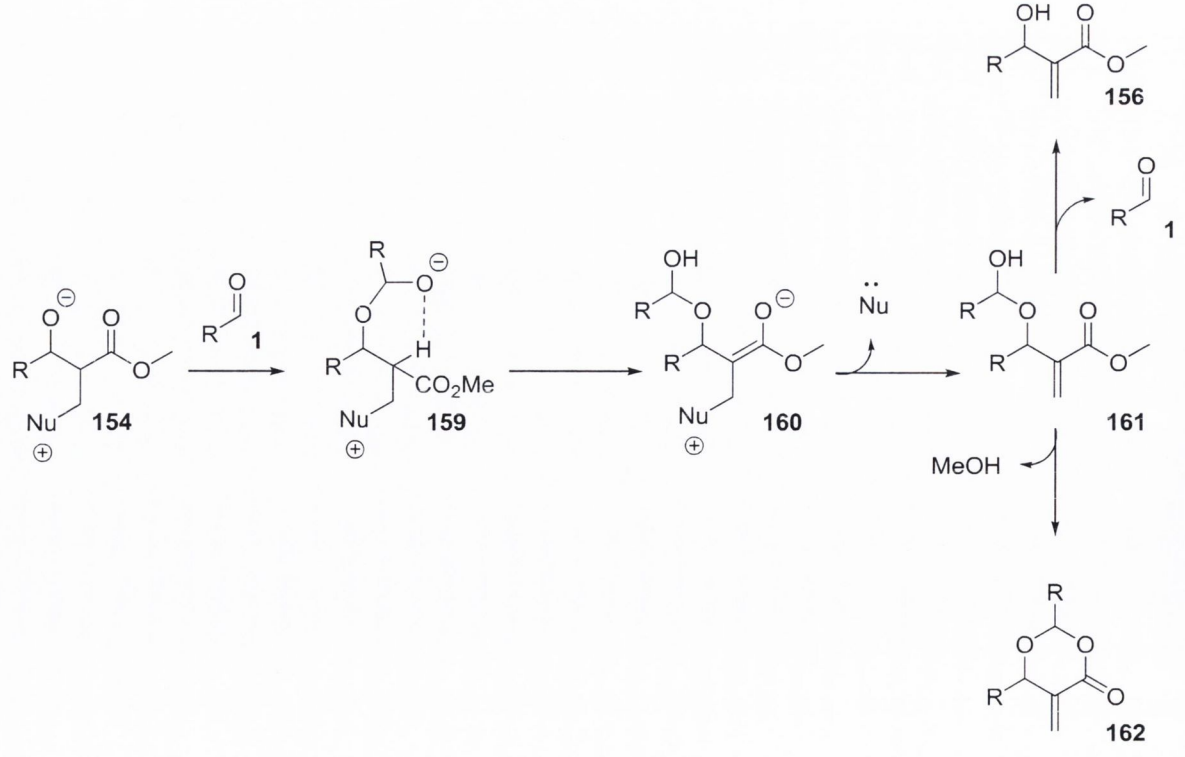


Aggarwal *et al.* reported a revised mechanism to explain why protic solvents accelerate the reaction.[43] Using the kinetic isotope effect (KIE), it was determined that the elimination step was rate-limiting for the early stages of the reaction (up to 20% conversion), at which point formation of the MBH adduct **154** became rate-limiting. They hypothesised that alcohol functionalities were assisting in the proton transfer (*i.e.* **158**, Scheme 1.28). It was noted that the MBH adduct **154** is unlikely to undergo intramolecular elimination, as the formation of

the four-membered ring required would be sterically disfavoured. They attribute the shift in rate-limiting step to the incorporation of an alcohol functionality in the MBH product **156**, which acts as the protic autocatalyst for the intermolecular proton transfer step.

However, the mechanism of the MBH reaction in the absence of protic solvent was still in question. When Aggarwal *et al.* doubled the catalyst loading they found a rate increase of 175%, suggesting that all of the catalyst is tied up in the formation of **153**, and therefore cannot act as a shuttle base in the proton transfer or elimination step. They later reported evidence for the aldehyde concentration-dependant elimination of the nucleophile catalyst (Scheme 1.32).[44] The intermediate **159**, initially proposed by McQuade *et al.*,[45] is formed from the addition of the MBH adduct **154** to a molecule of aldehyde **1**, forming a hemiacetal conjugate base which can undergo intramolecular proton transfer *via* a postulated six-membered transition state. Deprotonation followed by extrusion of the catalyst furnishes the hemiacetal **161**, which eliminates a molecule of aldehyde to form the MBH product **156**. It was also noted that this may explain the formation of the previously reported dioxanone product **162**.[46]

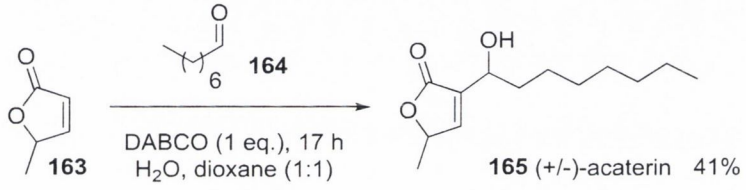
Scheme 1.32 Proposed mechanism of the aldehyde concentration dependant elimination of the nucleophile catalyst



1.3.2 Selected examples

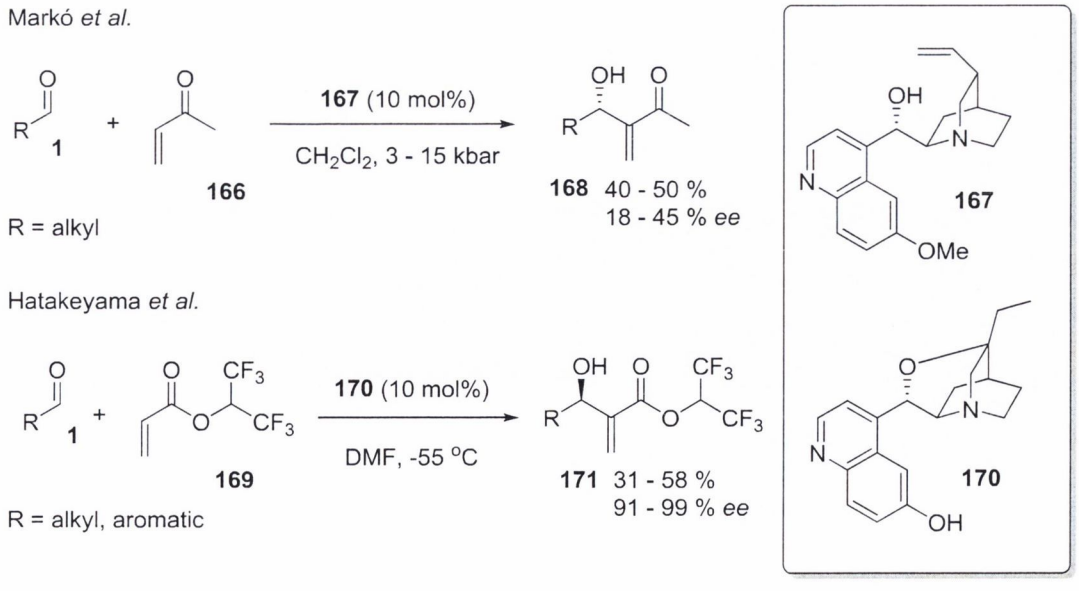
As the MBH reaction is a carbon – carbon bond forming reaction, its applications in organic synthesis are limitless: from the one step synthesis of the (+/-)-Acaterin **165**, an acyl-CoA cholesterol acyltransferase inhibitor from **163** and octanal (**164**, Scheme 1.33); to the generation of key molecules in the total synthesis of natural products.[47] As such, the development of novel enantioselective variants of the reaction has been studied extensively.

Scheme 1.33 One pot synthesis of (+/-)-Acaterin



Initial studies with chiral tertiary amine catalysts by Markó *et al.* reported poor yields and enantioselectivity, however, they found that using quinidine (**167**) as a catalyst, they could achieve low - moderate yields of the MBH product **168** with some enantiocontrol (Scheme 1.34).[48] They attributed the low enantioselectivity to the high pressures required by the reaction.

Scheme 1.34 Selected cinchona alkaloid catalysed MBH reactions



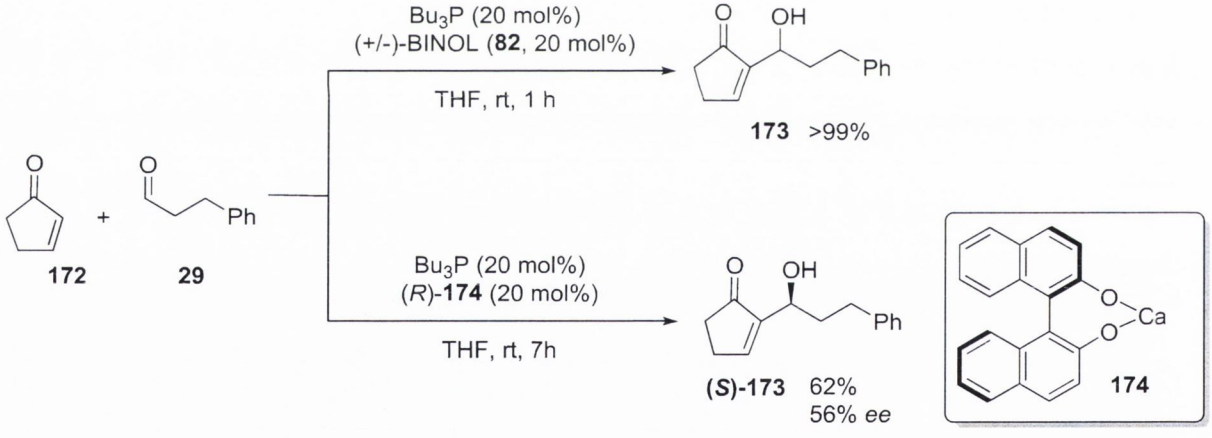
Later Hatakeyama *et al.* reported that β-isocupreidine (**171**) was an efficient catalyst for the enantioselective MBH reaction of acrylic esters with aliphatic and aromatic aldehydes.[49]

They found that the *bis*-trifluoromethyl-substituted acrylate **169** was capable of undergoing the MBH reaction at much lower temperatures compared to methyl acrylate (**152**) and as such the stereochemical outcome of the reaction could be controlled to a much higher degree by the catalyst, *i.e.* allowing the lowest energy transition state to be favoured to produce only one enantiomer. As such high enantioselectivities of MBH product **170** were obtained, at the expense of product yield.

1.3.3 BINOL-derived enantioselective catalysts

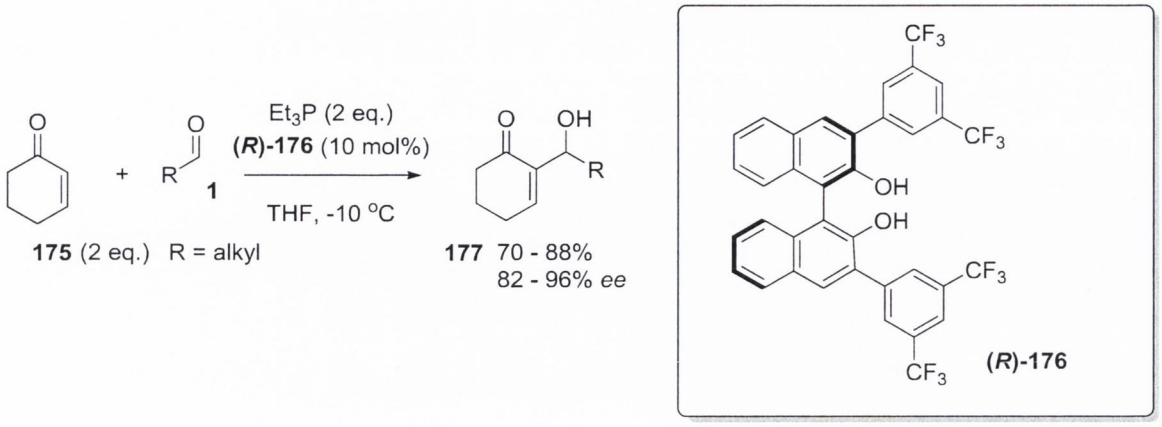
Ikegami *et al.* were the first to report the use of phenols and BINOL as additives in the tributylphosphine-catalysed MBH reaction (Scheme 1.35).[50] They found that quantitative yields of MBH product **173** were isolated in one hour when **82** was used as a co-catalyst in the reaction of cyclopentenone (**172**) and hydrocinnamaldehyde (**29**).

Scheme 1.35 The use of BINOL in the tributylphosphine catalysed MBH reaction



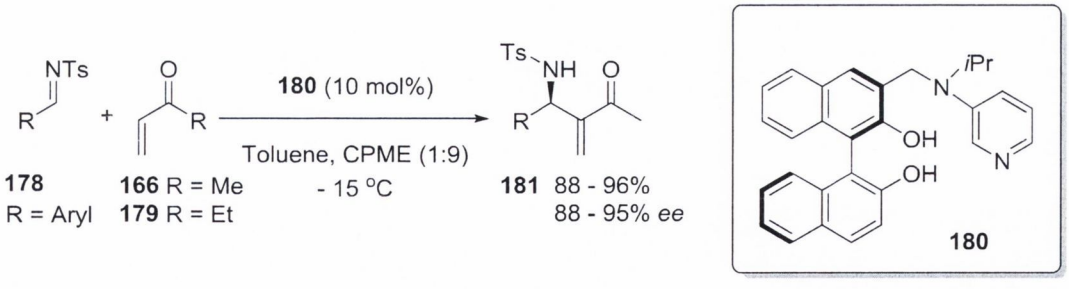
In addition, it was demonstrated that the *bis*-calcium salt of (*R*)-BINOL **174**, when used as an additive, allowed the formation of the MBH product **173** in moderate *ee* and yield. Furthering this research, Schaus *et al.* were able to generate MBH products of **177** in moderate – high yields using super-stoichiometric quantities of triethylphosphine and 3,3'-substituted BINOL catalyst **176** (Scheme 1.36).[51]

Scheme 1.36 3,3'-substituted BINOL co-catalysed MBH reaction



The aza-MBH reaction is a variant of the MBH reaction, where the aldehyde component is replaced by an imine, resulting in the formation of a C-N bond. Much research has been performed on this subject as the products are of significant synthetic utility.[52] One of the most efficient catalysts for this reaction was reported by Sasai *et al.*: a BINOL derived tertiary amine (*i.e.* **181**, Scheme 1.37).[53] They were able to demonstrate the catalytic aza-MBH reaction of *N*-tosyl imines **179** with methyl- and ethylvinylketones (**166** and **179**). A variety of electron-rich, electron-deficient and halogen-substituted aromatic *N*-tosyl imines were employed in this reaction.

Scheme 1.37 The aza-MBH reaction of N-tosyl imines and methylvinylketone

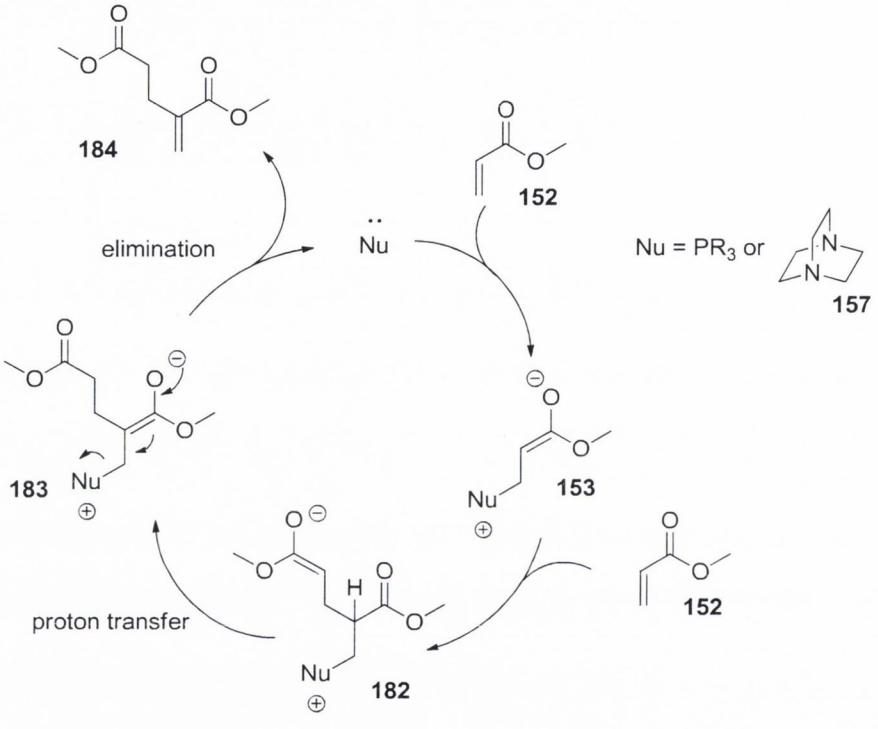


1.3.4 The Rauhut-Currier reaction

The Rauhut-Currier (RC) reaction predates the discovery of the MBH reaction, but as the products derived from it are not as useful, it has not received as much attention as the MBH reaction.[54] Originally discovered by Rauhut and Currier, the reaction involves the dimerisation of Michael acceptors (*e.g.* acrylonitrile and ethyl acrylate) by a tertiary phosphine or amine.[55] The reaction mechanism is very similar to that of the MBH reaction:

initial 1,4-conjugative addition of the nucleophile catalyst to the acrylate **152** forms intermediate **153** (Scheme 1.38). Subsequent attack of the enolate **153** on another molecule of methyl acrylate (**152**) generates enolate **182**, which undergoes proton transfer to furnish **183**. Retro-Michael reaction then yields the RC product **184** and regenerates the catalyst.

Scheme 1.38 Reaction mechanism of the Rauhut-Currier reaction



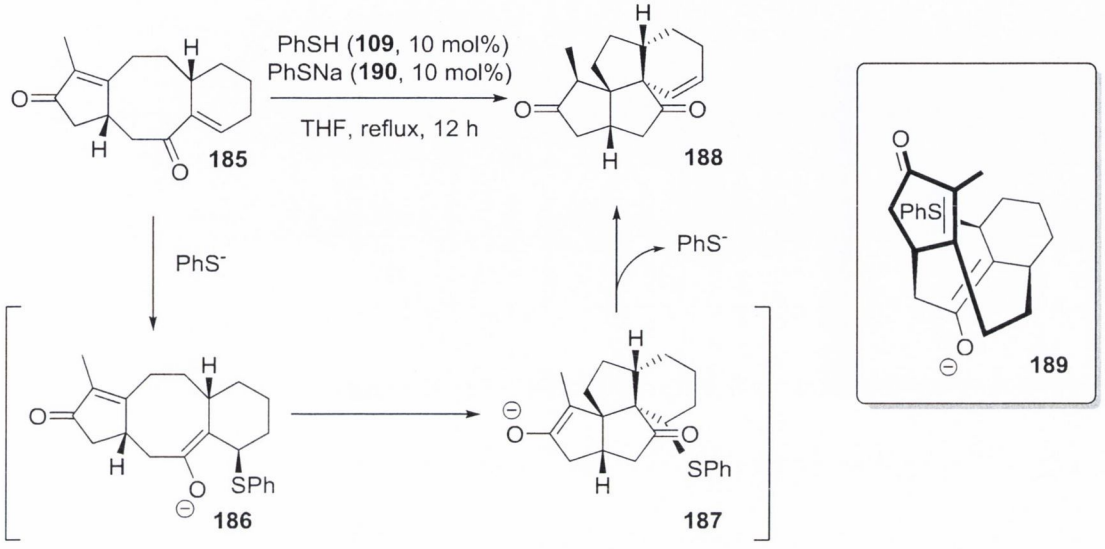
The Rauhut-Currier reaction has seen many improvements in recent years,[56] but for the purposes of this thesis we will limit the topics discussed to that of the thiolate catalysed reaction.

1.3.4.1 Thiolate-catalysed intramolecular Rauhut-Currier reactions

An intramolecular Rauhut-Currier-type reaction was reported by Moore *et al.* as the key transformation in the formation of tetraquinanes.[57] When compound **185** was treated with a catalytic amount of thiophenol (**109**) and sodium thiophenolate (**190**), the tetraquinane **188** was formed in 93% yield (Scheme 1.39). They postulate that the reaction proceeds through intermediate **186**, formed from the conjugate addition of **190** to the less sterically congested alkene. It was proposed that it is the spatial proximity of the enolate and the second alkene (see **189**) that allows the intramolecular conjugate addition to proceed, furnishing the

tetracycle **187** exclusively. Elimination of the thiolate yields the tetraquinane **188** as a single enantiomer.

Scheme 1.39 Sodium thiolate catalysed formation of tetraquinanes

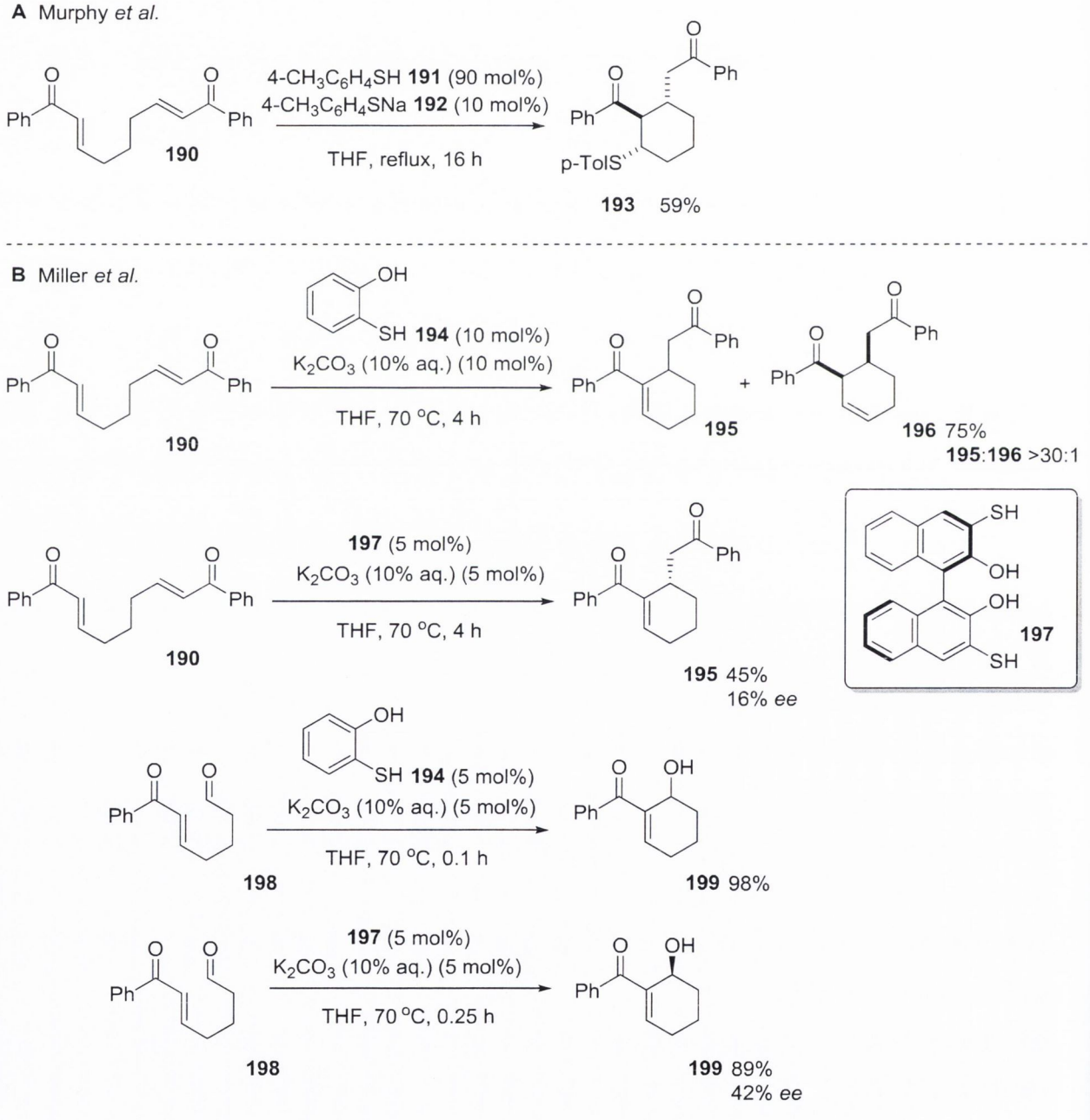


When the reaction was repeated with stoichiometric **109** and catalytic **190** the reaction was found to halt at the formation of the conjugate acid of enolate **187**, *i.e.* elimination of the thiolate did not occur.

Later, Murphy *et al.* reported a general procedure for the formation of intramolecular Rauhut-Currier adduct **193** using 4-methylthiophenol (**192**) and its sodium salt **193** (**A**, Scheme 1.40).[58] Subsequently, they were able to demonstrate the intramolecular RC reaction of electron-rich and electron deficient aryl-substituted analogues of **190**. In agreement with the observations made by Moore *et al.*, they noted that no elimination to form the RC product was observed when near quantitative amounts of thiol were used. Miller *et al.* were the first to demonstrate the catalytic intramolecular thiolate-catalysed RC reaction in quantitative yield (**B**, Scheme 1.40).[59] They found that the optimum catalyst for the reaction was 2-hydroxythiophenol (**194**), which furnished the intramolecular RC product **195** in high yield with trace amounts of the regioisomer **196**. As with the MBH reaction, it is thought that the presence of hydroxyl groups can increase the rate of the proton transfer step.[51] In this case the hydroxyl group is on the catalyst and may not only act as a proton shuttle, but it may increase the rate of elimination through its proximity to the thiol. Support for this hypothesis came from the finding that 4-hydroxythiophenol was completely inactive as a catalyst. Use of the

(*R*)-BINOL-derived thiol **197** furnished the RC product **195** in low enantiomeric excess and low yield. Miller *et al.* were also able to demonstrate the rapid thiolate-catalysed intramolecular MBH reaction of compound **198** to afford **199**. Further optimisation of this reaction using catalyst **197** led to the generation of the MBH product **199** in high yield with significant *ee*.

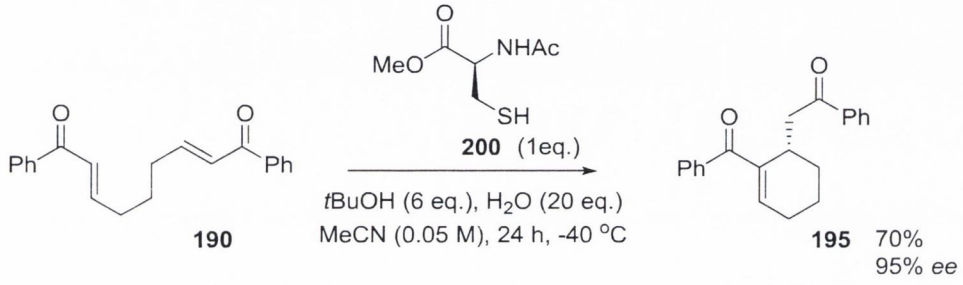
Scheme 1.40 Thiolate catalysed Rauhut-Currier and Morita-Baylis-Hillman reactions



Miller *et al.* later published an extension of this work: where the use of a cysteine-derived thiol **200** promoted the intramolecular RC reaction of **190** in high *ee* and moderate yield

(Scheme 1.41).[60] It was noted that the reaction could be performed under catalytic conditions (20 mol% of thiol **200**) to furnish the product in 92% *ee* and 75% yield. However, in substrates where the phenyl groups are electron-rich or electron-poor aromatics, or esters, stoichiometric quantities of promoter **200** are required to achieve these moderate yields and high *ee*'s.

Scheme 1.41 Enantioselective thiolate promoted intramolecular Rauhut-Currier reaction



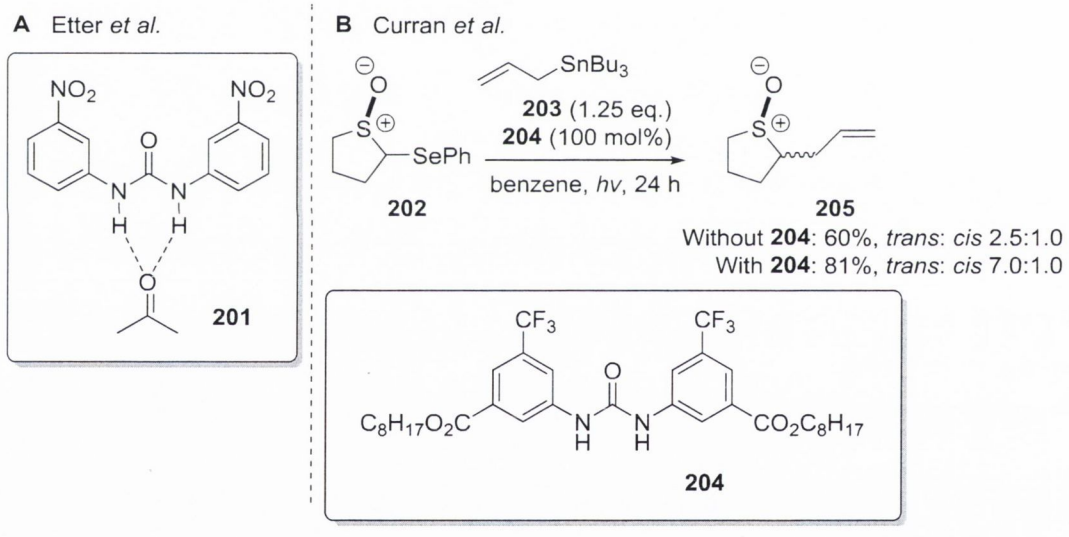
1.3.5 Summary

The MBH and RC reactions, though notoriously slow, have their respective places in organic synthesis; however, there is still room for improvement *via* the expansion of substrate scopes and increasing the reaction rates. Of particular note for the purposes of this thesis is the thiolate-catalysed methodology developed by Miller *et al.* as it may hold the potential for solving these problems.

1.4 Organocatalysis

An organocatalysed reaction can be loosely defined as a reaction that may be catalysed by a compound that contains no metal elements. The concept of organocatalysis is nearly as old as the concept of chemistry itself, one just has to look at the Fischer esterification, where an alcohol and a carboxylic acid are heated together under reflux with sulphuric acid as the catalyst.[61] This field has seen a resurgence of late, with many varieties of catalysts being published to promote a plethora of reactions.[62] Many catalyst types have been reported to date: phase transfer catalysts,[63] amine-based catalysts,[64] and bifunctional catalysts. This thesis will focus on the latter of these catalyst types.

Scheme 1.42 Functionalised ureas acting as a weak Lewis acid hydrogen bond donor

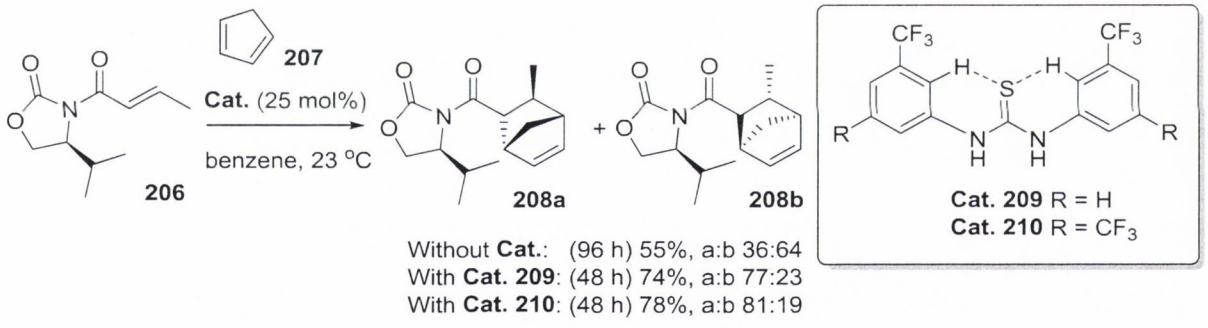


Early work in this field focused on Lewis acids, as it could be seen from the Fischer esterification the potential utility of a simple acid catalyst. The major drawback to using strong Brønsted acids as catalysts, however, is the lack of selectivity observed towards different reaction components (*e.g.* nucleophilic substrates and bases) and products (*i.e.* leading to product degradation).[65] Etter *et al.* were the first to demonstrate, using x-ray crystallography, the hydrogen bond donating/ weak-acid activity of ureas by demonstrating that they readily complex with Lewis bases (*i.e.* carbonyl functional groups) **201** (**A**, Scheme 1.42), this discovery would later spark a renaissance in the field of organocatalysis.[66] Curran *et al.* were the first to demonstrate the use of ureas as catalysts in the photochemical reaction

of α-phenylselenide sulfoxides with alkyl tin reagents and they noted that a shift in selectivity was observed in the ratio of the *cis* and *trans* products of **205** (**B**, Scheme 1.42).[67]

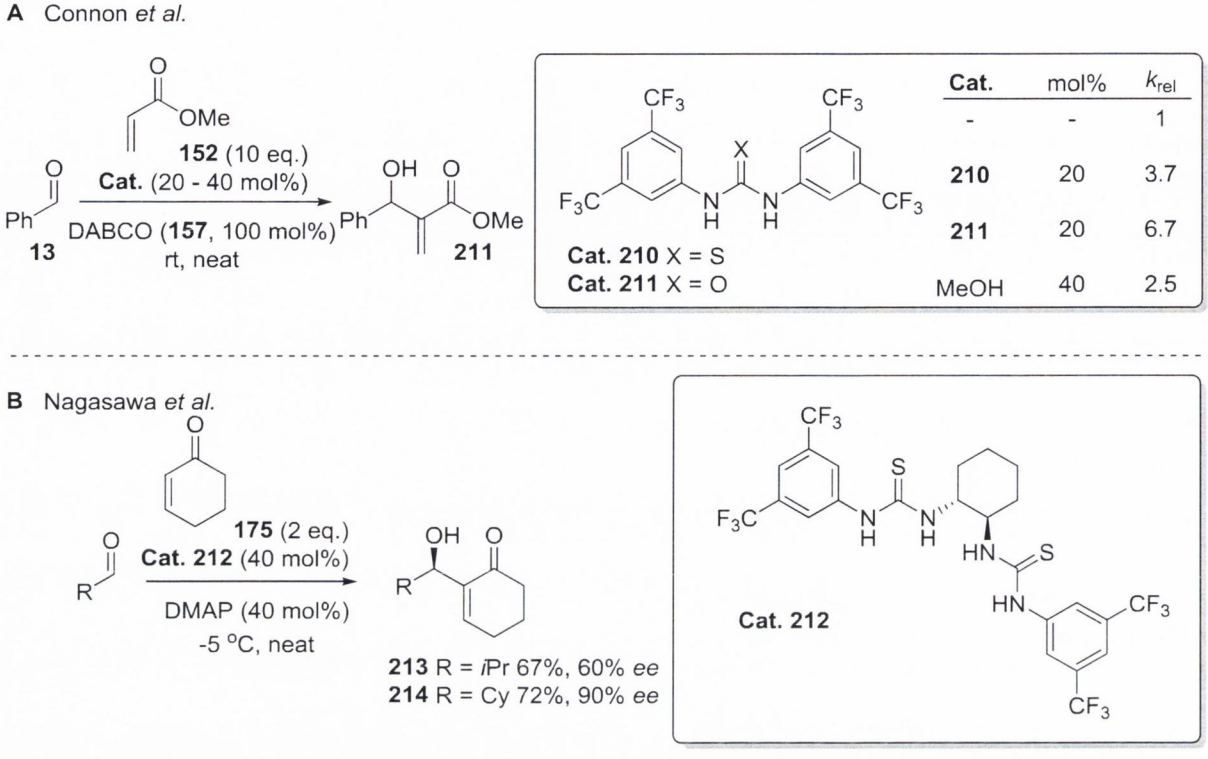
Schreiner *et al.* were the first to demonstrate that functionalised thioureas **Cat. 209/210** were capable of accelerating the rate of the Diels-Alder (DA) reaction between cyclopentadiene (**207**) and α,β-unsaturated ketones **206** (Scheme 1.43).[68] Interestingly, the opposite *trans*:*cis* selectivity was observed in DA product **208** when catalyst was used, compared with performing the reaction without catalyst. Schreiner *et al.* later demonstrated that thioureas with electron-withdrawing substituents on the aromatic rings were capable of promoting the DA reaction at a higher rate than catalysts incorporating electron-donating substituents.[69] With this observation they propose that the S-H interaction, illustrated below (*i.e.* **Cat. 209/210**), prevents rotation of the phenyl groups and increased the acidity of the N-H bonds.

Scheme 1.43 The functionalised thiourea catalysed Diels-Alder reaction



Connon *et al.* were able to demonstrate that ureas and thioureas were able to increase the rate of the MBH reaction to a higher degree than protic solvents (**A**, Scheme 1.44).[70] They found in this case that urea **211** outperformed the thiourea **210** in the catalysis of the MBH reaction of benzaldehyde (**13**) and methyl acrylate (**152**). Nagasawa *et al.* were the first to report the chiral thiourea catalysed MBH reaction of aromatic and aliphatic aldehydes with cyclohexenone (**175**) (**B**, Scheme 1.44).[71] They demonstrated that **Cat. 212** is capable of furnishing MBH products **213** and **214**, from aliphatic aldehydes, in moderate yields and moderate to high enantioselectivity.

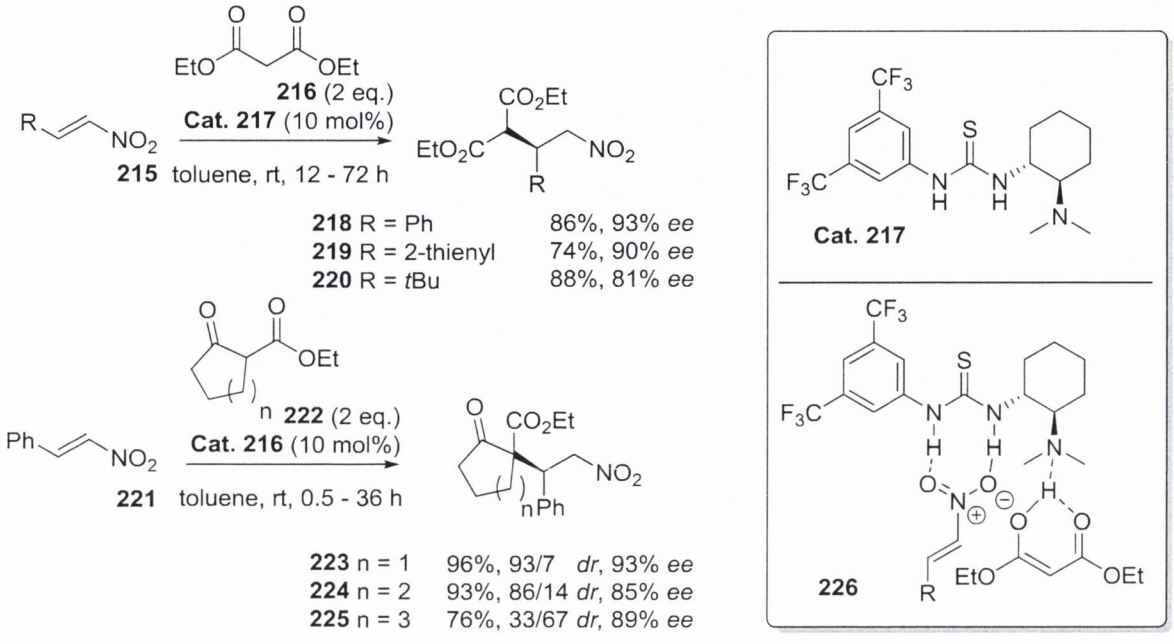
Scheme 1.44 The use of ureas and thioureas as catalysts for the tertiary amine-promoted MBH reaction



1.4.1 Bifunctional organocatalysis

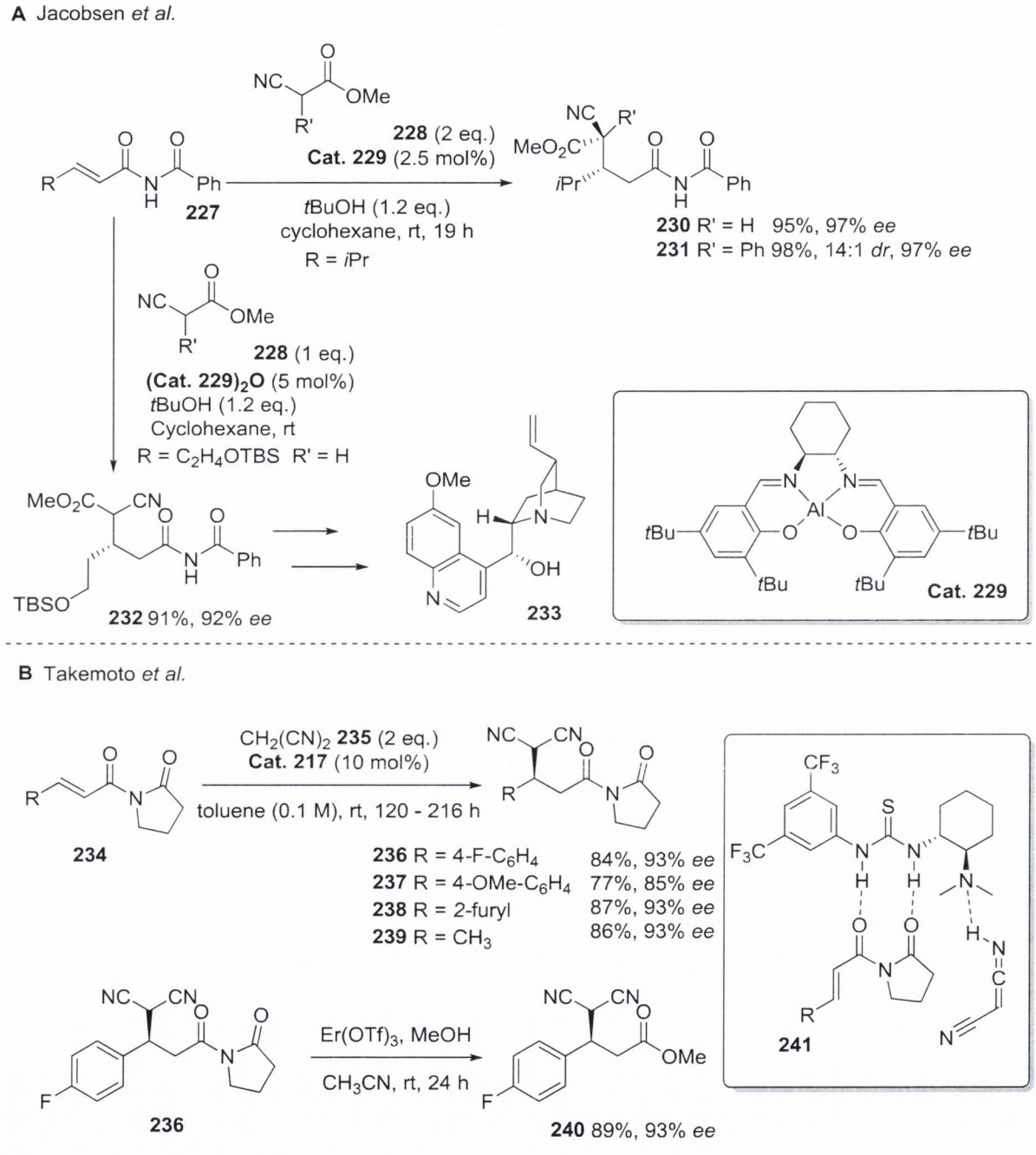
The concept of bifunctionality refers to the ability of the catalyst to activate both the nucleophile and the electrophile at the same time; a concept which is by no means novel as metal-ligand complexes have relied on this approach to promote many asymmetric reactions.[72] Takemoto *et al.* were the first to report a bifunctional organocatalyst capable of promoting the enantioselective 1,4-conjugate addition of malonate esters to nitroolefins (**216**, Scheme 1.45).[73] The authors demonstrated that their thiourea catalyst **216** is capable of promoting the formation of the Michael-type adducts **218** – **220** in significant yields with high *ee*. They were later able to extend the substrate scope of the reaction to include β-ketoesters similar to **222**.[74] It was found that diastereo- and enantioselectivity were generally good to excellent, for instance, adducts **223** – **225** were produced in 85 – 93% *ee*. They proposed that the binding interaction illustrated in complex **226** explains the stereochemical outcome of the reaction: the negatively charged oxygen of the nitro group binds to the Lewis acidic thiourea moiety, increasing the electrophilicity of the alkene, allowing the enol of the malonate to attain orbital overlap at the Bürgi-Dunitz angle with the LUMO of the nitroolefin.

Scheme 1.45 Asymmetric Michael addition reactions catalysed by bifunctional thiourea catalyst



Jacobsen and coworkers demonstrated that the α,β-unsaturated imide **227** was capable of being alkylated, in the presence of **Cat. 229**, to form the Michael addition products **230** and **231** in high yields and enantioselectivity with cyanoacetate ester pronucleophiles of general type **228** (**A**, Scheme 1.46).[75] They were later able to show that compound **232**, the product of the Michael addition of methyl cyanoacetate to **227**, could be used to form the chiral quinuclidine ring in the total synthesis of the natural product quinine (**233**).[76] Following on from the metal-catalysed Michael additions of pronucleophiles to α,β-unsaturated imides by Jacobsen and also Kanemasa,[77] Takemoto *et al.* reported that their bifunctional thiourea catalyst **217** could catalyse the addition of malononitrile (**235**) to α,β-unsaturated imides (**B**, Scheme 1.46).[78] Having evaluated a variety of α,β-unsaturated imides they found that analogues of **234**, containing cyclic imides that have limited degrees of freedom, performed best producing high yields of Michael products **236 – 239** in excellent *ee*. Interestingly, they were able to demonstrate methanolysis of the imide **236** using the Lewis acid $Er(OTf)_3$ to give the otherwise difficult to synthesize methyl cinnamate derivative **240**.

Scheme 1.46 Organocatalysed Michael addition of malononitrile to α,β-unsaturated imides



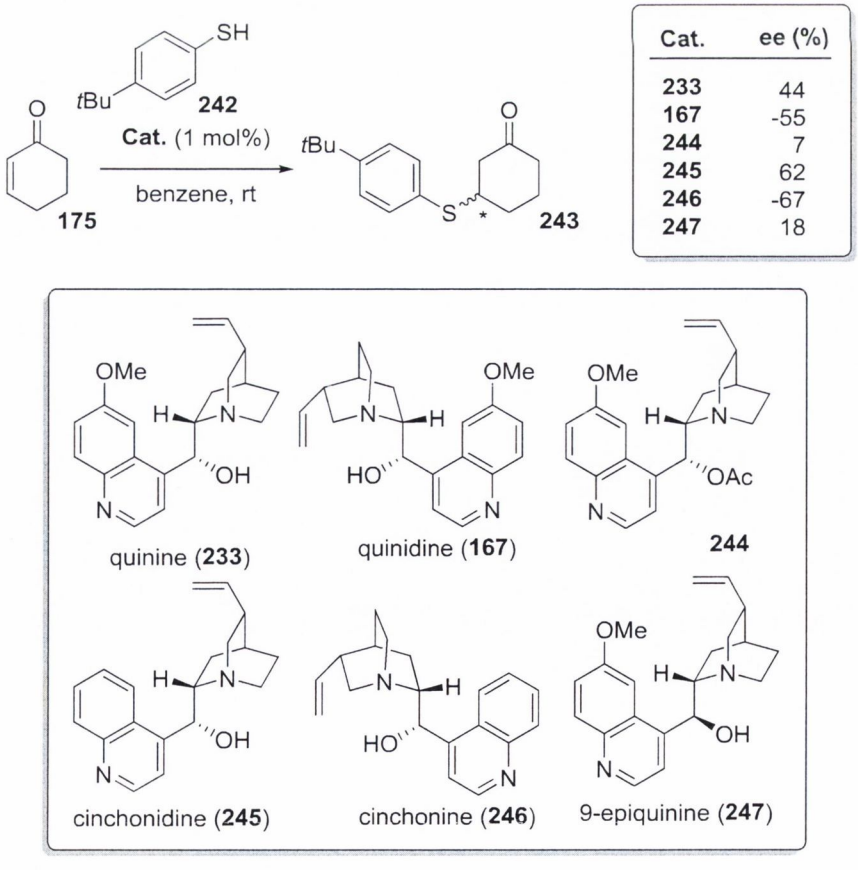
The authors attributed the high product enantioselectivity observed to the strong likelihood of forming the hydrogen bonding interaction between the imide and the thiourea moiety of the catalyst illustrated in complex **241**. All products in the process were generated with greater than 84% *ee*, indicating that this bonding interaction is highly favourable and that the angle of attack of the nucleophile must be fixed by the catalyst. Berkessel *et al.* later showed that the urea analogue of the bifunctional catalyst **Cat. 217** was highly effective in promoting the dynamic kinetic resolution of azlactones.[79]

1.4.2 Cinchona alkaloid-derived organocatalysts

Cinchona alkaloids have been used as a source of chiral information for decades, most prevalently as ligands for asymmetric metal-catalysed transformations producing enantioenriched products.[80]

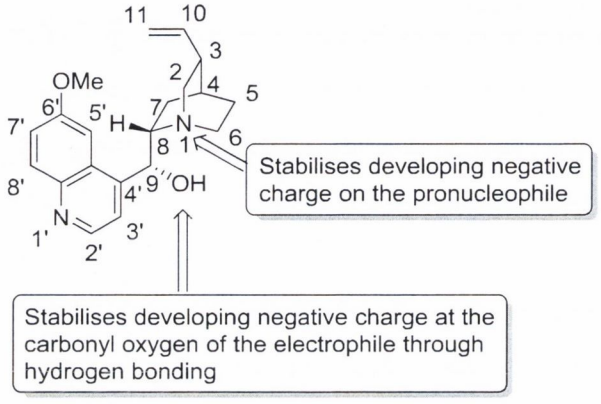
Wynberg *et al.* were the first to systematically demonstrate the capabilities of quinine and its analogues in catalysing asymmetric reactions.[81] They demonstrated that the natural products quinine (**233**) and quinidine (**167**), which are readily attainable from the bark of the cinchona tree, act as efficient catalysts for the sulfa-Michael reaction between 4-*t*butylthiophenol (**242**) and cyclohexene-one (**175**), furnishing the conjugate addition product **243** in moderate *ee* (Scheme 1.47). Interestingly, they found that the analogues cinchonidine (**245**) and cinchonine (**246**) afforded the sulfa-Michael product **243** in highest *ee*.

Scheme 1.47 The cinchona alkaloid catalysed sulfa-Michael addition reaction



Cinchona derivative **244** is of particular note: removal of the hydroxyl functionality has a detrimental effect on the observed *ee* of the sulfa-Michael product **243**, indicating that this catalyst must be bifunctional. In time this would be proved correct; the generally accepted mode of action of these catalyst types is illustrated in Figure 1.2.[62]

Figure 1.2 Mode of action of bifunctional quinine catalysts



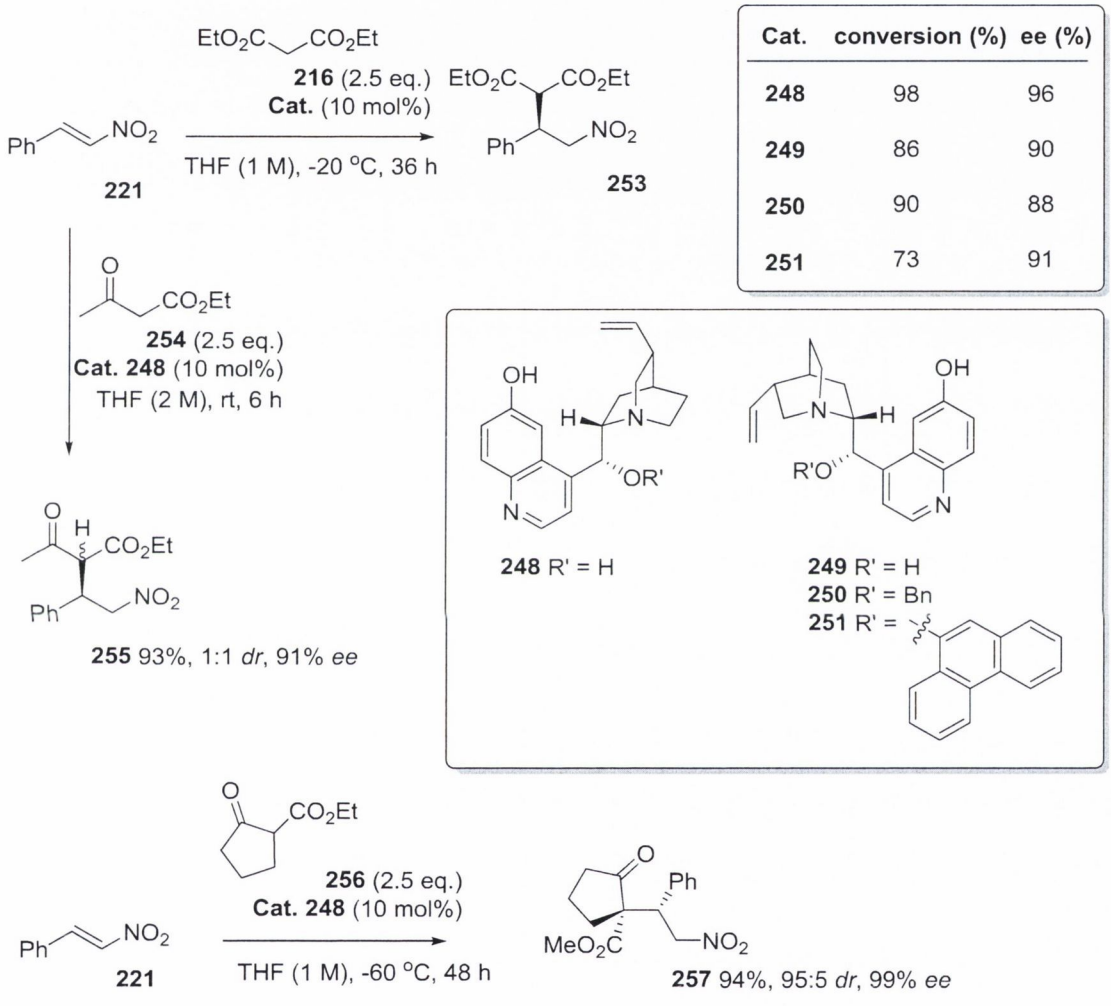
1.4.2.1 Functionalisation of cinchona alkaloids effecting catalyst activity

Deng *et al.* were the first group to disclose the use of a modified cinchona alkaloid catalyst to increase the enantiocontrol of Michael-type addition reactions.[82] Through a simple demethylation at the C-6' position of quinine (**233**) and quinidine (**167**), they generated a class of catalyst capable of promoting the enantioselective Michael addition of malonates to nitroolefins (Scheme 1.48). The authors found that the C-9 hydroxyl group appeared to play a smaller role in the reaction when the C-6'hydroxyl group is present (**248** and **249**), which may be due to their relative pK_as. The C-6' hydroxyl is much more acidic compared with the C-9 hydroxyl, as such it is expected that it would be the C-6' hydroxyl that would stabilise the developing negative charge in the transition state.[83] C-9 alkylated cinchona alkaloid analogues **250** and **251** promoted the formation of **253** in similar *ee* to that observed using the C-9 hydroxyl-based catalyst **248**.

Deng *et al.* found that a wide range of aliphatic and aromatic β-nitrostyrenes could be used to generate malonate ester-based Michael adducts in near quantitative yields and excellent *ee* (>90 %). When β-ketoester **254** was utilised as the pronucleophile, they found that the Michael product **255** readily formed in high yield and *ee* but in low *dr*. They attribute this to epimerisation of the γ-position under the basic reaction conditions, a theory which they later proved correct using the cyclic β-ketoester **256**. With this pronucleophile they could generate

contiguous quaternary and tertiary stereocenters on the Michael product **257** in high yield, exceptional *dr* and excellent *ee*.[84]

Scheme 1.48 C-6' modified cinchona alkaloid catalysts as promoters of the Michael-type reactions

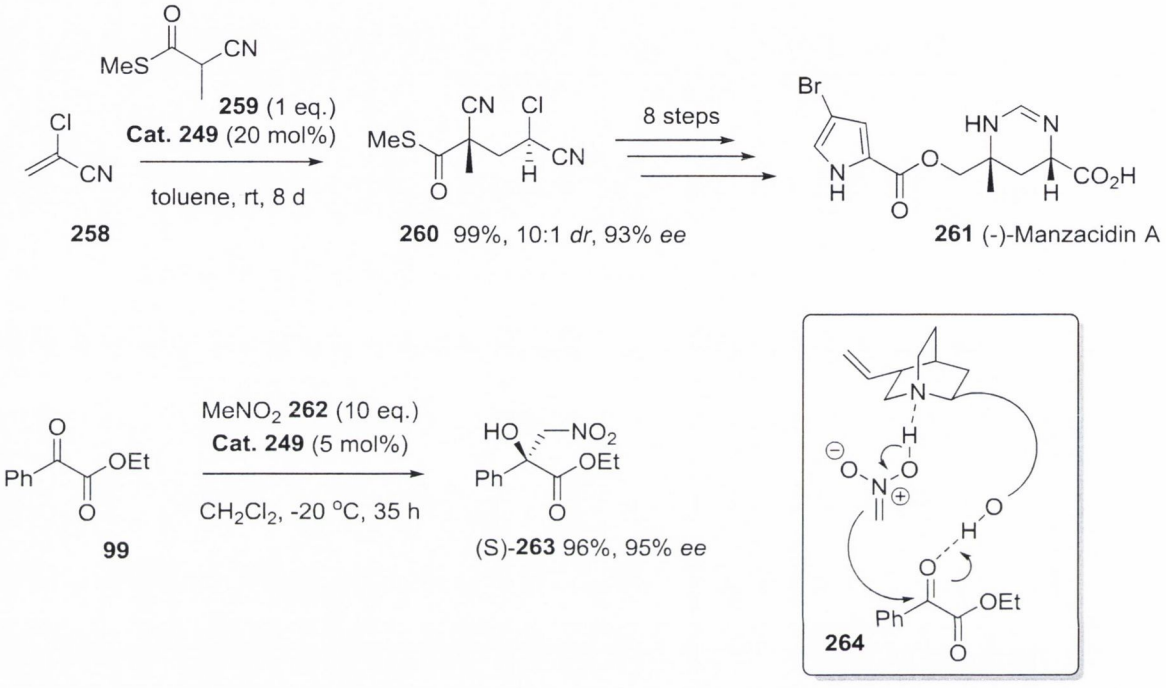


Cat.	conversion (%)	ee (%)
248	98	96
249	86	90
250	90	88
251	73	91

Deng *et al.* have reported that their C-6' hydroxyl quinine-based catalysts can also be used in a variety of other asymmetric tranformations with a diverse range of α,β-unsaturated substrates including: dialkyl azodicarboxylates and the often difficult MVK.[85] The authors were also able to exhibit the potential of their Michael addition methodology by synthesising the key intermediate **259** in the synthesis of the natural product (-)-Manzacidin A **261** (Scheme 1.49).[86] They were also able to demonstrate their catalyst's utility in the Henry reaction of nitromethane **263** and pyruvates.[87] The Henry reaction proceeds *via* the deprotonation of a nitroalkane and subsequent addition of the nitro-enolate to the carbonyl of another molecule, (*e.g.* the reaction assembly **264**). They found that both aliphatic and

aromatic pyruvate-like substrates were amenable to this protocol, furnishing high yields and excellent *ee*'s of Henry products.

Scheme 1.49 Synthesis of (-)-Manzacidin A and a cinchona alkaloid catalysed asymmetric Henry reaction

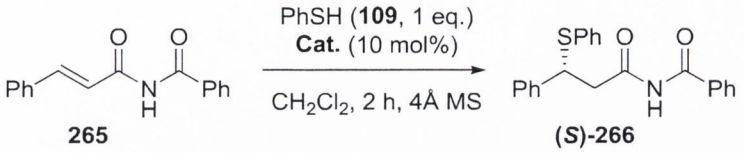


1.4.2.2 Functionalisation at C-9

What followed in the aftermath of Deng's original publication was a veritable 'arms race' to incorporate urea and thiourea functional groups onto cinchona alkaloids. The first group to incorporate a thiourea at the C-9 position of cinchonidine and cinchonine was Chen *et al.*, generating a catalyst capable of efficiently promoting the sulfa-Michael addition of thiols to α,β-unsaturated imides (**A**, Scheme 1.50). They found that quantitative yields of product **266** could be formed in a short period of time, however, only low product enantioselectivities were observed.[88] The authors were able to demonstrate that the reaction could be performed using Takemoto's catalyst **217**, producing product **266** in 95% yield and 75% *ee*.

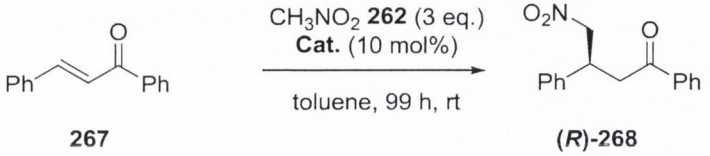
Scheme 1.50 Development of C-9 substituted ureas and thioureas

A Chen *et al.*



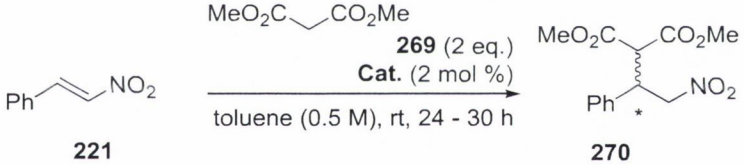
Cat.	yield (%)	*ee* (%)
Q-270	99	7
epiQ-270	99	17

B Soós *et al.*



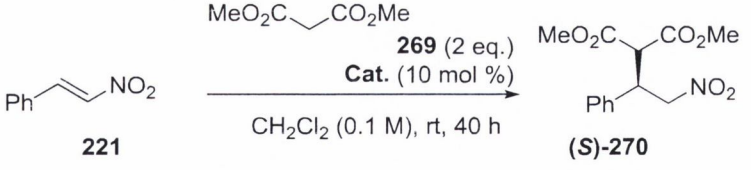
Cat.	yield (%)	*ee* (%)
epiQ-270	71	95 (*R*)
epiQ-272	93	96 (*R*)
Q-270	0	
epiQD-270	59	86 (*S*)

C Connon *et al.*

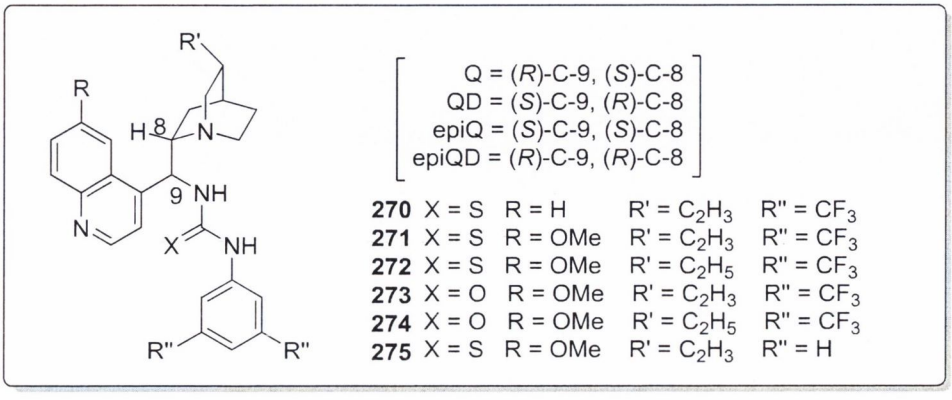


Cat.	conv. (%)	*ee* (%)
epiQ-274	>98	88 (*R*)
epiQD-274	>98	79 (*S*)
epiQ-272	>98	90 (*R*)
epiQD-272	>98	85 (*S*)

D Dixon *et al.*



Cat.	yield (%)	*ee* (%)
epiQ-275	96	87
epiQ-271	98	87



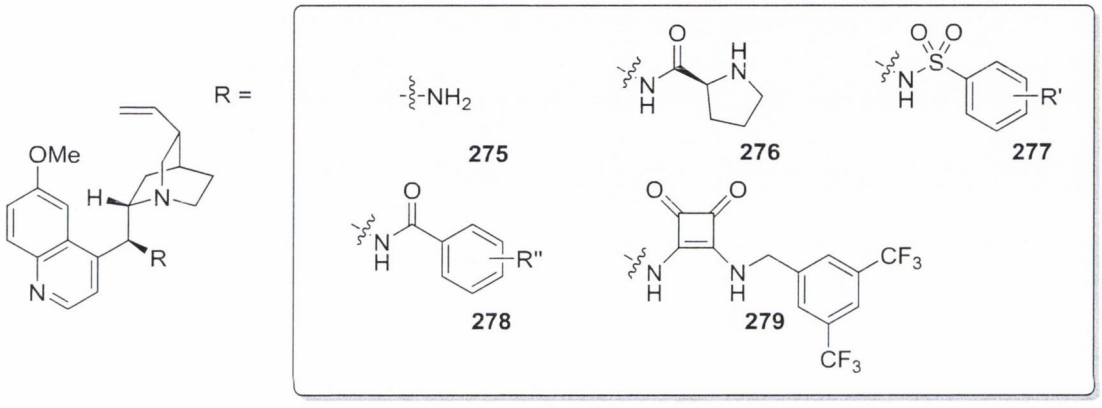
Shortly after, Soós *et al.* published the C-9 thiourea functionalised quinine and quinidine catalysts for the Michael-type reaction of nitromethane (**262**) to chalcone (**267**) (**B**, Scheme 1.50).[89] They reported for the first time that cinchona alkaloid-based catalysts were capable of promoting enantioselective Michael-type addition reactions. It is also noted that products of these reactions, where Ph = 4-Cl-C_6H_4, are key intermediates in the synthesis of γ-amino acids, and also the pharmaceutical Baclofen.[90]

Interestingly, Soós *et al.* noticed that compound **Q-270**, the natural configuration of quinine, exhibited no catalytic activity in the reaction. This observation ties in with that of Chen *et al.*, where the natural configuration of the cinchona alkaloid promotes the formation of the product in lower *ee*. The fact that the natural cinchona alkaloid configuration shows little or no catalytic activity, whereas its C-9 epimer promotes the reaction to high yield and enantioselectivity strongly indicates the presence of a bifunctional catalyst mode of action.

Connon *et al.* and Dixon *et al.* both demonstrated the cinchona alkaloid catalysed addition of malonates to nitroalkenes almost simultaneously. Connon *et al.* found promising initial results using urea and thiourea functionalised catalysts derived from quinine and quinidine (**C**, Scheme 1.50).[91] The superior catalyst proved to be the thiourea catalyst **epiQ-272**, allowing the formation of product **270** in up to 90% *ee* at room temperature. When the reaction was performed at -20 °C it was found that the product **270** was formed in 93% yield and 99% *ee*. Dixon *et al.* observed similar results with their thiourea catalyst **epiQ-271**, which promoted that same transformation in 87% *ee* at room temperature (**D**, Scheme 1.50).[92] Interestingly, when the CF_3 groups are not present on the thiourea moiety, the reaction proceeds in lower yield compared with when they are present, lending more credence to previously discussed studies on thiourea configuration, see Scheme 1.43. The authors also found that on cooling the reaction to -20 °C they could increase the observed *ee* to 94%. Both research groups were able to demonstrate a considerable substrate scope for the reaction including electron-rich/poor aromatic, heteroaromatic and aliphatic nitroalkenes. Since these discoveries, C-9 functionalised thioureas and ureas have been shown to be efficient catalysts of a wide variety of chemical transformations, and have been applied to the syntheses of many natural products and pharmaceuticals.[93]

Other functionalities at the C-9 position of quinine have been demonstrated to effect chemical reactions. C-9 amine-derived catalysts have been shown to undergo efficient iminium-type catalysis on compounds containing carbonyl functionalities (**275**, Figure 1.3).[94,95] The prolinamide functional group **276** at C-9 was also demonstrated to be a highly active catalyst for iminium-type catalysis.[96] Sulfonamide and amide C-9 functionalised quinine-derived catalysts, **277** and **278** respectively, have been utilised as asymmetric promoters of Michael reactions, desymmetrisation reactions and the synthesis of pharmaceuticals.[97,98]

Figure 1.3 Variation in functionalisation of cinchona alkaloids at C-9

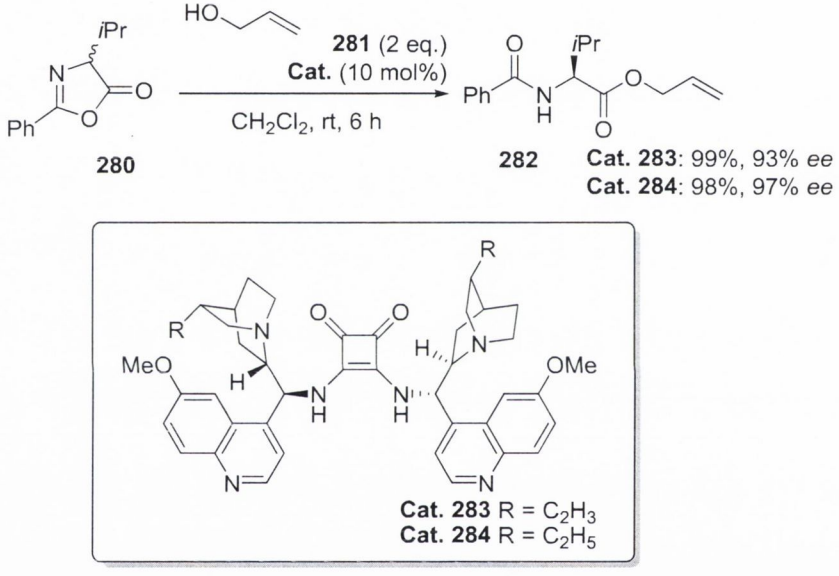


The use of squaramide functionalities on quinine-based catalysts, *e.g.* **279**, was first demonstrated by Rawal *et al.* in the asymmetric Michael addition of enolisable pronucleophiles to nitroalkenes.[99] They demonstrated that the squaramide moiety is a much more effective hydrogen bond-donating group than the thiourea group, in that the reaction could be performed with catalyst loadings as low as 0.1 mol%. This augmented activity was attributed to the ~0.6 Å increase in distance between the N-H bonds in the case of the squaramide, allowing more effective hydrogen bonding to the nitro-functionality of the substrate. It is also believed that the preferred conformation of the squaramide is the *anti/anti* form depicted. Though some *anti/syn* conformations have been observed in specifically engineered systems, the *syn/syn* system has never been observed and as such has been determined to be disfavoured.[100]

Since Rawal *et al.*'s initial incorporation of the squaramide moiety into catalyst **279**, a large interest has been sparked in the field, with a myriad of new catalyst designs being reported for a variety of reactions.[101] The most pertinent for the purposes of this thesis is that

developed by Song *et al.*, which was published soon after Rawal *et al.* Their C_2 symmetric, C-9 squaramide functionalised quinine catalyst (**Cat. 283**) was demonstrated to be a highly efficient catalyst for the dynamic kinetic resolution of the azlactone **280**, furnishing near enantiopure amino acid derivative **282** (Scheme 1.51).[102] The authors were able to improve the *ee* of this reaction to 97% with little expense to the isolated yield (98%) by cooling the reaction to -20 °C and by employing the C-3 ethyl analogue **Cat. 284** as the promoter.

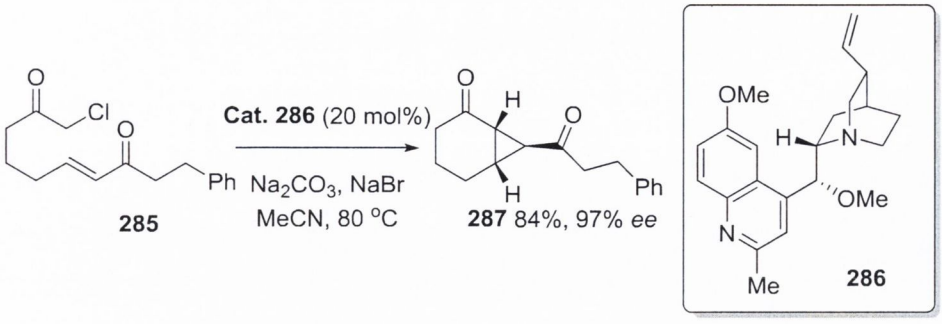
Scheme 1.51 DKR of azlactones catalysed by C_2 symmetric, squaramide functionalised quinine-derived catalyst



1.4.2.3 Functionalisation at C-2'

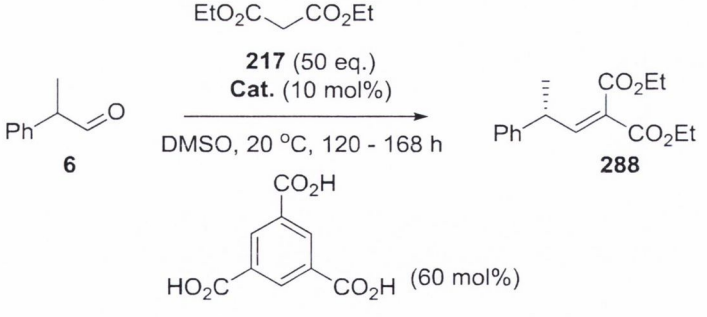
Gaunt *et al.* were the first to report the use of quinine-derived catalysts functionalised at the C-2' position (**286**, Scheme 1.52).[103] They theorised that when this position is alkylated, nucleophilic attack of the quinoline nitrogen would be disfavoured, allowing ylide formation at the quinuclidine nitrogen exclusively. This theory proved correct; high *ee* could only be expected from ylide formation at the quinuclidine N-atom, which is close to the stereochemical information.

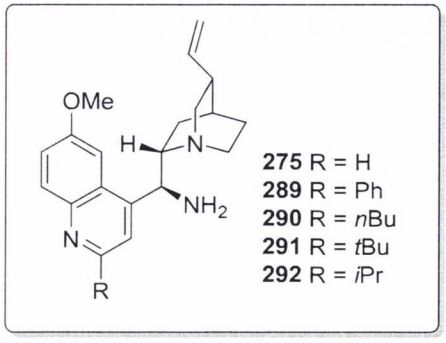
Scheme 1.52 An organocatalysed enantioselective cyclopropanation reaction



Recently List *et al.* reported that quinine amines functionalised at C-2' with bulky groups, were capable of catalysing the Knoevenagel condensation of aldehydes and malonate esters in excellent enantiomeric excess (Scheme 1.53).[104] The substituted quinine-derived amines **289 - 292** are readily synthesised *via* the reaction of the amine **275** with the corresponding alkyl lithium species. General increases in enantioselectivity were observed in the product **288** when these C-2' functionalisations were incorporated into the amine catalyst. This class of C-2' substituted quinine-derived amine catalysts have since been used to promote the asymmetric epoxidation of α,β-unsaturated ketones and 1,6-conjugate addition reactions of cyclic dienones.[105,106]

Scheme 1.53 C-2' functionalised quinine-derived amine catalysed Knoevenagel condensation

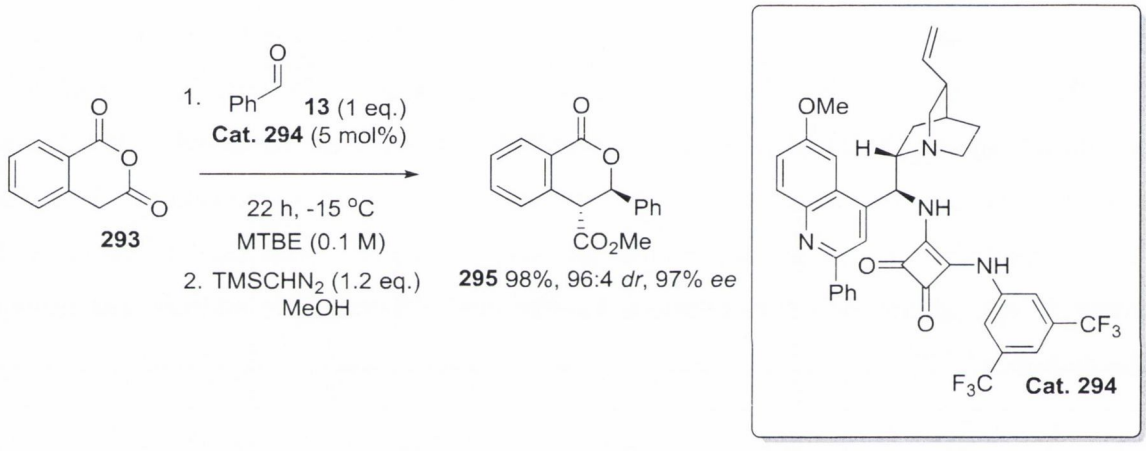




Cat.	yield (%)	ee (%)
275	90	88
289	87	91
290	92	90
291	86	89
292	91	91

Connon *et al.* reported the first C-2' functionalised squaramide catalyst **294**, which was employed in the enolisation of anhydrides and subsequent asymmetric addition to aldehydes.[107] The authors demonstrated that the lactone product **295** could be formed, largely as the *trans* isomer in high yield, *dr* and excellent *ee* (Scheme 1.54). They demonstrated that a large variety of aromatic, aliphatic and heterocyclic aldehydes were amenable to this methodology, furnishing lactones in moderate to high yields, and excellent *ee* (>91%). They were later able to extend the scope of the methodology to incorporate succinic anhydride substrates.[108]

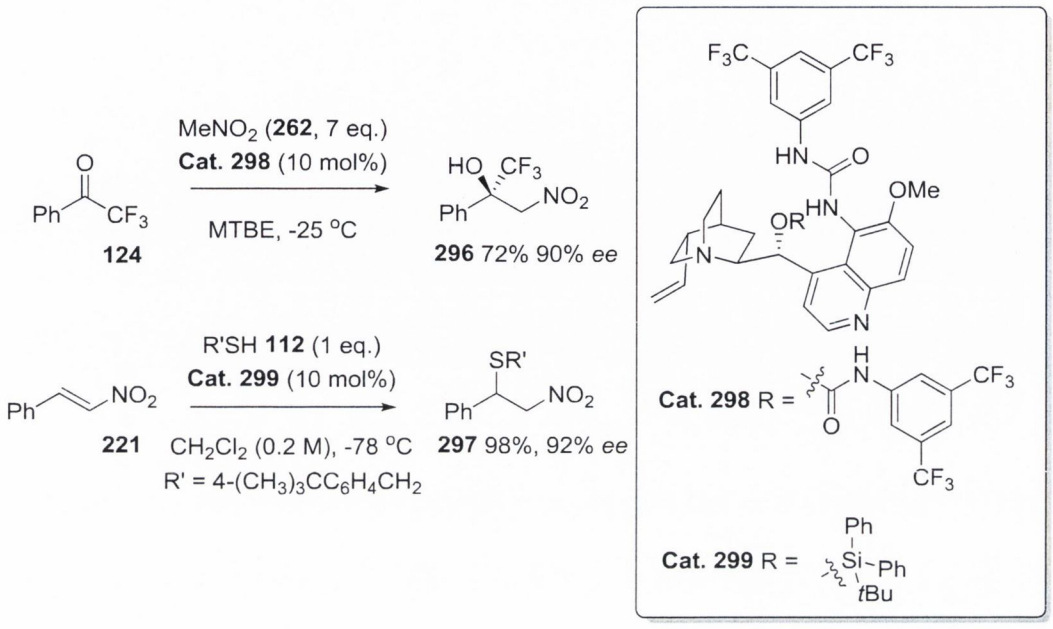
Scheme 1.54 The enolisation of anhydrides *via* the bifunctional quinine-derived catalyst **294**



1.4.2.4 Functionalisation at C-5'

Recently, urea functionalities have been installed at the C-5' position of quinine. The resulting compounds, **298** and **299**, have been shown to be efficient promotors of the asymmetric Henry and sulfa-Michael reactions (Scheme 1.55).[109,110] These catalysts were shown to exhibit a high degree of enantiocontrol at low temperatures, furnishing products **296** and **297** in high *ee*.

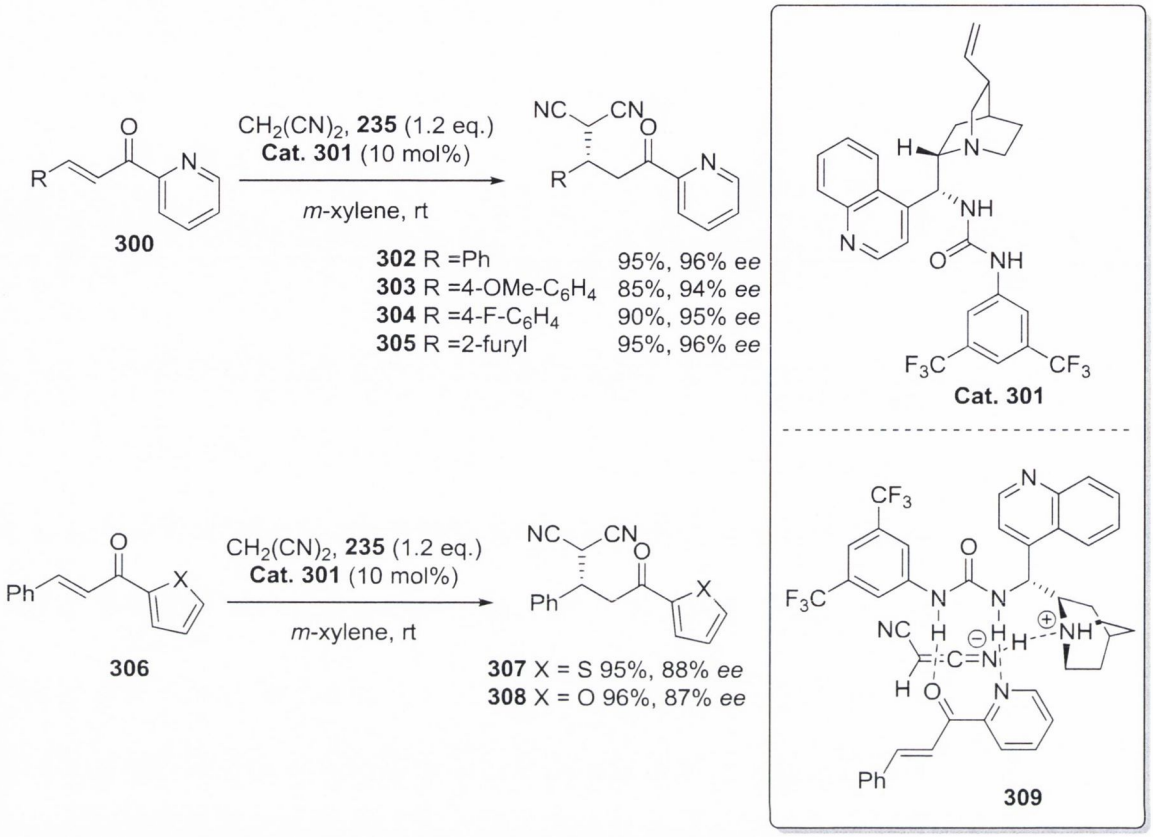
Scheme 1.55 C-5' substituted quinine-derived catalyst for the asymmetric Henry and sulfa-Michael reactions



1.4.3 The use of directing groups in asymmetric catalytic transformations

As described in Section 1.4.1, Takemoto used α,β-unsaturated imide substrates that were capable of binding to the Lewis acidic thiourea moiety of a bifunctional catalyst. Recently Singh *et al.* reported the addition of malononitrile (**235**) to 2-enoylpyridines **300**, furnishing Michael addition products **302** - **305** in high enantiopurity, using a cinchonine derived catalyst **301** (Scheme 1.56).[111] The authors also demonstrated that 2-enoylfurans and 2–enoylthiophenes could also be used to generate Michael addition products **307** and **308** in excellent *ee*. The proposed pre-transition state assembly (*i.e.* **309**) of this reaction is analogous to that proposed by Takemoto *et al.* in Scheme 1.46; the urea moiety binds both of the electrophiles Lewis basic functionalities as the malononitrile (**235**) pronucleophile is activated by the quinuclidine nitrogen, thereby conferring the facial selectivity observed.

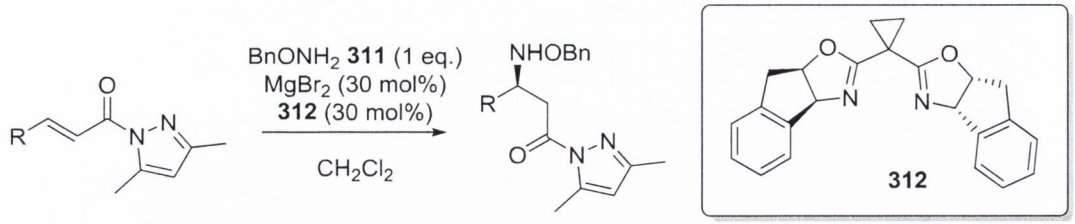
Scheme 1.56 Asymmetric 1,4-conjugate addition of malononitrile to 2-enoylpyridines



1.4.3.1 The use of pyrazoles as directing groups

In 1998, Sibi *et al.* reported the first use of 3,5-dimethylpyrazoles as directing groups for 1,4-conjugate addition reactions.[112] The authors demonstrated that the simple catalytic system of $MgBr_2$ and chiral ligand **312** were capable of promoting the 1,4-conjugate addition of the *O*-benzyl protected hydroxyl amine **311** to α,β-unsaturated acylpyrazoles **310**, in moderate yield and high *ee* (Scheme 1.57). It was noted that aliphatic products **313** and **314** formed readily in appreciable yield, however, aromatic-substituted product **315** proved difficult to generate, though a high *ee* was still observed.

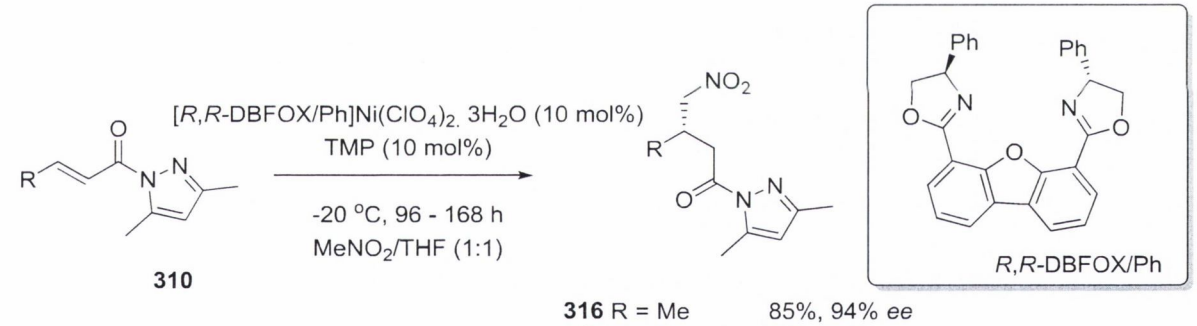
Scheme 1.57 1,4-Conjugate addition of amines to acylpyrazoles catalysed by a $MgBr_2$ ligand complex



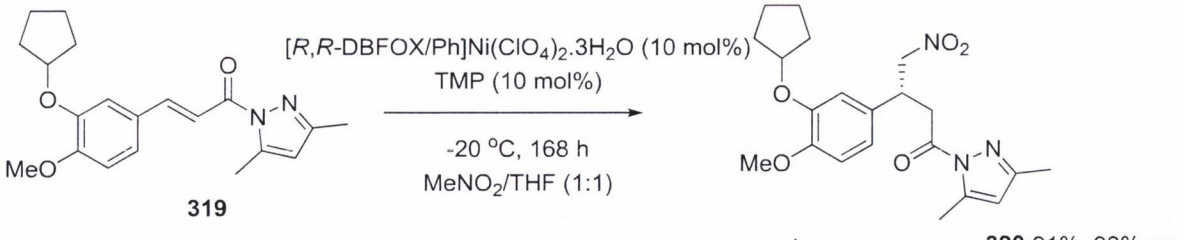
313 R = Me 80%, 92% *ee*
314 R = *i*Pr 76%, 87% *ee*
315 R = Ph 24%, 83% *ee*

Kanemasa *et al.* demonstrated the 1,4-conjugate addition of nitromethane to the same acylpyrazole substrates using a nickel-derived complex (Scheme 1.58).[113]

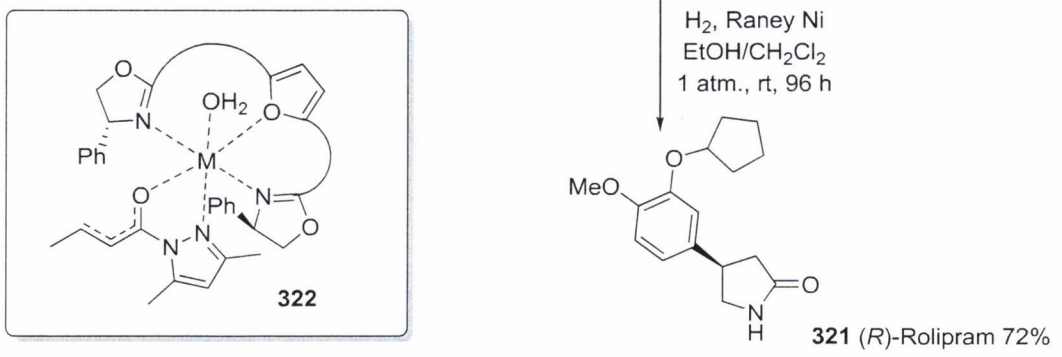
Scheme 1.58 1,4-conjugate addition of nitromethane to acylpyrazoles catalysed by a nickel R,R-DBFOX/Ph complex



316 R = Me 85%, 94% *ee*
317 R = Ph 90%, 93% *ee*
318 R = 2-C_4H_3O 75%, 97% *ee*



320 91%, 98% *ee*

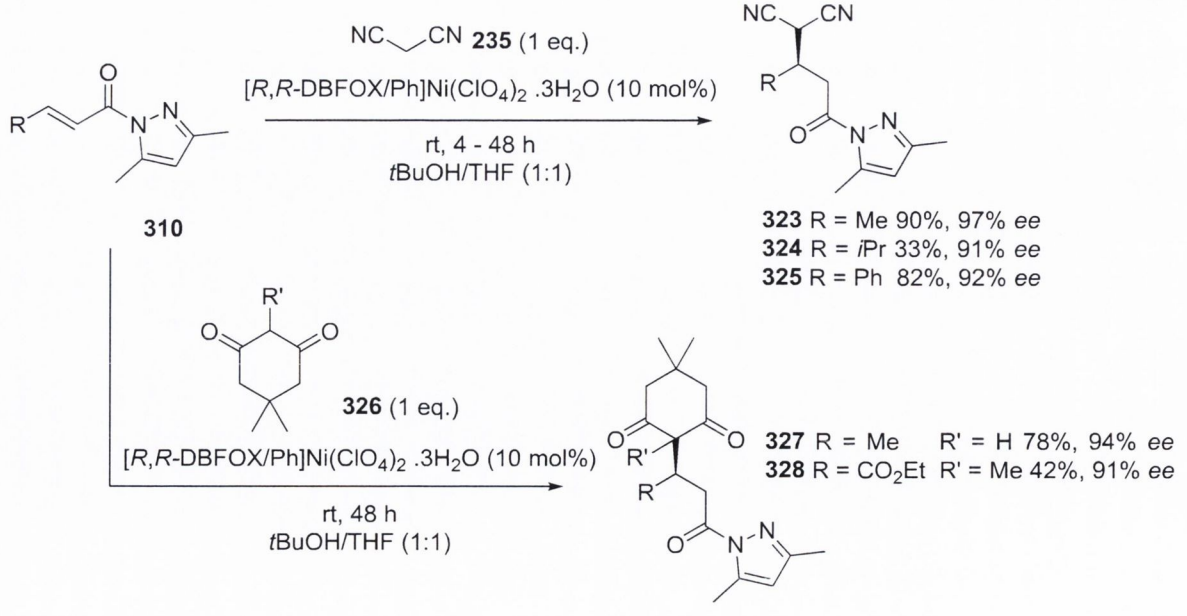


321 (*R*)-Rolipram 72%

It was found that the reaction only proceeded when nitromethane was used as a co-solvent, nevertheless, high yields and exceptional enantioselectivity were observed in the Michael addition products **316 – 318**. It is noteworthy that the substrate scope of this methodology encompasses the previously recalcitrant aromatic substituted acylpyrazoles. Using this methodology, Kanemasa *et al.* were able to execute the enantioselective synthesis of (*R*)-rolipram, a selective phosphodiesterase inhibitor.[114] Both Sibi and Kanemasa proposed similar modes of action of their metal catalysts for the reaction: the acylpyrazole displaces two water ligands at the metal centre and the Lewis acidity of the metal activates the β-position of the alkene by inductive withdrawal, (see **322**). In the case of the methodology developed by Kanemasa *et al.*, *Re* face addition the nitroalkane is favoured, furnishing the Michael addition product.

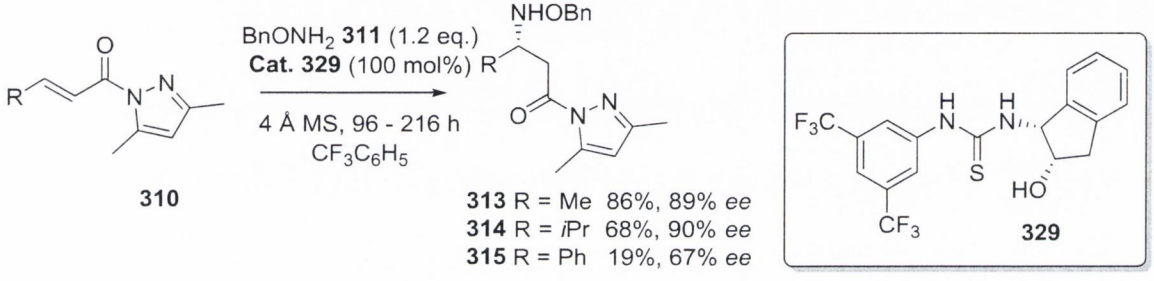
Later, Kanemasa *et al.* reported an extension to this methodology, where other pronucleophiles could be used in the 1,4-conjugate addition to acylpyrazoles (Scheme 1.59).[115] Initially they demonstrated the efficient catalysis of the addition of malononitrile to acylpyrazoles, furnishing Michael addition products **323** - **325** in excellent *ee*. The authors also reported the 1,4-conjugate addition of substituted and unsubstituted dimedones **326** to acylpyrazoles to afford products **327** and **328** in excellent *ee*.

Scheme 1.59 Nickel DBFOX/Ph ligand complex catalysed 1,4-conjugate addition of pronucleophiles to acylpyrazoles.



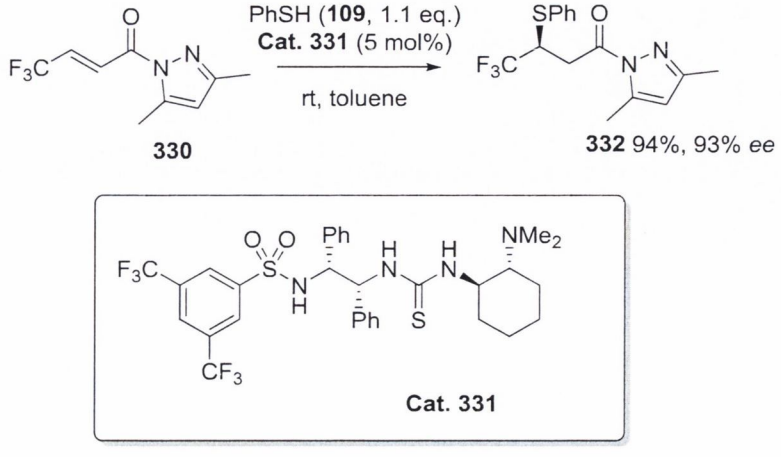
Sibi *et al.* disclosed the first organocatalytic version of their magnesium bromide ligand complex-catalysed 1,4-conjugate addition reaction of the *O*-benzyl protected hydroxyl amine **314** to α,β-unsaturated acylpyrazoles **310** (Scheme 1.60). On employing the thiourea functionalised organocatalyst **329**, the authors found that they could generate the Michael addition products **311** and **312** in high *ee*, although overall yields were lower compared with their metal-catalysed procedure.

Scheme 1.60 1,4-conjugate addition of amines to acylpyrazoles catalysed by a thiourea functionalised organocatalyst



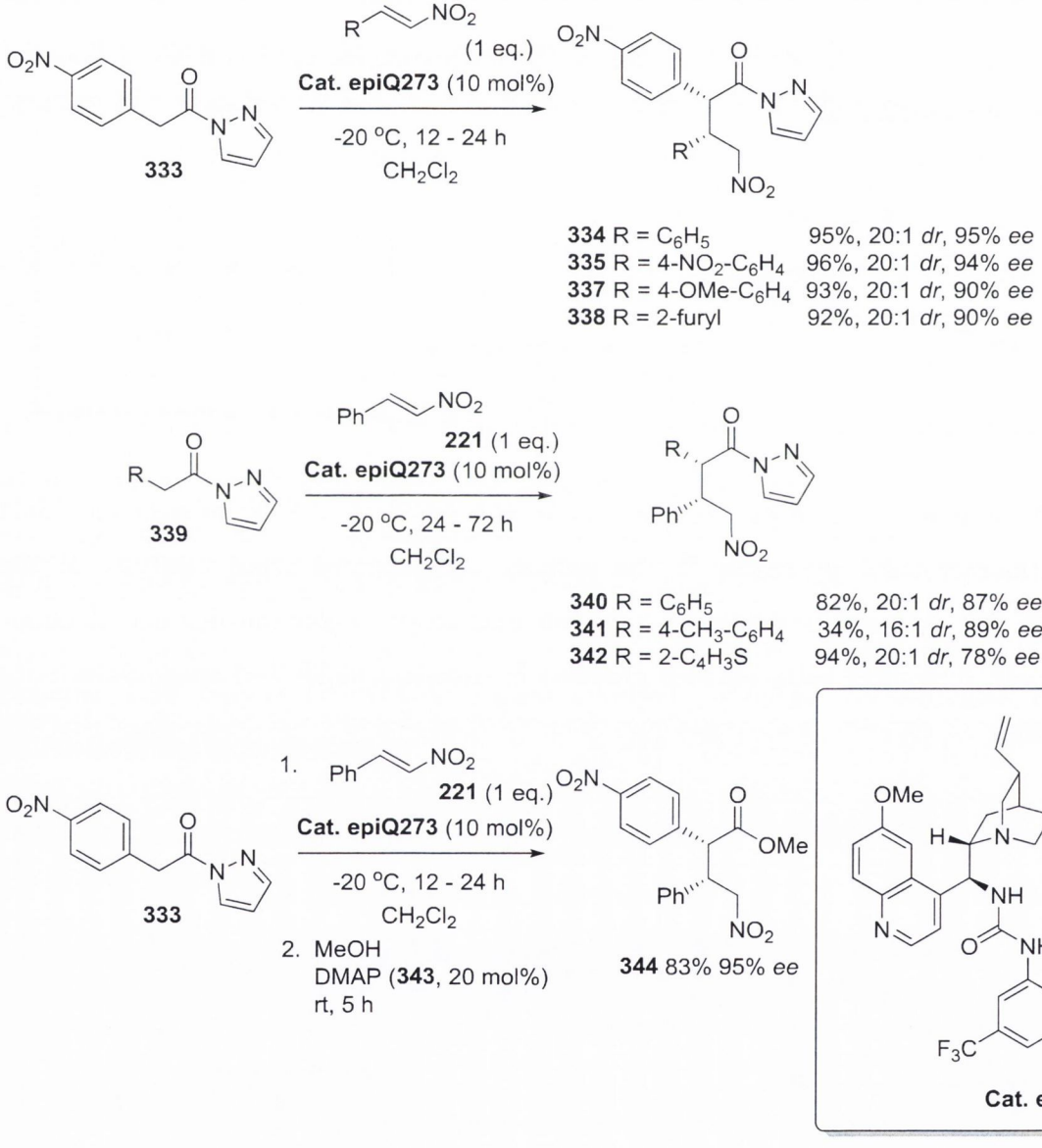
Recently, Wang *et al.* reported the organocatalytic sulfa-Michael addition of aromatic thiols to 4,4,4-trifluorocrotonyl pyrazoles.[116] The authors demonstrated rapid catalysis of the reaction with **Cat. 331** and established a large substrate scope of electron-rich and electron-deficient thiols, furnishing sulfa-Michael products in excellent yields and enantioselectivity (Scheme 1.61).

Scheme 1.61 Organocatalytic sulfa-Michael addition of aromatic thiols to 4,4,4-trifluorocrotonyl pyrazole



Barbas *et al.* demonstrated that benzylic acylpyrazoles could be used as pronucleophiles in an organocatalysed Michael addition reaction with β-nitrostyenes (Scheme 1.62).[117] The authors found that the Michael products **334** – **338** formed readily from the corresponding β-nitrostyenes and acylpyrazole **333**.

Scheme 1.62 Benzylic acylpyrazoles as pronucleophiles in the Michael addition reaction with β-nitrostyenes



They found, however, when electron-rich aromatic substituted acylpyrazoles were employed in the reaction with the β-nitrostyene **221**, the yields and enantioselectivity of the products **340** and **341** were observed to be lower. When a heterocycle-substituted acylpyrazole was used, the reaction proceeded to give product **342** in high yield but only moderate *ee*. These observations allowed the authors to propose that the rate of enolisation of the acylpyrazole

was dependant on the pK_a of the methylene proton, which electron withdrawing groups would lower significantly. Of particular synthetic interest is the methanolysis of the acylpyrazole under mild conditions with DMAP (**343**) to give the otherwise difficult to synthesise ester product **344** in high yield and excellent *ee*.

1.4.4 Summary

Though significant advances in the field of organocatalytic Michael addition reactions have been achieved through the enantioselective additions of pronucleophiles to, in the main, nitrostyrenes and chalcones, there's still much room for improvement. Specifically, these nitrostyrenes and chalcones are of little use and their utility as substrates is due to their high electrophilicity. It would be more advantageous to have a substrate which was stable, yet reactive enough under bifunctional catalysis and which could be readily further functionalised to yield products formally derived from α,β-unsaturated esters, amides and acids (which are currently beyond the scope of bifunctional organocatalytic methodologies). It will be within the scope of this thesis to investigate such substrates.

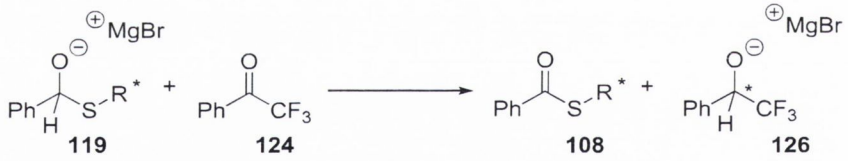
Chapter 2: The development of novel methodologies for the Tishchenko reaction

2.0 The use of chiral thiols in the crossed intermolecular Tishchenko reaction

2.1 Rationale and design of catalysts

The primary objective of this project was to devise a methodology for an asymmetric crossed intermolecular Tishchenko reaction based upon previous group work on the bromomagnesium thiolate-catalysed reaction (see Section 1.2.2). Assuming that the postulated reaction mechanism is valid, the most straightforward approach to achieve this would be through an asymmetric hydride transfer reaction (Scheme 2.1). We predicted that by using an enantioenriched thiolate, the hemithioacetal anion **119** would be capable of transferring a hydride, with a degree of facial discrimination, to the trifluoroketone **124** to generate the enantioenriched alkoxide **126**.

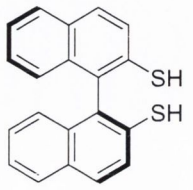
Scheme 2.1 Proposed mechanism of intermolecular hydride transfer using an enantioenriched thiolate catalyst



119 **124** **108** **126**

On careful study of the catalysts used in the crossed intermolecular Tishchenko reaction, we noted that for efficient enantioselective catalysis the thiolate must be aromatic, allowing a faster rate of acyl transfer. The obvious choice therefore was an axially chiral BINOL-derived thiol. Another valid choice that was considered was a ferrocene-derived chiral thiol, of which there are a few described in the literature.[118]

Figure 2.1 Proposed prototype catalyst for the asymmetric crossed intermolecular Tishchenko reaction



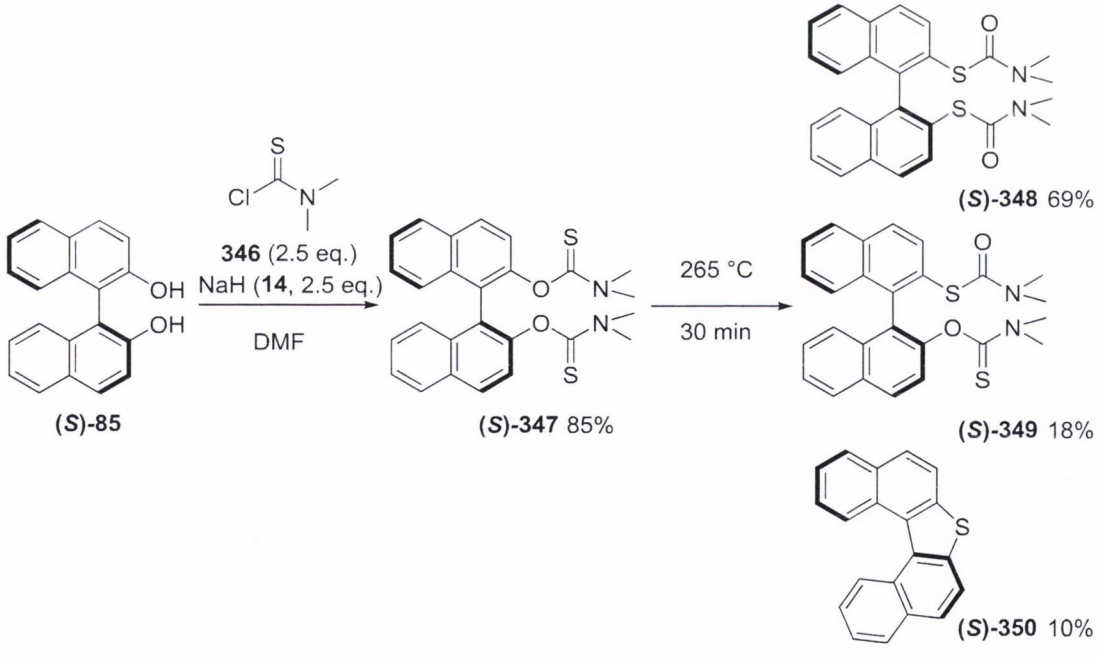
(*S*)-345

As a proof of concept, it was decided to synthesise a chiral BINOL-derived thiol that has been described in the literature and could be quickly acquired. **(*S*)-345** Had been synthesised by many groups and seemed ideal for our purposes.[119]

2.1.1 Synthesis of prototype catalyst

Following the synthetic route outlined by De Lucchi *et al.*, the chiral (*S*)-BINOL-derived **(*S*)-345** was prepared from (*S*)-BINOL (**(*S*)-85**). Treatment of (*S*)-BINOL (**(*S*)-85**) 2.5 equivalents of both sodium hydride (**14**) and *N*,*N*-dimethylthiocarbamoyl chloride (**346**) furnished the functionalised BINOL derivative **(*S*)-347**.

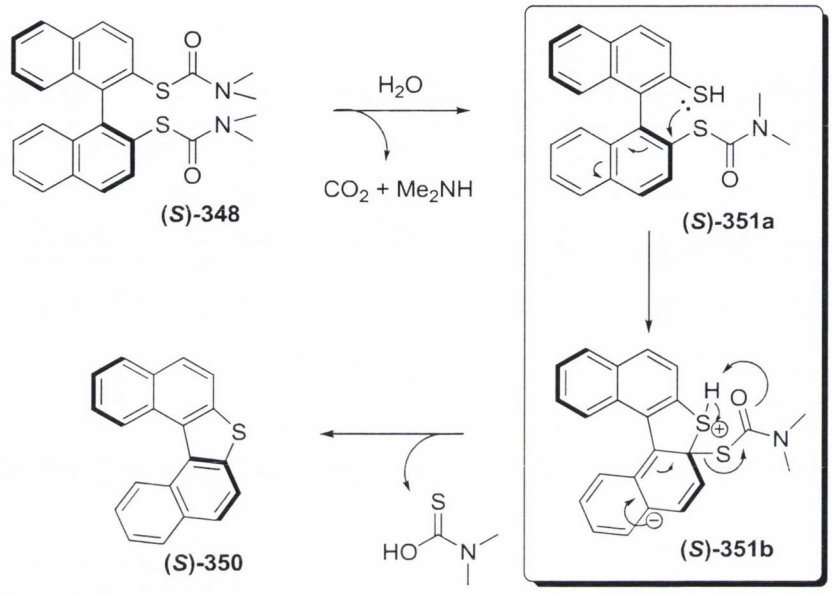
Scheme 2.2 *O*-Functionalisation and subsequent Newman-Kwart reaction on enantiopure BINOL



The next step proceeds *via* the heating of neat **(*S*)-347** at 265 °C to give the *bis*-rearranged product **(*S*)-348** in 69% yield, the *mono*-rearranged product **(*S*)-349** in 18% yield and the thiophene **(*S*)-350** in 10% yield. The thiophene **(*S*)-350** is a common side product in this reaction; its formation is attributed to adventitious water in the reaction vessel, which at high temperatures would favour cleavage of the S-CON(Me)$_2$ to form compound **(*S*)-351a** and

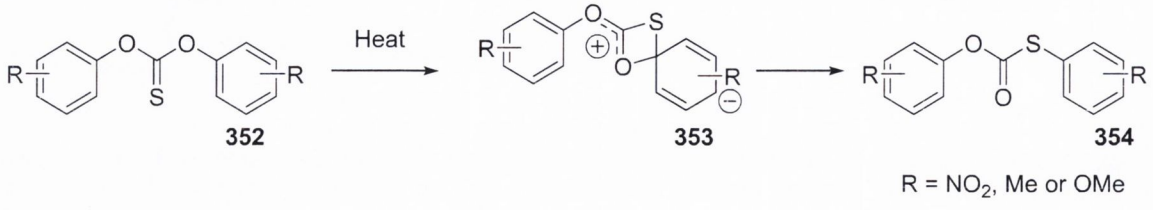
subsequent intramolecular S_NAr reaction *via* complex **(*S*)-351b** (Scheme 2.3).[120] It is for this reason that the reaction vessel was preheated to 130 °C under vacuum.

Scheme 2.3 Proposed reaction mechanism for the formation of thiophene **(*S*)-350**



The rearrangement is commonly referred to as a Newman-Kwart reaction and is a conventional means of forming aromatic C-S bonds.[121] Kwart *et al.* were the first to report that the reaction proceeds through the four-membered transtition state **353**, following the observation that the reaction proceeds at an accelerated rate in cases where electron-withdrawing groups are present on the aromatic rings (Scheme 2.4).[122] Newman *et al.* first demonstrated the use of thiocarbamoyl groups as substrates in this rearrangement.[123]

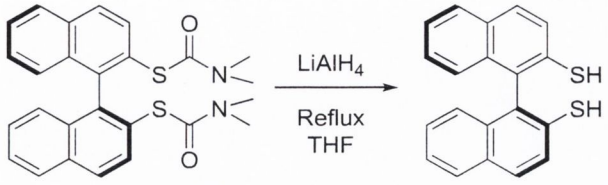
Scheme 2.4 The intramolecular cyclisation of aromatic thiocarbamates



The BINOL-derived thiol **(*S*)-345** was generated from the reduction with lithium aluminium hydride ($LiAlH_4$) in refluxing THF. The crude product was found to be of sufficient purity by ^1H NMR spectroscopic analysis for use as a catalyst for the Tishchenko reaction, however, over time impurities arose in the product (likely through oxidation of the thiol) and

repurification through a short column of silica furnished the pure thiol **(*S*)-345** in greatly diminished yield but high purity (Scheme 2.5).

Scheme 2.5 Formation of prototype catalyst

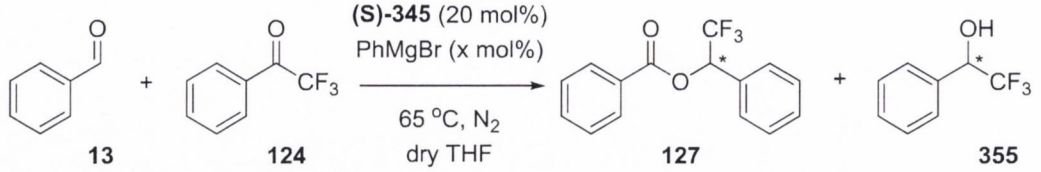


(*S*)-348 **(*S*)-345** 90%

2.1.2 Evaluation of the prototype enantioenriched catalyst in the asymmetric crossed intermolecular Tishchenko reaction

On evaluation of the thiol precatalyst **(*S*)-345** (Table 2.1), it was found that the catalyst was not as active as those used for this reaction previously. This is likely due to the increased steric bulk of the thiolate. It was observed that the rate of the crossed intermolecular reaction catalysed by the magnesium bromide thiolate of **(*S*)-345** was dependant on the amount of Grignard reagent used (entries 1 and 2, Table 2.1). When only one thiol is deprotonated, the reaction rate is much slower compared with when both thiols were deprotonated. This is probably due to the protonation of the conjugate base of alcohol **355** by the acidic thiol proton, thereby lowering the rate of the already rate-limiting acyl transfer step. Longer reaction times produced higher yields of the crossed ester **127**, however, after three days a paltry 42% yield was obtained (entry 3). A five day reaction time with one equivalent of PhMgBr furnished the ester product **127** in 83% yield but negligible *ee* (entry 4). The four day reaction time of the crossed-Tishchenko reaction catalysed by the *bis*-deprotonated thiol produced the crossed ester **127** in 85% yield and 6% *ee*. This is a very low level of asymmetric induction but it represents the first reaction of its kind to date and thus prompted us to attempt to design a catalyst which would augment the level of *ee* observed in the crossed ester product **127**.

Table 2.1 Evaluation of the prototype catalyst in the crossed intermolecular Tishchenko reaction



entry	x (mol%)	time (h)	yield of alcohol **355** (%)[a]	yield of ester **127** (%)[a]	*ee* of ester **127** (%)[c]
1	20	24	20	10[b]	N/D[c]
2	40	24	20	30[b]	N/D[c]
3	20	72	16	42[b]	N/D[c]
4	20	120	14	83	0
5	40	96	10	85	6

[a]Isolated by silica gel column chromatography. [b]Determined by ^{1}H NMR spectroscopy with reference to 2,5-diphenyl furan as internal standard. [c]Determined by CSP-HPLC analysis. [d]N/D: not determined.

2.1.3 Design and synthesis of functionalised BINOL-derived thiol precatalysts

The rationale for the design of the next generation of catalysts was simple: synthesise a diverse range of thiols so as to obtain the largest amount of data from the functional groups employed (Figure 2.2). Firstly, the commercially available cysteine derivative **356**, a chiral analogue of which *N*-acetylcystamine had previously been demonstrated to be a moderately effective catalyst for the crossed intermolecular Tishchenko reaction (**128**, Section 1.2.1.3). Secondly, the BINOL-derived thiol **(*S*)-357** containing a hydroxyl group which may be capable of hydrogen bonding also seemed worthy of investigation.[124] Thirdly, *O*-functionalised BINOL-derived thiols were also evaluated: **(*S*)-358** containing a benzyl group, thereby increasing steric bulk near the thiol; and **(*S*)-359**; a Lewis basic carbamoyl group with potential to bind the magnesium cation. The *bis*-thiol **360** showed promise as a precatalyst for the crossed-Tishchenko reaction; the reduced rings of which have been known to increase the angle between the two rings.[125] Finally, the 2,2'-phenyl-substituted *bis*-thiol

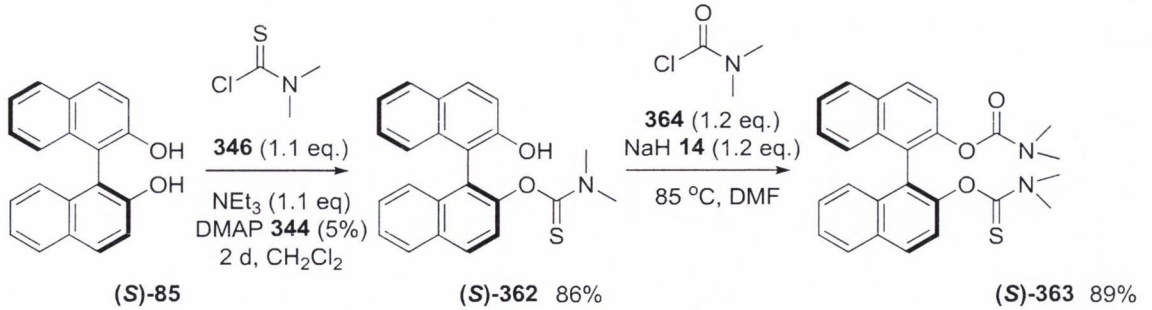
(*S*)-361, the steric bulk of which may provide more enantiocontrol.[126] It was at this point that Mr. F. Manoni was asked to synthesise (*S*)-360 and (*S*)-361, and as such, a report on their synthesis will not be commented on.

Figure 2.2 Prospective catalysts for asymmetric crossed intermolecular Tishchenko reaction

356 (*S*)-357 (*S*)-358 R = Bn (*S*)-359 R = $CON(Me)_2$ (*S*)-360 (*S*)-361

The *mono*-carbamoyl-functionalised BINOL derivative (*S*)-362 was generated in 86% yield from (*S*)-BINOL on stirring in *N*,*N*-dimethylthiocarbamoyl chloride (**346**), triethylamine and dichloromethane, with DMAP **344** as a nucleophilic catalyst (Scheme 2.6). Functionalisation of the free hydroxyl of (*S*)-362 using sodium hydride (**14**), *N*,*N*-dimethylcarbamoyl chloride (**364**) in DMF conditions, furnished the mixed carbamoyl-substituted BINOL derivative (*S*)-363 in 89% yield. It was found that the C-2' hydroxyl group needed to be protected, as it would impede the subsequent Newman-Kwart reaction.

Scheme 2.6 Synthesis of the carbamoyl-substituted BINOL derivative

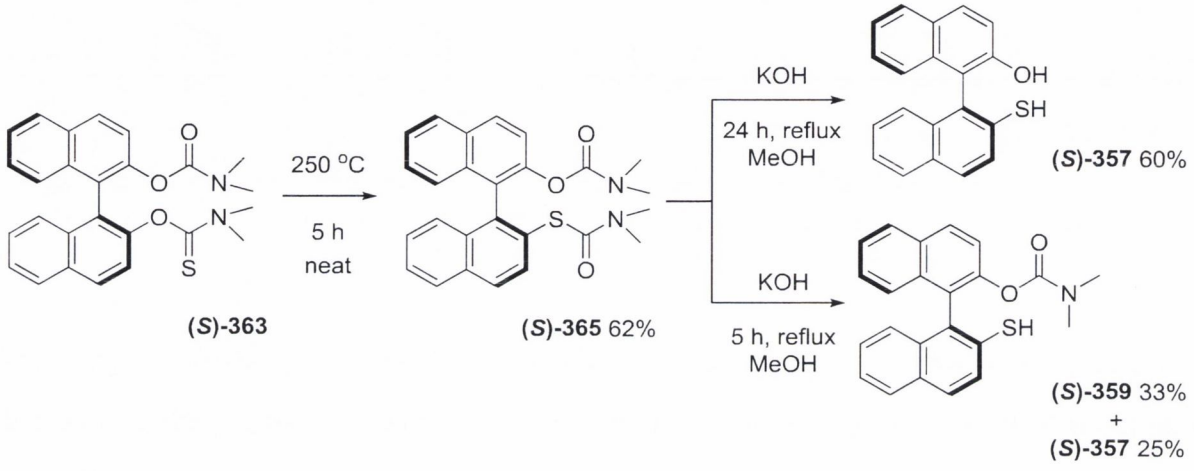


(*S*)-85 (*S*)-362 86% (*S*)-363 89%

Newman-Kwart thermal rearrangement of (*S*)-363 furnished the *S*,*O*-carbamoyl substituted BINOL (*S*)-365 (Scheme 2.7).[127] On treatment of this product with $LiAlH_4$ in THF under reflux, a black tar-like substance was obtained, from which the free-thiol compound (*S*)-357 could not be isolated either by recystallisation or flash chromatography. Smrčina *et al.* reported the cleavage of the carbamoyl groups using a KOH/methanol system, which furnished the free-thiol (*S*)-357 in 60% yield.[128] It was found that if (*S*)-365 was heated for 5

hours, the *O*-functionalised thiol **(*S*)-359** could be generated in 33% yield along with the *bis*-deprotected thiol **(*S*)-357** in 25% yield. Extension of the reaction time to 24 hours furnished the thiol **(*S*)-357** exclusively in 60 % yield.

Scheme 2.7 The Newman-Kwart reaction and subsequent carbamoyl removal *via* hydrolysis

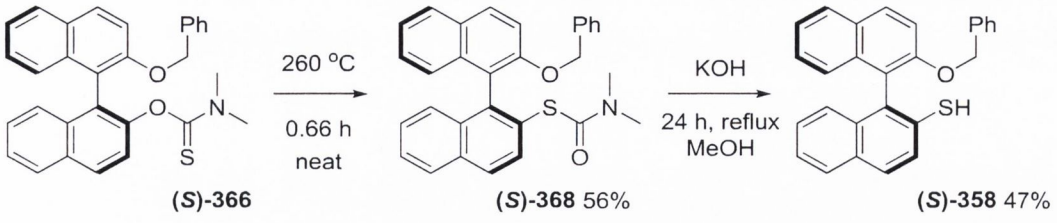


The *O*-benzyl thiol **(*S*)-358** was synthesised *via* a similar methodology: C-2' *O*-benzylation using sodium hydride **(14)** and benzyl bromide (**367**), furnished the thiocarbamoyl derivative **(*S*)-366** in 70% yield (Scheme 2.8).

Scheme 2.8 The benzylation of *mono*-thiocarbamoyl protected BINOL derivative **(*S*)-362**

The rapid thermal rearrangement of **(*S*)-366** furnished the Newman-Kwart product **(*S*)-368** in 56% yield. Subsequent hydrolysis furnished the *O*-benzyl-functionalised thiol **(*S*)-358** in 47% yield (Scheme 2.9).

Scheme 2.9 The Newman-Kwart reaction and subsequent hydrolysis of the carbamoyl moiety

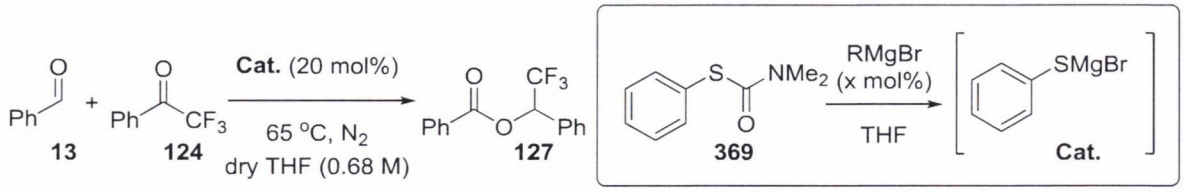


(*S*)-366 (*S*)-368 56% (*S*)-358 47%

2.1.4 A study on a tandem deprotection-Tishchenko reaction

As it was difficult to isolate the free thiols in acceptable yields and high purity (*i.e.* no disulphide impurities), we thought it prudent to probe the possibility of the *in situ* deprotection of the thiocarbamoyl functional group and subsequent Tishchenko reaction in one pot. For this we used a compound of known reactivity in the Tishchenko reaction, *i.e.* thiophenol, the bromomagnesium thiolate of which catalyses the production of the crossed-Tishchenko ester from the reaction of benzaldehyde (**13**) and 2,2,2-trifuoroacetophenone (**124**) under our standard conditions in 24 hours in 90% yield. Using conditions that would mimic the concentration of the thiolate catalysed Tishchenko reaction (0.68 M), we began evaluating the one pot deprotection-Tishchenko reaction (Table 2.2). It was found that PhMgBr deprotected **369** to generate the thiolate catalyst in 8 hours, under reflux conditions, but only when two equivalents were added (entries 1 and 2).

Table 2.2 The tandem one-pot deprotection-Tishchenko reaction



entry	R	x (mol %)	T (°C) deprotection	conv.[a]	yield **127** (%)[a]
1	Ph	20	80	50	N/D[b]
2	Ph	40	80	100	0
3	Ph	40	20	0	N/D[b]
4	Et	20	20	50	N/D[b]
5	Et	40	20	100	13

[a]Determined by ^{1}H NMR spectroscopy with reference to *E*-stilbene as internal standard. [b] N/D: not determined.

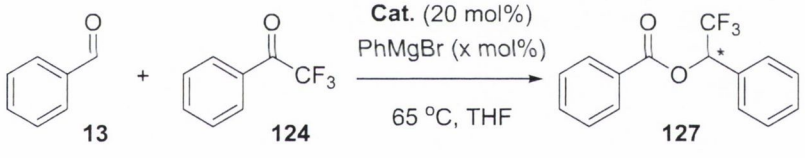
However, on addition of the aldehyde and ketone it was found that no ester was formed. Initially, this was attributed to air entering the reaction vessel and oxidising the thiol, as the reagents were added at just below reflux temperature. It was for this reason that room temperature deprotections were investigated. PhMgBr does not react with the protected thiol **369** at this temperature so a more reactive Grignard reagent was evaluated. Ethyl magnesiumbromide was found to cleave the carbamoyl group of the protected thiol **369** with two equivalents in twenty hours reaction time, however, on addition of benzaldehyde (**13**) and ketone **124**, very little of the Tishchenko ester product **127** was produced. It is likely therefore, that the product of the deprotection of **369** is inhibiting the Tishchenko reaction.

2.1.5 Evaluation of the functionalised BINOL-derived thiol precatalysts in the crossed Tishchenko reaction

On evaluation of the catalysts in the crossed Tishchenko reaction, it was found that none of the catalysts promoted the formation of the crossed ester **127** efficiently (Table 2.3). The

cysteine-derived thiol precatalyst **356** was found to be completely ineffective as a catalyst for the crossed-Tishchenko reaction (entry 1). The *mono*-deprotonated 2'-hydroxyl thiol **(*S*)-357** was also observed to be an ineffectual catalyst for the reaction (entry 2). However, it was found that the *bis*-deprotonated 2'-hydroxyl thiol **(*S*)-357** catalysed the formation of **127** in a paltry 5% yield (entry 3). The two *O*-functionalised thiol precatalysts **(*S*)-358** and **(*S*)-359** were found not to be catalysts for the crossed-Tishchenko reaction (entries 4 and 5). Interestingly, on formation of the thiolates of catalysts **(*S*)-358** and **(*S*)-359**, intense colours were observed: C-2' *O*-benzyl functionalised thiol **(*S*)-358** turned deep red/brown and C-2' *O*-(*N*,*N*-dimethylcarbamoyl) thiol **(*S*)-359** exhibited a dark green colour. As such, it is likely that there is a strong chelation of the magnesium metal ion in these cases, preventing thiolate addition to the aldehyde. The thiols that F. Manoni prepared were found to exhibit no activity in the promotion of the crossed Tishchenko reaction.

Table 2.3 Evaluation of functionalised enantioenriched thiols in the crossed Tishchenko reaction



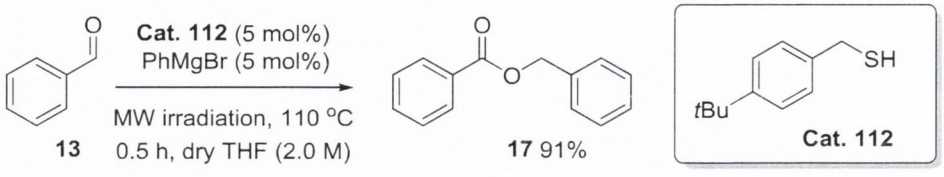
entry	catalyst	x (mol%)	time (h)	yield (%)[a]	*ee* (%)
1	**356**	20	24	0[b]	N/D[c]
2	**(*S*)-357**	20	24	0[b]	N/D[c]
3	**(*S*)-357**	40	48	5	0
4	**(*S*)-358**	20	24	0[b]	N/D[c]
5	**(*S*)-359**	20	24	0[b]	N/D[c]

[a]Isolated by silica gel column chromatography. [b]Determined by ^{1}H NMR spectroscopy with reference to *E*-stilbene as internal standard. [c]N/D: not determined.

2.2 The microwave accelerated Tishchenko reaction

One of the main drawbacks associated with the thiolate-catalysed Tishchenko chemistry discussed in Section 1.2.1 is the long reaction times required (sometimes up to 4 days for the more difficult substrates). For this reason considerable effort was exerted in an attempt to shorten these reaction times. Dr. Con O' Connor found that the disproportionation of benzaldehyde (**13**) to benzyl benzoate (**17**) could be performed in ten minutes in a 300W microwave in 70% yield at 0.68 M. On increasing the concentration of the reaction he found that the reaction proceeded to 91% yield (Scheme 2.10). Interestingly it was found that the catalyst loadings could be lowered to 5 mol%, a significant improvement over the 10 mol% required in the thermal reaction.

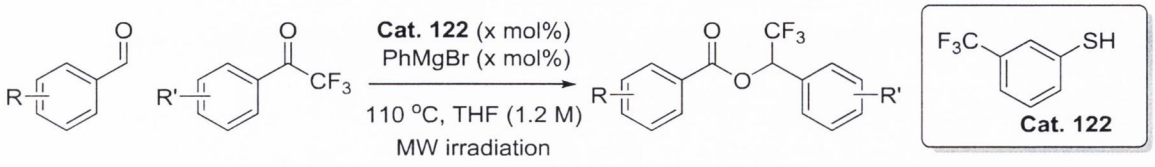
Scheme 2.10 Microwave accelerated thiolate catalysed disproportionation of benzaldehyde

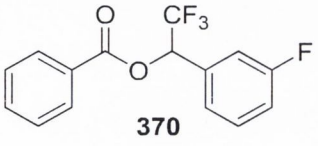
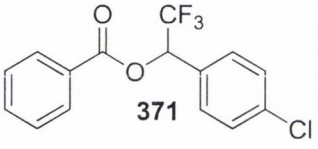
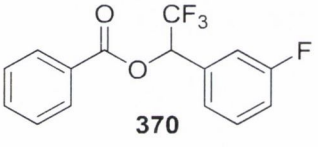
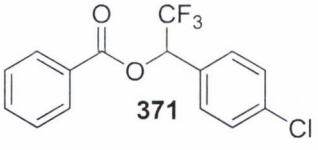
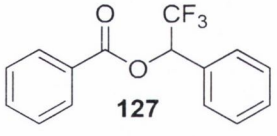
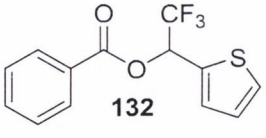
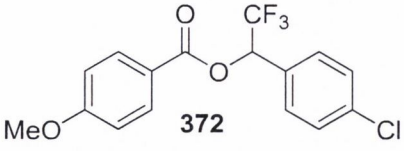
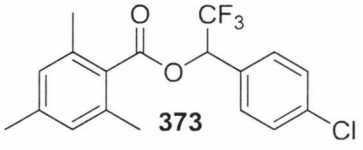


Evaluation of the crossed-intermolecular reaction was divided between F. Manoni and the author, of which only the reactions I performed will be discussed below.

We found that longer reaction times, relative to those required in the dimerisation of benzaldehyde, were required for the reaction to reach full conversion (entries 1 and 2, Table 2.4). Again, this is likely due to the rate-limiting acyl transfer step as relatively large concentrations of the reduced ketone were observed in these reactions. Increasing the reaction time to three hours furnished the products **370** and **371** in moderate to high yields (entries 3 and 4). Formation of the unfunctionalised crossed ester **127** in 82% yield was observed in 3 hours, however, when the heterocyclic thiophene-derived ketone was employed, the ester product **132** was generated in only 51% yield (entries 5 and 6).

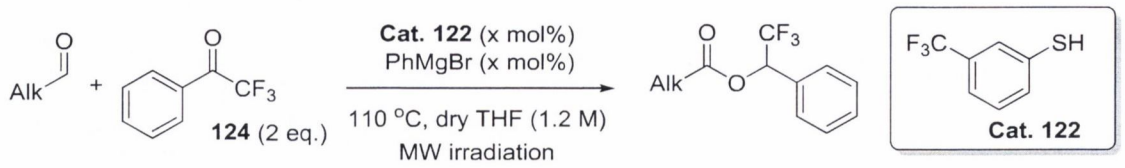
Table 2.4 Microwave accelerated crossed Tishchenko reaction

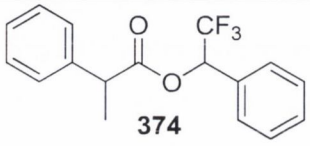
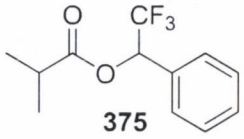
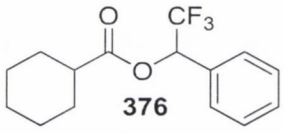
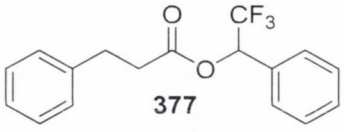


entry	product	x (mol %)	time (h)	yield (%)[a]
1	 **370**	10	2	30[b]
2	 **371**	20	2	72[b]
3	 **370**	20	3	63
4	 **371**	20	3	81
5	 **127**	20	3	82
6	 **132**	20	3	51[b]
7	 **372**	20	3	32[b]
8	 **373**	20	3	0[b]

[a]Isolated by silica gel column chromatography. [b]Determined by ^{1}H NMR spectroscopy with reference to *E*-stilbene as internal standard

Table 2.5 Microwave assisted crossed Tishchenko reaction with aliphatic aldehydes



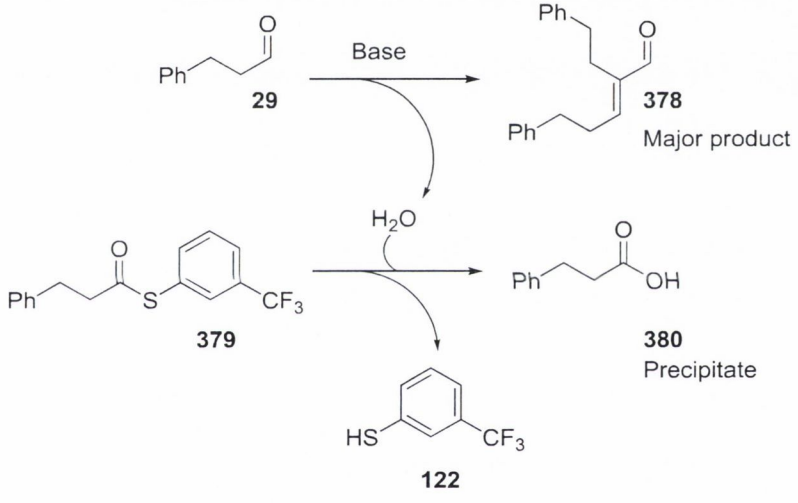
entry	product	x (mol%)	time (h)	yield (%)[a]
1	 **374**	20	3	34[b]
2	 **375**	20	3	34[c]
3[d]	 **376**	20	3	56
4	 **377**	20	3	0[b]

[a]Isolated by silica gel column chromatography. [b]Isolated as a 4:1 mixture of diastereomers. [c]Identified by ^{1}H NMR spectroscopy with reference to *E*-stilbene as internal standard. [d]Performed by F. Manoni.

Formation of the multi-functionalised crossed ester **372** was catalysed in low yield, likely due to the combined effect of the sluggish acyl transfer and the slower rate of addition of the thiolate catalyst to the relatively electron-rich *p*-methoxybenzaldehyde (entry 7). The highly sterically demanding 2,4,6-trimethylphenyl ester product **373** was impossible to form *via* this methodology (entry 8). F. Manoni demonstrated that 2-naphthyl and halogen-substituted aldehydes were amenable to this methodology. For the first time we were able to demonstrate the crossed Tishchenko reaction between an aliphatic aldehyde and the trifluoroketone **124** (Table 2.5). It was found that 2-substituted aliphatic aldehydes form crossed ester products **374 - 376** in low to moderate yields (entries 1 to 3). It appears that the aldol side reaction observed in the thermal thiolate mediated Tishchenko reaction is less problematic in the case of the microwave assisted methodology, thereby allowing the formation of crossed ester

products from secondary aliphatic aldehydes. However, α-unbranched aldehydes were found to be incompatible with this methodology, with the aldol condensation reaction predominating over the Tishchenko reaction. Having identified the α,β-unsaturated aldehyde **378** as the major product in the reaction by ^{1}H NMR spectroscopic analysis, it is probable that the formation of this product is responsible for the hydrolysis of the thioester **379** and subsequent formation of the carboxylic acid **380** (Scheme 2.11).[129,130] As the thiolate catalyst has been reprotonated, the Tishchenko reaction could not continue and the aldol condensation reaction would predominate.

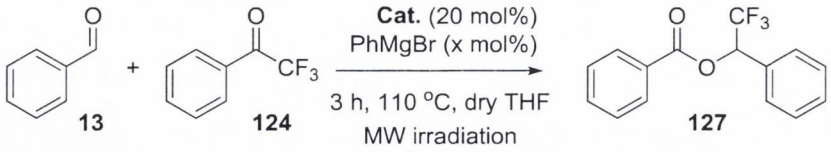
Scheme 2.11 Probable reaction mechanism of α-unbranched aldehydes in the crossed Tishchenko reaction



2.3 Evaluation of functionalised enantioenriched thiols in the microwave assisted Tishchenko reaction

As none of the chiral thiol catalysts exhibited satisfactory activity in catalysing the thermal crossed Tishchenko reaction, we became interested in the evaluation of the catalysts under the microwave accelerated conditions. The aliphatic cysteine-derived thiol **356** again proved to be inactive as a catalyst for the crossed Tishchenko reaction (entry 1, Table 2.6).

Table 2.6 Evaluation of enantioenriched thiol catalysts in the microwave assisted Tishchenko reaction



entry	**Cat.**	x (mol%)	conc. (M)	yield (%)[a]	*ee* (%)[c]
1	**356**	20	0.9	0[b]	N/D[d]
2	**(*S*)-357**	20	0.9	63	2
3	**(*S*)-357**	40	0.9	78	1
4	**(*S*)-358**	20	0.9	0[b]	N/D[d]
5	**(*S*)-359**	20	0.9	0[b]	N/D[d]
6	**(*S*)-357**	20	0.68	49	7
7	**(*S*)-357**	20	0.58	50	10
8	**(*S*)-357**	40	0.58	75	5
9	**(*S*)-357**	20	0.29	0[b]	N/D[d]
10	**(*S*)-357**[e]	100	0.1	0[b]	N/D[d]

[a]Isolated by silica gel column chromatography. [b]Determined by ^{1}H NMR spectroscopy with reference to *E*-stilbene as internal standard. [c]Determined by CSP-HPLC analysis. [d]N/D: not determined. [e]Performed with stoichiometric quantities of thiol precatalyst.

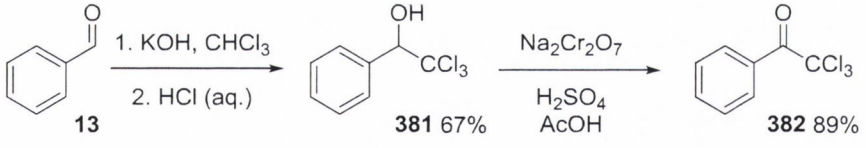
The C-2' hydroxyl BINOL-derived thiol **(*S*)-357** exhibited activity as a catalyst for the reaction though negligible *ee* was observed in the ester product **127** (entries 2 and 3). The C-2' *O*-functionalised BINOL-derived thiols **(*S*)-358** and **(*S*)-359** still proved to be completely inactive as catalysts for the crossed Tishchenko reaction (entries 4 and 5). We postulated that by lowering the concentration of the reactions catalysed by **(*S*)-357**, an increase in *ee* of the product might be observed. This proved correct: 0.68 M concentration furnished the product in 7% *ee*; while a 0.58 M concentration gave the product in an observed *ee* of 10%, a new

benchmark for this reaction (entries 6 and 7). The *bis*-deprotonated **(*S*)-357**-catalysed crossed Tishchenko reaction furnished the ester product **127** in higher yield but low *ee* (entry 8). Further lowering the concentration produced no product whatsoever (entry 9), and stoichiometric loadings of the catalyst at 0.1 M yielded no product (entry 10).

2.4 Synthesis and evaluation of the more sterically demanding 2,2,2-trichloroacetophenone in the crossed Tishchenko reaction.

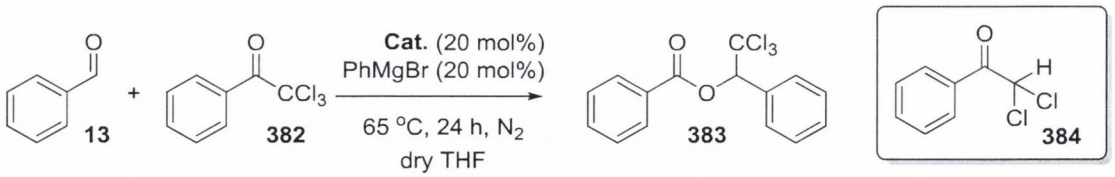
We postulated that the introduction of a more sterically demanding non-enolisable ketone, 2,2,2-trichloroacetophenone (**382**), which was synthesised in two steps from benzaldehyde (**13**) may produce a higher *ee* of crossed ester product (Scheme 2.12). The aldehyde was treated with chloroform and base, forming dichlorocarbene *in situ*, and a workup in aqueous HCl furnished alcohol **381** in 67% yield. Oxidation of this alcohol, using sodium dichromate in acid, produced the trichloroketone **382** in 89% yield.

Scheme 2.12 The synthesis of 2,2,2-trichloroacetophenone



On evaluation of the trichloroketone as a substrate for the Tishchenko reaction, it was found that, under standard thermal conditions, the crossed trichloroester product **383** was not formed, though a precipitate was observed (entries 1 and 2, Table 2.7). Interestingly, it was also noted that the trichloroalcohol intermediate **381** was not observed in the reactions, but a broad singlet was present at 6.85 ppm in the ^{1}H NMR spectrum of the crude reaction mixture.

Table 2.7 Evaluation of the trichloroketone as a hydride acceptor in the crossed Tishchenko reaction



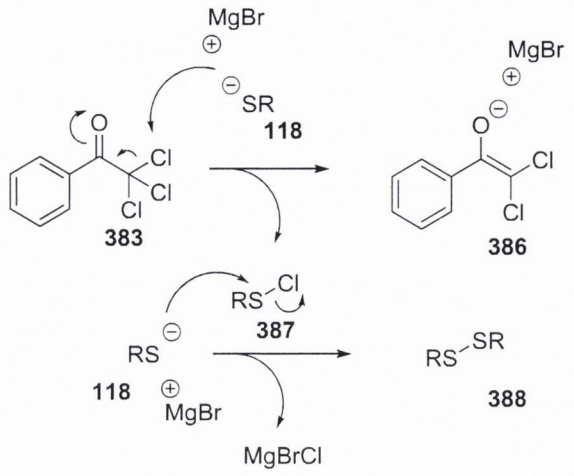
entry	**Cat.**	time (h)	yield **383** (%)[a]	yield **384** (%)[a]
1	$3\text{-}CF_3\text{-}C_6H_4SH$	24	0	7
2	C_6H_5SH	24	0	7
3	C_6H_5SH[b]	2	0	29

[a]Determined by ^1H NMR spectroscopy with reference to *E*-stilbene as internal standard. [b]Performed with stoichiometric quantities of thiolate catalyst.

The reaction performed at stoichiometric loading of thiolate catalyst furnished no product but the dechlorinated ketone **384** was identified as the major product by ^1H NMR spectroscopic analysis on quenching with acid (entry 3). A possible mechanism for the formation of this ketone product may be the attack of the thiolate **118** on the trichloro-moiety of the ketone **383** to furnish the enolate **386** (Scheme 2.13). This reaction could potentially generate the chlorinated intermediate **387** which would react rapidly with any remaining thiolate to yield the disulphide **388**. This would explain the absence of any benzyl benzoate, *via* the disproportionation reaction of benzaldehyde, in the crude product and the formation of the MgBrCl salt would explain the precipitate observed.

These results, coupled with the previous studies under thermal and microwave conditions, indicate that the use of chiral thiolate catalysts may not be the best solution for the production of enantioenriched crossed ester products. We therefore decided to try another approach that would not be as time consuming: the use of a chiral additive to the reaction.

Scheme 2.13 Possible mechanism for the formation of the dechlorinated ketone **384**

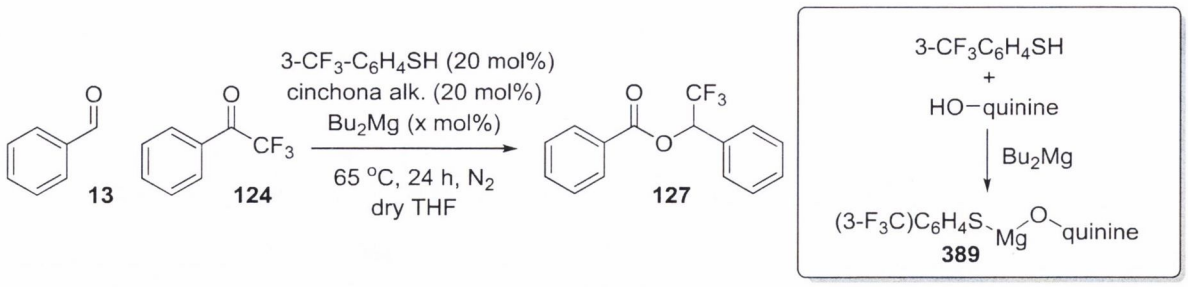


2.5 The incorporation of chiral alcohols into the thiolate catalysed crossed Tishchenko reaction

As previously mentioned, a readily available source of chirality is the natural product quinine (**233**) and its *pseudo*-enantiomer quinindine (**168**). We envisaged that if it was tethered to the magnesium ion chelating the catalyst, a degree of enantioselectivity may be observed. We hoped to accomplish this by the use of the dibasic Grignard reagent Bu_2Mg which would deprotonate the thiol and the C-9 alcohol functional group of quinine to furnish (to some degree) the mixed magnesium metal complex **389**.

A simple test to prove whether this type of catalyst would exhibit activity in the crossed reaction was performed using only the thiol and half an equivalent of Bu_2Mg to generate a *bis*-thiolate magnesium species. This *bis*-thiolate species proved to be as effect a catalyst as the magnesium bromide thiolate, furnishing the crossed ester product **127** in 91 % yield (entry 1, Table 2.8). Employment of the cinchona alkaloids in the reaction furnished the crossed ester product **127** in varying yields depending on the concentration used, though no asymmetric induction was observed in any case (entries 2 – 5).

Table 2.8 Evaluation of chiral auxiliaries in the crossed Tishchenko reaction



entry	cinchona alkaloid	x (mol %)	conc. (M)	yield (%)[a]	*ee* (%)[b]
1	-	10	0.68	91	N/A
2	quinine (**233**)	20	0.68	40	0
3	quinidine (**168**)	20	0.68	76	1
4	quinine (**233**)	20	1.0	42	0
5	quinidine (**168**)	20	1.0	73	0

[a]Isolated by silica gel column chromatography. [b]Determined by CSP-HPLC analysis.

2.6 Conclusion

In conclusion, we were able to achieve the first synthesis of enantioenriched crossed ester products using BINOL-derived thiols, though only low level of enantioselectivity was obtained.Further research on this topic was abandoned due to the low potential for success in achieving high enantioselectivity with this class of catalysts. In the case of the microwave accelerated Tishchenko reaction, the previously long reaction times were considerably shortened and the substrate scope of the crossed intermolecular reaction was extended to include aliphatic aldehydes. However, problems such as moderate product yields and a requirement for high catalyst loadings remained.

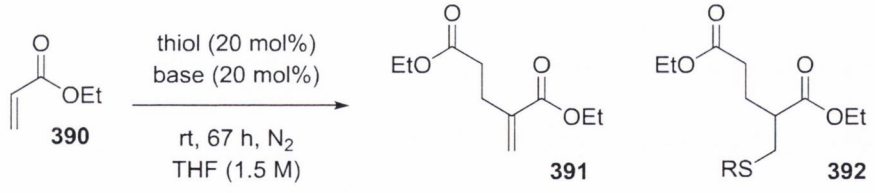
3.0 The use of thiols and selenols in the intermolecular Morita-Baylis-Hillman and Rauhut-Courier reactions

Inspired by the research conducted by Miller *et al.*, described in Section 1.3.4.1, we decided to use the knowledge we had gained through extensive research on the thiolate catalysed Tishchenko reaction on the intermolecular MBH and RC reactions. Thiolates seemed, in theory, to be optimum catalysts for these reactions as they are highly nucleophilic and are also classified as leaving groups in elimination chemistry.[131] We theorised that if the methodology could be perfected, substrates that are not amenable to other methodologies, such as β-substituted α,β-unsaturated esters, could be utilised.

3.1 Evaluation of thiolates in the intermolecular RC reaction

As a quick proof of concept study we chose the simple thiophenol **109** as precatalyst and varied the base employed to generate Table 3.1.

Table 3.1 Evaluation of thiolates in the intermolecular RC reaction



entry	thiol	base	yield **391** (%)[a]	yield **392** (%)[a]
1	C_6H_5SH **109**	NaH	10	10
2	C_6H_5SH **109**	KH	28	17
3	C_6H_5SH **109**	*t*BuOK	46	16
4	C_6H_5SH **109**	PhMgBr	0	16
5	C_6H_5SH **109**	CaH_2	0	19
6	$3\text{-}CF_3C_6H_4SH$ **122**	*t*BuOK	38	11

[a]Determined by ^1H NMR spectroscopy with reference to *E*-stilbene as internal standard.

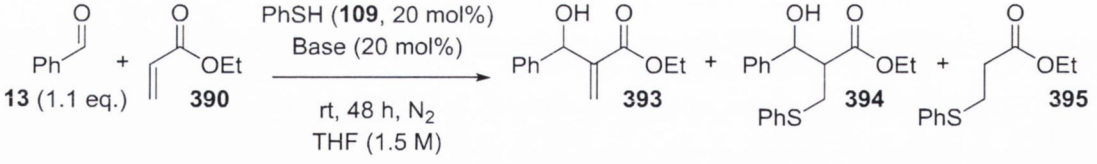
It was found that the alkali metal hydrides furnished the RC product **391** in 10% yield in the case of sodium hydride and 28% yield in the instance of potassium hydride (entries 1 and 2). On employment of potassium *tert*-butoxide as the base the RC product **391** was formed in 46% yield (entry 3). Interestingly the alkali earth metal counterions furnished the RC adduct **392** exclusively, with no elimination of the thiolate occurring (entries 4 and 5).

Theorising that the elimination of the thiolate may be rate limiting, as is the case in other methodologies (see Section 1.3.4), the optimum thiol for the crossed Tishchenko reaction, thiol **122** was employed as catalyst, however, lower yield of RC product **391** was obtained in this reaction (entry 6). Inspired by these results, we decided to focus on the more synthetically useful MBH reaction.

3.2 Evaluation of thiolates in the intermolecular MBH reaction

Using the same reaction conditions as those employed in the RC reaction, thiophenol was evaluated as a catalyst for the intermolecular MBH reaction between ethyl acrylate (**390**) and benzaldehyde (**13**).

Table 3.2 Evaluation of catalytic thiophenolate anions in the intermolecular MBH reaction



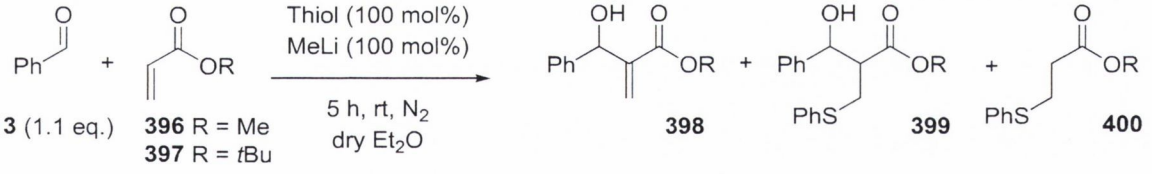
entry	base	yield **393** (%)[a]	yield **394** (%)[a]	yield **395** (%)[a]
1	NaH	0	7	6
2	KH	6	5	17
3	*t*BuOK	6	6	20
4	PhMgBr	0	10	3
5	CaH_2	0	0	20

[a]Determined by ^{1}H NMR spectroscopy with reference to *E*-stilbene as internal standard.

The sodium counterion furnished the MBH adduct **394** in a paltry 7% yield but no MBH product **393** was detected (entry 1, Table 3.2). The potassium counterion proved to be better but still only 6% of the MBH product **393** was observed in each case (entries 2 and 3). The magnesiumbromide counterion furnished the MBH adduct **394** in 10% yield but again without any MBH product **393** detectable (entry 4). Finally the calcium counterion furnished the 1,4-conjugate addition product **395** exclusively in 20% yield (entry 5).

To gain a greater insight into the reaction, more specifically, the lack of formation of the adduct which should ideally be forming in 20% yield (*i.e.* the amount of catalyst employed), a stoichiometric evaluation of multiple thiolates was performed on the MBH reaction. We hypothesised that as the thiolate is highly nucleophilic, some of the acrylate may be polymerising, forming RC-type products. As such we decided to appraise an acrylate that would readily self-polymerise, methyl acrylate (**396**), and an acrylate whose self-polymerisation would be less favoured, *t*-butyl acrylate (**397**).

Table 3.3 Evaluation of thiolates under stoichiometric conditions in the intermolecular MBH reaction



entry	thiol	R	conv. (%)[ab]	yield **398** (%)[a]	yield **399** (%)[a]
1	C_6H_5SH **109**	Me	98	0	71
2	3-CF_3-C_6H_4SH **122**	Me	100	0	49
3	3,5-CF_3-C_6H_3SH **401**	Me	100	0	20
4	C_6H_5SH **109**	*t*Bu	99	0	95
5	3-CF_3-C_6H_4SH **122**	*t*Bu	64	0	48
6	3,5-CF_3-C_6H_3SH **401**	*t*Bu	85	0	50

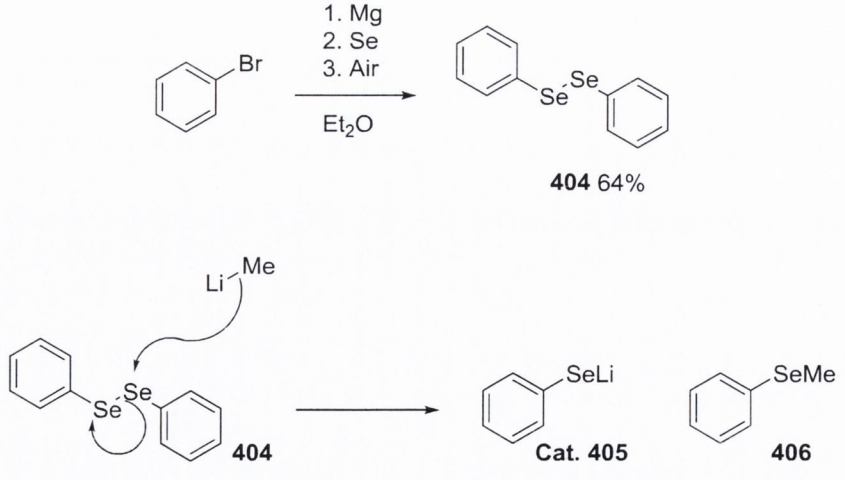
[a]Identified by ^1H NMR spectroscopy with reference to *E*-stilbene as internal standard. [b]Relative to the consumption of acrylate.

As expected, methyl acrylate (**396**) formed low to moderate yields of MBH adduct (entries 1 – 3, Table 3.3). All three reactions with this acrylate consumed the Michael acceptor, but not all of the acrylate was converted to product, making our earlier hypothesis plausible. It appears that polymerisation of the acrylate is favoured using more electron-deficient thiophenolates, with the MBH adduct forming in only 20% yield using the highly electron-deficient thiol 3,5-*bis*-CF_3-C_6H_3SH **401**. Conversely, the bulky acrylate **397** formed the MBH adduct **399** in near quantitative yield when thiophenol (**109**) was employed as the precatalyst. The electron-deficient thiol **122** furnished the MBH adduct **399** in 48% yield, with the remaining conversion percentage being accounted for in the formation of the 1,4-conjugate addition product **400**. Finally the highly electron-deficient thiol **401** formed the adduct **399** in 50 % yield, though some polymerisation was observed.

3.3 Evaluation of selenide ions in the intermolecular MBH reaction

As selenide ions act similarly to thiolate ions, being both highly nucleophilic and being effective leaving groups in elimination chemistry,[132] we proposed that they might be efficient catalysts for the intermolecular MBH reaction.

Scheme 3.1 Synthesis of diphenyl diselenide and subsequent *in situ* formation of lithium phenyl selenide-ion catalyst

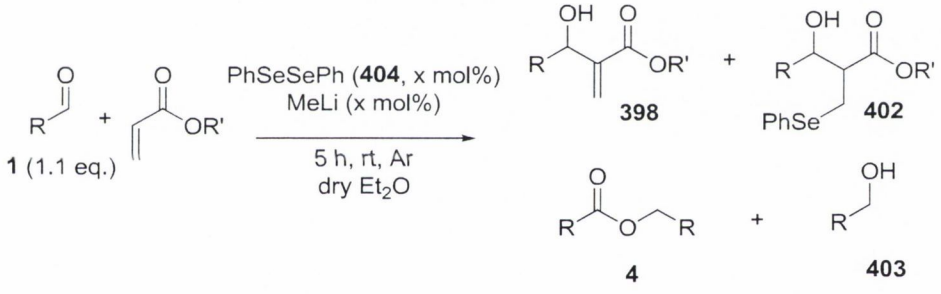


The diphenyl diselenide precatalyst **404** was synthesised in 64% yield *via* the formation of phenylmagnesium bromide, subsequent nucleophilic addition to molecular selenium and oxidation of the produced magnesium bromide phenylselenide-ion by bubbling air through the solution overnight (Scheme 3.1).[133] The lithium selenide catalyst **Cat. 405** is generated

prior to the reaction by the S_N2 cleavage of the diselenide **404** which forms the phenyl methyl selenide **406** as a side product.[134]

On evaluation of the lithium selenide **Cat. 405** using the three previously employed acrylates under stoichiometric conditions, it was found that the MBH adduct **402** was afforded in low to moderate yields and in the cases of ethyl and *tert*-butyl acrylate some MBH product **398** was observed (entries 1 – 3, Table 3.4). Examination of the ^{1}H NMR spectra of these reactions gave further insight into the reason why such low yields of MBH adduct **402** were formed. It was found that varying levels of benzyl alcohol and benzyl benzoate were present, likely formed *via* a Tishchenko-type reaction at room temperature; an observation which had never been noted in the bromomagnesium thiolate catalysed Tishchenko chemistry.

Table 3.4 Evaluation of selenide-ion-derived catalysts in the intermolecular MBH reaction



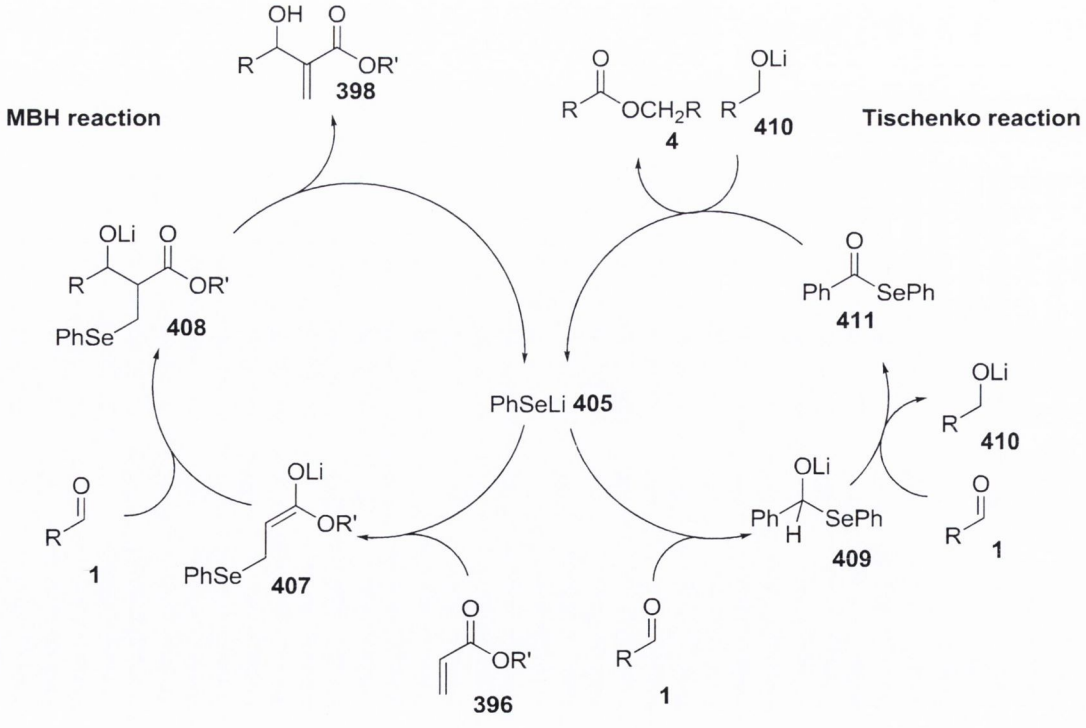
entry	x	R	R'	yield **398** (%)[a]	yield **402** (%)[a]	yield **14** (%)[a]	yield **403** (%)[a]
1	100	C_6H_5	*t*Bu	10	40	0	0
2	100	C_6H_5	Et	8	35	9	27
3	100	C_6H_5	Me	0	54	5	30
4	20	C_6H_5	*t*Bu	5	9	11	10
5	20	3-NO_2-C_6H_4	Et	0	0	15	21
6[b]	20	C_6H_5	Et	0	0	0	0

[a]Determined by ^{1}H NMR spectroscopy with reference to *E*-stilbene as internal standard. [b]Performed in the presence of MeOH (20 eq.).

On assessment of the lithium selenide catalyst at catalytic loading, it was found that when *tert*-butyl acrylate was employed together with benzaldehyde, all four of the products were observed in low yields (entry 4). However, when a highly electron-deficient aldehyde was used, only the Tishchenko products were observed (entry 5). We hypothesised that the addition of a protic additive (*i.e.* methanol) would supress the Tishchenko reaction and increase the rate of the MBH reaction, as the Tishchenko reaction cannot proceed in protic solvents and protic solvents have been shown to be beneficial in the MBH reaction (see Section 1.3.1). This proved inaccurate however, as the addition of methanol suppressed all catalytic activity (entry 6).

Based on these findings, we theorised that a catalytic cycle such as that depicted in Scheme 3.1 must be occurring. The lithium selenide **Cat. 405**, being immensely nucleophilic, attacks the most electrophilic carbon. This is highly evident in the case of 3-nitrobenzaldehyde, the use of which only led to the formation of Tishchenko products in the presence of the lithium selenide catalyst.

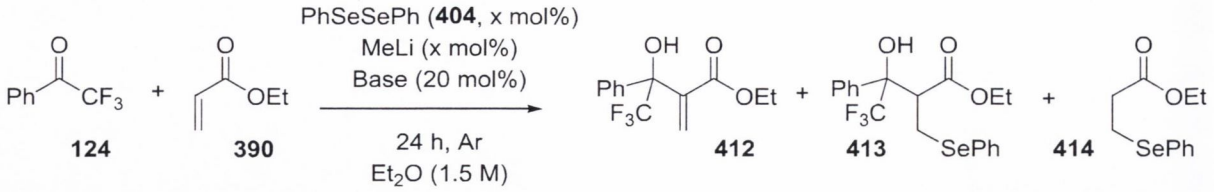
Scheme 3.1 Proposed catalytic pathway for the selenide-ion-catalysed Tishchenko and MBH reactions.



As two completing reactions are occurring in the presence of **Cat. 405**, it would be difficult to control either one under these conditions. Therefore, it was decided that the two reactions should be studied independently of one another; the selenide-ion-mediated Tishchenko reaction will be discussed further in Section 4.1.

As the presence of aldehyde functional groups appeared to promote the Tishchenko reaction, in competition with the MBH reaction, we theorised that replacing this with a carbonyl functional group that was not capable of undergoing a hydride transfer reaction would allow the further study of the selenide-ion-mediated MBH reaction. Therefore it was decided to evaluated the reaction employing 2,2,2-trifluoroacetophenone (**124**) in place of benzaldehyde. This trifluoroketone was chosen for its high electrophilicity, as demonstrated by its utility in the crossed-Tishchenko reaction. On evaluation of the lithium phenylselenide **Cat. 405** catalysed MBH reaction between ethyl acrylate (**390**) and 2,2,2-trifluoroacetophenone (**124**) it was found that, under stoichiometric conditions, the MBH adduct **413** was formed in 91% yield (entry 1, Table 3.5). Under sub-stoichiometric catalytic conditions however, only low yields of the 1,4-conjugate addition product **414** were observed (entries 2 and 3).

Table 3.5 Evaluation of 2,2,2-trifluoroacetophenone as an aldehyde equivalent in the intermolecular MBH reaction



entry	x	base	yield **412** (%)[a]	yield **413** (%)	yield **414** (%)[a]
1	100	-	0	91	0
2	20	-	0	0[a]	14
3	40	-	0	0[a]	35
4	50	K_2CO_3	0	0[a]	46
5	50	P_2	0	9[a]	36

[a]Determined by ^{1}H NMR spectroscopy with reference to *E*-stilbene as internal standard. [b]Isolated by silica gel column chromatography

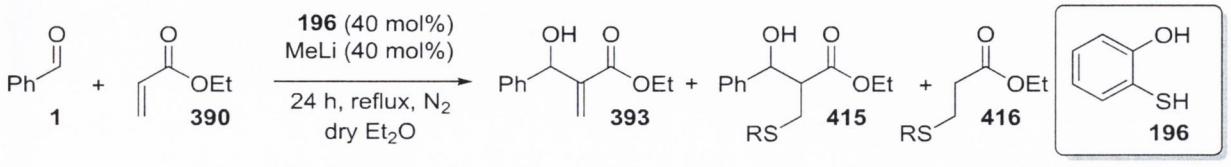
As no MBH product **412** was observed in any case, we theorised that the elimination reaction may be hindered by the steric bulk of the alcohol moiety, therefore we decided to use a catalytic amount of base to assist in this step. When potassium carbonate was employed, only the 1,4-conjugate addition product **414** was observed (entry 4). The the use of phosphazene base furnished both the 1,4-conjugate addition product **414** and the MBH adduct **413**, but no MBH product (*i.e.* **412**) was observed (entry 5).

3.4 Evaluation of the 2-hydroxythiophenol as a precatalyst for the intermolecular MBH reaction

It was decided that we should evaluate the 2-hydroxythiophenol precatalyst (**196**) that Miller *et al.* reported previously for the intramolecular MBH reaction (see Section 1.3.4.1) under our conditions. On evaluation of the lithium conjugate base of thiol **196**, the MBH product **393** was observed to form in 3% yield (entry 1, Table 3.6). Increasing the concentration of the

reaction did not furnish the MBH product **393**, however, the MBH adduct **415** and 1,4-conjugate addition product **416** were observed in 15 and 21% yield respectively (entry 2).

Table 3.6 Evaluation of 2-hydroxylthiophenol as a catalyst for the intermolecular MBH reaction



entry	conc. (M)	yield **393** (%)[a]	yield **415** (%)[a]	yield **416** (%)[a]
1	0.58	3	11	33
2	1.2	0	15	21

[a]Determined by ^{1}H NMR spectroscopy with reference to *E*-stilbene as internal standard.

3.5 Conclusion

In conclusion, we have found that the thiolate-catalysed MBH reaction showed little promise in becoming an efficient, synthetically useful protocol, due to poor overall yields of the MBH adduct obtained from the reactions. Though efficient formation of the MBH adduct could be attained, it was most likely the elimination step to form the MBH product and regenerate the catalyst that was rate-determining. Considerable efforts to increase the rate of this step were exerted to no avail, including: introduction of protic solvents and electron deficient aldehydes; the use of external bases to promote an E2 elimination reaction; and evaluating multiple acrylate esters.

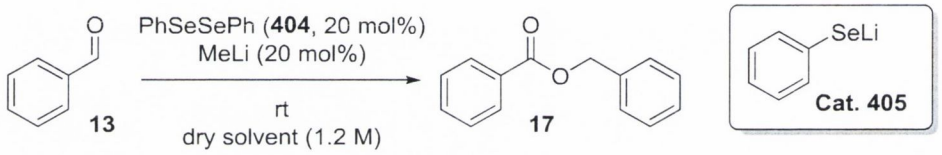
The discovery of the selenide-ion-catalysed Tishchenko reaction proved interesting, further optimisation of which will be discussed in the following section.

4.0 The selenide-ion catalysed Tishchenko reaction

4.1 Optimisation of catalytic conditions for the disproportionation of benzaldehyde

Continuing on from the discovery of the room temperature, selenide-ion catalysed Tishchenko reaction discussed in Section 3.3, it was attempted to optimise the reaction conditions, using the disproportionation of benzaldehyde as a starting point. Initial evaluation with commercial anhydrous ether solvent furnished the ester product **17** in 46% yield (entry 1, Table 4.1).

Table 4.1 Optimisation of the reaction conditions for the lithium selenide-ion-catalysed Tishchenko reaction



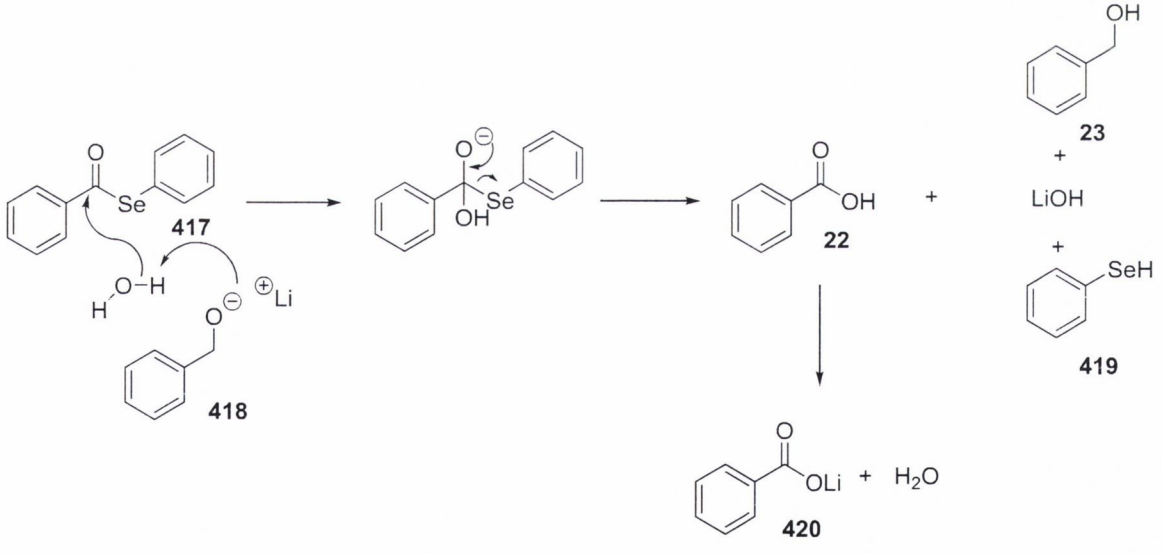
entry	additive (20 mol%)	conditions	solvent	time (h)	yield ester **17** (%)[a]
1	-	Ar balloon	Et_2O	18	46
2	**DMAP**	Ar balloon	Et_2O	18	45
3	-	Ar balloon	Et_2O	36	40
4	-	Ar balloon	THF	18	4
5	-	Ar balloon	Et_2O (degassed)	18	15
6	-	Schlenk, Ar	Et_2O	24	31
7	**DMAP**	Schlenk, Ar	Et_2O	24	54
8	-	Schlenk, Ar	Et_2O	48	46
9	**DMAP**	Schlenk, Ar	Et_2O	48	60

[a]Determined by ^{1}H NMR spectroscopy with reference to *E*-stilbene as internal standard.

Neither incorporation of the acyl transfer catalyst DMAP into the reaction or increasing the reaction time resulted in an augmented yield of benzyl benzoate (**17**) obtained (entries 2 and 3).[135] A change of solvent to THF, distilled over sodium/benzophenone, produced the ester in a paltry 4% yield (entry 4). Theorising that oxygen content may be a factor detrimental to catalytic activity (by oxidising the catalyst to the diselenide precatalyst **404**), we decided to use a sample of degassed, commercially dried diethyl ether solvent, however; only 15% of ester was formed (entry 5).

As no selenoester **417** was observed by ^{1}H NMR spectroscopic analysis, we theorised that water may be present in the reaction, which would cleave the highly electrophilic[136] selenoester into benzoic acid (**22**), benzyl alcohol (**23**) and selenophenol (**419**) (Scheme 4.1). This theory is supported by the observation of the formation of lithium benzoate (**420**) precipitate in all of reactions summarised in Table 4.1.

Scheme 4.1 Plausible mechanism for the hydrolysis of the selenoester intermediate

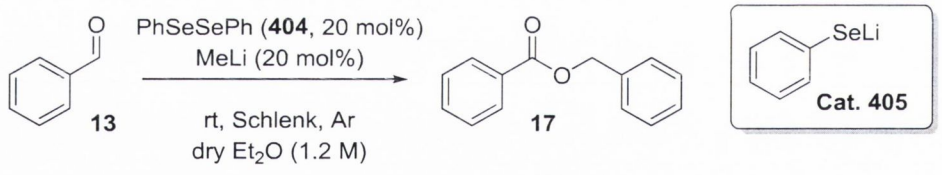


To test this hypothesis, it was decided to perform the lithium selenide ion catalysed Tishchenko reaction under Schlenk tube conditions, *i.e.* flame dried tube evacuated under vacuum and refilled with argon repeatedly prior to the reaction, which was performed under an argon bubbler. Under these conditions it was found that a low yield of ester product **17** was observed (entry 6, Table 4.1). Incorporation of DMAP into an identical reaction performed in parallel furnished benzyl benzoate (**17**) in an augmented yield of 54% (entry 7). Increasing the reaction times, however, did not furnish the ester dimer **17** in significantly

better yields (entries 8 and 9). It was noted that the selenoester **417** was still absent from the crude ^{1}H NMR spectra of the reactions performed under Schlenk conditions, indicating that the catalyst was being degraded prematurely.

Continuing in the same vein, we began focusing on the elimination of adventitious water from the reaction. It has been previously reported that the storage of solvent over activated molecular sieves (M.S.) has had a marked effect of the water content of the solvent, with the 3Å pore size being optimum for water removal.[137] A comparison with the previously employed commercially dried solvent demonstrated a clear superiority in water content suppression, with the ester product being furnished in 67% yield (entries 1 and 2, Table 4.2). Incorporation of 3Å molecular sieves into the reaction produced the ester **17** in very slightly raised yield, but addition of the acyl transfer catalyst, DMAP, did not increase the yield observed (entries 3 and 4).

Table 4.2 Evaluation of solvent drying methods on the lithium selenide-ion-catalysed Tishchenko reaction



entry	solvent drying method	additive	time (h)	yield ester **17** (%)[a]
1	commercial	-	24	35
2	3Å M.S.	-	24	67
3	3Å M.S.	3Å M.S.	24	68
4	3Å M.S.	**DMAP** (20 mol%)	24	66

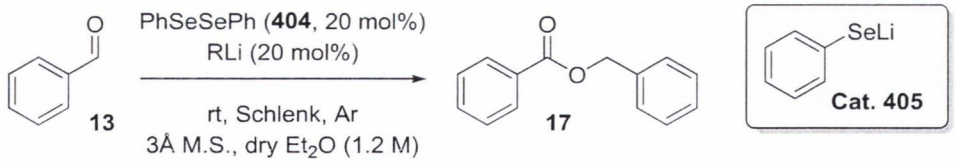
[a]Determined by ^{1}H NMR spectroscopy with reference to *E*-stilbene as internal standard.

Until this point the same bottle of methyl lithium was being used, and we began noting that increasingly depreciable yields of ester product **17** were being formed. Having eliminated water from the reaction, utilising activated 3Å molecular sieves from this point on as the standard for solvent drying, we decided to evaluate an old bottle of methyl lithium against a

new, previously unopened bottle. The difference in yield of product obtained between each reaction was determined to be 42% (entries 1 and 2, Table 4.3).

Upon comparison with a bottle of butyl lithium that was previously opened once, showed a similar, though not as drastic, difference in the yield of ester formed (entries 3 and 4). The most plausible explanation for this decrease in activity is the lithium hydroxide content of the alkyl lithium, the amount of which increases with each use of the reagent through the introduction of water. In normal alkyl lithium chemistry this content usually does not affect the reaction, except stoichiometry, as the alkyl lithium base is several orders of magnitude more basic/nucleophilic than the hydroxide.[138] However, as previously discussed, it can have a detrimental effect on the selenide-ion catalysed Tishchenko reaction as it can hydrolyse the selenoester and interrupt the catalytic cycle. We theorised that the solvent the alkyl lithium is stored in may have a direct relationship with the lithium hydroxide content, with more polar solvents containing a larger content of hydroxide ions, thereby forming lower yields of Tishchenko ester product.

Table 4.3 Evaluation of new and old bottles of commercial alkyl lithium bases for the formation of the lithium selenide catalyst



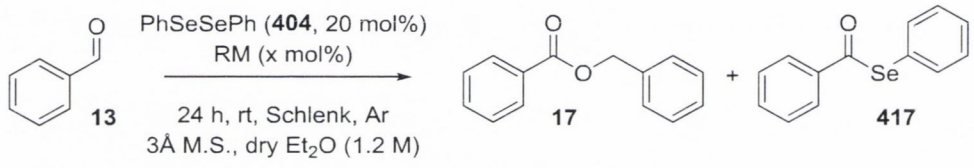
entry	RLi	additive (20 mol%)	time (h)	yield ester **17** (%)[a]
1	MeLi (Et_2O)	-	24	18
2	MeLi[b] (Et_2O)	-	24	60
3	*n*BuLi (*n*-hexane)	-	24	33
4	*n*BuLi (*n*-hexane)	**DMAP**	24	41

[a]Determined by ^{1}H NMR spectroscopy with reference to *E*-stilbene as internal standard. [b]New bottle

Evaluation of the lithium hydroxide content of the alkyl lithium species was performed and assessed by observing the yield of ester **17** and selenoester **417** observable in the ^{1}H NMR

spectra of the reaction crude. The reaction utilising *n*-butyllithium in hexanes formed the ester product **17** in 38% yield, with observable selenoester **417** (entry 1, Table 4.4). The employment of *sec*-butyllithium in cyclohexane and phenyllithium in dibutylether led to the formation of the benzyl benzoate (**17**) in lower yields (entries 2 and 3). The less basic lithium phenylacetylide solution in THF furnished the product in 44%, an increase which we attributed to the lower basicity of the anion, leading to a lower hydroxide content in the solution (entry 4). The use of the commercially available lithium triethylborohydride in THF produced only trace amounts of the ester product **17**, however, for the first time, we were able to identify the selenoester **417** in the ^{1}H NMR spectrum of the reaction crude (entry 5).

Table 4.4 Evaluation of previously unopened alkyl lithium species in the selenide-ion catalysed Tishchenko reaction



entry	RM	x (mol%)	yield ester **17** (%)[a]	yield ester **417** (%)[a]
1	*n*BuLi (*n*-hexane)	20	38	0
2	*sec*-BuLi (*c*-hexane)	20	32	0
3	PhLi (Bu_2O)	20	24	0
4	PhC_2Li (THF)	20	44	0
5	$LiBEt_3H$ (THF)	40	2	20
6	*i*PrMgCl (Et_2O)	20	11	21
7	Bu_2Mg (*n*-heptane)	10	62	18

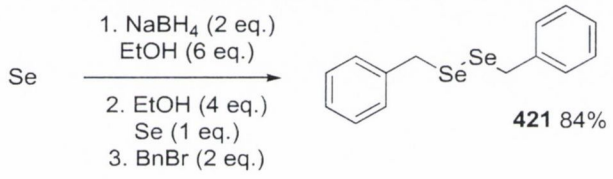
[a]Determined by ^{1}H NMR spectroscopy with reference to *E*-stilbene as internal standard.

Swapping the lithium counterion for the magnesium ion previously employed in the thiolate catalysed Tishchenko methodology furnished the ester product **17** in 11% yield and the selenoester **417** in 21% yield (entry 6). Use of the dibutylmagnesium in heptane produced the ester in 62% yield but also the selenoester **417** was present in 18% yield (entry 7). This

represents the highest yields of both benzyl benzoate (**17**) and selenoester **417** to be observed using this methodology, which indicates that this may be the optimum base for formation of the selenide-ion catalyst.

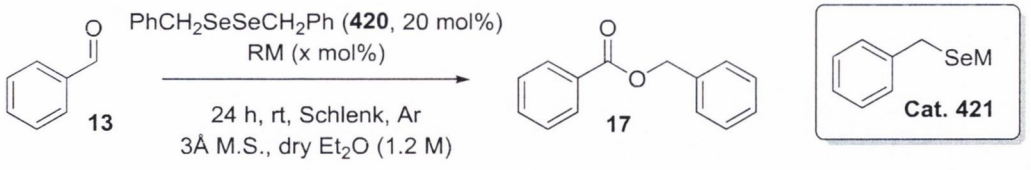
We speculated that the changes which were found to be efficacious in the corresponding thiolate-mediated reactions would be sensible modifications to attempt in the selenide-ion-catalysed reactions. In which case, a benzyl-derived selenide-ion would be the optimum catalyst for the disproportionation of aldehydes. The corresponding precatalyst, dibenzyl diselenide (**421**) was formed, *via* a literature methodology, in 84% yield (Scheme 4.2).[139]

Scheme 4.2 Synthesis of dibenzyl diselenide



Evaluation of the dibenzyl diselenide precatalyst under the optimum dry conditions (3Å molecular sieves) with lithium phenylacetylide as the deprotection agent, gave 34% yield of ester product **17** (entries 1, Table 4.5).

Table 4.5 Evaluation of dibenzyl diselenide as a precatalyst for the disproportionation of benzaldehyde



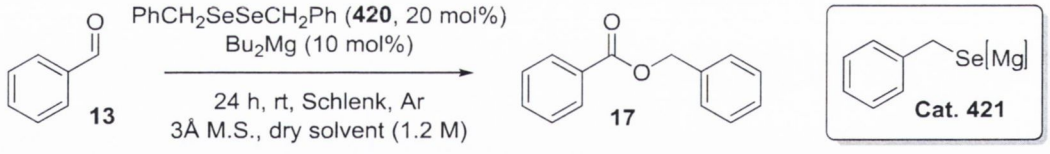
entry	additive (20 mol%)	RM	x (mol%)	yield ester **17** (%)[a]
1	-	PhC_2Li	20	34
2	**DMAP**	PhC_2Li	20	25
3	-	Bu_2Mg	10	84
4	**DMAP**	Bu_2Mg	10	84

[a]Determined by ^{1}H NMR spectroscopy with reference to *E*-stilbene as internal standard.

Enigmatically, it was found that in the presence of the DMAP additive only 25% yield was obtained (entry 2). Evaluation with the dibasic di-*n*-butyl magnesium (*i.e.* only requires half an equivalent to generate 1 equivalent of catalyst) as the deprotection agent, benzyl benzoate was furnished in 84% yield in both the presence and absence of DMAP (entries 3 and 4).

A repeat of the selenide-ion catalysed Tishchenko reaction in ether furnished the ester **17** in the same yield observed previously, (*i.e.* 84%), which demonstrates the robustness of the methodology utilising the magnesium counterion (entry 1, Table 4.6). We attributed this to the insolubility of $Mg(OH)_2$ in heptane; a theory that is supported by the salt that develops in the bottom of the bottle over time. Ongoing utilisation of this salt containing solution incurs no depreciation in yield of the ester product. The use of dry *t*-butyl methyl ether as solvent allowed the formation of benzyl benzoate (**17**) in 90% yield (entry 2). Employment of dry THF as the solvent for the magnesium selenide-ion catalysed Tishchenko reaction allowed the product **17** to be formed in quantitative yield (entry 3).

Table 4.6 Evaluation of different dry solvents for the magnesium selenide-ion catalysed Tishchenko reaction



entry	solvent	yield ester **17** (%)[a]
1	Et_2O	84[b]
2	*t*BuOMe	90[b]
3	THF	99

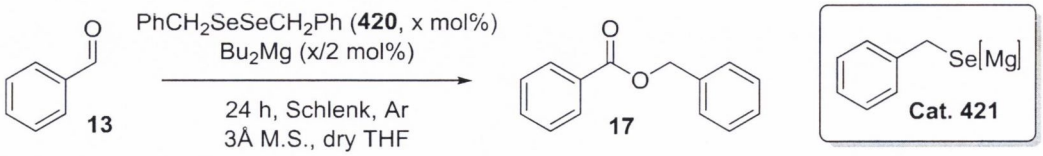
[a]Isolated by column chromatography. [b]Determined by ^1H NMR spectroscopy with reference to *E*-stilbene as internal standard.

We theorised that the magnesium selenide-ion should be more nucleophilic than the corresponding thiolate anion, as the negative charge is held within a higher energy p orbital; the 4p orbital. This would explain the increased rate of the hydride transfer reaction and also its occurance at room temperature. Also the increased leaving group ability of the selenide-ion should allow a more efficient acyl-transfer reaction to regenerate the catalyst. As such,

these catalysts should be capable of more efficient catalysis, promoting the reaction at lower loadings than the bromomagnesium thiolate-catalysed methodology, whose catalytic loadings at their lowest were 10 mol%.

Initially decreasing the loading of the selenide to 10 mol% at a standard controllable temperature of 25 °C furnished the product **17** in only 6% yield (entry 1, Table 4.7). An identical experiment run in parallel with the DMAP additive afforded the product in the slightly higher yield of 19% (entry 2). As expected, further decreasing these loadings to 5 mol% produced the product **17** in lower yields in the presence and absence of DMAP (entries 3 and 4). Evaluation of the reaction at 10 mol% catalyst loading in THF at reflux furnished the ester product in 42% yield (entry 5). As expected from the previous examples, further lowering of the catalyst loading to 5 mol% gave a much depreciated yield of ester (entry 6). Up until this point we had assumed, to our detriment, that the catalyst was acting independently of concentration, *i.e.* previously we had halved the amount of catalyst added, effectively halving the concentration with respect to the catalyst. However, if the catalyst is concentration dependant then this would have a marked effect on the catalyst activity, which is what was observed (entries 1 to 6, Table 4.7). Acting on this theory, the reaction was performed under the exact same conditions as those of entry 3, Table 4.6, except that two equivalents of aldehyde substrate were introduced (effectively halving the catalyst loading to 10 mol%) and gratifyingly it was found that benzyl benzoate (**17**) was formed in 94% isolated yield (entry 7). Employment of four equivalents of aldehyde (effectively 5 mol% catalyst) produced the product **17** in exactly the same isolated yield, (94%, entry 8).

Table 4.7 Evaluation of lower loadings of the selenide-ion catalyst



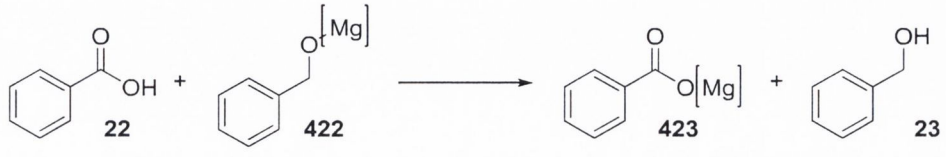
entry	x (mol%)	additive (20 mol%)	conc. of **13** (M)	temperature (°C)	yield ester **17** (%)[a]
1	10	-	1.2	25	6[b]
2	10	**DMAP**	1.2	25	19[b]
3	5	-	1.2	25	0[b]
4	5	**DMAP**	1.2	25	7[b]
5	10	-	1.2	65	42[b]
6	5	-	1.2	65	2[b]
7	10	-	2.4	25	94
8	5	-	4.8	25	94
9	2.5	-	9.6	25	90
10	1.25	-	10	25	0[b]
11[c]	2.5	-	9.6	25	99

[a]Isolated by column chromatography. [b]Determined by ^{1}H NMR spectroscopy with reference to *E*-stilbene as internal standard. [c]Aldehyde washed with Na_2CO_2 prior to distillation.

Further doubling of the substrate equivalents (2.5 mol% catalyst loading) furnished the product in 90% yield, however, this proved to be the limit of the catalyst activity, with 1.25 mol% catalyst loading having no catalytic activity (entries 9 and 10). It was noted that all of these reactions had a precipitate in the flask at the conclusion of the reaction. As previously discussed this indicates that the catalytic pathway is being interrupted, usually by water or base, however in this instance we had ruled out both of those possibilities with previous testing. We theorised that benzoic acid, being introduced from the oxidation of benzaldehyde,

might be the cause of this pathway interruption, an effect which would be most significant at lower catalyst loadings (Scheme 4.3).

Scheme 4.3 Possible mechanism for the formation of precipitate in low catalyst loading systems



To remove any adventitious acid from the reaction, the aldehyde was washed with a solution sodium carbonate prior to its purification by distillation and, gratifyingly, the disproportionation at 2.5 mol% catalyst loading proceeded in near quantitative yield (entry 11, Table 4.7).

Electrophilic selenium-based catalysts have been previously described, but to the best of our knowledge this represents only the second example of nucleophilic selenium-derived catalysts to be reported.[140,141]

4.1.1 Evaluation of the substrate scope of the magnesium selenide-ion-catalysed Tishchenko reaction

The disproportionation of 3-chlorobenzaldehyde furnished the ester product **424** in 99% isolated yield at the low catalyst loading of 2.5 mol% (entry 1, Table 4.8). However, the formation of the 2-chlorosubstituted benzaldehyde-derived ester **425** proved impossible at both 2.5 and 5 mol% catalyst loadings (entries 2 and 3). We attributed this to a S_NAr type reaction, where the 2-chloro moiety is substituted for the highly nucleophilic selenide-ion catalyst, with the extrusion of MgBrCl. Enigmatically, the electron-deficient nitro-substituted ester product **426** was also not produced in appreciable yields at 5 mol% catalyst loading (entry 4). It was noted that the reaction mixture contained a large proportion of crystals, as such, we initially thought that the reaction concentration may have been too high, thereby favouring crystallisation of the aldehyde. To prevent this, the reaction was diluted to the catalyst loading of 10 mol%, however only 48% yield of **426** was obtained and the crystallisation was observed again (entry 5). This observation made us consider another

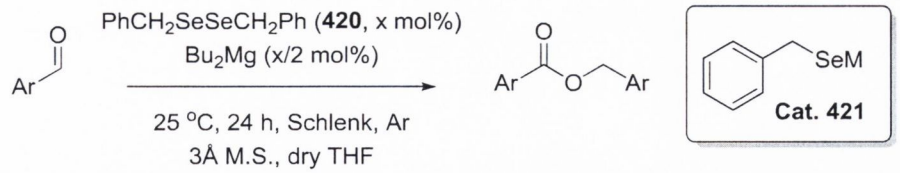
possibility; that another S_NAr-type reaction was occurring with the nitro group being substituted for the nucleophilic selenide-ion catalyst.[142]

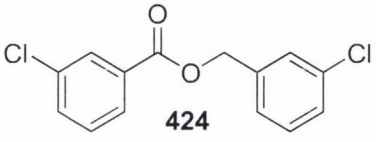
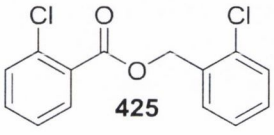
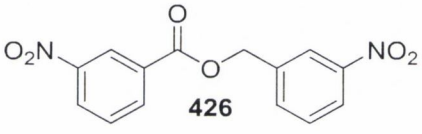
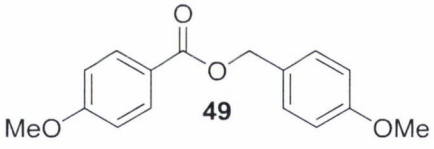
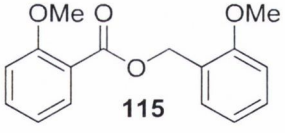
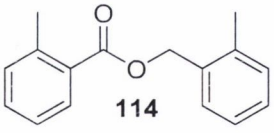
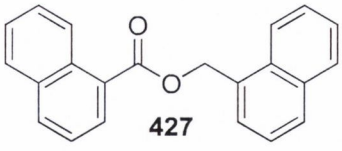
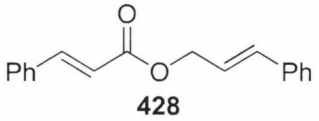
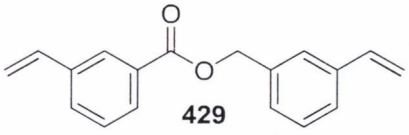
The electron-rich 4-methoxybenzaldehyde did not produce appreciable yields of ester dimer **49** at low catalyst loadings of 2.5 and 5 mol% (entries 6 and 7). Gratifyingly however; the excellent yield of 91% was obtained at 10 mol% catalyst loading (entry 8). The disproportionation of 2-methoxybenzaldehyde furnished the ester **115** in low yield (23%) at 10 mol% catalyst loading, and 48% yield at 20 mol% catalyst loading (entries 9 and 10). This substrate was the most challenging substrate reported in the bromomagnesium thiolate-catalysed methodology (see Section 1.2.1.1), owing to the proposed chelation of the bromomagnesium conjugate base hemithioacetal, preventing hydride transfer.

The sterically hindered 2-methylbenzaldehyde did not undergo the disproportionation reaction in acceptable yield at 20 mol% catalyst loading (entry 11). The 1-naphthaldehyde substrate furnished the ester **427** in high yields at 5 and 10 mol% catalyst loadings, however, the product could not be isolated in high purity from the aldehyde starting material *via* either flash chromatography or *in vacuo* distillation (entries 12 and 13).

On review of our earlier research on the selenide-ion-catalysed MBH reaction (see Section 3.3), we theorised that the selenide ion may favour addition to the aldehyde over 1,4-conjugate addition. Attempting to prove this theory we utilised the cinnamaldehyde substrate, which would theoretically produce ester **428**, however its dimerisation did not occur at catalyst loadings of 2.5 and 5 mol% (entries 14 and 15). The alkene substituted ester **429** was produced in excellent yield at 5 mol% catalyst loading, the appeal of which is that this functional group may be used as a synthetic handle to furnish more complex compounds, *e.g. via* ozonolysis and Grubbs-type catalysis (entry 16).[143,144]

Table 4.8 Investigation of the substrate scope for the disproportionation of aldehydes



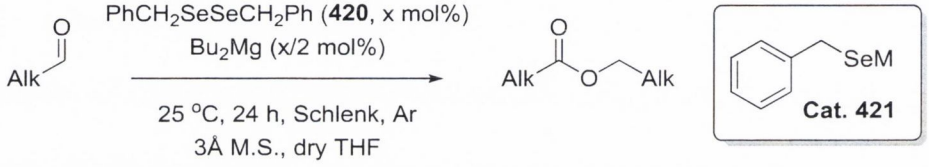
entry	product	x (mol%)	conc. of aldehyde (M)	yield (%)[a]
1	 **424**	2.5	9.6	99
2	 **425**	2.5	9.6	0[b]
3		5	4.8	2[b]
4	 **426**	5	4.8	12[b]
5		10	2.4	48[b]
6	 **49**	2.5	9.6	2[b]
7		5	4.8	11[b]
8		10	2.4	91
9	 **115**	10	2.4	23[b]
10		20	1.2	48[b]
11	 **114**	20	1.2	17[b]
12	 **427**	5	4.8	84[b]
13		10	2.4	88[b]
14	 **428**	2.5	9.6	0[b]
15		5	4.8	0[b]
16	 **429**	5	4.8	93

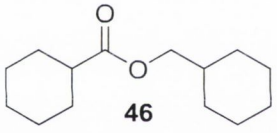
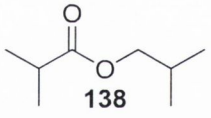
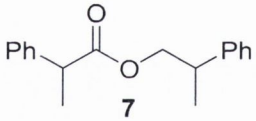
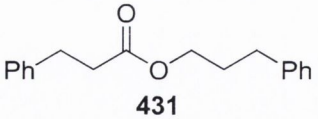
[a]Isolated by silica gel column chromatography. [b]Determined by ^{1}H NMR spectroscopy with reference to *E*-stilbene as an internal standard.

4.1.2 Evaluation of alkyl aldehydes as substrates for the magnesium selenide-ion-catalysed disproportionation reaction

As selenide ions are much less basic than the corresponding thiolate anions, we theorised that the deprotonation of the α-proton of aliphatic aldehydes and subsequent aldol reaction may be suppressed.[145]

Table 4.9 Evaluation of aliphatic aldehydes in the magnesium selenide-ion catalysed Tishchenko reaction conditions



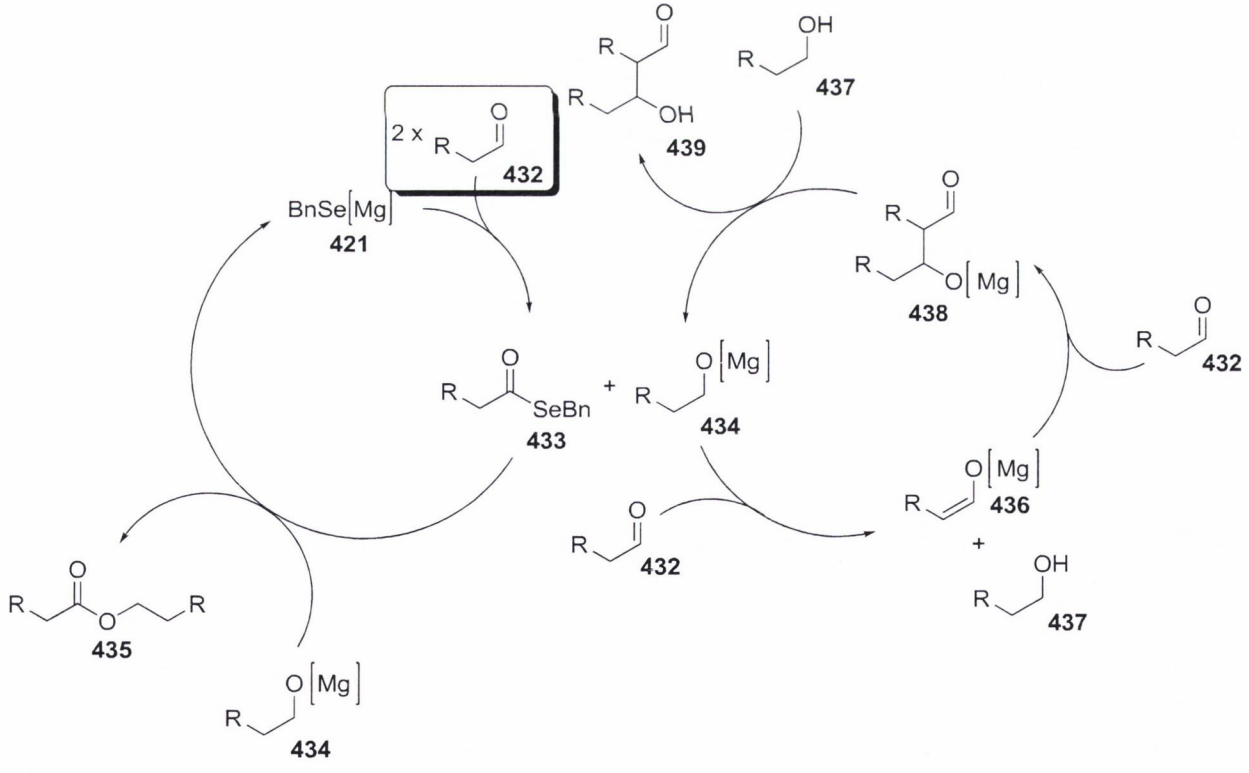
entry	product	x (mol%)	conc. of aldehyde (M)	yield (%)[a]
1	 **46**	5	4.8	23[b]
2		10	2.4	98
3	 **138**	10	2.4	35[b]
4	 **7**	10	2.4	0[b]
5		20	1.2	0[b]
6	 **431**	20	1.2	0[b]

[a]Isolated by silica gel column chromatography. [b]Determined by ^{1}H NMR spectroscopy with reference to *E*-stilbene as internal standard.

The dimerisation of cyclohexanecarboxaldehyde, furnishing ester **46**, proceeded in 23% yield at 5 mol% catalyst loading (entry 1, Table 4.9). Surprisingly however, a catalyst loading of 10 mol% allowed the production of **46** in the excellent yield of 98% yield (entry 2). Furthermore, the ester product **138** formed in low yield (35%) at 10 mol% catalyst loading (entry 3). The disproportionation reaction of 2-phenylpropionaldehyde, which theoretically

produces ester **7**, furnished no ester product at 10 or 20 mol% catalyst loadings (entries 4 and 5). Finally, the unbranched alkyl aldehyde, 3-phenylpropionaldehyde, did not furnish the ester product **431** at 20 mol% catalyst loading (entry 6). This lead us to believe that in both the thiolate and selenide-ion-catalysed reactions, the basic component that was propagating the aldol reaction is not the chalcone-derived catalyst but is more likely the alkoxide intermediate produced by the reaction of catalyst with aldehyde-type **432**: alkoxide **434** (pK_aH 30 – 31 in DMSO)[146] (Scheme 4.4). This alkoxide is a much stronger base than the catalyst and is therefore more likely to propagate the aldol reaction *via* the deprotonation and enolisation of aldehyde **432** to form the magnesium enolate **436** and alcohol **437**. This enolate will react with another molecule of aldehyde to furnish compound **438** which is reprotonated by alcohol **437** to generate the aldol product **439** and reform the alkoxide **434**.

Scheme 4.4 Possible mechanism for the competing aldol reaction from the products of the selenide-ion-derived Tishchenko reaction

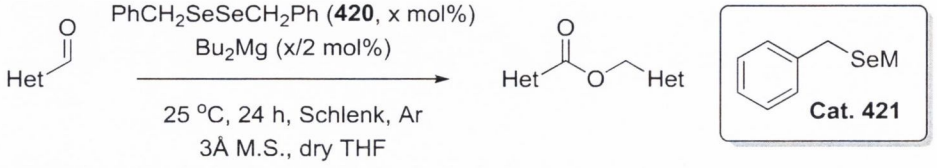


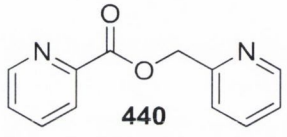
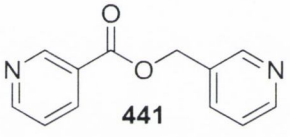
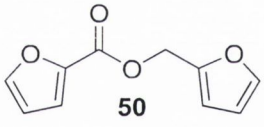
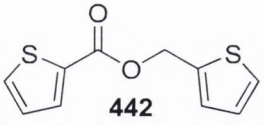
4.1.3 Evaluation of heterocyclic aldehydes as substrates

Previously, heterocyclic aldehydes were found to be incompatible with the magnesium thiolate-catalysed Tishchenko methodology, or indeed many other methodologies due to their varied electron properties (see Section 1.1).[147] The ester **440** was found to be difficult to

prepare *via* the selenide-ion-catalysed methodology, forming in only 6% yield with 20 mol% catalyst loading (entry 1, Table 4.10).

Table 4.10 Evaluation of heterocyclic aldehydes as substrates in the magnesium selenide-ion-catalysed Tishchenko reaction

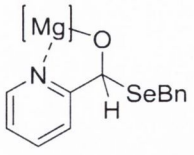


entry	product	x (mol%)	conc. of aldehyde (M)	yield (%)[a]
1	 **440**	20	1.2	6[b]
2	 **441**	5	4.8	95
3		10	2.4	99
4	 **50**	2.5	9.6	0[b]
5		5	4.8	8[b]
6		10	2.4	48
7		20	1.2	62
8	 **442**	2.5	9.6	87[b]
9		5	4.8	96
10		10	2.4	98[b]

[a]Isolated by silica gel column chromatography. [b]Determined by ^{1}H NMR spectroscopy with reference to *E*-stilbene as internal standard.

The regio-isomer ester **441**, formed from the disproportionation of pyridine-3-carboxaldehyde, was produced in excellent yields at catalyst loadings of 5 and 10 mol% (entries 2 and 3). This demonstrates that the position of the nitrogen atom drastically changes the efficiency of the reaction. We hypothesised that a similar effect to that observed using 2-methoxybenzaldehyde may be occurring with this substrate: *i.e.* chelation of the conjugate base hemiselenacetal *via* the lone pair of the hetero-atom (Figure 4.1).

Figure 4.1 Possible chelation of magnesium conjugate base hemiselenoacetal of pyridine-2-carboxaldehyde



Little or no furan-derived ester product **50** was observed to form in the presence of 2.5 and 5 mol% catalyst loading (entries 4 and 5). Gratifyingly, a moderate yield (48%) of ester **50**, was obtained with a catalyst loading of 10 mol%, furthermore, increasing the catalyst loading to 20 mol% afforded the product in 62% yield (entries 5 and 6). This substrate has generally been considered to be very difficult to dimerise *via* a Tishchenko-type reaction, as such this result demonstrated to us the superiority of this magnesium selenide-ion-catalysed methodology.[148] Finally, it was found that the thiophene-derived ester **442** could be produced in the high yield of 87% yield at catalyst loading of 2.5 mol% (entry 8). Increasing the catalyst loadings to 5 and 10 mol% afforded the ester product in excellent yields, 96% and 98% resectively (entry 4).

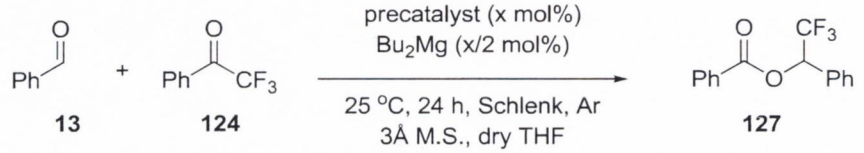
4.2 Optimisation of conditions for the crossed intermolecular Tishchenko reaction between benzaldehyde and 2,2,2-trifluoroacetophenone

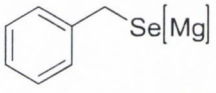
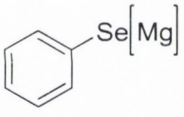
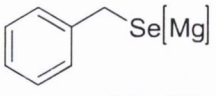
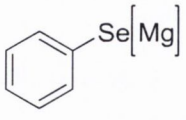
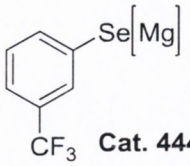
The previous bromomagnesium thiolate-catalysed crossed Tishchenko methodology between an aldehyde and a 2,2,2-trifluoroketone was demonstrated to be highly selective but only a narrow substrate scope of both aldehydes and ketones was available and high catalyst loadings (20 mol%) were required for efficient catalysis. These limitations directly effect the synthetic utility of the reaction and as such it was decided to address them using the superior magnesium selenide-ion-catalysed methodology.

Initial screening of the reaction with the benzyl-derived magnesium selenide-ion **421** as catalyst allowed the production of the crossed ester product **127** in 7% yield (entry 1, Table 4.11). The phenyl-substituted selenide-ion **435** catalysed the production of the ester **127** in a slightly augmented yield of 12% yield (entry 2). Again, we theorised that water may be an issue in this reaction and as such the reactions were repeated in the presence of ketone that was distilled and stored on 3Å molecular sieves. Encouragingly, the benzyl-derived

magnesium selenide-ion **421** catalyst propagated the formation of the crossed ester **127** in 39% yield (entry 3). The use of the phenyl-derived magnesium selenide-ion **435** as catalyst at 5 and 10 mol% loading proved unfruitful, however, evaluation at 20 mol% loading allowed the production of **127** in 96% yield (entries 4, 5 and 6).

Table 4.11 Evaluation of magnesium selenide-ion catalysts in the crossed intermolecular Tishchenko reaction with 2,2,2-trifluoroactophenone



entry	Cat.	x (mol%)	conc. of aldehyde (M)	yield **127** (%)[a]
1	 **Cat. 421**	20	1.2	7[b]
2	 **Cat. 443**	20	1.2	12[b]
3[c]	 **Cat. 421**	20	1.2	39[b]
4[c]	 **Cat. 443**	5	4.8	0[b]
5[c]		10	2.4	16[b]
6[c]		20	1.2	96
7[c]	 **Cat. 444**	2.5	9.6	0[b]
8[c]		5	4.8	38[b]
9[c]		10	2.4	92
10[c]		20	1.2	98

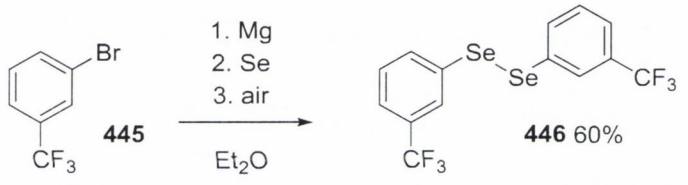
[a]Isolated by silica gel column chromatography. [b]Determined by ^{1}H NMR spectroscopy with reference to *E*-stilbene as an internal standard. [c]Ketone distilled prior to reaction.

As the previous trend of catalytic properties in the bromomagnesium thiolate-catalysed methodology had so far proved itself to be similar to that observed in the magnesium

selenide-ion catalysed reaction, it was decided to utilise the 3-(trifluoromethyl)-phenyl-substituted selenide-ion catalyst **444** which, dissapointingly, did not furnish any ester product at 2.5 mol% catalyst loading (entry 7). However, 28% yield of ester **127** was observed to form in the presence of 5 mol% catalyst (entry 8). Further increase of the catalyst loading to 10 mol% demonstrated that the product could be formed in the excellent yield of 92% (entry 9). As expected, the production of ester **127** at 20 mol% proceeded to 98% yield (entry 10).

The synthesis of precatalyst **446** was achieved by the formation of the Grignard reagent from 3-(trifluoromethyl)-bromobenzene **445**, subsequent addition to molecular selenium and bubbling of air through the solution overnight furnished the diselenide product in 60 % yield (Scheme 4.5).

Scheme 4.5 Synthesis of 3-CF_3-phenyl-derived diselenide precatalyst



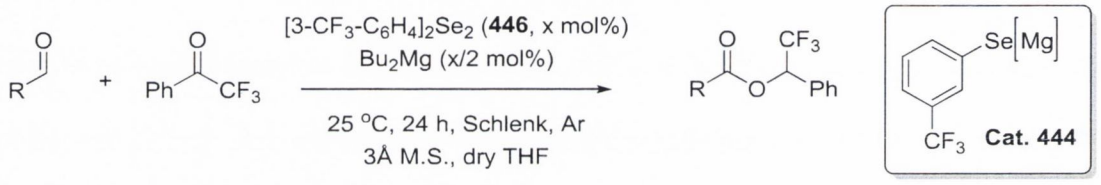
4.2.1 Evaluation of aldehyde substrate scope for the magnesium selenide-ion catalysed crossed intermolecular Tishchenko reaction between 2,2,2-trifluoroacetophenone and various aldehydes

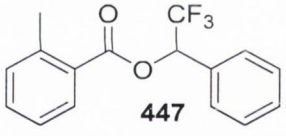
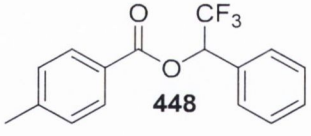
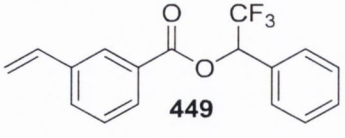
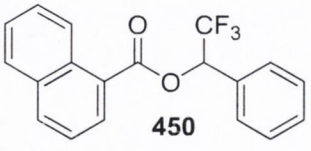
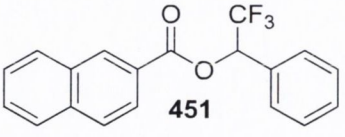
As both the thermal bromomagnesium thiolate-catalysed and microwave bromomagnesium thiolate-catalysed crossed intermolecular Tishchenko reactions had narrow substrate scopes, we decided to focus on substrates that were previously considered difficult. This would not only demonstrate the power and utility of this methodology, but also we hoped to make the products demonstrably obtainable from this reaction more synthetically useful.

The sterically hindered product **447**, formed from the previously incompatible 2-methylbenzaldehyde (see Section 4.1.2), was found to form in a paltry 12% yield (entry 1, Table 4.12). We next decided to subject the regio-isomer 4-methylbenzaldehyde to the crossed intermolecular Tishchenko conditions, and found that the respective product **448** only formed in 26% yield in the presence of 20 mol% catalyst loading, with 10 mol% catalyst loading producing only trace amounts of product (entries 2 and 3). This demonstrates that this

magnesium selenide ion-catalysed methodology is not entirely compatible with methyl-substituted aromatics. The alkene substituted product **449** was formed in high yield of 84% at 20 mol% catalyst loading (entry 4). Disappointingly, the crossed ester **450** derived from the sterically hindered 1-naphthaldehyde was not observed to form at 10 mol% catalyst loading and formed in only 7% yield at 20 mol% catalyst loading (entry 5 and 6). However, the crossed ester **451**, derived from the regio-isomer 2-naphthaldehyde, was furnished in the high yield of 87% at 20 mol% catalyst loading (entry 7).

Table 4.12 Evaluation of various hydrocarbon-substituted aldehydes in the crossed intermolecular Tishchenko reaction with 2,2,2-trifluoroacetophenone

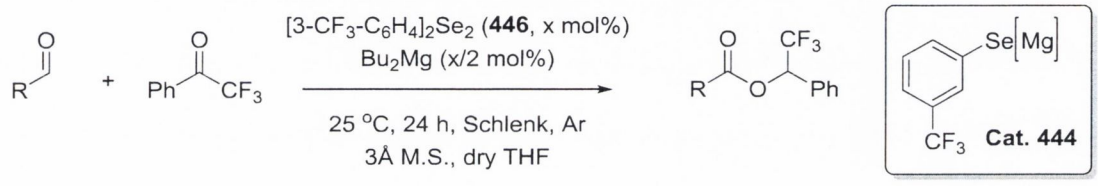


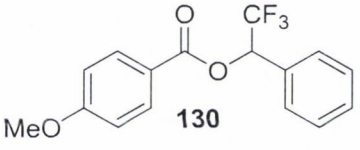
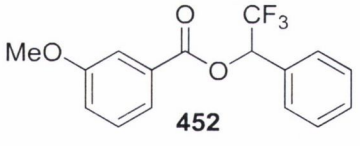
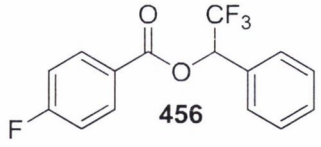
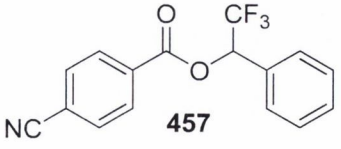
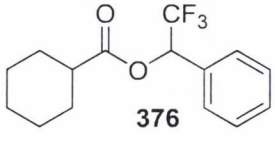
entry	product	x (mol%)	conc. of aldehyde (M)	yield (%)[a]
1	 **447**	20	1.2	12[b]
2	 **448**	10	2.4	2[b]
3		20	1.2	26[b]
4	 **449**	20	1.2	84
5	 **450**	10	2.4	0[b]
6		20	1.2	7[b]
7	 **451**	20	1.2	87

[a]Isolated by silica gel column chromatography. [b]Determined by ^{1}H NMR spectroscopy with reference to styrene as an internal standard.

Next, it was decided to evaluate a series of aldehydes with differing electronic properties in the crossed Tishchenko reaction with 2,2,2-trifluoroacetophenone. It was found that ester **130**, previously found to require long reaction times using the magnesium thiolate-catalysed methodology, was formed in low yield (25%) at 20 mol% catalyst loading (entry 1, Table 4.13).

Table 4.13 Evaluation of substituted aldehydes as substrates in the crossed intermolecular Tishchenko reaction with 2,2,2-trifluoroacetophenone



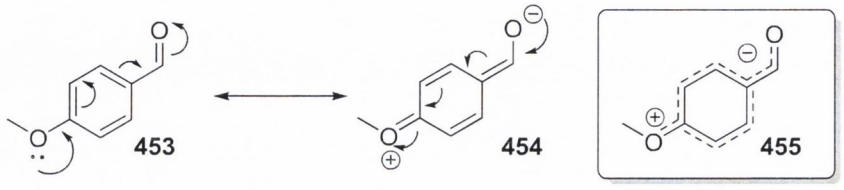
entry	product	x (mol%)	conc. (M)	yield (%)[a]
1	 **130**	20	1.2	25[b]
2	 **452**	20	1.2	94
3	 **456**	20	1.2	87
4	 **457**	20	1.2	73
5	 **376**	20	1.2	13[b]

[a]Isolated by silica gel column chromatography. [b]Determined by ^{1}H NMR spectroscopy with reference to styrene as an internal standard.

The isomer **452**, however, was formed in the excellent yield of 94% at 20 mol% catalyst loading (entry 2). This indicates that it is most likely the resonance stabilisation resulting

from the 4-methoxy-substituted aldehyde that disfavours addition of the nucleophilic catalyst, *i.e.* the contribution of resonance structure **454** to the overall structure of aldehyde **453** explains the poor reactivity of this aldehyde in the Tishchenko reaction, where the aldehyde serves as the electrophilic component twice in the catalytic cycle (Scheme 4.6).

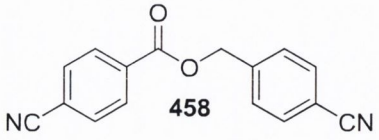
Scheme 4.6 Possible rationale for the resonance stabilisation of 4-methoxy substituted benzaldehydes



This may also be explained by a sufficiently lowered LUMO in the case of electron-deficient aromatic carbonyl systems and a correspondingly raised LUMO in the case of electron-rich aromatic aldehydes.

The formation of crossed ester **456** from 4-fluorobenzaldehyde, proceeded with the high yield of 87% at 20 mol% catalyst loading (entry 3). Ester **457** was formed in an appreciable yield of 73% at 20 mol% catalyst loading (entry 4), with the remainder of the aldehyde likely being consumed in a competing aldehyde disproportionation reaction to form the homo-Tishchenko product **458** (Figure 4.2). Previously, ester **457** was not synthesisable *via* either the magnesium thiolate-catalysed methodologies under either thermal of microwave irradiation conditions. It is likely that due to the highly electron-deficient nature of the 4-cyanobenzaldehyde, the hydride transfer step of the reaction became unselective to a small degree.

Figure 4.2 Side product from the crossed intermolecular reaction of 4-cyanobenzaldehyde and 2,2,2-trifluoroacetophenone



Disappointingly, the crossed ester **376** (derived from cyclohexanecarboxaldehyde) could not be produced in satisfactory yields at 20 mol% catalyst loading; with the aldehyde forming the aldol side-product almost exclusively (entry 5).

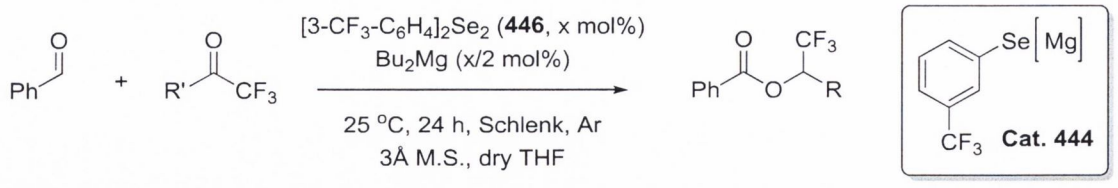
4.2.2 Evaluation of the substrate scope of substituted trifluoroketones

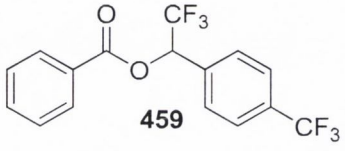
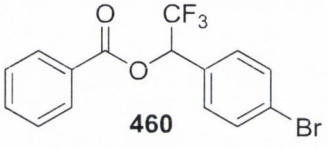
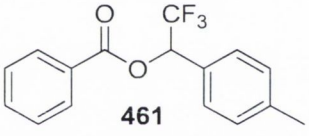
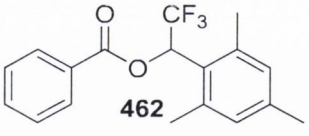
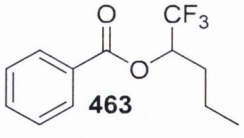
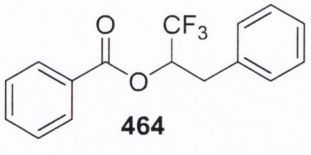
The crossed ester **459** was furnished in low yield (*i.e.* 5%) from benzaldehyde and the exceptionally electron-deficient 4'-trifluoromethyl-2,2,2-trifluoroacetophenone at 10 mol%, however, only 93% yield was obtained on lowering the catalyst loading to 20 mol% (entries 1 and 2, Table 4.14). We attributed this reduced yield at 10 mol% catalyst loading to the rate limiting acyl transfer step which would be retarded further by the reduced nucleophilicity of the alkoxide after hydride transfer to the trifluoromethylketone.

The bromo-substituted crossed ester **460** formed in a meagre 9% yield at 20 mol% catalyst loading and was undetectable in the reaction performed at 10 mol% catalyst loading (entries 3 and 4). This is likely due to a competing S_NAr-type reaction similar to that observed in the aldehyde disproportionation reaction (see Section 4.1.2). Surprisingly, the 4'-methylsubstituted 2,2,2-trifluoroacetophenone furnished the ester product **461** in 95% isolated yield at 10 mol% catalyst loading and quantitative yield at 20 mol% catalyst loading (entries 5 and 6). This is interesting as the methyl-substituted aldehydes furnished little or no ester product, when exposed to the magnesium selenide ion. The crossed ester **462**, derived from the extremely sterically hindered 2',4',6'-trimethyl-2,2,2-trifluoroacetophenone, was found to be impossible to form *via* this methodology (entry 7).

In an effort to expand the reaction scope to include aliphatic trifluoroketones, the esters **463** and **464** were attempted to be synthesised *via* the magnesium selenide-ion catalysed crossed Tishchenko reaction, however, only aldol products were observed in the crude ^{1}H NMR spectra (entries 8 and 9).

Table 4.14 Evaluation of 1-substituted 2,2,2-trifluoroketones in the crossed intermolecular Tishchenko reaction with benzaldehyde



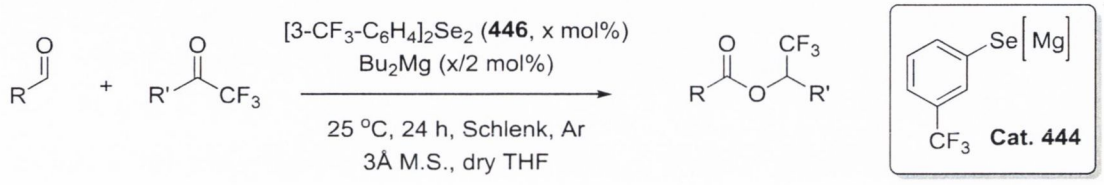
entry	product	x (mol%)	conc. of aldehyde (M)	yield (%)[a]
1	 **459**	10	2.4	5[b]
2		20	1.2	93
3	 **460**	10	2.4	0[b]
4		20	1.2	9[b]
5	 **461**	10	2.4	95
6		20	1.2	99[b]
7	 **462**	20	1.2	0[b]
8	 **463**	20	1.2	0[b]
9	 **464**	20	1.2	0[b]

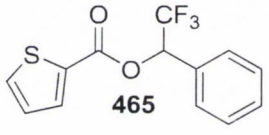
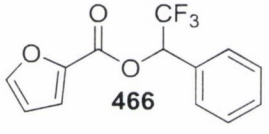
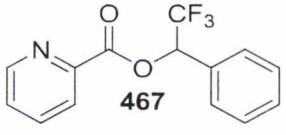
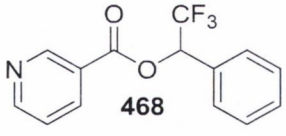
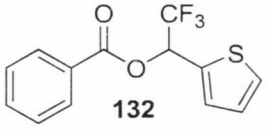
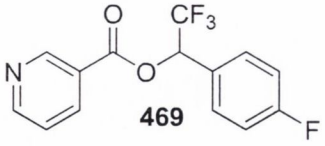
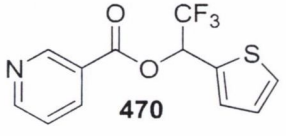
[a]Isolated by silica gel column chromatography. [b]Determined by ^{1}H NMR spectroscopy with reference to styrene as internal standard.

Previously, heterocyclic aldehydes were found to be incompatible with the bromomagnesium thiolate-catalysed Tishchenko reaction and their incompatibility with the methodology severly limited its synthetic utility. As such, it was decided to evaluate a variety of heterocyclic aldehydes in the selenide-ion-catalysed crossed Tishchenko reaction. It was

gratifying to observe the formation of **465** in 97% yield at 10 mol% catalyst loading, and 92% isolated yield at 20 mol% catalyst loading (entries 1 and 2, Table 4.15).

Table 4.15 Evaluation of heterocyclic aldehyde substrates in the crossed intermolecular Tishchenko reaction



entry	product	x (mol%)	conc. of aldehyde (M)	yield (%)[a]
1	 **465**	10	2.4	97
2		20	1.2	92
3	 **466**	10	2.4	33[b]
4		20	1.2	93
5	 **467**	20	1.2	0[b]
6	 **468**	10	2.4	71[b]
7		20	1.2	80
8	 **132**	10	2.4	0[b]
9		20	1.2	25[b]
10	 **469**	20	1.2	63[b]
11	 **470**	20	1.2	56

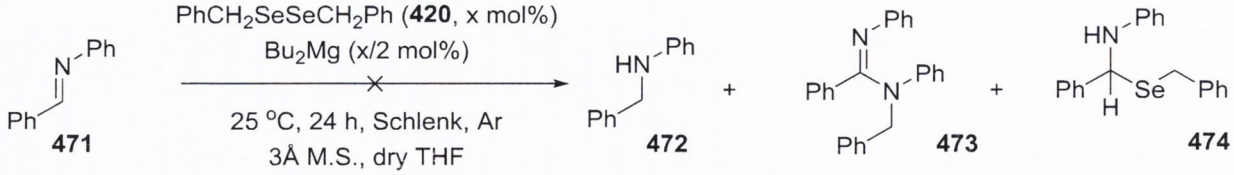
[a]Isolated by silica gel column chromatography. [b]Determined by ^{1}H NMR spectroscopy with reference to styrene as an internal standard.

The recalcitrant furfural, was subjected to crossed reaction conditions with 2,2,2-trifluoroacetophenone, from which the product **466** was obtained in excellent yield at 20 mol% catalyst loading, although the use of 10 mol% catalyst loading did not allow the formation of the product in acceptable yield (entries 3 and 4). Ester product **467**, derived from the previously difficult to dimerise 2-pyridinecarboxaldehyde, was not observed under these conditions (entry 5). Its isomer **468**, however, formed in 71% yield at 10 mol% catalyst loading and appreciable yield at 20 mol% catalyst loading (entries 6 and 7). Disappointingly, the crossed ester **132** only formed in only 25% yield at 20 mol% catalyst loading and was not observed at 10 mol% catalyst loading (entries 8 and 9). The crossed ester **469** was found to form in moderate yield at 20 mol% catalyst loading (entry 10). Finally, the mixed heterocyclic ester **470** was found to form in 56% isolated yield at 20 mol% catalyst loading (entry 11).

4.3 Further studies on the expansion of substrate scope of the homo and crossed Tishchenko reaction

Previously, F. Manoni had evaluated a variety of *N*-substituted imines as substrates for the magnesium thiolate-catalysed disproportionation reaction, to no avail. Subsequently, it was decided to subject one such imine, **471**, to the corresponding selenide-ion catalysed methodology (Scheme 4.7). After 24 hours, it was found that no hydride transfer reaction had occurred to generate **472** and, surprisingly, nor was the adduct **474** present.

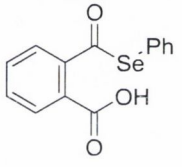
Scheme 4.7 The attempted Tishchenko-type reaction of an *N*-phenyl-substituted imine



Following this, we decided to focus on selective intermolecular hydride transfer reactions from benzaldehyde to other carbonyl-functionalised compounds. It was decided that the phenyl-substituted selenide-ion catalyst should be used for the evaluation of potential substrates as it was unclear whether the 3-(trifluoromethyl)-phenyl substituted selenide-ion catalyst would be active under these conditions. Initial evaluation of the trichloromethylketone **383** in the selenide-ion catalysed crossed Tishchenko reaction resulted

in no observable reduced product (entry 1, Table 4.16). Interestingly, no diselenide was observed in the product of this reaction, the formation of which might have been predicted from the results discussed in Section 2.4. Theorising that phthalic anhydride (**475**) might be electron-deficient enough to favour reduction *via* hydride transfer over benzaldehyde; it was evaluated under the magnesium selenide-ion conditions (entry 2). Disappointingly, the reduced anhydride was not observed in the ^{1}H NMR spectrum of the crude reaction mixture. The adduct derived from the attack of selenide-ion catalyst on the anhydride, was theorised to be major side product (Figure 4.3).

Figure 4.3 Proposed side product from the reaction of phthalic anhydride and the selenide-ion catalyst



Inspired by the work of Scheidt *et al.* discussed in Section 1.2.1, we decided to evaluate a range of 1,2-diketones in the crossed Tishchenko reaction. Gratifyingly, the reduced product of benzil (*i.e.* benzoin **476**) was observed in 3% yield, though no selenoester was observed, likely due to the presence of water in the deuterated solvent (entry 3). The use of the planar acenaphthoquinone (**477**) in the reaction resulted in no reduced carbonyl product (entry 4). Finally, the pyruvates **478** and **489**, when subjected to the crossed Tishchenko conditions, did not furnish any reduced products (entries 5 and 6). We theorised that the catalyst may be tied up by the formation of the adduct depicted in Figure 4.4, the presence of which would explain the absence of benzyl benzoate (formed *via* the disproportionation of benzaldehyde in the absence of other carbonyls capable of reduction by hydride transfer).

Figure 4.4 The proposed side product of the addition of the selenide-ion catalyst to the 1,2-diketone substrates

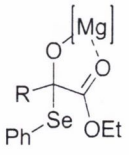
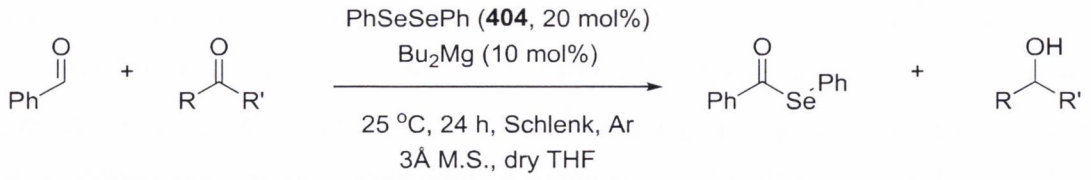
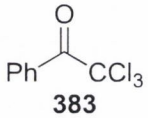
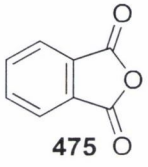
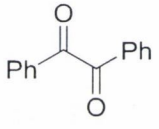
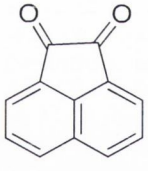
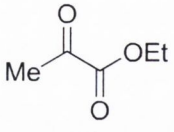
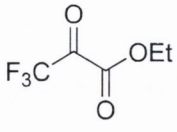


Table 4.16 Evaluation of various carbonyl functionalised substrates in the crossed Tishchenko reaction



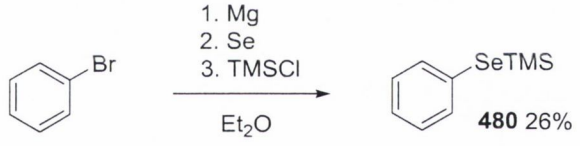
entry	substrate	yield (%)[a]	reduced product yield (%)[a]
1	 **383**	0	0
2	 **475**	0	0
3	 **476**	0	3
4	 **477**	0	0
5	 **478**	0	0
6	 **479**	0	0

[a]Determined by ^{1}H NMR spectroscopy with reference to (*E*)-stilbene as an internal standard.

4.3.1 Examination of counterion effects

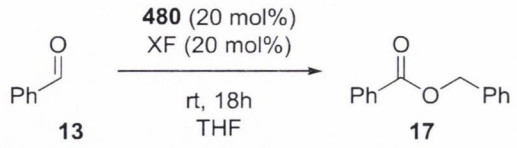
On examination of Tishchenko methodologies previously reported, we theorised that the counterion of the reaction may be important with respect to the potential substrate scope of the reaction (see Section 1.1). For instance, we theorised that a lithium metal counterion to the selenide-ion-derived catalyst may promote the disproportionation of furfural more efficiently than would a magnesium metal counterion. Our rationale for this is the much decreased size of the lithium ion and also the favourablilty of the lithium hemiselenacetal coordinating the oxygen lone-pair of the furan ring in the transition state would be much reduced. In order to generate other counterions we designed a silyl-protected precatalyst (*i.e.* **480**) which we theorised could be easily deprotected *in situ* using fluoride-based deprotecting agents.[149] This was synthesised in low yield *via* the formation of the magnesiumbromide selenide-ion and subsequent S_N2 reaction with trimethylsilylchloride (TMSCl, Scheme 4.8).

Scheme 4.8 The synthesis of the silyl-protected selenide



We were disappointed to find however, that the clean, anhydrous deprotection of this silyl-protected selenide could not be carried out *in situ* with the alkali fluorides (entries 1 – 3, Table 4.17). These reactions furnished no benzyl benzoate (**17**) and contained large amounts of precipitate, which was most likely the undissolved fluoride salts. In order to confirm this, tetrabutylammonium fluoride (TBAF), a known silyl-deprotection agent, was employed as a deprotecting agent in the reaction; the result of which was the formation the ester product in 7% yield (entry 4).[150]

Table 4.17 The tandem silyl-deprotection and Tishchenko reaction of TMS-protected phenylselenide

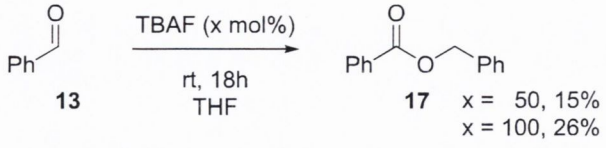


entry	XF	yield **17** (%)[a]
1	LiF	0
2	NaF	0
3	KF	0
4	TBAF (75% *w/v* in water)	7

[a]Determined by ^{1}H NMR spectroscopy with reference to (*E*)-stilbene as an internal standard.

To confirm that the reactivity being observed in the TBAF deprotection reaction is wholly attributed to the action of the selenide-ion, the reaction was performed in the absence of the silyl-protected selenide. On exposure of benzaldehyde (**13**) to 50 mol% TBAF overnight, it was found that 15% isolated yield of benzyl benzoate was formed (Scheme 4.9). When the reaction was performed with stoichiometric quantities of TBAF the ester product was formed in 26% yield. This experiment demonstrates that TBAF is acting as a catalyst for the Tishchenko reaction.

Scheme 4.9 Evaluation of the TBAF reaction in the absence of the silyl-protected selenide



This work will be further discussed in the following chapter.

4.4 Conclusion

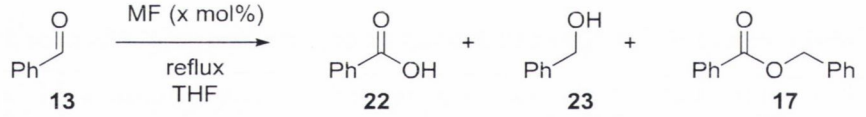
In conclusion, a highly active magnesium selenide-ion-catalysed methodology for the Tishchenko reaction has been described. Overall the substrate scope of the previous magnesium thiolate-catalysed methodology has been greatly expanded upon to generate

crossed heterocyclic esters and other potentially synthetically useful ester products. The catalyst loadings of the selenide-ion-catalysed methodology have been lowered to 2.5 mol% and the reaction times are generally much shorter than those previously required in the magnesium thiolate-catalysed methodology. Disapppointingly however, the efforts to evaluate other, potentially more reactive, counterions for the selenide-ion catalysed Tishchenko reaction were deemed too difficult and time-consuming at this point due to the insolubility of the fluoride salts.

5.0 The fluoride-catalysed hydride transfer reactions

As discussed as the end of the previous chapter, it was found that TBAF (75% *w/v* in water) catalysed the Cannizarro reaction of benzaldehyde. Theorising that this was due to the presence of water in the reaction, it was decided to evaluate other sources of fluoride under similar conditions. A repeat of the TBAF-mediated reaction at 50 mol% loading furnished acid **22** in 25% yield and alcohol **23** in the comparable yield of 24% (entry 1, Table 5.1). A reaction performed in parallel under a nitrogen atmosphere furnished the hydride transfer products in slightly improved yields (entry 2). Surprisingly, lithium fluoride mediated the formation of benzyl benzoate (**17**) in 15% yield under reflux in air, however, the reaction performed in parallel under a nitrogen atmosphere contained no observable hydride transfer products (entries 3 and 4). Sodium fluoride catalysed the formation of benzoic acid in 20% yield and benzyl alcohol in 14% yield, though the parallel reaction performed under nitrogen did not contain any hydride transfer products (entries 5 and 6).

Table 5.1 Evaluation of fluoride salts in the disproportionation of benzaldehyde



entry	M	x (mol%)	atmosphere	yield **22** (%)[a]	yield **23** (%)[a]	yield **17** (%)[a]
1	$N(Bu)_4$	50	O_2	25	24	1
2	$N(Bu)_4$	50	N_2	31	32	1
3	Li	50	O_2	7	2	15
4	Li	50	N_2	0	0	0
5	Na	50	O_2	20	14	2
6	Na	50	N_2	trace	0	1

[a]Determined by ^{1}H NMR spectroscopy with reference to styrene as an internal standard.

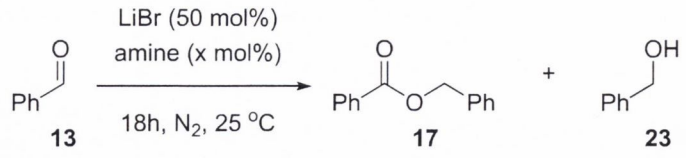
It appears from these results that TBAF is acting as a catalyst for the Tishchenko reaction, but the excess of water is promoting the hydrolysis of the ester **17** into its constituent acid (**22**)

and alcohol (**23**). This side reaction limits the utility of the methodology as products of this reaction have few novel synthetic applications. As the lithium and sodium salts appeared to only show activity in reactions performed in air, it is likely that they are occuring *via* a Cannizarro-type reaction mechanism.[151]

5.1 The lithium bromide-mediated Tishchenko reaction

This research led us to consider the work of Abaee *et al.* previously discussed in Section 1.1.4.1, *i.e.* the lithium bromide and triethylamine-mediated Tishchenko reaction. We theorised that this methodology may have some previously unlocked potential in catalysing the crossed intermolecular Tishchenko reaction, both in selectivity and in substrate scope due to the lithium counterion. However, we first needed to better understand the reaction mechanism before any further research could be performed. Theorising, like the authors, that the role of the lithium metal is to coordinate between both of the oxygen atoms of the two aldehyde carbonyls, it was decided to investigate the role of the amine. As a baseline indicator of how far the reaction would progress in 18 hours (reported reaction time is two days), triethylamine mediated the formation of ester **17** in 33% yield and benzyl alcohol (**23**) in 10% yield (entry 1, Table 5.2). The more sterically hindered diisopropylethylamine allowed the formation of the ester in the significantly lowered yield of 11%, however, the alcohol **23** was furnished in the augmented yield of 41% (entry 2). Finally, the nucleophilic amine DBU mediated the formation of the ester in 76% yield after only 18 hours (entry 3). Halving the loading of DBU allowed the formation the ester in 61% yield, while further lowering of the loading produced **17** in only 37% yield (entries 4 and 5). As a final confirmation of the catalytic activity of the amine, a reaction was performed in its absence, from which no hydride transfer products were obtained (entry 6). This demonstrates that the reaction cannot be performed in the absence of amine base and, as such, these catalysts (*i.e.* amine and salt) must be acting in a co-operative fashion.

Table 5.2 Investigation into the role of amines in the catalysis of the lithium bromide mediated Tishchenko reaction

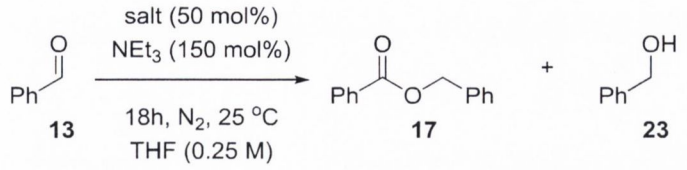


entry	amine	x (mol%)	yield **17** (%)[a]	yield **23** (%)[a]
1	NEt_3	150	33	10
2	$(iPr)_2NEt$	150	11	41
3	DBU	150	76	7
4	DBU	75	61	23
5	DBU	37.5	37	39
6	-	-	0	0

[a]Determined by ^{1}H NMR spectroscopy with reference to styrene as an internal standard.

To investigate the role of the metal counterion, it was decided to utilise other sources of lithium cations, however, in the cases of LiF, LiCl and Li_2CO_3 little or no ester product was formed (entries 1 – 3, Table 5.3). The sterically crowded tetraethylammonium cation was also found to be ineffective in the mediation of the disproportionation reaction (entry 4, Table 5.3). It is noteworthy that the respective lithium salts in each of these four reactions did not dissolve in the medium; however, the reactions performed in Table 5.2 were all a homogenous pale yellow solution.

Table 5.3 Investigation of the role of the salt

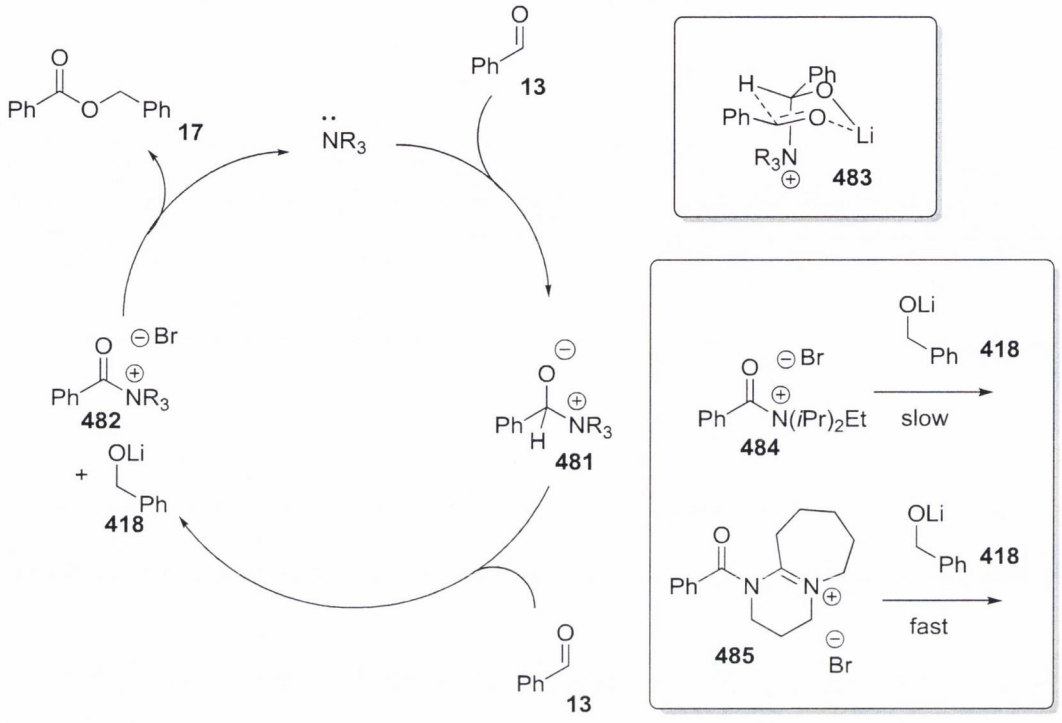


entry	salt	yield **17** (%)[a]	yield **23** (%)[a]
1	LiF	trace	0
2	LiCl	0	1
3	Li_2CO_3	3	0
4	NEt_4I	1	0

[a]Determined by ^{1}H NMR spectroscopy with reference to styrene as an internal standard.

On evaluation of the data compiled in Table 5.2 and Table 5.3, we theorised that the reaction must proceed through nucleophilic addition of the amine to the aldehyde, forming the zwitterionic species **481** (Scheme 5.1). Subsequently, hydride transfer occurs to form the alkoxide **418** and the acyl ammonium ion **482** *via* the six-membered transition state indicated **483**, a similar version of which was proposed by Abaee *et. al.* Finally, acyl transfer would furnish the ester **17** and regenerate the amine catalyst. This step is of particular interest as the sterically hindered $(i\text{Pr})_2\text{NEt}$ would theoretically form acyl amide **484** the reaction of which with the lithium alkoxide **418** would be much slower than the corresponding reaction with the DBU-derived acyl ammonium ion **485** as it is a much more sterically constrained intermediate. This would account for the poor yield of ester **17** obtained from the reaction mediated by $(i\text{Pr})_2\text{NEt}$.

Scheme 5.1 Possible catalytic cycle for the amine and lithium bromide catalysed Tishchenko reaction

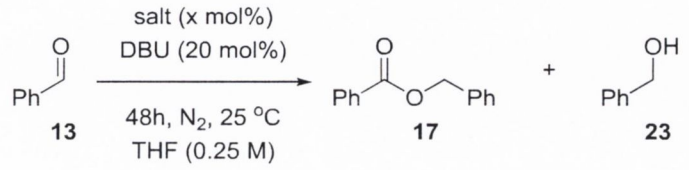


5.1.1 Optimisation of the DBU catalysed Tishchenko reaction

As the catalyst loadings of 75 mol% DBU and 50 mol% LiBr were exceptionally high, we decided to evaluate the effect of lower loadings on catalysis. Disappointingly, the yield of the ester product **17** depreciated to 53% and 56% yield at 20 mol% loading of DBU (entries 1 and 2, Table 5.4). The lithium chloride salt mediated the formation of the benzyl benzoate in low overall yields of 11% and 34% (entries 3 and 4). The lithium iodide salt proved to be a slightly better mediator of the reaction, allowing the ester to be afforded in 22% yield (entry 5). Lithium acetate proved an ineffective facilitator of the reaction, allowing only trace amounts of the ester to be formed after 48 hours (entry 6). Lithium perchlorate proved a better catalyst than lithium bromide at 50 mol% loading, however, it was not as effective at 20 mol% loading (entries 7 and 8). It is unclear whether this increased activity is due in part to the oxidative potential of the perchlorate anion.[152] Lithium azide, which was prepared *via* precipitation from a solution of sodium azide and lithium sulfate,[153] proved to be nearly completely ineffective at 20 mol% loading but an excellent co-catalyst for the reaction at a loading of 50 mol%, catalysing the formation of the ester product in 86% yield (entries 9 and

10). Evaluation of the sodium and potassium salts demonstrated a complete absence of catalytic activity (entries 11 – 13).

Table 5.4 Optimisation studies on the DBU catalysed Tishchenko reaction



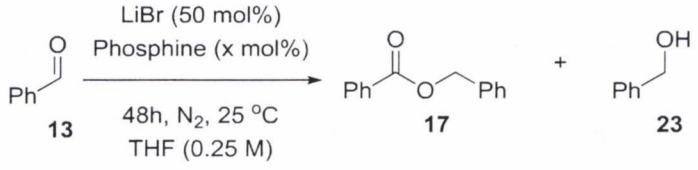
entry	salt	x (mol%)	yield **17** (%)[a]	yield **23** (%)[a]
1	LiBr	20	53	20
2	LiBr	50	56	28
3	LiCl	20	11	9
4	LiCl	50	34	9
5	LiI	20	22	20
6	LiOAc	20	2	1
7	$LiClO_4$	20	16	4
8	$LiClO_4$	50	66	13
9	LiN_3	20	1	8
10	LiN_3	50	86	6
11	NaBr	20	3	3
12	KBr	20	5	6
13	NaN_3	50	0	2

[a]Determined by ^{1}H NMR spectroscopy with reference to styrene as internal standard.

As phosphines are known to be similar, and sometimes more effective nucleophiles to amines,[154] it was decided to evaluate two different phosphines in the lithium bromide

mediated Tishchenko reaction. It was found that triphenylphosphine was a completely ineffective catalyst for the reaction, promoting the formation of neither benzyl benzoate (**17**), nor benzyl alcohol (**23**) in any observable yield (entries 1 and 2, Table 5.5). The more nucleophilic alkyl-substituted tributylphosphine proved to be only slightly effective in catalysing the formation of benzyl alcohol (**23**), predictably however, due to the steric bulk of the produced acylphosphine, it would appear that acyl transfer to form ester **17** is not favourable (entries 3 and 4).

Table 5.5 Evaluation of phosphines in the lithium bromide mediated Tishchenko reaction



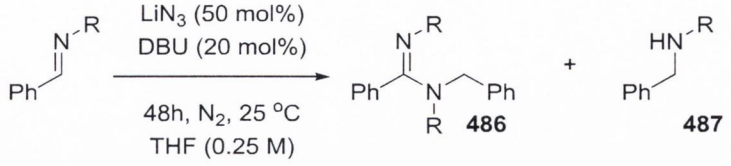
entry	phosphine	x (mol%)	ester yield (%)[a]	alcohol yield (%)[a]
1	PPh_3	20	0	0
2	PPh_3	50	0	0
3	PBu_3	20	0	1
4	PBu_3	50	1	6

[a]Determined by ^{1}H NMR spectroscopy with reference to styrene as an internal standard.

5.2 Evaluation of the potential substrate scope amenable to the DBU and lithium bromide catalysed Tishchenko reaction

It became apparent that this optimised methodology, though an improvement over the process reported by Abaee *et al.*, is not overall a significant contribution to the sum of knowledge on the Tishchenko reaction. Therefore, it was decided to focus on more ambitious goals, such as increasing the substrate scope to include substrates previously incompatible with the Tishchenko reaction; primary among these is the hydride transfer between imines.

Table 5.6 Evaluation of substituted imines in the DBU and lithium azide-catalysed Tishchenko-type reaction



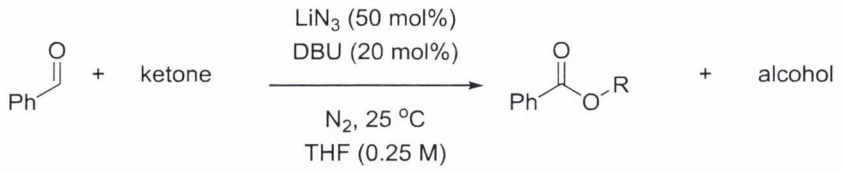
entry	R	yield **486** (%)[a]	amine yield (%)[a]
1	Ph	0	0
2	Ts	0	0

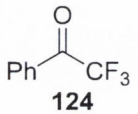
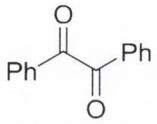
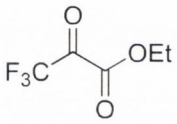
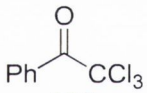
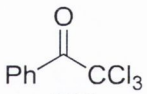
[a]Determined by ^{1}H NMR spectroscopy with reference to styrene as internal standard.

Disappointingly, the *N*-phenyl substituted imine, previously evaluated in the magnesium selenide-ion-catalysed methodology (see Section 4.3), was again found to be an incompatible substrate in this aza-Tishchenko-type reaction (entry 1, Table 5.6). The electron-deficient, tosyl-substituted imine, when subjected to the conditions of the reaction, appeared to decompose to its corresponding aldehyde and amine, as such no formation of the hydride transfer products was observed (entry 2).

As the imines proved to be ineffectual substrates for the hydride transfer reaction, it was decided to focus on selective intermolecular hydride transfer reactions. Initial evaluation with the trifluoromethylketone **124**, which previously exhibited excellent reactivity in both the magnesium thiolate and selenide-ion derived methodologies, proved incompatible with this methodology (entry 1, Table 5.7). The 1,2-diketone benzil (**477**) was also found to be inapplicable in this reaction, forming the corresponding alcohol in only trace amounts (entry 2). The CF_3-substituted pyruvate **480** was found to be of no utility in the reaction also (entry 3). The trichloromethyl-substituted ketone **383**, which was previously found to be useless in the magnesium thiolate and selenide-ion-catalysed methodologies, formed the crossed ester in 48% yield after 24 hours under the DBU and lithium azide-catalysed methodology (entry 5). This yield was further augmented to 71% yield after 48 hours (entry 6).

Table 5.7 Evaluation of various ketone substrates in the selective crossed Tishchenko reaction

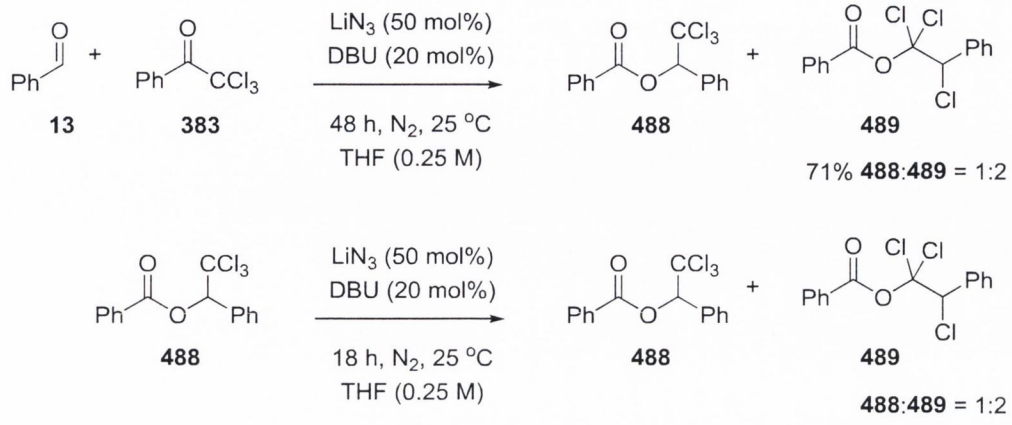


entry	ketone	time (h)	ester yield (%)[a]	alcohol yield (%)[b]
1	 **124**	24	0[b]	1
2	 **477**	24	0[b]	1
3	 **480**	24	0[b]	0
4	 **383**	24	48	20
5	 **383**	48	71[c]	13

[a]Isolated by silica gel column chromatography. [b]Identified by ^{1}H NMR spectroscopy with reference to styrene as an internal standard. [c]Isolated as a mixture of regio-isomers in a 1:2 ratio.

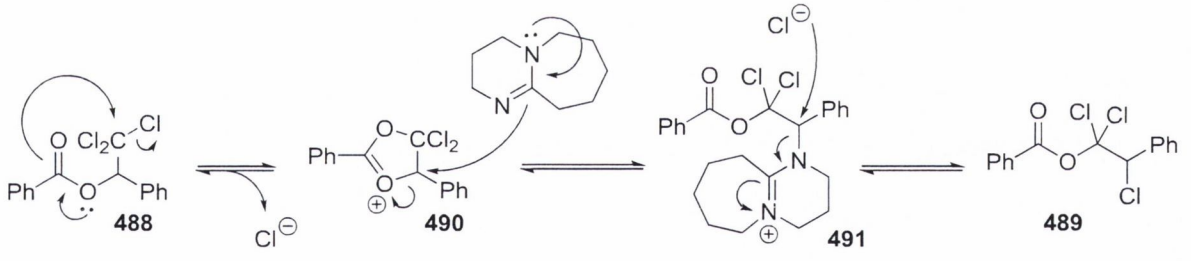
However, on isolation it was found that the ester obtained was a mixture of two regio-isomers in a ratio of 1:2 (Scheme 5.2). To ascertain whether product **489** is forming post-hydride transfer, the ester product **488** was synthesised separately; *via* the addition of benzoyl chloride to the corresponding trichloro-alcohol catalysed by DMAP, and was exposed to the DBU and LiN_3 reaction conditions. It was found that the regio-isomer **489** was formed in the same ratio as that observed in the hydride transfer reaction.

Scheme 5.2 The selective DBU and lithium azide-catalysed selective Tishchenko reaction between benzaldehyde and 2,2,2-trichloroacetophenone



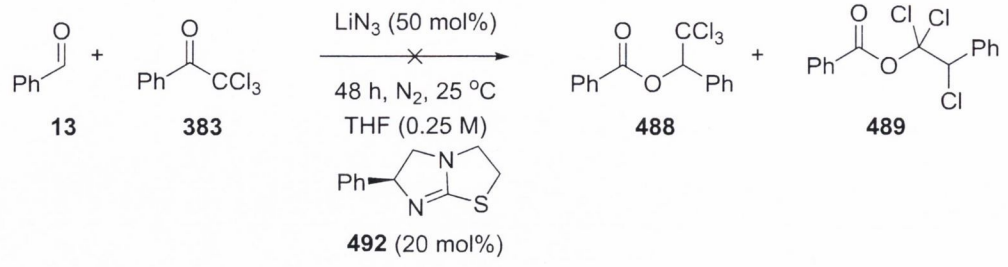
We theorised that the most likely mechanism for the formation of **489** from **488** is the oxa-cyclisation *via* the extrusion of chloride, to form the positively charged five membered ring **490** (Scheme 5.3). This is likely cleaved by DBU to furnish the ester **491**, which may in turn reaction *via* the S_N2-type reaction with chloride to generate the ester regio-isomer **489**.

Scheme 5.3 Possible mechanism for the formation of the ester regio-isomer **489** from **488**



Since the initial discovery that DBU is an effective amine catalyst for this methodology we theorised that chiral analogues of it may potentially be able to furnish enantioenriched crossed esters. Considering previously reported chiral DBU analogues used for the kinetic resolution of alcohols, it was decided to use (-)-tetramisole (**492**) as a test catalyst, commercially available as the hydrochloride salt and commonly used as a veterinary drug (Scheme 5.4).[155,156] Disappointingly however, no hydride transfer reaction was observed in the presence of this catalyst.

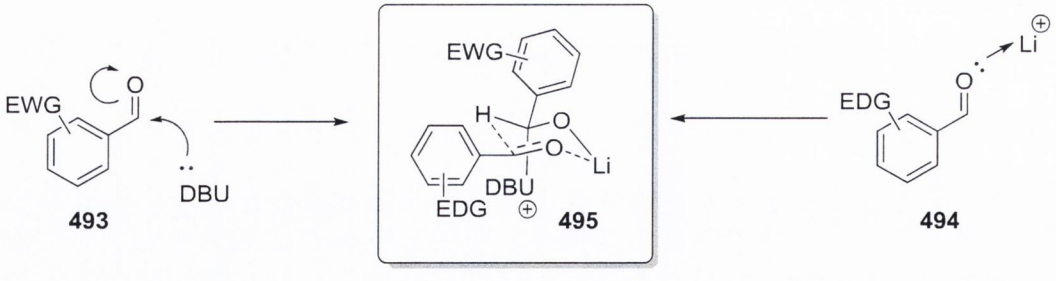
Scheme 5.4 Catalysis of the Tishchenko reaction with the enantioenriched DBU analogue, (-)-tetramisole



5.3 Catalysis of the selective Tishchenko reaction between two different aldehydes

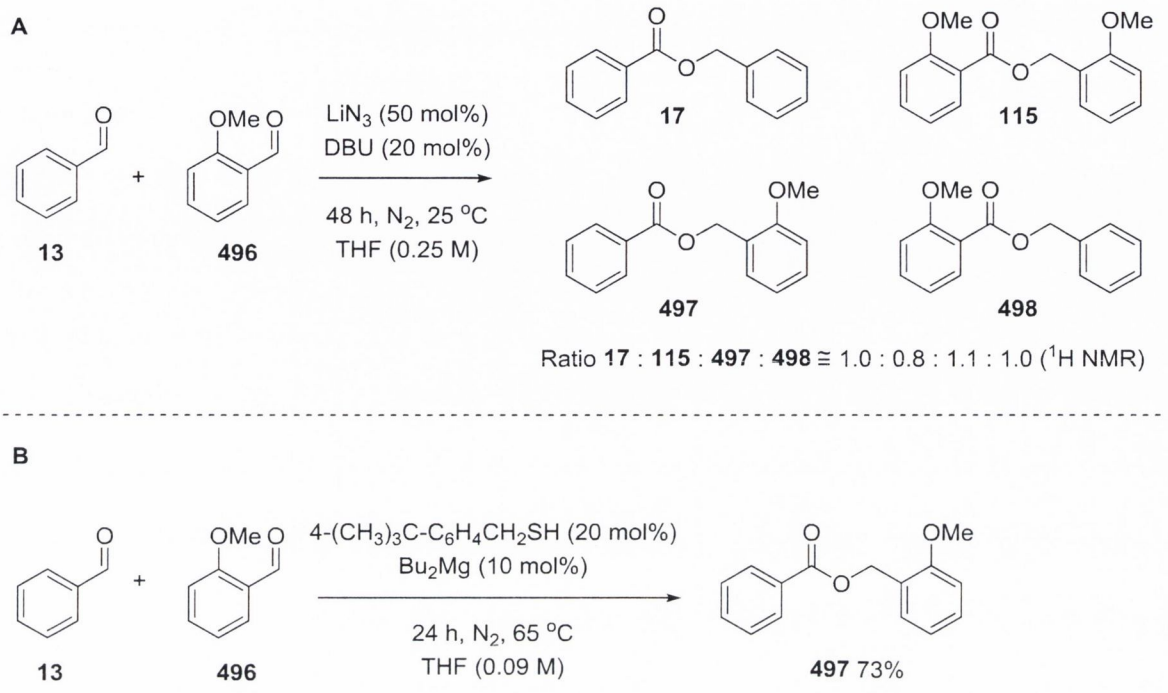
We theorised that this methodology may have the potential to catalyse the selective hydride transfer between two different aldehydes. Our rationale for this theory stemmed from the theoretical bimolecular mode of action of the co-catalysts. We posited that an electron-deficient aldehyde **493** would favour addition of the nucleophilic DBU, whereas an electron-rich aldehyde **494** would favour coordination to the lithium cation. Therefore for hydride transfer to occur these two adducts must interact to form the six-membered transition state **495**, thereby effecting a selective hydride transfer.

Scheme 5.5 Theorised mechanism for the selective Tishchenko reaction between two different aldehydes



On putting this theory into practice however, we were disappointed to find that on reaction of aldehydes **17** and **496** under the DBU and lithium azide-catalysed hydride transfer conditions, all four possible ester products were obtained in comparable ratios, and the conversion of the reaction only reached 74% (**A**, Scheme 5.6). Interestingly however, the reaction performed in parallel under the magnesium thiolate catalysed conditions contained a single product. On isolation, the ester was characterised as ester **497** and was obtained in 73% isolated yield, (**B**, Scheme 5.6). This discovery will be discussed further in Chapter 6.

Scheme 5.6 The selective Tishchenko reaction between 2 different aldehydes



As the DBU and lithium azide methodology did not furnish an excellent yield of benzyl benzoate (the maximum yield obtained was 86%) in the disproportionation reaction of benzaldehyde, and the crossed reaction with 2,2,2-trichloroacetophenone was fraught with complications, it was decided to abandon further research on this topic in favour of the much more ambitious selective Tishchenko reaction between two different aldehydes.

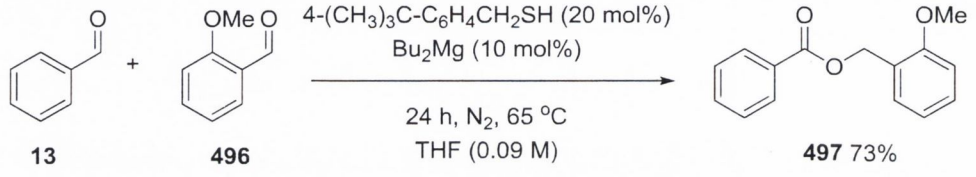
5.4 Conclusion

In conclusion, the improvement of a known, reported amine and lithium salt-catalysed methodology has been described here. Though much effort was exerted in the further expansion of this protocol, it was found that unsatisfactory novel applications could be found and the yields of ester products obtained were found to be relatively low compared with other methodologies. Attempts to develop a rationally designed methodology for the selective Tishchenko reaction between two different aldehydes failed using the lithium azide and DBU-catalysed methodology, with the formation of 4 unselective ester products being observed. However, the discovery of the magnesium thiolate-catalysed Tishchenko reaction appeared to hold considerable promise.

6.0 Studies on the origins of the chemoselectivity observed in the magnesium thiolate catalysed selective Tishchenko reaction between two different aldehydes

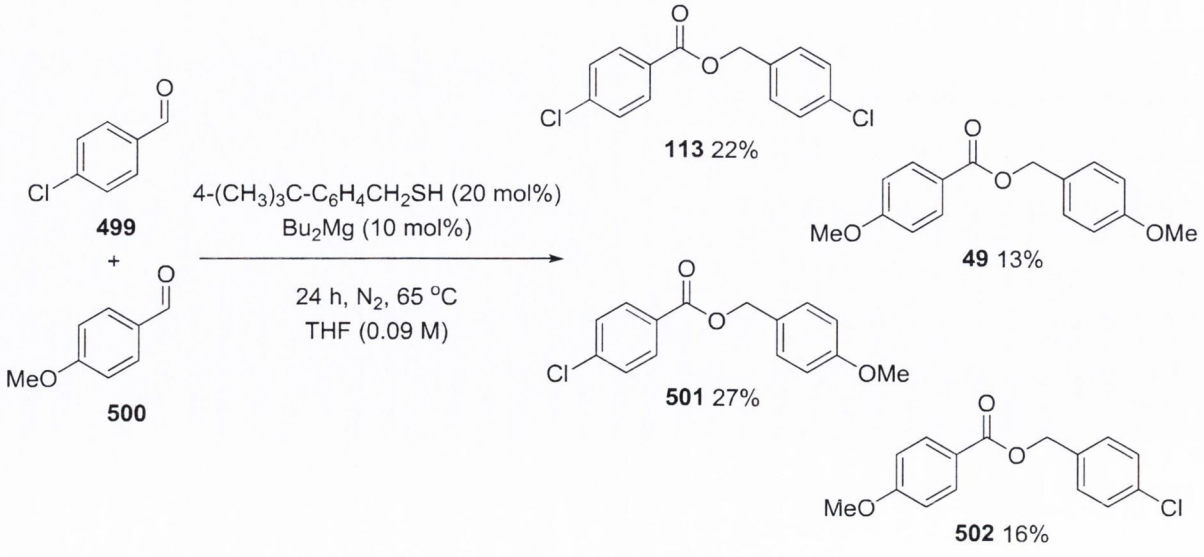
As previously discussed, the magnesium thiolate-catalysed methodology was found to promote the selective hydride transfer reaction between two different aldehydes (Scheme 6.1).

Scheme 6.1 Discovery of the selective Tishchenko reaction between two different aldehydes



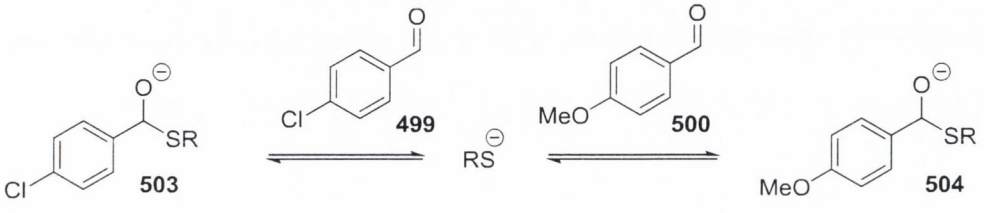
In order to understand the origin of this selectivity, it was decided to design a variety of experiments from which the selectivity of the reaction, and the products observed would allow us to formulate a theory. The first of such experiments was to determine if the electronic properties of the aromatic aldehyde substrates influence the chemoselectivity of the reaction (Scheme 6.2). It was found that when the electron-deficient aldehyde **499** and the electron-rich aldehyde **500** were exposed to the thiolate catalyst, all four of the possible products of the reaction were formed.

Scheme 6.2 Investigation of the electronic properties of the aldehyde substrates as the origin of the reaction chemoselectivity



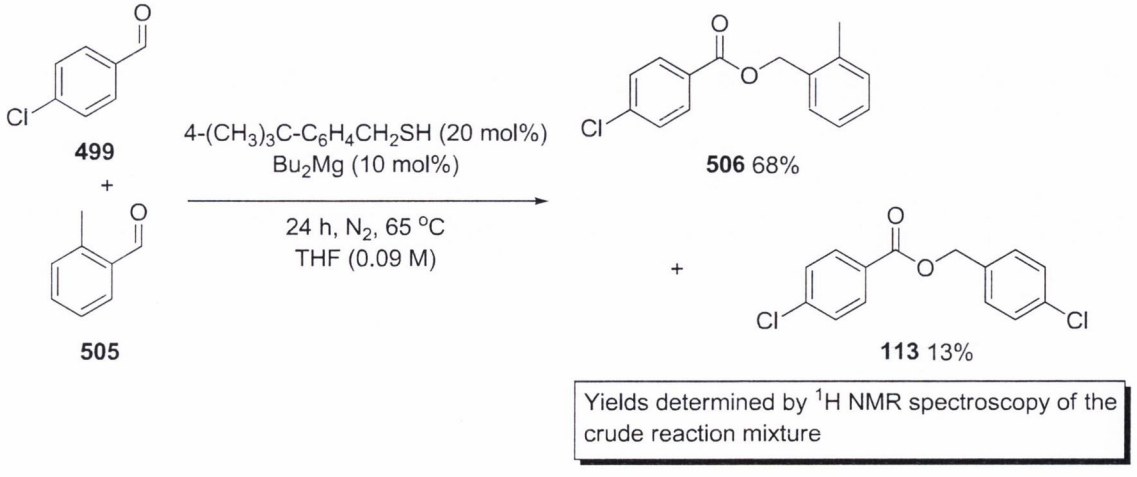
It is interesting to note that there does appear to be a slight electronic bias, with the formation of the products with oxidised chloro-substituted aldehydes (**113** and **501**) forming in higher yields than those of oxidised methoxy-substituted aldehydes (**49** and **502**). From these results, we postulated that the addition to electron-deficient aldehydes to form the conjugate base hemithioacetal **503** must be faster than the addition to electron-rich aldehydes to form the corresponding conjugate base hemithioacetal **504** (Scheme 6.3). It is likely therefore that the similar reactivity of both hemithioacetal conjugate bases (**503** and **504**) in the hydride transfer step, lead to the formation of multiple ester products.

Scheme 6.3 Rationale for the slight preferential formation of ester products



Failing to extract enough information from this, we decided to examine the influence of steric bulk. The reaction of the electron-deficient aldehyde **499** and the sterically encumbered aldehyde **505** furnished the ester **506** with reasonable selectivity; though it could not be separated chromatographically from the chloro-substituted ester dimer **113** (Scheme 6.4).

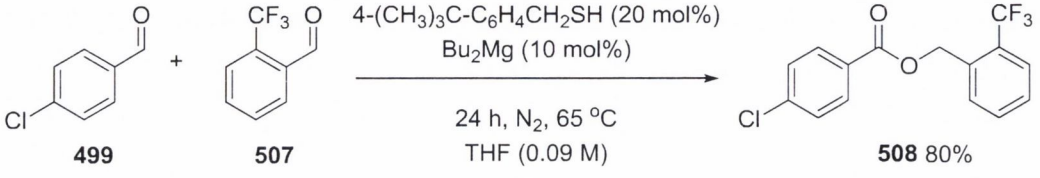
Scheme 6.4 Investigation of the steric bulk of the aldehyde substrate as the origin of the reaction chemoselectivity



Furthering this line of enquiry, the highly sterically hindered 2-trifluoromethyl-substituted aldehyde **507** was found to be a highly selective hydride acceptor on reaction with aldehyde

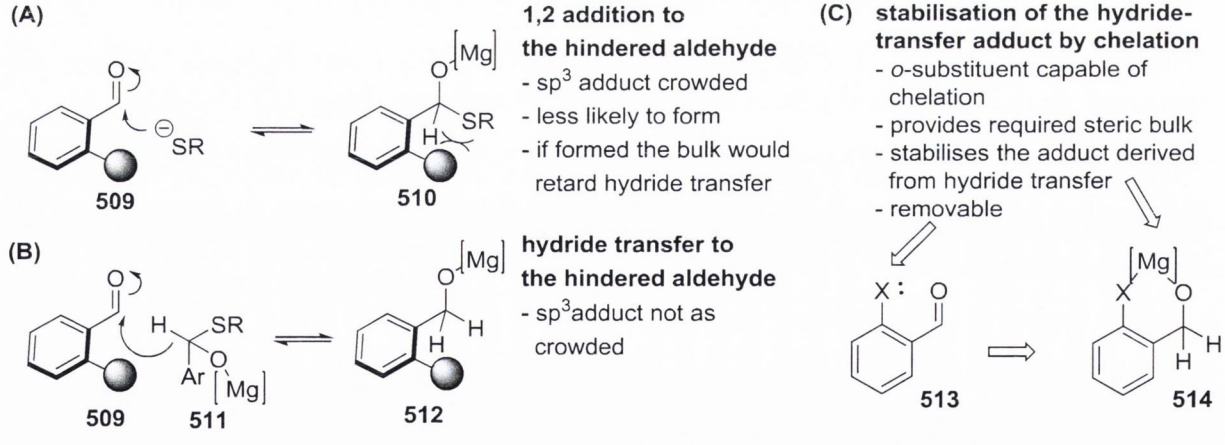
499 in the presence of the thiolate catalyst. As such, the ester **508** was isolated in 80% yield, which at the time represented the most selective Tishchenko reaction that we had knowledge of.

Scheme 6.5 Further study on the steric bias of the chemoselective crossed Tishchenko reaction between two different aldehydes



This suggests that steric bias is a major contributing factor in the reaction; however, it is not wholly responsible for the selectivity previously observed. We next decided to rationalise our findings mechanistically.

Scheme 6.6 Rationalisation of the observed chemoselectivity and the proposed influence of an *ortho* chelating group

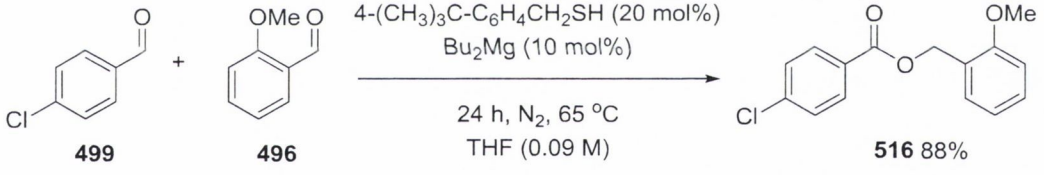


We posited that if the 1,2 addition of the thiolate to the aldehyde and the hydride transfer steps are reversible, then the chemoselectivity of the reaction could be due to the difference in stability of the sp^3 adducts arising from these steps. The addition of the thiolate catalyst to the hindered aldehyde **509** would generate **510**, a hemithioacetal conjugate base species that would be incapable of avoiding the steric strain associated with the interaction of the *ortho* substituent and the methane group (**A**, Scheme 6.6). Conversely the alkoxide **512**, derived from the hydride transfer from the hemithioacetal conjugate base **511**, is less sterically congested than **510** and therefore steric effects have lower influence over its formation (**B**,

Scheme 6.6). This rationale explains the formation of **506** (Scheme 6.4), however, it does not account for the fact that the homodimer **113** is not the major product. The increased chemoselectivity of the reactions containing groups capable of chelating the magnesium ions in the *ortho* position (*i.e.* methoxy) may be explained by the required steric component being fulfilled and the resultant stabilisation of the alkoxide adduct **514** (**C**, Scheme 6.6).

We postulated, if this mechanism was indeed correct, that if we performed the original selective Tishchenko reaction in the presence of an electron-deficient aldehyde instead of benzaldehyde, the crossed ester product-derived from this reaction would be formed in higher yield. Gratifyingly, it was found that the reaction of the chloro-substituted aldehyde **499** and aldehyde **496** under the magnesium thiolate-catalysed conditions, furnished the selective ester product **516** in 88% yield.

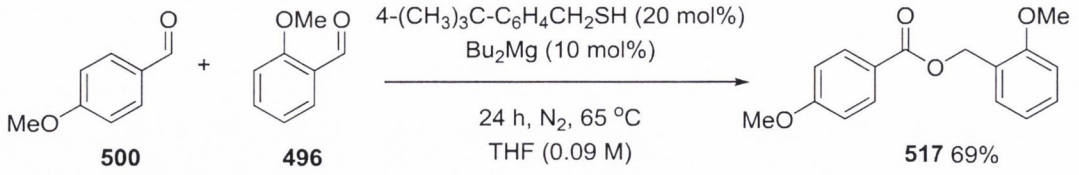
Scheme 6.7 The selective magnesium thiolate Tishchenko reaction between an electron-deficient aldehyde and 2-anisaldehyde



499 **496** **516** 88%

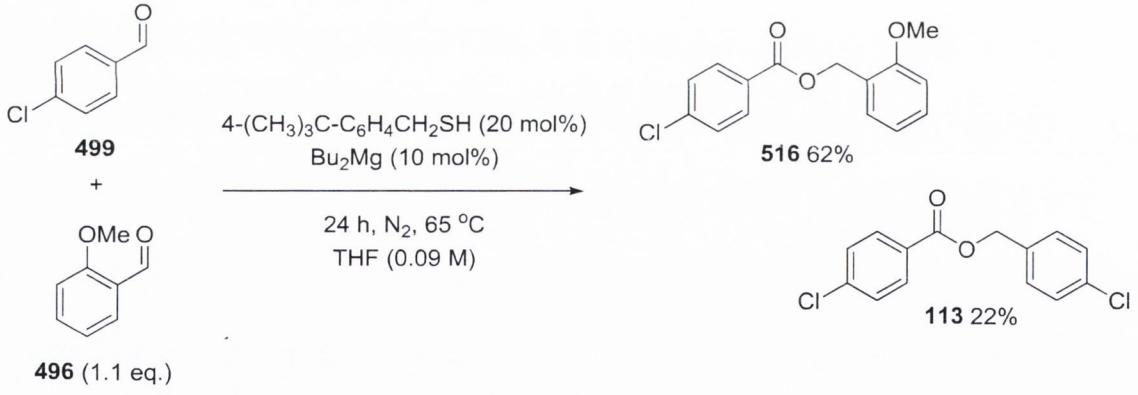
Conversely, we theorised that two electron-rich aldehyde substrates should be less selective due to a decrease in the rate of hemithioacetal conjugate base formation. Again, this proved correct, with the ester **517** forming in 69% yield (Scheme 6.8).

Scheme 6.8 The selective magnesium thiolate-mediated Tishchenko reaction between an electron-rich aldehyde and 2-anisaldehyde



In an effort to increase the observed selectivity we hypothesised that the introduction of a slight excess of the hydride accepting 2-anisaldehyde (**496**) would improve selectivity further as it may further favour the formation of the stabilised magnesium alkoxide. Disappointingly however, this was not the case as the yield of the crossed ester observed was decreased to 62% (Scheme 6.9).

Scheme 6.9 Initial evaluation of excess substrate loading on the observed selectivity of the reaction

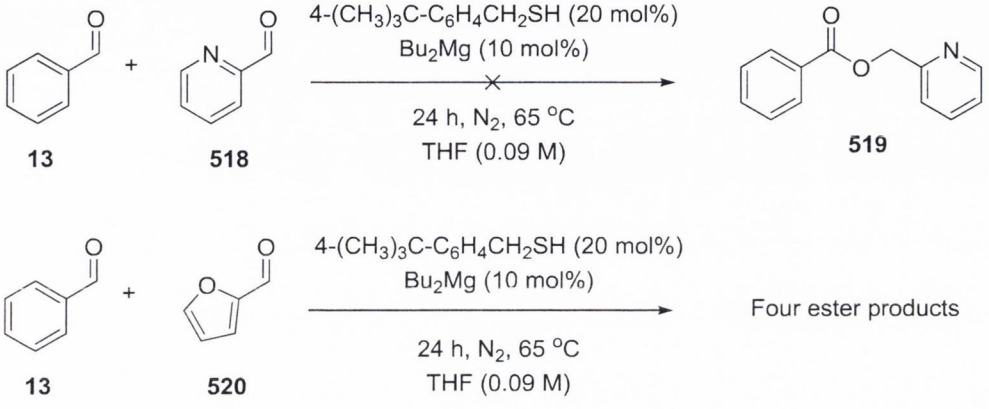


6.1 Evaluation of heterocyclic aldehydes in the selective crossed Tishchenko reaction between two different aldehydes

As lone-pair containing 2-substituted aldehydes were particularly selective in this reaction, we posited that 2-substituted heterocyclic aldehydes may exhibit the same propensity to undergo reduction in the selective Tishchenko reaction. It was found that 2-pyridinecarboxaldehyde (**518**) did not furnish any ester product, on reaction with benzaldehyde (**13**), in appreciable yield (Scheme 6.10). Conversely, furfural (**520**) was highly reactive but underwent completely unselective Tishchenko chemistry, forming all of the

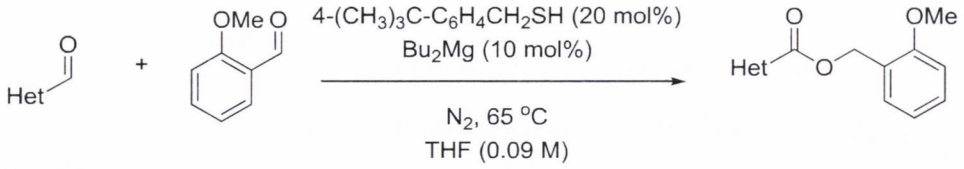
possible ester products in comparable yields (as determined by ^{1}H NMR spectroscopic analysis of the reaction crude mixture).

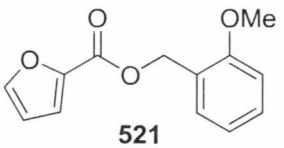
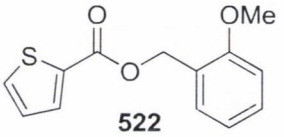
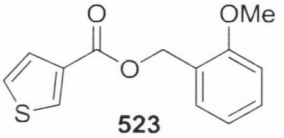
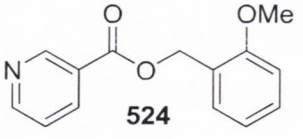
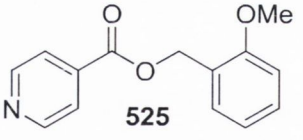
Scheme 6.10 Evaluation of heterocyclic aldehydes in the magnesium thiolate catalysed selective Tishchenko reaction between two different aldehydes



Following these studies, it was decided to evaluate heterocyclic aldehydes in the magnesium thiolate-catalysed Tishchenko reaction with 2-anisaldehyde. It was found that the 2-furyl-derived product **521** was formed in a paltry 16% yield (entry 1, Table 6.1). Similarly the 2-thiophene aldehyde produced the crossed ester product **522** in low yield (entry 2). This demonstrates that there must be some degree of stabilisation of the hemithioacetal conjugate base formed from the addition of thiolate to the heterocyclic aldehydes, however, not enough to prevent the formation of the six-membered ring required for hydride transfer. Production of the 3-thiophene-derived product **523** was found to proceed in 71% yield (entry 3). The 3-substituted pyridine aldehyde-derived product **524** was found to form in 61% yield after 36 hours (entry 4). Similarly, the 4-substituted pyridine regio-isomer product **525** was furnished in 63% yield (entry 5).

Table 6.1 Evaluation of heterocyclic aldehydes with 2-anisaldehyde in the Tishchenko reaction



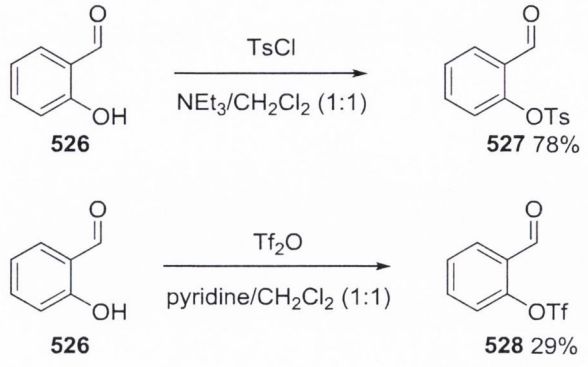
entry	product	time (h)	yield (%)[a]
1	 **521**	24	16[b]
2	 **522**	24	38[b]
3	 **523**	24	71
4	 **524**	36	61
5	 **525**	36	63

[a]Isolated by silica gel column chromatography. [b]Determined by ^{1}H NMR spectroscopy with reference to styrene as an internal standard.

6.1.1 The evaluation of 2-substituted aldehydes with 4-chlorobenzaldehyde in the Tishchenko reaction

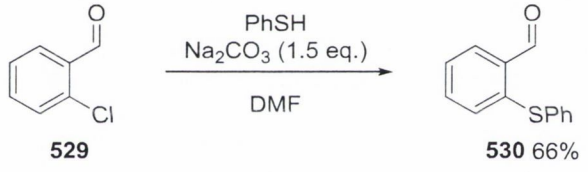
It seemed prudent at this point to evaluate other 2-substituted aldehydes as hydride acceptors in this methodology. We theorised that functional groups similar to methoxy would be most likely to be effective in the methodology. As such, the 2-*O*-tosyl substituted aldehyde **527** and the 2-*O*-triflyl substituted aldehyde **528** were synthesised in 78% and 29% yield respectively from salicylaldehyde (**526**, Scheme 6.11). [157]

Scheme 6.11 Synthesis of 2-*O*-substituted aldehydes from salicylaldehyde



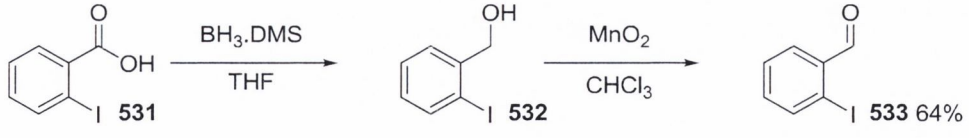
The 2-phenylthioether aldehyde **530** was synthesised in 66% yield *via* the S_NAr reaction of thiophenol and 2-chlorobenzaldehyde (**529**) in the presence of sodium carbonate (Scheme 6.12).

Scheme 6.12 Synthesis of 2-thiophenylether-substituted benzaldehyde



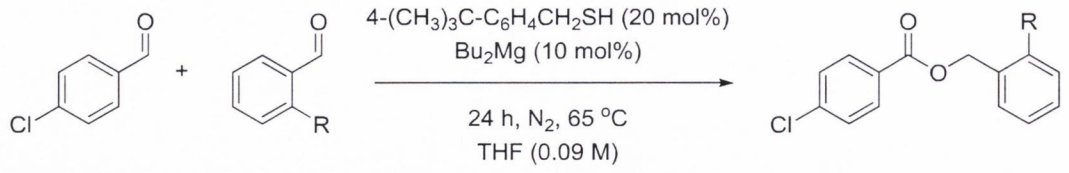
The 2-iodo-substituted aldehyde **533** was synthesised in 64% overall yield *via* the reduction of the corresponding commercially available substituted benzoic acid **531**, followed by the mild oxidation of the resulting alcohol **532** (Scheme 6.13).

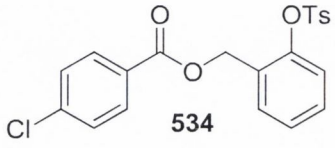
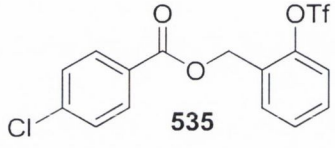
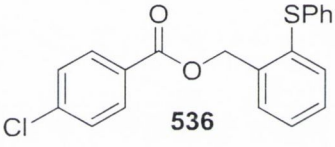
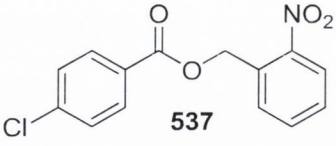
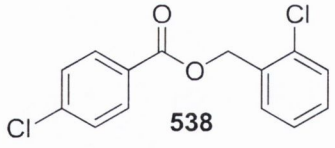
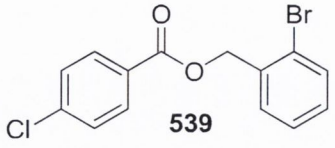
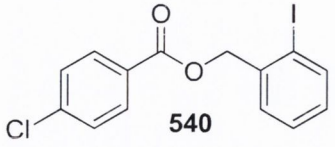
Scheme 6.13 Synthesis of 2-iodobenzaldehyde



The 2-*O*-tosyl substituted aldehyde **527** was found to furnish the selective crossed ester product **534** in the excellent yield of 93% on reaction with 4-chlorobenzaldehyde (entry 1, Table 6.2). Spurred on by this, the more synthetically useful 2-triflate-substituted aldehyde was evaluated with 4-chlorobenzaldehyde, disappointingly however, the Tishchenko product **535** was only produced in 64% yield, with the remainder favouring the formation of the chloro-substituted ester dimer (entry 2).

Table 6.2 Evaluation of lone-pair containing 2-substituted aldehydes with 4-chlorobenzaldehyde in the selective Tishchenko reaction



entry	product	yield (%)[a]
1	 **534**	93
2	 **535**	64[b]
3	 **536**	71
4	 **537**	65[b]
5	 **538**	78[b]
6	 **539**	94
7	 **540**	56[b]

[a]Isolated by silica gel column chromatography. [b]Determined by ^{1}H NMR spectroscopy with reference to styrene as an internal standard.

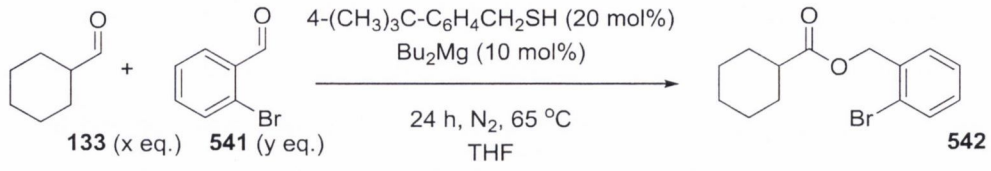
Evaluation of the 2-thiophenylbenzaldehyde (**530**) in the selective Tishchenko reaction with 4-chlorobenzaldehyde furnished the ester product **536** in 71% yield (entry 3, Table 6.2).

When 2-nitrobenzaldehyde was employed in the reaction, it was found that the ester product **537** was produced in 65% yield, though it could not be separated from the 4-chloro-substituted homo-Tishchenko product. Postulating that 2-halo-substituted aldehydes might exhibit similar selectivity to 2-methoxy-derived aldehydes in the Tishchenko chemistry (due to their relative size and the presence of lone pair electrons) it was decided to evaluate a selection of them in the crossed intermolecular Tishchenko reaction between two aldehydes. The ester product **538** was obtained in 78% yield, though it could not be separated from the 4-chlorobenzaldehyde homo-Tishchenko product (entry 5). The bromo-substituted ester product **539** was produced in the excellent yield of 94% (entry 6). Bromo-substituted ester products similar to **539** have previously been used as synthons for the production of substituted benzophenones.[158] The iodo-substituted ester product **540** was observed to form in 56% yield, the competing formation of the chloro-substituted ester dimer accounting for the remainder of the 4-chlorobenzaldehyde (entry 7).

6.1.2 Evaluation of α-branched aliphatic aldehydes in the selective Tishchenko reaction with 2-bromobenzaldehyde

As previously observed, α-branched- and unbranched-alkyl aldehydes had undergone aldol condensation reactions under these thiolate-catalysed conditions. On reaction of cyclohexanecarboxaldehyde (**133**) and 2-bromobenzaldehyde (**541**), the ester product **542** was formed in only 58% yield (entry 1, Table 6.3). In an effort to suppress the aldol reaction, a variety of conditions were employed to augment this yield. On doubling the equivalents of aliphatic aldehyde, it was found that ester **542** was formed in a slightly lower yield of 55% (entry 2). Gratifyingly, it was found that the ester **542** was produced in 72% isolated yield in the presence of 2 equivalents of 2-bromobenzaldehyde (entry 3). As expected, the yield of ester produced at half the concentration was drastically lower (entry 4). On doubling the concentration however, ester **542** was formed in 63% yield (entry 5).

Table 6.3 Optimisation of conditions for the selective Tishchenko reaction between cyclohexanecarboxaldehyde and 2-bromobenzaldehyde



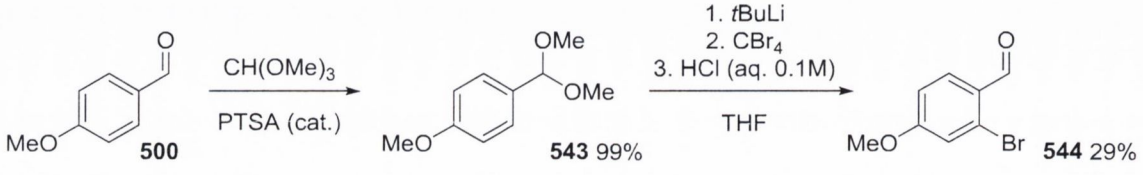
entry	x	y	conc. (M)	yield of **542** (%)[a]
1	1	1	0.09	58
2	2	1	0.09	55[b]
3	1	2	0.09	72
4	1	1	0.045	33[b]
5	1	1	0.18	63[b]

[a]Isolated by silica gel column chromatography. [b]Determined by ^{1}H NMR spectroscopy with reference to styrene as an internal standard.

6.2 The synthesis of 2-substituted aldehyde substrates

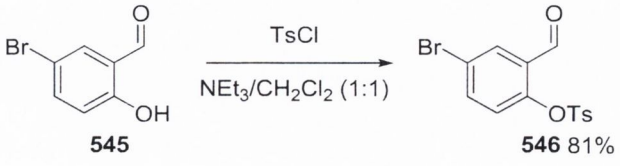
Having developed this highly selective methodology for the formation of crossed Tishchenko products derived from the reaction of two different aldehydes, it was decided that a large range of potentially synthetically useful aldehydes should be procured in order to demonstrate the utility of this methodology. The first of such was the di-substituted aldehyde **544**, which was synthesised from 4-anisaldehyde (**500**) in two steps: acetal protection of the aldehyde functional group using trimethyl orthoformate in catalytic acid to furnish compound **543** in 99% yield; followed by, *ortho*-lithiation, subsequent bromination and deprotection in aqueous HCl to furnish **544** in 29% yield (Scheme 6.14). [159]

Scheme 6.14 The synthesis of 2-bromo substituted aldehyde **544**



The 2-*O*-tosyl-substituted aldehyde **546** was furnished in 81% yield from the tosylation of the commercially available 5-bromo-substituted salicylaldehyde **545** (Scheme 6.15).

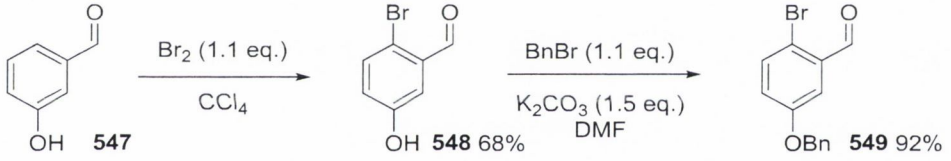
Scheme 6.15 The synthesis of 2-*O*-tosyl-substituted aldehyde **546**



545 **546** 81%

Bromination of the commercially available 3-hydroxybenzaldehyde **547** using molecular bromine furnished 2-bromo-4-hydroxybenzaldehyde (**548**) in 68% yield (Scheme 6.16). On reaction of this aldehyde with benzyl bromide and base in DMF the multi-substituted aldehyde **549** was furnished in 92% yield.[160]

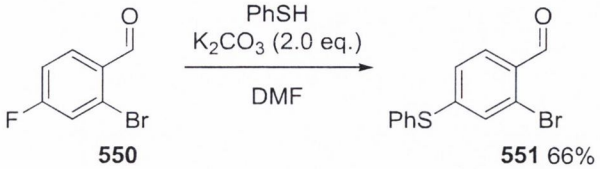
Scheme 6.16 The synthesis of 2-bromo-5-*O*-benzylbenzaldehyde (**549**)



547 **548** 68% **549** 92%

The commercially available 2-bromo-4-fluorobenzaldehyde (**550**) furnished the 2-bromo-4-thiophenyl-substituted benzaldehyde **551** in 66% yield *via* the S_NAr reaction with thiophenol and base in DMF (Scheme 6.17).[161]

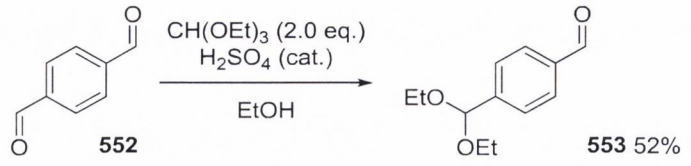
Scheme 6.17 The synthesis of the 2-bromo-4-thiophenylether-substituted benzaldehyde



550 **551** 66%

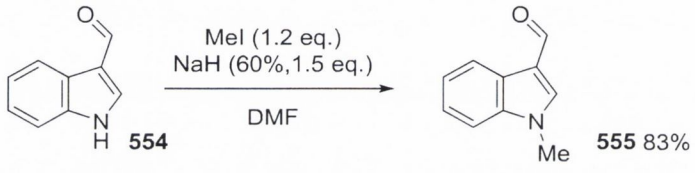
The acetal-protected benzaldehyde **553** was prepared in 52% yield from terephthaldehyde (**552**) on stirring in trimethyl orthoformate and catalytic amounts of acid (Scheme 6.18).[162]

Scheme 6.18 The synthesis of the *mono*-ortho ester protected terephthaldehyde



The *N*-methyl 3-formylindole **555** was synthesised *via* the methylation of 3-formylindole (**554**) using a small excess of methyl iodide and sodium hydride (Scheme 6.19).[163]

Scheme 6.19 The synthesis of the methylated 3-formyl-substituted indole **555**

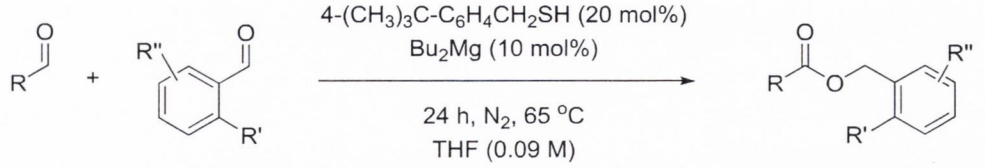


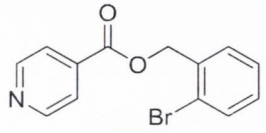
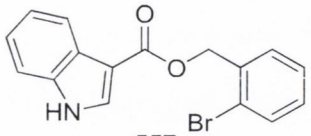
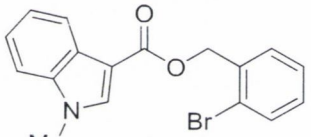
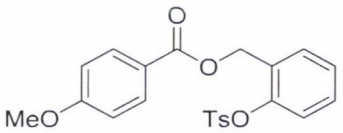
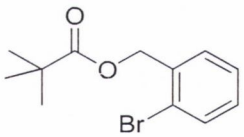
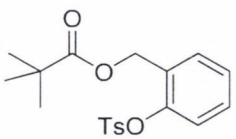
All of the other aldehydes employed from this point on were commercially available and purified by either distillation or recrystallisation prior to the reaction.

6.3 Evaluation of the full substrate scope

It was decided that these aldehydes, along with other commercially procured aldehydes, should be evaluated under the Tishchenko reaction conditions and the ratio of ester products formed would allow us to determine the reaction selectivity (*i.e.* ester selectivity ratio: the relative ratio of ester products observed in the ^{1}H NMR spectrum of the crude reaction mixture). The 4-pyridine-substituted ester **556** was formed in 78% yield (entry 1, Table 6.4). The reaction with indole-based aldehyde **554** proved to be selective in the formation of a majority of one ester product on reaction with 2-bromobenzaldehyde, furnishing the ester product **557**, though a high yield was not observed in the reaction (entry 2). The methylated derivative **555** did not prove much better; ester **558** was formed in low yield (entry 3). Both of these reactions contained only one observable major ester product, though neither reaction reached full conversion. Therefore, it is likely that the electron-rich nature of the indole-derived aldehyde may prevent its reaction with the catalyst. Similarly, the formation of ester **559** proceeded selectively, however, the rate of reaction was greatly lowered in the presence of the electron-rich 4-anisaldehyde (entry 4).

Table 6.4 Evaluation of the substrate scope of the crossed Tishchenko reaction

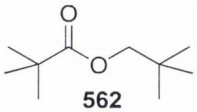


entry	product	ester selectivity ratio[a]	yield (%)[b]
1	 **556**	1.0 : 0.1 : 0.1: 0	78[c]
2	 **557**	1.0 : 0.2 : 0.21 : 0.1	30[c]
3	 **558**	1.0 : 0.15 : 0.15 : 0	31[c]
4	 **559**	1.0 : 0.30 : 0.16 : 0.1	42[c]
5	 **560**	1.0 : 0.22 : 0.12 : 0	63
6	 **561**	1.0 : 0.24 : 0.07 : 0	32[c]

[a]Determined by integration of the ^{1}H NMR spectrum of the crude product. [b]Isolated by silica gel column chromatography. [c]Determined by ^{1}H NMR spectroscopy with reference to styrene as an internal standard.

Reaction of the sterically hindered pivaldehyde with 2-bromobenzaldehyde produced the ester **560** in 63% isolated yield (entry 5). The ester **561** was formed in poor yield from the reaction of pivaldehyde and the *O*-tosyl-substituted benzaldehyde (entry 6). The major side product of this reaction was determined to the ester dimer of pivaldehyde **562** (Figure 6.1).

Figure 6.1 The major side product of the reaction of pivaldehyde and 2-substituted benzaldehydes

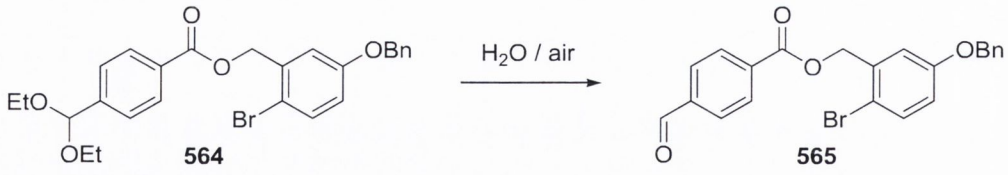


562

In an attempt to evaluate an electron-rich aldehyde as the hydride donor and an electron-deficient aldehyde as the hydride acceptor on the chemoselectivity of the process, the ester **563** was formed in 45% yield (entry 1, Table 6.5). As expected, the selectivity of this reaction was much lower than that observed in the previous table. This must be due to the decreased rate of thiolate addition to 4-anisaldehyde.

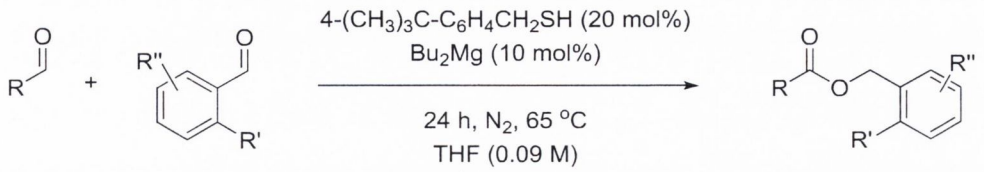
However, the orthogonally protected ester **564** was found to form highly selectively and in excellent yield (entry 3). This ester may be easily deprotected to form the aldehyde *via* the hydrolysis of the orthoester, and occurs readily on exposure to air (Scheme 6.20).[164]

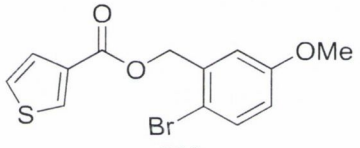
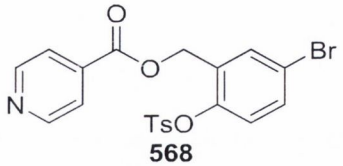
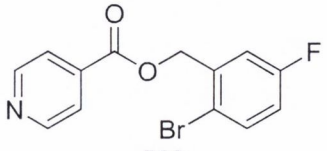
Scheme 6.20 Degradation of the orthoester moiety of ester **564**



Gratifyingly, the heterocyclic thiophene-derived esters **566** and **567** were obtained with excellent selectivity and yield, with **567** being furnished in near quantitative yield (entries 4 and 5). The pyridine-derived ester **568**, however, was generated in 72% yield (entry 6).

Table 6.5 Evaluation of the substrate scope of the selective Tishchenko reaction

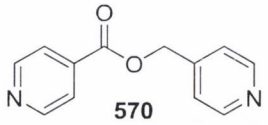


entry	product	ester selectivity ratio[a]	yield (%)[b]
1	 **563**	1.0 : 0.43 : 0.22 : 0.05	45[c]
2	 **564**	N/D[d]	92
3	 **566**	N/D[d]	95
4	 **567**	N/D[d]	99
5	 **568**	1.0 : 0.1 : 0.04 : 0	72
6	 **569**	1.0 : 0.15 : 0.01 : 0	69

[a]Determined by integration of the ^{1}H NMR spectrum of the crude product [b]Isolated by silica gel column chromatography. [c]Determined by ^{1}H NMR spectroscopy with reference to styrene as an internal standard. [d]N/D = not determined.

The pyridine-derived ester **569** was obtained in 69% yield and lower selectivity (entry 6). It is likely that the reduced selectivity is due to the generation of the 4-pyridine ester dimer **570** (Figure 6.2), the formation of which would be preferred by the electron-deficient nature of the aldehyde, favouring both reduction by hydride transfer and nucleophilic attack by the thiolate catalyst. This theory was supported by the presence of corresponding proton resonances in the ^{1}H NMR spectrum of the crude reaction mixture.

Figure 6.2 The major side-product formed in the Tishchenko reactions involving 4-pyridinecarboxaldehyde

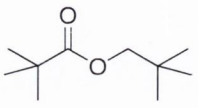


570

As expected, the Tishchenko reaction of α-branched-alkyl aldehydes and 2-substituted benzaldehydes proved difficult. It was found that ester **571** was obtained in only 11% yield (entry 1, Table 6.6). Similarly, ester **572** was also formed in a paltry 11% yield (entry 2). The cyclohexanecarboxaldehyde-derived ester **573** was generated in 26% yield and low selectivity (entry 3). In each of these reactions the aliphatic aldehyde reaction component was completely consumed, indicating that the formation of the aldol products is again predominating.

The reaction of pivaldehyde and the electron-deficient 2-bromo-5-fluorobenzaldehyde generated the crossed ester in **574** in 35% yield and low selectivity (entry 4). This was attributed to the production of the pivaldehyde ester dimer **562** previously observed in such reactions and, once the pivaldehyde had been consumed, the formation of the ester dimer of the electron-deficient 2-bromo-5-fluorobenzaldehyde **575** predominated (Figure 6.3)

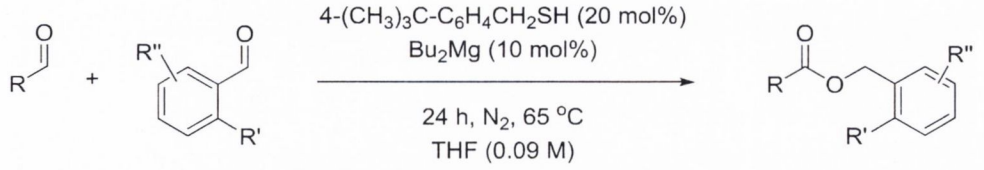
Figure 6.3 Side products of the reaction to form ester **574**

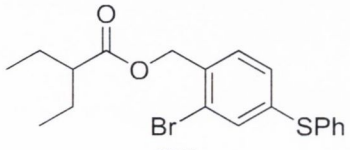
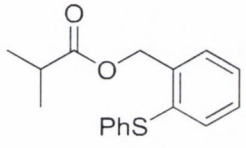
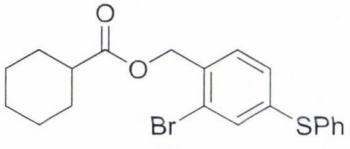
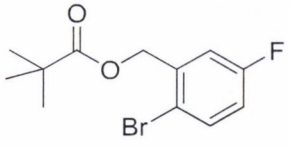
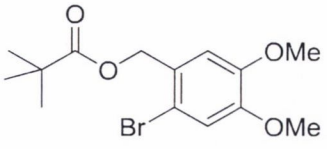
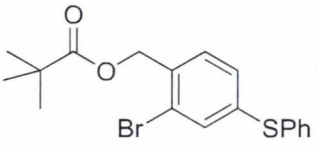


562

575

Table 6.6 Evaluation of 2-functionalised aldehydes in the crossed Tishchenko reaction



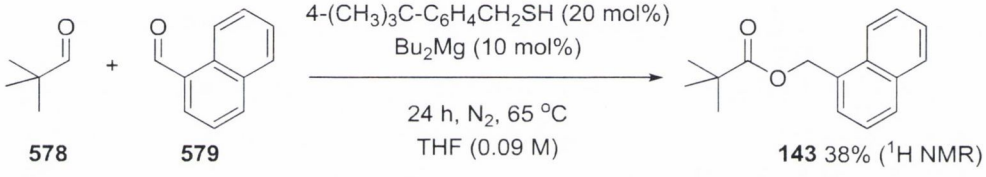
entry	product	ester selectivity ratio[a]	yield (%)[b]
1	 **571**	N/D[c]	11[d]
2	 **572**	N/D[c]	11[d]
3	 **573**	1 : 0.4 : 0 : 0	26[d]
4	 **574**	1 : 0.39 : 0.25 : 0	35[d]
5	 **576**	1 : 0.27 : 0.02 : 0	40[d]
6	 **577**	1 : 0.31 : 0 : 0	62

[a]Determined by integration of the ^{1}H NMR spectrum of the crude product. [b]Isolated by silica gel column chromatography. [c]N/D = not determined. [d]Determined by ^{1}H NMR spectroscopy with reference to styrene as internal standard.

Ester **576** was generated in 40% yield and the selectivity was not found to be optimum, with the formation of the pivaldehyde ester dimer side product **562** predominating again (entry 5). Finally, it was found that ester **577** was formed in 62% yield, with the major side product, again, being identified as ester **562** by ^{1}H NMR spectroscopy (entry 6).

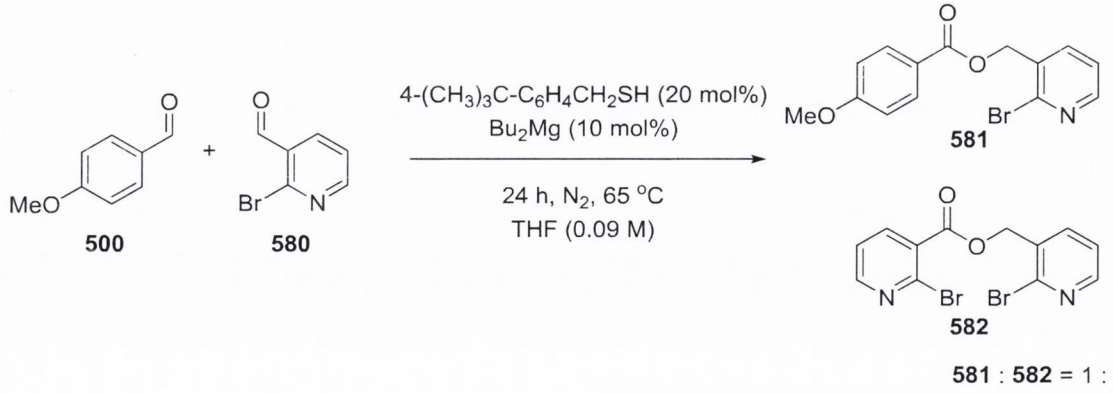
On review of the publication by Ogoshi *et al.*,[39] it was decided to evaluate the reaction of pivaldehyde (**578**) with 1-naphthaldehyde (**579**) using our magnesium thiolate-catalysed methodology (Scheme 6.21). Disappointingly however, it was found that the yield of the ester product **143** was found to be 38%, whereas Ogoshi *et al.* reported a yield of 65%.

Scheme 6.21 Evaluation of pivaldehyde and 1-naphthaldehyde in the crossed Tishchenko reaction



In an effort to extend the substrate scope to include 2-bromo-substituted heterocyclic aldehydes, the reaction of 4-anisaldehyde (**500**) and 2-bromo-3-pyridinecarboxaldehyde (**580**) was performed under the thiolate-catalysed conditions (Scheme 6.22). Disappointingly however, ^{1}H NMR spectroscopic analysis indicated that **581** and **582** were formed in roughly equal amounts.

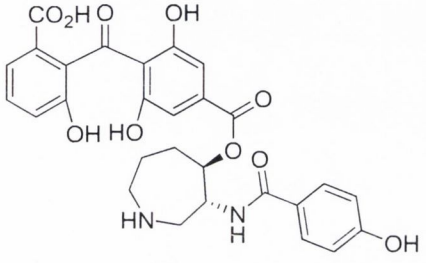
Scheme 6.22 Evaluation of 2-bromo-3-pyridinecarboxaldehyde as a substrate in the crossed Tishchenko reaction



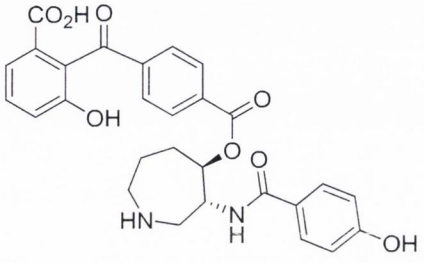
6.4 The attempted synthesis of the key intermediate in the formation of dideoxybalanol

Nicolaou *et al.* were the one of first groups to synthesise the protein kinase C inhibitor balanol (**583**) and its derivative 4'', 6''-dideoxybalanol (**584**, Figure 6.4).[165]

Figure 6.4 Balanol and its 4'', 6''-dideoxy derivative



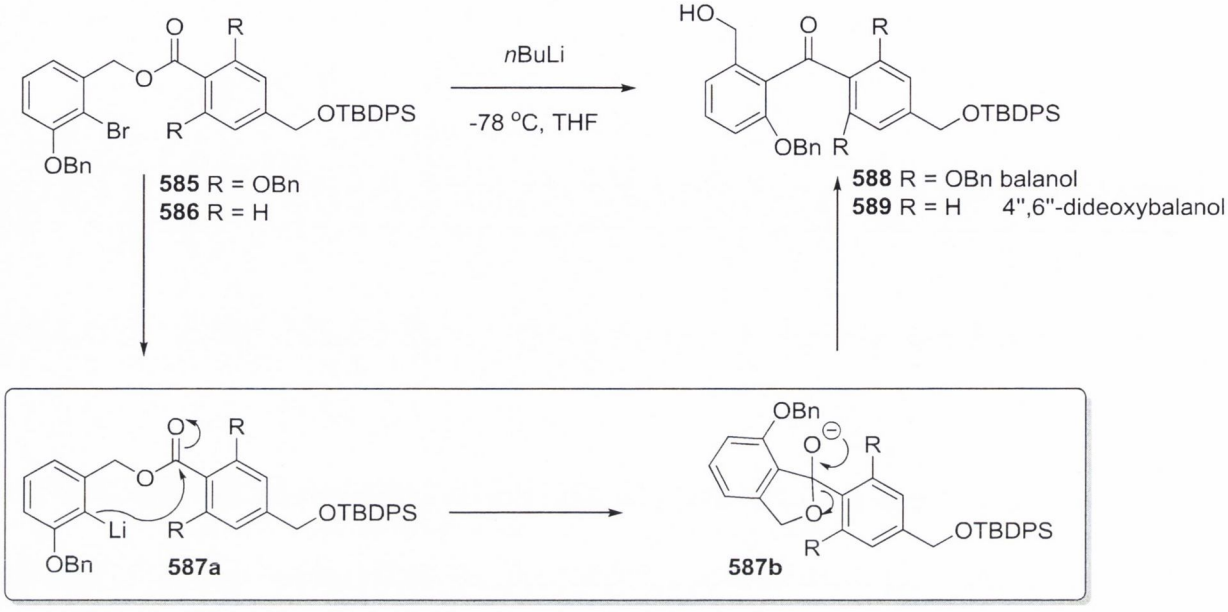
583 balanol



584 4", 6"-dideoxybalanol

The key intermediate for the formation of the benzophenones present in the structure of balanol is the bromo-substituted benzyl ester **585**, which on treatment at -78 °C with *n*-butyllithium formed the metal-halogen transfer product **587a** (Scheme 6.23). On formation of this intermediate the intramolecular ester cleavage occurs *via* the tetrahedral intermediate **587b** to form the substituted benzophenone **588**. As our magnesium thiolate-catalysed methodology for the crossed Tishchenko reaction forms similar bromo-substituted esters, we postulated that the synthesis of these intermediates may be performed *via* a catalytic Tishchenko reaction.

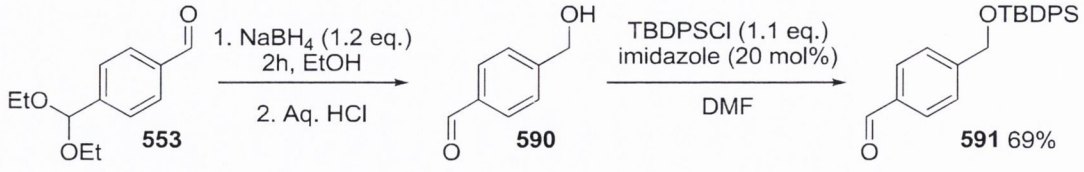
Scheme 6.23 The key step in the synthesis of the benzophenone portion of balanol and its derivatives



However, on evaluation of the aldehydes involved, it became apparent that the two aldehydes required for the synthesis of ester **585** were incompatible with our methodology as they both contained chelating *ortho*-substituents. It was for this reason that we focused our attention on the selective synthesis of ester **586**, which would furnish 4'', 6''-dideoxybalanol.

The first required aldehyde (*i.e.* **591**) was synthesised in 69% overall yield in two steps; initial reduction of aldehyde **553** to form **590** in quantitative yield, which was used without further purification in the protection reaction with TBDPS chloride and imidazole.

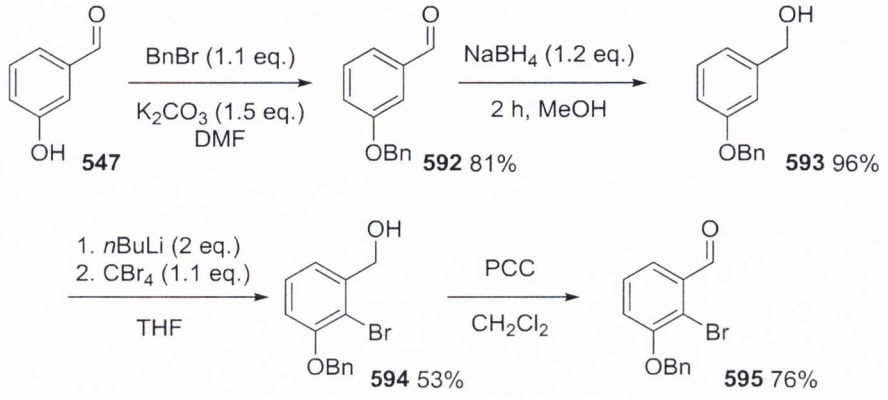
Scheme 6.24 Synthesis of the protected aldehyde **591**



The second required aldehyde **595** was synthesised *via* benzylation of aldehyde **547** using benzyl bromide and potassium carbonate in DMF, affording the 3-*O*-benzyl-substituted benzaldehyde **592** in 81% yield (Scheme 6.25). Reduction of this aldehyde produced the corresponding substituted benzyl alcohol **593** in 96% yield. Ortho-lithiation and subsequent

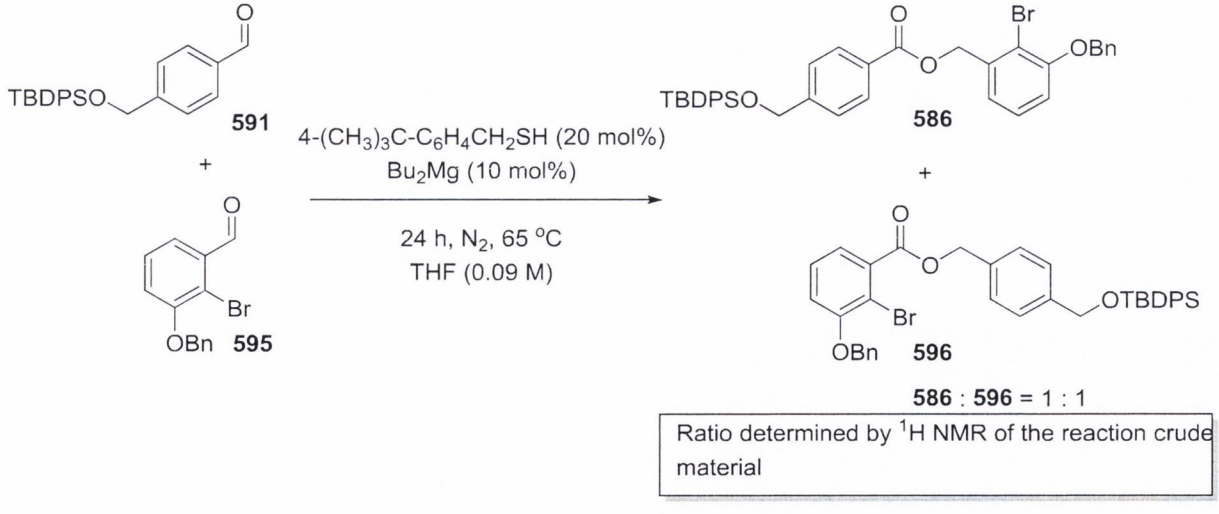
bromination with CBr_4 furnished the 2-bromo-3-*O*-benzyl-substituted benzyl alcohol **594** in 53% yield. Finally, oxidation using PCC produced the required aldehyde **595** in 76% yield.

Scheme 6.25 Synthesis of the 2-bromo-3-*O*-benzyl-substituted benzaldehyde



On reaction of these two aldehydes under our magnesium thiolate-catalysed conditions, we were disappointed to find that the desired ester **586** formed in equal amounts to the alternative crossed ester **596** (Scheme 6.26).

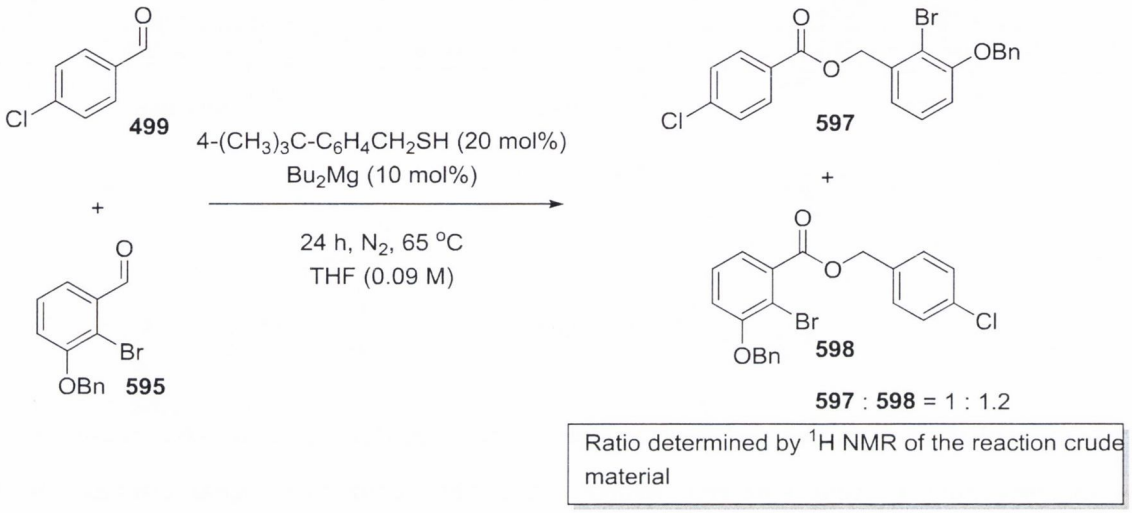
Scheme 6.26 Attempted synthesis of the key intermediate for the synthesis of balanol



In an attempt to further understand this, the TBDPS-protected aldehyde **591** was substituted for the simpler, previously employed 4-chlorobenzaldehyde (**499**) (Scheme 6.27). It was found however, that the desired product ester was formed in reduced selectivity, a ratio of 1:1.2 was observed in favour of the undesired ester. Combining these results with that obtained with the 2-bromo-3-pyridinecarboxaldehyde employed previously (Scheme 6.22),

we posited that 2,3-disubstituted benzaldehydes may not be compatible with the magnesium thiolate-catalysed Tishchenko methodology.

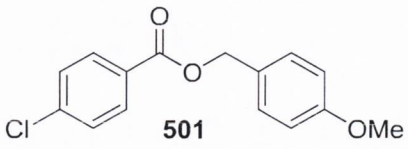
Scheme 6.27 The reaction between the 2-bromo-3-*O*-benzyl-substituted benzaldehyde **595** and 4-chlorobenzaldehyde



6.5 Removal of the bromo-functional group from the crossed Tishchenko ester product

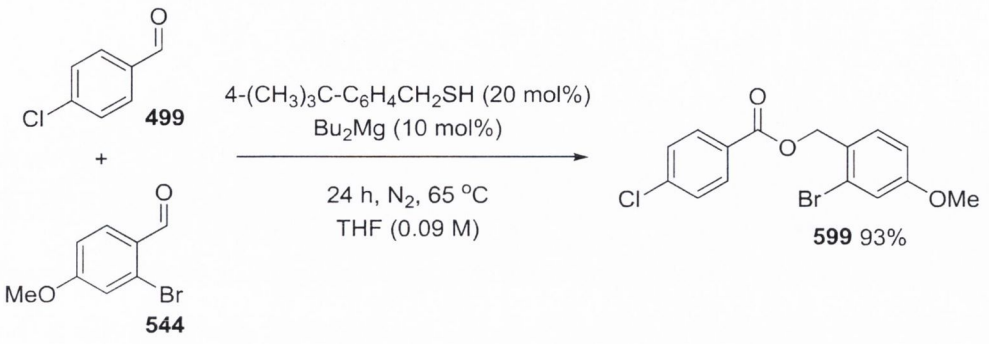
As mentioned previously, the formation of ester **501** from the unselective Tishchenko reaction between 4-chlorobenzaldehyde and 4-anisaldehyde proceeded in 27% yield (Figure 6.5). We proposed that if a selective reaction could be performed with 2-bromo-4-anisaldehyde, the bromo-functional group may be then removed to furnish the previously impossible to form ester **501** in high yield.

Figure 6.5 The crossed product **501** which is impossible to form selectively from the Tishchenko reaction of **499** with **500**



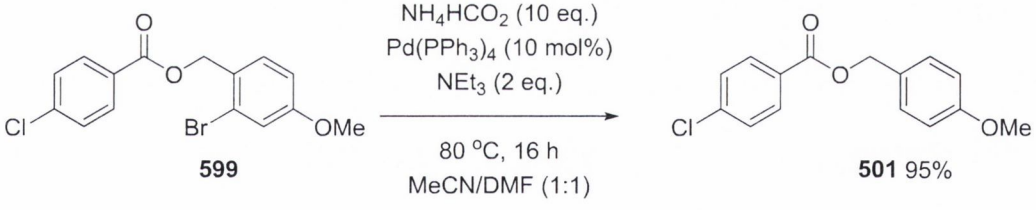
We were gratified to find that the magnesium thiolate-catalysed reaction between 4-chlorobenzaldehyde (**499**) and 2-bromo-4-anisaldehyde (**544**) gave 93% yield of the selective **599** (Scheme 6.28).

Scheme 6.28 The magnesium thiolate-catalysed Tishchenko reaction between 4-chlorobenzaldehyde and 2-bromo-4-anisaldehyde



The removal of the bromine atom group was achieved by exposure to $Pd(PPh_3)_4$, triethylamine and the reductant ammonium formate in a mixed solvent system of DMF and acetonitrile at 80 °C. The product **501** was formed in 95% yield, meaning that the overall yield for the two steps is 88%; a significantly more efficient process than the unselective Tishchenko reaction of the two constituent aldehydes.

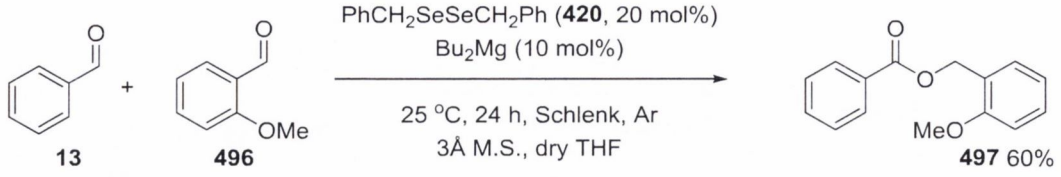
Scheme 6.29 Debromination of ester **599**



6.6 Evaluation of the corresponding selenide-ion-derived catalysts in the selective Tishchenko reaction between two aldehydes

As the magnesium selenide-ion catalysed methodology, previously described in Section 4, proved to have significant advantages over the corresponding magnesium thiolate-catalysed methodology, it was decided to evaluate its potential in the selective Tishchenko reaction between two different aldehydes. The most prudent starting point was the first selective reaction that was discovered, *i.e.* the production of ester **497** from benzaldehyde (**13**) and 2-anisaldehyde (**496**, Scheme 6.30). It was found however, that the formation of this ester did not proceed with as high a product yield as previously observed; 60% yield was obtained using the selenide-ion catalyst whereas previously 73% yield was obtained using a thiolate promotor.

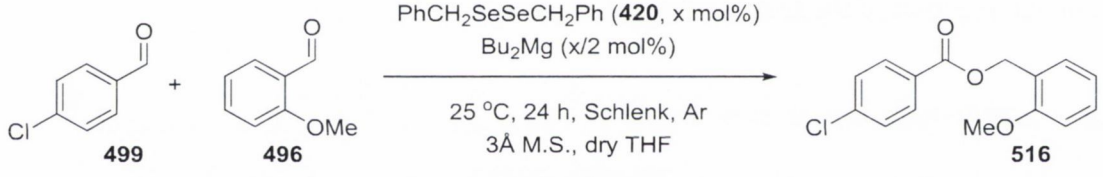
Scheme 6.30 Investigation of the magnesium selenide-ion-catalysed reaction of benzaldehyde and 2-anisaldehyde



13 **496** **497** 60%

Disappointed by this result, we decided to investigate the reaction of 4-chlorobenzaldehyde and 2-anisaldehyde at various catalyst loadings. At 20 mol% catalyst loading the crossed ester product **516** was generated in 63% yield, whereas previously the magnesium thiolate catalyst promoted the same reaction with 88% yield (entry 1, Table 6.7).

Table 6.7 Evaluation of selenide-ion catalyst in the Tishchenko reaction between 4-chlorobenzaldehyde and 2-anisaldehyde at different catalyst loadings



499 **496** **516**

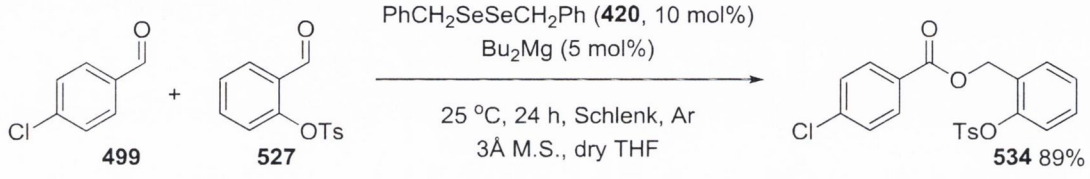
entry	x (mol%)	conc. (M)	ester selectivity ratio[a]	yield (%)[b]
1	20	1.2	1 : 0.29 : 0.02 : 0	63
2	10	2.4	1 : 0.31 : 0.02 : 0	62
3	5	4.8	1 : 0.43 : 0.02 : 0	54

[a]Determined by integration of the ^{1}H NMR spectrum of the crude product [b]Determined by ^{1}H NMR spectroscopy with reference to styrene as internal standard.

When performed at 10 mol% catalyst loading, it was found that the ester was formed in 62% yield (entry 2). Finally, 5 mol% catalyst loading furnished the product in the low yield of 54% (entry 3). It was noted that the chemoselectivity of these reactions decreased with the catalyst loading, indicating that concentration may be an issue in these reactions. As the selectivity of the magnesium selenide-ion appeared to drop drastically between 10 and 5 mol% catalyst loading it was decided to perform any further experiments at 10 mol% catalyst loading.

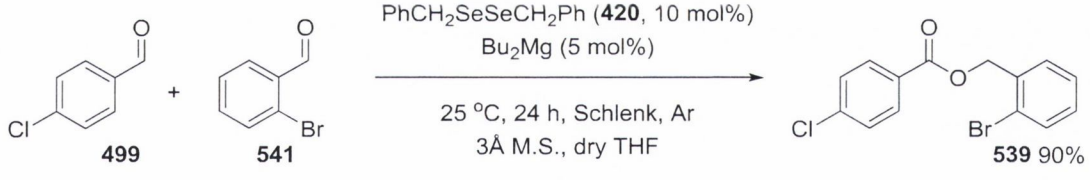
It was found that the magnesium selenide-ion-catalysed reaction of 4-chlorobenzaldehyde with the 2-*O*-tosyl-substituted benzaldehyde **527** furnished ester **534** in 89 % yield (Scheme 6.31). Again, this is a lower isolated yield than that observed using the analogous magnesium thiolate-catalysed methodology, in which the product was prepared in 93% isolated yield.

Scheme 6.31 The magnesium selenide-ion catalysed reaction to form ester **534**



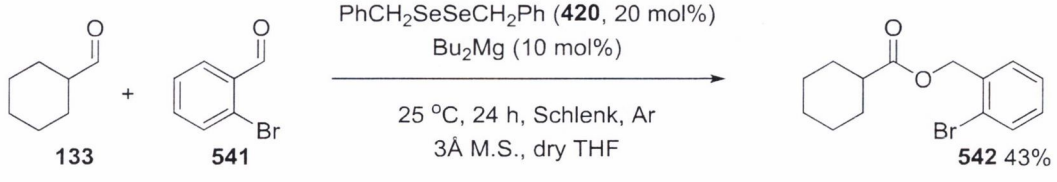
The bromo-substituted ester **539** was obtained in 90% yield at 10 mol% catalyst loading, which was again lower than that attained under catalysis with the magnesium thiolate catalyst (Scheme 6.32).

Scheme 6.32 The magnesium selenide-ion-catalysed reaction to form ester **539**



Finally, we posited that the reaction with cyclohexanecarboxaldehyde (**133**) might produce a higher yield of ester **542** due to the previous work on the magnesium selenide-ion catalysis furnishing some aliphatic ester products in higher yield (Scheme 6.33). Disappointingly however, the product was only formed in 43% yield, whereas previously, it was preparable in 58% yield *via* the magnesium thiolate-catalysed methodology.

Scheme 6.33 The magnesium selenide-ion-catalysed reaction to form ester **542**



As the magnesium selenide-ion-catalysed methodology produced esters in decreased yield and selectivity, it was deemed futile to continue with this research.

6.7 Conclusion

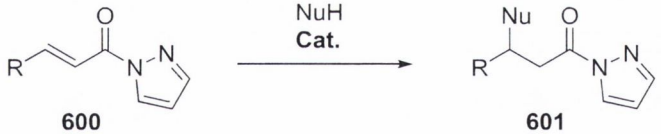
In conclusion, here is described the first methodology for the selective formation of crossed benzyl esters from two different aromatic aldehydes. It was found that when both aldehyde substrates were unhindered no selectivity was observed in the formation of the products, however when one of the reaction components incorporates a *o*-substituent one major ester product is observed. A relatively broad substrate scope was demonstrated and potentially useful orthogonally protected aldehydes were shown to be amenable. Though considerable efforts were exerted, it was found that the 4'', 6''-dideoxybalanol precursor could not be synthesised by the selective Tishchenko reaction of the two corresponding aldehydes. Finally a product which was impossible to be formed selectively from the corresponding aromatic aldehydes could be formed in high yield in two steps *via* the selective Tishchenko reaction and removal of the bromo-functional group from which selectivity is derived. Though significant effort was exerted in the optimisation of the corresponding magnesium selenide-ion catalysed methodology, overall lower yields and selectivity's were observed.

Chapter 3: The development of a novel organocatalytic methodology

7.0 The use of pyrazoles as directing groups for the enantioselective 1,4-conjugate addition of pronucleophiles

We theorised that acylpyrazoles may be excellent directing groups for organocatalysed 1,4-conjugate addition reactions (Scheme 7.1); as previously Kanemasa *et al.* had demonstrated their utility in metal-catalysed reactions,[113] and Barbas *et al.* employed them as pronucleophiles in organocatalysed reactions (see Section 1.4.3.1).[117] Like Barbas *et al.*, we proposed that the acylpyrazole functional group may have improved hydrogen bonding potential, thereby conferring much more control in the catalyst transition state. The advantages of this reaction would be that the pyrazole unit could be easily substituted by nucleophiles to furnish ester and amide functionalities, potentially providing one-pot access to products formally derived from α,β-unsaturated esters and amides; which are notoriously recalcitrant substrates in organocatalytic Michael addition reactions, due to their poor electrophilicity.[166]

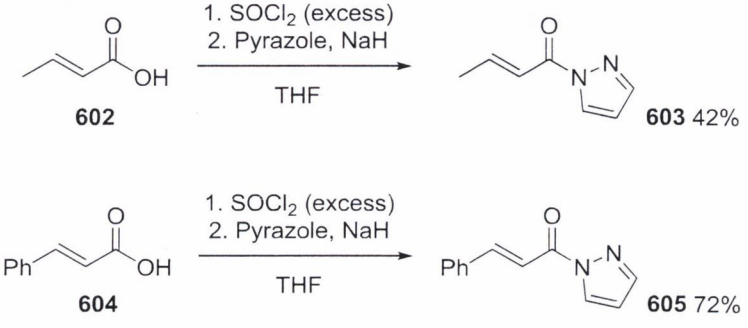
Scheme 7.1 Proposed reaction scheme



600 **601**

The acylpyrazole substrates were synthesised from the corresponding α,β-unsaturated carboxylic acids (Scheme 7.2).

Scheme 7.2 Synthesis of α,β-unsaturated acylpyrazoles from α,β-unsaturated carboxylic acids



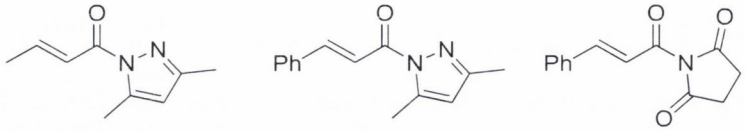
602 **603** 42%

604 **605** 72%

Crotonic acid (**602**) was functionalised *via* the formation of the corresponding acid chloride by the action of thionyl chloride, and subsequently was treated with the pyrazole sodium salt (obtained from the reaction of pyrazole and sodium hydride) to furnish acylpyrazole **603** in 42% yield. The corresponding phenyl-substituted α,β-unsaturated acylpyrazole **605** was prepared under the same conditions, from cinnamic acid (**604**).

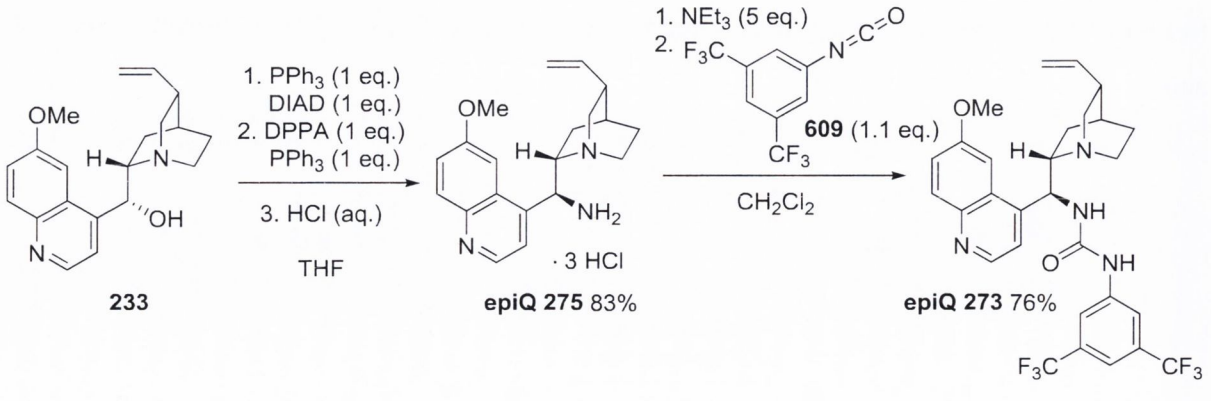
Other α,β-unsaturated acylpyrazole compounds derived from 3,5-dimethylpyrazoles and acylsuccinamide substrate with synthesised by Brendan Fallon, a senior sophister student whose project I helped to supervise (Figure 7.1).

Figure 7.1 The α,β-unsaturated acylpyrazole and acylsuccinamide substrates synthesised by Brendan Fallon



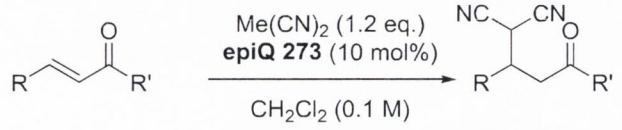
We deemed that an ideal initial catalyst for the reaction would be the urea **epiQ 273**, which was successfully employed by Barbas *et al.* and which was synthesised by known literature methods.[167] Quinine (**233**) was first converted to the corresponding C-9 azide and subsequent *in situ* Staudinger reduction furnished the tri-hydrochloride salt of amine **epiQ 275** (Scheme 7.3). On formation of the free-base of this amine and treatment with isocyanate **609**, urea catalyst **epiQ 273** was obtained.

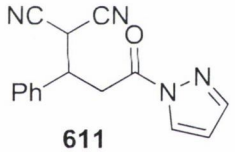
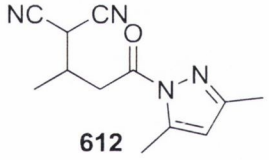
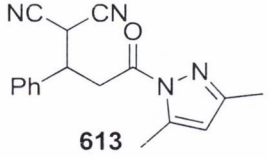
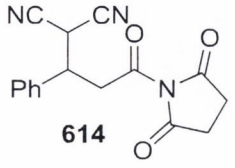
Scheme 7.3 The synthesis of urea catalyst **epiQ 273**



The α,β-unsaturated acylpyrazole and acylsuccinamide substrates were evaluated in the **epiQ 273** catalysed reaction with malononitrile as the pronucleophile as its chemical properties are well understood in Michael addition reactions. Surprisingly, product **610** was produced in 59% yield and 96% *ee* (entry 1, Table 7.1). Similarly, 1,4-addition product **611** was afforded in 83% yield and 95% *ee* (entry 2).

Table 7.1 Evaluation of α,β-unsaturated acyl-substituted in 1,4-conjugate addition reactions



entry	product	time (h)	yield (%)[a]	*ee* (%)[b]
1	 **610**	36	59	92
2	 **611**	90	83	91
3[c]	 **612**	36	70	86
4[c]	 **613**	36	86	86
5[c]	 **614**	36	0[d]	-

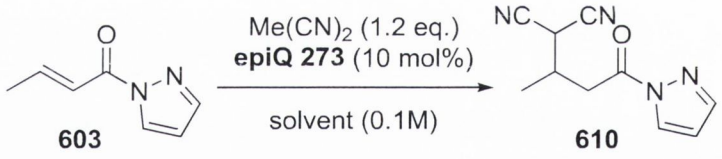
[a]Isolated by silica gel column chromatography. [b]Determined by CSP-HPLC analysis. [c]Performed by Brendan Fallon. [d]Determined by ^{1}H NMR spectroscopy.

We hypothesised that the 3,5-dimethylacylpyrazole derivatives (**606** and **607**) would allow the production of 1,4-addition products in higher *ee* as the methyl-substituted pyrazole might

might confer further control in the catalyst transition state. However, products **612** and **613** were formed in lower enantioselectivty (86%,entries 3 and 4). Finally, the acylsuccinamide **608** was found to be completely inactive as a substrate, no trace of the 1,4-conjugate addition product **614** could be detected (entry 5).

Having identified that the products of these reactions are formed in excellent enantioselectivity, it was decided to focus on increasing the yield. Determination of the optimum solvent took precedence therefore, and on repeat of the reaction in dichloromethane it was found that the same results as previously obtained, were observed (entry 1, Table 7.2). A similar reaction, performed in parallel, with tetrahydrofuran (THF) as solvent performed poorly, with product **610** forming in 40% yield and 78% *ee* (entry 2). Finally, the reaction performed in MTBE produced a roughly equal amount of product yield to that of dichloromethane, however, a marginal reduction in product *ee* was observed (entry 3).

Table 7.2 Evaluation of solvent effects on the organocatalysed addition of malononitrile to the crotonic acid-derived acylpyrazole **603**



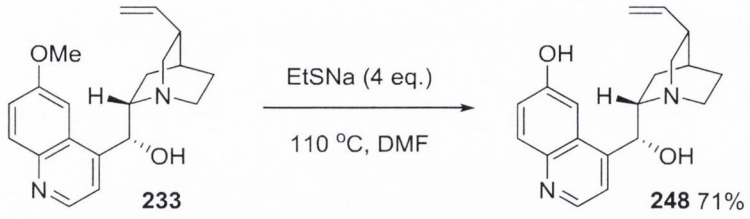
603 **610**

entry	solvent	time (h)	yield (%)[a]	*ee* (%)[b]
1	CH_2Cl_2	36	59	92
2	THF	36	40	78
3	MTBE	36	59	91

[a]Isolated by silica gel column chromatography. [b]Determined by CSP-HPLC analysis.

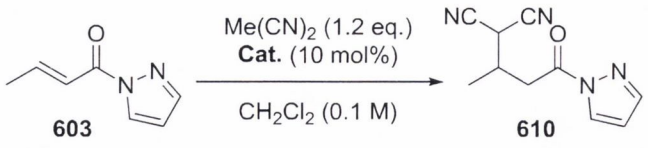
As no increase in the reaction rate was observed on changing solvent, it was decided that dichloromethane would remain the standard solvent. Next it seemed prudent to evaluate the performance other catalysts. Deng *et al.* reported that the demethylated quinine catalyst **248** was highly efficient in the 1,4-conjugate addition reaction of acetoacetate esters to β-nitrostyrenes.[84] This catalyst was synthesised from quinine (**233**) in 71% yield *via* the action of excess sodium ethanethiolate at 110 °C in DMF (Scheme 7.4).

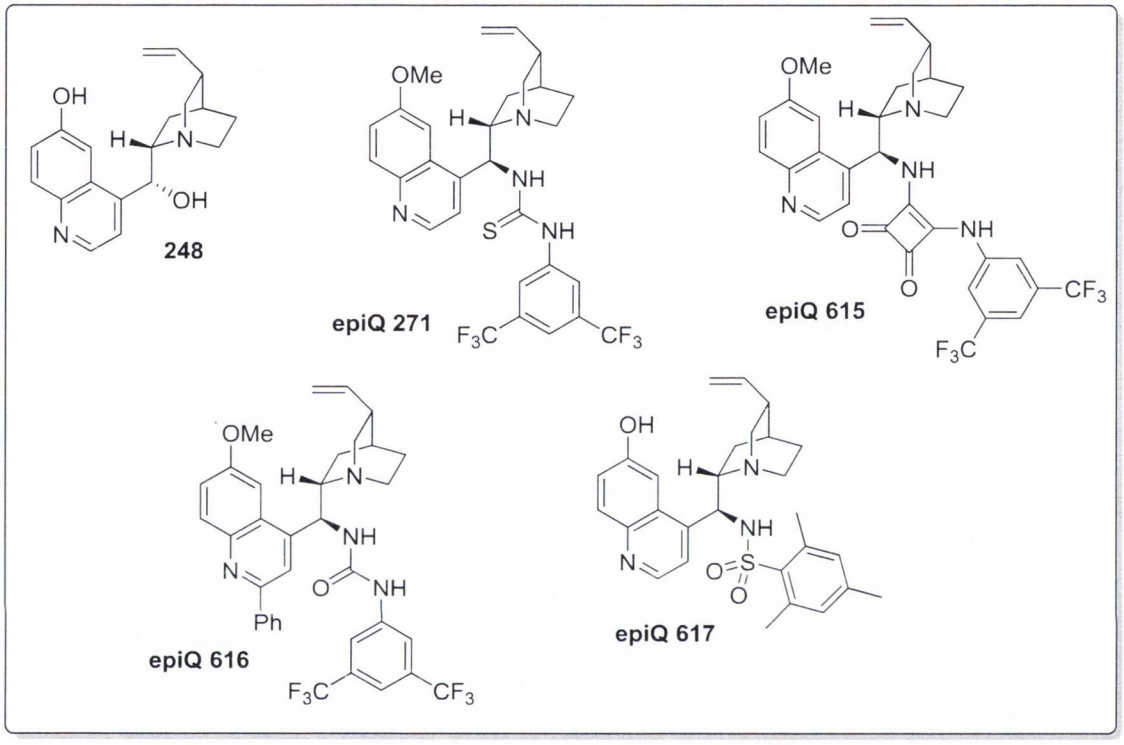
Scheme 7.4 The synthesis of the demethylated quinine catalyst **248**



Disappointingly however, it was found that product **610** was furnished in 45% yield and 13% *ee* (entry 1, Table 7.3). In addition the major enantiomer of **610** was the opposite antipode to that preffered when the reaction was catalysed by **epiQ 273**. The rest of the quinine-derived catalysts discussed in this paragraph were obtained in high purity from Dr. Sean Tallon. The thiourea-derived catalyst **epiQ 271** was found to produce the 1,4-conjugate addition product **610** in excellent yield and *ee* in a reduced reaction time of 24 hours (entry 2). The squareamide-analogue of urea-based catalyst **epiQ 273** (*i.e.* **epiQ 615**), was found to promote the formation of **610** in similarly excellent yield and an augmented *ee* of 95% (entry 3). The use of C-2' phenyl-substituted urea **epiQ 616** allowed the production of **610** in quantitative yield and 89% *ee* after 36 hours (entry 4). The sulfonamide catalyst **epiQ 617**, previously found to be effective in desymmetrisation reactions,[97] was found to be completely inactive as a catalyst in this reaction (entry 5). From this study it was decided that catalyst **615** was optimum for the reaction.

Table 7.3 Evaluation of various alkaloid-derived catalysts in the addition of malononitrile to **603**





entry	**Cat.**	time (h)	yield (%)[a]	*ee* (%)[b]
1	**248**	36	45	-13
2	**epiQ 271**	24	94	91
3	**epiQ 615**	24	94	95
4	**epiQ 616**	36	99	89
5	**epiQ 617**	36	0	-

[a]Isolated by silica gel column chromatography. [b]Determined by CSP-HPLC analysis.

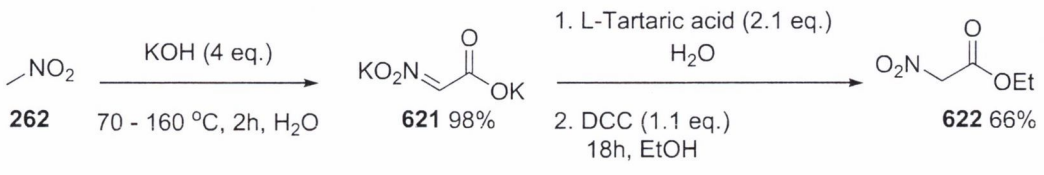
7.1 Evaluation of pronucleophile substrate scope

In an effort to investigate the potential scope of pronucleophiles amenable to this methodology it was decided to evaluate a selection of these under the best available catalytic conditions. Dimethyl malonate (**269**, pK_a 15.9 in DMSO)[168] and its chloro-substituted analogue **618** were found to be poor nucleophiles for addition to this Michael acceptor (entries 1 and 2, Table 7.4). Similarly, acetyl acetone (**619**, pK_a 13.3 in DMSO)[169] and ethyl acetoacetate (**254**, pK_a 14.2 in DMSO)[170] also proved to be poor pronucleophiles, furnishing no observable 1,4-conjugate addition products (entries 3 and 4). Ethyl cyanoacetate (**618**, pK_a 13.1 in DMSO), like the previous pronucleophiles, was found be incompatible with this methodology (entry 5).

Theorising that the relative size of these pronucleophiles prevented the Michael addition reaction, nitromethane (**262**, pK_a 17.2 in DMSO)[171] was employed as a pronucleophile without success (entry 6). It was decided to evaluate homophthalic anhydride as a pronucleophile for the reaction (see Section 1.4.2.3), disappointingly however, no conjugate addition product was observed from this reaction (entry 7)

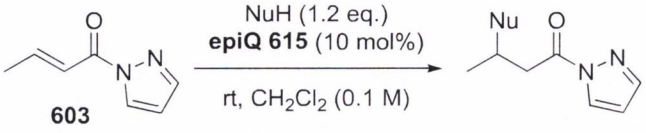
As malononitrile is a relatively acidic pronucleophile (pK_a 11.1 in DMSO),[47] we posited that its acidity may be the main contributing factor to its reactivity. As such, other highly acidic pronucleophiles should be effective pronucleophiles in this reaction. Ethyl nitroacetate (**622**) (pK_a 9.1 in DMSO)[172] was synthesised in two steps from nitromethane (**262**). First the dipotassium salt **621** was prepared in 98% yield,[173] then mild protonation of this salt using (L)-tartaric acid furnished the corresponding nitroacetic acid, which was promptly subjected to DCC coupling conditions in the presence of ethanol to furnish ethyl nitroacetate (**622**) in 66% yield (Scheme 7.5).

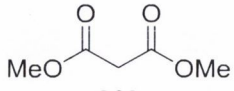
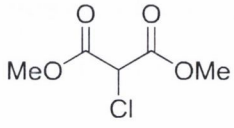
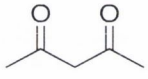
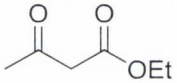
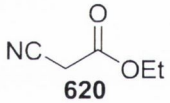
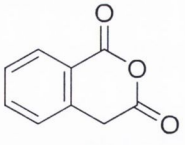
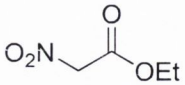
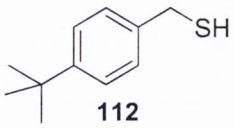
Scheme 7.5 The synthesis of ethyl nitroacetate (**622**)



262 **621** 98% **622** 66%

Table 7.4 Evaluation of pronucleophiles in the 1,4-conjugate addition reaction

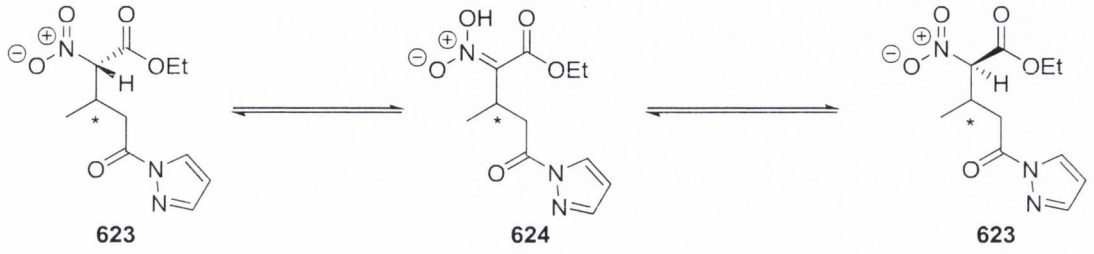


entry	NuH	time (h)	yield (%)[a]	dr[b]	*ee* (%)[c]
1	 **269**	72	0[b]	N/A[d]	-
2	 **618**	72	0[b]	N/A[d]	-
3	 **619**	72	0[b]	N/A[d]	-
4	 **254**	72	0[b]	-	-
5	 **620**	72	0[b]	-	-
6	 **262**	72	0[b]	N/A[d]	-
7	 **293**	20	0[b]	-	-
8[c]	 **622**	36	96	50:50	N/D[e]
9	 **112**	72	trace[b]	N/A[d]	-

[a]Isolated by silica gel column chromatography. [b]Determined by ^{1}H NMR spectroscopy with reference to styrene as an internal standard. [c]Performed by Brendan Fallon. [d]N/A = not applicable. [e]N/D = not determined.

On evaluation of ethyl nitroacetate in the organocatalysed 1,4-conjugate addition reaction, we were pleasantly surprised to observe (when Brendan Fallon performed the reaction) that the product **623** was formed in excellent yield. However, this product was obtained in a 50:50 diastereomeric ratio (entry 8). We proposed that the acidity of the α-nitromethine centre favoured the rapid epimerisation of the product *via* the nitroenol **624**. For the same reason this product was found to be inapplicable to HPLC analysis *i.e.* the diastereomers and enantiomers could not be resolved using CSP-HPLC (Scheme 7.6).

Scheme 7.6 Rapid epimerisation of the nitroenolate chiral centre *via* enolisation

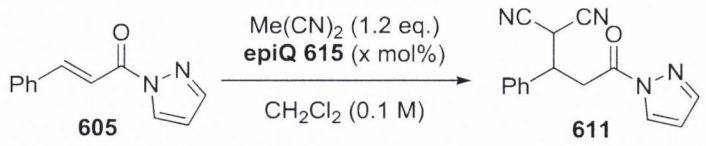


Finally, the catalysed sulfa-Michael addition reaction of 4-*t*-butylbenzylmercaptan (**112**) with the crotonic acid derived acylpyrazole did not proceed to any great extent under these conditions, with the product forming in only trace amounts (entry 9).

7.2 Evaluation of various pyrazole substrates

The use of the cinnamic acid-derived acylpyrazole **605** was evaluated under the optimum catalytic conditions with malononitrile and, disappointingly, the product **611** was obtained in only 51% yield at 10 mol% catalyst loading after 24 hours (entry 1, Table 7.5). As expected, the use of 5 mol% catalyst loading led to the production of **611** in a lower yield (entry 2). Theorising that increasing the temperature might produce higher product yields, it was decided to evaluate reactions at 30 °C. Catalyst loadings of 10 mol% produced **611** in 66% isolated yield and 92% *ee* (entry 3). 5 % catalyst loadings at 30 °C allowed the production of **611** in lower yield and slightly lower *ee* (entry 4). Increasing the temperature to 40 °C and performing the reactions in sealed tubes to prevent loss of solvent, afforded **611** in 51 and 80% yield, at 10 and 5 mol% catalyst loading respectively, and identical *ee* of 92% (entries 5 and 6).

Table 7.5 The catalysed addition of malononitrile to the cinnamic acid-derived acylpyrazole **605**: optimisation of the reaction conditions

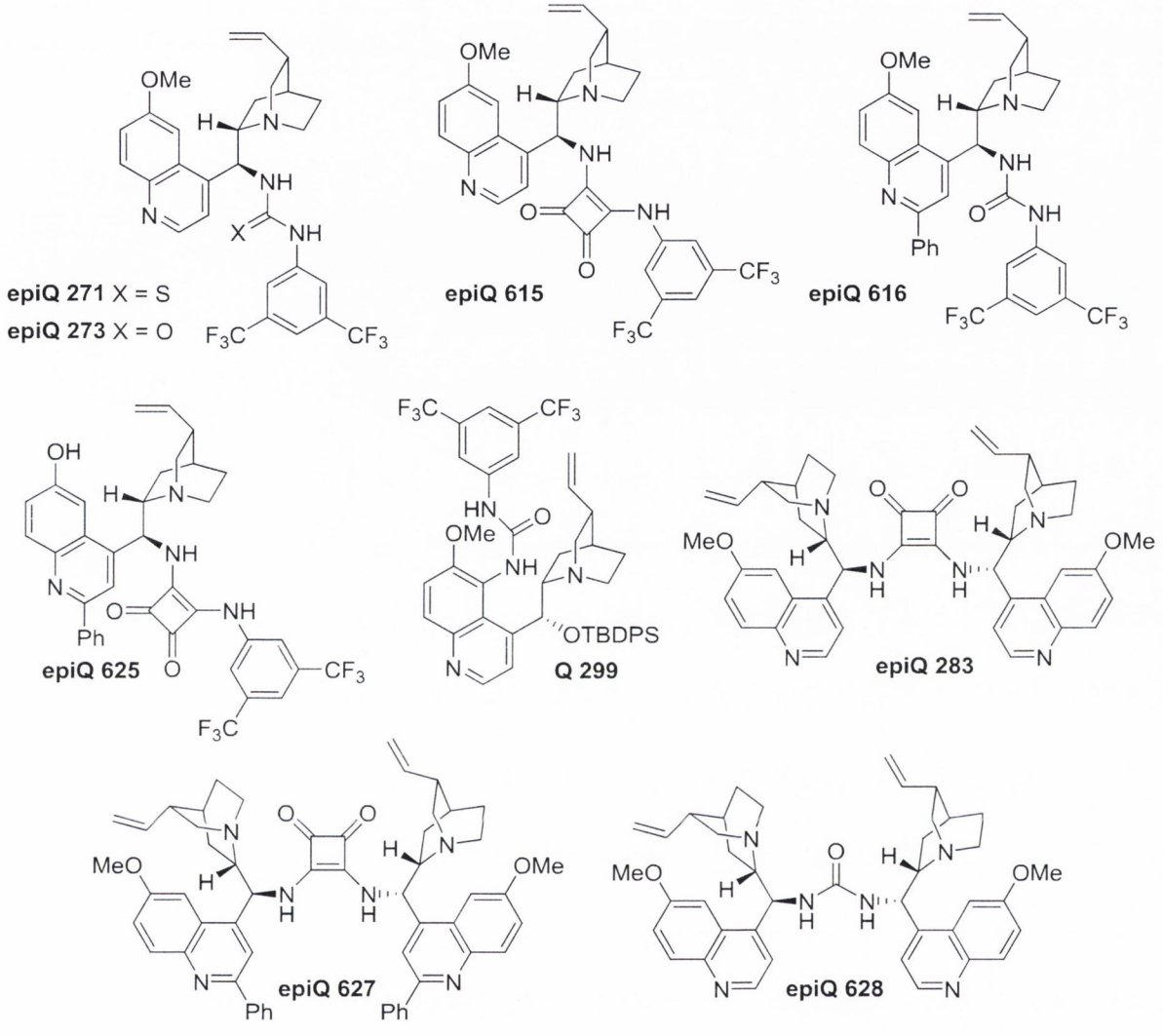


entry	x (mol%)	temp. (°C)	time (h)	yield (%)[a]	*ee* (%)[c]
1	10	20	24	51[b]	-
2	5	20	24	41[b]	-
3	10	30	24	66	92
4	5	30	24	61	91
5	10	40[b]	24	51	92
6	5	40[b]	36	80	92

[a]Isolated by silica gel column chromatography. [b]Determined by ^{1}H NMR spectroscopy with reference to styrene as internal standard. [c]Performed in sealed, low volume RBF flasks.

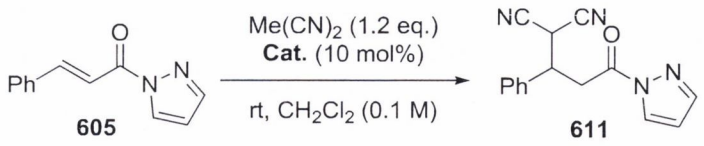
Despite attempts to optimise reaction conditions, it appeared that catalyst **epiQ615** was capable of highly enantioselective catalysis of the addition of malononitrile to **605**, however product yields were unsatisfactory. Therefore, our attention turned to related but alternative catalyst structures (Figure 7.2). The thiourea-substituted catalyst **epiQ 271** promoted the formation of the 1,4-conjugate addition product in 74% yield and 87% *ee* after 30 hours (entry 1, Table 7.6). Its urea-derived analogue **epiQ 273** was found to be a slightly superior, allowing the production of **611** in 83% yield and 89% *ee* (entry 2). The squareamide-derived analogue **epiQ 615** promoted the formation of the product in 81% yield and 92% *ee* (entry 3). Product **611**was afforded in only 66% yield and 92% *ee via* the use of The C-2' phenyl-substituted urea **epiQ 616** (entry 4).

Figure 7.2 Catalysts employed in Table 7.6 for optimisation studies



The C-2' phenyl-substituted squareamide-derived **epiQ 625** also proved to be an inefficient catalyst, with product **611** forming in only 57% yield, though the product had the highest *ee* compared with products furnished from reactions with other catalysts (entry 5). The C-5' urea-substituted catalyst **Q 299**, previously observed by our group to be highly efficient in the enantioselective sulfa-Michael reaction, was found to be a poor catalyst for this reaction, with **611** forming in a paltry 18% *ee* (entry 6).

Table 7.6 Further optimisation studies: the influence of catalyst structure



entry	Cat.	time (h)	yield (%)[a]	*ee* (%)[b]
1	**epiQ 271**	36	74	87
2	**epiQ 273**	36	83	89
3	**epiQ 615**	36	81	92
4	**epiQ 616**	36	66	92
5	**epiQ 625**	36	57	95
6	**Q 299**	42	18	N/D[d]
7	**epiQ 283**	30	98	91
8	**epiQ 627**	30	0[c]	-
9	**epiQ 628**	24	87	0

[a]Isolated by silica gel column chromatography. [b]Determined by CSP-HPLC analysis. [c]Determined by ^{1}H NMR spectroscopy with reference to styrene as internal standard. [d]N/D = not determined.

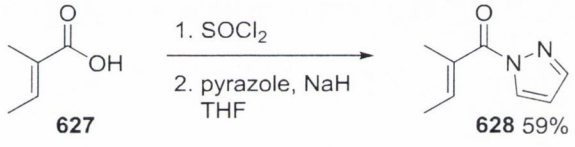
The C_2-symmetric squareamide-derived catalyst **epiQ 283** which was reported by Song *et al.* in the DKR of azlactones,[102] was found to be an excellent promoter of the reaction; the 1,4-conjugate addition product **611** was generated in 98% yield and 91% *ee* (entry 7). Spurred on by this result, the C-2' phenyl-substituted C_2-symmetric squareamide **epiQ 627** (synthesised by Dr. Sean Tallon) was evaluated and was found to be completely inactive as a catalyst (entry 8). Finally, the C_2-symmetric urea **epiQ 628** was found to be a highly efficient catalyst, with product **611**being produced in the high yield of 87% yield and 0% *ee* (entry 9). This suggests that the catalyst is too sterically constrained and, as such, is acting exclusively as a

base instead of a bifunctional catalyst. It was decided, therefore, that the optimum catalyst for this reaction is that reported by Song *et al.*, the C_2-symmetric squareamide **epiQ 283**.

7.3 The synthesis of functionalised α,β-unsaturated acylpyrazoles

It was decided that a variety of α,β-unsaturated acylpyrazoles should be synthesised in order to chart the potential substrate scope of this organocatalysed 1,4-conjugate addition reaction. The 2',3'-dimethyl-substituted acylpyrazole **628** was synthesised in 59% yield from the commercially available tiglic acid (**627**), *via* the formation of the corresponding acid chloride with thionyl chloride, and subsequent substitution by the pyrazole sodium salt (Scheme 7.8).

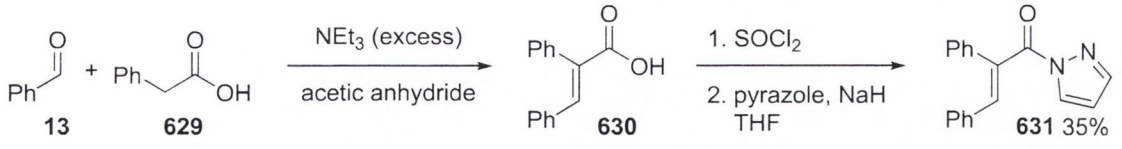
Scheme 7.8 The synthesis of the 2',3'-dimethyl-substituted acylpyrazole **628**



627 **628** 59%

The production of 2,3-diphenylacrylic acid (**630**) was executed in the poor yield of 26% *via* the Knoevenagel condensation of phenylacetic acid (**629**) and benzaldehyde (**13**).[174] As before, on treatment of this acid with thionyl chloride and pyrazole sodium salt, the desired acylpyrazole **631** was obtained as a viscous bright red oil in 35% yield (Scheme 7.9).

Scheme 7.9 The synthesis of the 2',3'-diphenyl-substituted acylpyrazole **631**

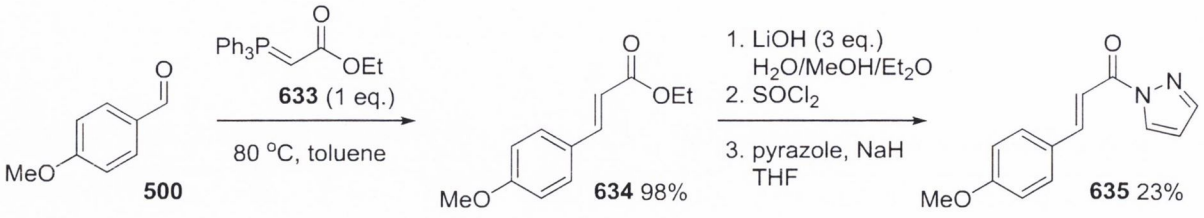


13 **629** **630** **631** 35%

As not all of the following α,β-unsaturated carboxylic acid derivatives were commercially available, it was decided to design a simple, flexible synthesis from cheap, commercially available starting materials. We decided that a Wittig-type reaction between an ester-substituted ylide and the required substituted aldehyde would furnish the desired substitution motif.[175] Implementing this plan, the Wittig- reaction of 4-anisaldehyde (**500**) and the ylide **633** furnished the α,β-unsaturated ester **634**, and mild hydrolysis of which, followed by

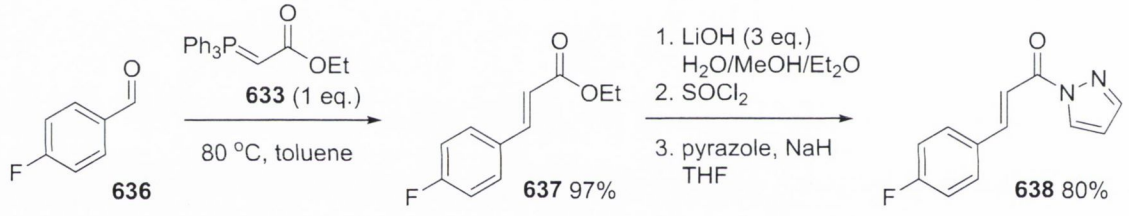
pyrazole functionalisation, afforded the desired acylpyrazole **635** in 23% yield (Scheme 7.11).

Scheme 7.11 The synthesis of the methoxy-substituted acylpyrazole **635**



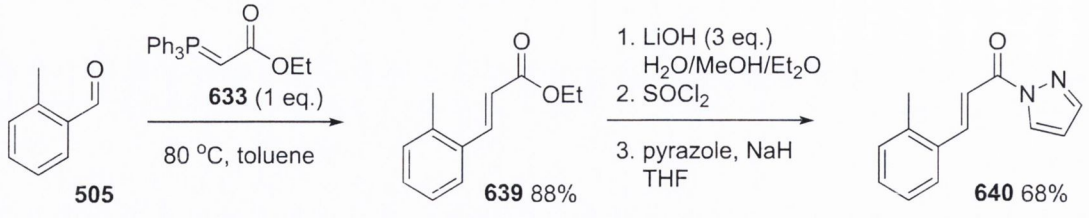
The fluoro-substituted α,β-unsaturated ester **637** was produced in 97% yield *via* the Wittig reaction with 4-fluorobenzaldehyde (**636**), subsequent functionalisation in a similar fashion, afforded acylpyrazole **638** in 80% yield (Scheme 7.12).

Scheme 7.12 The synthesis of the fluoro-substituted acylpyrazole **640**



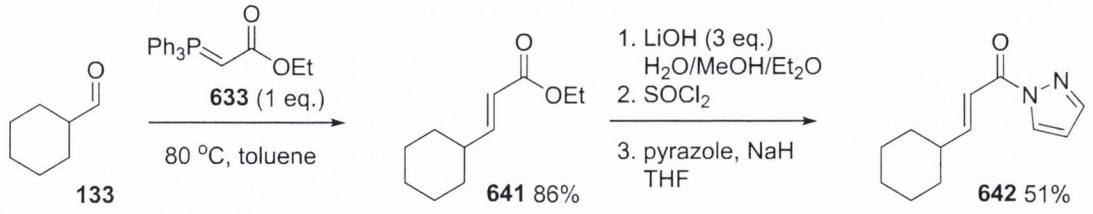
The same strategy allowed the synthesis of the *o*-methyl substituted derivative **640** from **505** *via* ester **639** in good yield (Scheme 7.13).

Scheme 7.13 The synthesis of the methyl-substituted acylpyrazole **642**



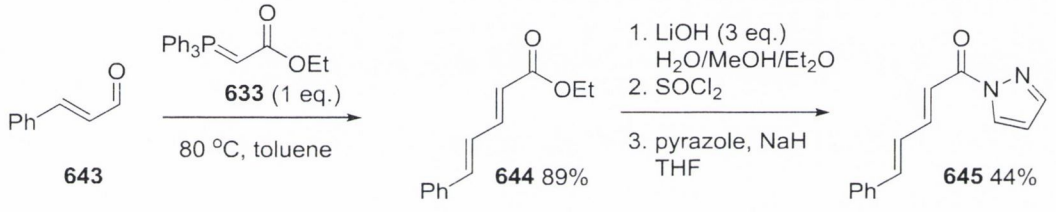
The formation of the cyclohexyl-substituted α,β-unsaturated ester **641** proceeded to the high yield of 86% yield and subsequent pyrazole functionalisation afforded the desired cyclohexyl-substituted acylpyrazole **642** in 51% yield (Scheme 7.14).

Scheme 7.14 The synthesis of the cyclohexyl-substituted acylpyrazole **642**



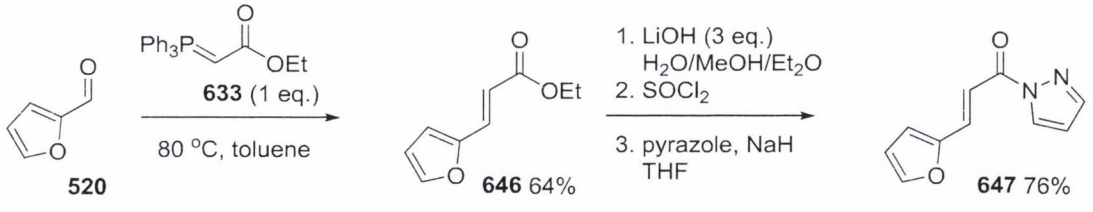
The treatment of cinnamaldehyde (**643**) under the Wittig conditions produced the ester **644** in 89% yield, further functionalisation afforded the highly conjugated acylpyrazole **645** in 44% yield (Scheme 7.15).

Scheme 7.15 The synthesis of the α,β,γ,δ-unsaturated acylpyrazole **647**



Finally, the same strategy allowed the synthesis of the furan-substituted acylpyrazole derivative **647** in 76% yield (Scheme 7.16).

Scheme 7.16 The synthesis of the furan-substituted acylpyrazole



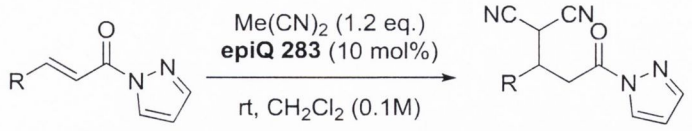
7.4 Evaluation of the various functionalised α,β-unsaturated acylpyrazoles in the 1,4-conjugate addition of malononitrile

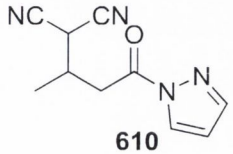
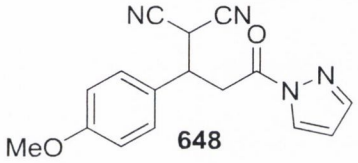
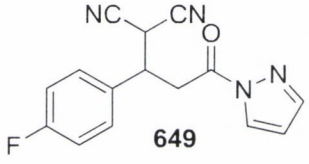
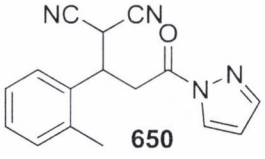
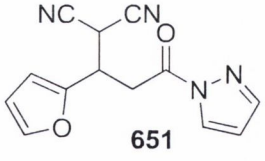
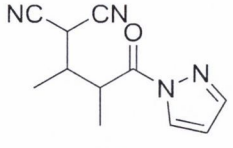
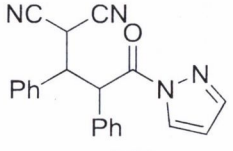
The addition of malononitrile to the crotonic acid-derived acylpyrazole to afford product **610** under catalysis of **epiQ 283** proceeded in quantitative yield and 75% *ee* (entry 1, Table 7.7). This demonstrates that **epiQ 283** is not the ideal catalyst for the enantioselective addition of pronucleophiles to β-alkyl substituted α,β-unsaturated acylpyrazoles.

The methoxy-substituted conjugate addition product **648** was formed in 82% yield and 89% *ee* (entry 2). Surprisingly, the relatively electron-deficient fluoro-substituted product **649** formed in poor yield at 20 mol% catalyst loading, though the product *ee* of 94% excellent (entry 3). The sterically hindered product **650** was produced in 61% yield at 10 mol% catalyst loading and 70% yield at 20 mol% catalyst loading; the product *ee* determined in these reactions was 92% (entry 4). Finally, the heterocyclic, furan-substituted product **653** was furnished in 63% yield and 95% *ee* at 10 mol% catalyst loading, and 67% yield and 91% *ee* at 20 mol% catalyst loading (entry 5).

Disappointingly, the addition of malononitrile to the 2',3'-dimethyl-substituted acylpyrazole to form product **652** did not proceed under these conditions (entry 6). Unsurprisingly, from the previous results, the formation of the phenyl analogue **653** was also found to be disfavoured (entry 7).

Table 7.7 The catalysed addition of malononitrile to β-substituted α,β-unsaturated acylpyrazoles

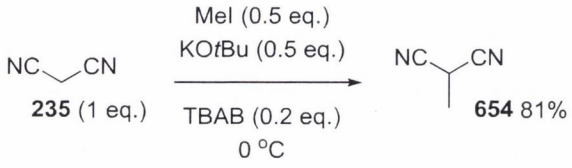


entry	product	x (mol%)	time (d)	yield (%)[a]	*ee* (%)[b]
1	 **610**	10	3	99	75
2	 **648**	10	3	82	89
3	 **649**	20	5	55	94
4	 **650**	10 20	5 5	61 70	92 92
5	 **651**	10 20	3 5	63 67	95 91
6	 **652**	10	14	0	-
7	 **653**	10	14	0	-

[a]Isolated by silica gel column chromatography. [b]Determined by CSP-HPLC analysis.

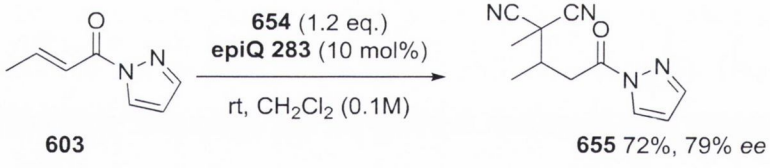
It was decided to evaluate a substituted malononitrile pronucleophile in the 1,4-conjugate addition reaction to α,β-unsaturated acylpyrazoles. As such, the methyl-substituted malononitrile **654** was synthesised in 81% yield *via* the methylation of malononitrile with potassium *t*-butoxide, methyl iodide and the phase transfer catalyst tetrabutylammonium bromide (TBAB) (Scheme 7.17).

Scheme 7.17 The methylation of malononitrile under basic phase transfer conditions



Disappointingly however, it was found that the product of the 1,4-conjugate addition reaction (*i.e.* **655**) was formed in 72% yield and 79% *ee* (Scheme 7.18).

Scheme 7.18 The organocatalytic 1,4-conjugate addition of the methyl-substituted malononitrile pronucleophile **654** to **603**

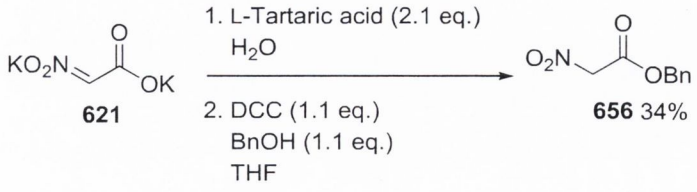


7.5 Evaluation of nitroacetates in the 1,4-conjugate addition reactions with α,β-unsaturated acylpyrazoles

As the only other pronucleophile to add to the α,β-unsaturated acylpyrazoles in appreciable yield was the highly acidic ethyl nitroacetate (**622**, Table 7.4), it was decided to focus on evaluating the *ee* of these products. Previously, it was found that the diastereomers of such products were demonstrated to be inseparable (due to the epimerisation of the α-nitro benzyl ester centre) and the enantiomeric excesses could not be determined. We theorised that the introduction of a removable ester protecting group might allow the determination of the *ee* of the deprotected product.

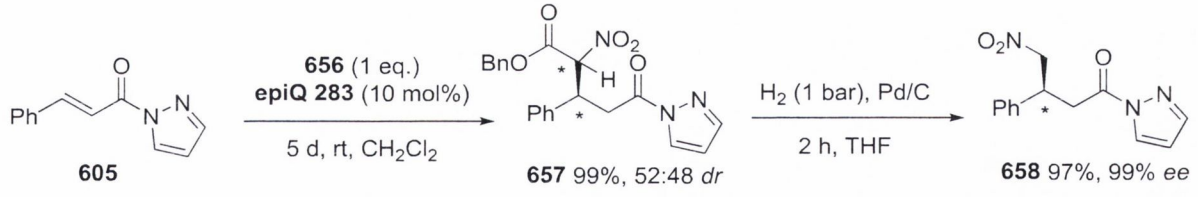
Benzyl nitroacetate (**656**) was synthesised in the poor yield of 34% *via* the formation of the nitroacetic acid and a subsequent DCC-coupling reaction with benzyl alcohol (Scheme 7.19).

Scheme 7.19 The synthesis of benzyl nitroacetate



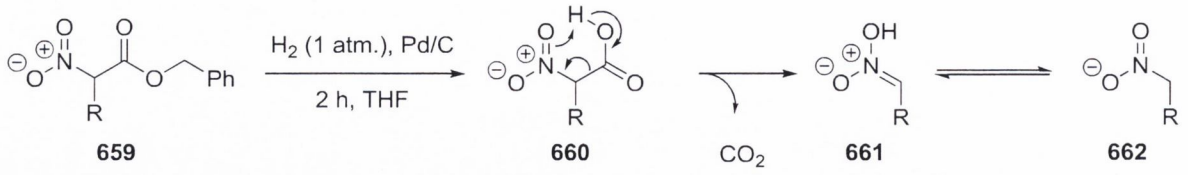
The addition of benzyl nitroacetate (**656**) to the phenyl-substituted α,β-unsaturated acylpyrazole **605**, catalysed by **epiQ 283**, afforded the addition product **657** in quantitative yield with a *dr* of 52:48 (Scheme 7.20). Removal of the benzyl protecting group by hydrogenolysis with palladium on carbon as a catalyst, furnished the corresponding nitro product **658** in excellent yield. The *ee* of the product was 99%, demonstrating that the addition of benzyl nitroacetate to these α,β-unsaturated acyl pyrazoles in completely enantioselective and the diastereomers formed are epimers of the α-carbon to the nitro group (formed by nitro-enol tautomerisation).

Scheme 7.20 The 1,4-conjugate addition of benzyl nitroacetate to the α,β-unsaturated acylpyrazole **605** and subsequent ester deprotection



The decarboxylation reaction, though not unexpected, is nonetheless surprising as it is analogous to the decarboxylation of β-keto acids, although under milder conditions and without specific acid catalysis.[176] This is likely formed *via* the initial deprotection of the benzyl group to form the corresponding nitro acid **660**, which undergoes a rapid decarboxylation reaction to furnish the nitro-enol **661**. Tautomerisation affords the nitroalkane **662** (Scheme 7.21).

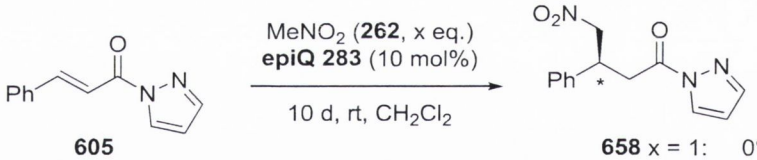
Scheme 7.21 Rationale for the formation of the nitroalkane from the deprotection of the benzyl ester



659 660 661 662

This strategy therefore represents a novel approach for the formation of nitroalkanes. We wished to demonstrate the potential of such a pronucleophile and as such repeated the 1,4-conjugate addition reaction with nitromethane in place of benzyl nitroacetate and found that product **658** was not formed in the presence of one equivalent of nitromethane (Scheme 7.22). Increasing the amount of nitromethane to ten equivalents furnished the same product in a paltry 16% yield and 98% *ee*. This represents quite a significant achievement, as several literature reports indicate that high concentrations of nitromethane are required to facilitate various organocatalytic and metal catalysed reactions.[177]

Scheme 7.22 The 1,4-conjugate addition of nitromethane to acylpyrazole **605**

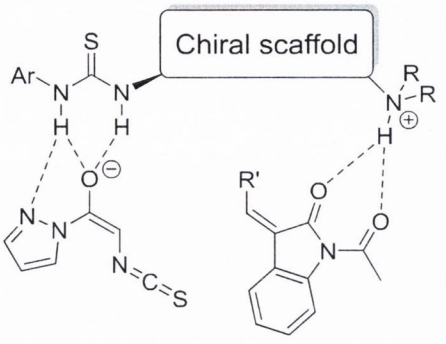


605

658 x = 1: 0%
x = 10: 16%, 98% *ee*

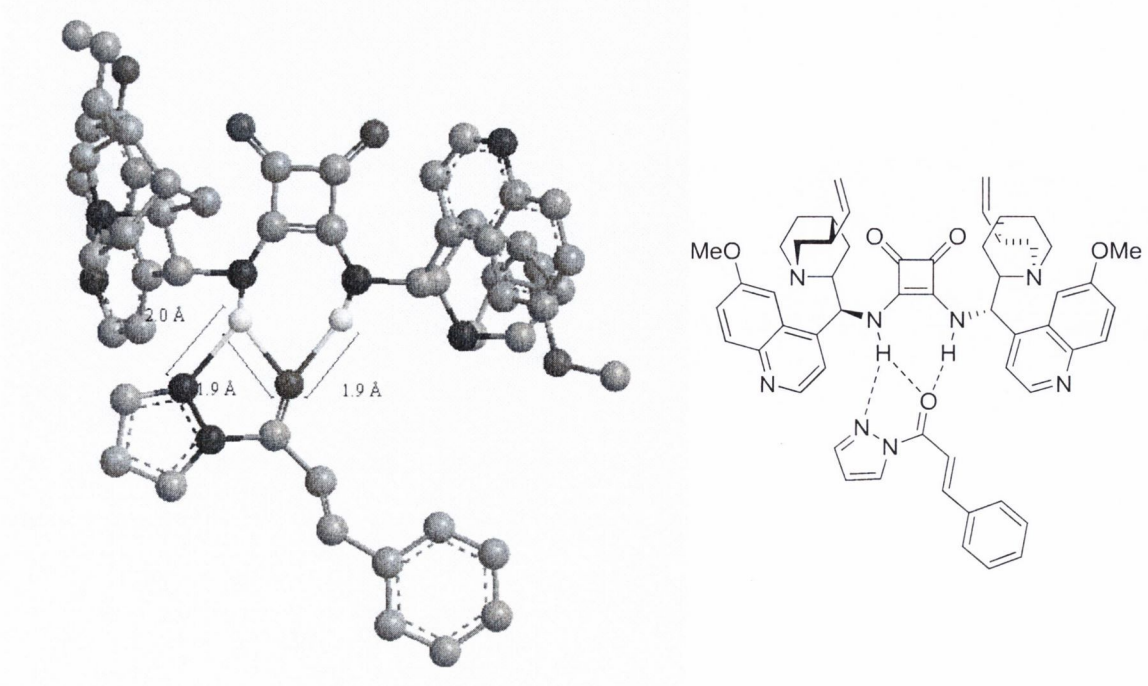
Using all the information gathered thus far, we wished to generate a proposed catalytic transition state that would account for not only the stereochemistry observed in the product but also the high level of enantioselectivity observed. Barbas *et al.* proposed that the mode of action of the catalyst was akin to that proposed by Takemoto *et al.*,[178,179] where the thiourea functional group is involved in a hydrogen bonding interaction with the orbitals of the carbonyl and that of the nitrogen in the pyrazole ring (Figure 7.2).

Figure 7.2 The catalytic transition state proposed by Barbas *et al.*



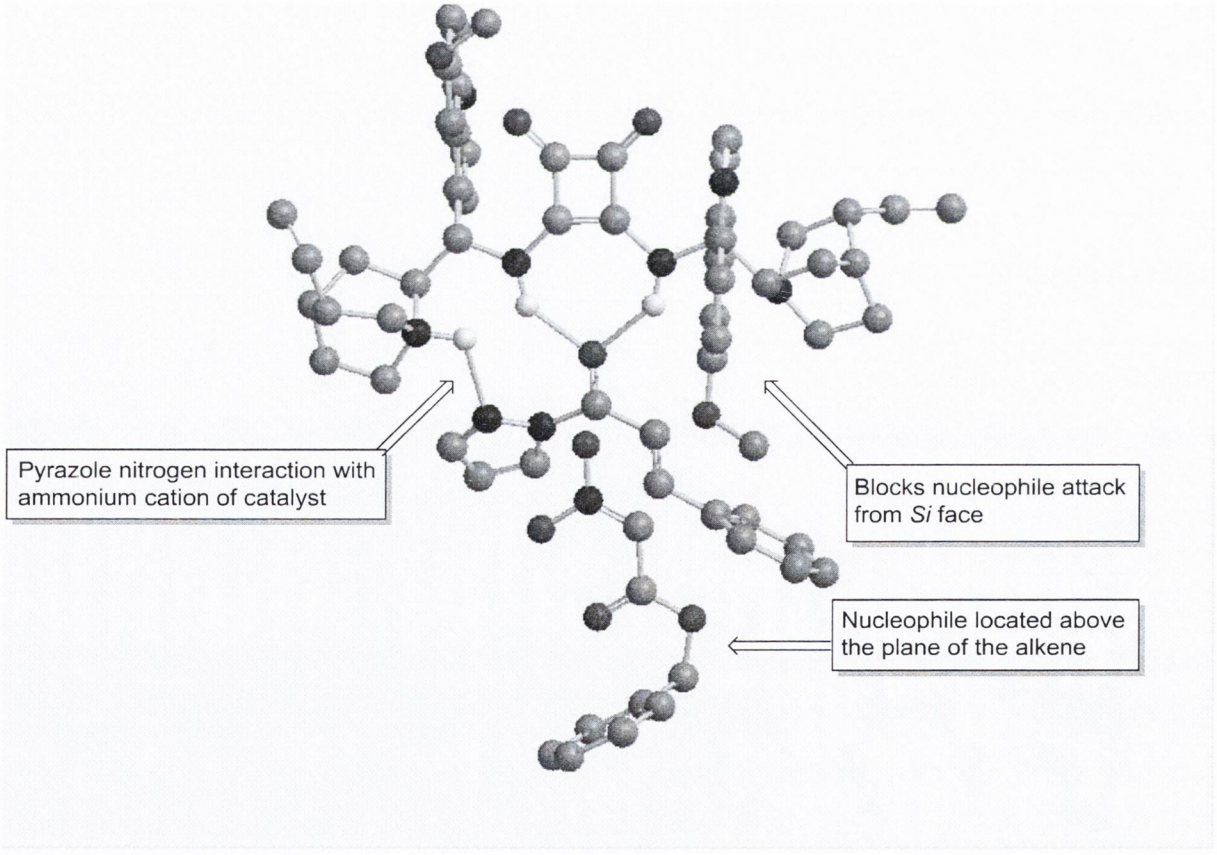
However, when we attempted to produce a three-dimensional model (using Chemdraw to generate a simple visual representation) of this interaction the results obtained were unsatisfactory as the hydrogen bond between the N-H and the nitrogen of the pyrazole, at the optimum distance for hydrogen bonding, is not favourable (Figure 7.3). For this model to be accurate, the hydrogen bonding interaction of the two lone pair orbitals of the carbonyl oxygen must be sufficiently weakened (to the point where one of the orbitals is no longer capable of interaction) to allow the pyrazole nitrogen to participate. This is an inadequate explanation for the exceptional enantioselectivity obtained in the products of the Michael addition reaction.

Figure 7.3 A model of the hydrogen bonding interaction proposed by Barbas *et al.* between catalyst **epiQ 283** and acylpyrazole **605**



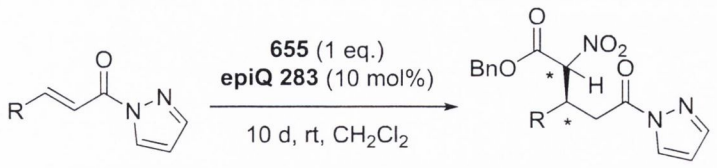
It became apparent that under the reaction conditions it is likely that benzyl nitroacetate, being highly acidic, would be deprotonated by the catalyst thereby forming its respective ammonium cation. We theorised that this cation may provide another hydrogen bonding node, to which the nitrogen of the pyrazole can bind. We believe that it is this electrostatic interaction coupled with the hydrogen bonding interaction between the squareamide and the carbonyl oxygen lone pairs that holds the acylpyrazole substrate in the catalytic transition state (Figure 7.4). While the *Si* face alkene is blocked by the unprotonated quinamine functional group, the nucleophile can only reach the required Burgi-Dunitz angle for addition at the *Re* face, therefore only the *R*-enantiomer of the product is observed.

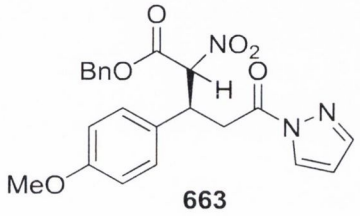
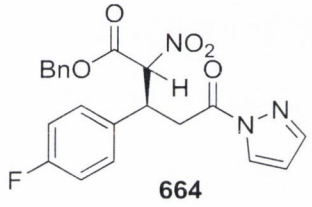
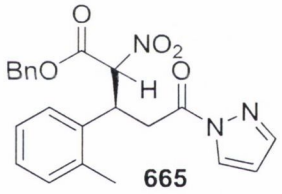
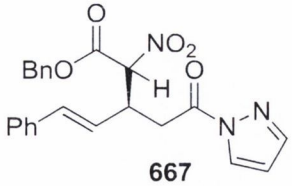
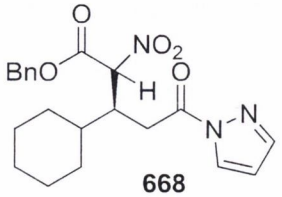
Scheme 7.4 Proposed catalytic transition state for the addition of benzyl nitroacetate to acylpyrazole **605**



Evaluation of the various β-substituted α,β-unsaturated acylpyrazoles under that organocatalysed conditions with benzyl nitroacetate was undertaken. The formation of the electron-rich methoxy-substituted nitroacetate product **663** was found to proceed to 91% isolated yield and 53:47 *dr* (entry 1, Table 7.8).

Table 7.8 Evaluation of the addition of benzyl nitroacetate to α,β-unsaturated acylpyrazoles



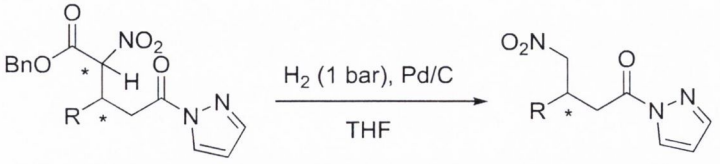
entry	product	yield (%)[a]	*dr*[b]
1	 **663**	91	53:47
2	 **664**	88	52:48
3	 **665**	74	56:44
4	 **666**	78	70:30
5	 **667**	66	52:48
6	 **668**	61[c]	50:50

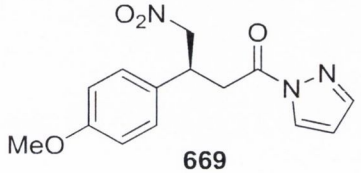
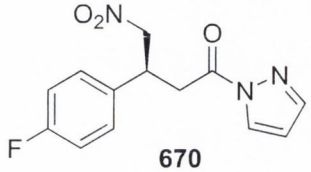
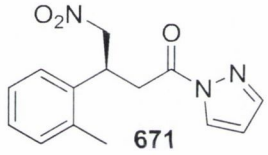
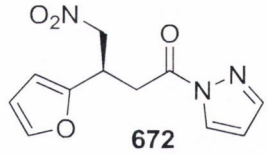
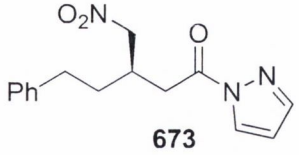
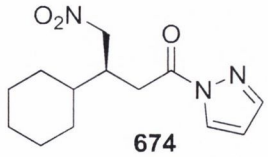
[a]Isolated by silica gel column chromatography. [b]Determined by ^{1}H NMR spectroscopic analysis. [c]Determined by ^{1}H NMR spectroscopic analysis with reference to styrene as internal standard.

The relatively electron-deficient fluoro-substituted adduct **664** was afforded in 88% isolated yield and 52:48 *dr* (entry 2). The sterically hindered methyl-substituted product **665** was furnished in the moderate yield of 74% and 56:44 *dr* (entry 3). The heterocyclic, furan-derived product **666** was produced in 78% yield and, surprisingly, a diasteriomeric ratio of 70:30 (entry 4). The use of the α,β,γ,δ-unsaturated acylpyrazole electrophile **647** furnished the 1,4-addition product **667** on the addition of benzyl nitroacetate (instead of the 1,6-conjugate addition product which might have been formed) in 66% yield and 52:48 *dr* (entry 5). Finally, the cyclohexyl-derived product **668** was generated in 61% yield, though it was inseparable from the remaining benzyl nitroacetate pronucleophile starting material (entry 6).

The hydrogenolysis of product **663** afforded the nitroalkane **669** in 97% yield and 99% *ee* (entry 1, Table 7.9). The fluoro-substituted product **670** was similarly prepared in 89% yield and 99% *ee* (entry 2). The sterically hindered, methyl-substituted nitroalkane **671** was produced in 92% yield and 97% *ee* (entry 3). The furan-derived nitroalkane **672** was generated in 98% yield and 96% *ee*, though it was found that longer reaction times caused the reduction of the furan ring (entry 4). The overnight reduction of the styrene-substituted nitroacetate **667** nitroalkane **673** in 97% yield and 97% *ee* (entry 5). As demonstrated in Table 7.7, this methodology appears to be less enantioselective when β-alkyl substituted α,β-unsaturated acylpyrazoles are utilised as substrates. Therefore the use of β-alkene substituted α,β-unsaturated acylpyrazoles represents a possible pathway for the production of enantiopure alkane substituted products. Finally, the cyclohexyl-derived product **674** was furnished *via* the reduction of the impure (*i.e.* contained unreacted benzyl nitroacetate) product **668** in 89% isolated yield and 88% *ee* (entry 6).

Table 7.9 The debenzylation of the products of Table 7.9



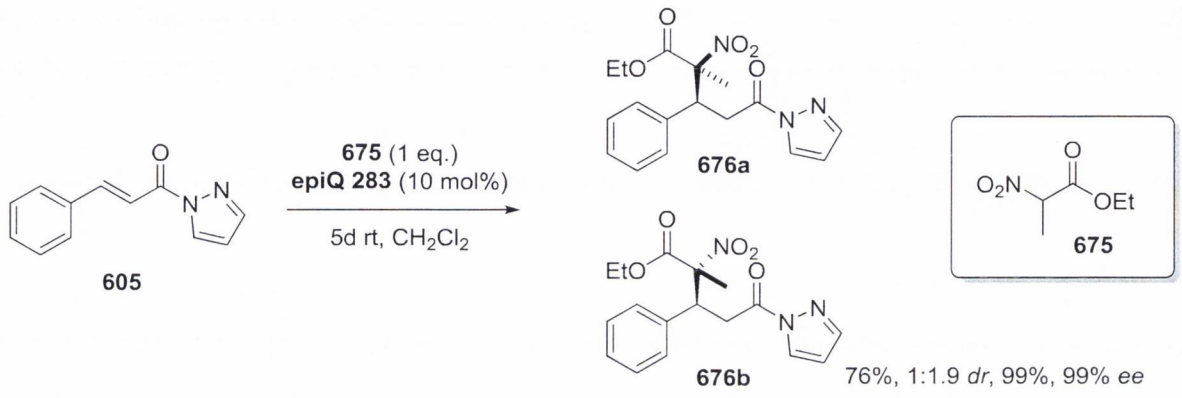
entry	product	time (h)	yield (%)[a]	*ee* (%)[b]
1	 **669**	2	97	99
2	 **670**	2	89	99
3	 **671**	2	92	97
4	 **672**	1	98[c]	96
5	 **673**	18	97	97
6	 **674**	2	89	88

[a]Isolated by filtering through a plug of silica gel. [b]Determined by CSP-HPLC analysis. [c]Product was isolated with ca. 10% impurity which was determined to be the product of the reduction of the furan ring.

In an effort to determine whether the acidity of the nitroacetate moiety was indeed the cause of the inseparability of the two diastereomers of the product, it was decided to attempt to synthesise a non-enolisable product *via* the same reaction. Product **676** was produced in the

moderate yield of 76% from the commercially available ethyl 2-nitropropanoate (**675**) and it was found that the diastereomers could be separated and evaluated by HPLC analysis separately. Both diastereomers were formed in 99% *ee* (Scheme 7.22).

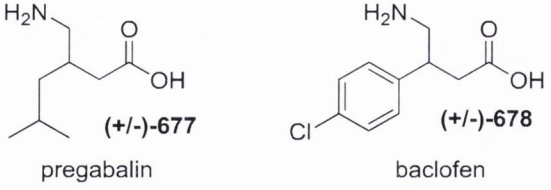
Scheme 7.22 The addition of ethyl 2-nitropropanoate to acylpyrazole **605**



7.6 The synthesis of pharmaceutical precursors

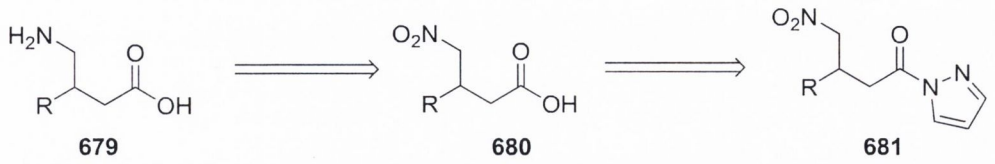
It was decided that some emphasis should be placed on the synthetic utility of this methodology. We posited that the gamma-aminobutyric acid (GABA) derivatives pregabalin (**677**) and baclofen (**678**) could be synthesised in high yield and *ee via* this 1,4-conjugate addition methodology (Figure 7.1).

Figure 7.2 The GABA-derivatives pregabalin and baclofen



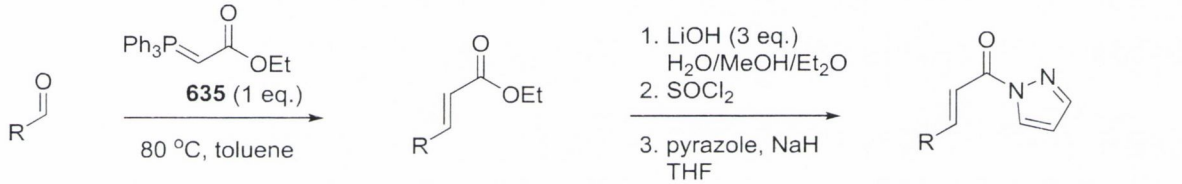
Analysis of the literature precendent indicates that the reduction of the nitro group (**680**) to form the GABA-derivatives (**679**) has been previously reported (Scheme 7.22).[180] As Barbas *et al.* previously reported the conversion of the acylpyrazole moiety into a methyl ester,[117] we theorised that the conversion to the carboxylic acid (**678**) should be facile.

Scheme 7.23 Retrosynthetic analysis of the GABA-derivatives



The required α,β-unsaturated acylpyrazoles were synthesised *via* the Wittig reaction with iso-valeraldehyde (**682**) and 4-chlorobenzaldehyde (**499**) to furnish the α,β-unsaturated esters in excellent yields. Subsequent hydrolysis functionalisation with pyrazole sodium salt afforded the acylpyrazole products **685** and **686** proceeded in moderate yield (Scheme 7.23).

Scheme 7.23 The synthesis of the α,β-unsaturated acylpyrazoles required for the production of the desired GABA-derivatives



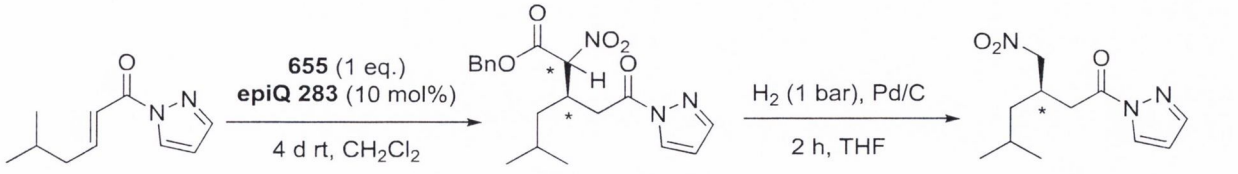
682 R = $CH_2CH(CH_3)_2$
499 R = 4-Cl-C_6H_4

683 R = $CH_2CH(CH_3)_2$ 94%
684 R = 4-Cl-C_6H_4 97%

685 R = $CH_2CH(CH_3)_2$ 66%
686 R = 4-Cl-C_6H_4 87%

The 1,4-conjugate addition of benzyl nitroacetate (**655**) to the α,β-unsaturated acylpyrazole **685** formed product **687** in 98% yield and 53:47 *dr* with 10 mol% catalyst loading after 4 days (Scheme 7.24). The debenzylation of this compound afforded the nitroalkane **688** in 94% yield. Though the product *ee* was a disappointing 80%.

Scheme 7.24 The formation of the pregabalin precursor **676**



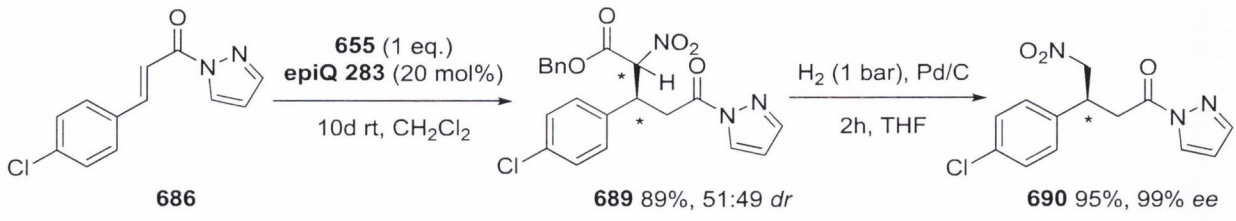
685

687 98%, 53:47 *dr*

688 94%, 80% *ee*

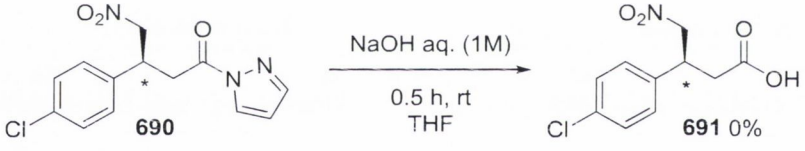
The product **689** was generated in 89% yield and 51:49 *dr via* the 1,4-conjugate addition reaction with 20 mol% catalyst loading. Subsequent reduction furnished the baclofen precursor in excellent yield (95%) and 99% *ee* (Scheme 7.25).

Scheme 7.25 The formation of baclofen precursor **678**



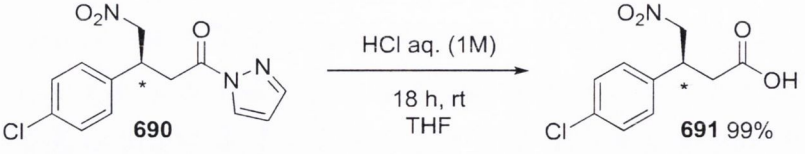
As the baclofen precursor was demonstrated to form in 99% *ee* it was decided to focus exclusively on the formation of this GABA-derivative. However, on treatment of the acylpyrazole **690** with aqueous 1 M sodium hydroxide, no formation of acid **691** was observed (Scheme 7.26). All of the starting material was consumed in this reaction, indicating that some kind of degradation reaction is occurring and most likely a Nef-type reaction, which is known to arise from the treatment of nitro-functionalised alkane compounds under basic conditions.[181]

Scheme 7.26 The hydrolysis of the acylpyrazole under basic conditions



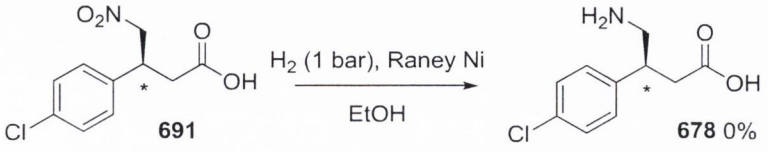
Gratifyingly however, the acid product **691** was produced in quantitative yield *via* the treatment of acylpyrazole **690** with 1M aqueous HCl at room temperature for 18 hours (Scheme 7.30). The desired acid product was isolated in high purity (by ^{1}H NMR spectroscopic analysis) *via* extraction with dichloromethane. The stereochemistry of this product was determined by polarimetric techniques and, by extension, the stereochemistry assigned to all of the products related to it (*i.e.* Tables 7.8 and 7.9).

Scheme 7.30 The hydrolysis of the acylpyrazole under acidic conditions



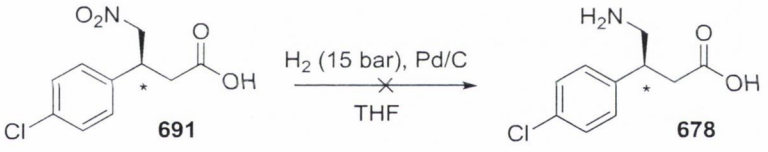
Disappointingly however, on attempted reduction of acid **689** using the literature reported method, *via* Raney nickel reduction, it was found that no product was observeable after filtration through celite (Scheme 7.31).[182]

Scheme 7.31 Reduction of **691** using Raney nickel



Furthermore, it was found that the attempted reduction of acid **691** under increased pressure of hydrogen and with palladium on carbon as the catalyst only produced the starting material on work-up (Scheme 7.31).

Scheme 7.31 Increased pressure of hydrogen for the reduction of the nitro-functional group



7.7 Conclusion

Here is described the enantioselective addition of highly acidic pronucleophiles to α,β-unsaturated acylpyrazoles and their subsequent utility in the synthesis of potential precursors to pregabalin and baclofen in substantial *ee*. It was found that the use of malononitrile as a pronucleophile substrate in the reaction furnished products in high enantiomeric excess, though in the main only moderate yields were obtained. The use of nitroacetate esters as pronucleophiles however, allowed the production of adducts which could be deprotected *via* hydrogenolysis to furnish highly enantiopure materials in moderate to high yield. This methodology negates the use of large, and wasteful, concentrations of nitromethane to effect efficient catalysis.

As for the acylpyrazole substrates, it was found that β-aryl-substituted α,β-unsaturated acylpyrazoles were excellent in the formation of products in high enantioselectivity. However, β-alkyl-substituted substrates were found to form products with lower *ee*. We were able to show that β-alkene-substituted substrates could furnish the corresponding β-alkyl-

substituted products after hydrogenation, thereby effecting a methodology for producing the β-alkyl-substituted products in high enantiopurity.

Also, here described, is the enantiopure synthesis of a known precursor to the pharmaceutical agent Baclofen. This represents a novel approach to the formation of this compound and may, in time, be suitable for the production of enantiopure pregabalin; the synthesis of which was hampered by the 1,4-conjugate addition reaction forming the adduct in only moderate enantioselectivity.

8.0 Published works

C. J. O' Connor, F. Manoni, S. P. Curran, S. J. Connon, *New J. Chem*, 2011, **35**, 551 -553

S. P. Curran, S. J. Connon, *Org. Lett.*, 2012, **14**, 1074 - 1077

S. P. Curran, S. J. Connon, *Angew. Chem. Int. Ed.*, 2012, **51**, 10866 - 10870

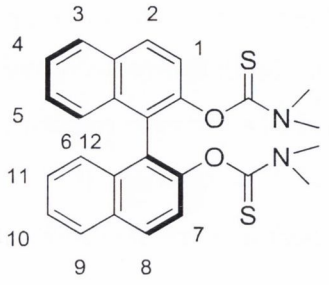
9.0 Experimental

General

Melting points were determined using a standard melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin Elmer Spectrum 100 FT-IR spectrometer equipped with a universal ATR sampling accessory. Proton nuclear magnetic resonance (NMR) spectra were recorded on: Bruker Avance III 400 MHz, Bruker Avance II 600 MHz and Bruker DPX400 400 MHz (^{1}H NMR spectra were recorded at 400.23 MHz and 400.13 MHz respectively). Chemical shifts are reported in ppm and coupling constants (J) are quoted in Hertz. Carbon NMR spectra were recorded on the previously mentioned 400 MHz instruments (100.64 MHz and 100.61 MHz respectively) with total proton decoupling. Fluorine NMR spectra were recorded on the Bruker DPX400 machine at 376.5 MHz). HSQC, HMBC, TOCSY and nOe NMR experiments were used to aid assignment of NMR peaks when required. Spectra recorded in $CDCl_3$ were referenced to residual $CHCl_3$ at 7.26 ppm for ^{1}H and 77.0 ppm for ^{13}C. A Waters micromass LCT-TOF mass spectrometer was used in ESI positive and ESI negative modes for electrospray ionization mass spectrometry. Electron Impact mass spectra were recorded on the same machine in EI mode. Flash chromatography was carried out using silica gel, particle size 0.04-0.063 mm and using a stepwise solvent polarity gradient (hexane-CH_2Cl_2 unless otherwise stated) correlated with TLC mobility. TLC analysis was performed on precoated 60F254 slides, and visualised by either UV irradiation or $KMnO_4$ staining. All of the aldehydes used were purified by distillation or recrystalisation prior to use. Optical rotation measurements are quoted in units of 10^{-1} deg cm^2 g^{-1}.

9.1 BINOL-derived products

(*S*)-*O*,*O*'-1,1'-Binaphthyl-2,2'-diyl bis(dimethylcarbamothioate) ((*S*)-347)



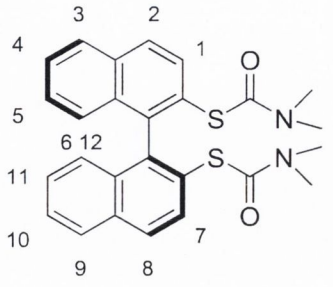
An ice-cooled solution of (*S*)-(-)-1,1'binaphthol (1.00 g, 3.5 mmol) in dry DMF (25 mL) in a 250 mL round bottom flask under N_2 was treated with NaH (60%, 350 mg, 8.75 mmol) (added in small portions) and allowed to stir for 30 minutes. To the resulting yellow mixture *N*,*N*-dimethylthiocarbamoyl chloride (1.08 g, 8.75 mmol) was added and the soln. was heated to 85 °C. After 1.5 hours the reaction was cooled to room temperature and poured over a solution of 2M KOH (aq.) (100 mL). The white precipitate was filtered, washed with water, dissolved in CH_2Cl_2 (50 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow solid which was recrystallised from CH_2Cl_2 and hexanes to afford **(*S*)-347** as white crystals (85%, 1.41 g). M.p. 205 - 207 °C. (lit. 206 - 208 °C[119]) [αD] = -149 (c = 1.08, $CHCl_3$). [lit. [αD] = -154 (c = 1, $CHCl_3$)[128]]

δ_H (400 MHz, $CDCl_3$): 2.51 (s, 6H, $N(CH_3)_2$), 3.08 (s, 6H, $N(CH_3)_2$), 7.30 (app. dt, 2H, H-4 and H-10), 7.46-7.43 (m, 4H, H-5, H-6, H-11 and H-12), 7.62 (d, 2H, *J* 9.0, H-2 and H-8), 7.90 (d, 2H, *J* 8.5, H-3 and H-9), 7.96 (d, 2H, *J* 9.0, H-1 and H-7).

δ_C (100 MHz, $CDCl_3$): 38.4 ($N(CH_3)_2$), 43.1 ($N(CH_3)_2$), 124.1 (CH), 124.4 (C), 126.1 (CH), 126.8 (CH), 127.2 (CH), 128.1 (CH), 128.7 (C), 131.8 (CH), 133.7 (C), 149.9 (C), 186.9 (C).

The NMR spectral data are consistent with those in the current literature.[119]

(*S*)-*S*,*S*'-1,1'-Binaphthyl-2,2'-diyl bis(dimethylcarbamothioate) ((*S*)-348)



Compound **(*S*)-347** (1.00 g, 2.2 mmol) was placed in a glass vial and preheated to 130 °C under vacuum for 10 minutes. The vial was then placed under argon and then heated to 265 °C for 30 minutes. The black residue was extracted with CH_2Cl_2 (70 mL), purified by flash chromatography and recrystallised from CH_2Cl_2/*n*-hexane to afford **(*S*)-348** as white crystalline solid in (69%, 690 mg). M.p. 241 - 242 °C. (lit. M.p 241 - 243 °C[183]) [αD] = + 70.4 (c = 0.9, $CHCl_3$).

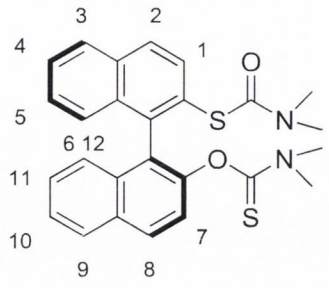
δ_H (400 MHz, $CDCl_3$): 2.77 (br. app. d, 12H, *J* 41.9, $N(CH_3)_2$), 7.08 (d, 2H, *J* 8.0, H-6 and H-12), 7.23 (app. t, 2H, H-4 and H-10), 7.46 (app. t, 2H, H-5 and H-11), 7.80 (d, 2H, *J* 8.7, H-2 and H-8), 7.91 (d, 2H, *J* 7.8, H-3 and H-9), 7.98 (d, 2H, *J* 8.7, H-1 and H-7).

δ_C (100 MHz, $CDCl_3$): 37.2 ($N(CH_3)_2$), 126.7 (CH), 126.9 (CH), 127.2 (CH), 128.1 (CH), 128.5 (CH), 128.7 (C), 133.5 (CH), 133.5 (C), 141.2 (C), 166.5 (C).

HMBC analysis indicates that the resonance at 133.5 ppm represents 2 carbon atoms, one of which is quaternary.

The NMR spectral data are consistent with those in the current literature.[119]

(*S*)-*O*,*O*'-1,1'-Binaphthyl-2,2'-diyl bis(dimethylcarbamothioate) ((*S*)-349)



This product was obtained as a side product of the reaction to form **(*S*)-348** and was isolated as a white solid (10 %, 100 mg). M.p. 181 – 184 °C. (lit. M.p. 183 - 184 °C)[128]

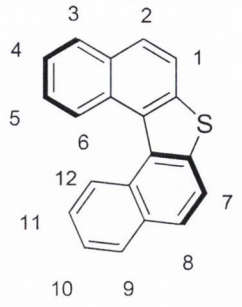
δ_H (400 MHz, $CDCl_3$): 1.60 (s, 3H, $OCSN(CH_3)_2$) and 1.82 (s, 3H, $OCSN(CH_3)_2$), 2.91 (s, 3H, $SCON(CH_3)_2$), 3.00 (s, 3H, $SCON(CH_3)_2$), 6.90 (d, *J* 8.5 Hz, 1H, H-6), 7.11 (d, *J* 8.8 Hz, 1H and H-12), 7.22 (app. t, 1H, H-4), 7.41 (app. t, 1H, H-5), 7.52 (app. t, 1H, H-11), 7.74 (d, *J* 8.5 Hz, 1H), 7.88-8.09 (m, 5H, H-1, H-2, H-3, H-8 and H-10), 8.40 (d, *J* 8.8 Hz, 1H, H-7).

δ_C (100 MHz, $CDCl_3$): 23.9 ($N(CH_3)_2$), 36.8 ($N(CH_3)_2$), 37.2 ($N(CH_3)_2$), 122.0 (CH), 124.8 (CH), 124.8 (CH), 125.3 (CH), 126.4 (CH), 126.7 (CH), 127.3 (CH), 127.5 (CH), 127.9 (C), 128.07 (CH), 128.6 (C), 129.5 (C), 130.6 (CH), 133.13 (CH), 133.16 (C), 133.4 (CH), 134.1 (CH), 134.9 (CH), 140.7 (C), 168.6 (C), 169.2 (C).

HMBC analysis indicates that the resonances at 23.9 and 127.9 ppm represent 2 carbon atoms; of which 127.9 ppm contains a quaternary carbon.

The NMR spectral data are consistent with those in the current literature.[128]

Dinaphtho[2,1-b:1′,2′-d]thiophene ((*S*)-350)



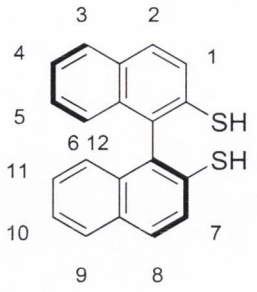
This product was obtained as a side product of the reaction to form **(*S*)-348** and was isolated as a yellow crystalline solid (18 %, 184 mg). M.p. 203 – 206 °C. (lit. M.p. 203 - 204 °C)[184]

δ_H (400 MHz, $CDCl_3$): 7.53 – 7.64 (m, 4H, H-4, H-5, H-10 and H-11), 7.93 (d, 2H, *J* 8.6 Hz, H-6 and H-12), 7.96 (d, 2H, *J* 8.6 Hz, H-3 and H-9), 8.03 (m, 2H, H-2 and H-8), 8.87 (m, 2H, H-1 and H-7).

δ_C (100 MHz, $CDCl_3$): 120.8 (CH), 124.8 (CH), 125.2 (CH), 126.0 (CH), 127.4 (C), 128.6 (CH), 129.8 (C), 131.4 (CH), 132.1 (C), 138.4 (C).

The NMR spectral data are consistent with those in the current literature.[184]

(*S*)-1,1'-Binaphthyl-2,2'-dithiol ((*S*)-345)



To a solution of recrystallised **(*S*)-348** (600 mg, 1.3 mmol) in dry THF (9 mL) in an oven dried 50 mL flask, $LiAlH_4$ (300 mg, 7.8 mmol) was added slowly under a stream of N_2. The reaction was heated at reflux overnight, quenched in degassed 1N HCl (20 mL), dried in $MgSO_4$ and concentrated *in vacuo* to afford **(*S*)-345** as a yellow solid (90%, 372 mg). M.p. 151 - 152 °C. (lit. M.p. 150 - 152 °C[184]) [αD] = +28.4 (c = 0.22, $CHCl_3$). (lit. [αD] = +54 (c = 0.8, $CHCl_3$[185]).

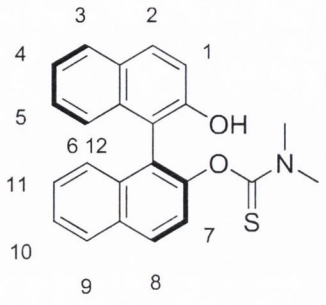
δ_H (400 MHz, $CDCl_3$): 3.32 (s, 2H, SH), 7.07 (d, 2H, *J* 8.4 Hz, H-6 and H-12), 7.33 (app. t, 2H, H-4 and H-10), 7.47 (app. t, 2H, H-5 and H-11), 7.62 (d, 2H *J* 8.7 Hz, H-3 and H-9), 7.93 (m, 4H, H-1, H-2, H-7 and H-8).

δ_C (100 MHz, $CDCl_3$): 125.15 (CH), 125.81 (CH), 127.48 (CH), 127.71 (CH), 128.59 (CH), 129.38 (CH), 131.66 (C), 132.10 (C), 132.17 (C), 132.90 (C).

HRMS (*m/z* - ESI$^-$) Found: 317.0435 (M^-- H $C_{20}H_{13}S_2$ Requires: 317.0435).

The NMR spectral data are consistent with those in the current literature.[120]

(*S*)-*O*-2'-Hydroxy-1,1'-binaphthyl-2-yl dimethylcarbamothioate ((*S*)-362)



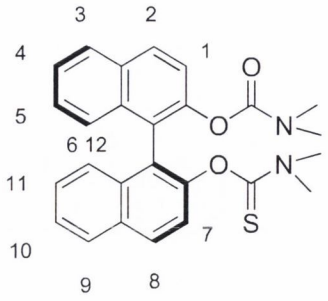
A 250 mL round bottomed flask was charged with (*S*)-1,1'binaphthol (10.00 g, 35 mmol), *N*,*N*-dimethylthiocarbamoyl chloride (4.32 g, 35 mmol) and DMAP (424 mg, 3.5 mmol), dry CH_2Cl_2 (130 mL) and distilled NEt_3 (5.43 mL, 38.5 mmol). The reaction was stirred under argon for 48 hours and quenched in a saturated solution of NH_4Cl (50 mL), extracted with CH_2Cl_2 (2 x 100 mL) and concentrated *in vacuo*. The product **(*S*)-362** was purified by column chromatography eluting in 10% EtOAc in hexanes and was isolated as a yellow solid (85%, 11.20 g). M.p. 145 - 147 °C. (lit. M.p. 143 - 144 °C[120]). [αD] = -84 (c = 1.0, $CHCl_3$).

δ_H (400 MHz, $CDCl_3$): 2.64 (s, 3H, $N(CH_3)_2$), 3.22 (s, 3H, $N(CH_3)_2$), 5.86 (s, 1H, OH), 7.16 (d, 1H, *J* 8.4, H-6), 7.27 – 7.30 (m, 2H, H-10 and H-12), 7.32 – 7.38 (m, 3H, H-4, H-5 and H-8), 7.45 (d, 1H, *J* 8.9, H-3), 7.53 (t, 1H, *J* 6.9, H-11), 7.87 (d, 1H, *J* 8.1, H-9), 7.91 (d, 1H, *J* 8.9, H-2), 7.99 (d, 1H, *J* 7.9, H-7), 8.09 (d, 1H, *J* 8.9, H-1).

δ_C (100 MHz, $CDCl_3$): 37.2 ($N(CH_3)_2$), 42.2 ($N(CH_3)_2$), 113.9 (C), 118.4 (CH), 122.1 (CH), 122.6 (CH), 123.0 (CH), 123.9 (CH), 125.0 (CH), 125.4 (CH), 125.6 (C), 126.5 (CH), 127.1 (CH), 127.5 (CH), 128.2 (C), 129.3 (CH), 130.6 (CH), 131.3 (C), 132.7 (C), 132.9 (C), 150.5 (C), 151.3 (C), 186.5 (C).

The NMR spectral data are consistent with those in the current literature.[120]

(*S*)-2'-(Dimethylcarbamothioyloxy)-1,1'-binaphthyl-2-yl dimethylcarbamate ((*S*)-363)



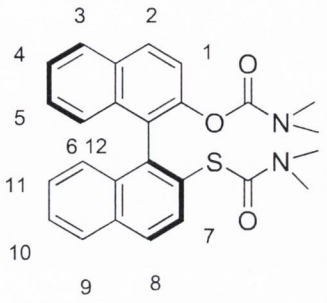
To an ice-cooled solution of **(*S*)-363** (10.0 g, 26.8 mmol) in a 2:1 mixture of dry THF/DMF (100 mL) under N_2, NaH (60%, 1.20 g, 29.5 mmol) was added slowly under a stream of argon and stirred for 30 minutes at room temperature. *N,N* dimethylcarbamoyl chloride (2.70 ml, 29.5 mmol) was added in one portion and the reaction was stirred overnight. The reaction mixture was then poured over aqueous KOH and extracted with CH_2Cl_2 (3 x 50 mL), dried over $MgSO_4$, concentrated *in vacuo* and purified by column chromatography eluting in 10% EtOAc in hexanes to give **(*S*)-363** as a white solid (90%, 9.65 g). M.p. 163 - 165 °C. (lit. M.p. 123 - 125 °C[120]) [αD] = -132 (c = 0.7, $CHCl_3$).

δ_H (400 MHz, $CDCl_3$): 2.22 (s, 3H, $N(CH_3)_2$), 2.47 (app. d, 3H, $N(CH_3)_2$), 2.68 (s, 3H, $N(CH_3)_2$), 3.07 (app. d, 3H, $N(CH_3)_2$), 7.29 – 7.32 (m, 3H, H-6, H-10 H-12), 7.40 – 7.47 (m, 3H, H-4, H-5 and H-11), 7.59 (app. dt, 2H, H-8 and H-9), 7.88 – 8.00 (m, 4H, H-1, H-2, H-7 and H-3).

δ_C (100 MHz, $CDCl_3$): 35.8 ($N(CH_3)_2$), 36.3 ($N(CH_3)_2$), 37.8 ($N(CH_3)_2$), 42.8 ($N(CH_3)_2$), 122.6 (CH), 123.0 (C), 123.7 (CH), 125.4 (CH), 125.6 (CH), 125.7 (CH), 126.1 (CH), 126.3 (C), 126.5 (CH), 126.6 (C), 126.8 (CH), 127.8 (CH), 127.9 (CH), 128.4 (CH), 128.9 (CH), 131.1 (C), 131.5 (C), 133.4 (C), 147.4 (C), 147.5 (C), 154.1 (C), 186.4 (C).

The NMR spectral data are consistent with those in the current literature.[120]

(*S*)-2'-(Dimethylcarbamoylthio)-1,1'-binaphthyl-2-yl dimethylcarbamate ((*S*)-365)



In a commercial Kugelrohr apparatus compound **(*S*)-363** (6.00 g, 13.5 mmol) was preheated to 130 °C under vacuum, it was then placed under an argon atmosphere and heated at 250 °C for 5 hours. The resulting black residue was extracted with CH_2Cl_2 (200 mL) and stirred over activated charcoal. The mixture was filtered, concentrated *in vacuo* and purified by column chromatography eluting in 10% EtOAc in hexanes to give a light yellow solid (70%, 4.20 g). M.p. 154 - 159 °C. (lit. M.p. 169 - 171 °C[120]) [αD] = -143 (c = 0.9, $CHCl_3$).

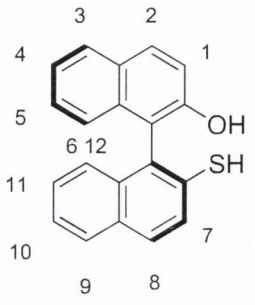
δ_H (400 MHz, $CDCl_3$): 2.22 (s, 3H, $N(CH_3)_2$), 2.69 – 2.89 (m, 9H, $N(CH_3)_2$), 7.20 – 7.25 (m, 2H, H-6 and H-12), 7.28 – 7.32 (m, 3H, H-4, H-10 and H-11), 7.44 – 7.52 (m, 2H, H-5 and H-8), 7.64 (d, 1H, *J* 8.9, H-2), 7.82 (d, 1H, *J* 8.6, H-9), 7.95 (t, 1H, *J* 8.6, H-7), 7.99 – 8.03 (m, 2H, H-1 and H-3).

δ_C (100 MHz, $CDCl_3$): 35.7 ($N(CH_3)_2$), 36.4 ($N(CH_3)_2$), 36.9 ($N(CH_3)_2$), 122.5 (CH), 125.3 (CH), 126.1 (CH), 126.4 (CH), 126.5 (CH), 126.7 (CH), 126.8 (CH), 127.8 (CH), 128.0 (CH), 128.1 (C), 129.1 (CH), 131.1 (C), 133.1 (C), 133.3 (C), 133.5 (C), 133.6 (C), 138.1 (C), 147.2 (C), 154.0 (C), 166.5 (C).

HSQC analysis indicates that the resonances at 126.7, 122.5 and 36.9 ppm represent 2 carbon atoms each.

The NMR spectral data are consistent with those in the current literature.[120]

(*S*)-2'-Mercapto-1,1'-binaphthyl-2-ol ((*S*)-357)



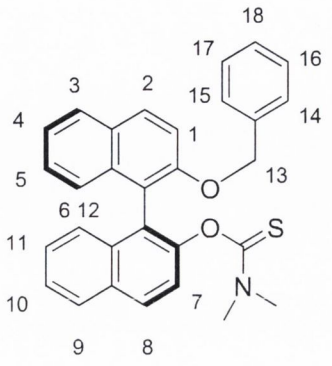
In a 250 ml flask, compound **(*S*)-365** (3.00 g, 6.75 mmol) was dissolved in anhydrous methanol (60 mL) under a N_2 atmosphere. To this was added 20 mL of a solution of KOH in MeOH (5 g/20 mL). The reaction was allowed to heat under reflux for 24 hours and was quenched with a degassed solution of 1N HCl (100 mL). The resulting colourless precipitate was filtered, dissolved in CH_2Cl_2 (70 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified by flash chromatography with CH_2Cl_2 as eluent to give **(*S*)-357** as a white solid (60% yield, average of 2 columns: 62% & 58%). M.p. 148 - 150 °C. (lit. M.p. 150 - 152 °C[120]) [αD] = -128.7 (c = 1.00, $CHCl_3$). (lit. [αD] = -27.9 (c = 0.10, $CHCl_3$)[120])

δ_H (400 MHz, $CDCl_3$): 3.43 (s, 1H, SH), 4.88 (s, 1H, OH), 7.03 – 7.06 (m, 1H, H-12), 7.15 – 7.18 (m, 1H, H-6), 7.31 – 7.35 (m, 2H, H-4 and H-10), 7.37 – 7.42 (m, 2H, H-5 and H-11), 7.47 (app. t, 1H, H-8), 7.62 (d, 1H, *J* 8.8, H-2), 7.92 – 7.94 (m, 3H, H-3, H-7 and H-9), 8.00 (d, 1H, *J* 8.8, H-1).

δ_C (100 MHz, $CDCl_3$): 116.2 (C), 117.3 (CH), 123.4 (CH), 123.8 (CH), 124.6 (CH), 125.2 (CH), 126.1 (C), 126.5 (CH), 126.7 (CH), 127.2 (CH), 127.9 (CH), 127.9 (CH), 128.9 (C), 129.3(CH), 130.4 (CH), 131.4 (C), 132.2 (C), 133.2 (C), 133.3 (C), 150.6 (C).

The NMR spectral data are consistent with those in the current literature.[120]

(*S*)-*O*-2'-(Benzyloxy)-1,1'-binaphthyl-2-yl dimethylcarbamothioate ((*S*)-366)



To an ice-cooled solution of **(*S*)-362** (5.00 g, 13.4 mmol) in a 2:1 mixture of dry THF/DMF (60 mL) under N_2, NaH (60%, 0.60 g, 14.8 mmol) was added slowly under a stream of nitrogen and stirred for 30 minutes at room temperature. Benzyl bromide (1.76 mL, 14.8 mmol) was added in one portion and the reaction was stirred overnight. The reaction was then poured over aqueous KOH and extracted with CH_2Cl_2 (3 x 50 mL), dried over $MgSO_4$, concentrated *in vacuo* and purified by column chromatography eluting (10% EtOAc/*n*-hexane) to afford **(*S*)-366** as a yellow solid (70%, 4.34 g). M.p. 72 - 75 °C. [αD] = +26.2 (c = 0.5 $CHCl_3$).

δ_H (400 MHz, $CDCl_3$): 2.55 (s, 3H, $N(CH_3)_2$), 3.10 (s, 3H, $N(CH_3)_2$), 5.11 (app. q, 2H, H-13), 7.05 - 7.14 (m, 2H, H-16 and H17), 7.16 - 7.24 (m, 3H, H-14, H-15 and H-18), 7.29 - 7.43 (m, 6H, H-5, H-6, H-8, H-10, H-11 and H-12), 7.49 (app. t, 1H, H-4), 7.67 (d, 1H, *J* 8.6, H-2), 7.86 (d, 1H, *J* 7.6, H-9), 7.94 (d, 1H, *J* 8.7, H-7), 8.00 (d, 1H, *J* 8.0, H-3), 8.06 (d, 1H, *J* 8.6, H-1).

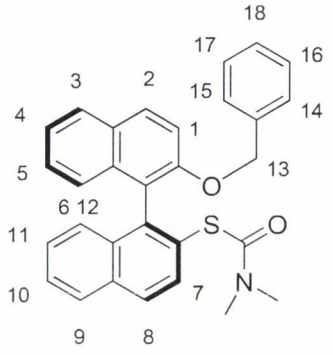
δ_C (100 MHz, $CDCl_3$): 37.3 ($N(CH_3)_2$), 42.3 ($N(CH_3)_2$), 70.7 (CH_2), 114.9 (CH), 118.5 (C), 123.1 (CH), 123.5 (CH), 125.0 (C), 125.9 (CH), 126.2 (CH), 126.4 (CH), 126.6 (CH), 127.8 (CH), 127.9 (CH), 128.1 (CH), 128.5 (CH), 128.6 (CH), 129.3 (CH), 131.3 (C), 133.3 (C), 133.5 (C), 137.1 (C), 149.2 (C), 153.7 (C), 186.1 (C).

HSQC analysis indicates that the resonance at 126.4 ppm represents 3 carbon atoms and the resonance at 126.6 represents 2 carbons.

HRMS (*m/z* - ESI$^+$) Found: 486.1492 (M^+ + Na $C_{30}H_{25}O_2NS$ Requires: 486.1504).

vmax (film)/cm^{-1}: 3218, 1637, 1416, 1309, 884, 750.

(*S*)-*S*-2'-(Benzyloxy)-1,1'-binaphthyl-2-yl dimethylcarbamothioate ((*S*)-368)



In a commercial Kugelrohr apparatus compound **(*S*)-366** (2.00 g, 4.3 mmol) was preheated to 130 °C under vacuum, it was then placed under an argon atmosphere and heated at 260 °C for 40 minutes. The resulting black residue was extracted with CH_2Cl_2 (100 mL) and stirred over activated charcoal. The resulting mixture was filtered, concentrated *in vacuo*, purified by column chromatography eluting in 50% CH_2Cl_2/*n*-hexane to produce **(*S*)-368** as an orange solid (56%, 1.11 g). M.p. 64 - 66 °C. [αD] = +12.7 (c = 1.03 $CHCl_3$).

δ_H (400 MHz, $CDCl_3$): 2.79 (br. app. d, 6H, $N(CH_3)_2$), 5.09 (app. q, 2H), 7.07 - 7.09 (m, 2H, H-16 and H-17), 7.19 - 7.22 (m, 4H, H-12, H-14, H-15 and H-18), 7.25 - 7.29 (m, 3H, H-6, H-8 and H-10), 7.37 (app. t, 1H, H-5), 7.44 (d, 1H, *J* 8.7, H-2), 7.50 (app. t, 1H, H-11), 7.88 - 7.98 (m, 4H, H-3, H-4, H-7 and H-9), 8.04 (d, 1H, *J* 8.7, H-1).

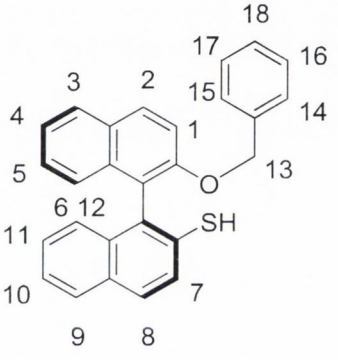
δ_C (100 MHz, $CDCl_3$): 38.01 ($N(CH_3)_2$), 43.0 ($N(CH_3)_2$), 71.45 (CH_2), 115.7 (CH), 119.3 (C), 123.8 (CH), 124.3 (CH), 125.8 (CH), 126.6 (CH), 126.7 (CH), 127.2 (CH), 127.7 (CH), 127.8 (CH), 128.5 (CH), 128.5 (CH), 128.6 (CH), 130.0 (C), 132.1 (C), 134.0 (C), 134.2 (C), 137.9 (C), 150.0 (C), 154.5 (C).

HSQC and HMBC analyses indicates that the resonance at 126.6 ppm contains 3 carbon atoms, the resonances at 126.7 and 128.5 ppm contain 2 carbon atoms each and the resonance at 125.8 ppm represents 2 carbons 1 of which is quaternary.

HRMS (*m/z* - EI^+) Found: 464.1687 (M^+ + H $C_{30}H_{27}O_2NS$ Requires: 464.1684).

νmax (film)/cm^{-1}: 2924, 1723, 1506, 1357, 1137, 1045, 910, 746.

(*S*)-2'-(Benzyloxy)-1,1'-binaphthyl-2-thiol ((*S*)-358)



In a 250 mL flask fitted with a reflux condenser, Compound **(*S*)-368** (150 mg, 0.32 mmol) was dissolved in anhydrous methanol (2 mL) under a N_2 atmosphere. To this was added 1 mL of a solution of KOH in MeOH (2.5 g/10 mL). The reaction was allowed to heat under reflux overnight and was quenched in a degassed solution of 1N HCl (20 mL). The resulting colourless precipitate was filtered, dissolved in CH_2Cl_2 (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified by flash chromatography by eluting in gradient 100% *n*-hexane to 10% $CHCl_3$ as eluent to afford **(*S*)-358** as a yellow solid (47%, 59 mg). M.p. 72 - 73 °C. [αD] = -37.3 (c = 0.42 $CHCl_3$)

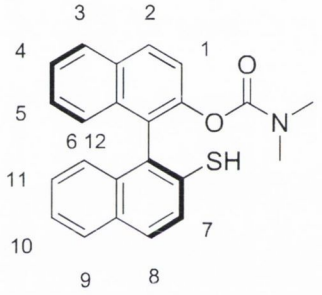
δ_H (400 MHz, $CDCl_3$): 3.31 (s, 1H, SH), 5.11 - 5.18 (m, 2H, H-13), 7.05 - 7.07 (m, 2H, H-16 and H-17), 7.12 (d, 1H, *J* 3.4, H-12), 7.17 - 7.18 (m, 3H, H-14, H-15 and H-18), 7.44 (m, 6H, H-4 H-5, H-6, H-8, H-10 and H-11), 7.60 (d, 1H, *J* 8.6, H-9), 7.87 - 7.92 (m, 3H, H-2, H-3, H-7), 7.99 (d, 1H, *J* 9.1, H-1).

δ_C (100 MHz, $CDCl_3$): 70.6 (CH_2), 114.6 (C), 115.4 (CH), 116.3 (C), 117.1 (CH), 122.8 (CH), 124.0 (CH), 124.5 (CH), 124.6 (C), 126.0 (CH), 126.4 (CH), 126.9 (CH), 127.2 (CH), 127.6 (CH), 127.7 (CH), 127.9 (CH), 128.7 (C), 129.2 (C), 129.4 (CH), 130.4 (CH), 133.4 (C), 133.6 (C), 136.5(C), 150.8 (C), 154.5 (C).

HRMS (*m/z* - ESI^+) Found: 821.2236 (M^+ + K $C_{54}H_{38}O_2S_2K$ Requires: 821.2211).

vmax (film)/cm^{-1}: 2923, 1590, 1452, 1328, 1172, 1017, 807.

(*S*)-2'-Mercapto-1,1'-binaphthyl-2-yl dimethylcarbamate ((*S*)-359)



Compound **(*S*)-365** (300 mg, 0.68 mmol) was dissolved in anhydrous methanol (8 mL) in a 50 mL round bottom flask, fitted with a reflux condenser and placed under an argon atmosphere. The flask was then charged with a 10% *w/v* solution of KOH in methanol (2 mL), and the reaction mixture was heated under reflux for 24 hours. The reaction was quenched using a degassed solution of 1N HCl (aq.) (40 mL) and the precipitate was collected by suction filtration. The precipitate was then dissolved in CH_2Cl_2 (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography eluting in 25% CH_2Cl_2 and hexanes to afford **(*S*)-359** as a white solid (33%, 83 mg) and **(*S*)-357** in 25% yield. M.p. 63 - 65 °C. [αD] = -77.1 (c = 1.2, $CHCl_3$)

δ_H (400 MHz, $CDCl_3$): 2.30 (s, 3H, $N(CH_3)_2$), 2.68 (s, 3H, $N(CH_3)_2$), 3.38 (s, 1H, SH), 7.13 (d, 1H, *J* 8.5, H-12), 7.21 (d, 1H, *J* 8.5, H-6), 7.24 - 7.28 (m, 1H, H-10), 7.33 (app. dt, 1H, H-4), 7.39 (app. dt, 1H, H-11), 7.48 (app. dt, 1H, H-5), 7.54 (d, 1H, *J* 8.6, H-8), 7.64 (d,

1H, *J* 8.9, H-2), 7.82 - 7.86 (m, 2H, H-7 and H-9), 7.97 (d,1H, *J* 8.1, H-3), 8.04 (d, 1H, *J* 9.0, H-1).

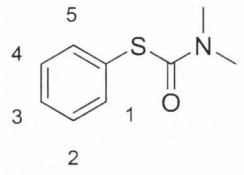
δ_C (100 MHz, $CDCl_3$): 35.6 ($N(CH_3)_2$), 36.3 ($N(CH_3)_2$), 122.7 (CH), 125.1 (CH), 125.5 (CH), 125.7 (CH), 126.3 (C), 126.8 (CH), 127.0 (CH), 127.8 (CH), 128.3 (CH), 128.4 (CH), 129.7 (CH), 129.9 (C), 131.2 (C), 131.4 (C), 131.7 (C), 132.4 (C), 133.5 (C), 147.45 (C), 154.0 (C).

HSQC analysis indicates that the resonances at 126.97 and 125.67 ppm represent 2 carbon atoms each.

HRMS (*m/z* - EI^+) Found: 396.1040 (M^+ + Na $C_{23}H_{19}O_2NSNa$ Requires: 396.1034).

νmax (film)/cm^{-1}: 2564, 1852, 1239, 932, 873, 786.

Thiophenol *N,N*-dimethylcarbamate (369)



To a solution of thiophenol (5 mmol, 0.51 mL) in CH_2Cl_2 (10 mL) was added *N,N*-dimethylcarbamyl chloride (5.5 mmol, 0.51 mL), NEt_3 (5.5 mmol, 0.767 mL) and DMAP (20 mg). The reaction was allowed to stir overnight and was poured into a solution of 1N HCl. Extraction with CH_2Cl_2 (3 x 20 mL) followed by concentration *in vacuo* afforded the crude material which was purified by column chromatography (10% EtOAc in hexanes) to furnish the product as a pale yellow solid (87%, 0.792 mg). M.p. 49 - 51 °C. (lit. 47.5 – 49 °C[186]).

δ_H (400 MHz, $CDCl_3$): 3.04 (s, 6H, $N(CH_3)_2$), 7.26 - 7.41 (m, 3H, H-2, H-3 and H-4), 7.47 - 7.50 (m, 2H, H-1 and H-5).

δ_C (100 MHz, $CDCl_3$): 36.8 ($N(CH_3)_2$), 128.7 (C), 128.8 (CH), 129.0 (CH), 135.6 (CH), 167.0 (C).

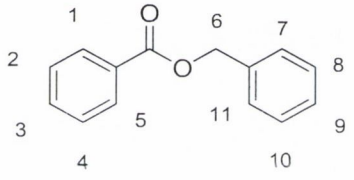
The NMR spectral data are consistent with those in the current literature.[187]

9.2 Tishchenko ester products

General procedure 1: the magnesium selenide-ion-catalysed Tishchenko reaction

To a oven dried flask charged with activated 3Å molecular sieves, a magnetic stirrer and dibenzyl diselenide (0.48 mmol, 163.3 mg) under a strict atmosphere of argon was added THF (1.6 mL, 1.2 M; 0.8 mL, 2.4 M; 0.4 mL, 4.8M; 0.2 mL, 9.6 M). To this yellow solution was added di-*n*-butylmagnesium (1M solution in *n*-heptane, 0.24 mmol, 0.24 mL) dropwise while stirring. To the resulting colourless solution, the aldehyde was added, and was allowed to stir at 25 °C for 24 hours. The reaction mixture was diluted with ethyl acetate and concentrated *in vacuo*.

Benzyl benzoate (17)



This product was obtained from the reaction of benzaldehyde (19.2 mmol, 1.95 mL), *via* general procedure 1. The product was isolated as a colourless oil (99%, 2.013 g) by column chromatography eluting in gradient 0 - 20% dichloromethane in hexanes.

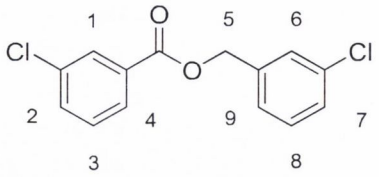
δ_H (400 MHz, $CDCl_3$): 5.40 (s, 2H, H-6), 7.37 - 7.49 (m, 7H, H-2, H-4, H-7, H-8, H-9, H-10 and H-11), 7.59 (t, 1H, *J* 7.5 Hz, H-3), 8.11 (d, 2H, *J* 7.6 Hz, H-1 and H-5).

δ_C (100 MHz, $CDCl_3$): 66.3 (CH_2), 127.7 (CH), 127.8 (CH), 127.9 (CH), 128.2 (C), 129.3 (CH), 129.7 (CH), 132.6 (CH), 135.7 (C), 166.0, (C).

HRMS (*m/z* - EI^+) Found: 212.0842 (M^+ $C_{14}H_{12}O_2$ requires: 212.0837).

The NMR spectral data are consistent with those in the current literature.[37]

3-Chlorobenzyl 3-chlorobenzoate (424)



This product was obtained from the reaction of 3-chlorobenzaldehyde (19.2 mmol, 2.18 mL), *via* general procedure 1. The product was isolated as a pale yellow oil (99%, 2.669 g) by column chromatography eluting in gradient 0 - 20% dichloromethane in hexanes.

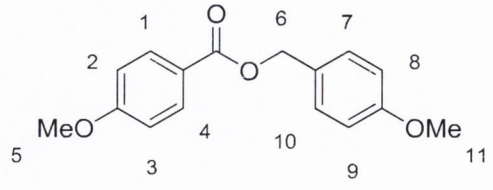
δ_H (400 MHz, $CDCl_3$): 5.32 (d, 2H, *J* 2.2 Hz, H-5), 7.32 – 7.42 (m, 5H, H-3, H-6, H-7, H-8, H-9), 7.53 (d, 1H, *J* 7.8 Hz, H-2), 7.95 (d, 1H, *J* 7.5 Hz, H-4), 8.03 (s, 1H, H-1).

δ_C (100 MHz, $CDCl_3$): 65.7 (CH_2), 125.9 (CH), 127.4 (CH), 127.8 (CH), 128.1 (CH), 129.3 (CH), 129.4 (CH), 129.5 (CH), 131.1 (C), 132.8 (CH), 134.1 (C), 134.2 (C), 137.2 (C), 164.6 (C).

HRMS (*m/z* - ESI^+) Found: 280.0059 (M^+ $C_{14}H_{10}Cl_2O_2$ requires: 280.0058).

The NMR spectral data are consistent with those in the current literature.[37]

4-Methoxybenzyl 4-methoxybenzoate (49)



This product was obtained from the reaction of 4-anisaldehydealdehyde (4.8 mmol, 0.585 mL), *via* general procedure 1. The product was isolated as a yellow oil (91%, 0.593 g) by column chromatography eluting in gradient 0 - 20% dichloromethane in hexanes.

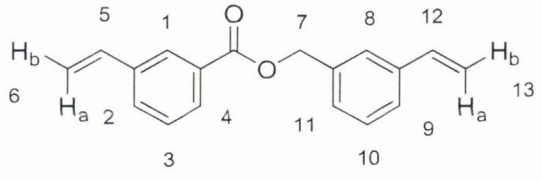
δ_H (400 MHz, $CDCl_3$): 3.84 (s, 3H, H-11), 3.87 (s, 3H, H-5), 5.29 (s, 2H, H-6), 6.92 - 6.95 (m, 4H, H-7, H-8, H-9 and H-10), 7.41 (d, 2H, *J* 8.8 Hz, H-2 and H-3), 8.03 (d, 2H, *J* 8.8 Hz, H-1 and H-4).

δ_C (100 MHz, $CDCl_3$): 54.9 (OMe), 55.0 (OMe), 65.8 (CH_2), 113.1 (CH), 113.5 (CH), 122.2 (C), 128.0 (C), 129.6 (CH), 131.3 (CH), 159.1 (C), 162.9 (C), 165.8 (C).

HRMS (*m/z* - EI^+) Found: 272.1049 (M^+ $C_{16}H_{16}O_4$ requires: 272.1049).

The NMR spectral data are consistent with those in the current literature.[37]

3-Vinylbenzyl 3-vinylbenzoate (429)



This product was obtained from the reaction of 3-vinylbenzaldehyde (9.6 mmol, 0.90 mL), *via* general procedure 1. The product was isolated as a pale yellow oil (93%, 1.178 g) by column chromatography eluting in gradient 0 - 20% dichloromethane in hexanes.

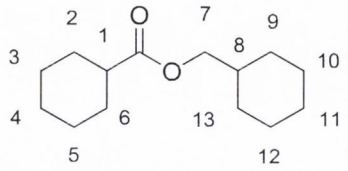
δ_H (400 MHz, $CDCl_3$): 5.31 (m, 4H, H-7 and H-13), 5.85 (dd, 2H, *J* 17.6, 14.0 Hz, H-6), 6.74 - 6.82 (m, 2H, H-5 and H-12), 7.39 - 7.45 (m, 4H, H-3, H-9, H-10 and H-11), 7.53 (s, 1H, H-8), 7.63 (d, 1H, *J* 7.8 Hz, H-2), 8.01 (d, 1H, *J* 7.8 Hz, H-4), 8.16 (s, 1H, H-1).

δ_C (100 MHz, $CDCl_3$): 66.3 (CH_2), 114.0 (CH_2), 114.8 (CH_2), 125.6 (CH), 125.7 (CH), 127.1 (CH), 127.2 (CH), 128.1 (C), 128.2 (CH), 128.4 (CH), 130.0 (C), 130.2 (CH), 135.5 (CH), 135.9 (CH), 136.0 (C), 137.4 (CH), 137.5 (C), 165.9 (C).

HRMS (*m/z* - EI^+) Found: 264.1150 (M^+ $C_{18}H_{16}O_2$ requires: 264.1150).

νmax (film)/cm^{-1}: 2925, 1713, 1587, 1374, 1263, 1105, 907, 748.

Cyclohexylmethyl cyclohexanecarboxylate (46)



This product was obtained from the reaction of cyclohexanecarboxaldehyde (4.8 mmol, 0.55 mL), *via* general procedure 1. The product was isolated as a pale yellow oil (98%, 0.525 g) by column chromatography eluting in gradient 0 - 20% dichloromethane in hexanes.

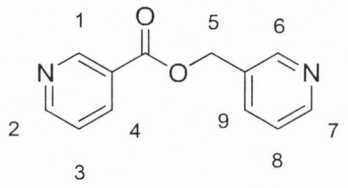
δ_H (400 MHz, $CDCl_3$): 0.90 - 1.02 (m, 2H, H-11), 1.16 - 1.34 (m, 6H, H-4, H-10 and H-12), 1.40 - 1.49 (m, 2H, H_a-9, and H_a-13), 1.64 - 1.76 (m, 9H, H_a-2, H-3, H-5, H_a-6, H-8, H_b-9 and H_b-13), 1.90 - 1.94 (m, 2H, H_b-2, H_b-6), 2.27 - 2.35 (tt, 1H, *J* 3.5, 11.6 Hz, H-1), 3.88 (d, 2H, *J* 6.5 Hz, H-7).

δ_C (100 MHz, $CDCl_3$): 25.0 (CH_2), 25.2 (CH_2), 25.3 (CH_2), 25.9 (CH_2), 28.6 (CH_2), 29.2 (CH_2), 36.7 (CH), 42.9 (CH), 68.8 (CH_2), 175.8 (C).

HRMS (*m/z* - EI$^+$) Found: 224.1764 (M^+ $C_{14}H_{24}O_2$ requires: 224.1776).

The NMR spectral data are consistent with those in the current literature.[37]

Pyridin-3-ylmethyl nicotinate (441)



This product was obtained from the reaction of 3-pyridinecarboxaldehyde (9.6 mmol, 0.9 mL), *via* general procedure 1. The product was isolated as an orange oil in (95%, 1.02 g) by column chromatography eluting in ethyl acetate in hexanes.

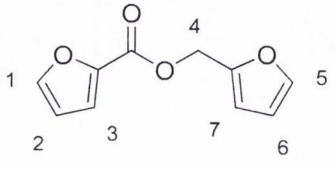
δ_H (400 MHz, $CDCl_3$): 5.43 (s, 2H, H-5), 7.34 - 7.43 (m, 2H, H-3 and H-8), 7.81 (d, 1H, *J* 7.8 Hz, H-9), 8.31 - 8.33 (m, 1H, H-6), 8.63 (d, 1H, *J* 4.0 Hz, H-7), 8.74 (s, 1H, H-2), 8.80 (d, 1H, *J* 4.6 Hz, H-4), 9.26 (s, 1H, H-1).

δ_C (100 MHz, $CDCl_3$): 64.1 (CH_2), 122.9 (CH), 123.2 (CH), 125.2 (C), 130.7 (C), 135.8 (CH), 136.7 (CH), 149.3 (CH), 149.5 (CH), 150.5 (CH), 153.3 (CH), 164.5 (C).

HRMS (*m/z* - ESI^+) Found: 214.0744 (M^+ $C_{12}H_{10}N_2O_2$ requires: 214.0742).

The NMR spectral data are consistent with those in the current literature.[188]

Furan-2-ylmethyl furan-2-carboxylate (50)



This product was obtained from the reaction of furfural (2.4 mmol, 0.20 mL), *via* general procedure 1. The product was isolated as a pale yellow oil (63%, 0.145 g) by column chromatography eluting in gradient 0 - 20% dichloromethane in hexanes.

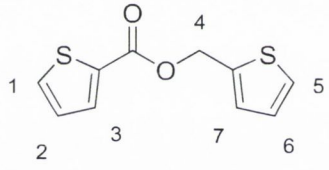
δ_H (400 MHz, $CDCl_3$): 5.31 (s, 2H, H-4), 6.40 - 6.41 (m, 1H, H-6), 6.51 - 6.53 (m, 2H, H-5 and H-7), 7.23 (app. d, 1H, *J* 3.5 Hz, H-2), 7.47 (app. s, 1H, H-1), 7.60 (app. s, 1H, H-3).

δ_C (100 MHz, $CDCl_3$): 57.8 (CH_2), 110.2 (CH), 110.8 (CH), 111.4 (CH), 118.0 (CH), 143.0 (CH), 143.8 (C), 146.1 (CH), 148.6 (C), 157.9 (C).

HRMS (*m/z* - EI^+) Found: 192.0420 (M^+ $C_{10}H_8O_4$ requires: 192.0423).

The NMR spectral data are consistent with those in the current literature.[24]

Thiophen-2-ylmethyl thiophene-2-carboxylate (442)



This product was obtained from the reaction of 2-thiophenecarboxaldehyde (9.6 mmol, 0.9 mL), *via* general procedure 1. The product was isolated as a pale yellow oil (96%, 1.036 g) by column chromatography eluting in gradient 0 - 20% dichloromethane in hexanes.

δ_H (400 MHz, $CDCl_3$): 5.48 (s, 2H, H-4), 7.00 - 7.02 (dd, 1H, *J* 1.0, 3.5, H-6), 7.08 - 7.10 (dd, 1H, *J* 0.8, 4.0, H-2), 7.17 - 7.18 (d, 1H, *J* 3.5, H-5), 7.33 - 7.35 (d, 1H, *J* 5.0 Hz, H-7), 7.54 - 7.56 (d, 1H, *J* 5.0 Hz, H-1), 7.82 - 7.83 (d, 1H, *J* 4.0 Hz, H-3).

δ_C (100 MHz, $CDCl_3$): 60.6 (CH_2), 126.4 (CH), 126.6 (CH), 127.4 (CH), 128.0(CH), 132.3 (CH), 133.0 (C), 133.4 (CH), 137.3 (C), 161.5 (C).

HRMS (*m/z* - ESI^+) Found: 223.9955 (M^+ $C_{10}H_{28}O_2S_2$ requires: 223.9966).

The NMR spectral data are consistent with those in the current literature.[180]

9.2.1 Crossed Tishchenko ester products

General procedure 2: the microwave assisted crossed Tishchenko reaction

To an oven-dried microwave-transparent reaction vessel charged with a magnetic stirring bar was added (*E*)-stilbene (95.4 mg, 0.53 mmol, 0.25 equiv.). The vessel was fitted with a rubber septum and then flushed with argon prior to the addition of 3-trifluoromethylbenzenethiol (57 μL, 0.42 mmol, 20 mol%). THF (1.2 ml) was introduced and once a homogenous solution was obtained a solution of phenylmagnesium bromide (3M solution in diethyl ether, 140 μL, 0.42 mmol, 20 mol%) was added dropwise. The reaction was stirred at ambient temperature for 5 min and then the 2,2,2-trifluoroketone (2.12 mmol) was added. After a further 2 min of stirring, freshly distilled aldehyde (2.12 mmol) was added. The rubber septum was then removed very quickly under a funneled heavy stream of argon and the reaction vessel was fitted with a microwave reaction vessel cap. The reaction was then irradiated for 3 h at 110 °C . Volatiles were removed *in vacuo* and the reaction mixture was purified by column chromatography eluting in gradient 100% hexanes to 10% CH_2Cl_2 in hexanes.

General procedure 3: the magnesium selenide-ion-catalysed crossed Tishchenko reaction

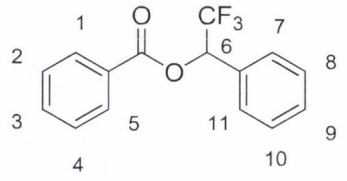
To a oven dried flask charged with activated 3Å molecular sieves, a magnetic stirrer and dibenzyl diselenide (0.48 mmol, 163.3 mg) under a strict atmosphere of argon was added THF (1.6 mL, 1.2 M; 0.8 mL, 2.4 M). To this yellow solution was added di-*n*-butylmagnesium (1M solution in *n*-heptane, 0.24 mmol, 0.24 mL) dropwise while stirring. To the resulting colourless solution, the 2,2,2-trifluoroketone was added and subsequently, the aldehyde. The reaction was allowed to stir at 25 °C for 24 hours and was diluted with ethyl acetate and concentrated in vacuo.

General procedure 4: the amine and lithium salt-catalysed crossed Tishchenko reaction

To an oven-dried flask fitted with a stirring bar under a N_2 atmosphere was charged with lithium azide (2 mmol, 95 mg), 1,8-diazabicyclo[5.4.0]undec-7-ene (2 mmol, 0.12 mL) and THF (1 mL). The ketone (4 mmol, 0.64 mL) was then added and subsequently the aldehyde

(4 mmol, 0.408 mL). The reaction mixture was allowed to stir for 48 hours at which point it was diluted with ethyl acetate and filtered through a plug of cotton wool. Volatiles were removed *in vacuo* and the reaction mixture was purified by column chromatography eluting in gradient 100% hexanes to 10% CH_2Cl_2 in hexanes.

2,2,2-Trifluoro-1-phenylethyl benzoate (127)



This product was obtained *via* general procedure 2, from the reaction of 2,2,2-trifluoroacetophenone and benzaldehyde, as a white solid (82%, 528 mg). M.p. 41 - 43 °C.

This product was obtained *via* general procedure 2, from the reaction of 2,2,2-trifluoroacetophenone and benzaldehyde, using **(*S*)-357** as the thiol precatalyst, as a white solid (50%, 528 mg, 10% *ee*).

This product was obtained from the reaction of 2,2,2-trifluoroacetophenone (4.8 mmol, 0.652 mL) and benzaldehyde (4.8 mmol, 0.488 mL), *via* general procedure 3. The product was isolated as a white solid (92%, 1.235 g) by column chromatography eluting in gradient 0 - 20% dichloromethane in hexanes.

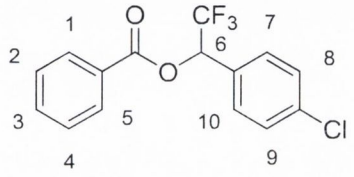
CSP-HPLC conditions CHIRALPAK OJ-H column (4.6 x 25 cm), hexane/IPA (95/5), 1 cm^3 min^{-1}, RT, UV detection at 220 nm, retention times: 10.5 min and 11.5 min.

δ_H (400 MHz, $CDCl_3$): 6.36 (q, 1H, *J* 6.7 Hz, H-6), 7.42 - 7.43 (m, 3H, H-8, H-9 and H-8), 7.49 (d, 2H, *J* 7.8 Hz, H-7 and H-11), 7.55 - 7.57 (m, 2H, H-2 and H-4), 7.63 (t, 1H, *J* 7.4 Hz, H-3), 8.14 (d, 2H, *J* 6.9 Hz, H-1 and H-5).

δ_C (100 MHz, $CDCl_3$): 72.8 (CH, *J* 33.4 Hz), 123.5 (CF_3, *J* 280.0 Hz), 128.4 (CH), 128.9 (C), 129.0 (CH), 129.1 (CH), 130.3 (C), 130.4 (CH), 131.6 (CH), 134.2 (CH), 164.7 (C).

The NMR spectral data are consistent with those in the current literature.[37]

1-(4-Chlorophenyl)-2,2,2-trifluoroethyl benzoate (371)



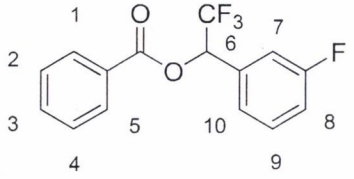
This product was obtained *via* general procedure 2, from the reaction of 2,2,2-trifluoro-4'-chloroacetophenone and benzaldehyde, as a white solid (81%, 540 mg). M.p. 62 - 64 °C.

δ_H (400 MHz, $CDCl_3$): 6.36 (q, 1H, *J* 6.7 Hz, H-6), 7.43 (d, 2H, *J* 8.5 Hz, H-8 and H-9), 7.51 - 7.55 (m, 4H, H-2, H-4, H-7 and H-10), 7.64 (t, 1H, *J* 7.4 Hz, H-3), 8.12 (d, 2H, *J* 7.4 Hz, H-1 and H-5).

δ_C (100 MHz, $CDCl_3$): 72.4 (CH, *J* 33.7 Hz), 123.4 (CF_3, *J* 280.6 Hz), 128.8 (C), 129.0 (CH), 129.4 (CH), 129.7 (CH), 130.2 (C), 130.4 (CH), 134.4 (CH), 136.5 (C), 164.6 (C).

The NMR spectral data are consistent with those in the current literature.[37]

2,2,2-Trifluoro-1-(3-fluorophenyl)ethyl benzoate (370)



This product was obtained from the reaction of 2,2,2-trifluoro-3'-fluoroacetophenone and benzaldehyde, as a yellow oil (63%, 391 mg) *via* general procedure 2.

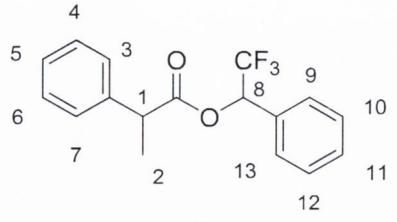
δ_H (400 MHz, $CDCl_3$): 6.36 (q, 1H, *J* 6.7 Hz, H-6), 7.11 - 7.15 (m, 1H, H-9), 7.28 (app. d, 1H, H-8), 7.34 (d, 1H, *J* 7.5 Hz, H-10), 7.37 - 7.43 (m, 1H, H-7), 7.50 (app. t, 2H, H-2 and H-4), 7.64 (t, 1H, *J* 7.5 Hz, H-3), 8.14 (d, 2H, *J* 7.8 Hz, H-1 and H-5).

δ_C (100 MHz, $CDCl_3$): 72.1 (CH, *J* 34.5), 115.4 (CH, *J* 23.5), 117.4 (CH, *J* 20.5), 123.4 (CF_3, *J* 280.4), 124.2 (CH, *J* 2.9), 128.8 (C), 129.1 (CH), 130.4 (CH), 130.8 (CH, *J* 7.8 Hz), 133.9 (q, *J* 6.9 Hz), 134.4 (C), 163.1 (CF, *J* 247.5 Hz), 164.6 (C).

HRMS (*m/z* - EI^+) Found: 298.0629 (M^+ $C_{15}H_{10}O_2F_4$ requires: 298.0617).

The NMR spectral data are consistent with those in the current literature.[37]

2,2,2-Trifluoro-1-phenylethyl 1-phenylpropionate (374)



This product was obtained *via* general procedure 2, from the reaction of 2,2,2-trifluoroacetophenone and 2-phenylpropionaldehyde, as a colourless oil (34%, 218 mg) in a 1:4 diastereomeric ratio.

Major diastereomer

δH (400 MHz, CDCl3): 1.58 (d, 3H, *J* 7.2 Hz, H-2), 3.92 (q, 1H, *J* 7.2 Hz, H-1), 6.08 - 6.16 (m, 1H, H-8), 7.17 - 7.19 (m, 2H, H-4 and H-6), 7.24 - 7.44 (m, 8H, H-3, H-5, H-7, H-9, H-10, H-11, H-12, H-13).

δC (100 MHz, CDCl3): 18.46 (CH_3), 45.61 (CH), 72.2 (CH, *J* 33.0 Hz), 123.2 (CF_3, *J* 280.7), 127.3 (CH), 127.5 (CH), 128.1 (CH), 128.5 (CH), 128.7 (CH), 129.6 (CH), 130.9 (C), 139.4 (C), 172.43 (C)

δF (377 MHz, CDCl3): -76.5 (CF_3).

Minor diastereomer

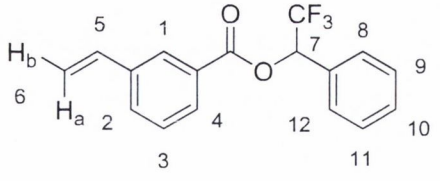
δH (400 MHz, CDCl3): ` 1.63 (d, 3H, *J* 7.1 Hz, H-2), 4.04 (q, 1H, *J* 7.1, H-1), 6.08 - 6.16 (m, 1H, H-8), 7.25-7.45 (m, 6H, H-4, H-5, H-6, H-10, H-11 and H-12), 7.53 - 7.57 (m, 2H, H-9 and H-13), 7.65 - 7.67 (m, 2H, H-3 and H-7).

δF (377 MHz, CDCl3): -63.2 (CF_3).

HRMS (*m/z* - EI^+) Found: 308.1028 (M^+ $C_{17}H_{15}O_2F_3$ Requires: 308.1024).

νmax (film)/cm^{-1}: 1685, 1562, 1419, 1302, 785.

2,2,2-Trifluoro-1-phenylethyl 3-vinylbenzoate (449)



This product was obtained from the reaction of 2,2,2-trifluoroacetophenone (2.4 mmol, 0.326 mL) and 3-vinylbenzaldehyde (2.4 mmol, 0.305 mL), *via* general procedure 3. The product was isolated as a colourless oil (84%, 0.621 g) by column chromatography eluting in gradient 0 - 20% dichloromethane in hexanes.

δ_H (400 MHz, $CDCl_3$): 5.40 (d, 1H, *J* 10.9 Hz, H_b-6), 5.88 (d, 1H, *J* 17.6 Hz, H_a-6), 6.42 (q, 1H, *J* 6.8 Hz, H-7), 6.80 (dd, 1H, *J* 10.9, 17.6 Hz, H-5), 7.46 – 7.51 (m, 4H, H-3, H-8, H-10 and H-11), 7.59 – 7.60

(app. t, 2H, H-9 and H-11), 7.69 (d, 1H, *J* 7.7 Hz, H-2), 8.05 (d, 1H, *J* 7.8 Hz, H-4), 8.17 (s, 1H, H-1).

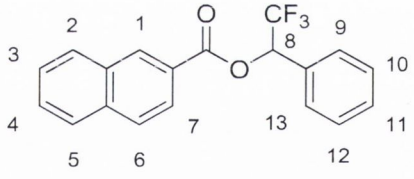
δ_C (100 MHz, $CDCl_3$): 72.3 (CH, *J* 33.0 Hz), 115.2 (CH_2), 122.9 (CF_3, *J* 279.1 Hz), 127.4 (CH), 127.6 (CH), 128.3 (CH), 128.4 (CH), 128.6 (C), 128.7 (CH), 129.5 (CH), 130.8 (C), 130.9 (CH), 135.2 (CH), 137.7 (C), 163.9, (C).

δ_F (376.5 MHz, $CDCl_3$): -76.3 (CF_3)

HRMS (*m/z* - EI^+) Found: 306.0866 (M^+ $C_{17}H_{13}O_2F_3$ requires: 306.0868).

νmax (film)/cm^{-1}: 1735, 1582, 1257, 1186, 1133, 1084, 989, 756.

2,2,2-Trifluoro-1-phenylethyl 2-naphthoate (451)



This product was obtained from the reaction of 2,2,2-trifluoroacetophenone (2.4 mmol, 0.326 mL) and 2-naphthaldehyde (2.5 mmol, 0.374g in a 0.75M solution of THF), *via* general procedure 3. The product was isolated as a white solid (87%, 0.688 g) by column chromatography eluting in gradient 0 - 15% dichloromethane in hexanes. M.p. 93 - 95 °C. (lit. 93 – 95 °C[37])

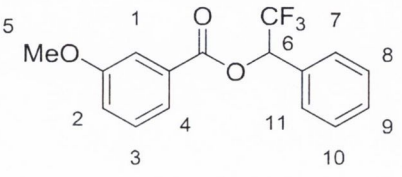
δ_H (400 MHz, $CDCl_3$): 6.45 (q, 1H, *J* 6.8 Hz, H-8), 7.43 - 7.45 (m, 3H, H-9, H-11 and H-13), 7.56 - 7.65 (m, 4H, H-3, H-4, H-10 and H-12), 7.91 (app. t, 2H, H-5 and H-6), 8.00 (d, 1H, *J* 8.0 Hz, H-2), 8.12 (dd, 1H, *J* 1.5, 8.6, H-7), 8.71 (s, 1H, H-1).

δ_C (100 MHz, $CDCl_3$): 72.9 (CH, *J* 33.4 Hz), 123.2 (CF_3, *J* 280.9 Hz), 125.5 (CH), 126.2 (C), 127.3 (CH), 128.2 (CH), 128.4 (CH), 128.9 (CH),

129.1 (CH), 129.2 (CH), 129.9 (CH), 130.3 (CH), 131.7 (C), 132.2 (CH), 132.7 (C), 126.2 (C), 164.9 (C).

The NMR spectral data are consistent with those in the current literature.[37]

2,2,2-Trifluoro-1-phenylethyl 3-methoxybenzoate (452)



This product was obtained from the reaction of 2,2,2-trifluoroacetophenone (2.4 mmol, 0.326 mL) and 3-anisaldehyde (2.4 mmol, 0.293 mL), *via* general procedure 3. The product was isolated as a yellow oil (94%, 0.697 g) by column chromatography eluting in gradient 0 - 30% dichloromethane in hexanes.

δ_H (400 MHz, $CDCl_3$): 3.89 (s, 3H, H-5), 6.39 (q, 1H, *J* 6.8 Hz, H-6), 7.19 (dd, 1H, *J* 2.5, 8.3 Hz, H-3), 7.41 – 7.46 (m, 4H, H-2, H-7, H-9 and H-11), 7.57 – 7.60 (m, 2H, H-8 and H-10), 7.66 (s, 1H, H-1), 7.77 (d, 1H, *J* 7.7 Hz, H-4).

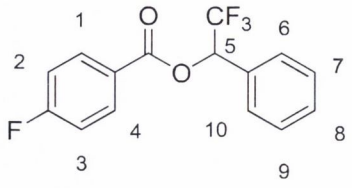
δ_C (100 MHz, $CDCl_3$): 55.0 (OCH_3), 72.3 (CH, *J* = 33.1 Hz), 114.2 (CH), 119.7 (CH), 121.5 (CH), 121.9 (CH), 122.8 (CF_3, *J* = 279.1 Hz), 127.6 (C), 128.3 (CH), 129.3 (CH), 129.5 (CH), 130.8 (C), 159.2 (C), 163.8 (C).

δ_F (376.5 MHz, $CDCl_3$): -76.3 (CF_3).

HRMS (*m/z* - EI^+) Found: 310.0826 (M^+ $C_{16}H_{13}O_3F_3$ requires: 310.0817).

νmax (film)/cm^{-1}: 2962, 1733, 1601, 1432, 1263, 1177, 1043, 916, 700.

2,2,2-Trifluoro-1-phenylethyl 4-fluorobenzoate (456)



This product was obtained from the reaction of 2,2,2-trifluoroacetophenone (2.4 mmol, 0.326 mL) and 4-fluorobenzaldehyde (2.4 mmol, 0.258 mL), *via* general procedure 3. The product was isolated as a pale yellow oil (87%, 0.623 g) by column chromatography eluting in gradient 0 - 30% dichloromethane in hexanes.

δ_H (400 MHz, $CDCl_3$): 6.37 (q, 1H, *J* 6.9 Hz, H-5), 7.17 (app. t, 2H, H-2 and H-3) 7.40 - 7.45 (m, 3H, H-6, H-8 and H-10), 7.55 - 7.57 (m, 2H, H-7 and H-9), 8.14 - 8.18 (dd, 2H, *J* 5.5, 8.8 Hz, H-1 and H-4).

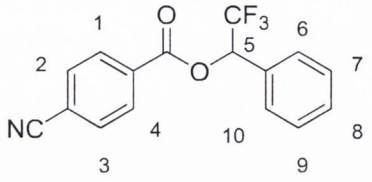
δ_C (100 MHz, $CDCl_3$): 72.2 (CH, *J* 33.0 Hz), 115.5 (CH, *J* 22.1 Hz), 123.2 (CF_3, *J* 278.9 Hz), 124.5 (C), 127.6 (CH), 128.3 (CH), 129.6 (CH), 130.7 (CH), 132.3 (q, *J* 9.4 Hz), 162.9 (C), 165.8 (CF, *J* 254.1 Hz).

δ_F (376.5 MHz, $CDCl_3$): -76.3 (CF_3).

HRMS (*m/z* - EI^+) Found: 298.0605 (M^+ $C_{15}H_{10}O_2F_4$ requires: 298.0617).

νmax (film)/cm^{-1}: 3072, 1737, 1604, 1508, 1255, 1182, 1088, 853, 701.

2,2,2-Trifluoro-1-phenylethyl 4-cyanobenzoate (457)



This product was obtained from the reaction of 2,2,2-trifluoroacetophenone (2.4 mmol, 0.326 mL) and 4-cyanobenzaldehyde (2.4 mmol, 0.315 g in a 0.75M solution of THF), *via* general procedure 3. The product was isolated as a colourless oil (74%, 0.543 g) by column chromatography eluting in gradient 0 - 50% dichloromethane in hexanes.

δ_H (400 MHz, $CDCl_3$): 6.40 (q, 1H, *J* 6.7 Hz, H-5), 7.47 – 7.59 (m, 5H, H-6, H-7, H-8, H-9 and H-10) 7.82 (d, 2H, *J* 8.3 Hz, H-2 and H-3), 8.26 (d, 2H, *J* 8.3 Hz, H-1 and H-4).

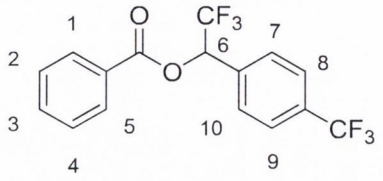
δ_C (100 MHz, $CDCl_3$): 72.6 (CH, *J* 33.2 Hz), 116.9 (C), 117.3 (C), 122.8 (CF_3, *J* 278.7 Hz), 127.6 (CH), 128.5 (CH), 129.8 (C), 130.1 (CH), 130.2 (C), 132.0 (CH), 162.4 (C).

δ_F (376.5 MHz, $CDCl_3$): -76.3 (CF_3).

HRMS (*m/z* - EI^+) Found: 305.0678 (M^+ $C_{16}H_{10}O_2F_3N$ requires: 305.0664).

νmax (film)/cm^{-1}: 2958, 2232, 1735, 13561255, 1128, 1019, 759.

2,2,2-Trifluoro-1-(4'-(trifluoromethyl)phenyl)ethyl benzoate (459)



This product was obtained from the reaction of 2,2,2,trifluoromethyl-(4'-trifluoromethyl)acetophenone (2.4 mmol, 0.488 mL) and benzaldehyde (2.4 mmol, 0.244 mL), *via* general procedure 3. The product was isolated as a yellow oil (93%, 0.778 g) by column chromatography eluting in gradient 0 - 10% dichloromethane in hexanes.

δ_H (400 MHz, $CDCl_3$): 6.45 (q, 1H, *J* 6.7 Hz, H-6), 7.54 (app. t, 2H, H-8 and H-9), 7.66 – 7.73 (m, 5H, H-2, H-3, H-4, H-7 and H-10), 8.17 (d, 2H, *J* 7.4 Hz, H-1 and H-5).

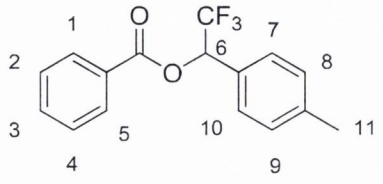
δ_C (100 MHz, $CDCl_3$): 71.4 (CH, *J* 33.3 Hz), 122.5 (CF_3, *J* 279.2 Hz), 123.2 (CF_3, *J* 271.0 Hz), 125.4 (C), 127.0 (CH), 127.8 (CH), 128.0 (CH), 129.2 (CH), 129.6 (C), 133.8 (CH), 134.7 (C), 163.8 (C).

δ_F (376.5 MHz, $CDCl_3$): -63.5 (CF_3), -76.2 (CF_3).

HRMS (*m/z* - EI^+) Found: 348.0576 (M^+ $C_{16}H_{10}O_2F_6$ requires: 348.0585).

νmax (film)/cm^{-1}: 1738, 1602, 1352, 1257, 1132, 1068, 875, 768.

2,2,2-Trifluoro-1-(p-tolyl)ethyl benzoate (461)



This product was obtained from the reaction of 2,2,2,trifluoromethyl-(4'-methyl)acetophenone (2.4 mmol, 0.734 mL) and benzaldehyde (2.4 mmol, 0.244 mL), *via* general procedure 3. The product was isolated as a white solid (95%, 1.335 g) by column chromatography eluting in gradient 0 - 10% dichloromethane in hexanes. M.p. 76 – 78 °C

δ_H (400 MHz, $CDCl_3$): 2.36 (s, 3H, H-11), 6.41 (q, 1H, *J* 6.9 Hz, H-6), 7.28 (d, 2H, *J* 8.0 Hz, H-8 and H-9), 7.50 – 7.55 (m, 4H, H-2, H-4, H-7 and H-10), 7.66 (t, 1H, *J* 7.3 Hz, H-3), 8.19 (d, 2H, *J* 7.5 Hz, H-1 and H-5).

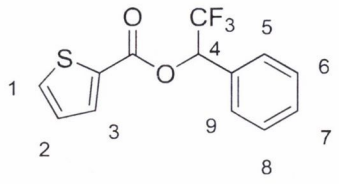
δ_C (100 MHz, $CDCl_3$): 20.8 (CH_3), 72.0 (CH, *J* 33.0 Hz), 122.9 (CF_3, *J* = 279.0 Hz), 127.5 (CH), 128.0 (C), 128.1 (CH), 128.2 (C), 129.0 (CH), 129.6 (CH), 133.4 (CH), 139.6 (C), 164.0 (C).

δ_F (376.5 MHz, $CDCl_3$): -76.3 (CF_3).

HRMS (*m/z* - EI^+) Found: 294.0860 (M^+ $C_{16}H_{13}O_2F_3$ requires: 294.0868).

νmax (film)/cm^{-1}: 1726, 1617, 1452, 1273, 1069, 1020, 912, 724.

2,2,2-Trifluoro-1-phenylethyl thiophene-2-carboxylate (465)



This product was obtained from the reaction of 2,2,2-trifluoroacetophenone (4.8 mmol, 0.652 mL) and 2-thiophenecarboxaldehyde (4.8 mmol, 0.451 mL), *via* general procedure 3. The product was isolated as a pale yellow oil (97%, 1.307 g) by column chromatography eluting in gradient 0 - 15% dichloromethane in hexanes.

δ_H (400 MHz, $CDCl_3$): 6.38 (q, 1H, *J* 6.8 Hz, H-4), 7.18 (app. d, 1H, H-2), 7.39 - 7.48 (m, 3H, H-5, H-7 and H-9), 7.53 - 7.61 (app. t, 2H, H-6 and H-8), 7.68 (d, 1H, *J* 1 Hz, H-1), 7.98 (d, 1H, *J* 1 Hz, H-3).

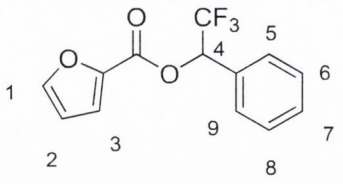
δ_C (100 MHz, $CDCl_3$): 71.9 (CH, *J* 33.1 Hz), 122.8 (CF_3, *J* 278.9 Hz), 127.6 (CH), 127.7 (CH), 128.3 (CH), 129.6 (CH), 130.7 (C), 131.4 (C), 133.5 (CH), 134.4 (CH), 159.5 (C).

δ_F (376.5 MHz, $CDCl_3$): -76.35 (CF_3).

HRMS (*m/z* - EI^+) Found: 286.0277 (M^+ $C_{13}H_9O_2F_3S$ requires: 286.0275).

νmax (film)/cm^{-1}: 2961, 1724, 1523, 1444, 1244, 1071, 860, 699.

2,2,2-Trifluoro-1-phenylethyl furan-2-carboxylate (466)



This product was obtained from the reaction of 2,2,2-trifluoroacetophenone (2.4 mmol, 0.326 mL) and furfural (2.4 mmol, 0.20 mL), *via* general procedure 3. The product was isolated as a pale yellow oil (93%, 0.602 g) by column chromatography eluting in gradient 0 - 15% dichloromethane in hexanes.

δ_H (400 MHz, $CDCl_3$): 6.35 (q, 1H, *J* 6.8 Hz, H-4), 6.54 (app. d, 1H, *J* 1.3 Hz, H-2), 7.39 – 7.40 (m, 1H, H-1), 7.35 - 7.43 (m, 3H, H-5, H-7, H-9), 7.54 - 7.56 (app. t, 2H, H-6 and H-8), 7.63 (app. s, 1H, H-3).

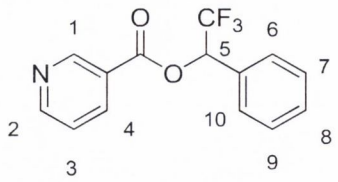
δ_C (100 MHz, $CDCl_3$): 71.6 (CH, *J* 33.2 Hz), 111.7 (CH), 119.4 (CH), 122.7 (CF_3, *J* 280.0 Hz), 127.6 (CH), 128.3 (CH), 129.6 (CH), 130.5 (C), 142.7 (C), 147.0 (CH), 155.8 (C).

δ_F (376.5 MHz, $CDCl_3$): -76.38 (CF_3).

HRMS (*m/z* - EI^+) Found: 270.0497 (M^+ $C_{13}H_9O_3F_3$ requires: 270.0505).

νmax (film)/cm^{-1}: 1732, 1579, 1470, 1350, 1295, 1100, 1007, 934, 885.

2,2,2-Trifluoro-1-phenylethyl nicotinate (468)



This product was obtained from the reaction of 2,2,2-trifluoroacetophenone (2.4 mmol, 0.326 mL) and 3-pyridinecarboxaldehyde (2.4 mmol, 0.226 mL), *via* general procedure 3. The product was isolated as a pale brown oil (80%, 0.539 g) by column chromatography eluting in gradient 0 - 20% ethyl acetate in hexanes.

δ_H (400 MHz, $CDCl_3$): 6.39 (q, 1H, *J* 6.8 Hz, H-5), 7.42 - 7.46 (m, 4H, H-3, H-7, H-8, H-9), 7.54 - 7.57 (m, 2H, H-6 and H-10), 8.37 (d, 1H, *J* 7.96 Hz, H-4), 8.84 (br. s, 1H, H-2), 9.34 (s, 1H, H-1).

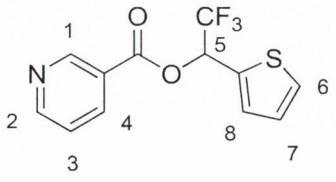
δ_C (100 MHz, $CDCl_3$): 72.4 (CH, *J* 33.2 Hz), 122.5 (CF_3, *J* 278.9), 123.1 (C), 124.4 (CH), 127.6 (CH), 128.4 (CH), 129.7 (CH), 130.4 (CH), 137.0 (C), 150.7 (CH), 153.8 (CH), 162.7 (C).

δ_F (376.5 MHz, $CDCl_3$): -76.30 (CF_3).

HRMS (*m/z* - EI^+) Found: 281.0660 (M^+ $C_{14}H_{10}O_2NF_3$ requires: 281.0664).

νmax (film)/cm^{-1}: 1739, 1591, 1421, 1256, 1130, 1024, 906, 710.

2,2,2-Trifluoro-1-(thiophen-2-yl)ethyl nicotinate (470)



This product was obtained from the reaction of 2-trifluoroacetylthiophene (2.4 mmol, 0.308 mL) and 3-pyridinecarboxaldehyde (2.4 mmol, 0.226 mL), *via* general procedure 3. The product was isolated as a pale yellow oil in 56% yield (0.388 g) by column chromatography eluting in gradient 0 - 10% ethyl acetate in hexanes.

δ_H (400 MHz, $CDCl_3$): 6.74 (q, 1H, *J* 6.5 Hz, H-5), 7.09 (dd, 1H, *J* 3.6, 1.2 Hz, H-7), 7.38 (d, 1H, *J* 3.6 Hz, H-7), 7.43 – 7.46 (m, 2H, H-3 and H-8), 8.37 (d, 1H, *J* 7.9 Hz, H-4), 8.87 (br. app. s, 1H, H-2), 9.33 (br. s, 1H, H-1).

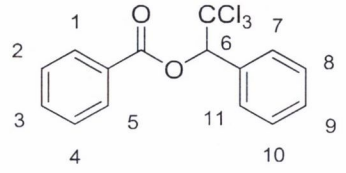
δ_C (100 MHz, $CDCl_3$): 68.3 (CH, *J* 35.0 Hz), 122.6 (CF_3, *J* 278.9), 123.1 (C), 124.2 (CH), 126.6 (CH), 127.8 (CH), 129.3 (CH), 131.4 (C), 137.1 (CH), 150.8 (CH), 153.8 (CH), 162.6 (C).

δ_F (376.5 MHz, $CDCl_3$): -76.54 (CF_3).

HRMS (*m/z* - EI^+) Found: 287.0238 (M^+ $C_{15}H_{10}O_2F_4$ requires: 287.0228).

νmax (film)/cm^{-1}: 1741, 1591, 1421, 1259, 1132, 1032, 908, 699.

2,2,2-Trichloro-1-phenylethyl benzoate (488)



The reaction of 2,2,2-trichloro-1-phenyl ethanol (8.87 mmol, 2 g) and benzoyl chloride (9.75 mmol, 1.13 mL) in NEt_3 (9.75 mmol, 1.35 mL), DMAP (50 mg) and CH_2Cl_2 (15 mL) afforded product **488** (76%, 2.212 g) after column chromatography in 20% CH_2Cl_2 in hexanes as a white solid. M.p. 97 – 99 °C. (lit. 96 – 97 °C[189])

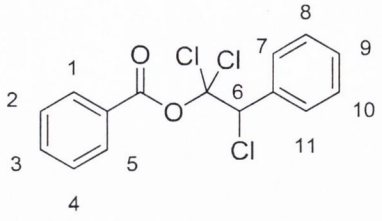
This product was obtained from the reaction of 2,2,2-trichloroacetophenone (4 mmol, 0.640 mL) and benzaldehyde (4 mmol, 0.408 mL) *via* general procedure 4. The product was isolated as a white solid (24%, 312 mg) by column chromatography eluting in gradient 0 – 20% CH_2Cl_2 in hexanes.

δ_H (400 MHz, $CDCl_3$): 6.61 (s, 1H, H-6), 7.42 – 7.44 (m, 3H, H-7, H-9 and H-11), 7.51 – 7.55 (app. t, 2H, H-8 and H-10), 7.66 (t, 1H, *J* 7.4 Hz, H-3), 7.73 (app. d, 2H, H-2 and H-4), 8.19 (d, 2H, *J* 7.85 Hz, H-1 and H-5).

δ_C (100 MHz, $CDCl_3$): 83.6 (CH), 99.8 (CCl_3), 128.4 (CH), 129.1 (CH), 129.4 (C), 130.0 (CH), 130.3 (CH), 130.5 (CH), 133.5 (CH), 134.2 (C), 164.7 (C).

The NMR spectral data are consistent with those in the current literature.[189]

1,1-Dichloro-2-chloro-2-phenylethyl benzoate (489)



This product was obtained from the reaction of 2,2,2-trichloroacetophenone (4 mmol, 0.640 mL) and benzaldehyde (4 mmol, 0.408 mL) *via* general procedure 4. The product was isolated as a white solid (47%, 609 mg) by column chromatography eluting in gradient 0 – 20% CH_2Cl_2 in hexanes. M.p. 91 – 94 °C.

δ_H (400 MHz, $CDCl_3$): 6.62 (s, 1H, H-6), 7.38 – 7.40 (m, 3H, H-8, H-9 and H-10), 7.48 – 7.51 (m, 2H, H-7 and H-11), 7.61 – 7.65 (m, 1H, H-3), 7.70 – 7.72 (m, 2H, H-2 and H-4), 8.10 (d, 2H, *J* 8.4 Hz, H-1 and H-5).

δ_C (100 MHz, $CDCl_3$): 92.6 (CH), 128.2 (CH), 128.3 (C), 128.6 (C), 129.0 (CH), 129.6 (CH), 130.3 (CH), 131.1 (CH), 134.0 (C), 134.8 (CH), 164.6 (C).

HRMS (*m/z* - EI^+) Found: (M^+ 327.9826 $C_{15}H_{11}Cl_3O_2$ requires: 327.9825)

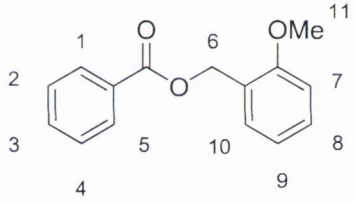
νmax (film)/cm^{-1}: 1728, 1637, 1599, 1451, 1315, 1244, 1104, 1067, 935, 853.

9.2.2 Tishchenko esters derived from the reaction of two different aldehydes

General procedure 5: the magnesium thiolate-catalysed Tishchenko reaction between 2 different aldehydes

To an oven dried flask, under an argon atmosphere, was added 4-*t*-butylbenzylmercaptan (0.2 mmol, 0.038 mL) and THF (1 mL). Dibutylmagnesium (0.1 mmol, 0.1 mL) was added to the solution slowly with stirring. After 10 minutes both aldehydes were added (1 mmol each) and the reaction was heated under reflux for the time indicated in the respective tables. The reaction mixture was concentrated *in vacuo* and the ester was purified by column chromatography in gradient dichloromethane in hexane (10 – 50%).

2-Methoxybenzyl benzoate (497)



This product was isolated as the major product from the reaction of benzaldehyde (1 mmol, 0.102 mL) and 2-anisaldehyde (1 mmol, 0.121 mL) *via* general procedure 5 and was isolated as a white solid (73%, 176 mg). M.p. 43 - 44 °C

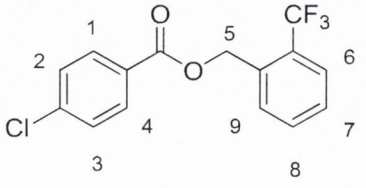
δ_H (400 MHz, $CDCl_3$): 3.89 (s, 3H, H-11), 5.46 (s, 2H, H-6), 6.94 - 7.03 (m, 2H, H-7 and H-9), 7.34 - 7.38 (app. dt, 1H, H-8), 7.45 - 7.49 (m, 3H, H-2, H-4 and H-10), 7.60 (app. t, 1H, H-3), 8.12 (d, 2H, *J* 6.4, H-1 and H-5).

δ_C (100 MHz, $CDCl_3$): 55.0 (OCH_3), 61.8 (CH_2), 110.0 (CH), 120.0 (CH), 123.9 (C), 127.9 (CH), 128.9 (CH), 129.0 (CH), 129.3 (CH), 129.9 (C), 132.5 (CH), 157.1 (C), 166.1 (C).

HRMS (*m/z* - EI^+) Found: 242.0936 (M^+ $C_{15}H_{14}O_3$ requires: 242.943).

V_{max} (film)/cm^{-1} 3010, 1718, 1602, 1459, 1270, 1243, 1109, 1023, 993, 754, 707, 674.

2-(Trifluoromethyl)benzyl 4-chlorobenzoate (508)



This product was isolated as the major product from the reaction of 4-chlorobenzaldehyde (1 mmol, 0.140 mg) and 2-trifluoromethylbenzaldehyde (1 mmol, 0.132 mL) *via* general procedure 5 and was isolated as a colourless oil (80%, 251 mg).

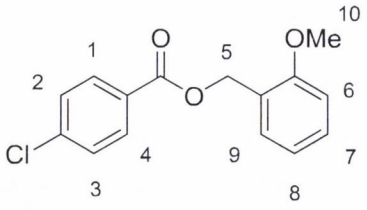
δ_H (400 MHz, $CDCl_3$): 5.58 (s, 2H, H-5), 7.44 – 7.51 (m, 3H, H-2, H-3 and H-6), 7.59 – 7.67 (m, 2H, H-7 and H-8), 7.75 (d, 1H, 7.8 Hz, H-9), 8.04 (d, 2H, 7.8 Hz, H-1 and H-4).

δ_C (100 MHz, $CDCl_3$): 62.9 (CH_2), 123.8 (CF_3, 272.3 Hz), 125.8 (CH), 127.8 (C), 128.0 (CH), 128.3 (CH), 128.4 (CH), 129.8 (C), 130.7 (CH), 131.7 (CH), 133.5 (C), 139.3 (C), 164.8 (C).

HRMS (*m/z* - EI^+) Found: 314.0324 (M^+ $C_{15}H_{10}O_2ClF_3$ requires: 314.0321).

V_{max} (film)/cm^{-1}: 1725, 1595, 1489, 1315, 1269, 1116, 1015, 849, 757.

2-Methoxybenzyl 4-chlorobenzoate (516)



This product was isolated as the major product from the reaction of 4-chlorobenzaldehyde (1 mmol, 0.140 mg) and 2-anisaldehyde (1 mmol, 0.121 mL) *via* general procedure 5 and was isolated as a white solid (88%, 244 mg). M.p. 53 - 55 °C.

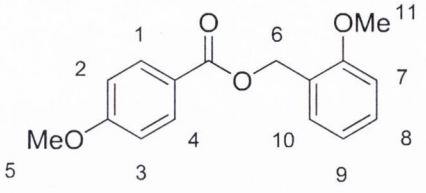
δ_H (400 MHz, $CDCl_3$): 3.88 (s, 3H, H-10), 5.45 (s, 2H, H-5), 6.94–7.03 (m, 2H, H-6 and H-8), 7.35-7.45 (m, 4H, H-2, H-3, H-7 and H-9), 8.04 (d, 2H, *J* 7.2 Hz, H-1 and H-4).

δ_C (100 MHz, $CDCl_3$): 55.0 (OCH_3), 62.0 (CH_2), 110.0 (CH), 120.0 (CH), 123.7 (C), 128.2 (CH), 128.4 (CH), 129.1 (C), 129.2 (CH), 130.7 (CH), 138.9 (C), 157.1 (C), 165.3 (C).

HRMS (*m/z* - EI^+) Found: 276.0554 (M^+ $C_{15}H_{13}O_3Cl$ requires: 276.0553).

V_{max} (film)/cm^{-1}: 2953, 1708, 1591, 1494, 1246, 1178, 1105, 1014, 900, 863, 749, 636.

2-Methoxybenzyl 4-methoxybenzoate (517)



This product was isolated as the major product from the reaction of 4-anisaldehyde (1 mmol, 0.121 mL) and 2-anisaldehyde (1 mmol, 0.121 mL) *via* general procedure 5 and was isolated as a pale yellow oil (69%, 188 mg).

δ_H (400 MHz, $CDCl_3$): 3.88 (s, 3H, H-5), 5.42 (s, 2H, H-6), 6.93 – 6.95 (m, 3H, H-2, H-3 and H-10), 7.00 (app. t, 1H, H-8), 7.35 (app. t, 1H, H-9), 7.44 (d, 1H, 7.4 Hz, H-7), 8.07 (d, 2H, 8.8 Hz, H-1 and H-4).

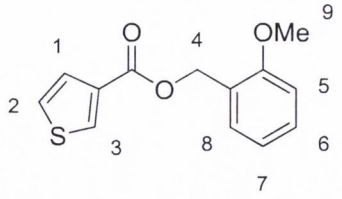
δ_C (100 MHz, $CDCl_3$): 55.0 (OCH_3), 61.4 (CH_2), 110.0 (CH), 113.1 (CH), 120.0 (CH), 122.4 (C), 124.2 (CH), 125.4 (C), 128.9 (CH), 131.3 (CH), 157.0 (C), 162.9 (C), 165.9 (C).

HSQC analysis indicates that the resonance at 55.0 ppm represents 2 carbon atoms.

HRMS (*m/z* - EI^+) Found: 272.1044 (M^+ $C_{16}H_{16}O_4$ requires: 272.1049).

V_{max} (film)/cm^{-1}: 2838, 1708, 1604, 1439, 1166, 1098, 1027, 753.

2-Methoxybenzyl thiophene-3-carboxylate (523)



This product was isolated as the major product from the reaction of 3-thiophenecarboxaldehyde (1 mmol, 0.088 mL) and 2-anisaldehyde (1 mmol, 0.121 mL) *via* general procedure 5 and was isolated as a yellow oil (71%, 175 mg).

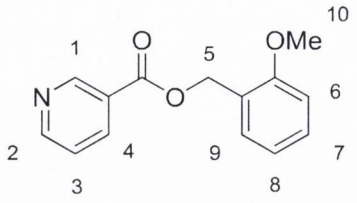
δ_H (400 MHz, $CDCl_3$): 3.88 (s, 3H, H-9), 5.41 (s, 2H, H-4), 6.94 (d, 8.2Hz, 1H, H-8), 7.00 (app. t, 1H, H-7), 7.31 – 7.37 (m, 2H, H-2 and H-6), 7.43 (d, 7.4Hz, 1H, H-5), 7.59 (d, 5.0 Hz, 1H, H-1), 8.17 – 8.18 (m, 1H, H-3).

δ_C (100 MHz, $CDCl_3$): 55.0 (CH_3), 61.4 (CH_2), 110.0 (CH), 120.0 (CH), 123.9 (C), 125.5 (CH), 127.6 (CH), 128.9 (CH), 129.0, (CH) 132.4 (CH), 133.3 (C), 157.0 (C), 162.3 (C).

HRMS (*m/z* - EI^+) Found: 248.0503 (M^+ $C_{13}H_{12}O_3S$ requires: 248.0507).

V_{max} (film)/cm^{-1} 2837, 1710, 1494, 1407, 1242, 1186, 1097, 1028, 864, 743.

2-Methoxybenzyl nicotinate (524)



This product was isolated as the major product from the reaction of 3-pyridinecarboxaldehyde (1 mmol, 0.094 mL) and 2-anisaldehyde (1 mmol, 0.121 mL) *via* general procedure 5 and was isolated as a colourless oil (61%, 149 mg).

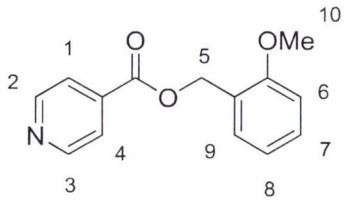
δ_H (400 MHz, $CDCl_3$): 3.87 (s, 3H, H-10), 5.46 (s, 2H, H-5), 6.93 (d, 1H, *J* 8.4 Hz, H-9), 6.99 (app. t, 1H, H-7), 7.33 – 7.43 (m, 3H, H-3, H-6 and H-8), 8.32 (d, 1H, *J* 8.0 Hz, H-4), 8.78 (br. app. s, 1H, H-2), 9.28 (br. s, 1H, H-1).

δ_C (100 MHz, $CDCl_3$): 55.8 (OCH_3), 63.1 (CH_2), 110.9 (CH), 120.8 (CH), 123.7 (CH), 124.1 (CH), 126.7 (C), 130.1 (CH), 130.3 (CH), 137.6 (CH), 151.4 (C), 153.7 (CH), 158.0 (C), 165.6 (C).

HRMS (*m/z* - EI^+) Found: 244.0978 (M^+ $C_{14}H_{14}O_3N$ requires: 244.0971).

νmax (film)/cm^{-1}: 1717, 1690, 1250, 1122, 1023, 751, 698.

2-Methoxybenzyl isonicotinate (525)



This product was isolated as the major product from the reaction of 4-pyridinecarboxaldehyde (1 mmol, 0.094 mL) and 2-anisaldehyde (1 mmol, 0.121 mL) *via* general procedure 5 and was isolated as a colourless oil (63%, 153 mg).

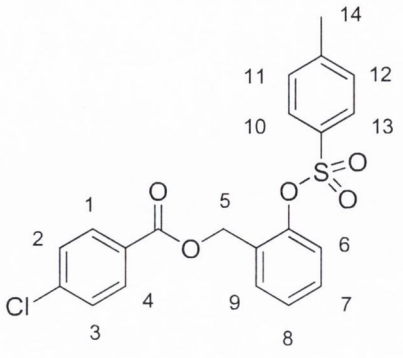
δ_H (400 MHz, $CDCl_3$): 3.88 (s, 3H, H-10), 5.46 (s, 2H, H-5), 6.94 (d, 1H *J* 8.2 Hz, H-9), 7.00 (app. t, 1H, H-7), 7.35 (app. t, 1H, H-8), 7.42 (d, 1H, *J* 7.4 Hz, H-6), 7.89 (d, 2H, *J* 4.6 Hz, H-1 and H-4), 8.78 (d, 2H, *J* 4.6 Hz, H-2 and H-3).

δ_C (100 MHz, $CDCl_3$): 55.0 (OCH_3), 62.6 (CH_2), 110.1 (CH), 120.0 (CH), 122.5 (CH), 123.1 (CH), 129.4 (C), 129.5 (CH), 137.1 (C), 150.1 (CH), 157.2 (C), 164.6 (C).

HRMS (*m/z* - EI^+) Found: 244.0969 (M^+ $C_{14}H_{14}O_3N$ requires: 244.0971).

V_{max} (film)/cm^{-1}: 2972, 1718, 1590, 1499, 1377, 1272, 1251, 1132, 1108, 1023, 983, 750, 698.

2-(Tosyloxy)benzyl 4-chlorobenzoate (534)



This product was isolated as the major product from the reaction of 4-chlorobenzaldehyde (1 mmol, 0.140 mg) and 2-*O*-tosylbenzaldehyde (1 mmol, 0.276 mg) *via* general procedure 5 and was isolated as a white solid (93%, 388 mg). M.p. 78-81 °C.

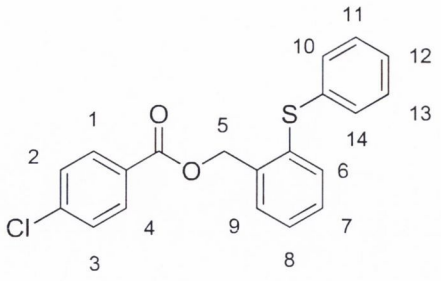
δ_H (400 MHz, $CDCl_3$): 2.42 (s, 3H, H-14), 5.22 (s, 2H, H-5), 7.18 (dd, 1H, *J* 1.7, 7.4, H-8), 7.28-7.37 (m, 4H, H-7, H-9, H-11 and H-12), 7.42 (d, 2H, *J* 8.5 Hz, H-2 and H-3), 7.48 (dd, 1H, *J* 2.1, 6.8, H-6), 7.79 (d, 2H, *J* 8.2 Hz, H-10 and H-13), 7.98 (d, 2H, *J* 8.5 Hz, H-1 and H-4).

δ_C (100 MHz, $CDCl_3$): 21.3 (CH_3), 61.1 (CH_2), 122.3 (CH), 126.9 (CH), 127.8 (C), 127.9 (CH), 128.3 (CH), 128.9 (C), 129.2 (CH), 129.5 (CH), 129.8 (CH), 130.7 (CH), 132.2 (C), 139.1 (C), 145.3 (C), 147.2 (C), 164.8 (C).

HRMS (*m/z* - EI^+) Found: 439.0373 (M^+ + Na $C_{21}H_{17}O_5ClSNa$ requires: 439.0383).

V_{max} (film)/cm^{-1} 1724, 1450, 1277, 1123, 975, 870, 772, 702, 660.

2-(Phenylthio)benzyl 4-chlorobenzoate (536)



This product was isolated as the major product from the reaction of 4-chlorobenzaldehyde (1 mmol, 0.140 mg) and 2-*S*-phenylbenzaldehyde (1 mmol, 0.214 mg) *via* general procedure 5 and was isolated as a colourless oil (71%, 235 mg).

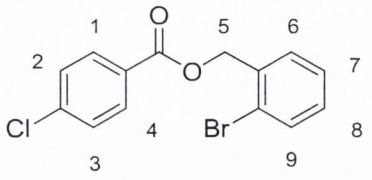
δ_H (400 MHz, $CDCl_3$): 5.52 (s, 2H, H-5), 7.17 – 7.43 (m, 10H, H-2, H-3, H-7, H-8, H-9, H-10, H-11, H-12, H-13 and H-14), 7.54 (dd, 1H *J* 1.0, 7.2 Hz, H-6), 7.91 (d, 2H, *J* 8.5 Hz, H-1 and H-4).

δ_C (100 MHz, $CDCl_3$): 65.3 (CH_2), 126.7 (CH), 128.2 (CH), 128.5 (C), 128.7 (C), 129.2 (CH), 129.3 (CH), 129.8 (CH), 129.9 (CH), 131.1 (CH), 134.1 (CH), 134.5 (CH), 135.1 (C), 137.3 (C), 139.4 (C), 165.4 (C).

HRMS (*m/z* - EI^+) Found: 354.0490 (M^+ $C_{20}H_{15}O_2ClS$ requires: 354.0481).

νmax (film)/cm^{-1}: 2956, 1721, 1594, 1477, 1400, 1267, 1101, 1092, 1015, 757.

2-Bromobenzyl 4-chlorobenzoate (539)



This product was isolated as the major product from the reaction of 4-chlorobenzaldehyde (1 mmol, 0.140 mg) and 2-bromobenzaldehyde (1 mmol, 0.116 mL) *via* general procedure 5 and was isolated as a pale yellow solid (71%, 235 mg). M.p. 68 - 71 °C.

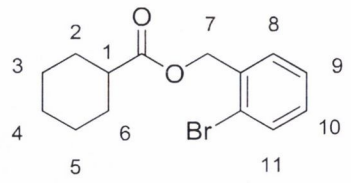
δ_H (400 MHz, $CDCl_3$): 5.46 (s, 2H, H-5), 7.23 (app. t, 1H, H-7), 7.37 (app. t, 1H, H-8), 7.44 (d, 2H, *J* 8.6 Hz, H-2 and H-3), 7.51 (dd, 1H, *J* 1.3, 7.6 Hz, H-6), 7.63 (dd, 1H, *J* 0.6, 8.0 Hz, H-9), 8.05 (d, 2H, *J* 8.6 Hz, H-1 and H-4).

δ_C (100 MHz, $CDCl_3$): 66.1 (CH_2), 123.2 (C), 127.1 (CH), 127.9 (C), 128.4 (CH), 129.5 (CH), 129.6 (CH), 130.7 (CH), 132.5 (CH), 134.7 (C), 139.2 (C), 164.9 (C).

HRMS (*m/z* - EI^+) Found: 323.9557 (M^+ $C_{14}H_{10}O_2ClBr$. requires: 323.9553).

V_{max} (film)/cm^{-1} 1717, 1593, 1402, 1267, 1127, 1090, 846, 743, 681.

2-Bromobenzyl cyclohexanecarboxylate (542)



This product was isolated as the major product from the reaction of cyclohexanecarboxaldehyde (1 mmol, 0.121 mL) and 2-bromobenzaldehyde (1 mmol, 0.116 mL) *via* general procedure 5 and was isolated as a pale yellow oil (58%, 173 mg).

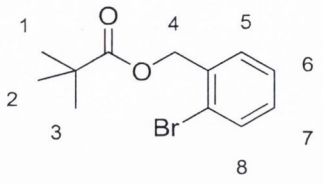
δ_H (400 MHz, $CDCl_3$): 1.17 - 1.46 (m, 5H, H_a-3, H-4 and H-5), 1.47 – 1.62 (m, 3H, H_a-2, H_b-3 and H_a-6), 1.71 – 1.75 (m, 2H, H_b-2, H_b-6), 2.36 (tt, 1H, *J* 3.6, 11.3 Hz, H-1), 5.14 (s, 2H, H-7), 7.15 (app. t, 1H, H-9), 7.29 (app. t, 1H, H-10), 7.36 (d, *J* 7.6 Hz, 1H, H-8), 7.53 (d, 1H, *J* 7.6 Hz, H-11).

δ_C (100 MHz, $CDCl_3$): 25.4 (CH_2), 25.7 (CH_2), 29.0 (CH_2), 43.1 (CH), 65.5 (CH_2), 123.3 (C), 127.4 (CH), 129.5 (CH), 129.6 (CH), 132.8 (CH), 135.6 (C), 175.6 (C)

HRMS (*m/z* - EI^+) Found: 296.0425 (M^+ $C_{14}H_{17}O_2Br$. requires: 296.0412).

νmax (film)/cm^{-1}: 2932, 2855, 1733, 1449, 1246, 1165, 1131, 1029, 751.

2-Bromobenzyl pivalate (560)



This product was isolated as the major product from the reaction of pivaldehyde (1 mmol, 0.109 mL) and 2-bromobenzaldehyde (1 mmol, 0.116 mL) *via* general procedure 5 and was isolated as a colourless oil (63%, 172 mg).

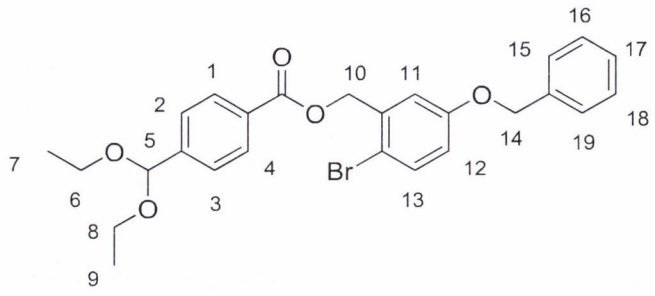
δ_H (400 MHz, $CDCl_3$): 1.25 (s, 9H, H-1, H-2 and H-3), 5.17 (s, 2H, H-4), 7.18 (app. t, 1H, H-6), 7.31 (app. t, 1H, H-7), 7.39 (d, 1H, *J* 7.6 Hz, H-5), 7.57 (d, 1H, *J* 7.6 Hz, H-8).

δ_C (100 MHz, $CDCl_3$): 27.2 (CH_3), 38.9 (C), 65.7 (CH_2), 123.3 (CH), 127.4 (CH), 129.5 (CH), 129.6 (CH), 132.8 (C), 135.7 (C), 178.0 (C).

HRMS (*m/z* - EI^+) Found: 270.0261 (M^+ $C_{12}H_{15}O_2Br$. requires: 270.0255).

V_{max} (film)/cm^{-1} 2972, 1731, 1479, 1367, 1282, 1146, 1030, 941, 750, 660.

5-(Benzyloxy)-2-bromobenzyl 4-(diethoxymethyl)benzoate (565)



This product was isolated as the major product from the reaction of 4-diethylorthoformylbenzaldehyde (1 mmol, 0.199 mL) and 2-bromo-4-(benyloxy)benzaldehyde (1 mmol, 0.291 mg) *via* general procedure 5 and was isolated as a colourless oil (92%, 457 mg).

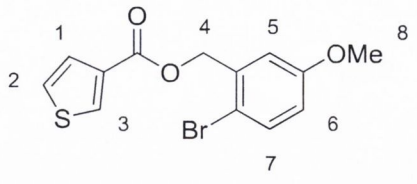
δ_H (400 MHz, $CDCl_3$): 1.14 – 1.17 (m, 6H, H-7 and H-9), 3.18 – 3.58 (m, 4H, H-6 and H-8), 5.14 (s, 2H, H-14), 5.34 (s, 2H, H-10), 5.58 (s, 1H, H-5), 7.01 (d, 1H, *J* 8.7 Hz, H-13), 7.24 (m, 1H, H-12), 7.32 – 7.44 (m, 5H, H-15, H-16, H-17, H-18 and H-19), 7.55 – 7.60 (m, 3H, H-2, H-3, H-11), 7.99 (d, 2H, *J* 8.2 Hz, H-1 and H-4).

δ_C (100 MHz, $CDCl_3$): 15.1 (CH_3), 60.9 (CH_2), 65.9 (CH_2), 69.5 (CH_2), 100.2 (CH), 113.2 (C), 116.6 (C), 117.1 (C), 126.9 (CH), 127.7 (CH), 127.9 (CH), 128.5 (CH), 129.0 (CH), 129.2 (CH), 133.5 (CH), 136.0 (C), 136.6 (CH), 144.6 (C), 157.8 (C), 165.1 (C).

HRMS (*m/z* - EI^+) Found: 521.0958 (M^+ + Na $C_{26}H_{27}O_5BrNa$ requires: 521.0940).

vmax (film)/cm^{-1}: 2975, 1723, 1574, 1475, 1270, 1102, 1019, 757, 697.

2-Bromo-5-methoxybenzyl thiophene-3-carboxylate (567)



This product was isolated as the major product from the reaction of 3-thiophenecarboxaldehyde (1 mmol, 0.088 mL) and 2-bromo-4-(methoxy)benzaldehyde (1 mmol, 0.215 mg) *via* general procedure 5 and was isolated as a white solid (99%, 327 mg). M.p. 74 - 77 °C.

δ_H (400 MHz, $CDCl_3$): 3.82 (s, 3H, H-8), 5.38 (s, 2H, H-4), 6.77 – 6.80 (m, 1H, H-7), 7.06 (s, 1H, H-5), 7.34 (app. s, 1H, H-2), 7.50 (d, 8.6 Hz, 1H, H-6), 7.61 (app. s, 1H, H-1), 8.21 (s, 1H, H-3).

δ_C (100 MHz, $CDCl_3$): 55.1 (CH_3), 65.4 (CH_2), 113.1 (C), 114.5 (C), 115.3 (CH), 125.7 (CH), 127.5 (CH), 132.8 (CH), 133.0 (CH), 135.8 (C), 158.5 (C), 161.8 (C).

HRMS (*m/z* - EI^+) Found: 325.9626 (M^+ $C_{13}H_{11}O_3BrS$ requires: 325.9612).

V_{max} (film)/cm^{-1} 2836, 1713, 1521, 1474, 1404, 1243, 1185, 1097, 1021, 869, 745.

2-Bromo-4,5-dimethoxybenzyl thiophene-3-carboxylate (368)

This product was isolated as the major product from the reaction of 3-thiophenecarboxaldehyde (1 mmol, 0.088 mL) and 2-bromo-3,4-(methoxy)benzaldehyde (1 mmol, 0.215 mg) *via* general procedure 5 and was isolated as a white solid (95%, 340 mg). M.p. 76 - 79 °C.

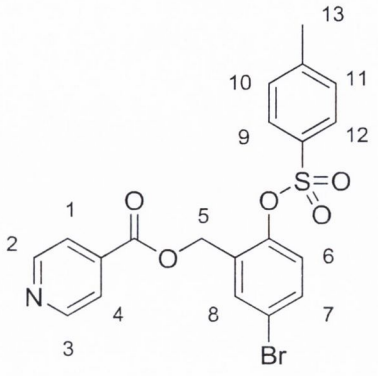
δ_H (400 MHz, $CDCl_3$): 3.90 (s, 6H, H-7 and H-8), 5.35 (s, 2H, H-4), 7.02 (s, 1H, H-5), 7.08 (s, 1H, H-6), 7.31 – 7.34 (m, 1H, H-2), 7.56 – 7.58 (m, 1H, H-1), 8.16 – 8.17 (m, 1H, H-3).

δ_C (100 MHz, $CDCl_3$): 55.7 (CH_3), 55.8 (CH_3), 65.7 (CH_2), 113.0 (CH), 114.1 (C), 115.1 (CH), 125.7 (CH), 126.8 (C), 127.5 (CH), 132.6 (CH), 132.9 (C), 147.9 (C), 149.2 (C), 162.0 (C).

HRMS (*m/z* - EI^+) Found: 355.9700 (M^+ $C_{14}H_{13}O_4BrS$ requires: 355.9718).

V_{max} (film)/cm^{-1} 2928, 1708, 1502, 1446, 1244, 1163, 967, 870, 744, 697.

5-Bromo-2-(tosyloxy)benzyl isonicotinate (569)



This product was isolated as the major product from the reaction of 4-pyridinecarboxaldehyde (1 mmol, 0.094 mL) and 2-bromo-3,4-(methoxy)benzaldehyde (1 mmol, 0.355 mg) *via* general procedure 5 and was isolated as a white solid (72%, 334 mg). M.p. 117 - 118 °C.

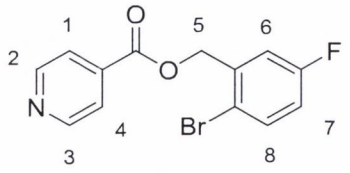
δ_H (400 MHz, $CDCl_3$): 2.40 (s, 3H, H-13), 5.19 (s, 2H, H-5), 6.99 (d, 1H, *J* 8.6 Hz, H-7), 7.32 (d, 2H, *J* 7.8 Hz, H-10 and H-11), 7.42 (d, 1H, *J* 8.6 Hz, H-6), 7.58 (s, 1H, H-8), 7.75 (d, 2H, *J* 7.8Hz, H-9 and H-12), 7.82 (d, 2H, *J* 4.5 Hz, H-1 and H-4), 8.78 (d, 2H, *J* 4.5 Hz, H-2 and H-3).

δ_C (100 MHz, $CDCl_3$): 21.3 (CH_3), 60.9 (CH_2), 120.2 (C), 122.5 (CH), 123.9 (CH), 128.0 (CH), 129.7 (CH), 130.7 (C), 131.7 (C), 132.4 (CH), 132.6 (CH), 136.3 (C), 145.7 (C), 146.1 (C), 150.3 (CH), 164.1(C).

HRMS (*m/z* - ESI^+) Found: 462.0007 (M^+ + H $C_{20}H_{16}O_5NSBr$. requires: 462.0011).

V_{max} (film)/cm^{-1} 1723, 1594, 1374, 1269, 1164, 1086, 991, 870, 815, 808, 723, 677.

2-Bromo-5-fluorobenzyl isonicotinate (570)



This product was isolated as the major product from the reaction of 4-pyridinecarboxaldehyde (1 mmol, 0.094 mL) and 2-bromo-3,4-(methoxy)benzaldehyde (1 mmol, 0.203 mg) *via* general procedure 5 and was isolated as a white solid (69%, 215 mg). M.p. 85 - 88 °C.

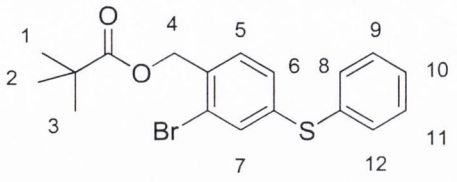
δ_H (400 MHz, $CDCl_3$): 5.45 (s, 2H, H-5), 6.97 – 7.01 (m, 1H, H-8), 7.22 – 7.25 (m, 1H, H-7), 7.57 - 7.61 (m, 1H, H-6), 7.92 (d, 2H, *J* 4.1 Hz, H-1 and H-4), 8.83 (d, 2H, *J* 4.1 Hz, H-2 and H-3).

δ_C (100 MHz, $CDCl_3$): 65.9 (CH_2), 116.3 (C), 116.5 (CH), 116.8 (CH), 122.5 (CH), 133.9 (CH, *J* 8 Hz), 136.2 (C), 136.3 (q, *J* 12 Hz), 150.3 (CH), 161.5 (CF, 246.3 Hz), 164.2 (C).

HRMS (*m/z* - EI^+) Found: 309.9892 (M^+ + H $C_{13}H_9O_2BrFN$ requires: 309.9879).

V_{max} (film)/cm^{-1} 2925, 1727, 1407, 1283, 1154, 1104, 963, 806, 738, 674.

2-Bromo-4-(phenylthio)benzyl pivalate (577)



This product was isolated as the major product from the reaction of pivaldehyde (1 mmol, 0.109 mL) and 2-bromo-4-(thiophenyl)benzaldehyde (1 mmol, 0.293 mg) *via* general procedure 5 and was isolated as a colourless oil (62%, 236 mg).

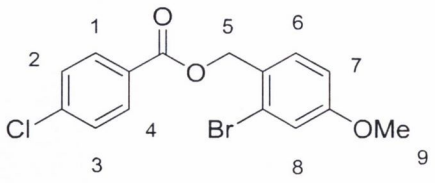
δ_H (400 MHz, $CDCl_3$): 1.21 (s, 9H, H-1, H-2 and H-3), 5.18 (s, 2H, H-4), 7.14 – 7.16 (m, 2H, H-6 and H-7), 7.20 – 7.33 (m, 6H, H-5, H-8, H-9, H-10, H-11 and H-12).

δ_C (100 MHz, $CDCl_3$): 27.2 (CH_3), 38.9 (C), 64.0 (CH_2), 127.7 (C), 128.6 (CH), 129.3 (CH), 129.4 (CH), 130.9 (CH), 133.2 (CH), 133.9 (CH), 134.7 (C), 136.0 (C), 137.7 (C), 178.1 (C).

HRMS (*m/z* - EI^+) Found: 378.0293 (M^+ $C_{18}H_{19}O_2S$ requires: 378.0289).

νmax (film)/cm^{-1}: 3020, 1722, 1478, 1214, 1153, 907, 749, 730, 668.

2-Bromo-4-methoxybenzyl 4-chlorobenzoate (599)



This product was isolated as the major product from the reaction of 4-chlorobenzaldehyde (1 mmol, 0.140 mg) and 2-bromo-4-(methoxy)benzaldehyde (1 mmol, 0.215 mg) *via* general procedure 5 and was isolated as a white solid (93%, 332 mg). M.p. 90 - 93 °C.

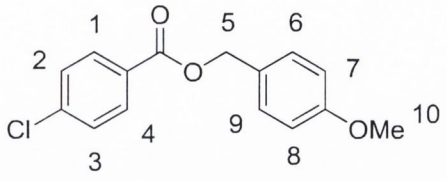
δ_H (400 MHz, $CDCl_3$): 3.83 (s, 3H, H-9), 5.40 (s, 2H, H-5), 6.89 (dd, 1H, *J* 2.2, 8.5 Hz, H-7), 7.19 (s, 1H, H-8), 7.41 – 7.44 (m, 3H, H-2, H-3 and H-6), 8.02 (d, 2H, *J* 8.4 Hz, H-1 and H-4).

δ_C (100 MHz, $CDCl_3$): 55.1 (OCH_3), 65.9 (CH_2), 112.9 (CH), 117.9 (CH), 124.3 (C), 126.7 (C), 128.1 (C), 128.3 (CH), 130.7 (CH), 131.2 (CH), 139.1 (C), 159.8 (C), 165.1 (C).

HRMS (*m/z* - EI^+) Found: 353.9638 (M^+ $C_{15}H_{12}O_3BrCl$ requires: 353.9658).

V_{max} (film)/cm^{-1} 3074, 1724, 1593, 1498, 1292, 1270, 1121, 1090, 853, 754.

4-Methoxybenzyl 4-chlorobenzoate (501)



A solution of ester **599** (0.3 mmol, 107 mg), tetrakis (triphenylphosphine) palladium (0.03 mmol, 17.7 mg), triethylamine (0.6 mmol, 0.05mL), ammonium formate (3 mmol, 190 mg) in 2 mL acetonitrile/DMF (1:1) was heated at 80 °C overnight. The solution was concentrated in vacuo, dissolved in DCM and filtered through a pad of silica to yield **501** as a yellow oil (95%, 79 mg).

δ_H (400 MHz, $CDCl_3$): 3.81 (s, 3H, H-10), 5.29 (s, 2H, H-5), 6.91 (d, 2H, *J* 8.4 Hz, H-7 and H-8), 7.38 – 7.40 (m, 4H, H-2, H-3, H-6 and H-9), 7.98 (d, 2H, *J* 8.4 Hz, H-1 and H-4)

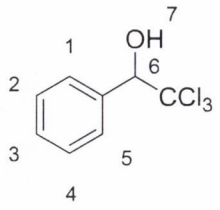
δ_C (100 MHz, $CDCl_3$): 55.3 (OCH_3), 66.8 (CH_2), 114.0 (CH), 127.9 (C), 128.6 (CH), 128.7 (C), 130.2 (CH), 131.1 (CH), 139.4 (C), 159.7 (C), 165.6 (C).

HRMS (*m/z* - EI^+) Found: 276.0553 (M^+ $C_{15}H_{13}O_3Cl$ requires: 276.0553).

νmax (film)/cm^{-1}: 1719, 1594, 1515, 1401, 1270, 1249, 1100, 1015, 826, 758.

9.3 Tishchenko substrate synthesis

2,2,2-Trichlorobenzylalcohol (381)



To a solution of benzaldehyde (0.04 mol, 4.20 mL) and $CHCl_3$ (7 mL) in DMF (30 mL) was added dropwise a solution of potassium hydroxide (0.04 mol, 2.24 g) in MeOH (10 mL) at -10°C. The solution was allowed to stir for one hour and was quenched with 2N HCl and was extracted with toluene (3 x 20 mL). The extracts were stirred in activated charcoal, filtered through a pad of celite and concentrated *in vacuo*. The product was isolated as a yellow oil (67%, 6.03 g) by column chromatography in 20% ethyl acetate in hexanes.

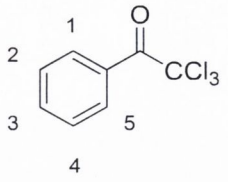
δ_H (400 MHz, $CDCl_3$): 5.25 (d, 1H, *J* 4.0 Hz, H-6), 5.33 (app. s, 1H, H-7), 7.40 – 7.46 (m, 3H, H-1, H-3 and H-5), 7.64 – 7.67 (app. t, 2H, H-2 and H-4)

δ_C (100 MHz, $CDCl_3$): 84.5 (CH), 103.1 (CCl_3), 127.8 (CH), 129.2 (CH), 129.5 (CH), 134.8 (C).

HRMS (*m/z* - EI^+) Found: 223.9557 (M^+ $C_8H_7OCl_3$ requires: 223.9562).

The NMR spectral data are consistent with those in the current literature.[181]

2,2,2-Trichloroacetophenone (382)



To a solution of alcohol **381** (5 mmol, 1.12 g) in sulphuric acid (0.5 mL) and acetic acid (20 mL) was added sodium dichromate (5 mmol, 1.49 g) in one portion. The solution was allowed to stir overnight and was poured over brine (40 mL). The aqueous layer was extracted with CH_2Cl_2 (4x 20 mL) and concentrated *in vacuo*. The ketone product was isolated as a colourless oil (89%, 0.998 g) by column chromatography eluting in 40% CH_2Cl_2 in hexanes.

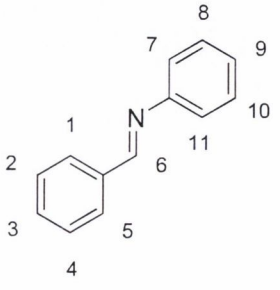
δ_H (400 MHz, $CDCl_3$): 7.53 (app. t, 2H, H-2 and H-4), 7.67 (t, 1H, *J* 7.2 Hz, H-3), 8.29 (d, 2H, *J* 7.2 Hz, H-1 and H-5)

δ_C (100 MHz, $CDCl_3$): 96.0 (CCl_3), 128.5 (CH), 129.1 (CH), 131.6 (CH), 134.4 (C), 181.3 (C).

HRMS (*m/z* - EI^+) Found: 186.9716 (M^+ - Cl $C_8H_5OCl_2$ requires: 186.9717).

The NMR spectral data are consistent with those in the current literature.[190]

***N*-Phenyl-benzaldehyde imine (471)**



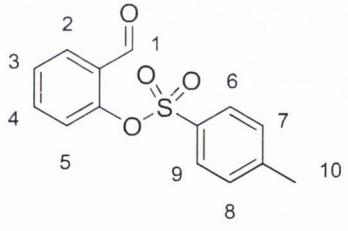
To a solution of benzaldehyde (5 mmol, 0.525 mL) and aniline (5 mmol, 0.456 mL) in toluene (30 mL) in a 50 mL round bottomed flask was added PTSA (50 mg). A Dean-Stark apparatus was attached to the flask and the solution was heated at reflux overnight at which point it was allowed to cool to room temperature. The solution was washed with a 0.1 M solution $NaHCO_3$ and was concentrated *in vacuo* to afford the product as a yellow solid (88%, 797 mg). M.p. 64 – 66 °C. (lit. 65 – 67 °C[191]).

δ_H (400 MHz, $CDCl_3$): 7.14 - 7.17 (app. t, 2H, H-8 and H-10), 7.18 (t, 1H, *J* 8.8 Hz, H-9), 7.33 (d, 2H, *J* 8.2 Hz, H-7 and H-11), 7.40-7.43 (m, 3H, H-2, H-3 and H-4), 7.85 (d, 2H, *J* 5.4 Hz, H-1 and H-5), 8.40 (s, 1H, H-6).

δ_C (100 MHz, $CDCl_3$): 121.1 (CH), 126.1 (CH), 129.0 (CH), 129.0 (CH), 129.4 (CH), 131.6 (CH), 136.4 (C), 152.4 (C), 160.6 (CH).

The NMR spectral data are consistent with those in the current literature.[191]

2-*O*-Tosyl-salicylaldehyde (527)



To a solution of salicylaldehyde (0.05 mol, 6.11 g) and 4-toluenesulfonyl chloride (0.05 mol, 9.53 g) in CH_2Cl_2 (100 mL) was added NEt_3 (0.055 mol, 7.72 mL) and DMAP (100 mg) and the solution was allowed to stir overnight. The solution was washed with 2N HCl and concentrated *in vacuo*. The crude material was recrystallised from diethyl ether to furnish the product as a white crystalline solid (78%, 10.75 g). M.p. 60 – 61 °C. (lit. 61 – 62 °C).[192]

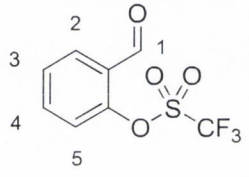
δ_H (400 MHz, $CDCl_3$): 2.47 (s, 3H, H-10), 7.21 (d, 1H, *J* 8.0 Hz, H-5), 7.35 (d, 2H, 8.4 Hz, H-7 and H-8), 7.41 (app. t, 1H, H-3), 7.60 (app. dt, 1H, H-

4), 7.72 (d, 2H, *J* 8.4 Hz, H-6 and H-9), 7.88 (dd, 1H, *J* 2.0, 8.0 Hz, H-2), 10.0 (s, 1H, H-1).

δ_C (100 MHz, $CDCl_3$): 21.8 (CH_3), 123.7 (CH), 127.5 (CH), 128.5 (CH), 128.6 (CH), 129.3 (C), 130.1 (CH), 131.3 (C), 135.3 (CH), 146.3 (C), 151.2 (C), 187.3 (CH).

The NMR spectral data are consistent with those in the current literature.[192]

2-*O*-Triflyl-salicylaldehyde (528)



To a solution of salicylaldehyde (0.025 mol, 3.20 g) and triflic anhydride (0.025 mol, 5.00 mL) in CH_2Cl_2 (12 mL) was added pyridine (12 mL) and the solution was allowed to stir overnight. The solution was poured into water (60 mL), extracted with diethyl ether (3 x 30 mL) and concentrated *in vacuo*. The crude material was purified by column chromatography eluting in 5% ethyl acetate in hexanes to furnish the product as a yellow oil (29%, 2.07 g).

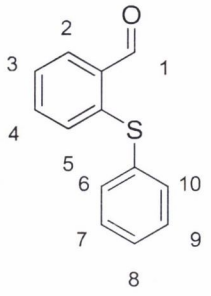
δ_H (400 MHz, $CDCl_3$): 7.44 (d, 1H, *J* 8.4 Hz, H-5), 7.59 (app. t, 1H, H-3), 7.75 (app. t, 1H, H-4), 8.03 (d, 1H, *J* 8.0 Hz, H-2), 10.30 (s, 1H, H-1)

δ_C (100 MHz, $CDCl_3$): 118.9 (CF_3, *J* 318.0 Hz), 122.4 (CH), 128.5 (C), 128.9 (CH), 130.9 (CH), 135.8 (CH), 149.8 (C), 186.5 (CH).

HRMS (*m/z* - EI^+) Found: 254.9926 (M^+ + H $C_8H_6O_4F_3S$ requires: 254.9939)

The NMR spectral data are consistent with those in the current literature.[193]

2-(Thiophenyl)-benzaldehyde (530)



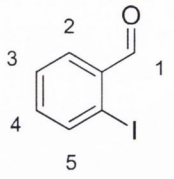
To a solution of 2-chlorobenzaldehyde (7.1 mmol, 1.00 g), sodium carbonate (11.8 mmol, 1.25 g) in DMF (5 mL), was added thiophenol (9.1 mmol, 1.00 g) and the reaction was heated overnight at 80 °C. The reaction mixture was allowed to cool to room temperature and was poured into water (50 mL). The crude product was extracted from the water with diethyl ether (2 x 10 mL), concentrated *in vacuo* and purified by recrystallisation in diethyl ether and hexanes to afforded the product as a yellow solid (66%, 1.01 g). M.p. 44 – 45 °C. (lit. 43 – 48 °C[194]).

δ_H (400 MHz, $CDCl_3$): 7.09 (d, 1H, *J* 8.0 Hz, H-5), 7.44-7.31 (m, 7H, H-3, H-4, H-6, H-7, H-8, H-9 and H-10), 7.88 (d, 1H, *J* 8.0 Hz, H-2), 10.39 (s, 1H, H-1).

δ_C (100 MHz, $CDCl_3$): 126.4 (CH), 128.6 (CH), 129.8 (CH), 129.9 (C), 130.4 (CH), 132.1 (CH), 133.3 (CH), 133.8 (CH), 134.2 (C), 141.7 (C), 191.7 (CH).

The NMR spectral data are consistent with those in the current literature.[194]

2-Iodobenzaldehyde (533)



A solution of 2-iodobenzoic acid (0.03 mol, 7.40 g) in THF (40 mL), was charged with a stirring bar and borane-dimethyl sulphide (0.033 mol, 3.11 mL). The reaction was allowed to stir for 4 hours and was then poured into water. The crude product was extracted with CH_2Cl_2 (3 x 20 mL), washed with 2M sodium carbonate and concentrated *in vacuo*. The crude alcohol product was used as without further purification.

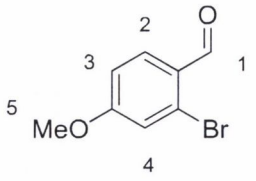
The crude alcohol product was dissolved in chloroform (50 mL) and manganese dioxide (0.06 mol, 5.21 g) was added to the vessel. The reaction mixture was heated under reflux for 3 days and filtered under gravity. The filtrate was then concentrated *in vacuo* and the product was isolated by column chromatography, eluting in 5% ethyl acetate in hexanes, as a yellow solid (64%, 4.45 g). M.p. 34 – 37 °C. (lit. 38 – 39 °C[195]).

δ_H (400 MHz, $CDCl_3$): 7.29 – 7.33 (m, 1H, H-4) 7.49 (app. t, 1H, H-3), 7.90 (d, 1H, *J* 8.0 Hz, H-5), 7.98 (d, 1H, *J* 8.0 Hz, H-2), 10.09 (s, 1H, H-1)

δ_C (100 MHz, $CDCl_3$): 100.7 (CH), 128.7 (CH), 130.3 (CH), 135.4 (CH), 135.1 (C), 140.7 (C), 197.7 (CH).

The NMR spectral data are consistent with those in the current literature.[195]

2-Bromo-4-anisaldehyde (544)



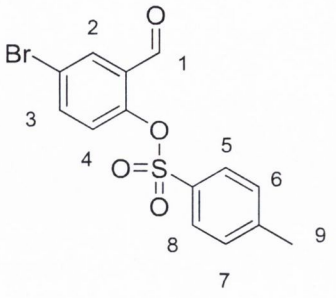
A solution of 4-anisaldehyde (0.06 mol, 15.00 mL) stirred overnight in trimethylorthoformate (7.90 mL) and *p*-toluenesulfonic acid (60 mg). The remaining trimethylorthoformate was removed under vacuum and the crude product was used without further purification.

The crude dimethylorthoester was dissolved in distilled THF (140 mL) and cooled to -78 °C. To this solution was added *t*-butyllithium (1.5 M in pentane, 40 mL) and was allowed to stir for 1 hour at which point carbontetrabromide (0.06 mol, 20.00 g) was added. The solution was allowed to warm to room temperature slowly and was poured into a 1N HCl solution (150 mL). The crude aldehyde product was extracted with CH_2Cl_2 (3 x 50 mL) and was purified by column chromatography, eluting in 5% ethyl acetate in hexanes, to afford a yellow solid (29%, 3.74 g). M.p. 76 – 79 °C. (lit. 77 – 79 °C[196]).

δ_H (400 MHz, $CDCl_3$): 3.90 (s, 3H, H-5), 6.96 (d, 1H, *J* 7.6 Hz, H-3), 7.15 (s, 1H, H-4), 7.90 (d, 1H, *J* 7.6 Hz, H-2), 10.23 (s, 1H, H-1).

The NMR spectral data are consistent with those in the current literature.[196]

2-*O*-Tosyl-5-bromo-salicylaldehyde (546)



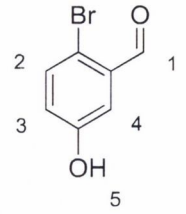
To a solution of salicylaldehyde (0.025 mol, 5.00 g) and 4-toluenesulfonyl chloride (0.038 mol, 7.10 g) in CH_2Cl_2 (20 mL) was added NEt_3 (0.03 mol, 4.2 mL) and DMAP (50 mg) and the solution was allowed to stir overnight. The solution was washed with 2N HCl and concentrated *in vacuo*. The crude material was recrystallised from diethyl ether to furnish the product as a yellow crystalline solid (81%, 7.20 g). M.p. 55 – 58 °C. (lit. 61 – 62 °C[197]).

δ_H (400 MHz, $CDCl_3$): 2.49 (s, 3H, H-9), 7.11 (d, 1H, *J* 8.8 Hz, H-4), 7.38 (d, 2H, *J* 8.8 Hz, H-6 and H-7) 7.68 – 7.74 (m, 3H, H-3, H-5 and H-8), 7.99 (d, 1H, *J* 2.4 Hz, H-2), 9.91 (s, 1H, H-1)

δ_C (100 MHz, $CDCl_3$): 22.2 (CH_3), 121.8 (C), 126.0 (CH), 128.9 (CH), 130.7 (CH), 130.9 (CH), 131.3 (C), 131.8 (C), 138.4 (CH), 147.0 (C), 150.4 (C), 186.3 (CH).

The NMR spectral data are consistent with those in the current literature.[197]

2-Bromo-5-hydroxybenzaldehyde (548)



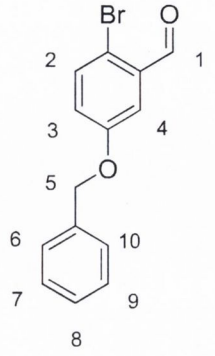
A solution of 3-hydroxybenzaldehyde (0.041 mol, 5.00 g) and chloroform (50 mL) in a 250 mL round bottomed flask was added dropwise from a pressure-equalising dropping funnel a solution of bromine (2.10 mL) in chloroform (50 mL). The resulting brown solution was allowed to sit overnight in the freezer to crystallise. The product was obtained by filtrate under vacuum as a yellow crystalline solid (68%, 5.61 g). M.p. 133 – 134 °C. (lit. 131 °C)[198]

δ_H (400 MHz, $CDCl_3$): 6.35 (br. s, 1H, H-5) 7.05 (dd, 1H, *J* 3.2, 8.8 Hz, H-3), 7.49 (d, 1H, *J* 3.2 Hz, H-2), 7.53 (d, 1H, *J* 8.8 Hz, H-2), 10.31 (s, 1H, H-1)

δ_C (100 MHz, $CDCl_3$): 115.8 (CH), 118.0 (C), 123.6 (CH), 134.3 (C), 135.3 (CH), 155.9 (C), 192.2 (CH).

The NMR spectral data are consistent with those in the current literature.[190]

2-Bromo-5-(benzyloxy)benzaldehyde (549)



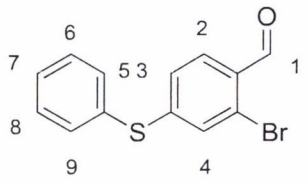
To a solution of aldehyde **548** (0.02 mol, 4.00 g) in DMF (25 mL) was added benzyl bromide (0.02, 2.50 mL) and potassium carbonate (0.03 mol, 8.90 g). The reaction mixture was heated to 80 °C and allowed to stir overnight, at which point it was cooled to room temperature, poured into water (100 mL) and extracted with diethyl ether (3 x 30 mL). The product was recrystallised from diethyl ether and hexanes to afford the product as a white solid (92%, 5.36 g). M.p 48 – 49 °C. (lit. 46 – 48 °C)[199]

δ_H (400 MHz, $CDCl_3$): 5.19 (s, 2H, H-5), 7.28 – 7.31 (d, 1H, *J* 8.7 Hz, H-3), 7.34 – 7.45 (m, 5H, H-6, H-7, H-8, H-9 and H-10), 7.49 – 7.52 (m, 2H, H-2 and H-4), 10.31 (s, 1H, H-1).

δ_C (100 MHz, $CDCl_3$): 70.4 (CH_2), 113.9 (CH), 118.2 (C), 123.7 (CH), 127.6 (CH), 128.3 (CH), 128.7 (CH), 134.0 (C), 134.6 (CH), 135.9 (C), 158.4 (C), 191.6 (CH).

The NMR spectral data are consistent with those in the current literature.[191]

2-Bromo-4-(thiophenyl)benzaldehyde (551)



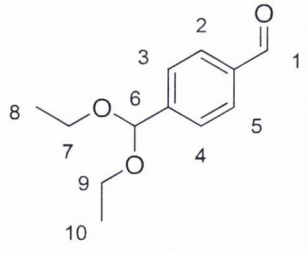
To a solution of 2-bromo-4-fluorobenzaldehyde (0.025 mol, 5.00 g) and thiophenol (0.031 mol, 5.00 g) in DMF (25 mL) was added potassium carbonate (0.072 mol, 10.0 g) and the solution was heated at 80 °C overnight. The solution was cooled to room temperature and poured over water (100 mL). The filtrate was extracted with diethyl ether (3 x 20 mL), washed with 1 M sodium carbonate and concentrated *in vacuo*. The pure product was recrystallised from diethyl ether to afford the product as a yellow solid (66%, 4.73 g). M.p. 54 – 61 °C

δ_H (400 MHz, $CDCl_3$): 6.62 (s, 1H, H-4), 7.03 (d, 1H, *J* 8.4 Hz, H-3), 7.28 – 7.41 (m, 5H, H-5, H-6, H-7, H-8 and H-9), 7.71 (d, 1H, *J* 8.4 Hz, H-2), 10.24 (s, 1H, H-1).

δ_C (100 MHz, $CDCl_3$): 123.5 (CH), 126.1 (C), 129.7 (CH), 129.8 (CH), 131.7 (C), 132.5 (CH), 133.9 (CH), 134.7 (CH), 143.2 (CH), 147.5 (C), 190.3 (CH).

The NMR spectral data are consistent with those in the current literature.[200]

4-diethylformylbenzaldehyde (553)



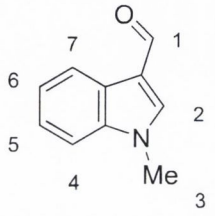
A solution of terephthalaldehyde (75 mmol, 10.00 g) and triethylorthoformate (77 mmol, 12.80 mL) in distilled THF (30 mL) was stirred overnight and concentrated *in vacuo*. The product was isolated directly by column chromatography, eluting in 5% ethyl acetate in hexanes, to furnish the product as a colourless oil (52%, 8.14 g).

δ_H (400 MHz, $CDCl_3$): 1.24 (t, 6H, *J* 7.6 Hz, H-8 and H-10), 3.58 – 3.71 (m, 4H, H-7 and H-9), 5.59 (s, 1H, H-6), 7.75 (d, 2H, *J* 7.9 Hz, H-3 and H-4), 7.91 (d, 2H, *J* 7.9 Hz, H-2 and H-5), 10.03 (s, 1H, H-1).

HRMS (*m/z* - EI^+) Found: 208.1094 (M^+ $C_{12}H_{16}O_3$ requires: 208.1099)

The NMR spectral data are consistent with those in the current literature.[201]

_N_-Methyl-3-indolecarboxaldehyde (555)



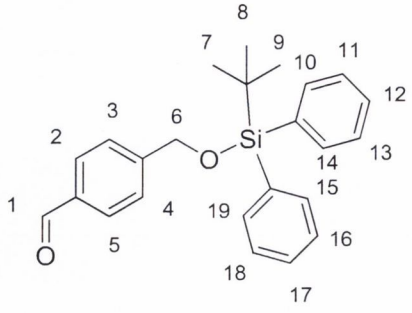
To a solution of indole-3-carboxaldehyde (7 mmol, 1.00 g) in DMF (30 mL) at 0 °C was added sodium hydride (12 mmol, 0.50 g) and was allowed to stir for 10 minutes. Methyl iodide (9 mmol, 0.591 mL) was then added to this solution and it was allowed to stir overnight at room temperature. The solution was poured onto water (100 mL), extracted with CH_2Cl_2 (3 x 20 mL) and concentrated *in vacuo*. The pure aldehyde product was isolated by column chromatography, eluting in gradient 20 – 50% ethyl acetate in hexanes, as a yellow solid (83%, 928 mg). M.p. 68 – 71 °C. (lit. 68 – 71 °C[202]).

δ_H (400 MHz, $CDCl_3$): 3.87 (s, 3H, H-3), 7.26 – 7.37 (m, 3H, H-5, H-6 and H-7), 7.67 (s, 1H, H-2), 8.30 (d, 1H, *J* 7.2 Hz, H-4), 9.99 (s, 1H, H-1).

δ_C (100 MHz, $CDCl_3$): 33.6 (CH_3), 109.8 (CH), 118.0 (C), 121.9 (CH), 122.9 (CH), 123.9 (CH), 125.2 (C), 137.8 (C), 139.2 (CH), 184.6 (CH).

The NMR spectral data are consistent with those in the current literature.[202]

4-(*t*-Butyldiphenylsilanoxymethyl)benzaldehyde (591)



Aldehyde **553** (24 mmol, 5 g) was dissolved in ethanol (20 mL) at 0 °C and sodium borohydride (32 mmol, 1.2 g) was added in portions. The mixture was stirred for 1 hour and poured over 1N HCl (50 mL) slowly. The crude product was extracted with CH_2Cl_2 (3 x 30 mL), concentrated *in vacuo* and used without further purification.

The crude alcohol product was dissolved in DMF (20 mL), at which point *t*-butyldiphenylsilyl chloride (24 mmol, 4.2 mL) and imidazole (0.6 g) were added and the reaction was allowed to stir overnight. The mixture was poured into 1N HCl (50 mL), extracted with CH_2Cl_2 (3 x 20 mL) and concentrated *in vacuo*. The product was purified by column chromatography, eluting in 20% ethyl acetate in hexanes, affording a milky-white oil (69%, 8.99 g).

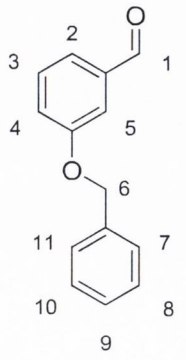
δ_H (400 MHz, $CDCl_3$): 1.12 (s, 9H, H-7, H-8 and H-9), 4.84 (s, 2H, H-6), 7.37 – 7.44 (m, 6H, H-11, H-12, H-13, H-16, H-17 and H-18), 7.51 (d, 2H, *J* 8.0 Hz, H-3 and H-4), 7.68 – 7.70 (m, 4H, H-10, H-14, H-15 and H-19), 7.85 (d, 2H, *J* 8.0 Hz, H-2 and H-5), 10.01 (s, 1H, H-1)

δ_C (100 MHz, $CDCl_3$): 19.3 (C), 26.8 (CH_3), 65.2, (CH_2), 125.8 (CH), 127.8 (CH), 129.9 (CH), 130.3 (CH) 133.2 (C), 134.8 (C), 135.5 (CH), 147.4 (C), 192.2 (CH).

HRMS (*m/z* - EI^+) Found: 374.1689 (M^+ $C_{24}H_{26}O_2Si$ requires: 374.1702)

The NMR spectral data are consistent with those in the current literature.[203]

3-(benzyloxy)benzaldehyde (592)



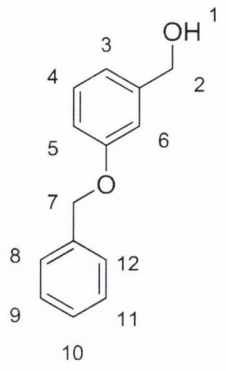
A solution of 3-hydroxybenzaldehyde (0.041 mol, 5 g) and benzyl bromide (0.042 mol, 5 mL) in DMF (20 mL) was added potassium carbonate (0.064 mol, 8.9 g) in one portion. The solution was heated at 80 °C overnight and diluted with water (200 mL). The crude product was extracted with diethyl ether (2 x 20 mL), concentrated *in vacuo* and was recrystallised from diethyl ether and hexane. The pure product was obtained as a white solid (81%, 7.05 g). M.p. 55 – 57 °C. (lit. 54 – 56 °C[204]).

δ_H (400 MHz, $CDCl_3$): 5.15 (s, 2H, H-6), 7.27 – 7.30 (m, 1H, H-4), 7.36 – 7.50 (m, 8H, H-2, H-3, H-5, H-7, H-8, H-9, H-10, H-11), 10.00 (s, 1H, H-1)

δ_C (100 MHz, $CDCl_3$): 70.8 (CH_2), 113.6 (CH), 122.7 (CH), 124.0(CH), 127.9 (CH), 128.6 (CH), 129.4 (CH), 130.4 (CH), 136.8 (C), 138.2 (C), 159.7 (C), 192.6 (CH).

The NMR spectral data are consistent with those in the current literature.[204]

3-(Benzyloxy)benzyl alcohol (593)



3-Hydroxybenzaldehyde (0.1 mol, 12.2 g) was added to a solution of benzyl bromide (0.11 mol, 13.1 mL) and potassium carbonate (0.15 mol, 20.7 g) in DMF (20 mL). The reaction mixture was heated overnight at 80 °C, then cooled to room temperature and poured into water (100 mL). The product was extracted with diethyl ether (3 x 30 mL), concentrated *in vacuo* and used without further purification.

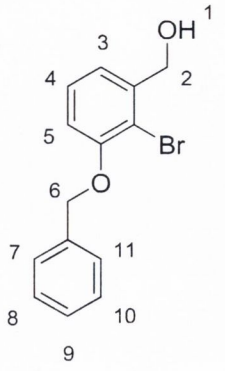
The crude material was dissolved in methanol (40 mL) at -10 °C and sodium borohydride (0.11 mol, 4.2 g) was added portionwise. The mixture was stirred for one hour and then poured into 1N HCl (50 mL). The crude product was extracted with CH_2Cl_2 (3 x 20 mL), washed with 0.1 M sodium carbonate (30 mL) and concentrated *in vacuo*. The product was isolated by column chromatography, eluting in gradient 20 – 40% ethyl acetate in hexanes, as a white solid (96%, 20.59 g). M.p. 48 – 50 °C. (lit. 49 °C[205]).

δ_H (400 MHz, $CDCl_3$): 4.70 (s, 2H, H-2), 5.10 (s, 2H, H-7), 6.93 – 6.99 (m, 2H, H-3 and H-5), 7.05 (s, 1H, H-6), 7.29 – 7.48 (m, 6H, H-4, H-8, H-9, H-10, H-11 and H-12)

δ_C (100 MHz, $CDCl_3$): 65.2 (CH_2), 69.9 (CH_2), 113.2 (CH), 114.1 (CH), 119.3 (CH), 127.4 (CH), 127.9 (CH), 128.5 (CH), 129.6 (CH), 136.9 (C), 142.6 (C), 159.0 (C)

The NMR spectral data are consistent with those in the current literature.[205]

`2-Bromo-3-(benzyloxy)benzyl alcohol (594)

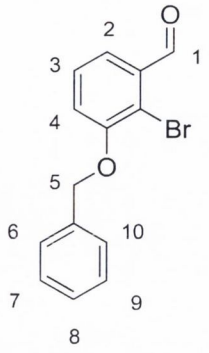


To a solution of alcohol **593** (0.09 mol, 19.3 g) in distilled THF (100 mL) at -78 °C under nitrogen, was added *n*-butyllithium (2.5 M in hexanes) (0.18 mol, 72 mL) and allowed to stir for 30 minutes. Carbon tetrabromide (0.1 mol, 33.2 g) was added in one portion, stirred for 1 hour and allowed to warm to room temperature slowly. The mixture was poured into water (200 mL), extracted with CH_2Cl_2 (3 x 50 mL), washed with brine and concentrated *in vacuo*. The product was isolated by column chromatography, eluting in gradient 20 – 40% ethyl acetate in hexanes, as a white solid (53%, 13.97 g). M.p. 118 - 122 °C. (lit. 123.5 – 124.5 °C[167]).

δ_H (400 MHz, $CDCl_3$): 4.79 (d, 2H, *J* 6.5 Hz, H-2), 5.18 (s, 2H, H-6), 6.90 (d, 1H, *J* 7.2 Hz, H-5), 7.11 (d, 1H *J* 7.8 Hz, H-3), 7.26 (app. t, 1H, H-4), 7.33 (t, 1H, *J* 7.6 Hz, H-9), 7.39 – 7.42 (app. t, 2H, H-8 and H-10), 7.51 (d, 2H, *J* 7.6 Hz, H-7 and H-11).

The NMR spectral data are consistent with those in the current literature.[167]

2-Bromo-3-(benzyloxy)benzaldehyde (595)



A solution of alcohol **594** (0.04 mol, 11.70 g), pyridinium chlorochromate (0.045 mol, 9.70 g) and CH_2Cl_2 (100 mL) was stirred overnight and then filtered under vacuum. The filtrate was concentrated *in vacuo* and purified by column chromatography, eluting in 5 – 20% ethyl acetate in hexanes, to afford a white solid (76%, 8.86 g). M.p. 126 – 127 °C. (lit. 130.5 – 132 °C[167]).

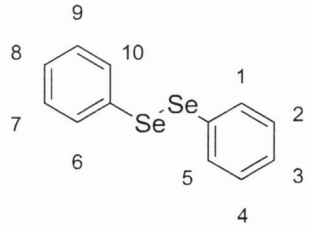
δ_H (400 MHz, $CDCl_3$): 5.20 (s, 2H, H-5), 7.15 (d, 1H, *J* 8.0 Hz, H-4), 7.31 – 7.40 (m, 2H, H-3 and H-8), 7.42 (app. t., 2H, H-7 and H-9), 7.51 (d, 2H, *J* 7.4 Hz, H-6 and H-10), 7.55 (d, 1H, *J* 7.8 Hz, H-2), 10.21 (s, 1H, H-1)

δ_C (100 MHz, $CDCl_3$): 70.4 (CH_2), 113.9 (CH), 118.2 (C), 123.7 (CH), 127.6 (CH), 128.3 (CH), 128.7 (CH), 134.6 (CH), 135.9 (C), 137.8 (C), 158.4 (C), 191.7 (CH).

The NMR spectral data are consistent with those in the current literature.[167]

9.4 Synthesis of diselenide precatalysts

Diphenyl diselenide (404)

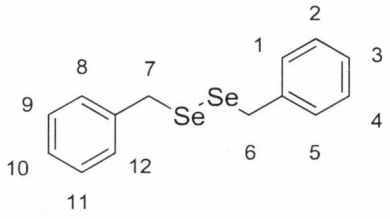


To a stirred solution of magnesium (35 mmol, 857 mg) in dry diethyl ether (50 mL) and a single crystal of iodine under a nitrogen atmosphere, was added bromobenzene (30 mmol, 3.16 mL) and the solution was heated under a gentle reflux for 1.5 hours. The solution was allowed to cool to room temperature and molecular selenium (35 mmol, 2.76 g) was added in portions. The resulting mixture was stirred for 30 minutes at room temperature and was quenched by the addition of 100 g ice. Concentrated hydrochloric acid (20 mL) was added and the solution was extracted with 100 mL diethyl ether. The extract was diluted with 200 mL methanol and stirred overnight with air bubbling through the solution. The solution was concentrated *in vacuo* and the crude material was recrystallised in hexanes to afford a yellow crystalline solid (64%, 6.02 g). M.p. 62 – 64 °C. (lit. 62 – 63 °C[206]).

δ_H (400 MHz, $CDCl_3$): 7.25 – 7.27 (m, 6H, H-2, H-3, H-4, H-7, H-8 and H-9), 7.60 – 7.62 (m, 4H, H-1, H-5, H-6 and H-10)

The NMR spectral data are consistent with those in the current literature.[207]

Dibenzyl diselenide (421)



This was synthesised using a modified literature procedure.[118]

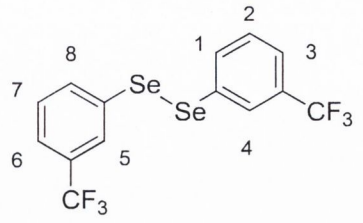
To a stirred solution of sodium borohydride (38.0 mmol, 1.44 g), and ethanol (114 mmol, 6.6 mL) in DMF (60 mL) in a 250 mL round bottomed flask at 0 °C, was added molecular selenium (19 mmol, 1.5 g). The solution was allowed to stir until the hydrogen evolution ceased and then ethanol (76 mmol, 4.4 mL) was added, whereupon the reaction was allowed to stir for a further 10 minutes before the addition of a molecular selenium (19 mmol, 1.5 g). To the resulting mixture was added benzyl bromide (0.38 mmol, 4.5 mL) dropwise which yielded a yellow solution which was poured over 400 mL water and extracted with 300 mL diethyl ether. The extract was washed with water (2 x 200 mL) and allowed to stir overnight open to the air. The yellow solution was dried over magnesium sulfate, evaporated under reduced pressure and the product was recrystallised from n-hexane to give a yellow crystalline solid (84%, 5.4g) which was stored under argon, in the dark at room temperature. Mp 97 - 101 °C. (lit. 90 - 93 °C[208]).

δ_H (400 MHz, $CDCl_3$): 3.85 (m, 4H, H-6 and H-7), 7.24 - 7.35 (m, 10H, H-1, H-2, H-3, H-4, H-5, H-8, H-9, H-10, H-11 and H-12).

δ_C (100 MHz, $CDCl_3$): 32.6 (CH_2), 127.1 (CH), 128.4 (CH), 129.0 (CH), 139.0 (C)

The NMR spectral data are consistent with those in the current literature.[140]

***Bis*-(3-trifluoromethyl)phenyl diselenide (446)**



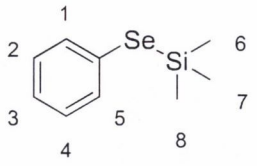
This was synthesised using a modified literature procedure.[209]

To a stirred solution of magnesium (36.8 mmol, 894 mg) in dry diethyl ether (50 mL) and a single crystal of iodine under a nitrogen atmosphere, was added m-trifluoromethylbromobenzene (33.5 mmol, 4.67 mL) and the solution was heated under a gentle reflux for 1.5 hours. The solution was allowed to cool to room temperature and molecular selenium (36.8 mmol, 2.9 g) was added in several portions. The resulting mixture was stirred for 30 minutes at room temperature and was quenched by the addition of 100 g ice. Concentrated hydrochloric acid (20 mL) was added and the solution was extracted with 100 mL diethyl ether. The extract was diluted with 200 mL methanol and stirred overnight with air bubbling through the solution. The resulting orange solution was dried over magnesium sulfate, evaporated under reduced pressure and the residue was distilled under reduced pressure using a commercial Kugelrohr apparatus to afford **446** as an orange liquid (8.98 g, 60%) which was stored under argon, in the dark at room temperature. B.p. 130 °C, 0.7 mbar (lit. 121 - 123 °C, 0.3 torr)

δ_H (400 MHz, $CDCl_3$): 7.43 (app. t, 2H, H-2 and H-7), 7.55 (d, 2H, *J* 7.8 Hz, H-1 and H-8), 7.79 (d, 2H, *J* 7.8 Hz, H-3 and H-6), 7.87 (s, 2H, H-4 and H-5).

The NMR spectral data are consistent with those in the current literature.[209]

***Se*-trimethylsilyl phenylselenide (480)**



To a stirred solution of magnesium (35 mmol, 857 mg) in dry diethyl ether (50 mL) and a single crystal of iodine under a nitrogen atmosphere, was added bromobenzene (30 mmol, 3.16 mL) and the solution was heated under a gentle reflux for 1.5 hours. The solution was allowed to cool to room temperature and molecular selenium (30 mmol, 2.37 g) was added in portions. The resulting mixture was stirred for 30 minutes at room temperature and chlorotrimethylsilane (35 mmol, 4.44 mL) was added dropwise with stirring. The product was distilled under vacuum in a commercially Kugelrohr apparatus to afford an orange oil (26%, 1.80 g). B.p 72 °C, 0.7 mbar (lit. 66 – 68 °C, 1 torr[210]).

δ_H (400 MHz, $CDCl_3$): 0.39 (s, 9H, H-6, H-7 and H-8), 7.21 – 7.29 (m, 3H, H-2, H-3 and H-4), 7.55 (d, 2H, *J* 6.8 Hz, H-1 and H-5).

δ_C (100 MHz, $CDCl_3$): 1.4 (CH_3), 125.3 (CH), 127.0 (CH), 128.9 (CH), 136.7 (C).

The NMR spectral data are consistent with those in the current literature.[201]

9.5 The synthesis of α,β-unsaturated acylpyrazoles

General procedure 6: the formation of α,β-unsaturated carboxylic acids

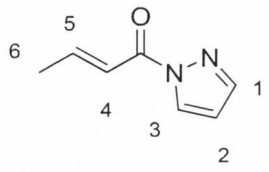
The ylide was formed from the extraction of ethyl 2-triphenylphosphoniumacetate bromide (0.025 mol, 10.7 g) from a solution of 2 M sodium hydroxide with CH_2Cl_2 (3 x 30 mL) and concentrated *in vacuo*. This crude product was dissolved in toluene (50 mL), the aldehyde (0.025 mol) was added and the reaction was heated overnight at 80 °C. The vessel was cooled to room temperature, poured into water and extracted with CH_2Cl_2 (3 x 30 mL). The extract was dried over magnesium sulfate and concentrated *in vacuo*.

General procedure 7: the formation of α,β-unsaturated acylpyrazoles

The α,β-unsaturated ester (0.015 mol) was dissolved in a mixed solvent solvent system of diethyl ether, THF and water (30 mL, 1:1:1). To this solution was added lithium hydroxide (0.045 mol, 1.08 g) and it was allowed to stir for 5 hours, at which point the mixture was diluted with water (50 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The crude product was dried over magnesium sulfate and recrystallised from ethyl acetate in hexanes.

The required α,β-unsaturated carboxylic acid (0.01 mol) was heated under reflux in thionyl chloride (15 mL) for 1 hour. The reaction was cooled slightly, a distillation apparatus was attached and the remaining thionyl chloroide was removed by distillation at atmospheric pressure, the remaining oil was dissolved in distilled THF and added in one portion to a solution of pyrazole (0.09 mol, 6.13 g) and sodium hydride (60% dispersion in oil, 0.1 mol, 4 g) in distilled THF at 0 °C. The solution was stirred for 2 hours and concentrated *in vacuo*. The crude product was purified by column chromatography, eluting in 10 – 25% ethyl acetate in hexanes.

(*E*)-1-(1H-Pyrazol-1-yl)but-2-en-1-one (603)



This product was obtained as a yellow oil (42%, 5.69 g) *via* general procedure 7 from crotonic acid.

Yellow oil.

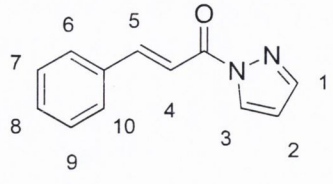
δ_H (400 MHz, $CDCl_3$): 2.0 (d, 3H, *J* 6.0 Hz, H-6), 6.42 – 6.43 (m, 1H, H-2), 7.28 – 7.32 (m, 2H, H-4 and H-5), 7.7 (app. s, 1H, H-3), 8.29 (d, 1H, *J* 2.4 Hz, H-1).

δ_C (100 MHz, $CDCl_3$): 18.7 (CH_3), 109.6 (CH), 120.8 (CH), 128.6 (CH), 143.7 (CH), 147.7 (CH), 163.1 (C).

HRMS (*m/z* – EI) Found 137.0717 ($M^+ + H$ $C_7H_8N_2O$ requires: 137.0715).

V_{max} (film)/cm^{-1} 3134, 2945, 1710, 1642, 1532, 1440, 1329, 1199, 1028, 908, 808, 765, 630.

(*E*)-3-Phenyl-1-(1H-pyrazol-1-yl)prop-2-en-1-one (605)



This product was obtained as a white solid (72%, 14.30 g) *via* general procedure 7 from cinnamic acid. M.p. 58 – 60 °C (lit. 68 °C[211]).

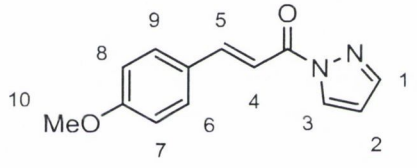
δ_H (400 MHz, $CDCl_3$): 6.46 – 6.47 (m, 1H, H-2), 7.38 – 7.41 (m, 3H, H-6, H-8 and H-10), 7.64 – 7.67 (m, 2H, H-7 and H-9), 7.75 (d, 1H, *J* 0.4 Hz, H-3), 7.88 (d, 1H, *J* 16.0 Hz, H-5), 8.0 (d, 1H, *J* 16.0 Hz, H-4), 8.36 (d, 1H, *J* 2.8Hz, H-1).

δ_C (100 MHz, $CDCl_3$): 109.5 (CH), 115.2 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 130.6 (CH), 134.0 (C), 143.4 (CH), 147.5 (CH), 163.2 (C).

HRMS (*m/z* – EI) Found 198.0799 (M^+ $C_{12}H_{10}N_2O$ requires: 198.0793).

Spectral data for this compound were consistent with those in the literature.[212]

(*E*)-3-(4-Methoxyphenyl)-1-(1H-pyrazol-1-yl)prop-2-en-1-one (637)



Ethyl 4'-methoxyphenyl-3-prop-2-enoate was obtained from 4-anisaldehyde *via* general procedure 6 as a yellow oil (98%, 5.05 g).

This product was obtained in as a pink solid (23%, 0.53 g) *via* general procedure 7 from 4'-methoxyphenyl-3-prop-2-enoic acid. M.p. 66 – 68 °C.

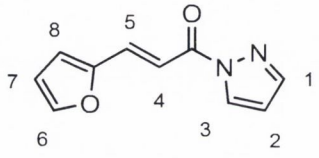
δ_H (400 MHz, $CDCl_3$): 3.83 (s, 3H, H-10), 6.45 (dd, 1H, *J* 2.4, 2.4 Hz, H-2), 6.91 (d, 2H, *J* 8.4 Hz, H-7 and H-8), 7.62 (d, 2H, *J* 8.4 Hz, H-6 and H-9), 7.72 – 7.75 (m, 3H, H-3, H-4 and H-5), 8.36 (d, 1H, *J* 2.4 Hz, H-1).

δ_C (100 MHz, $CDCl_3$): 55.4 (CH_3), 109.5 (CH), 113.0 (CH), 114.4 (CH), 127.3 (C), 128.6 (CH), 130.7 (CH), 143.6 (CH), 147.7 (CH), 162.1 (C), 163.8 (C).

HRMS (*m/z* – EI) Found 228.0896 (M^+ $C_{13}H_{12}N_2O_2$ requires: 228.0899).

V_{max} (film)/cm^{-1} 3120, 2931, 1700, 1595, 1595, 1417, 1384, 1238, 1093, 937, 866, 803, 768.

(*E*)-3-(Furan-2-yl)-1-(1H-pyrazol-1-yl)prop-2-en-1-one (649)



Ethyl furyl-3-prop-2-enoate was obtained from furfural *via* general procedure 6 as a yellow oil (64%, 2.66 g).

This product was obtained as a brown solid (76%, 1.43 g) *via* general procedure 7 from ethyl furyl-3-prop-2-enoate. M.p. 64 - 68 °C.

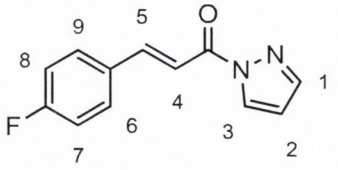
δ_H (400 MHz, $CDCl_3$): 6.45 – 6.50 (m, 2H, H-8 and H-7), 6.75 (app. d, 1H, H-2), 7.52 (d, 1H, *J* 0.8 Hz, H-6), 7.73 – 7.74 (m, 3H, H-3, H-4 and H-5), 8.34 (d, 1H, *J* 2.8 Hz, H-1).

δ_C (100 MHz, $CDCl_3$): 109.7 (CH), 112.7 (CH), 113.3 (CH), 116.7 (CH), 128.6 (CH), 133.4 (CH), 143.8 (CH), 145.6 (CH), 151.4 (C), 163.7 (C).

HRMS (*m/z* – EI^+) Found 211.0483 (M^+ + Na $C_{10}H_8N_2O_2Na$ requires: 211.0486).

V_{max} (film)/cm^{-1} 3120, 2914, 1688, 1615, 1531, 1413, 1381, 1345, 1206, 1159, 1091, 979, 928, 761.

(*E*)-3-(4-Fluorophenyl)-1-(1H-pyrazol-1-yl)prop-2-en-1-one (640)



Ethyl 4'-fluorophenyl-3-prop-2-enoate was obtained from furfural *via* general procedure 6 as a colourless oil (97%, 4.71g).

This product was obtained as a white solid (80%, 1.83 g) *via* general procedure 7 from ethyl 4'-fluorophenyl-3-prop-2-enoate. M.p. 114 - 118 °C.

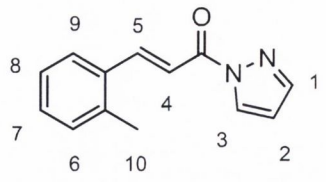
δ_H (400 MHz, $CDCl_3$): 6.48 (dd, 1H, *J* 2.8, 2.8 Hz, H-2), 7.08 – 7.12 (app. t, 2H, H-7 and H-8), 7.65 – 7.69 (m, 2H, H-6 and H-9), 7.76 (app. s, 1H, H-3) 7.82 (d, 2H, *J* 16.0 Hz, H-5), 7.96 (d, 1H, *J* 16.0 Hz, H-4), 8.37 (d, 1H, *J* 2.8 Hz, H-1).

δ_C (100 MHz, $CDCl_3$): 109.9 (CH), 115.5 (q, *J* 2.4 Hz), 116.1 (CH, *J* 21.8 Hz), 128.7 (CH), 130.7 (CH, *J* 2.3 Hz), 130.8 (CH, *J* 7.6 Hz), 143.9 (CH), 146.4 (CH, *J* 0.9 Hz), 163.5 (C), 164.3 (CF, d, *J* 251.4 Hz).

HRMS (*m/z* – EI^+) Found 216.0636 (M^+ $C_{12}H_9N_2OF$ requires: 216.0626).

V_{max} (film)/cm^{-1} 3149, 3044, 1696, 1622, 1592, 1507, 1415, 1382, 1348, 1221, 1203, 1092, 993, 911, 827, 768.

(*E*)-1-(1H-Pyrazol-1-yl)-3-(o-tolyl)prop-2-en-1-one (642)



Ethyl 2'-methylphenyl-3-prop-2-enoate was obtained from 2-methylbenzaldehyde *via* general procedure 6 as a colourless oil (88%, 4.18 g).

This product was obtained as a yellow solid in (68%, 1.44 g) *via* general procedure 7 from ethyl 2'-methylphenyl-3-prop-2-enoate. M.p. 42 - 46 °C.

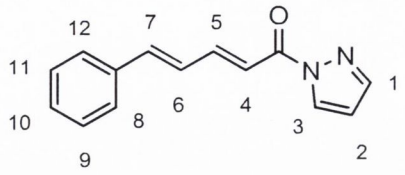
δ_H (400 MHz, $CDCl_3$): 2.49 (s, 3H, H-10), 6.47 (dd, 1H, 1.2, 2.8 Hz, H-2), 7.20 – 7.24 (app. t, 1H, H-8), 7.28 – 7.32 (app. t, 1H, H-7), 7.75 – 7.77 (m, 2H, H-3 and H-9), 7.83 (d, 1H, *J* 15.9 Hz, H-5), 8.31 (d, 1H, *J* 15.9 Hz, H-4), 8.37 – 8.38 (m, 1H, H-1).

δ_C (100 MHz, $CDCl_3$): 109.7 (CH_3), 118.8 (C), 126.6 (CH), 127.5 (CH), 128.6 (CH), 128.8 (CH), 128.9 (CH), 129.5 (CH), 135.8 (C), 142.7 (CH), 143.7 (CH), 147.8 (CH), 163.7 (C).

HRMS (*m/z* – EI^+) Found 235.0847 (M^+ + Na $C_{13}H_{12}N_2ONa$ requires: 235.0844).

V_{max} (film)/cm^{-1} 3112, 3018, 1697, 1618, 1597, 1382, 1347, 1232, 1200, 1093, 1027, 978, 933, 814, 758.

(2*E*,4*E*)-5-Phenyl-1-(1H-pyrazol-1-yl)penta-2,4-dien-1-one (647)



Ethyl phenyl-5-pent-2,4-dienoate was obtained from cinnamaldehyde *via* general procedure 6 as a colourless oil (86%, 4.51 g).

This product was obtained as a yellow solid (44%, 987 mg) *via* general procedure 7 from ethyl phenyl-5-pent-2,4-dienoate. M.p. 62 – 66 °C.

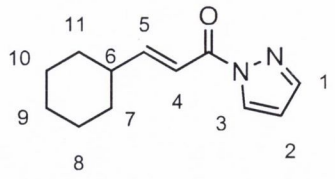
δ_H (400 MHz, $CDCl_3$): 6.44 – 6.45 (m, 1H, H-2), 7.03 – 7.04 (m, 2H, H-6 and H-7), 7.29 – 7.49 (m, 6H, H-5, H-8, H-9, H-10, H-11 and H-12), 7.74 – 7.80 (m, 2H, H-3 and H-4), 8.34 – 8.35 (m, 1H, H-1).

δ_C (100 MHz, $CDCl_3$): 109.7 (CH), 118.8 (CH), 126.6 (CH), 127.5 (CH), 128.6 (CH), 128.9 (CH), 129.5 (CH), 135.8 (C), 142.7 (CH), 143.7 (CH), 147.8 (CH), 163.6 (C).

HRMS (*m/z* – EI^+) Found 224.0950 (M^+ $C_{14}H_{12}N_2O$ requires: 224.0947).

V_{max} (film)/cm^{-1} 3120, 3029, 1689, 1601, 1531, 1448, 1382, 1335, 1243, 1086, 1027, 999, 836, 766, 685.

(*E*)-3-Cyclohexyl-1-(1H-pyrazol-1-yl)prop-2-en-1-one (644)



Ethyl cyclohexyl-3-prop-2-enoate was obtained from cyclohexanecarboxaldehyde *via* general procedure 6 as a colourless oil (86%, 3.92 g).

This product was obtained in colourless oil (51%, 1.05 g) *via* general procedure 7 from ethyl cyclohexyl-3-prop-2-enoate.

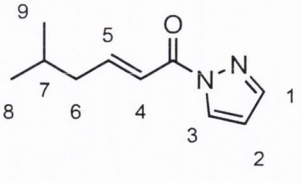
δ_H (400 MHz, $CDCl_3$): 1.12 – 1.35 (m, 4H, H_a-8, H-9 and H_b-10), 1.63 – 1.84 (m, 6H, H-7, H_b-8, H_b-10 and H-11), 2.22 – 2.31 (m, 1H, H-6), 6.41 (dd, 1H, *J* 1.5, 2.8 Hz, H-2), 7.17 – 7.30 (m, 2H, H-4 and H-5), 7.69 (app. s, 1H, H-3), 8.30 (d, 1H, *J* 2.8 Hz, H-1).

δ_C (100 MHz, $CDCl_3$): 25.6 (CH_2), 25.9 (CH_2), 31.6 (CH_2), 41.2 (CH), 109.6 (CH), 116.9 (CH), 128.6 (CH), 143.7 (CH), 158.4 (CH), 163.6 (C).

HRMS (*m/z* – EI^+) Found 227.1160 (M^+ + Na $C_{12}H_{16}N_2ONa$ requires: 227.1163).

V_{max} (film)/cm^{-1}: 1730, 1645, 1502, 1455, 1377, 1302, 1081, 992, 946, 897, 792.

(*E*)-5-Methyl-1-(1H-pyrazol-1-yl)hex-2-en-1-one (685)



Ethyl methyl-5-hex-2-enoate was obtained from valeraldehyde *via* general procedure 6 as a colourless oil (94%, 3.66 g).

This product was obtained as an orange oil (66%, 1.18 g) *via* general procedure 7 from ethyl methyl-5-hex-2-enoate.

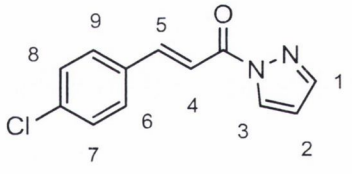
δ_H (400 MHz, $CDCl_3$): 0.96 (d, 6H, *J* 3.6 Hz, H-8 and H-9), 1.78 – 1.88 (sept, 1H, *J* 6.7 Hz, H-7), 2.24 (dd, 2H, *J* 2.8, 6.8 Hz, H-6), 6.43 (dd, 1H, *J* 1.6, 2.8 Hz, H-2), 7.22 – 7.34 (m, 2H, H-4 and H-5), 7.71 (app. s, 1H, H-3), 8.31 (d, 1H, *J* 2.8 Hz, H-1).

δ_C (100 MHz, $CDCl_3$): 22.0 (CH_3), 27.5 (CH), 41.7 (CH_2), 109.2 (CH), 119.7 (CH), 128.3 (CH), 143.3 (CH), 152.3 (CH), 162.7 (C).

HRMS (*m/z* – ESI^+) Found 179.1191 ($M^+ + H$ $C_{10}H_{15}N_2O$ requires: 179.1184).

V_{max} (film)/cm^{-1} 2957, 2871, 1713, 1640, 1531, 1414, 1381, 1353, 1241, 1198, 1093, 1017, 986, 889, 844, 795.

(*E*)-3-(4-Chlorophenyl)-1-(1H-pyrazol-1-yl)prop-2-en-1-one (686)



Ethyl 4'-chlorophenyl-3-prop-2-enoate was obtained from 4-chlorobenzaldehyde *via* general procedure 6 as a colourless oil (94%, 5.11 g).

This product was obtained as a yellow solid (87%, 2.02 g) *via* general procedure 7 from ethyl 4'-chlorophenyl-3-prop-2-enoate. M.p. 100 - 106 °C.

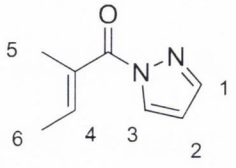
δ_H (400 MHz, $CDCl_3$): 6.47 – 6.48 (m, 1H, H-2), 7.37 (d, 2H, *J* 8.4 Hz, H-7 and H-8), 7.59 (d, 2H, *J* 8.4 Hz, H-6 and H-9), 7.76 (app. s, 1H, H-3), 7.84 (d, 1H, *J* 16.0 Hz, H-5), 7.94 (d, 1H, *J* 16.0 Hz, H-4), 8.36 (d, 1H, 2.8 Hz, H-1).

δ_C (100 MHz, $CDCl_3$): 109.9 (CH), 116.3 (CH), 128.7 (CH), 129.3 (CH), 129.9 (CH), 132.9 (C), 137.0 (C), 143.9 (CH), 146.2 (CH), 163.4 (C).

HRMS (*m/z* – EI^+) Found 232.0403 (M^+ $C_{12}H_9N_2OCl$ requires: 232.0405).

V_{max} (film)/cm^{-1} 3131, 2933, 1695, 1620, 1589, 1488, 1382, 1236, 1201, 1085, 1062, 992, 894, 819, 761.

(*E*)-2-Methyl-1-(1H-pyrazol-1-yl)but-2-en-1-one (628)



This product was obtained as a yellow oil (59%, 8.87 g) *via* general procedure 7 from 2-methyl-but-2-enoic acid.

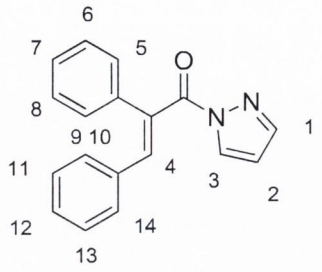
δ_H (400 MHz, $CDCl_3$): 1.87 (d, 3H, *J* 6.8 Hz, H-6), 2.01 (s, 3H, H-5), 6.40 (dd, 1H, *J* 1.6, 2.8 Hz, H-2), 6.77 (q, 1H, *J* 6.8 Hz, H-4), 7.69 (app. s, 1H, H-3), 8.22 (d, 1H, *J* 2.8 Hz, H-1).

δ_C (100 MHz, $CDCl_3$): 13.8 (CH_3), 14.6 (CH_3), 108.8 (CH), 130.1 (CH), 139.4 (C), 140.8 (CH), 143.7 (CH), 168.1 (C).

HRMS (*m/z* - ESI^+) Found: 173.0699 (M^+ + Na $C_8H_{10}N_2ONa$ requires: 173.0691)

νmax (film)/cm^{-1}: 1694, 1378, 1331, 1186, 1028, 935, 867, 722, 668.

(*E*)-2,3-Diphenyl-1-(1H-pyrazol-1-yl)prop-2-en-1-one (631)



A solution of phenylacetic acid (61 mmol, 8.3 g), benzaldehyde (50 mmol, 5 mL) and NEt_3 (5 mL) in acetic anhydride (11 mL) was heated for 24 hours. It was then cooled to room temperature, poured into 2N HCl (100 mL), extracted with CH_2Cl_2 and dried over magnesium sulfate. The solution was filtered, concentrated *in vacuo* and was precipitated from ethyl acetate and hexanes to afford 2,3-diphenylprop-2-enoic acid as a crude white solid (26%, 2.91 g).[213]

The acylpyrazole product **631** was obtained as a red oil (35%, 1.24 g) *via* general procedure 7 from 2,3-diphenylprop-2-enoic acid.

δ_H (400 MHz, $CDCl_3$): 6.44 (dd, 1H, *J* 1.6, 2.8 Hz, H-2), 7.10 – 7.24 (m, 5H, H-10, H-11, H-12, H-13 and H-14), 7.31 – 7.35 (m, 5H, H-5, H-6, H-7, H-8 and H-9) 7.52 (s, 1H, H-4), 7.71 (d, 1H, *J* 1.6 Hz, H-3), 8.28 (d, 1H, *J* 2.8 Hz, H-1).

δ_C (100 MHz, $CDCl_3$): 109.3 (CH), 128.2 (CH), 128.7 (CH), 129.0 (CH), 129.6 (CH), 130.3 (C), 130.4 (C), 135.7 (C), 140.8 (CH), 144.2 (CH), 167.5 (C).

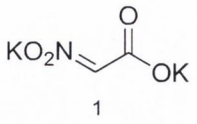
HSQC analysis indicates that the resonance at 128.7 ppm contains 3 carbon atoms, and the resonance at 129.0 contains 2 carbon atoms.

HRMS (*m/z* - EI^+) Found:297.1003 (M^+ + Na $C_{18}H_{14}N_2ONa$ requires 297.1004)

νmax (film)/cm^{-1}: 3046, 1695, 1410, 1210, 1055, 1031, 756, 691, 642.

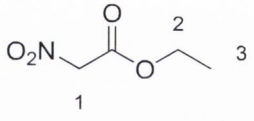
9.5.1 The synthesis of pronucleophiles for the addition to α,β-unsaturated acylpyrazoles

Dipotassium nitroacetate (621)



Nitromethane (0.2 mol, 10.8 mL) was added dropwise over 20 minutes to a solution of potassium hydroxide (0.8 mol, 44.8 g) in water (22.5 mL) at 70 °C. On completion of the addition the reaction vessel was fitted with a reflux condenser and was heated to 160 °C for 1 hour. The solution was then allowed to cool to room temperature and was filtered under vacuum. The filtered salt was washed with methanol (2 x 75 mL) and used without further purification. The salt was isolated as a beige solid (98%, 17.81 g). M.p. 238 – 241 °C. (lit. 240 °C[214]).

Ethyl nitroacetate (622)



To a solution of salt **621** (44 mmol, 8 g) in water (20 mL) at 0 °C, was added dropwise over 20 minutes, a solution of tartaric acid (88 mmol, 13.8 g) in water (20 mL). The solution was stirred for a further 20 minutes and then filtered under vacuum. The resulting filtrate was saturated with sodium chloride and extracted with ice-cold diethyl ether (5 x 50 mL). The extracts were combined, dried over magnesium sulfate and concentrated *in vacuo* under a low heat.

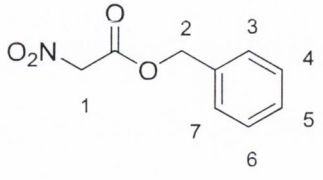
The crude nitroacetic acid (19 mmol, 2 g) was dissolved in distilled THF (40 mL) and ethanol (5 mL) at 0 °C. Then DCC (20 mmol, 4.0 g) was added in one portion and the reaction was allowed to stir overnight at room temperature. The solution was filtered under vacuum, concentrated *in vacuo* and purified by column chromatography, eluting in 10 - 25% ethyl acetate in hexanes, to afford a yellow oil (66%, 1.76 g).

δ_H (400 MHz, $CDCl_3$): 1.36 (t, 3H, *J* 7.2 Hz, H-3), 4.35 (q, 2H, *J* 7.2 Hz, H-2), 5.19 (s, 2H, H-1)

HRMS (*m/z* – EI^+) Found 87.0449 (M^+ - NO_2 $C_4H_7O_2$ requires: 87.0446).

Spectral data for this compound were consistent with those in the literature.[215]

Benzyl nitroacetate (656)



This product was obtained as a yellow oil (34%, 1.26 g) *via* the same procedure for the formation of **622**, substituting benzyl alcohol for ethanol.

δ_H (400 MHz, $CDCl_3$): 5.17 (s, 2H, H-1), 5.26 (s, 2H, H-2), 7.33 – 7.38 (m, 5H, H-3, H-4, H-5, H-6 and H-7)

δ_C (100 MHz, $CDCl_3$): 68.6 (CH_2), 68.7 (CH_2), 128.6 (CH), 128.8 (CH), 129.0 (CH), 134.0 (C), 161.6 (C).

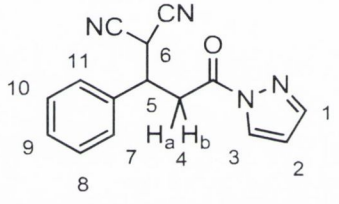
HRMS (*m/z* – EI^+) Found 194.0455 (M^+ - H $C_9H_8NO_4$ requires: 194.0453).

9.6 The products of the 1,4-conjugate addition reactions of malononitrile to α,β-unsaturated acylpyrazoles

General procedure 8: the 1,4-conjugate addition reaction of malononitrile to α,β-unsaturated acylpyrazoles.

A solution of malononitrile (0.48 mmol, 31 mg), α,β-unsaturated acylpyrazole (0.4 mmol) and **Cat. epiQ 283** (0.04 mmol, 29 mg) in CH_2Cl_2 (4 mL) was stirred for the time indicated in a sealed 5 mL round bottomed flask at room temperature. The product was purified by column chromatography, eluting in gradient 10 – 25% ethyl acetate in hexanes.

2-(3-Oxo-1-phenyl-3-(1H-pyrazol-1-yl)propyl)malononitrile (611)



This product was obtained as a white solid (98%, 104 mg, 91% *ee*) *via* general procedure 7. M.p. 88 – 90 °C. $[\alpha]_D^{20}$ +6.50 (*c* 0.60 $CHCl_3$).

CSP-HPLC conditions CHIRALPAK OD-H column (4.6 x 25 cm), hexane/IPA (90/10), 1 cm^3 min^{-1}, RT, UV detection at 220 nm, retention times: 35.4 min and 53.0 min.

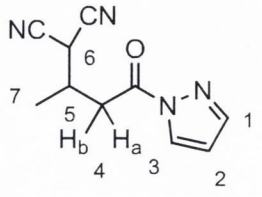
δ_H (400 MHz, $CDCl_3$): 3.75 – 3.82 (dd, 1H, *J* 9.6, 18.6 Hz, H_a-4), 3.91 – 3.97 (m, 2H, H_b-4 and H-5), 4.47 (dd, 1H, 1.2, 5.2 Hz, H-6), 6.45 – 6.46 (m, 1H, H-2), 7.37 – 7.41 (m, 5H, H-7, H-8, H-9, H-10 and H-11), 7.72 (app. s, 1H, H-3), 8.18 (d, 1H, *J* 2.0 Hz, H-1).

δ_C (100 MHz, $CDCl_3$): 29.1 (CH), 36.1 (CH), 41.7 (CH_2), 110.5 (CH), 111.6 (C), 127.9 (CH), 128.5 (CH), 129.3 (CH), 129.4 (CH), 135.7 (C), 144.8 (CH), 168.9 (C).

HRMS (*m/z* – ESI$^-$) Found 263.0933 (M^+ - H $C_{15}H_{11}N_4O$ requires: 263.0927).

V_{max} (film)/cm^{-1}: 2916, 1732, 1391, 1331, 1033, 920, 781, 700, 673.

2-(4-Oxo-4-(1H-pyrazol-1-yl)butan-2-yl)malononitrile (610)



This product was obtained as a yellow oil (99%, 80 mg, 75% *ee*) *via* general procedure 7. $[\alpha]_D^{20}$ +3.49 (*c* 0.63 $CHCl_3$).

CSP-HPLC conditions CHIRALPAK OD-H column (4.6 x 25 cm), hexane/IPA (90/10), 1 cm^3 min^{-1}, RT, UV detection at 220 nm, retention times: 33.7 min and 40.9 min.

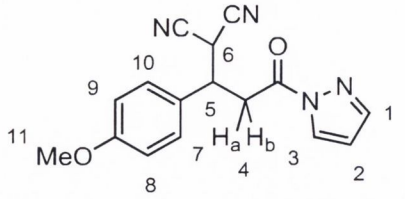
δ_H (400 MHz, $CDCl_3$): 1.40 (d, 3H, *J* 6.8 Hz, H-7), 2.81 – 2.88 (m, 1H, H-5), 3.34 (dd, 1H, *J* 8.0, 18.0, H_a-4), 3.45 (dd, 1H, *J* 5.6, 18.0 Hz, H_b-4), 4.33 (d, 1H, *J* 4.8 Hz, H-6), 6.47 – 6.48 (m, 1H, H-2), 7.73 (app. s, 1H, H-3), 8.22 (d, 1H, *J* 2.8 Hz, H-1).

δ_C (100 MHz, $CDCl_3$): 17.1 (CH_3), 28.0 (CH), 31.9 (CH), 37.0 (CH_2), 110.5 (CH), 112.0 (C), 128.4 (CH), 144.8 (CH), 169.3 (C).

HRMS (*m/z* – ESI$^-$) Found 201.0776 (M^+ - H $C_{10}H_9N_4O$ requires: 201.0778).

V_{max} (film)/cm^{-1}: 1761, 1676, 1518, 1186, 4040, 912, 742.

2-(1-(4-Methoxyphenyl)-3-oxo-3-(1H-pyrazol-1-yl)propyl)malononitrile (650)



This product was obtained as a white solid (82%, 96 mg, 89% *ee*) *via* general procedure 7. M.p. 78 – 82 °C. $[\alpha]_D^{20}$ -9.68 (*c* 0.31 $CHCl_3$).

CSP-HPLC conditions CHIRALPAK OD-H column (4.6 x 25 cm), hexane/IPA (90/10), 1 cm^3 min^{-1}, RT, UV detection at 220 nm, retention times: 40.5 min and 49.0 min.

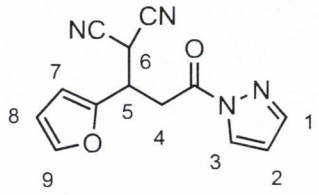
δ_H (400 MHz, $CDCl_3$): 3.71 – 3.78 (m, 4H, H-5 and H-11), 3.87 – 3.94 (m, 2H, H_a-4 and H_b-4), 4.42 (d, 1H, *J* 5.2 Hz, H-6), 6.45 (dd, 1H, *J* 2.4, 2.4 Hz, H-2), 6.90 (d, 2H, *J* 8.8 Hz, H-8 and H-9), 7.30 (d, 2H, *J* 8.8 Hz, H-7 and H-10), 7.72 (app. s, 1H, H-3), 8.17 (d, 1H, *J* 2.4 Hz, H-1).

δ_C (100 MHz, $CDCl_3$): 29.4 (CH), 36.3 (CH_2), 41.1 (CH), 55.3 (CH_3), 110.5 (CH), 111.4 (C), 111.7 (C), 114.7 (CH), 127.5 (C), 128.4 (CH), 129.1 (CH), 144.8 (CH), 160.1 (C), 168.9 (C).

HRMS (*m/z* – ESI-) Found 293.1039 (M^+ – H $C_{16}H_{13}N_4O_2$ requires: 293.1041).

V_{max} (film)/cm^{-1}: 3123, 2259, 1720, 1514, 1392, 1029, 829, 754, 599.

2-(1-(Furan-2-yl)-3-oxo-3-(1H-pyrazol-1-yl)propyl)malononitrile (653)



This product was obtained as a brown oil (63%, 64 mg, 95% *ee*) *via* general procedure 7. $[\alpha]_D^{20}$ +9.68 (*c* 0.31 $CHCl_3$).

CSP-HPLC conditions CHIRALPAK OD-H column (4.6 x 25 cm), hexane/IPA (90/10), 1 cm^3 min^{-1}, RT, UV detection at 220 nm, retention times: 35.2 min and 36.9 min.

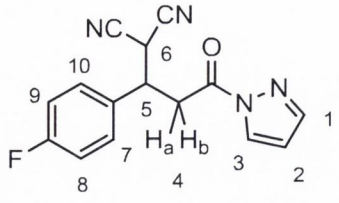
δ_H (400 MHz, $CDCl_3$): 3.72 (dd, 1H, *J* 7.2, 18 Hz, H_a-4), 3.92 (dd, 1H, *J* 6.8, 18 Hz, H_b-4), 4.13 (app. q, 1H, H-5), 4.50 (d, 1H, *J* 5.6 Hz, H-6), 6.35 – 6.37 (m, 1H, H-8), 6.43 (d, 1H, *J* 2.4 Hz, H-7), 6.46 – 6.48 (m, 1H, H-2), 7.41 – 7.42 (m, 1H, H-9), 7.73 (app. s, 1H, H-3), 8.20 (d, 1H, *J* 2.8 Hz, H-1).

δ_C (100 MHz, $CDCl_3$): 27.4 (CH), 34.8 (CH), 36.1 (CH_2), 109.5 (CH), 110.6 (CH), 110.8 (CH), 111.0 (C), 128.5 (CH), 143.6 (CH), 144.9 (CH), 148.6 (C), 168.5 (C).

HRMS (*m/z* – ESI$^-$) Found 253.0726 (M^+ – H $C_{13}H_9N_4O_2$ requires: 253.0733).

V_{max} (film)/cm^{-1}: 2016, 1645, 1513, 1155, 1039, 913, 744, 641.

2-(1-(4-Fluorophenyl)-3-oxo-3-(1H-pyrazol-1-yl)propyl)malononitrile (651)



This product was obtained as a yellow oil (55%, 62 mg, 94% *ee*) *via* general procedure 7. $[\alpha]_D^{20}$ -9.76 (*c* 0.41 $CHCl_3$).

CSP-HPLC conditions CHIRALPAK OD-H column (4.6 x 25 cm), hexane/IPA (90/10), 1 cm^3 min^{-1}, RT, UV detection at 220 nm, retention times: 37.9 min and 44.0 min.

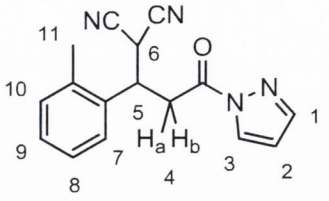
δ_H (400 MHz, $CDCl_3$): 3.73 – 3.81 (m, 1H, H-5), 3.88 – 3.97 (m, 2H, H-4), 4.45 – 4.48 (m, 1H, H-5), 6.47 (dd, 1H, *J* 1.6, 2.4 Hz, H-6) 7.10 (dd, 2H, *J* 1.6, 8.4 Hz, H-7 and H-10), 7.42 (ddd, 2H, *J* 1.6, 5.2, 8.4 Hz, H-8 and H-9), 7.73 (app. s, 1H, H-3), 8.18 (d, 1H, *J* 2.8 Hz, H-1).

δ_C (100 MHz, $CDCl_3$): 29.2 (CH, 1.1 Hz), 36.2 (CH_2), 41.0 (CH), 110.6 (CH), 111.3 (q, *J* 29.2 Hz), 116.4 (CH, *J* 21.6 Hz), 128.5 (CH), 129.8 (CH, *J* 8.4 Hz), 131.4 (CH, *J* 3.4 Hz), 144.9 (CH), 163.0 (CF, *J* 248.0 Hz), 168.8 (C).

HRMS (*m/z* – ESI⁻) Found 281.0839 (M^+ - H $C_{15}H_{10}N_4OF$ requires: 281.0843).

V_{max} (film)/cm^{-1}: 2144, 1647, 1518, 1364, 1155, 913, 744.

2-(3-Oxo-3-(1H-pyrazol-1-yl)-1-(o-tolyl)propyl)malononitrile (652)



This product was obtained as a colourless oil (61%, 68 mg, 92% *ee*) *via* general procedure 7. $[\alpha]_D^{20}$ -24.0 (*c* 0.10 $CHCl_3$).

CSP-HPLC conditions CHIRALPAK OD-H column (4.6 x 25 cm), hexane/IPA (90/10), 1 cm^3 min^{-1}, RT, UV detection at 220 nm, retention times: 21.1 min and 33.6 min.

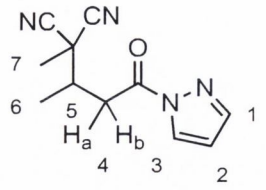
δ_H (400 MHz, $CDCl_3$): 2.47 (s, 3H, H-11), 3.76 (dd, 1H, *J* 4.8, 17.6 Hz, H_a-4), 3.96 (dd, 1H, *J* 7.6, 17.6 Hz, H_b-4), 4.10 (app. q, 1H, H-5), 4.31 (d, 1H, *J* 7.6 Hz, H-6), 6.44 (dd, 1H, *J* 2.8, 2.8 Hz, H-2), 7.22 – 7.24 (m, 3H, H-7, H-9 and H-10), 7.39 – 7.42 (app. t, 1H, H-8), 7.71 (app. s, 1H, H-3), 8.15 (d, 1H, *J* 2.8 Hz, H-1).

δ_C (100 MHz, $CDCl_3$): 19.6 (CH), 36.1 (CH_2), 43.6 (CH), 76.7 (CH_3), 111.2 (C) 125.7 (C), 126.7(CH), 127.1(CH), 127.9(C), 128.4(CH), 128.6 (CH), 131.1 (CH), 131.4, (CH) 144.4(CH), 169.8 (C).

HRMS (*m/z* – ESI$^-$) Found 277.1089 (M^+ – H $C_{16}H_{13}N_4O$ requires: 277.1091).

V_{max} (film)/cm^{-1} 1731, 1420, 1390, 1335, 1264, 1203, 1092, 1035, 920, 732, 703.

2-methyl-2-(4-oxo-4-(1H-pyrazol-1-yl)butan-2-yl)malononitrile (655)



This product was obtained as a colourless oil (72%, 62 mg, 79% *ee*) *via* general procedure 7. $[\alpha]_D^{20}$ -17.23 (*c* 0.47 $CHCl_3$).

CSP-HPLC conditions CHIRALPAK OD-H column (4.6 x 25 cm), hexane/IPA (90/10), 1 cm^3 min^{-1}, RT, UV detection at 220 nm, retention times: 20.6 min and 49.5 min.

δ_H (400 MHz, $CDCl_3$): 1.33 (d, 3H, *J* 6.8 Hz, H-6), 1.84 (s, 3H, H-7), 2.76 – 2.84 (m, 1H, H-5), 3.32 (dd, 1H, *J* 10.0, 17.0 Hz, H_a-4) 3.49 (dd, 1H, *J* 3.3, 17.0 Hz, H_b-4), 6.47 (dd, 1H, *J* 1.6, 2.8 Hz, H-2), 7.72 (d, 1H, *J* 1.6 Hz, H-3), 8.24 (d, 1H, *J* 2.8 Hz, H-1).

δ_C (100 MHz, $CDCl_3$): 15.8 (CH_3), 22.1 (CH_3), 36.3 (C), 36.7 (CH_2), 36.9 (CH), 110.0 (CH), 114.9 (C), 128.0 (CH), 144.2 (CH), 168.5 (C).

HRMS (*m/z* – ESI^+) Found 217.1089 (M^+ + H $C_{11}H_{13}N_4O$ requires: 217.1087).

V_{max} (film)/cm^{-1}: 3229, 2965, 1703, 1458, 1335, 1038, 914, 770.

9.7 The products of the 1,4-conjugate addition reactions of benzyl nitroacetate to α,β-unsaturated acylpyrazoles

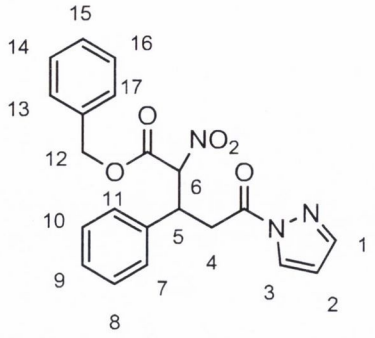
General procedure 8: the 1,4-conjugate addition reaction of benzyl nitroacetate to α,β-unsaturated acylpyrazoles.

A solution of benzyl nitroacetate (0.4 mmol, 78.1 mg), α,β-unsaturated acylpyrazole (0.4 mmol) and **Cat. epiQ 283** (0.04 mmol, 29 mg) in CH_2Cl_2 (4 mL) was stirred for the time indicated in a sealed 5 mL round bottomed flask. The product was purified by column chromatography, eluting in gradient 10 – 25% ethyl acetate in hexanes.

General procedure 9: the debenzylation-decarboxylation of products of the 1,4-conjugate addition reactions of benzyl nitroacetate to α,β-unsaturated acylpyrazoles.

A solution of the 1,4-conjugate addition product (0.2 mmol) and a trace amount of palladium on carbon in THF (3 mL) was fitted with a hydrogen balloon and left to stir for the time indicated. The solution was filtered through a celite plug, concentrated *in vacuo* and filtered through a plug of silica using CH_2Cl_2 as eluent.

Benzyl 2-nitro-5-oxo-3-phenyl-5-(1H-pyrazol-1-yl)pentanoate (657)



This product was obtained as a white solid (99.8%, 157 mg) as a mixture of diastereomers (52 : 48), *via* general procedure 8. M.p. 120 – 122 °C. $[\alpha]_D^{20}$ +19.50 (*c* 0.41 $CHCl_3$).

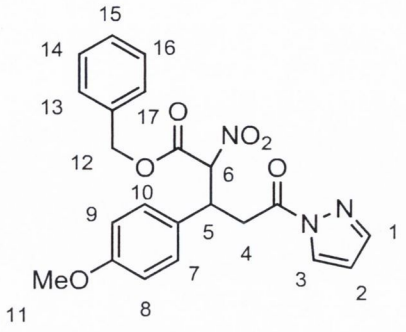
δ_H (400 MHz, $CDCl_3$): 3.65 – 3.78 (m, 1.5H, H-4), 3.94 (dd, 0.5H, *J* 9.6, 17.6 Hz, H-4), 4.42 – 4.48 (m, 1H, H-5), 4.94 – 5.03 (app. q, 1H, H-12), 5.17 – 5.26 (m, 1H, H-12), 5.24 (d, 0.5H, 9.2 Hz, H-6), 5.60 (d, 0.5H, 9.6 Hz, H-6), 6.37 (d, 1H, 0.8 Hz, H-2), 7.26 – 7.35 (m, 10H, H-7, H-8, H-9, H-10, H-11, H-13, H-14, H-15, H-16 and H-17), 7.65 (m, 1H, H-3), 8.01 (app. s, 1H, H-1).

HRMS (*m/z* – ESI^+) Found 416.1222 (M^+ + Na $C_{21}H_{19}N_3O_5Na$ requires: 416.1235).

V_{max} (film)/cm^{-1}: 1744, 1563, 1389, 1221, 1051, 740, 699, 577.

Due to coincident ^{13}C resonances associated with the two diastereometrically related constituents of the product mixture, a list of ^{13}C resonances is not provided here. The ^{13}C spectrum associated with these two diastereomers can be found in Appendix A.

Benzyl 3-(4-methoxyphenyl)-2-nitro-5-oxo-5-(1H-pyrazol-1-yl)pentanoate (663)



This product was obtained as a white solid (91%, 154 mg) as a mixture of diastereomers (53 : 47), *via* general procedure 8. M.p. 89 – 92 °C. $[\alpha]_D^{20}$ +58.64 (*c* 0.44 $CHCl_3$).

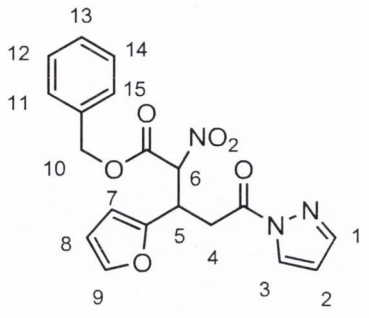
δ_H (400 MHz, $CDCl_3$): 3.54 – 3.81 (m, 4.5H, H-4 and H-11), 3.96 (dd, 0.5H, 1.2, 2.0 Hz, H-4), 4.44 – 4.48 (m, 1H, H-5), 5.04 (app. s, 1H, H-12), 5.22 – 5.31 (m, 1H, H-12), 5.53 (d, 0.5H, 0.8 Hz, H-6), 5.60 (d, 0.5H, 1.2Hz, H-6), 6.42 (app. s, 1H, H-2), 6.77 – 6.83 (m, 2H, H-8 and H-9), 7.19 – 7.29 (m, 2H, H-7 and H-10) 7.31 – 7.41 (m, 5H, H-13, H-14, H-15, H-16 and H-17), 7.70 (app. s, 1H, H-3), 8.13 – 8.15 (m, 1H, H-1).

HRMS (*m/z* – ESI^+) Found 446.1328 (M^+ + Na $C_{22}H_{21}N_3O_6Na$ requires: 446.1332).

V_{max} (film)/cm^{-1}: 1752, 1498, 1369, 1192, 1064, 914, 888, 768.

Due to coincident ^{13}C resonances associated with the two diastereometrically related constituents of the product mixture, a list of ^{13}C resonances is not provided here. The ^{13}C spectrum associated with these two diastereomers can be found in Appendix A.

Benzyl 3-(furan-2-yl)-2-nitro-5-oxo-5-(1H-pyrazol-1-yl)pentanoate (666)



This product was obtained as a grey solid (78%, 119 mg) as a mixture of diastereomers (70 : 30), *via* general procedure 8. M.p. 94 – 97 °C. $[\alpha]_D^{20}$ +20.85 (*c* 0.61 $CHCl_3$).

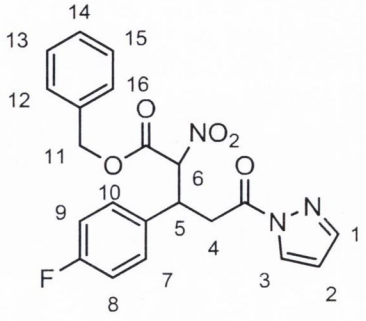
δ_H (400 MHz, $CDCl_3$): 3.55 – 3.69 (m, 1H, H-4), 3.84 (dd, 0.7H, 0.8, 4.0 Hz, H-4), 3.98 (dd, 0.3H, *J* 0.8, 4.0 Hz, H-4), 4.61 – 4.64 (m, 1H, H-5), 5.18 – 5.31 (m, 2H, H-10), 5.68 – 5.73 (m, 1H, H-6), 6.23 – 6.28 (m, 2H, H-2, H-8), 6.47 (app. s, 1H, H-7), 7.29 – 7.40 (m, 6H, H-9, H-11, H-12, H-13, H-14 and H-15), 7.72 (app. s, 1H, H-3), 8.21 (app. s, 1H, H-1).

HRMS (*m/z* – ESI^+) Found 406.1015 (M^+ + Na $C_{19}H_{17}N_3O_6Na$ requires: 406.1020).

V_{max} (film)/cm^{-1} 1746, 1564, 1389, 1328, 1206, 1016, 921, 819.

Due to coincident ^{13}C resonances associated with the two diastereometrically related constituents of the product mixture, a list of ^{13}C resonances is not provided here. The ^{13}C spectrum associated with these two diastereomers can be found in Appendix A.

Benzyl 3-(4-fluorophenyl)-2-nitro-5-oxo-5-(1H-pyrazol-1-yl)pentanoate (664)



This product was obtained as a white solid (88%, 145 mg) as a mixture of diastereomers (52 : 48), *via* general procedure 8. M.p. 80 – 82 °C. $[\alpha]_D^{20}$ +46.78 (*c* 0.59 $CHCl_3$).

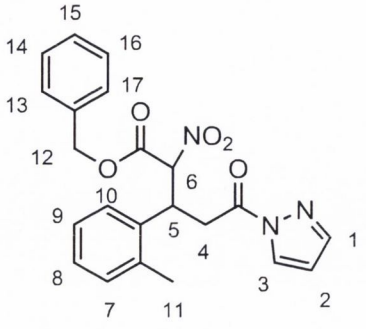
δ_H (400 MHz, $CDCl_3$): 3.48 –3.62 (m, 1H, H-4), 3.71 (d, 0.5H, 8.4 Hz, H-4), 3.86 – 3.93 (m, 0.5H, H-4), 4.42 – 4.44 (m, 1H, H-5), 5.18 (s, 1H, H-11), 5.22 – 5.27 (m, 1H, H-11), 5.49 (d, 0.5H, *J* 9.2 Hz, H-6), 5.56 (d, *J* 9.6 Hz, H-6), 6.39 (app. s, 1H, H-2), 6.88 - 6.96 (m, 2H, H-8 and H-9), 7.09 – 7.11 (m, 1H, H-7 and H-10), 7.19 – 7.36 (m, 6H, H-7, H-10, H-12, H-13, H-14, H-15 and H16), 7.65 – 7.66 (m, 1H, H-3), 8.08 – 8.10 (m, 1H, H-1).

HRMS (*m/z* – ESI^+) Found 410.1152 (M^+ – H $C_{21}H_{17}N_3O_5FNa$ requires: 410.1144).

V_{max} (film)/cm^{-1} 1743, 1563, 1511, 1389, 1232, 1203, 1093, 918, 838, 739, 699.

Due to coincident ^{13}C resonances associated with the two diastereometrically related constituents of the product mixture, a list of ^{13}C resonances is not provided here. The ^{13}C spectrum associated with these two diastereomers can be found in Appendix A.

Benzyl 2-nitro-5-oxo-5-(1H-pyrazol-1-yl)-3-(o-tolyl)pentanoate (665)



This product was obtained as a yellow oil (88%, 121 mg) as a mixture of diastereomers (56 : 44), *via* general procedure 8. $[\alpha]_D^{20}$ +52.08 (*c* 0.24 $CHCl_3$).

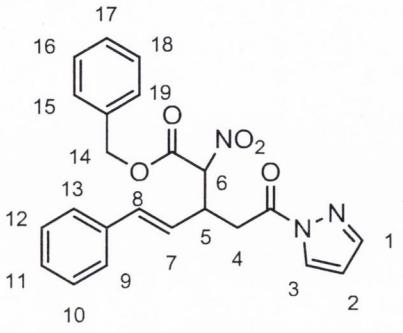
δ_H (400 MHz, $CDCl_3$): 2.48 (s, 1.5H, H-11), 2.52 (s, 1.5H, H-11), 3.54 (dd, 0.5H, *J* 3.6, 17.6 Hz, H-4), 3.65 – 3.80 (m, 1H, H-4), 3.98 (dd, 0.5H, *J* 10.0, 17.6 Hz, H-4), 4.73 – 4.83 (m, 1H, H-5), 4.98 (app. q, 1H, H-12), 5.22 – 5.31 (m, 1H, H-12), 5.55 (d, 0.4H, *J* 10.0 Hz, H-6), 5.64 (d, 0.6H, *J* 10.0 Hz, H-6), 6.414 (app. s, 1H, H-2), 7.07 – 7.41 (m, 9H, H-7, H-8, H-9, H-10, H-13, H-14, H-15, H-16 and H-17), 7.68 – 7.69 (m, 1H, H-3), 8.12 – 8.14 (m, 1H, H-1).

HRMS (*m/z* – ESI^+) Found 430.1379 (M^+ + Na $C_{22}H_{21}N_3O_5Na$ requires: 430.1376).

V_{max} (film)/cm^{-1} 3055, 1745, 1565, 1420, 1264, 896, 730, 702, 549.

Due to coincident ^{13}C resonances associated with the two diastereometrically related constituents of the product mixture, a list of ^{13}C resonances is not provided here. The ^{13}C spectrum associated with these two diastereomers can be found in Appendix A.

(*E*)-benzyl 2-nitro-3-(2-oxo-2-(1H-pyrazol-1-yl)ethyl)-5-phenylpent-4-enoate (667)



This product was obtained as a yellow solid (66%, 111 mg) as a mixture of diastereomers (52 : 48), *via* general procedure 8. M.p. 64 – 68 °C. $[\alpha]_D^{20}$ +20.54 (*c* 0.76 $CHCl_3$).

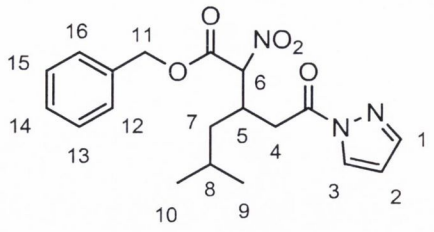
δ_H (400 MHz, $CDCl_3$): 3.38 – 3.49 (m, 1H, H-4), 3.56 – 3.68 (m, 1H, H-4), 3.86 – 4.00 (m, 1H, H-5), 5.17 – 5.30 (m, 2H, H-14), 5.49 – 5.51 (m, 0.5H, H-6), 5.59 – 5.61 (m, 0.5H, H-6), 6.08 (dd, 0.5H, *J* 9.1, 15.8 Hz, H-8), 6.20 (dd, 0.5H, *J* 9.1, 15.8 Hz, H-7), 6.41 – 6.43 (m, 1H, H-2), 6.54 (app. t, 1H H-6), 7.22 – 7.36 (m, 10H, H-9, H-10, H-11, H-12, H-13, H-15, H-16, H-17, H-18 and H-19), 7.67 – 7.68 (m, 1H, H-3), 8.18 – 8.19 (m, 1H, H-1).

HRMS (*m/z* – ESI^+) Found 420.1559 (M^+ + H $C_{21}H_{22}N_3O_5Na$ requires: 420.1566).

V_{max} (film)/cm^{-1} 1743, 1561, 1418, 1388, 1195, 969, 918, 748, 696, 535.

Due to coincident ^{13}C resonances associated with the two diastereometrically related constituents of the product mixture, a list of ^{13}C resonances is not provided here. The ^{13}C spectrum associated with these two diastereomers can be found in Appendix A.

Benzyl 5-methyl-2-nitro-3-(2-oxo-2-(1H-pyrazol-1-yl)ethyl)hexanoate (987)



This product was obtained as a yellow oil (98%, 146 mg) as a mixture of diastereomers (53 : 47), *via* general procedure 8. $[\alpha]_D^{20}$ +10.51 (*c* 0.39 $CHCl_3$).

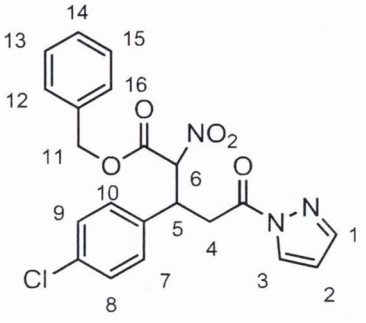
δ_H (400 MHz, $CDCl_3$): 0.83 – 0.89 (m, 6H, H-9 and H-10), 1.24 – 1.35 (m, 1H, H-8), 1.49 – 1.63 (m, 2H, H-7), 3.07 – 3.18 (m, 1H, H-4), 3.34 – 3.39 (m, 2H, H-4 and H-5), 5.18 – 5.27 (m, 2H, H-11), 5.48 (d, 0.5H, *J* 4.8 Hz, H-6), 5.53 (d, 0.5H, *J* 5.6 Hz, H-6), 6.40 – 6.44 (m, 1H, H-2), 7.30 – 7.38 (m, 5H, H-12, H-13, H-14, H-15 and H-16), 7.67 (app. s, 1H, H-3), 8.19 – 8.20 (m, 1H, H-1).

HRMS (*m/z* – ESI^+) Found 396.1535 (M^+ + Na $C_{19}H_{23}N_3O_5Na$ requires: 396.1526).

V_{max} (film)/cm^{-1} 2954, 1742, 1561, 1417, 1388, 1254, 1200, 1088, 921, 750, 698.

Due to coincident ^{13}C resonances associated with the two diastereometrically related constituents of the product mixture, a list of ^{13}C resonances is not provided here. The ^{13}C spectrum associated with these two diastereomers can be found in Appendix A.

Benzyl 3-(4-chlorophenyl)-2-nitro-5-oxo-5-(1H-pyrazol-1-yl)pentanoate (689)



This product was obtained white solid (89%, 152 mg) as a mixture of diastereomers (51 : 49), *via* general procedure 8. M.p. 102 – 105 °C. $[\alpha]_D^{20}$ +46.95 (*c* 0.59 $CHCl_3$).

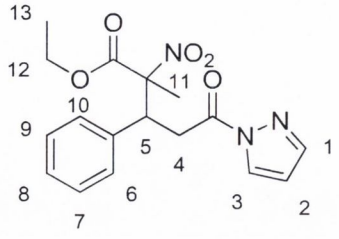
δ_H (400 MHz, $CDCl_3$): 3.48 (dd, 0.5H, *J* 4.0, 17.6 Hz, H-4), 3.59 (dd, 0.5H, *J* 5.2, 17.2 Hz, H-4), 3.73 (dd, 0.5H, *J* 8.8, 17.6, H-4), 3.89 (dd, 0.5 H, *J* 4.0, 18.0 Hz, H-4), 4.41 – 4.42 (m, 1H, H-5), 5.00 – 5.02 (m, 1H, H-11), 5.18 – 5.27 (m, 1H, H-11), 5.49 (d, 0.5H, *J* 9.6 Hz, H-6), 5.56 (d, 0.5H, *J* 9.6 Hz, H-6), 6.38 – 6.40 (m, 1H, H-2), 7.07 – 7.10 (m, 1H, H-8 and H-9), 7.16 – 7.37 (m, 8H, H-7, H-8, H-9, H-10, H-12, H-13, H-14, H-15 and H-16), 7.65 – 7.66 (m, 1H, H-3), 8.08 – 8.10 (m, 1H, H-1).

HRMS (*m/z* – ESI^+) Found 428.1013 (M^+ + H $C_{21}H_{19}N_3O_5Cl$ 428.1003).

V_{max} (film)/cm^{-1} 3125, 2934, 1747, 1550, 1382, 1295, 1198, 1039, 900, 828, 786.

Due to coincident ^{13}C resonances associated with the two diastereometrically related constituents of the product mixture, a list of ^{13}C resonances is not provided here. The ^{13}C spectrum associated with these two diastereomers can be found in Appendix A.

Benzyl 2-methyl-2-nitro-5-oxo-3-phenyl-5-(1H-pyrazol-1-yl)pentanoate (976)



1st diastereomer.

This product was obtained as a yellow solid (26%, 42 mg, 99% *ee*), *via* general procedure 8, utilising ethyl 2-nitropropanoate as pronucleophile in place of benzyl nitroacetate. M.p. 64 – 68 °C. $[\alpha]_D^{20}$ +61.88 (*c* 0.32 $CHCl_3$).

CSP-HPLC conditions CHIRALPAK OD-H column (4.6 x 25 cm), hexane/IPA (90/10), 0.5 cm^3 min^{-1}, RT, UV detection at 220 nm, retention times: 14.6 min and 16.2 min.

δ_H (400 MHz, $CDCl_3$): 1.20 (dt, 3H, *J* 2.0, 9.2 Hz, H-13), 1.75 (d, 3H, *J* 1.6 Hz, H-11), 3.65 (dd, 1H, *J* 2.0, 18 Hz, H-4), 4.11 – 4.20 (m, 3H, H-4 and H-12), 4.45 (dd, 1H, *J* 1.6, 6.8 Hz, H-5), 6.35 (app. d, 1H, H-2), 7.21 – 7.26 (m, 5H, H-6, H-7, H-8, H-9 and H-10), 7.67 (app. s, 1H, H-3), 8.07 (d, 1H, *J* 2.0 Hz, H-1).

δ_C (100 MHz, $CDCl_3$): 13.7 (CH_3), 20.9 (CH_3), 36.0 (CH_2), 45.9 (CH), 63.1 (CH_2), 95.1 (C), 109.7 (CH), 128.3 (CH), 128.4 (CH), 128.7 (CH), 129.7 (CH), 135.9 (C), 144.1 (CH), 166.8 (C), 169.4 (C).

HRMS (*m/z* – ESI^+) Found 431.1457 (M^+ + Na $C_{22}H_{22}N_3O_5Na$ requires: 431.1454).

V_{max} (film)/cm^{-1} 2975, 1736, 1551, 1386, 1201, 1098, 1016, 920, 857, 703.

2^{nd} diastereomer.

This product was obtained as a colourless oil (50%, 82 mg, 99% *ee*), *via* general procedure 8, utilising ethyl 2-nitropropanoate as pronucleophile in place of benzyl nitroacetate. $[\alpha]_D^{20}$ +63.60 (*c* 0.5 $CHCl_3$).

CSP-HPLC conditions CHIRALPAK OD-H column (4.6 x 25 cm), hexane/IPA (90/10), 0.5 cm^3 min^{-1}, RT, UV detection at 220 nm, retention times: 17.6 min and 19.0 min.

δ_H (400 MHz, $CDCl_3$): 1.28 (dt, 3H, *J* 0.8, 8.0 Hz, H-13), 1.77 (d, 3H, *J* 0.8 Hz, H-11), 3.63 (ddd, 1H, *J* 1.2, 2.8, 18 Hz, H-4), 4.07 – 4.14 (m, 1H, H-4), 4.26 – 4.33 (m, 2H, H-12), 4.54 – 4.57 (m, 1H, H-5), 6.35 – 6.36 (m, 1H, H-2), 7.23 – 7.27 (m, 5H, H-6, H-7, H-8, H-9 and H-10), 7.66 (app. s, 1H, H-3), 8.07 – 8.08 (m, 1H, H-1).

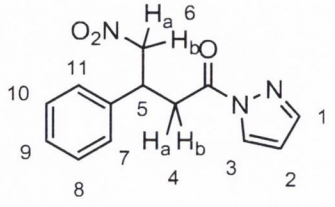
δ_C (100 MHz, $CDCl_3$): 13.7 (CH_3), 20.0 (CH_3), 35.8 (CH_2), 46.1 (CH), 63.1 (CH_2), 95.4 (C), 109.7 (CH), 128.3 (CH), 128.4 (CH), 128.7 (CH), 129.3 (CH), 135.9 (C), 144.0 (CH), 166.3 (C), 169.1 (C).

HRMS (*m/z* – ESI^+) Found 431.1457 (M^+ + Na $C_{22}H_{22}N_3O_5Na$ requires: 431.1454).

V_{max} (film)/cm^{-1} 2975, 1742, 1555, 1388, 1248, 1201, 1125, 922, 770, 703.

9.7.1 The debenzylation of the products of the 1,4-conjugate addition reactions of benzyl nitroacetate to α,β-unsaturated acylpyrazoles

4-Nitro-3-phenyl-1-(1H-pyrazol-1-yl)butan-1-one (658)



This product was obtained as a white solid (97%, 52 mg, 99% *ee*), *via* general procedure 9. M.p. 79 – 82 °C. $[\alpha]_D^{20}$ +27.65 (*c* 0.34 $CHCl_3$).

CSP-HPLC conditions CHIRALPAK OD-H column (4.6 x 25 cm), hexane/IPA (90/10), 0.5 cm^3 min^{-1}, RT, UV detection at 220 nm, retention times: 62.8 min and 66.1 min.

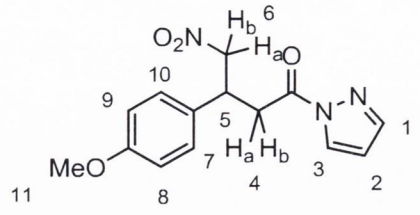
δ_H (400 MHz, $CDCl_3$): 3.54 (dd, 1H, *J* 7.2, 17.6 Hz, H_a-4), 3.71 (dd, 1H, *J* 7.6, 17.6 Hz, H_b-4), 4.21 (app. quin, 1H, H-5), 4.69 (dd, 1H, *J* 8.0, 12.8 Hz, H_a-6), 4.78 (dd, 1H, *J* 7.2, 12.8 Hz, H_b-6), 6.42 (dd, 1H, *J* 1.6, 2.8 Hz, H-2), 7.26 – 7.34 (m, 5H, H-7, H-8, H-9, H-10 and H-11), 7.69 (app. s, 1H, H-3), 8.17 (d, 1H, *J* 2.8 Hz, H-1).

δ_C (100 MHz, $CDCl_3$): 37.3 (CH_2), 39.5 (CH), 79.4 (CH_2), 110.0 (CH), 127.5 (CH), 128.1 (CH), 128.3 (CH), 129.1 (CH), 144.3 (CH), 157.0 (C), 169.1 (C).

HRMS (*m/z* – ESI^+) Found 278.0551 (M^+ + Na $C_{13}H_9N_3O_3Na$ requires: 278.0542).

V_{max} (film)/cm^{-1}: 1721, 1553, 1389, 1196, 1102, 1014, 927, 818.

3-(4-Methoxyphenyl)-4-nitro-1-(1H-pyrazol-1-yl)butan-1-one (669)



This product was obtained as a white solid (99%, 58 mg, 99% *ee*), *via* general procedure 9. M.p. 66 - 68 °C. $[\alpha]_D^{20}$ +35.71(*c* 0.14 $CHCl_3$).

CSP-HPLC conditions CHIRALPAK OD-H column (4.6 x 25 cm), hexane/IPA (90/10), 1 cm^3 min^{-1}, RT, UV detection at 220 nm, retention times: 73.2 min and 85.9 min.

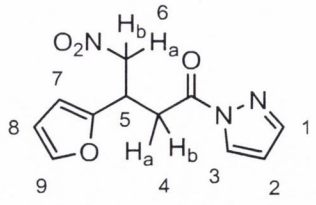
δ_H (400 MHz, $CDCl_3$): 3.50 (dd, 1H, *J* 6.8, 17.3 Hz, H_a-4), 3.65 – 3.75 (m, 4H, H_b-4 and H-11), 4.09 – 4.19 (m, 1H, H-5), 4.64 (dd, 1H, *J* 8.0, 12.2 Hz, H_a-6), 4.74 (dd, 1H, *J* 7.0, 12.2 Hz, H_b-6), 6.41 (app. s, 1H, H-2), 6.83 (d, 2H, *J* 8.4 Hz, H-8 and H-9), 7.18 (d, 2H, *J* 8.4 Hz, H-7 and H-10), 7.68 (app. s, 1H, H-3), 8.17 (app. s, 1H, H-1).

δ_C (100 MHz, $CDCl_3$): 37.4 (CH_2), 38.9 (CH), 55.2 (CH_2), 79.7 (CH_2), 110.0 (CH), 114.4 (CH), 128.3 (CH), 128.5 (CH), 130.0 (C), 144.3 (CH), 159.2 (C), 169.2 (C).

HRMS (*m/z* – ESI^+) Found 308.0659 (M^+ + Na $C_{14}H_{11}N_4O_3Na$ requires: 308.0647).

V_{max} (film)/cm^{-1} 1731, 1553, 1514, 1386, 1252, 1181, 1097, 1034, 920, 833, 756.

3-(Furan-2-yl)-4-nitro-1-(1H-pyrazol-1-yl)butan-1-one (672)



This product was obtained as a yellow oil (98%, 49 mg, 96% *ee*), *via* general procedure 9. $[\alpha]_D^{20}$ -20.60 (*c* 0.15 $CHCl_3$)

CSP-HPLC conditions CHIRALPAK OD-H column (4.6 x 25 cm), hexane/IPA (90/10), 0.5 cm^3 min^{-1}, RT, UV detection at 220 nm, retention times: 35.2 min and 38.5 min.

δ_H (400 MHz, $CDCl_3$): 3.56 (dd, 1H, *J* 7.1, 17.7 Hz, H_a-4), 3.74 (dd, 1H, *J* 7.0, 17.7 Hz, H_b-4), 4.28 – 4.35 (m, 1H, H-5), 4.77 (d, 2H, *J* 6.9 Hz, H-6), 6.20 (d, 1H, *J* 3.2 Hz, H-7), 6.27 – 6.28 (m, 1H, H-8), 6.45 (dd, 1H, *J* 1.4, 2.8 Hz, H-2), 7.32 – 7.33 (m, 1H, H-9), 7.70 (app. s, 1H, H-3), 8.21 (d, 1H, 2.8 Hz, H-1).

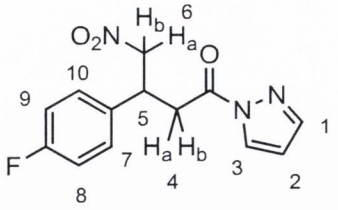
δ_C (100 MHz, $CDCl_3$): 33.0 (CH_2), 34.6 (CH), 107.0 (CH), 109.7 (CH), 110.1 (CH), 128.0 (CH), 142.1 (CH), 144.1 (CH), 150.6 (C), 168.6 (C).

The CH_2NO_2 resonance is obscured by the residual $CHCl_3$ resonances.

HRMS (*m/z* – ESI$^-$) Found 244.0371 (M^+ - H $C_{11}H_6N_3O_4$ requires: 244.0360).

V_{max} (film)/cm^{-1} 1720, 1499, 1354, 1099, 1028, 965, 789, 701

3-(4-Fluorophenyl)-4-nitro-1-(1H-pyrazol-1-yl)butan-1-one (670)



This product was obtained as a white solid (89%, 49 mg, 99% *ee*), *via* general procedure 9. M.p. 42 - 46 °C. $[\alpha]_D^{20}$ +38.0 (*c* 0.10 $CHCl_3$).

CSP-HPLC conditions CHIRALPAK OD-H column (4.6 x 25 cm), hexane/IPA (90/10), 1 cm^3 min^{-1}, RT, UV detection at 220 nm, retention times: 86.5 min and 106.9 min.

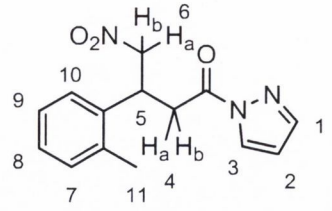
δ_H (400 MHz, $CDCl_3$): 3.51 (dd, 1H, *J* 6.9, 17.4 Hz, H_a-4), 3.68 (dd, 1H, *J* 7.6, 17.4 Hz, H_b-4), 4.16 – 4.23 (m, 1H, H-5), 4.65 (dd, 1H, *J* 8.2 12.6 Hz, H_a-6), 4.76 (dd, 1H, *J* 6.8, 12.6 Hz, H_b-6), 6.42 (dd, 1H, 1.4, 2.8 Hz, H-2), 6.98 – 7.03 (m, 2H, H-8 and H-9), 7.22 – 7.27 (m, 2H, H-7 and H-10), 7.68 (app. s, 1H, H-3), 8.16 (d, 1H, *J* 2.8 Hz, H-1).

δ_C (100 MHz, $CDCl_3$): 37.4 (CH_2), 38.9 (CH), 79.4 (CH_2), 110.2 (CH), 116.0 (CH, *J* 21.4 Hz), 128.4 (CH), 128.9 (C), 129.2 (CH, *J* 8.2 Hz), 144.4 (CH), 162.7 (CF, *J* 245.9), 169.0 (C).

HRMS (*m/z* – ESI$^-$) Found 272. 0540 (M^+ - H $C_{14}H_{10}N_3O_3$ requires: 272.0550).

V_{max} (film)/cm^{-1} 2921, 1727, 1554, 1507, 1389, 1263, 1223, 1092, 1022, 716, 698.

4-Nitro-1-(1H-pyrazol-1-yl)-3-(o-tolyl)butan-1-one (671)



This product was obtained as a yellow oil (92%, 50 mg, 97% *ee*), *via* general procedure 9. $[\alpha]_D^{20}$ +37.00 (*c* 0.10 $CHCl_3$).

CSP-HPLC conditions CHIRALPAK OD-H column (4.6 x 25 cm), hexane/IPA (90/10), 1 cm^3 min^{-1}, RT, UV detection at 220 nm, retention times: 69.4 min and 83.8 min.

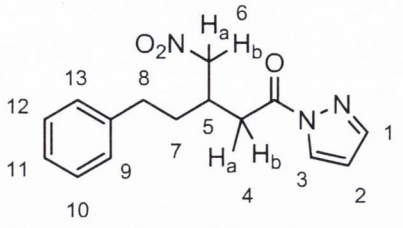
δ_H (400 MHz, $CDCl_3$): 2.45 (s, 3H, H-11), 3.50 (dd, 1H, *J* 6.8, 17.3 Hz, H_a-4), 3.72 (dd, 1H, *J* 7.6, 17.3 Hz, H_b-4), 4.51 (app. quin, 1H, H-5), 4.65 (dd, 1H, *J* 5.3, 12.7 Hz, H_a-6), 4.73 (dd, 1H, *J* 7.6, 12.7 Hz, H_b-6), 6.41 – 6.42 (m, 1H, H-2), 7.13 – 7.21 (m, 4H, H-7, H-8, H-9 and H-10), 7.68 (app. s, 1H, H-3), 8.15 (d, 1H, *J* 2.9 Hz, H-1).

δ_C (100 MHz, $CDCl_3$): 19.6 (CH_3), 34.5 (CH_2), 40.3 (CH), 77.2 (CH_2), 111.5 (C) 126.6 (CH), 127.0 (CH), 128.2 (CH), 128.5 (C), 131.1 (CH), 135.2 (CH), 136.0 (C), 136.3 (CH), 171.4 (C).

HRMS (*m/z* – ESI^+) Found 292.0689 (M^+ + Na $C_{14}H_{11}N_3O_3Na$ requires: 292.0698).

V_{max} (film)/cm^{-1} 2949, 1731, 1554, 1384, 1264, 947, 732, 703.

3-(Nitromethyl)-5-phenyl-1-(1H-pyrazol-1-yl)pent-4-an-1-one (673)



This product was obtained as a yellow oil (97%, 56 mg, 97% *ee*), *via* general procedure 9. $[\alpha]_D^{20}$ +8.89 (*c* 0.09 $CHCl_3$).

CSP-HPLC conditions CHIRALPAK OD-H column (4.6 x 25 cm), hexane/IPA (90/10), 1 cm^3 min^{-1}, RT, UV detection at 220 nm, retention times: 81.6 min and 86.7 min.

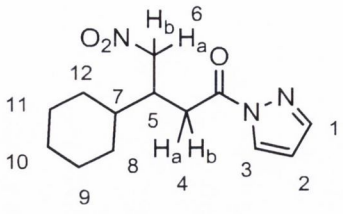
δ_H (400 MHz, $CDCl_3$): 1.81 – 1.86 (app. q, 2H, H-7), 2.70 – 2.74 (t, 2H, *J* 7.6 Hz H-8), 2.87 (app. quin, 1H, H-5), 3.35 – 3.37 (m, 2H, H-4), 4.52 – 4.62 (m, 2H, H-6), 6.45 – 6.46 (m, 1H, H-2), 7.14 – 7.28 (m, 5H, H-9, H-10, H-11, H-12 and H-13), 7.70 (app. s, 1H, H-3), 8.23 (d, 1H, *J* 2.4 Hz, H-1).

δ_C (100 MHz, $CDCl_3$): 32.7 (CH_2), 33.2 (CH_2), 33.3 (CH_2), 35.3 (CH), 78.2 (CH_2), 110.1 (CH), 126.3 (C), 128.2 (CH), 128.3 (CH), 128.6 (CH), 140.6 (CH), 144.3 (CH), 170.0 (C).

HRMS (*m/z* – ESI^+) Found 306.0866 (M^+ + Na $C_{15}H_{13}N_3O_3Na$ requires: 306.0855).

V_{max} (film)/cm^{-1} 2961, 2925, 2864, 1932, 1551, 1461, 1383, 1121, 952, 817.

3-Cyclohexyl-4-nitro-1-(1H-pyrazol-1-yl)butan-1-one (674)



This product was obtained as a yellow oil in 54% overall yield over two steps (0.4 mmol scale, 106 mg, 88% *ee*), *via* general procedure 9. $[\alpha]_D^{20}$ +1.85 (*c* 0.27 $CHCl_3$).

CSP-HPLC conditions CHIRALPAK OD-H column (4.6 x 25 cm), hexane/IPA (90/10), 1 cm^3 min^{-1}, RT, UV detection at 220 nm, retention times: 16.1 min and 17.3 min.

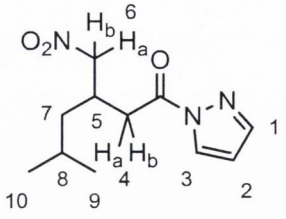
δ_H (400 MHz, $CDCl_3$): 1.00 – 1.55 (m, 6H, H-9, H-10 and H-11), 1.65 – 1.77 (m, 4H, H-8 and H-12), 2.21 – 2.28 (m, 1H, H-7), 2.28 – 2.83 (m, 1H, H-5), 3.18 (dd, 1H, *J* 8.0, 17.7 Hz, H_a-4), 3.36 (m, 1H, *J* 5.2, 17.7 Hz, H_b-4), 4.33 (app. t, 1H, H-2), 4.52 (app. d, 2H, H-6), 6.44 (dd, 1H, *J* 1.1, 2.9 Hz, H-3), 7.70 (d, 1H, *J* 1.1 Hz, H-3), 8.23 (d, 1H, *J* 2.9 Hz, H-1).

δ_C (100 MHz, $CDCl_3$): 26.2 (CH_2), 26.3 (CH_2), 29.3 (CH_2), 29.9 (CH), 33.2 (CH), 38.7 (CH_2), 39.2 (CH_2), 109.9 (CH), 128.3 (CH), 144.2 (CH), 159.6 (C).

HRMS (*m/z* – ESI^+) Found 306.0866 (M^+ + Na $C_{13}H_{15}N_3O_3Na$ requires: 284.1011).

V_{max} (film)/cm^{-1} 2964, 2930, 1734, 1551, 1388, 1278, 1094, 1020, 997, 798, 768.

5-Methyl-3-(nitromethyl)-1-(1H-pyrazol-1-yl)hexan-1-one (688)



This product was obtained as a colourless oil (94%, 48 mg, 80% *ee*), *via* general procedure 9. $[\alpha]_D^{20}$ +7.18 (*c* 0.39 $CHCl_3$).

CSP-HPLC conditions CHIRALPAK OD-H column (4.6 x 25 cm), hexane/IPA (90/10), 1 cm^3 min^{-1}, RT, UV detection at 220 nm, retention times: 18.1 min and 20.6 min.

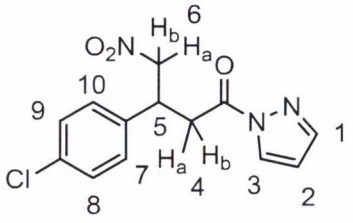
δ_H (400 MHz, $CDCl_3$): 0.93 (t, 6H, *J* 6.8 Hz, H-9 and H-10), 1.34 (q, 1H, *J* 7.1 Hz, H-7), 1.64 – 1.74 (m, 2H, H-8), 2.85 – 2.92 (m, 1H, H-5), 3.28 (d, 2H, *J* 6.4 Hz, H-4), 4.47 – 4.57 (m, 2H, H-6), 6.44 – 6.45 (m, 1H, H-2), 7.69 (app. s, 1H, H-3), 8.23 (d, 1H, *J* 2.8 Hz, H-1).

δ_C (100 MHz, $CDCl_3$): 22.2 (CH_3), 22.5 (CH_3), 25.1 (CH), 31.6 (CH_2), 35.6 (CH), 40.7 (CH_2), 78.7 (CH_2), 109.9 (CH), 128.3 (CH), 144.3 (CH), 170.3 (C).

HRMS (*m/z* – ESI^+) Found 306.0866 (M^+ + Na $C_{11}H_{13}N_3O_3Na$ requires: 258.0855).

V_{max} (film)/cm^{-1}: 1711, 1511, 1481, 1392, 1356, 1248, 935, 896.

3-(4-Chlorophenyl)-4-nitro-1-(1H-pyrazol-1-yl)butan-1-one (690)



This product was obtained as a white solid (95%, 55 mg, 99% *ee*), *via* general procedure 9. M.p. 74 - 78 °C. $[\alpha]_D^{20}$ +35.88 (*c* 0.34 $CHCl_3$).

CSP-HPLC conditions CHIRALPAK OD-H column (4.6 x 25 cm), hexane/IPA (90/10), 1 cm^3 min^{-1}, RT, UV detection at 220 nm, retention times: 76.2 min and 82.3 min.

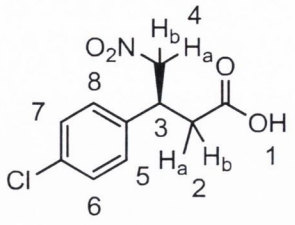
δ_H (400 MHz, $CDCl_3$): 3.53 (dd, 1H, *J* 2.4, 17.6 Hz, H_a-4), 3.67 (dd, 1H, *J* 3.6, 10.4 Hz, H_b-4), 4.07 – 4.22 (m, 1H, H-5), 4.65 (dd, 1H, *J* 8.0, 12.4 Hz, H_a-6), 4.76 (dd, 1H, *J* 6.8, 12.8 Hz, H_b-6), 6.42 – 6.43 (m, 1H, H-2), 7.21 – 7.29 (m, 4H, H-7, H-8, H-9 and H-10), 7.68 (app. s, 1H, H-3), 8.15 (d, 1H, *J* 2.8 Hz, H-1).

δ_C (100 MHz, $CDCl_3$): 37.2 (CH), 39.7 (CH_2), 79.7 (CH_2), 110.4 (CH), 128.8 (CH), 129.3 (CH), 129.7 (CH), 134.4 (C), 137.0 (C), 144.9 (CH), 169.3 (C).

HRMS (*m/z* – ESI^+) Found 292.0489 (M^+ - H $C_{13}H_{11}N_3O_3Cl$ requires: 292.0487).

V_{max} (film)/cm^{-1} 1728, 1544, 1421, 1386, 1322, 1095, 928, 801.

(*R*)-3-(4-Chlorophenyl)-4-nitro-butanoic acid (691)

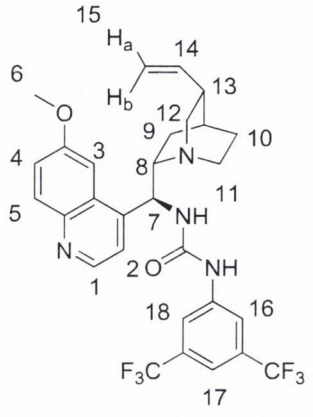


Acylpyrazole **690** (0.17 mmol, 50 mg) was stirred in THF (2 mL) and 2N HCl (5 mL) for 18 hours, diluted with 2N HCl (10 mL) and extracted with $CHCl_3$ (4 x 5 mL). The extracts were combined, dried over magnesium sulfate and concentrated *in vacuo* to afford the acid as a white solid in 99% yield (40 mg). M.p. 68 - 70 °C ($CHCl_3$). (lit. 79 – 81 °C[216]), $[\alpha]_D^{20}$ +5.20 (*c* 0.40 $CHCl_3$). (lit. $[\alpha]_D^{20}$ +10.10 (*c* 1.0 $CHCl_3$[217]).

δ_H (400 MHz, $CDCl_3$): 2.80 (app. quin, 2H, H-2), 3.95 (app. quin, 1H, H-3), 4.60 (ddd, 1H, *J* 0.8, 8.0, 12.6 Hz, H_a-4), 4.70 (ddd, 1H, *J* 0.7, 6.8, 12.6 Hz, H_b-4), 7.16 (d, 2H, *J* 8.1 Hz, H-6 and H-7), 7.31 (d, 2H, *J* 8.1 Hz, H-5 and H-8).

9.8 The synthesis of quinine-derived catalysts

1-(3,5-bis(trifluoromethyl)phenyl)-3-((S)-(6-methoxyquinolin-4-yl)((2S,4S,8R)-8-vinylquinuclidin-2-yl)methyl)urea (**epiQ 273**)



To a solution of quinine (**233**, 5 mmol) and triphenylphosphine (6 mmol) in THF (30 mL) was added diisopropyl azodicarboxylic acid (6 mmol) at 0 °C. The solution was allowed to stir for 10 minutes at this temperature and then diphenylphosphoryl azide (6 mmol) was added dropwise. The solution was then heated to 50 °C for 18 hours, triphenylphosphine (6 mmol) was added in one portion and the solution was stirred for a further 5 hours. The solution was cooled to room temperature and then filtered under vacuum. The filtrate was then acidified with aq. HCl (1M, 10 mL) and concentrated *in vacuo*. The resulting yellow solid was recrystallised from methanol to afford a white crystalline solid.

The solid was dissolved in a solution of CH_2Cl_2 (25 mL) and TEA (20 mmol). To the resulting solution was added 3,5-*bis*-trifluoromethylphenyl isocyanate (5 mmol) and the reaction was allowed to stir for 18 hours. The solution washed with water (20 mL) and concentrated *in vacuo* to afford the crude solid, which was purified by silica gel column chromatography eluting in gradient EtOAc/ MeOH (9/1) to EtOAc/ MeOH (9/1) in 5% TEA to afford a white solid. M.p. 133 - 134 °C (lit. 133.0 – 133.5 °C [218]).

δ_H (400 MHz, $CDCl_3$): 1.50 - 1.53 (m, 1H, H-10), 1.67 - 1.70 (m, 1H, H-10), 1.80 - 1.84 (m, 2H, H-11), 2.21 - 2.24 (m, 1H, H-13), 2.86 (t, 2H , *J* 8.0 Hz, H-12), 2.95 - 3.02 (m, 3H, H-7 and H-8), 3.99 (s, 3H, H-6), 5.12 - 5.15 (m, 2H, H-9 and H_a-15), 5.33 (app. br s, 1H,

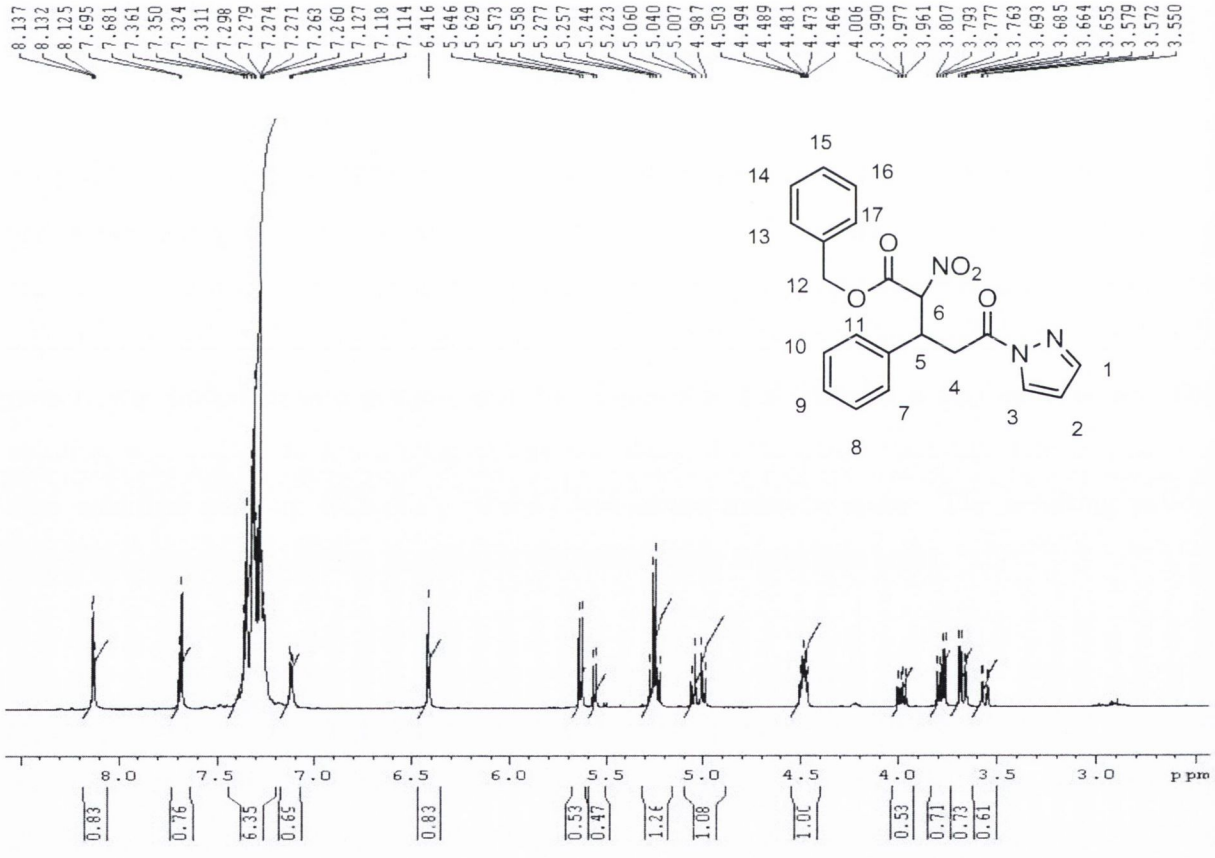
H_b-15), 5.88 (ddd, 1H, *J* 15.0, 10.0, 4.0 Hz, H-14), 6.29 (br s, 1H, N-H), 7.60 (s, 1H, H-17), 7.37 - 7.42 (m, 3H, H-2, H-3 and H-4), 7.78 (s, 2H, H-16 and H-18), 8.05 (d, 1H, *J* 9.5 Hz, H-5), 8.76 (d, 1H, *J* 4.5 Hz, H-1).

10.0 Appendix A

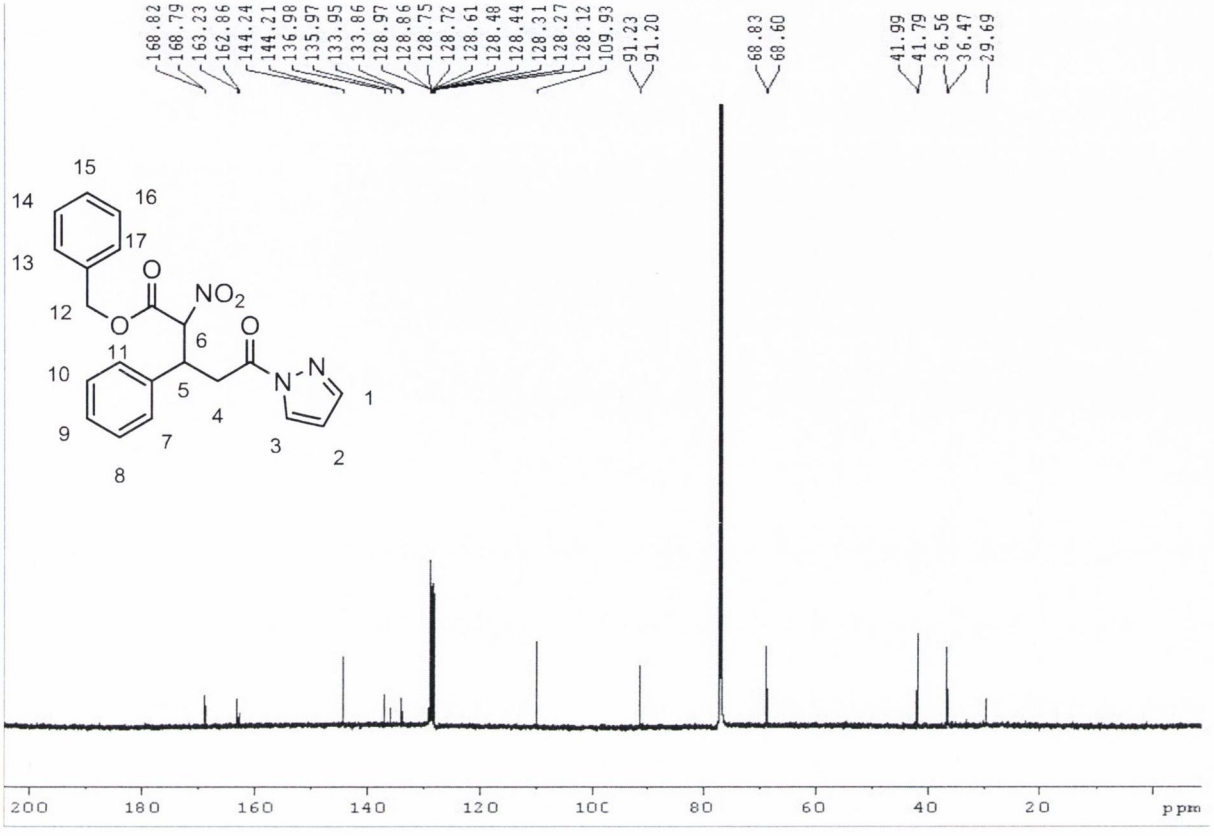
The purpose of this appendix is to demonstrate that the ^{1}H and ^{13}C NMR spectra of the class of diastereomeric compounds derived from the addition of benzyl nitroacetate to β-substituted α,β-unsaturated acylpyrazoles cannot be unambiguously assigned. It also supports the experimental characterisation of the ^{13}C spectra which were not quoted due to coincident unresolved resonances.

10.1 NMR spectra of compound **657**

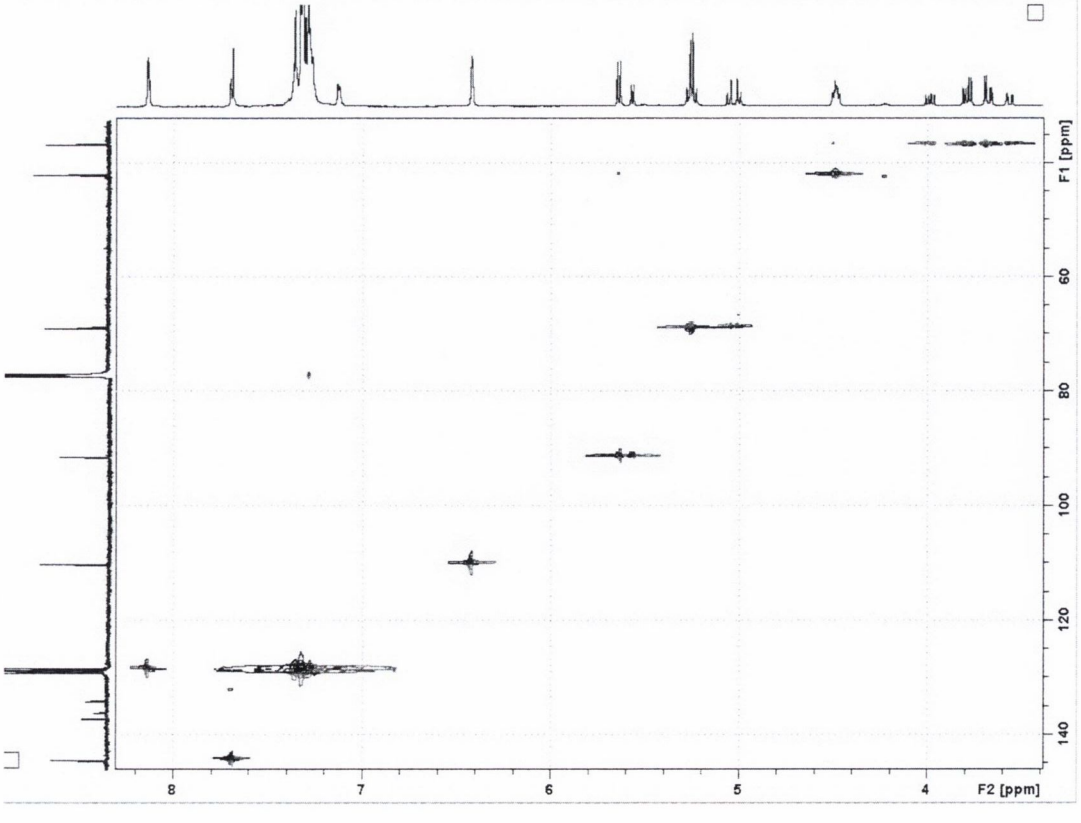
δ_H (400 MHz, $CDCl_3$)



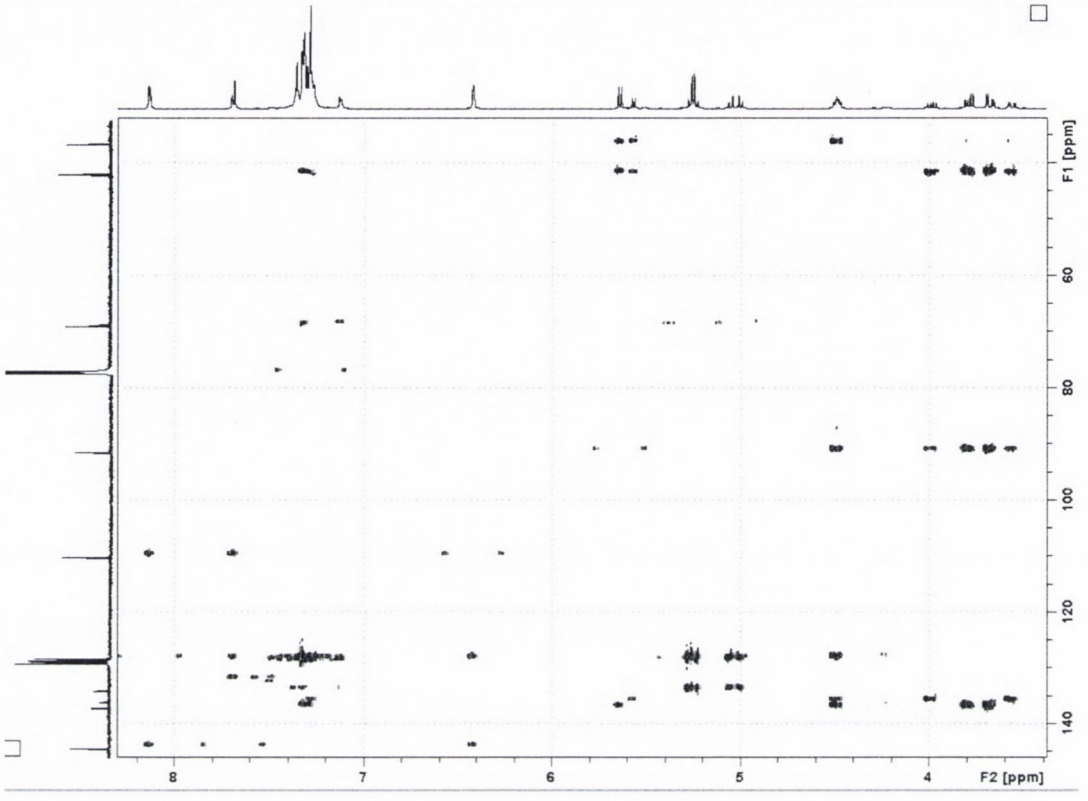
δ_C (100 MHz, $CDCl_3$)



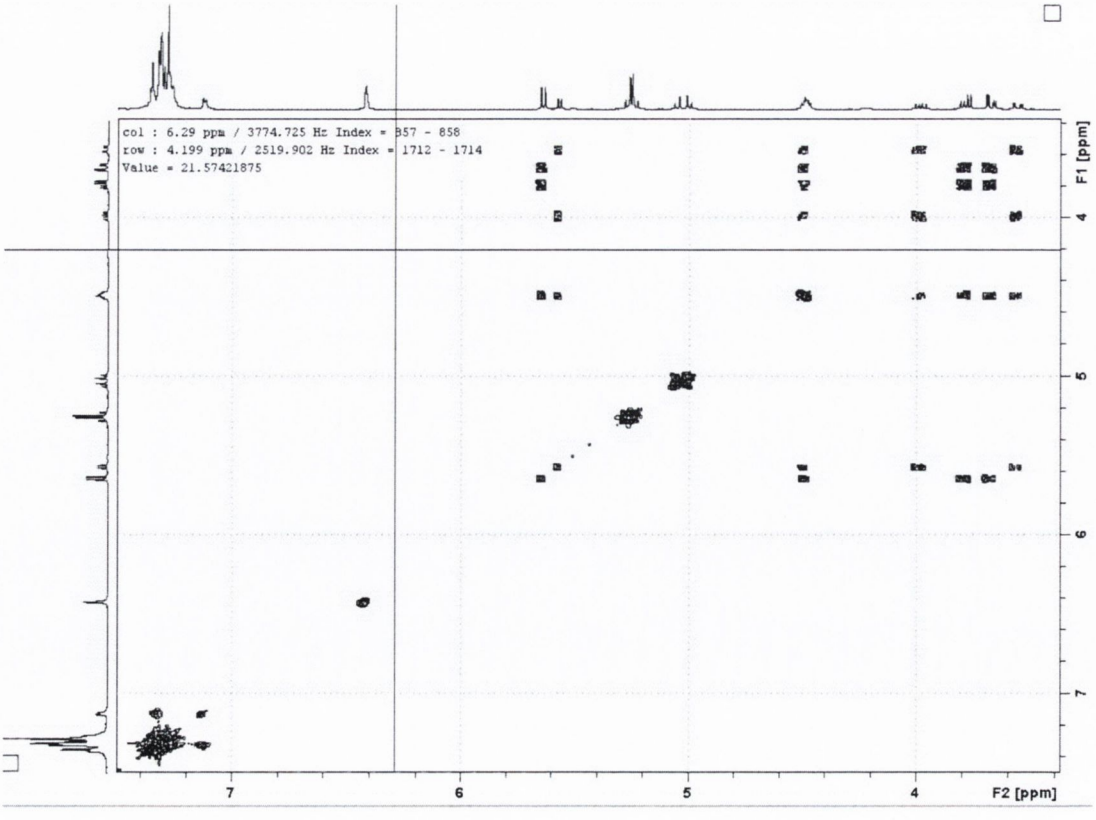
HSQC



HMBC

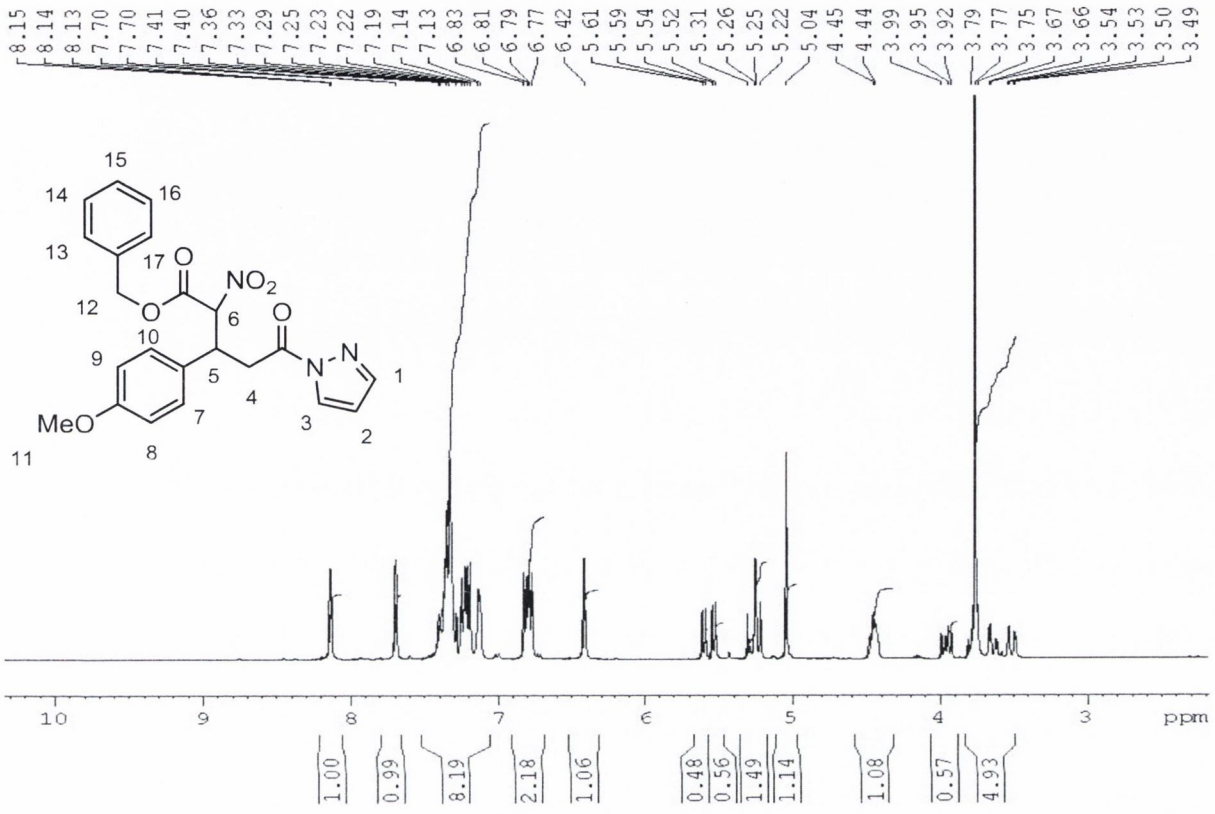

F1 [ppm]
60
80
100
120
140
8
7
6
5
4
F2 [ppm]

HH COSY

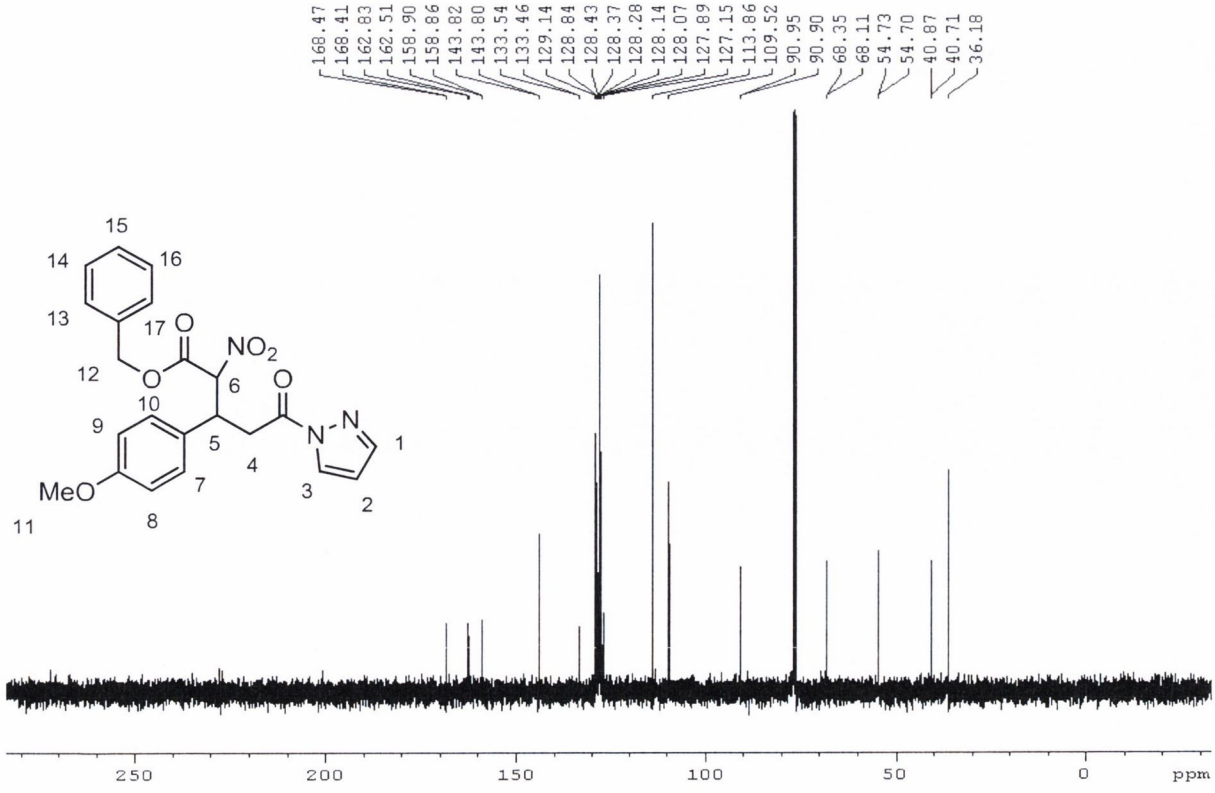

col : 6.29 ppm / 3774.725 Hz Index = 857 - 858
row : 4.199 ppm / 2519.902 Hz Index = 1712 - 1714
Value = 21.57421875
F1 [ppm]
4
5
6
7
7
6
5
4
F2 [ppm]

10.2 NMR spectra of compound **663**

δ_H (400 MHz, $CDCl_3$)

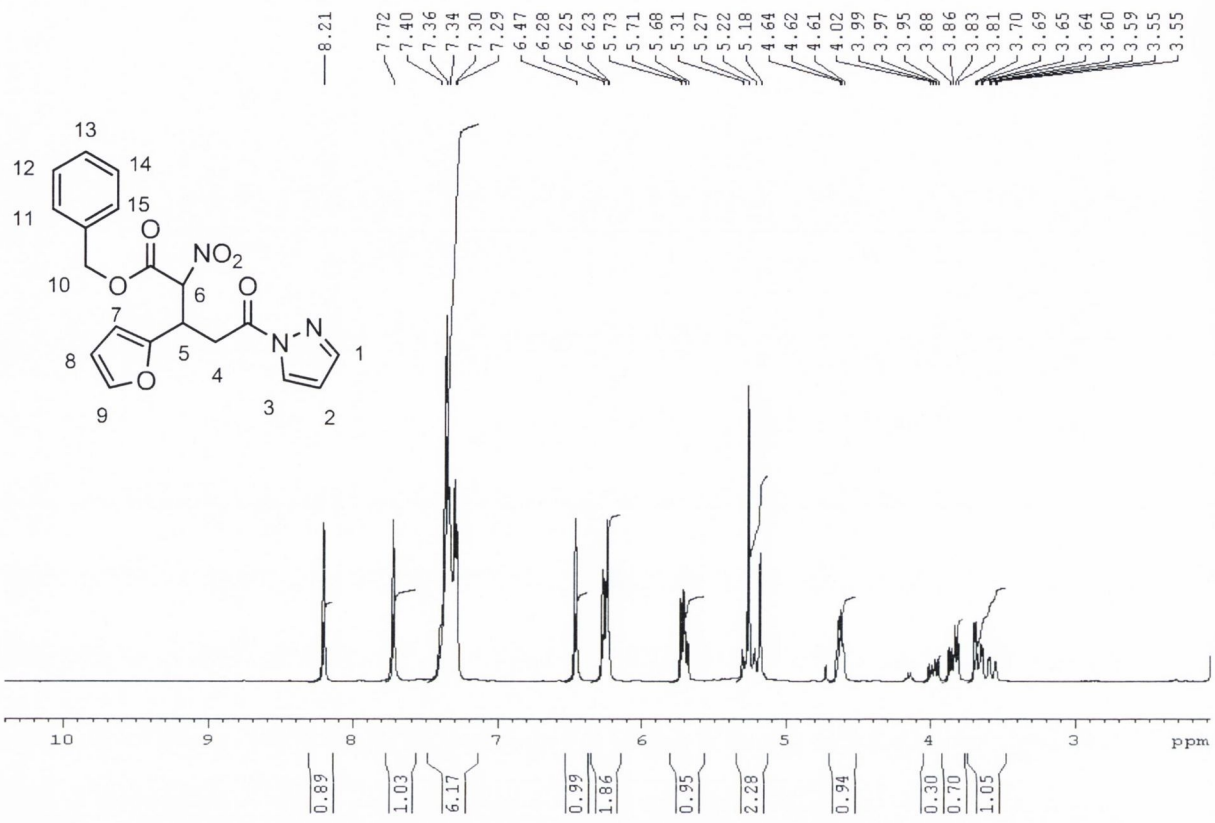


δ_C (100 MHz, $CDCl_3$)

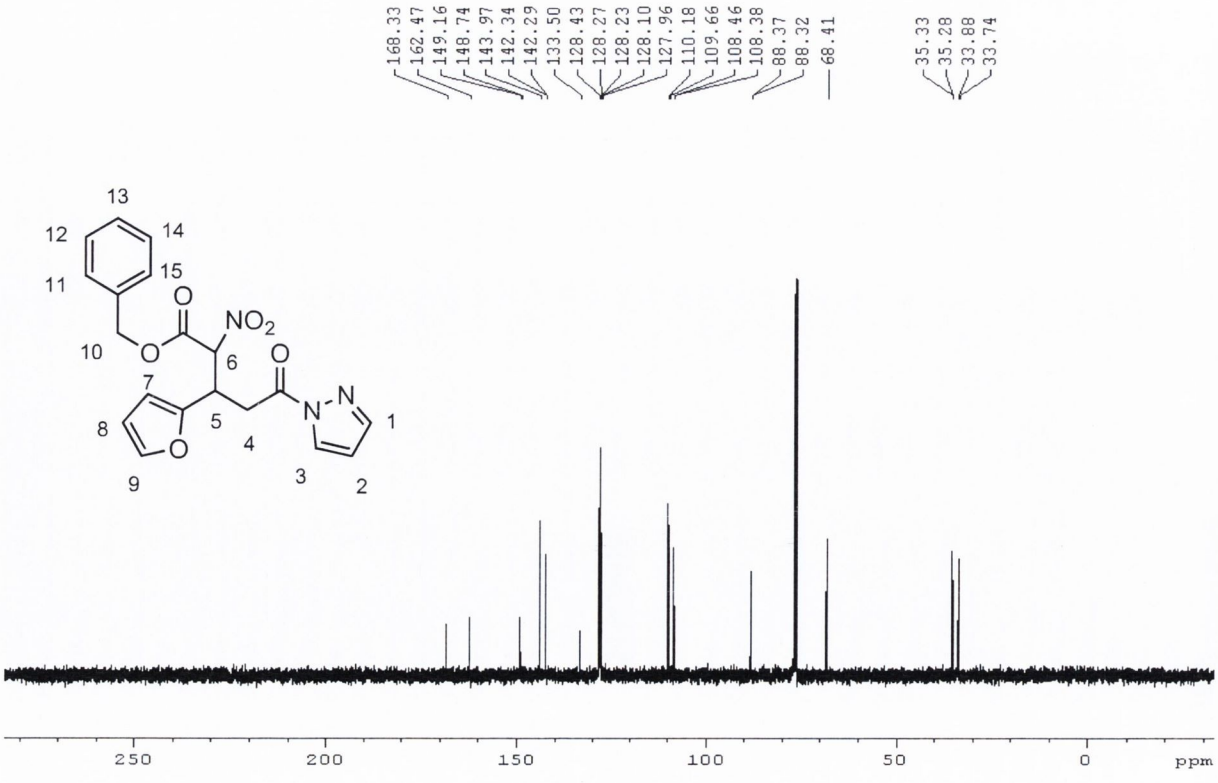


10.3 NMR spectra of compound **664**

δ_H (400 MHz, $CDCl_3$)

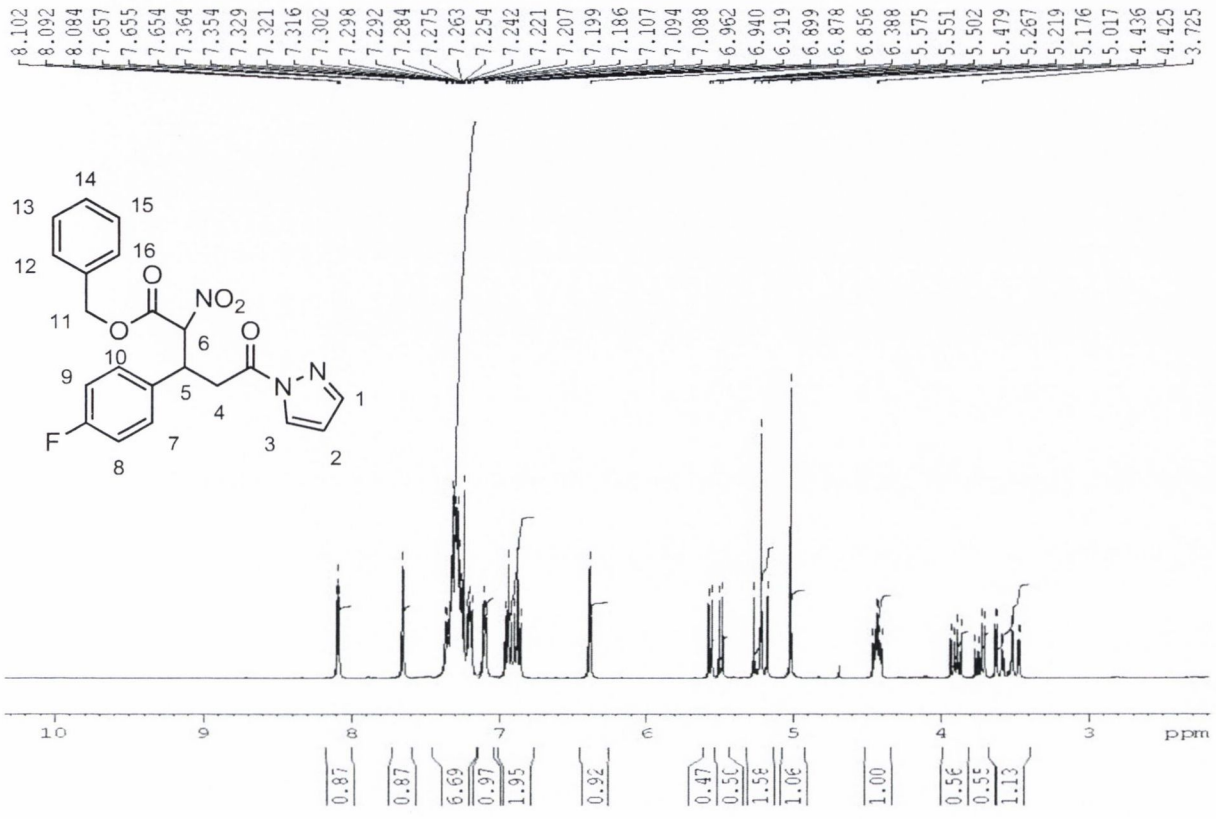


δ_C (100 MHz, $CDCl_3$)

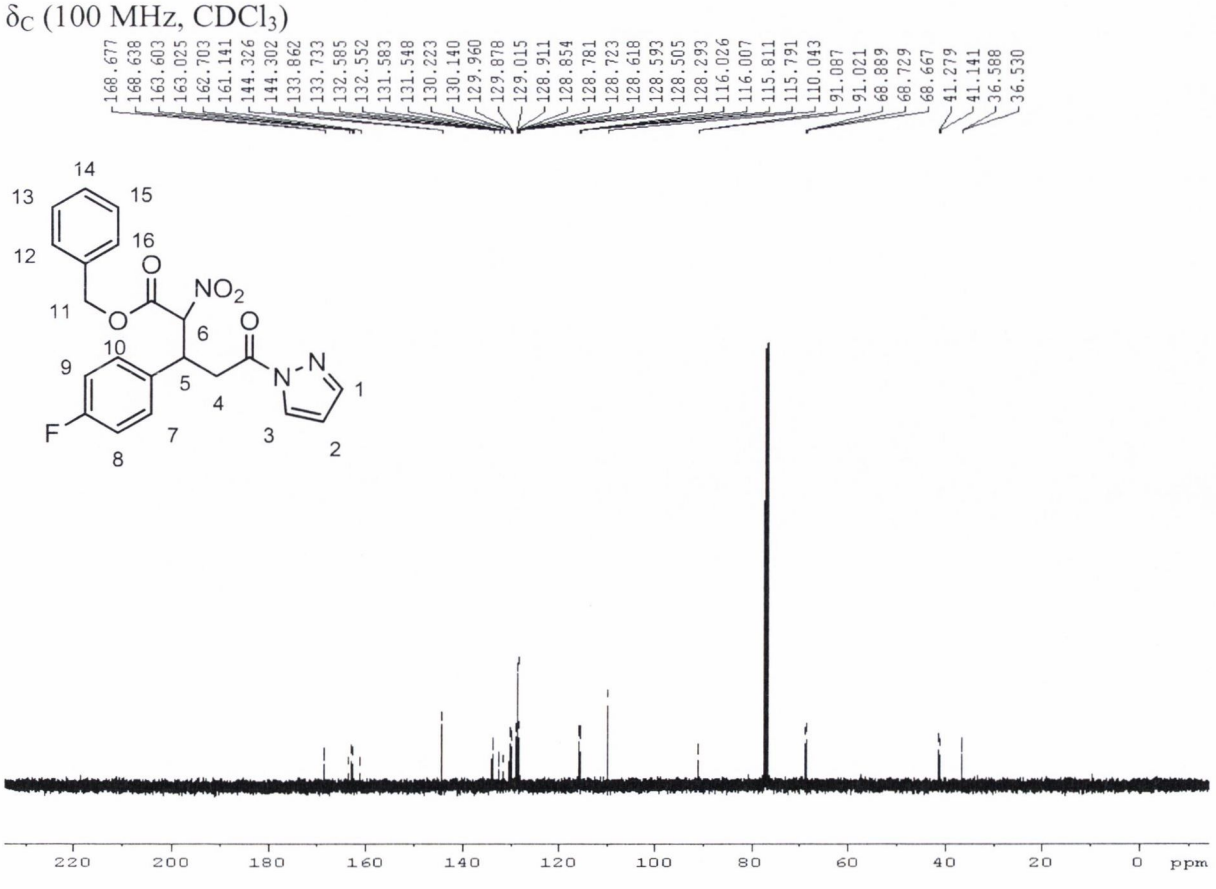


10.4 NMR spectra of compound **665**

δ_H (400 MHz, $CDCl_3$)

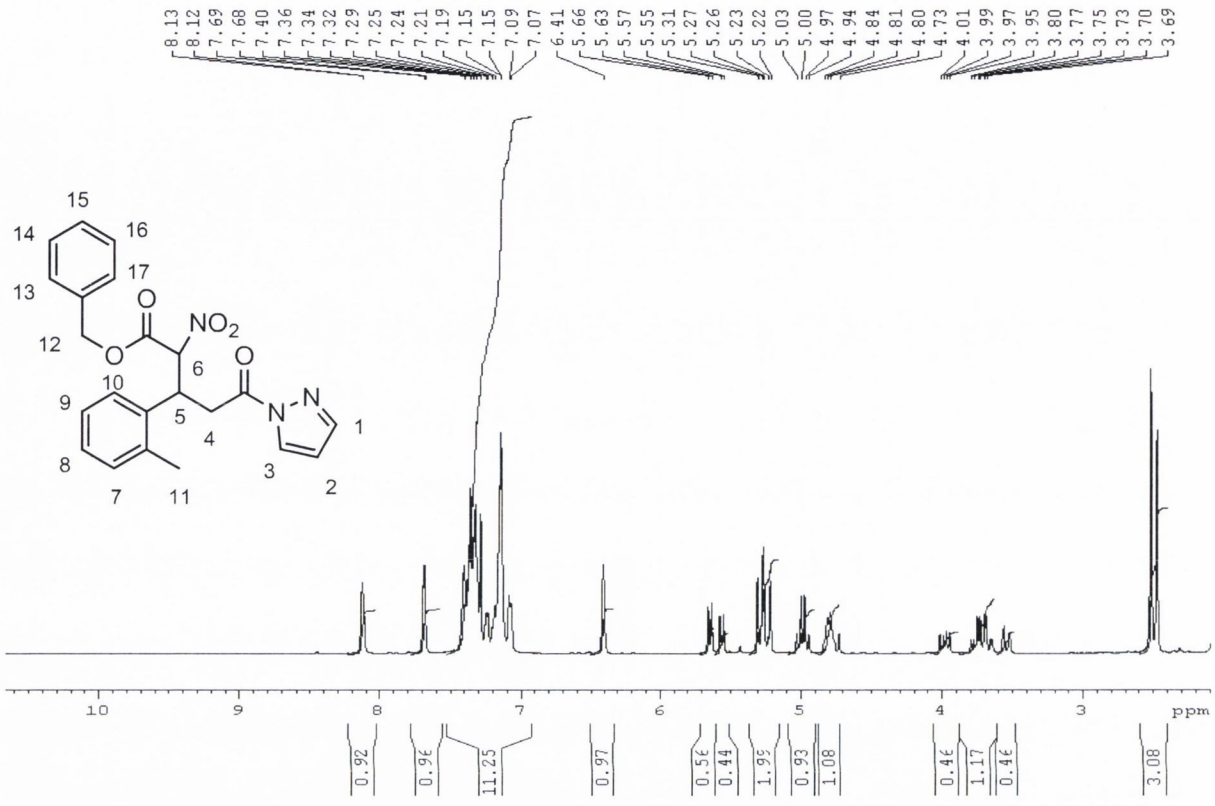


δ_C (100 MHz, $CDCl_3$)

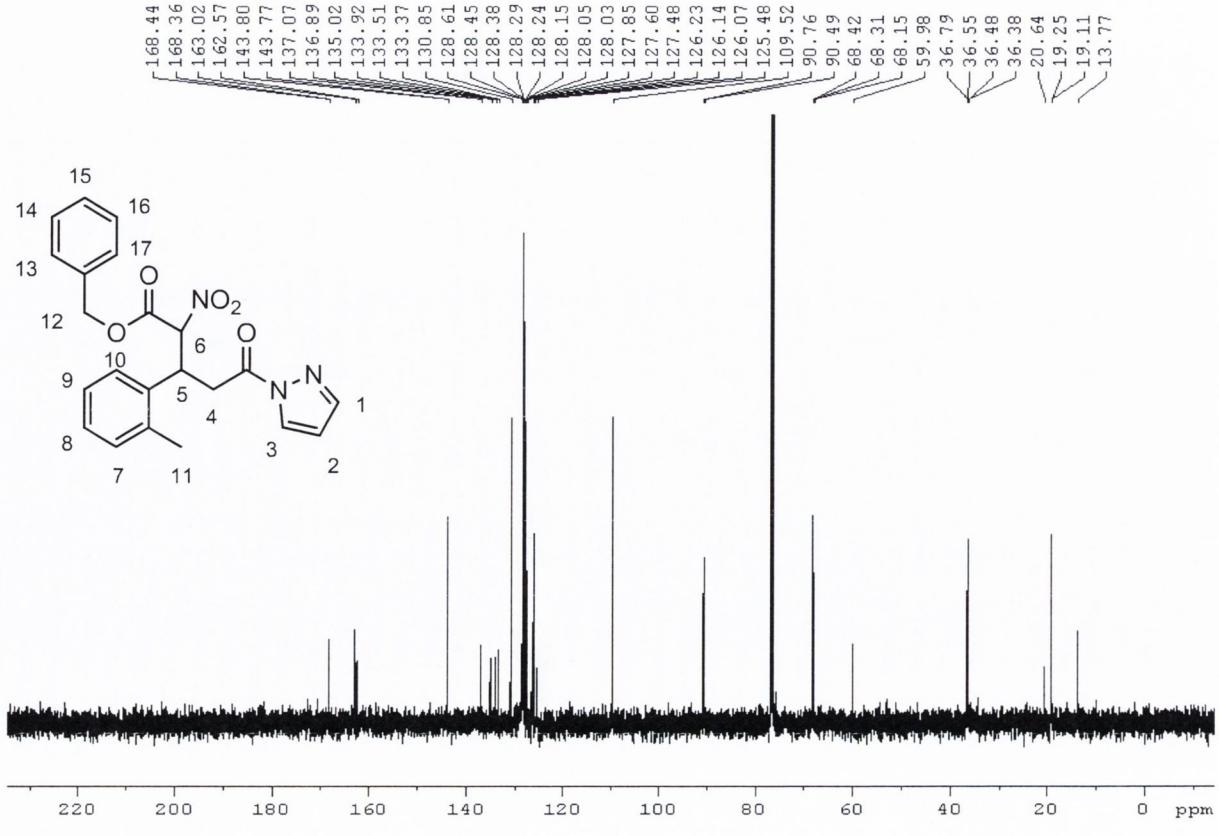


10.5 NMR spectra of compound **666**

δ_H (400 MHz, $CDCl_3$)

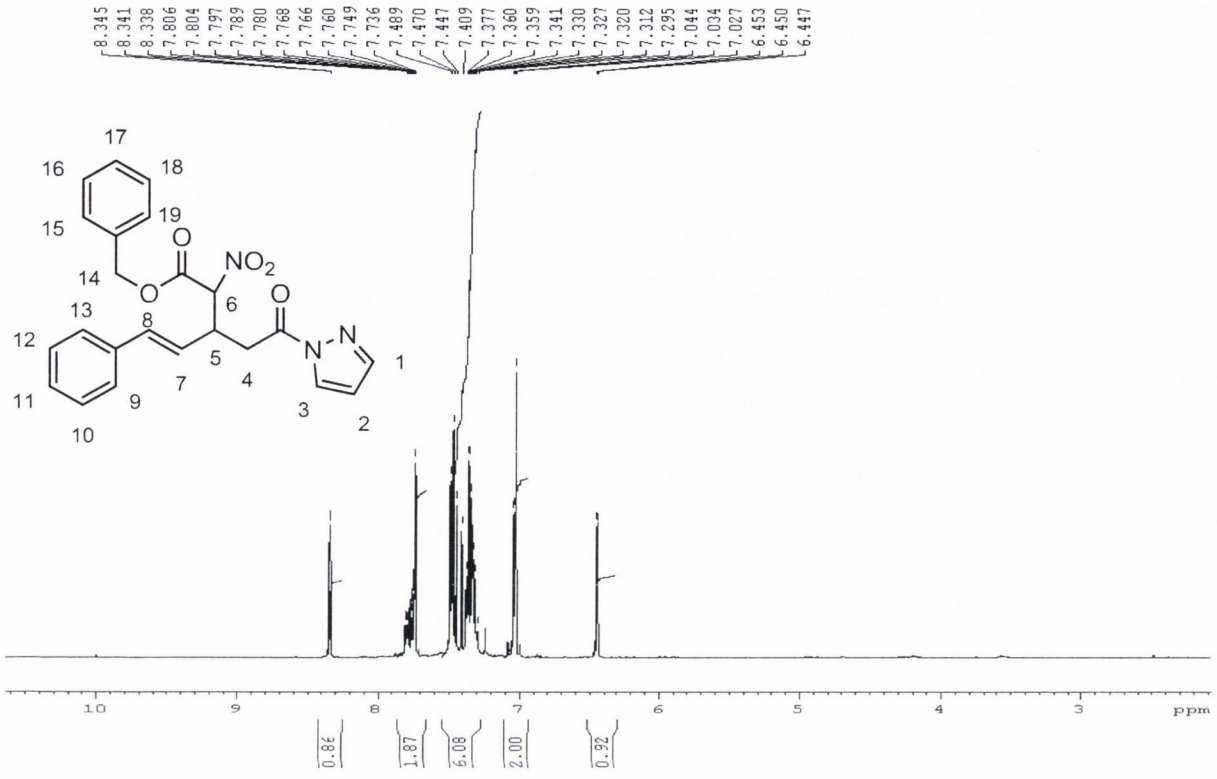


δ_C (100 MHz, $CDCl_3$)

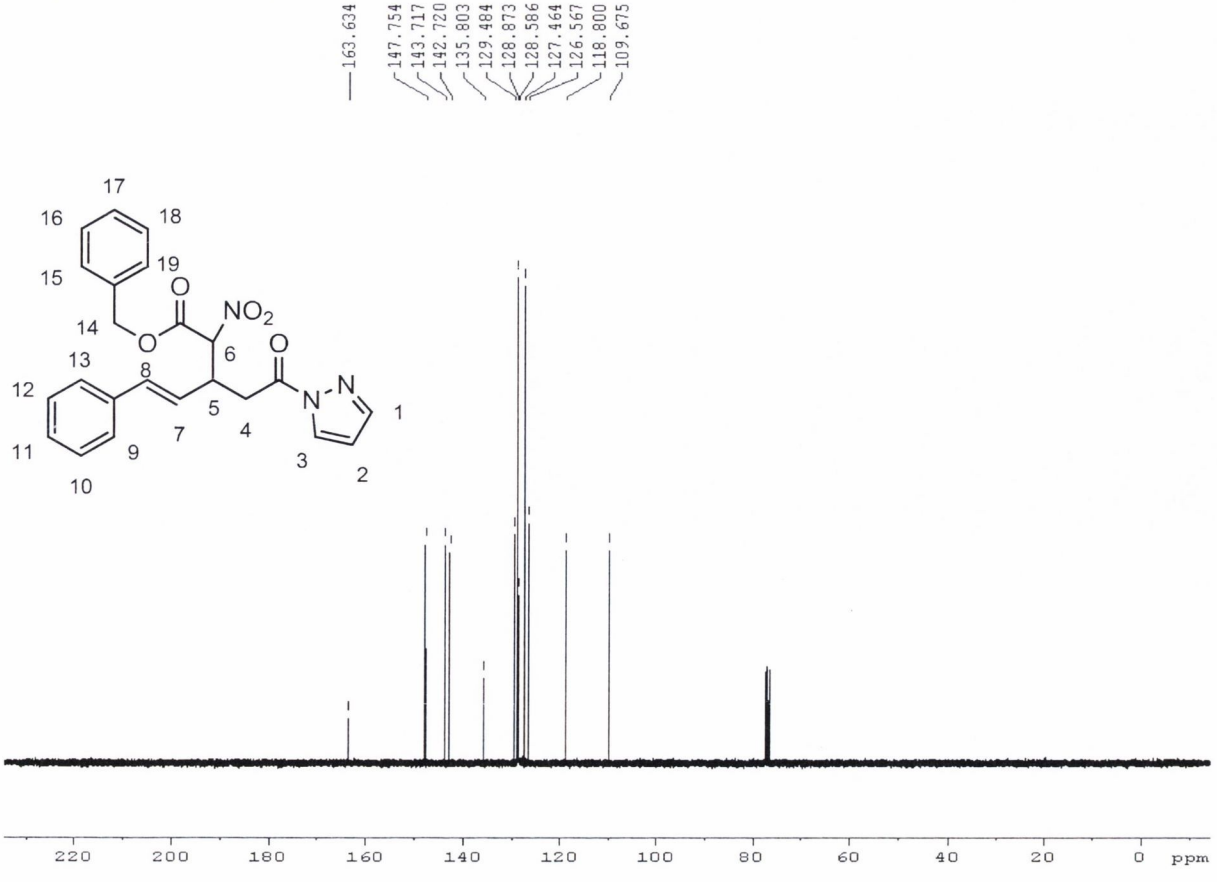


10.6 NMR spectra of compound **667**

δ_H (400 MHz, $CDCl_3$)

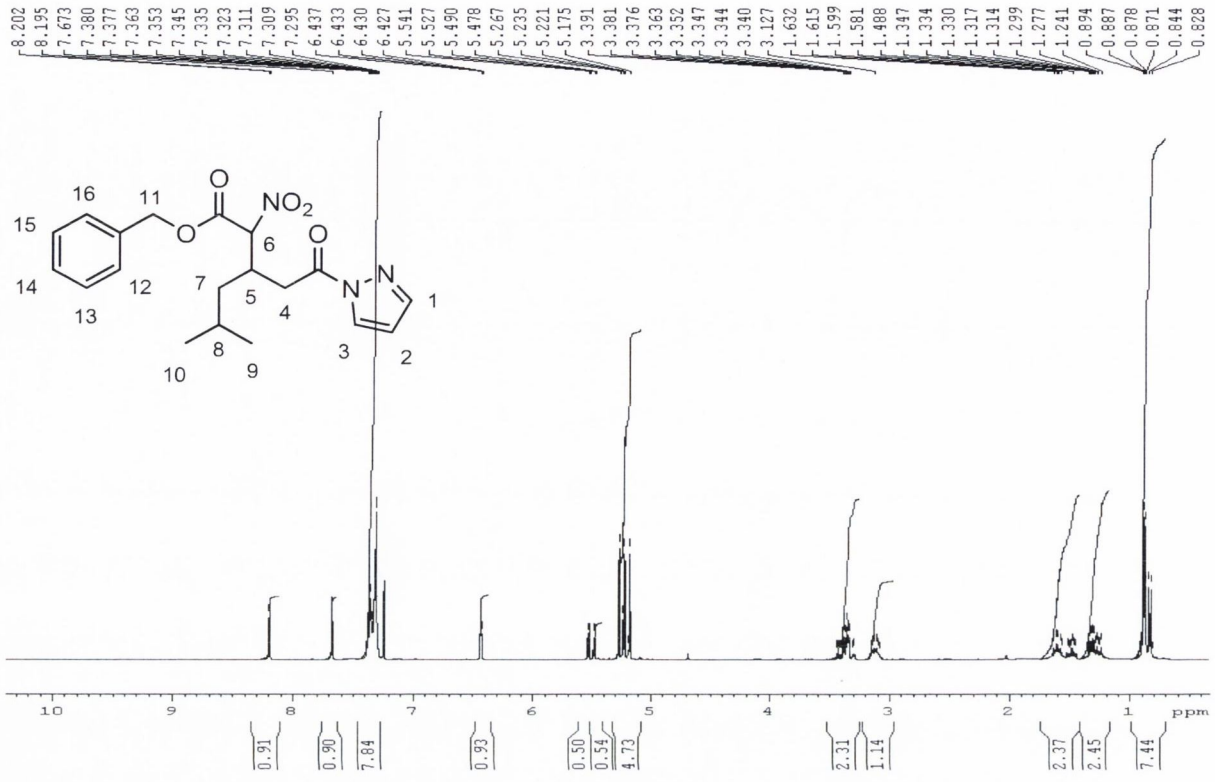


δ_C (100 MHz, $CDCl_3$)

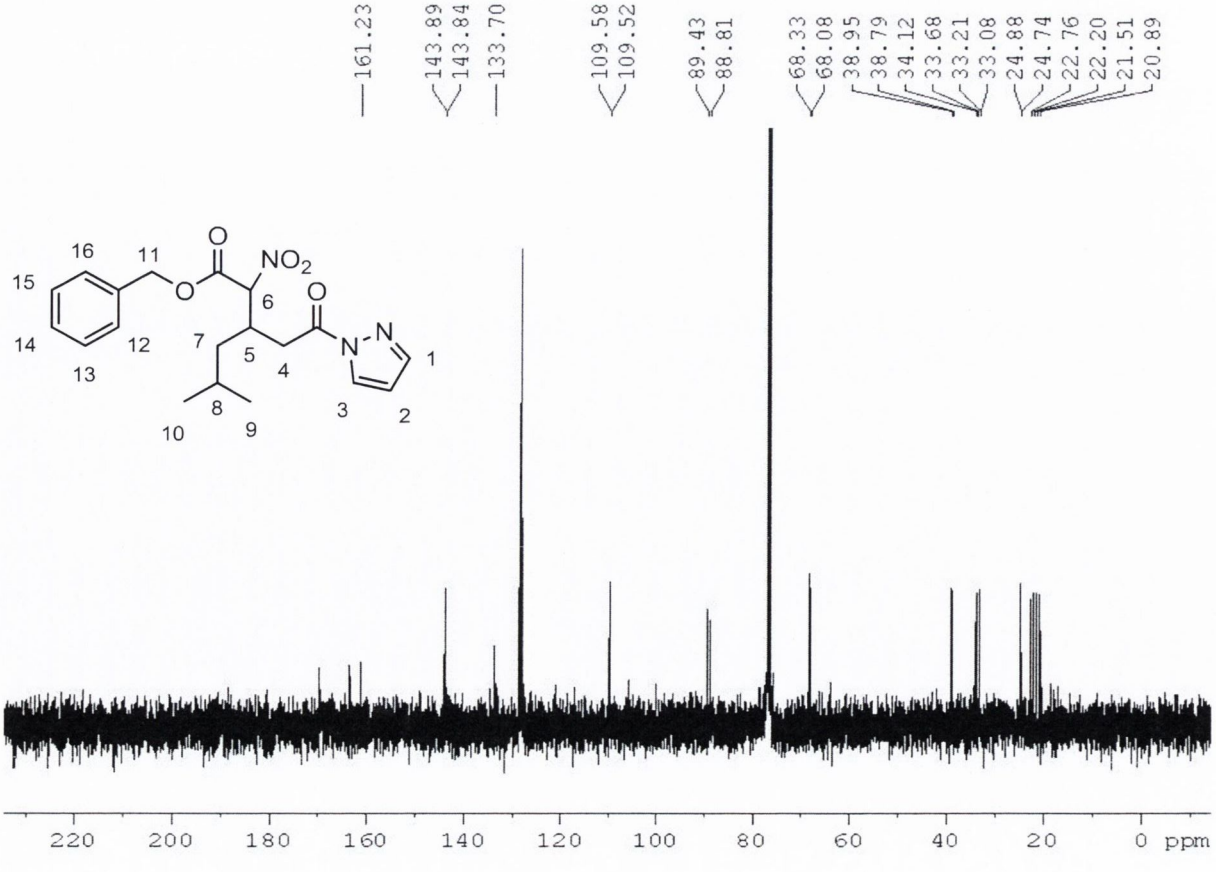


10.7 NMR spectra of compound **687**

δ_H (400 MHz, $CDCl_3$)

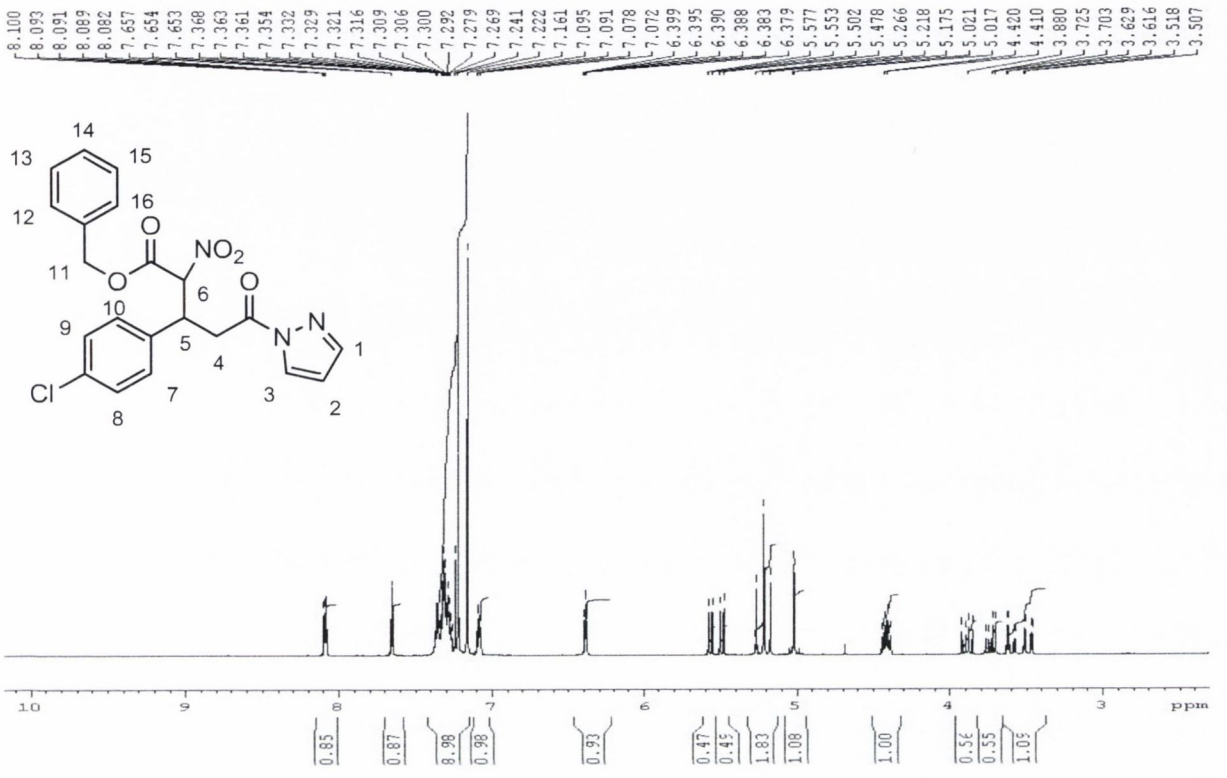


δ_C (100 MHz, $CDCl_3$)

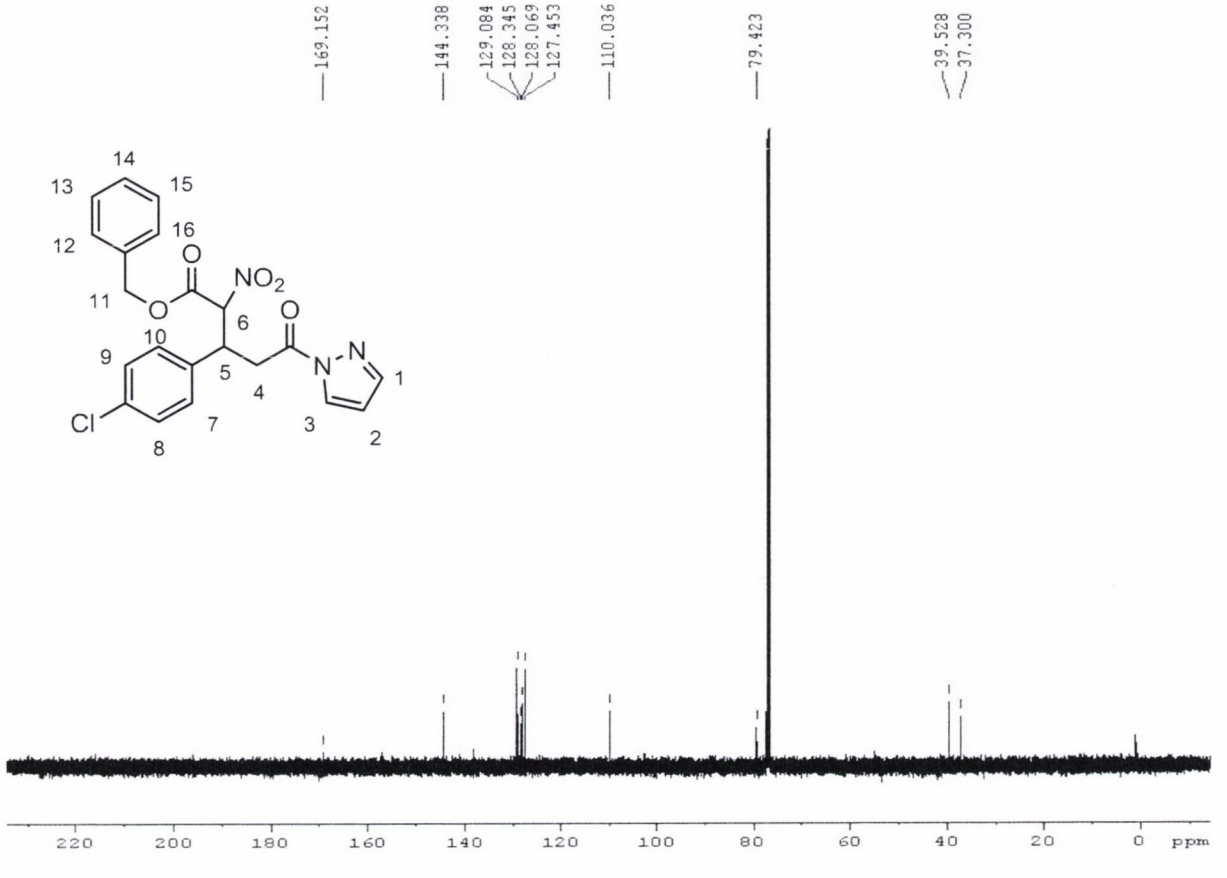


10.8 NMR spectra of compound **669**

δ_H (400 MHz, $CDCl_3$)



δ_C (100 MHz, $CDCl_3$)



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