The Synthesis and use of heterocycles in organocatalysis

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Abstract

This thesis is concerned with two sections: the first deals with the synthesis of quinolinones *via* a tandem VNS reaction. The second examines the aminocatalysis of the Baylis-Hillman reaction

Chapter 1: Provides an overview of aromatic chemistry. Focus is on the separate mechanisms of the substitution of aromatic compounds. An overview of VNS chemistry is also included to provide a basis for the investigations carried out.

Chapter 2: Describes the synthesis of a small library of *bis*-nitroaromatic compounds using the VNS reaction. An investigation into the cyclisation of the *bis*-nitroaromatic compounds to a range of biologically interesting quinolinones is also desribed.

Chapter 3: Introduces the concept of aminocatalysis and gives an overview of recent developments in the field including the Baylis-Hillman reaction, the reaction chosen for asymmetric catalyst development.

Chapter 4: Is split into three sections; the first describes an interesting solvent effect encountered during the course of the investigation. The second investigates the effect of the structure of secondary amines on the enantioselectivity of the reaction *via* iminium ion formation. The third section describes the investigation of the structure of Lewis bases on the enantioselectivity of the reaction.

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Abbreviations

Ac	acetyl		
AcOH	acetic acid		
APcI	atmospheric pressure chemical ionisation		
Ar	aromatic		
atm.	atmosphere(s)		
BHR	Baylis-Hillman reaction		
Bn	benzyl		
Boc	tert-butoxycarbonyl		
b.pt.	boiling point		
br	broad		
Bu	butyl		
BuOK	potassium butoxide		
cat.	catalyst		
Cbz	benzyloxycarbonyl		
CHCl ₃	chloroform		
column chromatography	flash column chromatography		
Су	cyclohexane		
d	doublet		
DCA	dichloroacetic acid		
DCC	dicyclhexyl carbodiimide		
DCM	dichloromethane		
DDQ	2,3-Dichloro-5,6-Dicyanobenzoquinone		
DMD	dimethyldioxirane		
DMF	dimethylformamide		
DMSO	dimethyl sulfoxide		
DNPH	2,4-dinitrophenylhydrazine		
Ε	electrophile		
Et	ethyl		
EtOH	ethanol		
ES	electrospray		
ether	diethyl ether		

EWG	electron withdrawing group		
e.e.	enantiomeric excess		
equiv. (eq.)	equivalent(s)		
GC	gas chromatography		
GLC	gas-liquid chromatography		
HCl	hydrochloric acid		
hr.	hour(s)		
HOBt	1-hydroxybenzotriazole		
НОМО	highest occupied molecular orbital		
HPLC	high performance liquid chromatography		
HRMS	high resolution mass spectrometry		
i	iso		
IR	infra red		
k	kilo		
LA	Lewis acid		
light petrol	petroleum ether 40–60 °C		
Lit.	literature		
LUMO	lowest unoccupied molecular orbital		
Μ	molar		
m	mass		
m	multiplet		
Ме	methyl		
min.	minute(s)		
MVK	methyl vinyl ketone		
mmol	millimole(s)		
NMR	nuclear magnetic resonance		
МО	molecular orbital		
mol	mole(s)		
mp	melting point		
MHz	megahertz		
MS	mass spectrometry		
Ms	mesyl		
NaH	sodium hydride		
NI-OUT	andine hudrowide		

NaHCO ₃	sodium hydrogencarbonate		
n	normal		
ONSH	oxidative nucleophilic substitution of hydrogen		
p	para		
р	pentet		
PES	potential energy surface		
Ph	phenyl		
РМР	<i>p</i> -methoxyphenyl		
Pr	propyl		
q	quartet		
quant.	quantitative		
RDS	rate determining step		
r.t.	room temperature		
S	singlet		
SAR	structure-activity relationship		
SERM	selective estrogen receptor modulators		
sept.	septet		
SMP	(S)-2-methoxymethylpyrrolidine		
sol ⁿ .	solution		
S _N Ar	nucleophilic aromatic substitution		
t	tertiary		
t	triplet		
TBDMS-Cl	tertiary butyl dimethylsilyl chloride		
tert	tertiary		
TFA	trifluoroacetic acid		
THF	tetrahydrofuran		
TLC	thin layer chromatography		
Ts	tosyl		
pTSA	para-toluene sulfonic acid		
vol.	volume(s)		
VS.	versus		
σ	sigma		
*	chiral		

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Chapter 1: VNS introduction

1. Introduction

1.1.Aromatic Chemistry

The synthesis of benzene derivatives is one of the largest fields of synthetic research studied by organic chemists. Since the beginning of the field of organic chemistry, scientists have been intrigued by different aromatic compounds. The synthesis of benzene derivatives has provided chemists with both an intellectual and synthetic challenge, which has led to some of the core named reactions taught to students today.

Benzene, unlike unsaturated compounds like cyclohexene, 1, doesn't react with bromine under ambient conditions to give a bis-brominated compound (Scheme 1).



Scheme 1

Instead, a Lewis acid such as aluminium trichloride, 6, must be added in order to form bromobenzene 4 (Scheme 2). The mechanism by which this addition proceeds is *via* Lewis acid activation of the bromine to give 7, which undergoes nucleophilic attack from the benzene (which breaks the aromaticity of the molecule). The driving force of the reaction becomes the restoration of the aromaticity of the benzene ring by the elimination of a proton from the cationic intermediate **8**.



Scheme 2

Another reaction that can be brought about by the addition of a Lewis acid is the Friedel-Crafts acylation¹ (Scheme 3). Formation of a σ -adduct, 10, between the carbonyl group and the Lewis acid which activates the acyl chloride, 9, toward electrophilic attack by the benzene ring. This addition breaks the aromaticity of the benzene ring. Restoration of the aromaticity by the loss of a proton provides a thermodynamic driving force for the overall transformation.



Scheme 3

1.2. Heterocyclic compounds

Not only are carbocyclic aromatic compounds a target for synthesis but rings containing heteroatoms are attractive, especially to the pharmaceutical industry, since the presence of heteroatoms facilitate drug absorption and binding. Many methods of heterocyclic synthesis have become a mainstay for teaching of synthetic organic chemistry. Some of these methods are named after their initial discoverer. One example of this class of well-known reaction is the Hantzsch pyridine synthesis,² in which relatively simple precursors are combined in one pot to form 3,5-disubstituted dihydropyridines 18. The dihydropyridines can be easily oxidised to the corresponding pyridines, 19, providing an efficient synthesis of highly substituted complex products (Scheme 4).



Scheme 4

Not only are one-ring systems easily available, the Fischer indole synthesis, a reaction discovered by Hermann Emil Fischer in 1883,³ provides a bicyclic [6,5] heterocycle **26** (Scheme 5).



Indoles are not the only important two-ring heterocycles. The bicyclic [6,6] heterocycle is called quinoline **32**, a naturally occurring compound found in coal tar and was first isolated from this source in 1834 by Runge.⁴ Quinolines can be synthesised in a variety of ways including the Skraup synthesis developed in 1880 (Scheme 6),⁵ the Doebner-Miller reaction, first published in 1881⁶ and the Combes quinoline synthesis published in 1888,⁷ all of which use aniline as a precursor.



Scheme 6

The growth in the synthesis of aromatic and heteroaromatic compounds has in the most part been driven by the pharmaceutical industry where the importance of such compounds is shown by the prevalence of aromatic moieties in the top 10 best selling drugs of 2005 (Figure 1).⁸ Each of the drugs shown has an aromatic group present which helps to explain why there is such interest in this class of compound.



Seroquel







Prevacid

Effexor

Figure 1

1.3. Synthesis and substitution of aromatic compounds

In order to fill the demand for new and more efficient methods for the generation of aromatic compounds, significant resources have been expended by research groups throughout the world. This interest has focussed on the different mechanistic opportunities to activate benzene.

There are 4 main classes of reactivity of aromatic compounds;

- i) Nucleophilic aromatic substitution (S_NAr),
- ii) Oxidative nucleophilic substitution of hydrogen (ONSH),
- iii) Electrophilic aromatic substitution,
- iv) Palladium mediated coupling,
- v) Diazonium salt formation
- vi) Metallation

The first four of these classes will be briefly discussed below.

1.3.1. Nucleophilic aromatic substitution

Nucleophilic substitution can occur in one of two ways; the first at positions occupied by halogens to form σ^X -adducts, and the second at positions occupied by hydrogen forming σ^H -adducts.

Substitution of halides proceeds rapidly by the elimination of X⁻ from the intermediate σ^{X} -adducts, with fluoride (F⁻) being the best leaving group. Substitution at ring positions occupied by Fluorine is faster than at those occupied by Bromine or Iodine due to the increased electronegativity of Fluorine compared to the other halides.

A typical S_NAr reaction is shown in scheme 7. Nucleophilic attack of hydroxide on 4-fluoronitrobenzene, 33, leads to the formation of intermediate σ^X -adduct, 34. Elimination of fluoride restores aromaticity leading to the observed 4-nitrophenol product 35. Substitution is greatly accelerated by the presence of electron withdrawing groups (such as nitro groups) situated *ortho* or *para* to the point of substitution. These groups stabilise negative charges at *ortho* and *para* positions but are unable to do so for reactions at *meta* positions. Several reviews have been published on this topic.⁹



1.3.2. Oxidative nucleophilic substitution of hydrogen

Reactions that proceed *via* σ^{H} -adducts are slightly different in that the elimination of hydride is an unfavoured process. The substitution of hydride is possible, even with carbons bearing halogens (or other good leaving groups) at the *ortho* and *para* positions, however, an additional reagent is required. Without the additional reagent the σ^{H} -adducts rapidly revert back to the starting material leading to no observed reaction. The removal of the hydride is a process that is analogous to oxidation and has given rise to the name for the process oxidative nucleophilic substitution of hydrogen (ONSH).

ONSH reactions suffer, however, due to the sensitivity of carbon nucleophiles (such as carbanions or Grignard reagents) to oxidation. This sensitivity can be overcome by the use of a different sub-set of ONSH reactions, namely, the vicarious nucleophilic substitution (VNS) reaction (see section 1.4).

An example of an ONSH reaction is the reaction of nitroarene, 36, with the carbanion of isopropyl phenyl acetate, 37, in which the use of different oxidants gives rise to a variety of products, 39-41, which have numerous opportunities for further synthetic elaboration (Scheme 8).¹⁰



1.3.3. Electrophilic aromatic substitution

Electrophilic aromatic substitution reactions also proceed via charged intermediates. These reactions have been known and studied for a long time, the major components of this class of reaction are briefly discussed here. The process can be split into two separate steps, the first involves the formation of a new σ -bond between the electrophile (E⁺) and the aromatic ring, **3**, to give the charged intermediate, **42**. The second step restores the aromaticity by removal of a proton to give the observed product, **43** (Scheme 9).



As with nucleophilic substitution reactions the presence of substituents on the ring can affect the rate and position of substitution. Electron donating groups (such as OH and NH₂) increase reactivity towards the electrophile, when compared to benzene. Conversely, electron withdrawing groups (such as NO₂) decrease reactivity making reactions slower than reactions of benzene. Both inductive and resonance effects control the regiochemistry of the disubstituted products formed as a result of electrophilic aromatic substitution reactions of substituted substrates. If the products formed by the nitration of anisole, halobenzenes and nitrobenzene are compared, it is possible to see the three types of effects in action.

Anisole 44 reacts at the *ortho* and *para* positions due to stabilisation of the intermediate carbocations 45 by donation of electrons from oxygen. No such stabilisation is available for reaction at the *meta* position. Halogens, 48 (where X=F, Cl, Br or I), while having both an inductive and a resonance effect, are *ortho/para* deactivating due to the strength of the inductive electron withdrawing effect outweighing the resonance effect. *Meta*-directing substituents, such as the electron-withdrawing nitro group of nitrobenzene 51 deactivate aromatic compounds towards reaction with electrophiles at the *ortho* and *para* positions since the resonance forms of the intermediate, 52, place the carbocation at the position occupied by the withdrawing group, which in turn causes the reaction only to occur at the *meta* position, 53.



1.3.4. Palladium mediated methods

Although a majority of functional groups can be attached using variations of the methods previously described above, there have been a number of methods developed using aryl halides and triflates with organometallic nucleophiles. Some of these variants, including the Suzuki (boron mediated),¹¹ Stille (tin mediated)¹² and the Sonogashira (copper mediated),¹³ form the cornerstone of synthesis in the pharmaceutical industry. Each of these named variants follows the same reaction pathway. Initially the palladium undergoes oxidative addition into the Ar-X bond to give **54**, transmetallation of the nucleophile to the palladium forms a *bis*-organic Pd(II)

complex 55. This intermediate complex gives the observed coupling product, 56, by reductive elimination (Scheme 11).



1.4. The VNS reaction

The VNS reaction was mentioned above as a mild alternative to the ONSH reaction. Here is presented a brief introduction to the vicarious nucleophilic substitution reaction and a brief overview of some of the advances made since its discovery.

The VNS reaction was first recognised as a distinct concept by Makosza in the late 1970's.¹⁴ The reaction takes place between a carbanion bearing a leaving group, **56**, and a nitroarene, **51**, at a carbon bearing a hydrogen atom. As with the ONSH reaction, substitution occurs *ortho* or *para* to the nitro group. There is no need for a separate reagent to act as an oxidant as the presence of the leaving group (X) allows for the elimination of HX to from the post-VNS anion, **58** which is then quenched by acid, to give **59**, or further functionalised by a suitable electrophile to give **60** (Scheme 12).



Scheme 12

The post-VNS anion, 58, due to its highly conjugated structure, can usually be observed as a highly coloured intermediate (Figure 2). The formation of this coloured intermediate is immediate on addition of base and can therefore be used as a qualitative indication of the reaction successfully taking place.



Figure 2

The VNS pathway can lead to *ortho* and *para* substitution, but what governs the selectivity of the reaction? Theoretically there should be a 2:1 *ortho:para* ratio of the VNS product, and in simple systems, where the nucleophile has only hydrogens at the anionic centre, this has been shown to be the case.¹⁵

In order for the elimination to take place the ring-hydrogen and the leaving group (X) must obtain an anti-periplanar arrangement (Scheme 13).



Scheme 13

where X=halogen Y=hydrogen, alkyl Z=electron withdrawing group

If Y is a hydrogen, i.e. a secondary carbanion is formed as a reaction intermediate, then the steric interaction between it and the nitro group is negligible enough to allow substitution to take place in both the *ortho* and *para* positions. Tertiary carbanions, however, do not substitute in the *ortho* position due to the interaction between Y and the nitro group. It is possible to force *ortho* substitution by adding a substituent in the *para* position of the nitroaromatic. This is only possible if Y is small (methyl or similar), and even in these cases the yield of the reaction doesn't reach the same levels as if Y is a proton.¹⁶

Vicarious substitution can dominate over conventional aromatic substitution in cases where the nitroaromatic contains a halogen in the *ortho* or *para* positions.¹⁶

Despite these general trends it is possible to substitute exclusively in the *ortho*-position. When ¹BuOK/THF is the chosen base/solvent combination then the vicarious substitution of nitrobenzene, **51**, by chloromethylphenyl sulphone, **63**, proceeds exclusively in the *ortho*-position to give **64** (Scheme 14).¹⁷



Unlike other base/solvent combinations that form a loose solvent separated ion-pair. THF forms a tight ion-pair between the carbanion and the potassium cation. During the reaction the

negatively charged oxygen atoms of the nitro group attract the potassium cation and thus the carbanion is delivered to the neighbouring *ortho* position (Figure 3).¹⁸



Figure 3

Interaction with the nitro group weakens the carbanion-cation link and therefore the carbanion adds to the nitroarene in the form of a loose-ion pair.

The regioselectivity of the VNS of carbanions where $Y \neq H$ can be explained by the relative rate of reaction at the *ortho* and *para* positions. It has been shown that the reaction of α -chloroethylphenyl sulphone, **65**, with nitrobenzene, **51**, in the presence of ¹BuOK/DMF proceeds 40 times slower at the *ortho* position compared to the *para* position (scheme 15).¹⁹



This field has been reviewed on numerous occasions²⁰ therefore only recent developments will be discussed here.

Previous work in our group has found that it is possible to form *E*-stilbenes by utilising a tandem VNS/Horner-Wittig reaction of chloromethyl diphenylphosphinoyl oxide and a range of nitro aromatics in the presence of sodium hydride and DMSO. The VNS products underwent a Horner-Wittig reaction in the presence of base and a range of benzaldehydes to give the stilbene products, **70** (Scheme 16). The *E*-stilbenes, **70**, were only obtained in modest yield. It was hypothesised that if the post-VNS anion, **69**, was treated directly with the benzaldehyde the same product would be obtained. This would effectively make the process a one-pot tandem reaction.

The yields were found to be significantly higher (up to 10%) than those obtained *via* the two-step process (up by 47%).²¹



Scheme 16

Indoprofen, 76, is a non-steroidal anti-inflammatory drug, and some of its derivatives can be synthesised in a four-step process that incorporates a VNS reaction (Scheme 17).²² The first step involves the VNS reaction of ethyl-2-chloro propionate 71 with nitrobenzene, 51, in the presence of NaII/DMF, the post-VNS anion was quenched either by acid or methyl iodide to give the VNS products 72 and 73. Following the VNS process, the product was reduced under hydrogenation conditions to give the anilines 74 and 75. The phthalimidine derivative was obtained *via* the Takahashi protocol²³ which involves reaction of the aniline with 1,2,3-1*II*-benzotriazole, 2-mercaptoethanol and *o*-phthalaldehyde. Saponification of the ester with sodium hydroxide gave Indoprofen 76 in a 24% overall yield. The protocol involving the methyl iodide quench gave rise to the α -methylated derivative 77 (43% overall yield).



Scheme 17

6,7-dihydroimidazo[4,5-d][1,3]diazepin-8(3*H*)-one, 78, (Figure 4) has been shown to be an important intermediate in organic synthesis. It has been used in the synthesis of the natural products pentostatin²⁴ and coformycin²⁵ both of which are *anti*-cancer and *anti*-viral nucleosides. The synthesis of this synthetically important compound can be carried out beginning with the VNS reaction of 4-nitroimidazole (which is commercially available).²⁶



Beginning with *N*-benzylation of 4-nitroimidazole, **79**, gave a compound, **80**, that could undergo the VNS process. Reaction of **80** with the anion generated by the action of potassium *tert*-butoxide on chloroform gave the expected VNS product, **81** (Scheme 18).



Treatment of **81** with formic acid followed by $NaClO_2/NH_2SO_3H$ gave the carboxylic acid **82**. CDI mediated coupling of nitromethane gave the dinitroketone, **83**. Reduction of the nitro groups was followed by benzyl deprotection to give the diamino ketone, **84**. Cyclisation of the diamine with ethyl formate in DMSO gave the desired product, **78**, as the mono hydrochloride salt in 20% overall yield (Scheme 19).



Scheme 19

The tricyclic indole-2-carboxylic acid, **90**, has been investigated to examined its activity as an *anti*-convulsant in the mouse NMDA-induced seizure model. The synthesis of the compound ncorporates a VNS reaction between 4-iodonitrobenzene, **85**, and *tert*-butyl chloroacetate in the presence of potassium *tert*-butoxide to give **86** (73% yield). Palladium catalysed cyanation of the product using $Zn(CN)_2$ gave, **87**. Three further steps gave the Boc-protected amine, **88** (Scheme 20).



Amide coupling of the diamine, **88**, with tricyclic indole, **89**, followed by Boc-deprotection and ester hydrolysis gave the product as the hydrochloride salt (Scheme 21).



Some further work in our group has also targeted indole based compounds.²⁷ The first step involves the VNS reaction of ethyl-2-chloropropionate, 71, with nitrobenzene, 51, in the presence of sodium hydride. The post-VNS anion was quenched with 2,4-dinitrofluorobenzene, 91, giving the trinitro compound, 92 (77% yield). Reduction of the three nitro groups with tin(11) chloride dihydrate gave the product of reduction and cyclisation, 93 (71% yield) (Scheme 22).



Scheme 22

This important discovery has applications within the pharmaceutical industry as the diarylmethane group can be found imbedded in several drugs,²⁸ for example 3-arylindoles. This also provides the background and incentive for my own work.

The need for methods to synthesise multiple ring heterocycles was exemplified by the synthesis of a series of selective estrogen receptor modulators (SERMs) by Grese *et al.*²⁹ These SERMs included a core of an *N*-arylbenzophenanthridine, **96**, which were further derivatised in order to obtain the desired compounds (Scheme 23).



Scheme 23

1.5. Aims and Objectives

It was believed that it was possible to utilise the chemistry developed for the aryl indole (Scheme 22) in order to synthesise an analogous series of compounds (Scheme 24).



Scheme 24

Chapter 2: VNS results and discussion

2. VNS results and discussion

2.1. Tandem VNS coupling

In order to begin to understand the nature of the compounds that were being attempted to be synthesised, it was decided that the first intermediate would be synthesised in a stepwise fashion (Scheme 25).



Nitrobenzene, 51, was reacted with ethyl-2-chloropropionate, 71, in the presence of a NaH/DMF base/solvent combination at 0°C. As soon as the base was introduced to the reaction vessel the typical VNS colouration appeared, which indicated that the reaction was proceeding as expected. After warming the reaction mixture to room temperature and stirring for 2 hrs, 1M HCl was added and the reaction mixture turned from the purple colour of the post-VNS anion to a cream suspension. Following basic aqueous work-up and column chromatography (eluting with 10% EtOAc/Petroleum Ether) the desired product was obtained in 79% yield. The identity of the product, 103, was proven by the 1H NMR spectrum in which 2 aromatic doublets at $\delta_{\rm H}$ 7.30 and 8.10 ppm had replaced the 3 signals in the aromatic region of the NMR spectrum of nitrobenzene, 51.

Another feature of the NMR of the product which was to become indicative of this class of compound belonged to the CH_2 of the ethyl ester. The presence of a stereogenic centre in the product gave rise to a diastereotopic methylene protons. Diastereotopic protons occur in compounds which contain a stereogenic centre, if one of the protons on a CH_2 group is substituted by another element (or group) diastereomers may be formed. Diastereotopic protons are not equivalent and therefore possess slightly different chemical shifts. In our case the slight inequivalence not only causes a difference in location of the peaks of the quartet formed due to coupling to the CH_3 of the ethyl ester, but also causes the protons to couple to each other adding

a further degree of complexity to the fine structure. In all the presence of 16 peaks which occur due to 2 sets of doublets of quartets was observed. This structure will be discussed further for a different compound below.

Once it had been ascertained that the initial VNS product had been isolated it was necessary to further derivatise the product by introducing a nitrobenzyl chloride group in order to alkylate the secondary centre (Scheme 26). An equivalent of NaH (the third overall) was added to the SM in a solution of DMF at 0°C and the reaction mixture allowed to stir for 30mins again producing a purple solution. The nitrobenzyl chloride was added and the solution stirred at room temperature for 1 hr. During the reaction the solution turned from dark purple to deep red in colour. The addition of 1M HCl again quenched the reaction giving a yellow/orange solution. Basic work-up followed by column chromatography (eluting with 20% EtOAc/Petroleum Ether) gave the product as an orange oil in 79% yield for an overall two-step yield of 62.5%. The product was identified by the absence of the 1H quartet of the benzylic proton $\delta_{\rm H} = 3.79$ and the presence of a methyl singlet $\delta_{\rm H} = 1.50$ along with the signals from the four extra aromatic protons between $\delta_{\rm H}$ 6.90 and 7.80 ppm.



The presence of a stereogenic centre in the product has generated some added complexity into the multiplicity of several signals in the NMR spectrum. Due to the proximity of the stereogenic centre to the two CH_2 groups in the product, namely the benzylic CH_2 and the CH_2 of the ethyl ester, the respective protons of these groups don't inhabit identical chemical environments. They are therefore diastereotopic and subsequently couple to each other (Figure 5).



Figure 5

The benzylic CH_2 is resolved into two discreet doublets with a coupling constant J value of 14.0Hz. The ester CH_2 however, is more complex, being an ethyl ester the methylenic protons classically exhibited a quartet multiplicity. The presence of the stereogenic centre had the same effect on this CH_2 as the benzylic CH_2 , the protons were not degenerate therefore coupled to each other, with a coupling constant J value of 10.8 Hz. This does not, however, completely explain the complexity exhibited by the NMR signal. The two protons also have slightly different chemical shifts, separated by 0.05 ppm. This meant that each proton was observed as a doublet of quartets. The chemical shift separation was not sufficient to completely de-convolute the multiplet resulting in the two sets of signals coalescing. All of this complexity caused a

fourfold increase in the number of signals expected from an ethyl ester CH_2 , there being sixteen peaks in place of the more usual four. These signals were shown to be indicative of this class of compound and were present in all of the analogues of this compound prepared throughout this work.

Following the success of forming the required di-nitroaryl compound, 104, in two steps, it was important to recreate the synthesis in one-pot (Scheme 27). The reagents used were identical to those used in the two-step process, with one important difference, only two molar equivalents of the base, NaH, were to be used compared to three used in the two-step procedure. The reason for the absence of the third equivalent of the base was that the driving force for the 'quench' step in the sequence is the restoration of aromaticity to the post-VNS anion 58. This restoration of the aromaticity of the compound is energetically favourable enough to make it unnecessary to isolate the intermediate aryl-ester, 103, therefore eliminating the need for the extra equivalent of base.



The initial procedure was identical to that in the two-process up to the point of the acid quench. In place of being quenched with an aqueous acid/ice mixture, 2-nitrobenzyl chloride, **100**, was added at this point in anhydrous DMF and the reaction allowed to proceed at room temperature for an hour. The same purple to dark red/orange colour change that occurred on the addition of the benzyl chloride previously was observed again. Following an hour the reaction was quenched with aqueous acid and purified *via* column chromatography (eluting with 20% EtOAc/Petroleum Ether) to yield an orange oil in 79% yield. The ¹H NMR data for this compound was compared to the spectrum of the product of the two-step process and found to be identical.

The success of the one-pot procedure not only generated the product in 16% greater yield, but it also eliminated one column chromatography stage with all its added waste in time and eluent. There is one drawback however; the purification is hindered by the presence of an extra precursor, 100, that needs to be removed from the crude reaction mixture.

Once a standard protocol for the synthesis of the di-nitroaryl intermediate that we required in order to synthesise our desired target was determined it was decided to experiment with the electronic nature of the precursor nitrobenzene in order to determine how widely applicable our procedure would be.

The VNS process generally requires a fairly electron deficient nitroaryl group in order to be successful. It was therefore decided to add an electron-donating group to the precursor and subject it to the standard procedure that had been developed (Scheme 28).



The reaction of 2-nitrotoluene, **105**, with ethyl-2-chloro propionate, **71**, in the presence of DMF and NaH at 0°C initially gave the purple reaction mixture indicating that the post-VNS anion had been formed. After stirring for two hours a solution of 2-nitrobenzyl chloride, **100**, in DMF was added and the reaction mixture stirred for a further hour causing the reaction mixture to turn to a red/orange colour. On addition of the 1M HCl quench solution the solution changed colour from red/orange to a cream colour. Basic work-up followed by column chromatography eluting with 20% EtOAc/Petroleum Ether gave the product as an orange oil in 59% yield. The ¹H NMR data showed similar 'fingerprint' multuplet splitting patterns as the nitrobenzene example allowing the product to be identified as the desired compound. The lower yield for this reaction compared with the previous example is due to the inductive electron-donation of the methyl group having a destabilising effect on the addition of the VNS anion. The inductive donation of negative charge into the nitroaryl ring would reduce the δ^+ of the carbon atoms *ortho* and *para* to the nitro group. This in turn would make it less favourable for the VNS anion to attack the ring.

Following the reaction of the 2-nitrotoluene, 105, under the reaction conditions, and since the VNS reaction requires an electron deficient phenyl group, it was decided to see what effect the addition of a second electron-withdrawing group to the precursor. 2-nitroanisole, 107, was reacted with ethyl-2-chloropropionate, 71, in the presence of the DMF/NaH slurry (scheme 29).

Again the purple coloured reaction mixture was observed. After 2 hours 2-nitrobenzyl chloride, 100, was added to the reaction mixture causing a colour change from purple to dark orange. Following acidic quench and basic work-up, column chromatography was performed to give the product in 47% yield product. It was thought that the addition of the methoxy group (an electron-withdrawing group) would reduce the facility the VNS reaction. This indeed proved to be the case, the product, 108, being isolated in lower 47% yield.



A method it was thought would possibly allow more efficient access to the 2-oxygenated products is shown in Scheme 30. It was believed a second phenyl group would reduce the effect of the oxygen lone pairs on the electronic nature of the reaction. The commercially available 2-nitrodiphenyl ether, **109**, was reacted with ethyl-2-chloropropionate, **71**, under the standard NaH/DMF conditions (scheme 30), giving the purple intermediate solution. After two hours the reaction was quenched by the addition of 2-nitrobenzyl chloride, **100**, turning the solution dark green. A 1M HCl quench of the reaction mixture followed by basic work up and column chromatography gave the desired product, **110**, as an orange oil in 42% yield.



The attempt to reduce the effect of the electron donation of alkoxy groups failed to have the desired outcome, the phenoxy group was presumably causing too large a steric interaction between the starting material and the incoming nucleophile.

In order that the products of our process could be of further use to organic chemists we decided to incorporate a group that would enable a range of further transformations to be carried out on the products. It was decided to examine 2-halonitro benzenes. VNS reaction (pathway a) has been shown to occur in preference to an S_NAr reaction (pathway b) between 4-fluoronitro benzene, 111, and carbon nucleophiles (scheme 31),³⁰ we wanted to see if this held true for the tandem coupling process.



Scheme 31

The second reason for examining halonitro benzenes was the ability of these types of compounds to undergo palladium mediated reactions such as the Suzuki coupling,³¹ in which the halo compound is firstly converted to the boronic acid, 117, (or boronate ester) and then further reacted to give a bi-aryl product, 119, (scheme 32). This simple change of structure allows us to open up a large range of possibilities for our products.



The reaction of 2-chloronitro benzene, 120, with ethyl-2-chloro propionate, 71 proceeds under the reaction conditions to give the desired chlorinated di-aryl compound, 121 (52% yield) (scheme 33). Our conditions followed the previously reported pattern of the VNS reaction proceeding preferentially in the presence of the substitution of the halide. The structure of the product was proven by examination of the 1H NMR of the isolated material, 7 aromatic protons were shown to be present (substitution would give 8) and the coupling pattern showed a 1,2,4substituted phenyl group was present in the molecule. Substitution of the halide would give a disubstituted compound. The mass spectrum of the product also gave us re-inforcement of the structure, the presence of the chloride gave rise to a distinctive isotope pattern with a peak at 410 for the hydrate of the ³⁵Cl isotope and 412 for the hydrate of the ³⁷Cl isotope present in a 3:1 ratio.



A similar yield for the fluoro analogue, 123 (Scheme 34) was seen. The product was obtained in 50% yield, proving that the reaction proceeds irrespective of the halide attached to the nitroaromatic.



After examining the reaction of ethyl-2-chloropropionate with a range of nitroaromatics it was decided to examine the reaction of the same 6 nitro compounds with methyl 2-chloropropionate in order to see if the same reactivity was seen with different CH-acids. The same reaction conditions were used as the ethyl ester and achieved similar results for all 6 nitroaromatics (Scheme 35, Table 1).



Scheme 35

Entry	R	Compound Number	Yield (%)
1	н	126	73
2	Me	127	59
3	ОМе	128	56
4	OPh	129	48
5	CI	130	50
6	F	131	49

Table 1

2.2. Quinolinone formation

Following the synthesis of the range of *bis*-nitroaromatic compounds *via* the tandem VNS coupling it was necessary to transform these compounds into the analogous quinalinone compounds.

Two methods were used to reduce and cyclise the *bis*-nitroaryl compounds in our guiding literature reference. The first was a standard palladium catalysed reduction (Scheme 36) and produced the desired oxindole in 54% yield.



The second involved the use of tin(II) chloride as the reducing agent and was slightly more successful in producing the oxidole, 93, (71%, Scheme 37).


Scheme 37

The initial thoughts were to examine each of these methods in order to reduce the quinolinone precursors (Scheme 38).



Scheme 38

The first method chosen was the tin(II) chloride method as this had previously proved to be the most efficient method of synthesis of the desired oxindole.



The *bis*-nitroaryl compound, **104**, was dissolved in a 3:1 mixture of ethanol and ethyl acetate with a drop of acid, added the tin compound and heated the mixture for 24 hours at reflux (Scheme 39). The reaction mixture was cooled to room temperature and filtered in order to remove any excess tin from the mixture. The solvent was removed in vacuo and the residue redissolved in EtOAc and washed with saturated aqueous NaHCO₃ in order to remove any trace of acid remaining. The crude product was then purified to yield the pure *bis*-aminoaryl compound, **132**, in 68% yield. The compound was identified by the shifting of the NMR signals due to the aryl protons of both rings upfield by approximately 1.0 ppm and the appearance of a signal due to the two NH₂ groups in the IR spectrum. This data confirms the reduction of the two nitro groups, it doesn't however prove or disprove the cyclisation; that is done by the presence of the signals due to the ethyl ester at 4.2 and 1.3 ppm. The cyclisation step had not occurred, therefore it was decided that the other published method would be attempted.



Unfortunately, the equipment necessary to carry out reactions at such high pressures was unavailable at the required time, therefore it was decided to carry out a standard hydrogenation method in order to see if the required quinolinone could be synthesised at room temperature and atmospheric pressure (Scheme 40).

The *bis*-nitroaryl compound, **104**, was dissolved in MeOH and stirred in the presence of palladium on carbon under an atmosphere of hydrogen for 16 hrs. The solution was filtered through celite and the solvent removed in vacuo, the crude product was purified in the same manner as described above, yielding 93% of the product, **132**. The ¹H NMR for this product agreed with the NMR of the previous reaction showing that the reduction had indeed taken place to give **132**, however, cyclisation had not occurred.



It was thought that having a slightly less polar solvent would improve the chances of the product cyclising, therefore the precursor was dissolved in ethyl acetate and the above procedure repeated. The purified product, 132, was obtained in 95% yield which was slightly higher than that previously obtained but the cyclisation had still not taken place as shown by examination of the ¹H NMR spectrum of the isolated product.

It was postulated that adding some acid into the reaction mixture would activate the ester towards cyclisation. Returning to the literature to find alternative methods of reducing the nitro groups to the corresponding amines that could also promote cyclisation to the quinolinone. Johnstone *et. al.* described in 1977^{32} that formic acid could be used as a co-catalyst in the palladium mediated reduction of aromatic nitro compounds to the corresponding anilines (Scheme 42)



The procedure was essentially the same as that used without the additive with the formic acid added at the beginning of the reaction. The *bis*-nitro arene, **104**, was reduced under the reported conditions. Following filtration and basic work up the product was obtained in 76% yield. Disappointingly, the addition of formic acid had not promoted the desired cyclisation.



It was again thought that having a slightly less polar solvent in the reaction mixture would improve the chances of the cyclisation taking place, therefore the reaction was run in ethyl acetate. This unfortunately proved not to be the case since the purified reaction product (obtained in 69% yield) was shown by ¹H NMR to be the uncyclised product previously obtained.

For the next experiment it was decided to change the additive in the mixture. Sodium hydroxide was chosen (Scheme 44) in order to investigate the action of a basic reaction medium on the cyclisation of the intermediate, since it was believed that the presence of an acidic reaction medium was interfering with the nucleophilic nature of the aniline by formation of a salt. The sodium hydroxide was added at the very beginning of the reaction. The reaction was allowed to stir under an atmosphere of hydrogen for 16 hrs and then the solids removed by filtration through

celite and the methanol removed in vacuo. The residue was then re-dissolved in DCM and subjected to acidic work up followed by column chromatography to again yield the *bis*-aminoaryl compound, 132, in 93%. Interestingly, the ethyl ester of the substrate had remained intact throughout this transformation (Scheme 44)



It was at this point that it was concluded that using palladium as catalyst was unsuitable to the process necessary to generate the desired quinolinone product. After returning to search the literature iron powder was found to have been used as a catalyst,³³ so it was decided to attempt our reaction with iron (Scheme 44). The iron was added to the acetic acid solution and immediately attached to the magnetic stirrer. During the course of the reaction the iron oxidised and detached from the stirrer leaving the solution a rust-orange colour. Following an hour of refluxing the mixture was cooled to room temperature, the oxidised iron removed via filtration and DCM added to the acidic solution. The mixture was washed with NaHCO3 and the crude product purified by column chromatography and yielded two products in a combined yield of 90%. The NMR spectra of the two isolated products differed only in the aromatic region between $\delta_{\rm H}$ 6.5 and 8.2 ppm. The first compound was identified as 133 by the presence of two doublets at 7.13 and 6.43 ppm and a set of signals integrating to 4 hydrogens between 8.10 and 7.42 ppm. The second identified by the same sets of signals but their position was slightly shifted in comparison to those of the starting material and compound 133, the signals were located at 8.23 and 7.60 ppm for the pair of doublets relating to the para substituted aromatic ring and between 7.10 and 6.79 ppm for the ortho substituted aromatic ring of compound 134. The NMR data proved that the reaction had not gone to completion and also that cyclisation had not occurred. It was believed that if the reaction was run for a longer period of time then the precursor would not only be completely reduced but the cyclisation step would also proceed.



Scheme 45

The procedure for the next reaction was the same as the previous reaction except for the longer reaction time (Scheme 46). The product of this reaction was again the *bis*-aniline (87% yield), 132, that had been synthesised repeatedly.



Zinc dust has been used in order to reduce o-nitroaniline, 135, to 1,2-diaminobenzene, 136.³⁴ Therefore it was decided that Zinc could be of interest in this investigation (Scheme 47).



Scheme 47

The precursor *bis*-nitro compound was dissolved in ethanol and the Zn dust added before adding a drop of conc. HCl prior to refluxing the mixture for 2.5 hours. Following the reflux the mixture was cooled to room temperature and filtered through celite to remove the zinc oxide formed in the reaction and any excess zinc that remained. After column chromatography the product, 137, was obtained in 75% yield. It was pleasing to find that analysis of the ¹H NMR data showed the absence of characteristic peaks due to the ester group along with the required aromatic peaks. The supposition that the required quinolinone had indeed been synthesised was reinforced by the ¹³C NMR, HRMS and IR spectroscopy.



Although the required product had been synthesised it was felt that we could improve the yield. The presence of the HCl in the mixture could be hindering the cyclisation step by fully protonating the NH₂ group that under went cyclisation to the ⁺NH₃ thereby preventing the attack on the carbonyl of the ester in some small degree. It was decided to utilise a slightly weaker acid (acetic acid, pka \approx 5) in order to see if this was the case (Scheme 49). The procedure was identical to the one used for the HCl (pka \approx -5) experiment. Following work-up and purification the product, 137, was indeed found to have a higher yield of 98%.



At this point the series of results obtained for the 3 acidic additives that had been added to the reaction mixture (namely formic acid, acetic acid and HCl) was slightly confusing. The greater success of the acetic acid in promoting the reaction would suggest that for the reaction to proceed a weak acid was needed, therefore the failure of the formic acid to promote the reaction was a surprise to us. Presumably only catalytic acid would be necessary to promote the reaction as higher concentrations of H^+ would be more likely to associate with the aniline nitrogen thereby reducing its nucleophilicity. After examining the reaction conditions employed the concentration of HCOOH used in the reaction was found to be 15 times higher than that found for both the HCl and acetic acid reactions. Although formic acid is only slightly stronger an acid (pKa ~ 4) than acetic acid the higher concentration of formic acid in the reaction was the cause for the reduced reactivity.

Once is was determined that the desired product had been formed the protocol was applied to the other members of the range of related *bis*-nitroaryl compounds that had been synthesised previously. All of the reactions were performed under the standard conditions (Zn dust, EtOH, AcOH under reflux for 2.5hrs) gave us the intended product in very good isolated yields (91-93%) (Table 2).



Scheme 50

Entry	R	Yield (%)
1	Me	93
2	OMe	93
3	OPh	92
4	F	91
5	Cl	93

In conclusion, this project has developed a facile one-pot tandem VNS coupling reaction that was used in order to synthesise a small range of related biologically significant compounds from fairly simple starting materials. These compounds possessed rich and diverse functionality suitable for further elaboration synthesise more complex systems. This effective two-step procedure to prepare densely functionalised quinolinone products proved to be both efficient and high yielding and provides a further example of the power of the VNS reaction within synthesis.

Chapter 3: Introduction to aminocatalysis

3. Introduction to aminocatalysis

3.1. Catalytic asymmetric synthesis

Asymmetric synthesis is a term given to the dedicated preparation of stereochemically pure compounds, which have a defined three-dimensional structure.³⁵ The quest for chemically defined, enantiopure compounds is of growing importance to organic chemists, specifically (but not confined to) the pharmaceutical industry where the need for optical purity in biologically active products has become one of the driving forces behind improvements in the control of the stereochemical result of chemical reactions. An indication of the importance of asymmetric synthesis to modern synthetic chemistry was the award of the 2001 Nobel Prize for Chemistry to K.B. Sharpless (chirally catalysed oxidation reactions), R. Noyori and W.S. Knowles (both for their work on catalytic chiral hydrogenation reactions) for their invaluable work in this critical and expanding area of science.³⁶



Initially, enantiopure compounds were only obtainable by isolation from nature, but gradually the ability of synthetic chemists to reproduce these biologically active compounds in the laboratory grew to the point where chemically complex molecules, such as Taxol,³⁷ could be synthesised from relatively simple building blocks. Now, an enantiomerically pure compound

can be obtained by reaction of a chirally pure starting material (e.g. an amino acid), resolution of a mixture of enantiomers (either by preparative HPLC with a chiral stationary phase or selective crystallisation), by the use of chiral auxiliaries, or by one of two types of catalytic reaction of prochiral precursors. These types can be characterised as: i) conversion of prochiral sp² compounds to enantiopure sp³ compounds (such as chiral carbon-carbon double bond reduction or nucleophilic addition to ketones) or ii) conversion of enantiotopic substrates into enantiomerically enriched compounds by breaking the symmetry of the precursors (for example allylic oxidation) (Scheme 51).³⁸



The formation of these enantiomerically enriched products can be generated either by the generation of a chiral compound by addition of a chiral auxiliary (e.g. Evans' oxazolidinone,³⁹ **153**) in stoichiometric quantities resulting in a lower atom efficiency of the overall process (Scheme 52), or by the use of a catalytic amount of a chrial substance (e.g. ADmix- α and ADmix- β for the Sharpless asymmetric dihydroxylation⁴⁰) (Scheme 53). Asymmetric catalysis has an advantage over chiral auxiliary addition due to the low loading of catalyst that can be achieved (frequently less than 1 mol%) to generate equally impressive results.



Scheme 53

3.2. Organocatalysis

The term organocatalysis was coined in the late 1970's in order to describe the field of organic synthesis that utilised relatively low molecular weight, simple organic molecules as catalysts in given transformations.



An example of such a molecule is 4-(N,N-dimethylamino) pyridine, 163, which can be used to catalyse the esterification of alcohols using acyl chlorides (Scheme 54). The DMAP, 163, first attacks the acyl chloride, 162, displacing the chloride to form the activated intermediate, 164. This activated intermediate is then attacked by the alcohol, 166, forming the ester, 165, and regenerating the DMAP which is then free to re-enter the catalytic cycle.⁴¹ Addition of a stoichiometric amount of a tertiary amine is also needed in these transformation to remove the HCl generated.

DMAP, in a chiral form, can also be used to resolve a racemic mixture of alcohols. This is accomplished by the selective acylation of one of the enantiomers. The groups of Spivey⁴² and Fu^{43} amongst others, have been successful in using chiral DMAP analogues in this manner.



Spivey's method concentrated on using 'axially chiral' analogues of DMAP, 173, which utilised the high restriction to rotation around the aryl-aryl bond to create atropisomers that allow the selective acylation of secondary alcohols (Scheme 56).



Fu's approach differed in the fact that instead of relying on the 'axial chirality' generated by Spivey, he generated a 'planar chiral' DMAP, 173, by using a metal complex in order to block the top or bottom face of the planar DMAP analogue thereby distinguishing between the left and right side of the molecule (Scheme 56). Both methods have their advantages, the Spivey type catalysts have a higher activity but the selectivity of the Fu type catalysts are 3-5 times more selective based on similar substrates.

The driving philosophy in synthetic organic chemistry is the development of cleaner, faster and more selective transformations. This guiding principle, along with the rate at which the detection limits of modern analytical equipment is improving, has seen the desire to develop metal-free functional-group transformations increase at a phenomenal rate in recent years. At the heart of any synthetic organic chemists work are a group of core reactions that over the last 2 decades have received considerable attention by utilising small organic molecules in order to make them more efficient and tolerant of ambient conditions. The field of organocatalysis has seen a rapid expansion from its beginnings as a concept to being a considerable contributor to the scientific literature today, due to the variety of cheap, widely available enantiomerically pure compounds that are suitable for use as catalysts. Another benefit of having an organocatalytic method for accelerating a given process is, that unlike many organometallic catalysts, reactions can be carried out in the presence of air and moisture removing the need to use specialised equipment such as Schlenk apparatus and glove boxes, which therefore make the methods more amenable to scale-up to the industrial level.

Despite the advantages of organocatalysts, namely the lack of residual metals in the products and tolerance of air/moisture, the field is not ready to completely replace metal-mediated processes that are prevalent in organic synthesis today. A lot of the newly developed organocatalytic processes that are reported in the literature are highly substrate dependant. Metal-mediated processes also currently lead the way with respect to catalyst loading where metal catalysts are generally used with a loading of <1 mol%, whereas the majority of organocatalytic processes operate in the 5-20 mol% catalyst loading range. Also the sheer number of metal ligand types available mean that it is relatively simple to tune the selectivity/activity of a metal centred catalyst by changing the ligands. An example of which can be seen in the increase of activity between the 1st and 2nd generation Grubbs catalyst, with the 2nd generation being designedby modification of the ligands on the initial catalyst.⁴⁴

Although it is unlikely that organometallic processes will be completely replaced by organic counterparts, as least in the near future, the development of novel catalysts for existing, well studied, core reactions can only be of assistance to the synthetic chemist in their quest to perform more complex chemistry in search of evermore potent and selective compounds.

3.3. Iminium ion catalysis

The concept of iminium ion catalysis can be easily understood form the use of Lewis acids to accelerate reactions involving α , β -unsaturated carbonyl compounds (Scheme 57). Addition of a Lewis acid, 175, to a carbonyl substrate, 176, forms a complex, 177, causing an increase in reactivity of the alkene portion of an α , β -unsaturated carbonyl compound by lowering the energy level of the LUMO associated with the π -system. In an analogous manner, the formation of an iminium ion, 180, between a secondary amine salt, 179, and an α , β -unsaturated carbonyl compound. The main difference between iminium ion and Lewis acid catalysis is the mode of binding between the catalyst and substrate. Lewis acids frequently bind *via* a σ -bond between the catalyst and the substrate

whereas amine catalysts bind *via* a covalent bond, this stronger binding allows iminium ions to be isolated and studied more closely. Additionally, along with the formation of the iminium ion, **180**, is the generation of a molecule of water, **181**. This means that iminium ion catalysis is inherently tolerant of moisture greatly adding to the practicality of the work



Scheme 57

The catalytic cycle for a typical iminium ion catalysed process consists of three steps. The first is the formation of an iminium ion, 183, from a secondary amine salt, 179, and an α,β -unsaturated carbonyl, 28. The second is the reaction of the iminium ion with in cycloadditions (e.g. Diels-Alder reaction, Scheme 58) or a nucleophile (conjugate addition, Scheme 59). The third step is the hydrolysis of the iminium ion of the product which reforms the secondary amine allowing it to re-enter the catalytic cycle.



In the case of the Diels-Alder reaction (Scheme 58) the process begins with the addition of a secondary amine salt, 179, to an α , β -unsaturated aldehyde, 28, displacing water and forming an iminium ion, 183. The formation of the iminium salt has the effect of lowering the energy level of the LUMO of the carbon-carbon double bond thereby activating the π -bond towards

cycloaddition.⁴⁵ Hydrolysis of the ensuing Diels-Alder adduct, 185, by the molecule of water generated in the first step regenerates the secondary amine, 179 allowing it to re-enter the catalytic cycle.

The first step of the catalytic cycle of the conjugate addition of a nucleophile to an α,β -unsaturated aldehyde, 28, (Scheme 59) is the same as in the Diels-Alder case, the formation of the iminium salt, 183. The formation of the iminium salt activates the carbon-carbon double bond towards nucleophilic attack, generating an enamine, 187. Hydrolysis of the enamine generates the conjugate addition product, 188, once again regenerating the amine catalyst, 179.



The group of MacMillan has extensively studied the use of chiral secondary amines as catalysts in the Diels-Alder reaction. In 2000 they published an article⁴⁶ describing the investigation of Diels-Alder reaction secondary amine catalysts for use in the between a, β-unsaturated aldehydes, 189, and a series of dienes, e.g. 184, (Scheme 60). They initially studied the use of amino acid based catalysts, 190, and found that they achieved high yields and high enantioselectivities, along with a respectable ratio of exo:endo products. The authors examined the generality of the process with respect to the α_{β} -unsaturated aldehyde and the nature of the diene and found that the process was reasonably tolerant of a wide range of functional groups.



Scheme 61

Within the paper the authors proposed a hypothesis to explain the selectivity of the reaction using an enantiopure imidazolidinone, 190. There is a possibility for the formation of two iminium ions from the reaction of cinnamaldehyde, 193, and the imidazolidinone, 190. In the article it was proposed that only one of the iminium ions was energetically favourable, the geminal dimethyl substituents of the catalyst and the alkene means that only the (E)-isomer of the iminium ion, 194, was formed. A rationale for the high level of asymmetric induction was provided by the position occupied by the benzyl substituent which allowed a π - π interaction between the phenyl group and the alkene. Consequently, the phenyl group effectively blocks the *Re*-face of the dienophile leaving the *Si*-face open to react with the incoming diene (Scheme 61).

One of the most difficult processes in synthesis is the formation of carbon-carbon bonds. This difficulty arises from the lack of functional group tolerance along with the substrate specificity afforded by many of the new synthetic methods currently being developed. The use of secondary amine based processes can somewhat alleviate these problems and highly selective processes have been developed. During the development of secondary amine catalysis two main classes of nucleophile have come to the fore in the conjugate addition of carbon nucleophiles to α - β -unstaurated carbonyl compounds; aryl or heteroaryl compounds which undergo Friedel-Crafts type addition and C-H acids such as 1,3-dicarbonyl compounds that undergo Michael type additions.

Following the development of the imidazolidinone catalyst, **190**, for the Diels-Alder reaction a method emerged in which the alkylation of electron rich heteroaromatic compounds by α,β -unstaurated aldehydes catalysed by a related imidazolidinone.⁴⁷



Within this paper the regiospecific alkylation of pyrroles was described (Scheme 62). The reaction conditions, functional group tolerance and the nature of the catalyst co-acid were examined. The optimum solvent system was found to be a mixture of THF and water while the temperature had to be kept low (-60 to -30 $^{\circ}$ C) in order to ensure chemoselectivity. Co-acid selection was also found to be crucial depending on the nature of the substrate.



Scheme 63

The addition of malonates to α - β -unstaurated ketones provides a simple first step in the formation of more complex substrates, such as δ -ketoesters and tetrahydroisoquinolines. The group of Jørgensen published the use of an imidazoline, 200, prepared from phenyl alanine, in order to catalyse the addition of dibenzyl malonate, 199, to α - β -unstaurated ketones, 198 (Scheme 63). The authors found that the reaction was fairly general, the only exception found was the presence of steric bulk around the reactive carbonyl centre. The quoted results were obtained only by using the malonate as the reaction solvent and reaction times of between 150 and 288hrs. As with other catalysts, the observed enantioselectivities were explained through the selective formation of the (*E*)-iminium ion, and the blocking of the *Re*-face of the π -system.

In order for asymmetric iminium catalysed processes to become part of the mainstream arsenal of the synthetic organic chemist, it must be demonstrated that the methods developed can be used for industrial processes and not just remain research laboratory curiosity. MacMillan and co-workers⁴⁸ have begun the process of making iminium catalysis accessible for industrial use by demonstrating that a secondary amine, **205**, can be used to prepare biologically significant compounds.



The imidazolinone, 205, was used in order to catalyse a Mukaiyama-Michael reaction between a silyloxyfuran, 203, and *tert*-butyl 4-oxobutenoate, 202, as the first step towards the synthesis of spiculisporic acid, 208, a commercially important biosurfactant for metal decontamination and fine polymer production (Scheme 64).

The paper also states that it is possible to reverse the stereoinduction generated by the catalyst by using methyl 4-oxobutenoate, 204, as the substrate. This product was then taken through the remainder of the synthesis to generate 5-epi-spiculisporic acid, 209.

3.4. Enamine catalysis

A particularly useful strategy for the utilization of carbonyl compounds involves the catalysis of their reactions with primary and secondary amines via enamine intermediates.⁴⁹1 The basis of *enamine catalysis* is the reversible and catalytic generation of enamines from amines and carbonyl compounds. Enamine formation is facilitated by the dramatic increase in C-H-acidity upon initial conversion of the carbonyl compound into an iminium ion. The catalytically generated enamine undergoes addition reactions with various electrophiles (X=Y and X-Y) via nucleophilic addition or substitution reactions, similarly to the well studied chemistry of

preformed enamines. The resulting new iminium ion furnishes after hydrolysis with in situ generated water the α -substituted carbonyl products.



Scheme 65

An example of an enamine catalysed process is the aldol reaction promoted by the addition of the amino acid proline (Scheme 16). The proline, 211, forms an iminium salt, 213, with the ketone, 216. The increased acidity of the α -proton (due to the iminium ion) allows deprotonation, under the reaction conditions, forming an enamine, 214. The enamine attacks the aldehyde, 215, forming a second iminium ion, 216, which is hydrolysed to the ketone product, 210, regenerating the catalytic amine.



Figure. 6

The product, **210** can be obtained in very high e.e's which has been explained using a metal free version of the Zimmerman-Traxler transition state (Figure 6) which promotes re-facial attack of the aldehyde by utilising the acid moiety of the proline holding the aldehyde in place.

3.5. Iminium ion/enamine dual catalysis

Within the catalytic cycle of iminium ion catalysis of conjugate addition reactions, the intermediate from the addition reaction is an enamine. The trapping of this intermediate with a variety of nucleophiles gives rise to the possibility of using this process to form a wider range of products.



Scheme 66

The initial steps of the dual catalytic cycle are the same as those in the iminium ion case. The first is addition of a secondary amine, 179, to an α , β -unsaturated carbonyl compound, 218, forming an iminium ion, 219. A nucleophile attacks the carbon-carbon double bond forming an enamine, 220. An electrophile is then used to trap the enamine intermediate. The second iminium ion, 221, is then hydrolysed to give the desired product, 217, leaving the secondary amine free to re-enter the catalytic cycle (Scheme 66).



Scheme 67

The work of Sharpless on allylic epoxidation⁵⁰ has inspired a large effort into developing an organocatalytic method to epoxidise both electron rich⁵¹ and electron deficient⁵² unsaturated systems. Catalytic asymmetric methods have also been developed⁵³ and these transformations make use of a dual iminium ion/enamine catalysed procedure to epoxidise electron deficient systems.



The group of Jørgensen made one of the first contributions to this area using a di-aryl prolinol derivative, **226**, as the catalyst in the epoxidation of α , β -unsaturated aldehydes (Scheme x).⁵⁴ The optimal conditions found by the authors used 35% hydrogen peroxide as the oxidant in a solution of DCM and the products of various α , β -unsaturated aldehydes were formed in good yield (63-90%) and enantiomeric excess (75-96%) by using only 10 mol% of the catalyst, **226**.



The formation of an aziridine is a relatively straight forward first step in the generation of β -amino esters, as shown in the work of Córdova.⁵⁵ The enantioselective aziridination of an α , β -unsaturated carbonyl compound, 225, using a protected hydroxylamine, 228, in the presence of a diaryl prolinol, 229, proceeded in upto 78% yield and 99% yield. The reaction was a two step process involving iminium ion formation, conjugate addition of the hydroxylamine followed by a 3-*exo*-tet cyclisation to eliminate acetate and give the desired aziridine following hydrolysis of the iminium species (Scheme 68).

3.6. Baylis-Hillman reaction



The Baylis-Hillman reaction has its origins in a German patent filed in 1972 to Baylis and Hillman.⁵⁶ It involves the formation of a carbon-carbon bond between an α,β -unsaturated carbonyl compound, 230, and a second carbonyl compound, 231, in the presence of a tertiary amine base, 232 (e.g. DABCO) (Scheme 69). The initial step of the process involves a conjugate addition of the base to the unsaturated carbonyl followed by addition of the resulting enolate to the second carbonyl. Elimination of the tertiary amine catalyst generates the product from the reaction, a highly functionalised compound, 233, containing a new stereogenic centre.

It is the formation of this stereogenic centre that has opened the Baylis-Hillman up to the development of a catalytic asymmetric variant of the reaction. There are 4 methods for influencing induction of the asymmetry; i) chiral activated alkene, ii) chiral electrophile, iii) chiral base and iv) chiral solvent.



Scheme 70

Two of these have received considerable attention. The reaction of menthyl acrylates, 235, with aldehydes (Scheme 70) was studied by Gowriswari⁵⁷ who obtained a maximum d.e. of 70%. A chiral variant of DABCO, 240, has also been studied.⁵⁸ It was found that 15 mol% of the catalyst generated the desired product with an e.e. of up to 47%.



Scheme x

The group of Hatakeyama⁵⁹ has developed a catalyst based on the structure of quinidine, 244, that generates the Baylis-Hillman adduct in upto 74% yield and upto 91% e.e. The authors rationalised that the formation of a hydrogen bond between the hydroxyl group of the catalyst and the intermediate Michael addition product gave the correct conformation for the E_2 or E_{1CB} elimination of the catalyst needed to furnish the product (Scheme 71).

The Baylis-Hillman reaction has also been investigated with respect to developing an iminium/enamine catalysed variant and this was to be the focus our investigations. In order to begin to examine efficacy of the enamine catalysed reaction we decided to follow the example of Shi, who despite having worked on the Lewis acid catalysis of the reaction,⁶⁰ had also been investigating the use of proline as a co-catalyst in order utilise iminium ion activation.⁶¹



Scheme 72

The authors showed that using DABCO as the base in the reaction resulted in a significant achiral background reaction. Instead, they examined less nucleophilic amines to see if they could slow down the reaction and allow the participation of iminium ion activation. The first step in the catalytic cycle was the formation of the iminium species, **246**, between proline, **211**, and the unsaturated ketone (MVK), **239**. Next was the conjugate addition of the base to give the zwitterionic enamine intermediate, **248**, followed by addition of the aldehyde to give a second iminium species, **249**. Elimination of the Lewis base catalyst and hydrolysis of the iminium ion gave the desired product, **250** (Scheme 72).

The reaction conditions, using 30 mol% proline, were examined to determine the best solvent, Lewis base and substrate tolerance with respect to the aldehyde. The results showed that the optimum solvent was DMF and in this solvent 30 mol% imidazole turned out to be the most effective Lewis base, giving the product in 91% yield. The conditions also proved to be fairly general for electron deficient aromatic aldehydes, with reactivity reduced for aliphatic and electron rich substrates.



Following the emergence of Shi's findings two further publications re-inforced the co-catalyst concept for the Baylis-Hillman reaction. Both papers came form the group of Miller.⁶² The first described the use of proline along with a π -(Me)Histidine, 251, which was incorporated into a polypeptide chain (Scheme x). Although the first thought was that the interactions of the proline with the peptide chain was responsible for the enantioselectivity of the reaction, the authors determined through reactions with both L- (78% e.e.) and D-proline (-39% e.e.) that it was the proline that was the dominant partner in imparting the observed enantioselectivity.



The second paper to involve the co-catalyst concept concentrated on the proline component. The imidazole was replaced by N-methyl imidazole, 254, and various proline analogues were examined. The main finding was that modifying the proline in any way was detrimental to the e.e. observed. Only pipicolinic acid, 253, was as active as proline, resulting in similar levels of selevtivity.

3.7.Aims and Objectives

It was these three publications combined that led us to investigate dual catalysis within the Baylis-Hillman reaction. The catalytic cycle (Scheme x) proposed in Shi's paper gave us a starting point. We envisaged that we could control the formation of the stereogenic centre by utilising the inherent stereochemistry present in the proline. The first step in the mechanism involved the formation of an iminium salt and an equivalent of water. This was followed by the conjugate addition of imidazole followed by addition of the resulting enamine, xx, to the aldehyde. The elimination of the imidazole and the hydrolysis of the proline by water gives the product and the catalysts are free to re-enter the cycle.



The control of the enamine addition would be the way to introduce any stereochemical information into the product. To do this we thought that we could form an ester/amide of the proline catalyst in order to attempt to block one face of the alkene and force the aldehyde to approach the activated intermediate from the opposite face.

The reaction of MVK, 239, with 4-nitrobenzaldehyde, 238, was ideal in the fact that Shi had developed conditions to synthesise the Baylis-Hillman adduct, 241, that would provide a base from which to begin our investigations (Scheme 76).



Our principle goal for this project was the development of a single catalyst with the properties of both proline (for its iminium ion forming ability) and the imidazole (for its nucleophilic properties). In order to do this we would have to examine the relationship between the two components when they were separated by varying length of alkyl linker (Figure 7).



By combining the two catalysts into one compound we hoped to be able to reduce the amount of catalyst needed to achieve the levels of activity and efficacy needed to make the process applicable not only on a research scale but on an industrial scale as well.

Chapter 4: Organocatalysis results and discussion

4. Organocatalysis Results and Discussion

4.1. Solvent effect on the aminocatalysis of the BHR

A recent report by Shi showed that a combination of 30 mol% imidazole, **256**, and 30 mol% L-proline, **211**, catalysed the Baylis-Hillman reaction between methyl vinyl ketone (MVK) and a series of benzaldehydes in good to excellent yield (Scheme 77, Table 3).⁶³



Entry	Lewis Base	Solvent	Time	Yield
			(hrs)	(%)
1	Imidazole	DMF	24	91
2	Imidazole	DMSO	24	90
3	Imidazole	THF	24	87
4	Imidazole	Chloroform	24	88
5	Benzimidazole	DMF	24	45
6	1 <i>H-benzimidazole</i>	DMF	36	-
7	NEt ₃	DMF	36	66
8	Pyridine	DMF	40	-

Scheme 77

Table :	3
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Shi found that by performing the Baylis-Hilmann reaction of methyl vinyl ketone (MVK), 239, and 4-nitrobenzaldehyde, 238, in the presence of 30 mol% of both L-proline, 211, and imidazole, 256, in a range of aprotic solvents gave the Baylis-Hilmann adduct, 241, in excellent yields (entries 1-4, Table 3). The authors also experimented with the nature of the co-catalyst in order to determine what effect lowering the Lewis basicity would have on the yield of the reaction. The efficacy of benzimidazole, *1H*-benzotriazole, triethylamine and pyridine (entries 5-8) were examined. All four of the amines gave a lower yield than that obtained using imidazole with *1H*-

benzotriazole (entry 6) and pyridine (entry 8) not providing any of the desired product. The lower the Lewis basicity for the four amines, compared to imidazole, was proposed as the reason for the reduced yields. The authors the proceeded to examine the generality of the conditions with respect to other aldehydes (Table 4).

Entry	Aldehyde	Reaction time (hrs)	Yield (%)
1	<i>m</i> -nitrobenzaldehyde	24	90
2	o-nitrobenzaldehyde	24	8 6
3	p-bromobenzaldehyde	48	85
4	p-chlorobenzaldehyde	60	67
5	benzaldehyde	72	45
6	<i>p</i> -ethylbenzaldehyde	80	30
7	2-pyridaldehyde	24	90
8	3-pyridaldehyde	24	80
9	trans-cinnamaldehyde	72	43
10	butyraldehyde	80	46

Table 4

The results achieved show that the Shi protocol was general to a range of aldehydes both aromatic (entries 1-9) and aliphatic (entry 10). Although the enantiomeric excesses reported by Shi were low (<5%), it was encouraging enough to believe that recent advances achieved in organocatalysed transformations involving secondary amines would allow us to begin to elucidate the mechanism of this intriguing process and investigate alternative amines to accelerate the reaction.

As a starting point we elected to replicate Shi's conditions in order to get a feel for the reaction and its products. Reaction of MVK, 239, with 4-nitrobenzaldehyde, 238, in the presence of 10 mol% of L-proline, 211, and 10 mol% imidazole, 256 (a lower catalyst loading than that reported by Shi) provided a convenient place to initiate this investigation (Scheme 78).



Scheme 78

Our first attempts using our variation of the Shi conditions proved less successful than expected, the adduct being isolated in 63% yield (Table 5, entry 1). We decided to repeat the reported conditions by increasing the catalyst loading of both the proline and the imidazole to 30 mol% each (Table 5, entry 2). To our surprise this led to a significantly lower isolated yield of the product (54%). In order to explain this anomalous result we speculated that the DMF used as solvent in the Shi reaction could have contained a small amount of water and sought to examine the effect of known quantities of water on reactivity. It has been shown previously that water has a beneficial role in the organocatalysed Diels-Alder reaction between α,β -unsaturated aldehydes and cyclopentadiene by both MacMillan⁶⁴ and Ogilvie,⁶⁵ we therefore carried out a series of reactions in the presence of 5 (entry 3), 10 (entry 4), 25 (entry 5), 50 (entry 6) and 100 vol% water (entry 7) to determine the effect on reactivity. We were pleased to see that adding 10 vol% water increased our yield significantly to 80% (entry 4) and from this optimum further water was detrimental to the isolated yield of the reaction (entries 5 and 6). Running the reaction in pure water gave the lowest yield of adduct observed (16%) (entry 7). As can be seen from the plot (Fig. x) the addition of water to the reaction mixture beyond the optimum 10% (v/v) results in a dramatic drop in reaction yield. This is due to the presence of competing reactions, and the formation of by-products, which are visible in the NMR spectrum, but we have not been able to identify these products due to difficulties in purifying the crude reaction mixtures from these 'high water' reactions.

Entry	Solvent	proline (mol%)	Imidazole (mol%)	Yield (%)
1	DMF	10	10	63
2	DMF	30	30	54
3	DMF/H ₂ O 19:1	10	10	63
4	DMF/H ₂ O 9:1	10	10	80
5	DMF/H ₂ O 7.5:2.5	10	10	40
6	DMF/H ₂ O 1:1	10	10	30
7	H ₂ O	10	10	16
8	THF	10	10	27
9	THF/H ₂ O 19:1	10	10	62
10	THF/H ₂ O 9:1	10	10	30
11	THF/H ₂ O 1:1	10	10	32

*all reactions carried out at 25°C, for 24 hrs at 1M concentration

Table 5



Figure 8

A recent report by Millar has shown THF to be an effective solvent for the proline catalysed BH reaction in the presence of a complex amine base, with the adducts being isolated in good yields and enantiomeric excess.⁶⁶ THF also provides a practical advantage over DMF in its ease of handling. We therefore examined THF and THF/water mixtures in our standard reaction of MVK and 4-nitrobenzaldehyde catalysed by proline and imidazole (entries 8-11). Again the addition of water improved the reaction yield up to a maximum THF:H₂O ratio of 19:1 (62% yield (entry 9). Addition of further amounts of water (entries 10 and 11) resulted in a similar fall in yield consistant with our observations with DMF. The experiments showed that THF/water mixtures were not as effective as DMF/water mixtures.

It was clear from the series of experiments carried out that water had an extremely important role to play in the reaction. We hypothesised that the water was acting as a proton transfer agent thereby promoting formation of the iminium ion due to the increased concentration of H^+ needed for iminium ion formation, this hypothesis was re-enforced by the observations of both MacMillan and Ogilvie.

Having established that water had a significant role to play in the proline/imidazole catalysed BH reaction of MVK and 4-nitrobenzaldehyde, we proceeded to investigate the generality of the phenomenon with alternative aldehydes (Scheme 79, Table 6).



The reaction was performed for a series of aldehydes in both anhydrous DMF and a mixture of DMF and water (9:1) with 10 mol% of both proline and imidazole. In all cases we observed an increase in yield with the addition of water (10 vol%) to the reaction mixture. In the case of para-fluorobenaldehyde anhydrous DMF gave the product in 67% yield while the DMF/water mixture gave the product in 87% yield (entries 1 and 2). The presence of the water in the reaction mixture of 2,4-dinitrobenzaldehyde reaction almost doubled the observed yield from 41% to 81% (entries 3 and 4). Reaction of 2,4-dichlorobenzaldehyde with MVK generated the product in 56% yield when conducted in anhydrous DMF, addition of water increased the yield to 80% (entries 5 and 6). Ortho-nitrobenzaldehyde behaved, as expected, in a similar fashion to paranitrobenzaldehyde with the anhydrous reaction generating the product in 58% yield and the 'wet' reaction mixture generating the product in 73% yield (entries 7 and 8). The most dramatic evidence of water being necessary for the BH reaction to take place was found when the reaction of pentafluorobenzaldehyde and MVK was attempted. The anhydrous reaction mixture failed to produce the desired adduct, whereas in the presence of water, the adduct was generated in 84% yield (entries 9 and 10). Changing the aldehyde further to incorporate a different functional group (the furan moiety) had an effect on the reaction with MVK, after 24 hrs the desired BH adduct did not form in the anhydrous reaction mixture, but in the 'wet' reaction mixture the adduct was obtained in 23% yield (entries 11 and 12) due to the disappointing results we retested the furfural under the reaction conditions for a total of 90 hrs and found that the yield increased to 33% (anhydrous DMF) and 83% (DMF/H₂O 9:1) (entries 13 and 14).

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		Reaction		Viald
Entry	Aldehyde	time	Solvent	<i>(04)</i>
		(hours)		(70)
1	p-fluoro benzaldehyde	24	DMF	67
2	<i>p</i> -fluoro benzaldehyde	24	DMF/H ₂ O (9:1)	87
2	2,4-dinitro	24	DMF	40
3	benzaldehyde			42
	2,4-dinitro	24	DMF/H ₂ O (9:1)	81
4	benzaldehyde			
E	2,4-dichloro	24	DMF	F (
3	benzaldehyde			20
(2,4-dichloro	24	DMF/H ₂ O (9:1)	80
0	benzaldehyde			
7	o-nitro benzaldehyde	24	DMF	58
8	o-nitro benzaldehyde	24	DMF/H ₂ O (9:1)	73
0	Pentafluoro	24	DMF	•
9	benzaldehyde			0
10	Pentafluoro	24	DMF/H ₂ O (9:1)	84
10	benzaldehyde			
11	Fufuraldehyde	24	DMF	0
12	Fufuraldehyde	24	DMF/H ₂ O (9:1)	23
13	Fufuraldehyde	90	DMF	33
14	Fufuraldehyde	90	DMF/H ₂ O (9:1)	89

*all reactions carried out at 25°C, for 24 hrs at 1M concentration

Table 6

Following the realisation of the role that water was playing we also needed to determine the enantiomeric excess (if any) of the products formed within these reactions. Our chosen method to achieve this was HPLC using a chiral stationary phase. Successful separation of the enantiomers of the BH adduct, **xx**, was achieved on a chiralcel OJ column (5% IPA in hexanes), $t_1 = 35.4$ mins; $t_2 = 38.1$ mins (Figure 9).



Figure 9

The adducts generated within this study were examined by HPLC for any indication of asymmetric induction within the transformations. Disappointingly each of the BH products was found to be racemic.

Despite this finding we were pleased with our initial observations that water was playing a cruicial (as yet undetermined) role within the overall reaction of MVK, 239, and a series of benzaldehyde derivatives.

4.2. Effect secondary amine catalyst structure

We had shown that water had an effect on the Baylis-Hillman reaction of MVK with a range of benzaldehyde derivatives. The observation that each of these adducts was racemic was somewhat disappointing we therefore elected to examine if alternative secondary amine catalysts would increase the efficiency of the reaction and also allow us to develop an asymmetric version of this transformation.

Previous work in the group⁶⁷ had shown that the rate of the Diels-Alder reaction between *trans*cinnamaldehyde, **193**, and cyclopentadiene, **184**, can be accelerated by the hydrazine derivative **266** (Scheme 80)



Within this paper the acceleration of the Diels-Alder reaction was explained by the α -effect. We believed that the same α -effect would increase the rate at which the Baylis-Hillman reaction would take place.

The work carried out in the group involving the hydrazine derivative, 266, also showed that varying the co-acid caused the length of time needed for the reaction to occur also vary. They showed that as the pK_a of the co-acid decreased the reaction time increased. We chose to include this variable in our investigations as well.



The catalyst was synthesised by the reaction of benzoic hydrazide, 268, with acetone, 267, and subsequent double bond reduction using PtO_2 as a hydrogenation catalyst, the catalyst was formed in 73% overall yield (Scheme 81). We initially performed the reaction with 10 mol% of the hydrazine derivative, 270, and 10 mol% imidazole in our optimum solvent 10% water in DMF (Scheme 82).


The co-acids we chose were (in decreasing order of pK_a) HCl (table 3, entry 1), MeSO₃H (entry 2), TFA (entry 3) and benzoic acid (entry 4). The results of the reactions showed that the yield increased slightly by decreasing the strength of the acid but with the weakest co-acid gave no product whatsoever.

E	X Lewis Base	I annia Basa		Yield
Entry		рп	(%)	
1	HC1	Imidazole	7	23
2	MeSO ₃ H	Imidazole	7	52
3	TFA	Imidazole	7	49
4	PhCO ₂ H	Imidazole	7	0
*all reactions ca	rried out at 25°C, for	24 hrs at 1M concentrati	on	

Table 7

In the Diels-Alder reaction between cyclopentadiene and *trans*-cinnamaldehyde the lower the pKa of the co-acid the slower the reaction rate, it was expected that the same observation would be made in this case. It was surprising to see the yield of the reaction initially increased (entries 1-3, Table 7) then decrease with the weakest co-acid (benzoic acid, entry 4). It is believed that the co-acid plays a role in the β -elimination of the accepted Baylis-Hilmann mechanism. It was hypothesised that the HCl was too strongly bound to the amine catalyst to be able to protonate the imidazole in order to facilitate its elimination form the intermediate. The methane sulphonic acid and trifluoroacetic acid were more weakly bound to the amine catalyst and therefore able to protonate the imidazole more easily.

Proline has been shown to promote stereoselective aldol reactions by the formation of a metal-free Zimmerman-Traxler type transition state which promotes *Re*-facial attack of the enamine (Figure 6, page 43). Another secondary amine catalyst that has been shown to activate the reaction of α,β -unsaturated aldehydes by a similar transition state is the imidazolidinone architechture, **190**, developed by MacMillan⁶⁸ This catalyst type was shown to increase both the rate of the Diels-Alder reaction between cyclopentadiene, **184**, and cinnamaldehyde. The imidazolidinone, **190**, was also to generate the product with an e.e. of 93% (Scheme 83).



We decided to experiment with the same imidazolidinone used by MacMillan to catalyse the BHR between MVK, 239, and 4-nitrobenzaldehyde, 238 (Scheme 94).



We chose to examine catalysis of the reaction by imidazolidinone, 190, since proline wasn't promoting a steroselective reaction. The imidazolidinone architecture prevents the formation of one of the two possible geometries, 271 and 272, of the iminium ion due to the steric interaction between the α -proton of the α , β -unsaturated aldehyde and the geminal dimethyl groups of the catalyst (Figure 10).



Figure 10

We initially experimented with the solvent combinations previously examined (table x, entries 1-6) but none of the reactions provided us with the desired product. We varied the solvent to incorporate other aprotic solvents with and without added water. Both MeCN (entries 7-9) and 1,4-dioxane (entries 10-12) gave us varying degrees of success again showing the need for water in order for the reaction to proceed. The reactions run in a 1:1 mixture of solvents gave the product on both occasions in 85% yield. We analysed the products using the HPLC assay we had developed and they again proved to be racemic.

Entry	Solvent	Yield %
1	DMF	0
2	DMF/H ₂ O 9:1	0
3	DMF/H ₂ O 1:1	0
4	THF	0
5	THF/H ₂ O 9:1	0
6	THF/H ₂ O 1:1	0
7	MeCN	5
8	MeCN/H ₂ O 9:1	10
9	MeCN/H ₂ O 1:1	85
10	1,4-Dioxane	0
11	1,4-Dioxane/H ₂ O 9:1	8
12	1,4-Dioxane/H ₂ O 1:1	8 5
*all reactions carried out at 25°C, for 24 hrs at 1M concentration		

Table 8

Despite only allowing one conformer of the iminium ion to form, the imidazolidinone, 190, does nothing to promote attack by the enamine on one face of the 4-nitrobenzaldehyde, 238, over the other leading to the observed racemic product. Despite the products that we obtained being racemic we observed a surprising solvent effect. Only reactions run in a 1:1 ratio of MeCN and water (entry 9, Table 8) and 1,4-dioxane and water (entry 12) gave significant yields of the Baylis-Hilmann adduct, 241. It was hypothesised that the water effect that had been previously observed (*section 4.1*) was more pronounced in reactions catalysed by MacMillans imidazolidinone.

All of the secondary amine catalysts that were examined during the investigation share a common property; they are all non-symetrical. This fact means that any iminium ion intermediate that forms can adopt 2 different geometries (273 and 274, Figure 10). The use of indoline carboxylic acid was thought to minimise the *E*-conformer due to a van der Waals interaction between the aldehyde proton and an aromatic hydrogen during the cyclopropanation reaction between $\alpha_{\alpha}\beta$ -unsaturated aldehydes and sulphur ylides.⁶⁹



Scheme 85

We experimented with a range of solvents (Table 9), from our standard DMF (entry 1) to water (entry 3). We found that although water gave the greatest yield (entry 3) we thought that the most promising results were those obtained from the reactions run in DMSO (entry 5) and MeCN (entry 7). We have seen previously that solutions of MeCN gave good conversions to the BH adduct. Much to our disappointment none of the different solvents that we used gave rise to any enantiomeric enrichment of the final product, showing that although we had two possibilities of controlling the stereochemistry neither of which was successful. We began to come to the realisation that the nature of the secondary amine might not influence the step in which the stereochemistry of the product is determined.

Entry	Solvent	Yield % (ee%)
1	DMF	44 (0)
2	Acetone	58 (0)
3	Water	92 (0)
4	Chloroform	0
5	DMSO	71 (0)
6	THF	8 (0)
7	MeCN	72 (0)
*all reactions carried out at 25°C, for 24 hrs at 1M concentration		
Table 9		

We thought that following the success of the indoline-2-carboxylic acid in the reaction between acrolein and 4-nitrobenzaldehyde reaction we would experiment with the generality of the reaction by changing the aldehyde. The addition of a substituent at the β -position of the alkene was the direction we chose since both crotonaldehyde (R=Me) and cinnamaldehyde (R=Ph) are commercially available compounds (Scheme 85).



Crotonaldehyde (Table x, odd entries) was found to be inert under our conditions. Similarly cinammaldehyde (even entries) also proved inert in a range of solvents. We initially believed that the presence of the carboxylic acid moiety in the indolyl compound was protonating the imidazole nitrogen thereby preventing Michael attack on to the alkene. This, however, proved to be unlikely as we found that it had been proven that the Baylis-Hillman reaction of β -substituted vinyl aldehydes can be difficult to perform, so much so that pressures in excess of 9bar can be needed.⁷⁰

Entry	R	Solvent	Yield %
1	Me	DMF	0
2	Ph	DMF	0
3	Ме	Acetone	0
4	Ph	Acetone	0
5	Ме	Water	0
6	Ph	Water	0
7	Ме	Chloroform	0
8	Ph	Chloroform	0
9	Ме	DMSO	0
10	Ph	DMSO	0
11	Ме	THF	0
12	Ph	THF	0
13	Ме	MeCN	0
14	Ph	MeCN	0
*all re	actions carried	out at 25°C for 24 hrs at 1	M concentration

Table 10

In order to determine if it was only our reaction system that was preventing the reaction taking place we decided to run the reaction using the parent Baylis-Hillman Lewis base, DABCO (Scheme 86)



The reactions (entries 1-14) showed that it was not only the decreased nucleophilicity of imidazole, 256, that caused the failure of the procedure. The presence of the substituent at the β -position hinders the Michael addition of the Lewis base thereby preventing the reaction from taking place.

*

Entry	R	Solvent	Yield % (ee%)
1	Me	DMF	0
2	Ph	DMF	0
3	Me	Acetone	0
4	Ph	Acetone	0
5	Me	Water	0
6	Ph	Water	0
7	Ме	Chloroform	0
8	Ph	Chloroform	0
9	Me	DMSO	0
10	Ph	DMSO	0
11	Me	THF	0
12	Ph	THF	0
13	Ме	MeCN	0
14	Ph	MeCN	0

*all reactions carried out at 25°C, for 24 hrs at 1M concentration

Table 11

4.3. Effect of the structure of the Lewis base on reactivity

One of the initial aims of this project was the development of a 'bi-dentate' catalyst which incorporated both the iminium ion forming component and the Lewis base component into the same molecule. With this in mind we decided to experiment with *N*-methyl imidazole as the Lewis base component in our reaction as an experiment into how the Lewis base interacts with the vinyl ketone. We utilised the reaction of MVK with 4-nitrobenzaldehyde as our test reaction (Scheme 87).



Scheme 87

We hypothesised that the presence of the N-methyl group of the imidazole would make the elimination step proceed more readily since the eliminated group would be the neutral molecule of N-methyl imidazole, 254, not a charged species (Scheme 88)



The reaction was tested using a range of solvents and we found that whilst no enantiomeric enrichment was seen by HPLC, we again found that water has a dramatic effect on the yield of the reaction (Table 12). The addition of 10% and 50% water to the reaction mixture containing THF allowed the generation of the BH adduct in 90% (entry 8) and 94% (entry 9) respectively.

Entre	Calvant	Yield %	
Entry	501Ve14	(ee%)	
1	DMF	52 (0)	
2	DMF/H ₂ O 9:1	53 (0)	
3	DMF/H ₂ O 1:1	78 (0)	
4	MeCN	66 (0)	
5	MeCN/H ₂ O 9:1	0	
6	MeCN/H ₂ O 1:1	69 (0)	
7	THF	87 (0)	
8	THF/H ₂ O 9:1	90 (0)	
9	THF/H ₂ O 1:1	94 (0)	
*all reaction	*all reactions carried out at 25°C, for 24 hrs at 1M concentration		
	Table 12		

Following the results of the proline catalysed reactions we decided to experiment again with MacMillan's imidazolidinone, **190**, in order to see if the transformation of the secondary amine centre of imidazole to a tertiary amine would allow us to form the desired BH adduct (Scheme 89).



As can be seen from Table 13, no BH adduct was generated by the reactions involving MacMillans imidazolidinone and N-methyl imidazole in the same way that the reactions using the imidazolidinone and imidazole were inert. From this data we can infer that the imidazolidinone while being a good catalyst for some iminium/enamine catalysed processes it is by no means a general catalyst for all amino-catalytic processes.

Entry	Solvent	Yield %
1	DMF	0
2	DMF/H ₂ O 1:1	0
3	DMF/H ₂ O 9:1	0
4	MeCN	0
5	MeCN/H ₂ O 1:1	0
6	MeCN/H ₂ O 9:1	0
7	THF	0
8	THF/H2O 1:1	0
9	THF/H2O 9:1	0

*all reactions carried out at 25°C, for 24 hrs at 1M concentration

Table 13

After seeing that *N*-methyl imidazole was capable of catalysing the Baylis-Hillman reaction in the presence of the secondary amine proline, we wanted to determine how much of the catalysis observed in the previous case was caused by the *N*-methyl imidazole and how much was possibly attributable to any iminium ion/enamine intermediate (Scheme 90)



From the results shown in Table 14, it is ambiguous whether the proline was playing any part on the reaction or not. If we compare the yield of BH adduct in Table 12 (with proline) to the analogous solvent system in Table 14 (without proline), we can see that the proline in DMF (entry 1 in both tables) is detrimental to the tune of 30%. The proline seems to have a less detrimental effect when the reaction mixture contains a proportion of water with the reactions run in MeCN:water 1:1 (entries 6 in both tables) and THF:water 1:1 (entries 9 in both tables) show similar activities both with and without proline. From this we can deduce that water not only has a beneficial effect on the reaction but can even counteract the detrimental effect caused by having the proline in the reaction mixture.

Entry	Solvent	Yield %
1	DMF	83
2	DMF/H ₂ O 9:1	64
3	DMF/H ₂ O 1:1	76
4	MeCN	83
5	MeCN/H ₂ O 9:1	39
6	MeCN/H ₂ O 1:1	78
7	THF	80
8	THF/H2O 9:1	85
9	THF/H ₂ O 1:1	73
*all reactions carried out at 25°C, for 24 hrs at 1M concentration		

Table 14

Following the success we had using indoline-2-carboxylic acid along with imidazole as the co-catalysts for the reaction of acrolein and 4-nitrobenzaldehyde we decided to attempt the reaction using N-methyl imidazole as well (Scheme 91).



Of the reactions attempted, it was the reactions run in solutions of MeCN (entries 4, 5 and 6) which gave the BH adduct in 63% for the anhydrous reaction mixture. The reactions run with added water gave a better result with an increase to 91% with 10% water and the addition of further caused a decrease in the obtained yield. The reaction that was run in a 1:1 solution of DMF and water (entry 3) also gave the BH adduct although in a lower yield (24%). None of the BH adducts obtained showed any trace of optical enrichment.

Entry	Solvent	Yield % (ee%)
1	DMF	0
2	DMF/H ₂ O 9:1	0
3	DMF/H ₂ O 1:1	24 (0)
4	MeCN	63 (0)
5	MeCN/H ₂ O 9:1	91 (0)
6	MeCN/H ₂ O 1:1	72 (0)
7	THF	0
8	THF/H ₂ O 9:1	0
9	THF/H ₂ O 1:1	0
*all reactions of	arried out at 25°C. for 24 hrs at	1M concentration

Table 15

As with the reaction of MVK and 4-nitrobenzaldehyde it was necessary to test the background activity of the *N*-methyl imidazole. The reactions were run in the same solvent systems to directly compare the effect (if any) of the secondary amine on the activity of the reaction (Scheme 92).



The reactions run in solutions containing DMF (entries 1-3) gave fair to good yields of the product whereas only the anhydrous MeCN and THF (entries 4 and 7) solutions gave any product at all. This showed that dependant on the solvent, the indoline carboxylic acid could have either a positive or negative effect on the yield of the reaction. This would prove to be the final negative point for the use of indoline carboxylic acid as a catalyst for the Baylis-Hillman reaction as it has proven to be an unreliable and very substrate specific catalyst.

Entry	Solvent	Yield %
1	DMF	80
2	DMF/H ₂ O 9:1	72
3	DMF/H ₂ O 1:1	44
4	MeCN	16
5	MeCN/H ₂ O 9:1	0
6	MeCN/H ₂ O 1:1	0
7	THF	27
8	THF/H ₂ O 9:1	0
9	THF/H ₂ O 1:1	0

^{*}all reactions carried out at 25°C, for 24 hrs at 1M concentration

After experimenting with *N*-methyl imidazole as the Lewis base we thought that putting a different substituent on the imidazole ring would give us further insight into the mechanistic pathway of the reaction. We also thought that introducing another acidic group into the molecule would promote the formation of the enamine intermediate since as in the case above (Scheme 92) the elimination step would be aided by the fact that the molecule eliminated would have been neutral in nature (Scheme 93).



After running the reaction under our standard conditions in three separate solvents (namely DMF, DMF/H₂O and THF) we determined that the imidazole carboxylic acid was inert as a catalyst for the BH reaction (Table 17).

Table 16

Entre	S-Luma	Yield %
Entry	Solveni	(ee%)
1	DMF	0
2	DMF/H ₂ O 9:1	0
3	THF	0
*all reactions carried out at 25°C, for 24 hrs at 1M concentration		

Table 17

We thought that a possible the reason that the imidazole carboxylic acid was the presence of the acid moiety existing as a zwitterion thereby occupying the N-lone pair that attacks the MVK/proline intermediate iminium ion. We therefore decided to form the methyl ester by reaction with MeOH in the presence of catalytic HCl (96% yield).



Again the same three solvents were used along with the standard conditions and again no BH adduct was observed. This failure was thought to be due to the electron withdrawing nature of the ester group making the imidazole too weak a nucleophile to attack the alkene, even in its activated state as an iminium species.

Eastan	Salvant	Yield %
Entry	soiveni	(ee%)
1	DMF	0
2	DMF/water 9:1	0
3	THF	0

*all reactions carried out at 25°C, for 24 hrs at 1M concentration Table 18 We hypothesised that having the acid group attached to the ring was affecting the electronic nature of the imidazole ring, thereby preventing the Michael addition of the catalyst to the alkene. In order to try and alleviate this detrimental effect an experiment was designed with the acid separated from the imidazole by a methylene group in order to see if the presence of the acid moiety would be able to influence the introduction of the aldehyde to the enamine. To this end we decided to employ imidazole acetic acid in place of imidazole (Scheme 95).



As with the imidazole carboxylic acid there is no indication of any catalytic activity in any of the three chosen solvents (Table 19).

Eastan.	Sahart	Yield %
Emry	Solveni	(ee%)
1	DMF	0
2	DMF/water 9:1	0
3	THF	0

*all reactions carried out at 25°C, for 24 hrs at 1M concentration Table 19

Again we postulated that the presence of the free acid group could be impeding the ability of the imidazole to catalyse the reaction, we therefore synthesised the methyl ester by the reaction of the acid with MeOH in the presence of a catalytic amount of HCl (89% yield).



The formation of the methyl ester did little to improve the activity of the imidazole analogue as we did not observe any BH adduct formation in any of the three chosen solvents (Table 20).

Eastern	Saharat	Yield %
Entry	Solveni	(ee%)
1	DMF	0
2	DMF/water 9:1	0
3	THF	0
all reactions car	rried out at 25°C, for 24 hrs a	at 1M concentration

Table	20
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With the failure of the previous two carboxylic acids, we decided to see if we could somehow prevent the acid group from interfering with the reaction by increasing the distance between it and the reactive centre of the molecule and to also reduce the degree of freedom with which it rotated in solution. The addition of a double bond between the acid group and the imidazole accomplished both of these objectives since the double bond has a fixed geometry and contained a further methylene group increasing the chain length between the two parts of the molecule. We were lucky not to have to synthesise the desired compound as Urocanic acid, **283**, is commercially available.



The reactions run with DMF (entry 1, Table 21) and DMF/water 9:1 (entry 2) gave 63 and 50% yield of the BH adduct respectively. The reaction run in THF (entry 3) gave none of the BH adduct. Neither of the successful reactions gave any enantiomeric enhancement.

Entry	Solvent	Yield %
		(ee%)
1	DMF	63 (0)
2	DMF/water 9:1	50 (0)
3	THF	0

We wanted to see if the methyl ester would be equally active therefore we set out to synthesise it *via* the same method as described above. The urocanic acid methyl ester was generated in 92% yield.



Having performed the catalytic test reactions in the same three solvents as previous reactions we saw that none of the BH adduct had been formed. This suggests that the presence of the acid moiety in the Lewis base aids the addition of the benzaldehyde to the enamine formed between MVK and proline. The failure of the methyl ester to yield any product suggests that the carboxylic acid is necessary as part of the catalysts but it also has to be sufficiently removed from the reactive centre as to not interfere with the reaction.

Frederer	Salvart	Yield %
Entry	Solveni	(ee%)
1	DMF	0
2	DMF/water 9:1	0
3	THF	0
*all reactions	carried out at 25°C, for 24 hrs at	M concentration
	Table 22	

After observing that the acid was a necessary component of the Lewis base we decided to attempt to synthesise some novel catalystsbased on the imidazole and 2 carbon chain skeleton derived from the urocanic acid. Fortunately the amino acid histidine contains both of these features. We decided to test the amino acid itself in the reaction and no product was observed under our standard conditions. We therefore decided to protect the acid group of histidine as the methyl ester, then couple the free amine to a simple carboxylic acid (namely benzoic acid) in the presence of HOBt and DCC with stirring in DCM at room temp for 3 days. The amide, **285**, was formed in 86% yield, and before having the methyl ester removed was used as Lewis base in the reaction shown in Scheme 99.



The reactions were all run in anhydrous THF, initially only the reaction of MVK with 4-nitrobenzaldehyde and L-proline (entry 1, Table 23), but when the isolated material was analysed by HPLC on a chiral stationary phase showed that the adduct was formed with an enantiomeric excess of 14%. Encouraged by this result we ran the reaction with both racemic proline (entry 2) and also D-proline (entry 3) in order to see if we could determine whether it

was the proline or the amide that was imparting the optical activity. We were initially pleased to see that the yields of all three reactions were very similar also after HPLC analysis we saw that the racemic proline gave racemic product, and the D-proline gave the same excess of the opposite enantiomer suggesting that it was indeed the proline that imparts the chirality and not the amide. With these results in mind we experimented with other aldehydes to see if our conditions were tolerant of other substrates. The reaction of MVK with 2,4-dinitrobenzaldehyde under the same conditions gave the BH adduct in 45% yield and 10% e.e. (entry 4). The furfural adduct was formed in 48% yield and 9% e.e. (entry 5). Of the halo substituted compounds the pentafluoro derivative was inactive to our conditions (entry 6), while the 4-fluoro- and 2,4-dichloro-benzaldehyde adducts were formed in 14 and 15% (entries 7 and 8) respectively while the dichloride was the only one of the three to give an enantiomerically enriched product.

Entry	Secondary	R	Yield %
	amine		(ee%)
1	L-proline	4-NO ₂	38 (14)
2	DL-proline	4-NO ₂	32 (0)
3	D-proline	4-NO ₂	30 (14*)
4	L-proline	2,4-diNO ₂	45 (10)
5	L-proline	Fufural	48 (9)
6	L-proline	F ₅	0 (0)
7	L-proline	4- F	14 (0)
8	L-proline	2,4-diCl	15 (5)

* - opposite enantiomer

*all reactions carried out at 25°C, for 24 hrs at 1M concentration

Table 23

After the successful catalytic tests involving the histidine-benzoic acid dimer we decided to investigate whether an amide with an *N*-substituted imidazole would be equally successful in providing an enantiomerically enriched product. The amide dimer, **286** (scheme 100), was generated in 76% yield by reaction of benzoic acid and 1-(3-aminopropyl)imidazole in the presence of DCC and HOBt in DCM for 2 days.



As with the previous example we began with the reaction of MVK and 4-nitrobenzaldehyde which generated the BH adduct in 93% yield with an e.e. of 11% (entry 1, Table 24, HPLC trace shown in fig 3). The yield was improved in comparison to the histidine reactions but the e.e. was slightly depressed. The yield of the 2,4-dinitro adduct was also substantially improved (entry 2) and the product had an e.e. of 9%. The reaction of pentafluorobenzaldehyde with MVK gave the product in 37% yield and 4% e.e. (entry 4) and the reaction of the 2,4-difluoro compound gave the BH-adduct in 55% yield with an e.e. of 9% (entry 6). The only inactive reaction mixture was that containing the 4-fluorobenzaldehyde (entry 5).

R	Yield % (ee%)
4-NO ₂	93 (11)
2,4-diNO ₂	96 (8)
Fufural	14 (9)
F5	37 (4)
4-F	0
2,4-diF	55 (9)
	R 4-NO ₂ 2,4-diNO ₂ Fufural F ₅ 4-F 2,4-diF

Table 24

We believe the activity of the reaction mixtures where a stereoselectivity was observed arises due to a joint effect of both the proline (as evidenced by the switching of the enantiomer formed by the use of D-proline) and also a π,π -interaction between the phenyl group of the benzoic amides synthesised and the alkene moiety of the enamine intermediate species (Figure 11).



Figure 11

Both of these intermediate structures partially obscure one face of the enamine causing the aldehyde to approach from the opposite face, this step forms the stereogenic centre in the product therefore any imbalance in the faces of the intermediate would give rise to an observed enrichment. Although no direct evidence of this hypothesis has been obtained a more thorough study involving the synthesis and testing of further analogues may be able to confirm or disprove our hypothesis.

4.4. Conclusions

During the course of our investigations into the work of Shi, we have shown that water is necessary for the Baylis-Hillman reaction of α,β -unsaturated carbonyl compounds with a range of electron deficient aromatic aldehydes. Our attempts to optimise the reaction conditions revealed that the reaction between MVK and 4-nitrobenzaldehyde catalysed by L-proline (10 mol%) in the presence of imidazole (10 mol%) was affected by the presence of water in the reaction solvent. We were able to quantify the optimum value of water for both reactions carried out in DMF (10% water v/v) and THF (5% water v/v). The presence of the water increased the yield of reaction by 20 and 40% respectively. Unfortunately all of the isolated products proved to be racemic in nature. After optimisation of a general reaction scheme we turned our attention to identifying a catalyst system that would allow the stereoselective formation of the Baylis-Hillman product.

We have also begun to show through both variation of the secondary amine catalyst and also the use of Lewis bases of different structures that any asymmetric iminium ion catalysed variant of the Baylis-Hillman reaction requires, not only an optically active amine to form the iminium species, but also a Lewis base containing an aliphatic chain in order to allow the aromatic moiety to adopt a conformation that would facilitate the interaction between its π -electrons and the C-C double bond of the aldehyde in order to induce chirality into the product.

The results of the experiments carried out by varying the Lewis base also lead us to believe there is a need for a group which has the propensity to form a π,π -interaction with the alkene of the unsaturated carbonyl compound. This interaction would effectively shield one face of the unsaturated species from attack by the electrophile giving rise to some stereo induction.

Although only the final two catalysts described above produced any stereo induction in the Baylis-Hilmann adduct generated, the reversible nature of the Baylis-Hilmann reaction itself may be masking any stereo control generated in the reaction. One relatively fast way to determine if this is indeed the case would be to subject some enantiopure Baylis-Hilmann adduct to the standard reaction conditions and observe the effect if any on the chiral purity of the obtained product at the end of the reaction.

Chapter 5: Expermental

5. Experimetal

5.1. General Instructions

Reagents were obtained from Aldrich, Avocado, Lancaster and Fluka chemical suppliers. Solvents and reagents were purified according to the procedures of Perrin, Armarego and Perrin.⁷¹ Dichloromethane was dried by refluxing over, and distilling from calcium hydride. Tetrahydrofuran was obtained dry by distillation from sodium benzophenone ketyl under nitrogen. Acetonitrile was dried by refluxing over, and distilling from calcium hydride. *N,N*-Dimethylformamide was dried by stirring over phosphorus pentoxide for 48 h followed by distillation from calcium hydride. The *iso*-propanol, hexanes and acetonitrile used for HPLC analysis were of analytical grade and >99% purity. The water used for HPLC analysis was deionised and distilled prior to use. Light petroleum refers to petroleum ether 40-60 °C; ether refers to diethyl ether; THF is tetrahydrofuran.

All reactions using air/moisture sensitive reagents were performed in oven-dried or flame-dried apparatus, under a nitrogen atmosphere. Catalytic runs were performed using a Radley's carousel, which consists of twelve test tubes with suba-seals and nitrogen inlets, a stirrer plate and a bath for cooling. The cryostat used for low temperature reactions was a HAAKE EK90 immersion cooler. All reactions were followed and monitored by TLC, ¹H NMR, ¹³C NMR and mass spectrometry as appropriate.

TLC analysis refers to analytical thin layer chromatography, using aluminium-backed plates coated with Merck Kieselgel 60 GF_{254} . Product spots were viewed either by the quenching of UV fluorescence, or by staining with a solution of 2% aqueous potassium permanganate.

Flash chromatography refers to column chromatography using head pressure by means of compressed air according to the procedure of Still,⁷² using Merck Kieselgel 60 H silica or Matrix silica 60.

Melting points were recorded using a Kofler Heated Stage Micro Melting Point Apparatus and are uncorrected. The abbreviation dec. is used for compounds that decomposed above the temperature specified.

The optical rotation, $[\alpha]_D^{20}$, of chiral non-racemic compounds, was analysed using an Optical Activity AA-1000 polarimeter at 20 °C, using the sodium D line.

Infra-red spectra were recorded in the range 4000-600 cm^{-1} using a Perkin-Elmer 1600 series FTIR instrument either as a thin film or as a nujol mull between sodium chloride plates. All absorptions are quoted in cm^{-1} .

¹H NMR spectra (δ_{H}) were recorded in deuteriochloroform (unless otherwise stated) using an Avance Bruker DPX 400 instrument (400 MHz) or an Avance Bruker DPX 500 (500 MHz), with ¹³C NMR spectra (δ_{C}) recorded at 100 MHz or 125 MHz respectively. Chemical shifts (δ_{H} and δ_{C}) were recorded in parts per million (ppm) from tetramethylsilane (or chloroform) and are corrected to 0.00 (TMS) and 7.27 (CHCl₃) for ¹H NMR and 77.30 (CHCl₃), centre line, for ¹³C NMR. The abbreviations s, d, t, q, sept., m, br and rot. denote singlet, doublet, triplet, quartet, septet, multiplet, broadened resonances and rotamer respectively; all coupling constants were recorded in hertz (Hz).

High pressure liquid chromatography (HPLC) was performed using a Hewlett Packard 1100 series chromatographic pump and injector, fitted with a chiralcel OJ column, eluting the column with 0-30% *iso*-propanol in hexanes.. Detection was *via* a selective wavelength UV detector.

Low resolution mass spectrometric data was determined using a Fisons VG Platform II Quadrapole instrument using electrospray ionisation (ES) unless otherwise stated. APCI refers to atmospheric pressure chemical ionisation; CI is chemical ionisation (ammonia); EI refers to electron ionisation; ES refers to electrospray.

High resolution mass-spectrometric data was obtained courtesy of the EPSRC Mass Spectrometry Service at the University of Wales, Swansea, UK, using the ionisation methods specified. Calculated accurate masses are of the parent ion (exclusive of an electron, mass = 0.00055Da).

5.2. Experimental Procedures

Ethyl 2-(4-nitrophenyl)propionate 103⁷³



In a flame dried 100 ml round bottomed flask was added a suspension of NaH (60% dispersion in oil, 0.37 g, 15.4 mmol) in anhydrous DMF (5 ml) and the mixture flushed with nitrogen and cooled to 0°C in an ice bath. Ethyl-2-chloro propionate (0.95 g, 7.75 mmol) and nitrobenzene (1.00 g, 7.75 mmol) were dissolved in anhydrous DMF (5 ml) and added dropwise to the sodium hydride slurry. The reaction mixture was stirred at 0°C for 30 mins. The mixture was then quenched using ice and HCl (1 M, 10 ml) and extracted using DCM (3 × 30 ml). The combined organic extracts were washed with saturated NaHCO₃ (3 × 50 ml) and distilled water (5 × 50 ml) and dried (sodium sulphate, approx 2.5 g). The solvent was removed in vacuo giving the crude product as an orange oil. The crude mixture was separated by column chromatography R_{f} = 0.35 (10% EtOAc/40-60 Petroleum Ether) giving the ethyl-2-(4-nitrophenyl)propanoate as a yellow oil (1.37 g, 79%); MS *m/e* 225 (10%) 224 (M+H)⁺ (100%); (EI) exact mass calculated for C₁₁H₁₄NO₄⁺ 224.0923, found 224.0925; ¹H NMR (400 MHz, CDCl₃) δ 8.10 (2H, d, J=8.8 Hz) 7.30 (2H, d, J=8.8 Hz), 4.09 (1H, dq, J=10, 8 Hz), 4.05 (1H, dq, J=10, 8Hz), 3.79 (1H, q, J=7.2Hz), 1.47 (3H, d, J=7.2Hz), 1.13 (3H, t, J=7.2Hz); ¹³C NMR δ 172.3, 148.0, 147.0, 128.5, 123.7, 61.2, 45.3, 18.3, 14.0

Ethyl 2-methyl-2-(4-nitrophenyl)-3-(2-nitrophenyl)propionate 104



In a flame dried 100 ml round bottomed flask was added a suspension of NaH (60% dispersion in oil, 0.11 g, 4.48 mmol) in anhydrous DMF (5 ml) and the mixture flushed with nitrogen and cooled to 0°C in an ice bath. 2-nitrobenzyl chloride (0.77 g, 4.48 mmol) and ethyl-2-(4nitrophenyl)propanoate (1.00 g, 4.48 mmolwere dissolved in anhydrous DMF (10 ml) and added dropwise to the sodium slurry. The mixture was allowed to warm to room temperature and stirred for 1hr. The mixture was subsequently quenched with ice and HCl (1 M, 10 ml) and extracted with Et₂O (3×30 ml). The combined organic extracts were washed with NaHCO₃ (2×30 ml). 50 ml) and distilled water (2 × 50 ml) and dried (sodium sulphate, approx 2.5 g). The solvent was removed in vacuo giving the product as an orange oil. The crude mixture was separated by column chromatography $R_f = 0.23$ (10% EtOAc/40-60 Petroleum Ether) giving ethyl 2-methyl-2-(4-nitrophenyl-3-(2-nitrophenyl)propionate as a yellow/orange oil (1.27 g, 79%); IR (film, cm⁻ ¹): 1726, 1606, 1526, 1016, 856; MS m/e 359 (M+H)⁺ (100%), 329 (65%), 193 (20%), 136 (18%); (EI) exact mass calculated for $(C_{18}H_{19}N_2O_6^+)$ 359.1243, found 359.1246; ¹H NMR (400 MHz, CDCl₃) 8 8.15 (dt, 2H, J=9, 2 Hz), 7.75 (dd, 1H, J=7.5, 2 Hz), 7.36 (m, 4H), 7.00 (dd, 1H, J=7, 2 Hz), 4.12 (1H, dq, J=11, 7 Hz), 4.09 (1H, dq, J=11, 7 Hz) 3.84 (d, 1H, J=14.0 Hz), 3.72 (1H, d, J=14.0 Hz), 1.50 (s, 3H), 1.18 (t, 3H, J=7 Hz); ¹³C NMR (CDCl₃) (62.5MHz) & 174.4, 151.1, 149.6, 146.9, 133.1, 132.1, 131.0, 128.1, 127.6, 124.7, 123.6, 61.8, 52.0, 39.8, 21.6, 14.0.

Ethyl 2-methyl-2-(4-nitrophenyl -3-(2-nitrophenyl)propionate 104



In a flame dried 100 ml round bottomed flask a suspension of NaH (0.37 g, 15.5 mmol, 2 eq) in DMF (5 ml) was stirred at 0°C for 10 mins. To it was added dropwise a solution of the nitrobenzene compound (7.75 mmol) and the chloro propionate (7.75 mmol) in DMF (5 ml) and stirred at 0°C for 30 mins. The solution was allowed to warm to room temperature and quenched with 2-nitrobenzyl chloride (7.75 mmol) in DMF (10 ml), then allowed to stir at room temperature for a further 2 hours. The reaction was quenched with 1M HCl (25 ml) and extracted with Et₂O (3×30 ml), the organic extracts were combined and washed with NaHCO₃ (2×25 ml) and H₂O (3×25 ml), then dried over MgSO₄ and solvent removed in vacuo yielding the crude product as a yellow oil. The crude mixture was separated by column chromatography $R_f = 0.23$ Petroleum Ether) giving ethyl 2-methyl-2-(4-nitrophenyl-3-(2-(10%) EtOAc/40-60 nitrophenyl)propionate as a yellow/orange oil (1.94 g, 70%); IR (film, cm⁻¹): 1726, 1606, 1526, 1016, 856; MS m/e 359 (M+H)⁺ (100%), 329 (65%), 193 (20%), 136 (18%); (EI) exact mass calculated for (C₁₈H₁₉N₂O₆⁺) 359.1243, found 359.1246; ¹H NMR (400 MHz, CDCl₃) δ 8.15 (dt, 2H, J=9, 2 Hz), 7.75 (dd, 1H, J=7.5, 2 Hz), 7.36 (m, 4H), 7.00 (dd, 1H, J=7, 2 Hz), 4.12 (1H, dq, J=11, 7 Hz), 4.09 (1H, dq, J=11, 7 Hz) 3.84 (d, 1H, J=14.0 Hz), 3.72 (1H, d, J=14.0 Hz), 1.50 (s, 3H), 1.18 (t, 3H, J=7 Hz); 13 C NMR (CDCl₃) (62.5MHz) δ 174.4, 151.1, 149.6, 146.9, 133.1, 132.1, 131.0, 128.1, 127.6, 124.7, 123.6, 61.8, 52.0, 39.8, 21.6, 14.0.

Ethyl 2-methyl-2-(3-methyl-4-nitrophenyl)-3-(2-nitrophenyl)propionate 107



In a flame dried 100ml round bottomed flask a suspension of NaH (0.37 g, 15.5 mmol, 2 eq) in DMF (5 ml) was stirred at 0°C for 10 mins. To it was added dropwise a solution of the nitrobenzene compound (1.06 g, 7.75 mmol) and the chloro propionate (1.05 g, 7.75 mmol) in DMF (5 ml) and stirred at 0°C for 30 mins. The solution was allowed to warm to room temperature and quenched with 2-nitrobenzyl chloride (1.33 g, 7.75 mmol) in DMF (10 ml), then allowed to stir at room temperature for a further 2 hours. The reaction was quenched with 1M HCl (25 ml) and extracted with Et₂O (3×30 ml), the organic extracts were combined and washed with NaHCO₃ (2×25 ml) and H₂O (3×25 ml), then dried over MgSO₄ and solvent removed in vacuo yielding the crude product as a yellow oil. The crude mixture was purified by column chromatography $R_f = 0.28$ (20% EtOAc/40-60 Petroleum Ether) giving ethyl 2-methyl-2-(3methyl-4-nitrophenyl)-3-(2-nitrophenyl)propionate as an orange oil (1.55 g, 57%); IR (film, cm⁻ ¹): 1745, 1612, 1535, 1011, 856; MS m/e 373 (M+H)⁺ (100%), 343 (80%), 207 (45%), 136 (25%) 29 (15%); (EI) exact mass calculated for $C_{19}H_{21}N_2O_6^+$ 373.1394, found 373.1398; ¹H 1H, J=8, 2 Hz, H-5'), 7.27 (td, 1H, 8, 2 Hz, H-4'), 7.07 (m, 2H, H-2+6), 6.96 (dd, 1H, J=8, 2 Hz, H-6'), 4.11 (1H, dq, J=11, 7 Hz, H-11), 4.05 (1H, dq, J=11, 7 Hz, H-11), 3.72 (d, 1H, J=14 Hz, H-8a), 3.64 (d, 1H, J=14 Hz, H-8b), 2.49 (s, 3H, H-13), 1.40 (s, 3H, H-9), 1.11 (t, 3H, J=7 Hz, H-12); ¹³C NMR (100 MHz, CDCl₃) & 173.2, 157.2, 155.3, 146.4, 143.0, 140.1, 138.5, 136.6, 130.2, 128.4, 124.2, 120.1, 119.7, 61.3, 52.8, 40.2, 38.1, 25.3, 14.6

Ethyl 2-methyl-2-(3-methoxy-4-nitrophenyl)-3-(2-nitrophenyl)propanoate 108



In a flame dried 100 ml round bottomed flask a suspension of NaH (0.37 g, 15.5 mmol, 2 eq) in DMF (5 ml) was stirred at 0°C for 10 mins. To it was added dropwise a solution of 2nitroanisole (1.19 g, 7.75mmol) and ethyl-2-chloro propionate (1.05 g, 7.75 mmol) in DMF (5 ml) and stirred at 0°C for 30 mins. The solution was allowed to warm to room temperature and quenched with 2-nitrobenzyl chloride (1.33 g, 7.75 mmol) in DMF (10 ml), then allowed to stir at room temperature for a further 2 hours. The reaction was quenched with 1M HCl (25 ml) and extracted with Et₂O (3×30 ml), the organic extracts were combined and washed with NaHCO₃ (2×25 ml) and H₂O (3×25 ml), then dried over MgSO₄ and solvent removed in vacuo yielding the crude product as a yellow oil. The crude mixture was separated by column chromatography $R_f = 0.29$ (10% EtOAc/40-60 Petroleum Ether) giving ethyl 2-methyl-2-(3-methoxy-4nitrophenyl)-3-(2-nitrophenyl)propanoate as an orange oil (1.19 g, 47%); IR (film, cm⁻¹): 1726, 1608, 1527, 1421, 1352, 1024; MS m/e 389 (M+H)⁺; (EI) exact mass calculated for C₁₉H₂₁N₂O₇⁺ 389.1347, found 389.1349; ¹H NMR (400 MHz, CDCl₃) 7.70 (d, 1H, J=8.5, H-3), 7.64 (dd, 1H, J=8, 1.5 Hz, H-3'), 7.33 (td, 1H, J=7.5, 1.5 Hz, H-5'), 7.27 (td, 1H, J=7.5, 1.5 Hz, H-4'), 7.00 (dd, 1H, J=7.5, 1.5 Hz, H-6'), 6.80 (d, 1H, J=2 Hz, H-6), 6.75 (dd, 1H, J=8.5, 2 Hz, H-2), 4.12 (1H, dq, J=10.8, 7.1, H-11), 4.05 (1H, dq, J=10.8, 7.1, H-11), 3.79 (s, 3H, H-13), 3.68 (s, 2H, H-8), 1.41 (s, 3H, H-9), 1.11 (t, 3H, J=7 Hz, H-12); ¹³C NMR (62.5 MHz, CDCl₃) 174.3, 152.8, 151.0, 149.3, 138.3, 133.2, 132.1, 131.0, 128.0, 125.8, 124.6, 118.4, 112.1, 61.7, 56.4, 52.1, 39.7, 21.5, 14.2.



Ethyl 2-methyl-2-(3-phenoxy-4-nitrophenyl)-3-(2-nitrophenyl)propanoate 110



In a flame dried 100 ml round bottomed flask a suspension of NaH (0.37 g, 15.5 mmol, 2 eq) in DMF (5 ml) was stirred at 0°C for 10 mins. To it was added dropwise a solution of 2nitrodiphenyl ether (1.68 g, 7.75 mmol) and ethyl-2-chloro propionate (1.05 g, 7.75 mmol) in DMF (5 ml) and stirred at 0°C for 30 mins. The solution was allowed to warm to room temperature and quenched with 2-nitrobenzyl chloride (1.33 g, 7.75 mmol) in DMF (10 ml), then allowed to stir at room temperature for a further 2 hours. The reaction was quenched with 1 M HCl (25 ml) and extracted with Et₂O (3×30 ml), the organic extracts were combined and washed with NaHCO₃ (2×25 ml) and H₂O (3×25 ml), then dried over MgSO₄ and solvent removed in vacuo yielding the crude product as a yellow oil. The crude mixture was separated by column chromatography $R_f = 0.35$ (20% EtOAc/40-60 Petroleum ether) giving ethyl 2-methyl-2-(3phenoxy-4-nitrophenyl)-3-(2-nitrophenyl)propanoate as an orange oil (0.88 g, 42%); IR (film, cm⁻¹): 1727, 1586, 1528, 1487, 1410, 1353, 1107, 1021; MS m/e 451 (M+H)⁺ (100%), 373 (54%), 237 (40%), 136 (40%), 77 (40%); (EI) exact mass calculated for $C_{24}H_{22}N_2O_7 + H^+$ 451.1427, found 451.1499; ¹H NMR (400 MHz, CDCl₃) δ : 7.82 (1 H, d, J = 9 Hz), 7.64 (1 H, dd, J = 8, 2 Hz), 7.34-7.19 (4H, m), 7.06 (1H, t, J = 7 Hz), 6.96-6.92 (2 H, m), 6.88-6.84 (2 H, m), 6.67 (1H, d, J = 2 Hz), 4.09-3.95 (2H, m), 3.60 (2H, s), 1.30 (3H, s), 1.16 (3H, t, J = 7.1Hz); ¹³C NMR (125 MHz, CDCl₃) 172.4, 155.7, 150.9, 150.2, 149.8, 141.0, 134.6, 132.5, 131.1, 130.6, 130.0, 129.4, 125.8, 125.4, 125.0, 121.3, 120.3, 116.3, 54.1, 53.2, 38.4, 22.7, 15.2

Ethyl 2-methyl-2-(3-chloro-4-nitrophenyl)-3-(2-nitrophenyl)propanoate 121



In a flame dried 100 ml round bottomed flask a suspension of NaH (0.37 g, 15.5 mmol, 2 eq) in DMF (5 ml) was stirred at 0°C for 10 mins. To it was added dropwise a solution of 2-chloronitrobenzene (1.22 g, 7.75 mmol) and ethyl-2-chloro propionate (1.05 g, 7.75 mmol) in DMF (5 ml) and stirred at 0°C for 30mins. The solution was allowed to warm to room temperature and quenched with 2-nitrobenzyl chloride (1.33 g, 7.75 mmol) in DMF (10 ml), then allowed to stir at room temperature for a further 2 hours. The reaction was quenched with 1 M HCl (25 ml) and extracted with Et₂O (3×30 ml), the organic extracts were combined and washed with NaHCO₃ (2×25 ml) and H₂O (3×25 ml), then dried over MgSO₄ and solvent removed in vacuo yielding the crude product as a yellow oil. The crude mixture was separated by column chromatography (20% EtOAc/40-60 Petroleum ether) giving ethyl 2-methyl-2-(3-chloro-4nitrophenyl)-3-(2-nitrophenyl)propanoate as an orange oil (1.30 g, 52 %); IR (film, cm⁻¹): 1728, 1581, 1529, 1444, 1421, 1353, 1049; MS m/e 412 (35%) 410 (M+H₂O)⁺ (100%); (EI) exact mass calculated for $(C_{18}H_{17}N_2O_6Cl + H_2O)^+$ 410.0875, found 410.1111; ¹H NMR (400 MHz, CDCl₃) δ 7.78 (d, 1H, J=8.5 Hz, H-3), 7.70 (dd, 1H, J=7.5, 1.5 Hz, H-3'), 7.36, (td, 1H, J=7.5, 1.5 Hz, H-5') 7.31 (td, 1H, J=7.5, 1.5 Hz, H-4'), 7.27 (d, 1H, J=2.0 Hz, H-6), 7.19 (dd, 1H, J=8.5, 2.0 Hz, H-2), 7.01 (dd, 1H, J=7.5, 1.5 Hz, H-6'), 4.14 (1H, dq, J=11, 7 Hz, H-11), 4.07 (1H, dq, J=11, 7 Hz, H-11), 3.74 (d, 1H, J=14 Hz, H-8a), 3.63 (d, 1H, J=14 Hz, H-8b), 1.42 (s, 3H, H-9), 1.13 (t, 3H, J=7 Hz, H-12; ¹³C NMR (125 MHz, CDCl₃) δ 173.9, 151.0, 148.7, 146.4, 133.1, 132.2, 130.7, 128.2, 127.2, 125.9, 125.7, 125.5, 124.8, 62.0, 51.8, 27.3, 21.6, 14.0

Ethyl 2-methyl-2-(3-fluoro-4-nitrophenyl)-3-(2-nitrophenyl)propanoate 123



In a flame dried 100 ml round bottomed flask a suspension of NaH (0.37 g, 15.5 mmol, 2 eq) in DMF (5 ml) was stirred at 0°C for 10 mins. To it was added dropwise a solution of 2-fluoronitrobenzene (1.09 g, 7.75 mmol) and ethyl-2-chloro propionate (1.05 g, 7.75 mmol) in DMF (5 ml) and stirred at 0°C for 30 mins. The solution was allowed to warm to room temperature and quenched with 2-nitrobenzyl chloride (1.33 g, 7.75 mmol) in DMF (10 ml), then allowed to stir at room temperature for a further 2 hours. The reaction was quenched with 1 M HCl (25 ml) and extracted with Et₂O (3×30 ml), the organic extracts were combined and washed with NaHCO₃ (2×25 ml) and H₂O (3×25 ml), then dried over MgSO₄ and solvent removed in vacuo yielding the crude product as a yellow oil. The crude mixture was separated by column chromatography $R_f = 0.22$ (20% EtOAc/Petroleum ether) giving ethyl 2-methyl-2-(3-fluoro-4nitrophenyl)-3-(2-nitrophenyl)propanoate as an orange oil (1.33 g, 50%); IR (film, cm⁻¹): 1728, 1603, 1529, 1351, 1265; MS m/e 378 (10%), 377 (M+H)⁺ (100%); (EI) exact mass calculated for C₁₈H₁₇N₂O₆F 376.1605, found 376.1605; ¹H NMR (125 MHz, CDCl₃) δ 8.01 (1H, t, J=8.0, H-3); 7.77 (1H, dd, J=7.9, 1.5, H-3'); 7.42 (1H, td, J=7.5, 1.5, H-5'); 7.37 (1H, td, J=7.5, 1.5, H-4') 7.13 (2H, m, H-6 & 6'); 7.06 (1H, dd, J=8.0, 1.4, H-2); 4.23-4.12 (2H, 2×dq, J=10.8, 7.1, H-11); 3.81 (1H, d, J=14.0, H-8a); 3.70 (1H, d, J=14.0, H-8b); 1.49 (3H, s, H-9); 1.19 (3H, t, J=7.13, H-12); ¹³C (CDCl₃, 125MHz) δ: 173.8, 155.3 (d, ¹J_{CF}=265 Hz), 151.6, 151.5, 151.0, 133.1, 132.3, 130.7, 128.3, 126.1, 124.8, 122.9, 116.9 (d, ²J_{CF}=20 Hz)

Methyl 2-methyl-2-(4-nitrophenyl)-3-(2-nitrophenyl)propanoate 126



In a flame dried 100 ml round bottomed flask a suspension of NaH (0.37 g, 15.5 mmol, 2 eq) in DMF (5 ml) was stirred at 0°C for 10 mins. To it was added dropwise a solution of nitrobenzene (1.00 g, 7.75mmol) and methyl-2-chloro propionate (0.95 g, 7.75 mmol) in DMF (5 ml) and stirred at 0°C for 30 mins. The solution was allowed to warm to room temperature and quenched with 2-nitrobenzyl chloride (1.33 g, 7.75 mmol) in DMF (10 ml), then allowed to stir at room temperature for a further 2 hours. The reaction was quenched with 1 M HCl (25 ml) and extracted with Et₂O (3×30 ml), the organic extracts were combined and washed with NaHCO₃ $(2 \times 25 \text{ ml})$ and H₂O $(3 \times 25 \text{ ml})$, then dried over MgSO₄ and solvent removed in vacuo yielding the crude product as a yellow oil. The crude mixture was separated by column chromatography (20% EtOAc/Petroleum giving 2-methyl-2-(4-nitrophenyl)-3-(2ether) methyl nitrophenyl)propanoate as an orange oil (1.94 g, 73%); IR (film, cm⁻¹): 1728, 1610, 1519, 895; MS m/e 345 (M+H)⁺; (EI) exact mass calculated for (C₁₇H₁₇N₂O₆⁺) 345.1086, found 345.1087; ¹H NMR (500 MHz, CDCl₃) δ 7.95 (2H, dd, J = 9, 2 Hz), 7.72 (2H, dd, J = 8, 2 Hz), 7.39-7.29 (1H, m), 7.09-7.03 (2H, m), 6.99 (1H, dd, J = 7.5, 2 Hz), 3.82 (3H, s) 3.60 (1H, d, J = 14 Hz), 3.20 (1H, d, J = 14 Hz), 1.39 (3H, s); ¹³C (CDCl₃, 125MHz) δ : 173.9, 151.6, 149.1, 147.2, 132.7, 131.8, 130.4, 128.4, 128.0, 125.0, 119.6, 62.6, 51.6, 37.2, 21.3.

Methyl 2-methyl-2-(3-methyl-4-nitrophenyl)-3-(2-nitrophenyl)propanoate 127



In a flame dried 100 ml round bottomed flask a suspension of NaH (0.37 g, 15.5 mmol, 2 eq) in DMF (5 ml) was stirred at 0°C for 10 mins. To it was added dropwise a solution of 2-nitroanisole (1.06 g, 7.75 mmol) and methyl-2-chloro propionate (0.95 g, 7.75 mmol) in DMF (5 ml) and stirred at 0°C for 30 mins. The solution was allowed to warm to room temperature and quenched with 2-nitrobenzyl chloride (1.33 g, 7.75mmol) in DMF (10 ml), then allowed to stir at room temperature for a further 2 hours. The reaction was quenched with 1M HCl (25 ml) and extracted with Et₂O (3×30 ml), the organic extracts were combined and washed with NaHCO₃ (2×25 ml) and H₂O (3×25 ml), then dried over MgSO₄ and solvent removed in vacuo yielding the crude product as a yellow oil. The crude mixture was separated by column chromatography (20% EtOAc/Petroleum ether) giving methyl 2-methyl-2-(3-methyl-4nitrophenyl)-3-(2-nitrophenyl)propanoate as an orange oil (1.54 g 59%); IR (film, cm⁻¹): 1716, 1574, 1541, 1010, 895; MS m/e 360 (10%), 359 (M+H)⁺ (100%); (EI) exact mass calculated for $(C_{18}H_{19}N_2O_6^+)$ 359.1243, found 359.1244; ¹H NMR (500 MHz, CDCl₃) δ 7.97 (1H, dd, J = 9, 2 Hz), 7.72 (1H, dd, J = 8, 1 Hz), 7.36-7.26 (2H, m), 7.09-7.01 (2H, m), 6.99 (1H, dd, J = 7, 1 Hz), 3.96 (3H, s), 3.52 (1H, d, J = 14 Hz), 3.11 (1H, d, J = 14 Hz), 1.44 (3H, s); ¹³C (CDCl₃, 125MHz) & 175.2, 157.8, 155.6, 145.4, 142.8, 140.4, 137.5, 136.9, 129.4, 127.9, 124.8, 119.7, 119.4, 62.3, 52.5, 41.0, 37.4, 24.9

Methyl 2-methyl-2-(3-methoxy-4-nitrophenyl)-3-(2-nitrophenyl)propanoate 128



In a flame dried 100 ml round bottomed flask a suspension of NaH (0.37 g, 15.5 mmol, 2 eq) in DMF (5 ml) was stirred at 0°C for 10 mins. To it was added dropwise a solution of 2nitroanisole (1.19 g, 7.75 mmol) and methyl-2-chloro propionate (0.95 g, 7.75 mmol) in DMF (5ml) and stirred at 0°C for 30 mins. The solution was allowed to warm to room temperature and quenched with 2-nitrobenzyl chloride (1.33 g, 7.75 mmol) in DMF (10 ml), then allowed to stir at room temperature for a further 2 hours. The reaction was quenched with 1 M HCl (25 ml) and extracted with Et₂O (3×30 ml), the organic extracts were combined and washed with NaHCO₃ (2×25 ml) and H₂O (3×25 ml), then dried over MgSO₄ and solvent removed in vacuo yielding the crude product as a yellow oil. The crude mixture was separated by column chromatography (20% EtOAc/Petroleum ether) giving methyl 2-methyl-2-(3-methoxy-4-nitrophenyl)-3-(2nitrophenyl)propanoate as an orange oil (1.37 g, 56%); IR (film, cm⁻¹): 1717, 1631, 1565, 1327, 1038, 895; MS m/e 376 (12%), 375 (M+H)⁺ (100%); (EI) exact mass calculated for $(C_{18}H_{19}N_2O_7^+)$ 375.1192, found 375.1196; ¹H NMR (500 Mhz, CDCl₃) δ 7.95 (1H, dd, J = 8, 2 Hz), 7.72 (1H, dd, J = 8, 1.5 Hz), 7.37-7.26 (2H, m), 7.11-7.01 (2H, m), 6.99 (1H, dd, J = 7.5, 2 Hz), 4.01 (3H, s), 3.54 (1H, d, J = 14 Hz), 3.11 (1H, d, J = 14 Hz) 1.40 (3H, s); ¹³C (CDCl₃, 125MHz) & 175.3, 151.9, 150.5, 149.6, 137.9, 133.0, 132.2, 131.3, 127.9, 126.0, 125.0, 118.1, 112.3, 62.0, 56.7, 52.4, 27.7, 21.5
Methyl 2-methyl-2-(3-phenoxy-4-nitrophenyl)-3-(2-nitrophenyl)propanoate 129



In a flame dried 100 ml round bottomed flask a suspension of NaH (0.37 g, 15.5 mmol, 2 eq) in DMF (5 ml) was stirred at 0°C for 10 mins. To it was added dropwise a solution of 2nitrodiphenyl ether (1.68 g, 7.75 mmol) and methyl-2-chloro propionate (0.95 g, 7.75 mmol) in DMF (5 1) and stirred at 0°C for 30 mins. The solution was allowed to warm to room temperature and quenched with 2-nitrobenzyl chloride (1.33 g, 7.75 mmol) in DMF (10 ml), then allowed to stir at room temperature for a further 2 hours. The reaction was quenched with 1M HCl (25 ml) and extracted with Et_2O (3×30 ml), the organic extracts were combined and washed with NaHCO₃ (2×25 ml) and H₂O (3×25 ml), then dried over MgSO₄ and solvent removed in vacuo yielding the crude product as a yellow oil. The crude mixture was separated by column chromatography (20% EtOAc/Petroleum ether) giving ethyl 2-methyl-2-(3-phenoxy-4nitrophenyl)-3-(2-nitrophenyl)propanoate as an orange oil (0.97 g 48%); IR (film, cm⁻¹); 1713, 1607, 1529, 1221, 1092, 902; MS m/e 437 (M+H)⁺; (EI) exact mass calculated for $(C_{23}H_{21}N_2O_7^+)$ 437.1349, found 437.1350; ¹H NMR (500 MHz, CDCl₃) δ : 8.20 (1H, d, J = 8 Hz), 8.01 (1H, d, J = 8 Hz), 7.83 (1H, td, J = 7, 2 Hz), 7.56-7.38 (3H, m), 7.39 (2H, t, J = 8 Hz), 7.25 (1H, dd, J = 8, 2 Hz), 7.09 (2H, d, 8 Hz), 3.83 (3H, s), 3.40 (1H, d, J = 14 Hz), 3.02 (1H, d, J = 14 Hz), 1.73 (3H, s); ¹³C (100 MHz, CDCl₃): 174.6, 155.7, 151.0, 150.4, 149.3, 140.0, 133.2, 132.1, 130.7, 130.1, 130.0, 128.1, 125.9, 124.7, 124.5, 121.6, 119.3, 119.0, 118.8, 52.7, 52.0, 39.7, 21.7

Methyl 2-methyl-2-(3-chloro-4-nitrophenyl)-3-(2-nitrophenyl)propanoate 130



In a flame dried 100 ml round bottomed flask a suspension of NaH (0.37 g, 15.5 mmol, 2 eq) in DMF (5 ml) was stirred at 0°C for 10 mins. To it was added dropwise a solution of 2chloronitrobenzene (1.22 g, 7.75 mmol) and methyl-2-chloro propionate (0.95 g, 7.75 mmol) in DMF (5 ml) and stirred at 0°C for 30 mins. The solution was allowed to warm to room temperature and quenched with 2-nitrobenzyl chloride (1.33 g, 7.75 mmol) in DMF (10 ml), then allowed to stir at room temperature for a further 2 hours. The reaction was quenched with 1M HCl (25 ml) and extracted with Et₂O (3×30 ml), the organic extracts were combined and washed with NaHCO₃ (2×25 ml) and H₂O (3×25 ml), then dried over MgSO₄ and solvent removed in vacuo yielding the crude product as a yellow oil. The crude mixture was separated by column chromatography (20% EtOAc/Petroleum ether) giving methyl 2-methyl-2-(3-chloro-4nitrophenyl)-3-(2-nitrophenyl)propanoate as an orange oil (1.20 g, 50%); IR (film, cm⁻¹): 1733, 1604, 1529, 895; MS m/e 380 (30%), 378 (100%) (M+H)⁺; (EI) exact mass calculated for $(C_{17}H_{16}N_2O_6Cl^{\dagger})$ 379.0697, found 379.0699; ¹H NMR (500 MHz, CDCl₃) δ : 7.96 (1H, dd, J = 8.8, 7.8 Hz), 7.72 (1H, dd, J = 7.8, 1.6 Hz), 7.40-7.28 (2H, m), 7.10-7.03 (2H, m), 6.99 (1H, dd, J = 7.5, 1.6 Hz), 3.83 (3H, s), 3.45 (1H, d, J = 14.0), 3.12 (1H, d, J = 14.0), 1.35 (3H, s); ¹³C NMR (125 MHz, CDCl₃): 174.2, 151.6, 149.0, 147.0, 133.3, 132.0, 131.0, 128.7, 127.5, 126.2, 125.9, 125.7, 124.4, 61.7, 51.3, 27.5, 22.0

Methyl 2-methyl-2-(3-fluoro-4-nitrophenyl)-3-(2-nitrophenyl)propanoate 131



In a flame dried 100ml round bottomed flask a suspension of NaH (0.37 g, 15.5 mmol, 2 eq) in DMF (5 ml) was stirred at 0°C for 10 mins. To it was added dropwise a solution of 2fluoronitrobenzene (1.09 g, 7.75 mmol) and methyl-2-chloro propionate (0.95 g, 7.75 mmol) in DMF (5 ml) and stirred at 0°C for 30 mins. The solution was allowed to warm to room temperature and quenched with 2-nitrobenzyl chloride (1.33 g, 7.75 mmol) in DMF (10 ml), then allowed to stir at room temperature for a further 2 hours. The reaction was guenched with 1M HCl (25 ml) and extracted with Et_2O (3×30 ml), the organic extracts were combined and washed with NaHCO₃ (2×25 ml) and H₂O (3×25 ml), then dried over MgSO₄ and solvent removed in vacuo yielding the crude product as a yellow oil. The crude mixture was separated by column chromatography $R_f = 0.22$ (20% EtOAc/Petroleum ether) giving methyl 2-methyl-2-(3-fluoro-4nitrophenyl)-3-(2-nitrophenyl)propanoate as an orange oil (1.26 g, 49%); IR (film, cm⁻¹): 1710, 1638, 1327, 895, 727; MS m/e 364 (10%), 363 (100%) (M+H)⁺; (EI) exact mass calculated for (C₁₇H₁₆N₂O₆F⁺) 363.0992, found 363.0995; ¹H NMR (500 MHz, CDCl₃) δ 7.95 (1H, dd, J = 9, 2 Hz), 7.72 (1H, dd, J = 8, 2 Hz), 7.39-7.29 (2H, m), 7.09-7.03 (2H, m), 6.99 (1H, dd, J = 7.5, 2 Hz), 3.76 (1H, d, J=14 Hz) 3.64 (1H, d, J = 14 Hz), 3.64 (3H, s), 1.44 (3H, s); ¹³C (CDCl₃, 125MHz): 171.6, 151.8 (d, ${}^{1}J_{CF} = 255$ Hz), 148.6, 147.2, 133.1, 132.6, 130.4, 127.7, 127.3, 126.5, 125.9, 125.3, 119.9 (d, ${}^{2}J_{CF} = 23Hz$), 62.1, 51.8, 26.0, 23.1

Methyl 2-methyl-2-(4-aminophenyl)-3-(2-aminophenyl)propanoate 132



Method a

To a 2-necked round bottom flask fitted with a condenser and N₂ bubbler was added tin(II) chloride dihydrate (6.30 g, 27.9 mmol), the ester (1.00 g, 2.79 mmol), ethanol (20 ml), ethyl acetate (7 ml) and conc. HCl (1 drop). The solution was heated under reflux and then cooled to room temperature. The solution was reduced in vacuo to give a yellow oil. Ethyl acetate (50 ml) was added followed by NaHCO₃ (50 ml). The product was extracted with ethyl acetate $(3 \times 25 \text{ ml})$ and then washed with water (50 ml) and saturated sodium chloride (50 ml). The solution was dried over MgSO₄ and reduced in vacuo to give the crude product, this was washed 2-methyl-2-(4-aminophenyl)-3-(2with chloroform, dried and pure ethvl aminophenyl)propanoate collected as a yellow oil (0.57 g, 68%); IR (film, cm⁻¹): 3462, 1718, 1612, 1554, 1382, 895; MS m/e 300 (10%) 299 (100%) (M+H)⁺; (EI) exact mass calculated for (C₁₈H₂₃N₂O⁺) 299.1754, found 299.1754; ¹H NMR (500 MHz, CDCl₃) δ: 10.30 (2H, br s), 9.90 (2H, br s), 7.47 (2H, d, J = 8 Hz), 7.19-7.11 (4H, m), 6.90 (2H, d, J = 8 Hz), 4.12 (2H, m), 3.74, 3.36 (1H, d, J = 14 Hz), 3.13 (1H, d, J = 14 Hz), 1.34, (3H, s), 1.14 (3H, t, J = 7 Hz); ¹³C NMR (CDCl₃) (125MHz): 172.6, 147.2, 141.3, 139.4, 136.5, 135.8, 132.1, 129.4, 128.5, 128.1, 122.6, 119.4 115.6, 62.5, 50.1, 32.8, 22.1, 14.6

Method b (MeOH) and c (EtOAc)

To a stirred slurry of 10% palladium on carbon (approx 1 g) in methanol (5ml) was added a solution of the *bis*-nitro aryl compound (1.00 g, 2.79 mmol) in methanol (10 ml). The flask was evacuated and charged with H₂. The mixture was then stirred at room temperature for 24 hrs. The mixture was filtered through celite to remove the excess palladium and the solvent removed in vacuo yielding ethyl 2-methyl-2-(4-aminophenyl)-3-(2-aminophenyl)propanoate the product as a yellow oil (0.77 g, 93% <0.79 g, 95% in EtOAc>)

Method d (MeOH) and e (EtOAc)

To a stirred slurry of 10% palladium on carbon (approx 1 g) in methanol (5 ml) was added a solution of the *bis*-nitro aryl compound (1.00 g, 2.79 mmol) in methanol (10 ml). To the flask

was added formic acid (1 drop). The flask was evacuated and charged with H₂. The mixture was then stirred at room temperature for 24 hrs. The mixture was filtered through celite to remove the excess palladium and the solvent removed in vacuo yielding ethyl 2-methyl-2-(4-aminophenyl)-3-(2-aminophenyl)propanoate as a yellow oil (0.63 g, 76% <0.57 g, 69% in EtOAc>).

Method f

To a stirred slurry of 10% palladium on carbon (approx 1 g) in methanol (5 ml) was added a solution of the *bis*-nitro aryl compound (1.00 g, 2.79 mmol) in methanol (10 ml). To the flask was added 6M NaOH (1 drop). The flask was evacuated and charged with H₂. The mixture was then stirred at room temperature for 24 hrs. The mixture was filtered through celite to remove the excess palladium and the solvent removed in vacuo yielding ethyl 2-methyl-2-(4-aminophenyl)-3-(2-aminophenyl)propanoate as a yellow oil (0.77 g, 93%).

Method g



To a solution of the *bis*-nitro aryl compound in glacial acetic acid (10 ml) was added Fe powder (375 mg) the reaction mixture was stirred at reflux for 1 hr. During the course of the reaction the Fe powder that had attached to the magnetic stirrer became orange and detached from the magnet. The residual iron oxide was removed by filtration through celite and the solvent was removed by co-evaporation with ethanol. The crude product was purified by colun chromatography eluting with 80% EtOAc/40-60 petroleum ether to yield two products;

a) an orange oil (93 mg, 45%) IR: 3462, 1743, 1643, 1620; MS *m/e* 330 (12%) 329 (100%) (M+H)⁺; (EI) exact mass calculated for ($C_{18}H_{23}N_2O_4^+$) 329.1501, found 329.1501; ¹H NMR (500 MHz. CDCl₃) δ : 10.30 (2H, br s), 8.10 (1H, dd, *J* = 8, 2 Hz), 7.82 (1H, td, *J* = 7, 2 Hz), 7.47-7.42 (2H, m), 7.13 (2H, d, *J* = 8 Hz), 6.43 (2H, d, *J* = 8 Hz), 4.13-4.09 (2H, m), 3.46 (1H, d, *J* = 14 Hz), 3.10 (1H, d, *J* = 14 Hz), 1.98 (3H, s), 1.39 (3H, t, *J* = 8 Hz); ¹³C NMR (125 MHz,

CDCl₃) & 175.1, 149.2, 141.3, 136.5, 135.5, 130.2, 129.1, 125.3, 122.6, 120.4 117.0, 62.1, 52.7, 31.8, 23.6, 14.0

b) an orange oil (92mg, 45%) IR: 3457, 1738, 1635, 1625; MS *m/e* 329 (100%) (M+H)⁺; (EI) exact mass calculated for ($C_{18}H_{23}N_2O_4^+$) (EI) 329.1501, found 329.1507; ¹H NMR (CDCl₃) (500MHz) δ : 9.73 (2H, br s), 8.23 (2H, d, J = 8 Hz), 7.60 (2H, d, J = 8 Hz), 7.10-7.01 (2H, m), 6.87-6.79 (2H, m), 4.13-4.09 (2H, m), 3.46 (1H, d, J = 14 Hz), 3.10 (1H, d, J = 14 Hz), 1.98 (3H, s), 1.39 (3H, t, J = 8 Hz); ¹³C (125 MHz, CDCl₃) δ : 173.0, 147.2, 145.6, 141.8, 132.4, 128.3, 126.1, 124.4, 124.2, 119.4, 62.1, 52.8, 31.6, 23.6, 14.0

3-(4-aminophenyl)-3-methyl-3,4-dihydroquinolin-2(1H)-one 137



Method i

In a 50 ml round bottom flask fitted with a condenser was charged with a solution of the *bis*-nitro aryl compound (500 mg, 1.40 mmol) dissolved in EtOH (10 ml). To the solution was added Zn dust (375 mg) and HCl_{cone} (2 ml) and the mixture refluxed for 4 hrs. The solution was cooled to room temperature and quenched with H₂O. The mixture was filtered through celite in order to remove any excess Zn or ZnO and the solvent removed in vacuo. The residue was re-dissolved in DCM (50 ml), washed with NaHCO₃ (3 × 30 ml) and water (3 × 30 ml) and dried with MgSO4. The solvent was removed in vacuo to yield the desired quinolinone as a yellow powder (264 mg, 73%); m.p. 237-239°C; IR (Nujol, cm⁻¹): 3442, 1673, 1352, 1279, 1013, 875; MS *m/e* 253 (100%) (M+H)⁺, 151 (10%), 139 (15%); (EI) exact mass calculated for (C₁₆H₁₇N₂O⁺) 253.1351 found 253.1335; ¹H NMR (500 MHz, DMSO d⁶) δ : 10.13 (1H, br s), 7.17 (1H, d, *J* = 7 Hz), 7.01 (1H, t, *J* = 8 Hz), 6.92 (2H, d, *J* = 9 Hz), 6.83 (1H, t, *J* = 7 Hz), 6.71 (2H, d, *J* = 8 Hz), 6.36 (2H, d, *J* = 9 Hz), 3.33 (1H, d, *J* = 16 Hz), 2.98 (1H, d, *J* = 16 Hz), 1.35 (3H, s); ¹³C (125 MHz, DMSO d⁶) δ : 176.8, 147.0, 135.4, 131.4, 129.4, 127.7, 126.3, 126.0, 125.8, 120.4, 117.3, 52.4, 43.5, 22.1.

Method j

In a 50 ml round bottom flask fitted with a condenser was charged with a solution of the *bis*-nitro aryl compound (500 mg, 1.40 mmol) dissolved in EtOH (10 ml). To the solution was added Zn dust (375 mg) and AcOH (2 ml) and the mixture refluxed for 4 hrs. The solution was cooled to room temperature and quenched with H₂O. The mixture was filtered through celite in order to remove any excess Zn or ZnO and the solvent removed in vacuo. The residue was re-dissolved in DCM (50 ml), washed with NaHCO₃ (3×30 ml) and water (3×30 ml) and dried with MgSO4. The solvent was removed in vacuo to yield the desired quinolinone as a yellow powder (345 mg, 98%)

3-(3-methyl-4-aminophenyl)-3-methyl-3,4-dihydroquinolin-2(1H)-one 138



In a 50 ml round bottom flask fitted with a condenser was charged with a solution of the *bis*-nitro aryl compound (250 mg, 0.67 mmol) dissolved in EtOH (10 ml). To the solution was added Zn dust (375 mg) and glacial acetic acid (2ml) and the mixture refluxed for 4 hrs. The solution was cooled to room temperature and quenched with H₂O. The mixture was filtered through celite in order to remove any excess Zn or ZnO and the solvent removed in vacuo. The residue was redissolved in DCM (50 ml), washed with NaHCO₃ (3 × 30 ml) and water (3 × 30 ml) and dried with MgSO4. The solvent was removed in vacuo to yield the desired quinolinone as a red powder (166 mg, 93%); m.p. 209-211°C IR (Nujol, cm⁻¹): 3452, 1661, 845, 736; MS *m/e* 267 (M+H)⁺; (EI) exact mass calculated for (C₁₇H₁₉N₂O⁺) 267.1497, found 267.1500; ¹H NMR (500 MHz, DMSO d⁶) δ : 10.18 (1H, br s), 7.20 (1H, d, *J* = 7 Hz), 7.05 (1H, t,

J = 7 Hz), 6.90 (2H, d, J = 8.5 Hz), 6.85 (1H, t, J = 7 Hz), 6.74 (2H, d, J = 7 Hz), 6.38 (2H, d, J = 8.5 Hz), 3.37 (1H, d, J = 16 Hz), 2.84 (1H, d, J = 16 Hz), 1.41 (3H, s); ¹³C (125 MHz, DMSO d^{6}) & 173.6, 143.5, 134.8, 132.0, 130.1, 128.1, 127.4, 127.0, 125.6, 122.2, 121.0, 116.9, 52.3, 44.5, 29.2, 20.2

3-(3-methoxy-4-aminophenyl)-3-methyl-3,4-dihydroquinolin-2(1H)-one 139



In a 50 ml round bottom flask fitted with a condenser was charged with a solution of the *bis*-nitro aryl compound (250 mg, 0.64 mmol) dissolved in EtOH (10 ml). To the solution was added Zn dust (375 mg) and glacial acetic acid (2 ml) and the mixture refluxed for 4 hrs. The solution was cooled to room temperature and quenched with H₂O. The mixture was filtered through celite in order to remove any excess Zn or ZnO and the solvent removed in vacuo. The residue was redissolved in DCM (50 ml), washed with NaHCO₃ (3 × 30 ml) and water (3 × 30 ml) and dried with MgSO4. The solvent was removed in vacuo to yield the desired quinolinone as a yellow/orange powder (169mg, 93%); m.p. 240-242°C; (IR (Nujol, cm⁻¹): 3459, 1659, 1239, 1146, 1031, 715; MS *m/e* 283 (100%) (M+H)⁺; (EI) exact mass calculated for C₁₈H₂₃N₂O₆⁺ 283.1446, found 283.1448; ¹H NMR (500 MHz, DMSO d⁶) δ : 8.12 (1H, br s), 7.12 (1H, d, J = 7 Hz), 7.01 (1H, t, J = 7 Hz), 6.87 (1H, t, J = 7 Hz), 6.71 (1H, s), 6.66 (1H, d, J = 8 Hz), 6.59 (1H, d, J = 7 Hz), 6.45 (1H, d, J = 8 Hz), 3.29 (1H, d, J = 16 Hz), 3.06 (1H, d, J = 16 Hz), 1.51 3H, s); ¹³C (DMSO d⁶, 125MHz) δ : 173.6, 146.5, 135.1, 132.0, 129.7, 128.2, 127.0, 126.7, 124.2, 120.8, 116.3, 51.3, 44.2, 37.2, 21.2

3-(3-phenoxy-4-aminophenyl)-3-methyl-3,4-dihydroquinolin-2(1H)-one 140



In a 50 ml round bottom flask fitted with a condenser was charged with a solution of the *bis*-nitro aryl compound (250 mg, 0.55 mmol) dissolved in EtOH (10 ml). To the solution was added Zn dust (375 mg) and glacial acetic acid (2 ml) and the mixture refluxed for 4 hrs. The solution was cooled to room temperature and quenched with H₂O. The mixture was filtered through celite in order to remove any excess Zn or ZnO and the solvent removed in vacuo. The residue was redissolved in DCM (50 ml), washed with NaHCO₃ (3 × 30 ml) and water (3 × 30 ml) and dried with MgSO4. The solvent was removed in vacuo to yield the desired quinolinone as an orange solid (176 mg, 92%); m.p. 246-248°C IR (Nujol, cm⁻¹): 3691, 1678, 1267, 749; MS *m/e* 346 (22%) 345 (100%) (M+H)⁺, 160 (65%), 141 (15%); (EI) exact mass calculated for (C₂₂H₂₀N₂O₂⁺) 345.1598, found 345.1599 ¹H NMR (500 MHz, DMSO d⁶) δ :10.53 (2H, br s), 7.86 (1H, d, *J* = 9 Hz), 7.68 (1H, dd, *J* = 8, 2 Hz), 7.37-7.25 (3H, m), 7.10 (1H, t, *J* = 7 Hz), 6.94 (2H, m), 6.91-6.87 (1H, m), 6.69 (1H, d, *J* = 2 Hz), 3.65 (2H, m), 3.57 (3H, s), 1.32 (3H, s); ¹³C (DMSO d⁶, 125MHz) δ : 177.0, 158.3, 140.9, 137.4, 135.9, 130.1, 128.4, 128.2, 127.0, 125.9, 125.0, 123.2, 122.2, 120.1, 117.9, 115.9, 53.3, 41.5, 23.9

3-(3-chloro-4-aminophenyl)-3-methyl-3,4-dihydroquinolin-2(1H)-one 141



In a 50ml round bottom flask fitted with a condenser was charged with a solution of the *bis*-nitro aryl compound (250 mg, 0.64mmol) dissolved in EtOH (10 ml). To the solution was added Zn dust (375 mg) and glacial acetic acid (2ml) and the mixture refluxed for 4 hrs. The solution was cooled to room temperature and quenched with H₂O. The mixture was filtered through celite in order to remove any excess Zn or ZnO and the solvent removed in vacuo. The residue was redissolved in DCM (50 ml), washed with NaHCO₃ (3 × 30 ml) and water (3 × 30 ml) and dried with MgSO4. The solvent was removed in vacuo to yield the desired quinolinone as a brown solid (169 mg, 93%); m.p. 223-225°C; IR (cm⁻¹): 3392, 1677, 895, 735 ; MS *m/e* 287 (M+H)⁺; exact mass calculated for (C₁₆H₁₆N₂OCl⁺) 287.0946, found 287.0945; ¹H NMR (500MHz, DMSO d⁶) δ : 10.27 (1H, s), 7.26 (1H, d, *J* = 7 Hz), 7.15-7.08 (2H, m), 7.01 (1H, dd, *J* = 8.5, 2 Hz), 6.92 (1H, dt, *J* = 7, 2 Hz), 6.80 (1H, d, *J* = 8 Hz), 6.68 (1H, d, *J* = 8.5Hz), 3.40 (1H, d, *J* = 16 Hz), 3.06 (1H, d, *J* = 16 Hz), 1.43 (3H, s); ¹³C (DMSO d⁶, 125MHz) δ : 173.2, 145.3, 133.2, 131.9, 128.8, 126.9, 126.0, 125.7, 123.8, 121.0, 118.1, 54.4, 43.1, 23.2

3-(3-fluoro-4-aminophenyl)-3-methyl-3,4-dihydroquinolin-2(1H)-one 142



In a 50 ml round bottom flask fitted with a condenser was charged with a solution of the *bis*-nitro aryl compound (250 mg, 0.66 mmol) dissolved in EtOH (10 ml). To the solution was added Zn dust (375 mg) and glacial acetic acid (2 ml) and the mixture refluxed for 4 hrs. The solution was cooled to room temperature and quenched with H₂O. The mixture was filtered through celite in order to remove any excess Zn or ZnO and the solvent removed in vacuo. The residue was redissolved in DCM (50 ml), washed with NaHCO₃ (3 × 30 ml) and water (3 × 30 ml) and dried with MgSO4. The solvent was removed in vacuo to yield the desired quinolinone as a purple solid (179 mg, 91%); m.p. 235-237°C; IR (cm⁻¹): 3472, 1675, 895, 737; MS *m/e* 271 (86%) (M+H)⁺, 233 (25%) 160 (100%); (EI) exact mass calculated for (C₁₆H₁₆N₂OF⁺) 271.1241, found 271.1241; ¹H NMR (CDCl₃) (500MHz) δ : 10.24 (1H, br s) 7.24 (1H, d, *J* = 7.3Hz), 7.08 (1H, t, *J* = 7.3Hz), 6.91 (2H, m), 6.82 (1H, dd, *J* = 8.3, 2.1Hz), 6.78 (1H, d, *J* = 7.9Hz), 6.61 (1H, d, *J* = 8.3Hz), 3.45-3.34 (4H, m), 3.04 (1H, d, *J* = 16.1 Hz), 1.41 (3H, s); ¹³C (DMSO *d*⁶, 125MHz) 173.8, 156.3 (d, ¹J_{CF} = 250 Hz), 154.2, 151.5, 151.0, 133.1, 132.3, 130.6, 128.3, 126.1, 124.8, 122.9, 117.0 (d, ²J_{CF} = 20Hz), 52.0, 39.7, 21.5

3-(Hydroxy(4-nitrophenyl)methyl)but-3-en-2-one 241⁷⁴



To a solution of L-proline (12 mg, 0.1 mmol), imidazole (7 mg, 0.1 mmol) and 4nitrobenzaldehyde (151 mg, 1mmol) in DMF/water (9:1) (1 mL) was added methyl vinyl ketone (0.25 mL, 3 mmol) and the resulting mixture was stirred at room temperature for 24 h at 25°C. The reaction was quenched with saturated sodium bicarbonate solution (5 mL) and extracted with dichloromethane (3 x 10 mL). The organic phase was washed with water (3 x 10 mL), dried over magnesium sulphate, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica, eluting with ethyl acetate/light petroleum (3:7), to give the title compound (176mg, 80%) as a pale yellow solid; mp = 79-81°C; IR (nujol) 3419, 2922, 1732, 1660, 1652 cm⁻¹; MS (CI, [M+NH₄]⁺) m/z 239.1 (100%); HRMS (CI, [M+NH₄]⁺): found 239.1028; (C₁₁H₁₅N₂O₄⁺) requires 239.1026; HPLC retention time 37.4mins (major), 40.4mins (minor); ¹H NMR (500 MHz, CDCl₃) δ : 8.17 (2H, d, J = 8.9Hz), 7.54 (2H, d, J = 8.9Hz), 6.30-6.22 (1H, m), 6.03 (1H, br s), 5.66 (1H, d, J = 5.0Hz), 3.37 (1H, d, J = 5.0Hz), 2.34 (3H, s); ¹³C NMR (125MHz, CDCl₃) δ : 200.0, 149.0, 148.9, 147.3, 127.7, 127.2, 123.5, 72.2, 26.3;

The absolute stereochemistry of the major adduct was determined by comparing the sign of the specific rotation with reported literature data. Measurement of the optical rotation and comparison to literature showed the sample to be of the (*R*)-configuration: $[\alpha]_D^{20} = -0.88$ (c = 4, CHCl₃) was calculated utilising the adduct obtained from the Baylis-Hillman reaction performed under the conditions described above catalysed with (S)-histidine derivate xxx (see section 4.3, Table 23, entry 1, 14% ee (R)); literature for 3-((R)-hydroxy(4-nitrophenyl)methyl)but-3-en-2-one (R)-134: $[\alpha]_D^{20} = -12.1$ (c = 0.53, CHCl₃)

3-(Hydroxy(4-fluorophenyl)methyl)but-3-en-2-one 24275



To a solution of L-proline (12 mg, 0.1 mmol), imidazole (7 mg, 0.1 mmol) and 4fluorobenzaldehyde (124 mg, 1mmol) in DMF/water (9:1) (1 mL) was added methyl vinyl ketone (0.25 mL, 3 mmol) and the resulting mixture was stirred at room temperature for 24 h at 25°C. The reaction was quenched with saturated sodium bicarbonate solution (5 mL) and extracted with dichloromethane (3 x 10 mL). The organic phase was washed with water (3 x 10 mL), dried over magnesium sulphate, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica, eluting with ethyl acetate/light petroleum ([DMF]-130mg, 67%; [DMF/water 9:1]-169mg, 87%) as a off-white solid; LRMS (CI, [M+H]⁺) m/z 195.1 (100%); HRMS (CI, [M+H]⁺): found 195.0820; (C₁₁H₁₂O₂F⁺) requires 195.0816¹H NMR (400 MHz, CDCl₃) δ : 7.26 (2H, d, J = 8.6Hz), 6.95 (2H, d, J = 8.6Hz), 6.13 (1H, s), 5.91 (1H, s), 5.53 (1H, s), 2.27 (3H, s). 3-(Hydroxy(2,4-dinitrophenyl)methyl)but-3-en-2-one 243⁷⁶



To a solution of L-proline (12 mg, 0.1 mmol), imidazole (7 mg, 0.1 mmol) and 2,4dinitrobenzaldehyde (196 mg, 1mmol) in DMF/water (9:1) (1 mL) was added methyl vinyl ketone (0.25 mL, 3 mmol) and the resulting mixture was stirred at room temperature for 24 h at 25°C. The reaction was quenched with saturated sodium bicarbonate solution (5 mL) and extracted with dichloromethane (3 x 10 mL). The organic phase was washed with water (3 x 10 mL), dried over magnesium sulphate, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica, eluting with ethyl acetate/light petroleum ([DMF]-112mg, 42%; [DMF/water 9:1]-215mg, 81%) as a yellow oil; IR (film): 3408, 3106, 2357, 1673, 1606, 1536, 1347; LRMS (CI, [M+H]⁺) m/z 267.1 (100%); HRMS (CI, [M+H]⁺): found 267.0617; (C₁₁H₁₁N₂O₆⁺) requires 267.0617; HPLC retention time 49.3mins (major), 58.1 (minor); ¹H NMR (400 MHz, CDCl₃) δ : 8.73 (1H, d, J = 2 Hz), 8.41 (1H, dd, J = 9, 2 Hz), 7.98 (1H, d, J = 9 Hz), 6.23 (1H, s), 6.17 (1H, s), 5.79 (1H, s), 2.31 (1H, s); 1³C NMR (100 MHz, CDCl₃) δ : 199.5, 148.1, 147.9, 147.2, 143.2, 130.6, 127.3, 127.1, 120.1, 67.4, 25.9. 3-(Hydroxy(2,4-dichlorophenyl)methyl)but-3-en-2-one 244⁷⁷



To a solution of L-proline (12 mg, 0.1 mmol), imidazole (7 mg, 0.1 mmol) and 2,4chlorobenzaldehyde (175 mg, 1mmol) in DMF/water (9:1) (1 mL) was added methyl vinyl ketone (0.25 mL, 3 mmol) and the resulting mixture was stirred at room temperature for 24 h at 25°C. The reaction was quenched with saturated sodium bicarbonate solution (5 mL) and extracted with dichloromethane (3 x 10 mL). The organic phase was washed with water (3 x 10 mL), dried over magnesium sulphate, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica, eluting with ethyl acetate/light petroleum (1:1) [DMF]-137mg, 56%; [DMF/water 9:1]-196mg, 80%) as a yellow solid; mp = 148-150°C; LRMS (CI, [M+H]⁺) m/z 245.0 (100%); HRMS (CI, [M+H]⁺): found 245.0136; (C₁₁H₁₁O₂Cl₂⁺) requires 245.0131; ¹H NMR (400 MHz, CDCl₃) &: 7.44 (1H, d, J = 8.4Hz), 7.29 (1H, d, J = 2.1Hz), 7.22 (1H, dd, J = 2.1, 8.4Hz), 6.11 (1H, s), 5,85 (1H, s), 5.60 (1H, s), 2.32 (1H, s)

3-(Hydroxy(2-nitrophenyl)methyl)but-3-en-2-one 24578



To a solution of L-proline (12 mg, 0.1 mmol), imidazole (7 mg, 0.1 mmol) and 2nitrobenzaldehyde (151 mg, 1mmol) in DMF/water (9:1) (1 mL) was added methyl vinyl ketone (0.25 mL, 3 mmol) and the resulting mixture was stirred at room temperature for 24 h at 25°C. The reaction was quenched with saturated sodium bicarbonate solution (5 mL) and extracted with dichloromethane (3 x 10 mL). The organic phase was washed with water (3 x 10 mL), dried over magnesium sulphate, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica, eluting with ethyl acetate/light petroleum (1:1) [DMF]-128mg, 58%; [DMF/water 9:1]-161mg, 73%) as a yellow oil; IR (film) 3414, 1675, 1525, 1351; LRMS (CI, [M+H]⁺) m/z 222.1 (100%); HRMS (CI, [M+H]⁺): found 222.0767; (C₁₁H₁₂NO₄⁺) requires 222.0761; HPLC retention time 25.8 (major), 28.5 (minor); ¹H NMR (400 MHz, CDCl₃) δ : 7.91 (1H, d, J = 7.7Hz), 7.72 (1H, d, J = 7.7Hz), 7.60 (1H, t, J = 7.7Hz), 7.40 (1H, t, J = 7.7Hz), 6.16 (1H, s), 6.11 (1H, s), 5.73 (1H, s), 2.32 (3H, s); ¹³C NMR (100 MHz, CDCl₃) δ : 199.5, 149.0, 147.8, 136.7, 133.5, 128.8, 128.5, 126.6, 124.5, 67.1, 26.2. 3-(Hydroxy(pentafluorophenyl)methyl)but-3-en-2-one 24679



To a solution of L-proline (12 mg, 0.1 mmol), imidazole (7 mg, 0.1 mmol) and 2nitrobenzaldehyde (151 mg, 1mmol) in DMF/water (9:1) (1 mL) was added methyl vinyl ketone (0.25 mL, 3 mmol) and the resulting mixture was stirred at room temperature for 24 h at 25°C. The reaction was quenched with saturated sodium bicarbonate solution (5 mL) and extracted with dichloromethane (3 x 10 mL). The organic phase was washed with water (3 x 10 mL), dried over magnesium sulphate, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica, eluting with ethyl acetate/light petroleum (1:1) [DMF]-0mg, 0%; [DMF/water 9:1]-223mg, 84%) as a orange solid; LRMS (CI, [M+H]⁺) m/z 267.0 (100%); HRMS (CI, [M+Na]⁺): found 289.0260; (C₁₁H₇F₅NaO₂⁺) requires 289.0258; NMR (400 MHz, CDCl₃) δ : 6.29 (1H, br s), 6.21 (1H, br s), 5.87 (1H, s), 2.31 (3H, s).

3-(Hydroxy(furan-2-yl)methyl)but-3-en-2-one 247⁸⁰



To a solution of L-proline (12 mg, 0.1 mmol), imidazole (7 mg, 0.1 mmol) and 2-fufural (96 mg, 1mmol) in DMF/water (9:1) (1 mL) was added methyl vinyl ketone (0.25 mL, 3 mmol) and the resulting mixture was stirred at room temperature for 24 h at 25°C. The reaction was quenched with saturated sodium bicarbonate solution (5 mL) and extracted with dichloromethane (3 x 10 mL). The organic phase was washed with water (3 x 10 mL), dried over magnesium sulphate, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica, eluting with ethyl acetate/light petroleum (1:1) (24h [DMF]-0mg, %; [DMF/water 9:1]-38mg, 23%; 96h [DMF]-55mg, 33%; [DMF/water 9:1]-148mg, 89%) as a pale yellow oil; IR (film) 3320, 2957, 2923, 2852, 1714, 1667, 1510, 1462, 1376; LRMS (CI, [M+H]⁺) m/z 167.1 (100%); HRMS (CI, [M+H]⁺): found 167.0708; (C₁₁H₁₁N₂O₆⁺) requires 167.0703; HPLC retention time 25.0 (major), 33.0 (minor); ¹H NMR (400 MHz, CDCl₃) &: 7.29 (1H, dd, J = 0.8, 1.8Hz), 6.26 (1H, dd, J = 1.8, 3.2Hz), 6.18 (2H, m), 6.03 (1H, d, J = 1.1Hz), 5.56 (1H, s), 2.32 (3H, s); ¹³C NMR (100 MHz, CDCl₃) &: 199.2, 154.2, 147.2, 141.6, 126.4, 109.9, 106.6, 65.2, 25.7.

N'-(Propan-2-ylidene)benzoic hydrazide 269⁸¹



Benzoic hydrazide 242 (5.00 g, 36.7 mmol) was stirred in an excess of acetone 60 (22 mL, 0.3 mmol), containing acetic acid (40 m, 0.7 mmol), for 48 hours at ambient temperature. Water (30 mL) was added and the reaction mixture was extracted with CH₂Cl₂ (3x30 mL). The combined organic extracts were dried (Na₂SO₄) and reduced *in vacuo* to afford the *title compound* 269 (5.57 g, 86%) as a colourless solid; mp (petrol/ether) 141–143 °C [lit.⁸¹ mp 142-143 °C]; \Box_{max} (nujol)/cm⁻¹ 3221, 1655, 1578, 1578, 1531, 1490; ¹H NMR (400 MHz, CDCl₃) δ_{H} 8.70 (1H, s, N<u>H</u>) 7.79 (2H, d, *J* = 7.1, Ar-<u>H</u>) 7.52 (1H, t, *J* = 7.1, Ar-<u>H</u>) 7.44 (2H, t, *J* = 7.1, Ar-<u>H</u>) 2.15 (3H, s, C<u>H₃</u>) 1.97 (3H, s, C<u>H₃</u>); ¹³C NMR (100 MHz, CDCl₃) δ_{C} 164.6 (C) 156.9 (C) 134.1 (C) 132.1 (CH) 129.0 (CH) 127.6 (CH) 26.0 (CH₃) 17.3 (CH₃); *m/z* (EI) [M]⁺ 176 (8%), 161 (50), 105 (100); HRMS (EI) (found 176.0950 [M]⁺; C₁₀H₁₂N₂O requires 176.0950).



Platinum(IV) oxide (68 mg, 0.3 mmol) was placed in a nitrogen flushed flask with ethanol (12 mL) and acetic acid (6 mL). *N*-(Propan-2-ylidene)benzoic hydrazide **181** (2.50 g, 14.2 mmol) was added, the flask was charged with hydrogen and stirred for 48 hours at ambient temperature. The reaction mixture was filtered over Celite and the filtrate was neutralised with saturated sodium bicarbonate solution (180 mL). The volatiles were removed under reduced pressure and the aqueous phase was extracted with diethyl ether (5x50 mL). The combined organic extracts were washed with brine (30 mL), dried (MgSO₄) and the volatiles were removed under reduced pressure to give the *title compound* **243** (2.18 g, 86%) as a colourless powder; mp (petrol/ether) 110–112 °C [lit.⁸¹ mp 115-117 °C]; \Box_{max} (nujol/cm⁻¹ 3289, 1640, 1537, 725, 693; ¹H NMR (400 MHz, CDCl₃) $\delta_{\rm H}$ 7.70 (1H, s, N<u>H</u>) 7.69 (2H, d, J = 7.7, Ar-<u>H</u>) 7.46 (1H, t, J = 7.7, Ar-<u>H</u>) 7.38 (2H, t, J = 7.7, Ar-<u>H</u>) 4.81 (1H, s, N<u>H</u>) 3.18 (1H, sept., J = 6.2, NC<u>H</u>(CH₃)₂); ¹³C NMR (100 MHz, CDCl₃) $\delta_{\rm C}$ 167.5 (C) 132.9 (C) 131.9 (CH) 128.7 (CH) 126.9 (CH) 51.4 (CH) 20.9 (CH₃); m/z (EI) [M]⁺ 178 (3%), 163 (9), 122 (13), 105 (100); HRMS (EI) (found 178.1105 [M]⁺; C₁₀H₁₄N₂O requires 178.1106).

Ethyl-1H-imidazole carboxylic acid 281⁸²



To a stirred solution of imidazole-4-carboxylic acid (1.00g, 8.19mmol) in MeOH (15ml) was added *conc*. H₂SO₄ (1 drop) and the reaction mixture heated at reflux overnight. The mixture was cooled to room temperature and concentrated in vacuo. The crude product was re-dissolved in DCM (25ml) and washed with sat. NaHCO₃ (25ml), and water (25ml). The product was obtained as a yellowish oil (990mg, 96%) ¹H NMR (CDCl₃, 400 MHz) $\delta_{\rm H}$ 8.02 (1H, s), 7.85 (1H, s), 3.48 (3H,s)

methyl-2(imidazol-4-yl)acetate 28383

To a stirred solution of imidazole-4-acetic acid (1.00g, 7.94mmol) in MeOH (15ml) was added *conc.* H₂SO₄ (1 drop) and the reaction mixture heated at reflux overnight. The mixture was cooled to room temperature and concentrated in vacuo. The crude product was re-dissolved in DCM (25ml) and washed with sat. NaHCO₃ (25ml), and water (25ml). The product was obtained as a clear oil (988mg, 89%); ¹H NMR (CDCl₃, 400MHz) δ : 8.93 (1H, s), 7.51 (1H, s), 3.92 (2H, s), 3.70 (3H, s)

(E)-methyl 3-(imidazol-4-yl)acrylate 284⁸⁴

To a stirred solution of urocanic acid (1.00g, 7.24mmol) in MeOH (15ml) was added *conc*. H_2SO_4 (1 drop) and the reaction mixture heated at reflux overnight. The mixture was cooled to room temperature and concentrated in vacuo. The crude product was re-dissolved in DCM (25ml) and washed with sat. NaHCO₃ (25ml), and water (25ml). The product was obtained as a white solid (1.01g, 92%). mp 91-93°C (*ref* 92-94°C) ¹H NMR (400 MHz, CDCl₃) δ : 7.69 (1H, s), 7.59 (1H, d, J = 15.6Hz), 7.27 (1H, s), 6.45 (1H, d, J = 15.6Hz), 5.24 (1H br s), 3.76 (3H, s)

(S)-methyl-2-(benzamido)-3-(1H-imidazol-4-yl)propanoate 285



To a stirred suspension of benzoic acid (490mg, 4mmol), 1-hydroxybenzotriazole hydrate (560mg, 4.2mmol), L-histidine methyl ester dihydrochloride (970mg, 4mmol), and Nmethylmorpholine (0.88mL, 8mmol) in dry tetrahydrofuran (50mL) at 0°C was added 1,3dicyclohexylcarbodiimide (827mg, 4mmol) in dry dichloromethane (12.5mL) and the mixture stirred at 0°C for 2h. The reaction mixture was allowed to warm to room temp. and stirring continued for 2 days. The reaction mixture was cooled to 0°C the resulting urea precipitate was removed by filtration and the filtrate concentrated under reduced pressure. The concentrated residue was washed with brine (2 x 30mL), sat. NaHCO₃ (2 x 30mL) and brine (30mL) once again. The organic phase was dried over MgSO₄, filtered and evaporated under reduced pressure to give the crude product as an orange gum. The crude product was purified by flash column chromatography, eluting with EtOAc/MeOH 100:0 to 80:20, to give the title compound (904 mg, 82%) as a pale yellow solid; mp (methanol) = 155-157 °C; IR (nujol): 3277, 1757, 1735, 1644, 1576, 1537, 1462, 1376, 1332, 1252, 1137 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ : 8.37 (1H, d, J =7.1Hz, NH amide), 7.80 (2H, d, J = 7.3Hz), 7.48 (1H, s, CH-imidazole), 7.43 (1H, dd, J = 7.3, 7.5Hz), 7.35 (2H, d, J = 7.5Hz), 6.75 (1H, s, CH-imidazole), 4.88 (1H, dd, J = 6.0, 15.0Hz, *NHCH*), 3.60 (3H, s), 3.15 (2H, dd, J = 6.0, 15.0Hz, *CHCH*₂); ¹³C NMR (126 MHz, CDCl₃) δ : 171.8, 167.5, 135.1, 134.2, 133.3, 131.5, 128.3, 126.9, 115.3 53.1, 52.0, 28.7; LRMS (APCI, $[M+H]^+$): m/z 274 (100%), 214 (30%); HRMS (ES, $[M+H]^+$): found m/z 274.1192. $(C_{14}H_{16}N_{3}O_{3}^{+})$ requires *m/z* 274.1192; $[\alpha]_{D}^{20} = -24.4$ (*c* 0.01g/ml, methanol)

N-(3-(1H-imidazol-1-yl)propyl)benzamide 286



To a stirred suspension of benzoic acid (500 mg, 4.10 mmol), 1-hydroxybenzotriazole hydrate (582 mg, 4.31 mmol), 1-(3-aminopropyl)imidazole (513 mg, 4.10 mmol), and Nmethylmorpholine (0.90 mL, 8.20 mmol) in dry tetrahydrofuran (50 mL) at 0°C was added 1,3dicyclohexylcarbodiimide (845 mg, 4.10 mmol) in dry dichloromethane (12.5 mL) and the mixture stirred at 0°C for 2 h. The reaction mixture was allowed to warm to room temp. and stirring continued for 2 days. The reaction mixture was cooled to 0°C the resulting urea precipitate was removed by filtration and the filtrate concentrated under reduced pressure. The concentrated residue was washed with brine (2 x 30 mL), sat. NaHCO₃ (2 x 30 mL) and brine (30mL) once again. The organic phase was dried over MgSO4, filtered and evaporated under reduced pressure to give the crude product as an orange gum which was purified by flash column chromatography, eluting with EtOAc/MeOH 100:0 to 85:15 yielding the title compound (715 mg, 76%) as a colourless oil; IR (DCM) 3426, 1642, 1580; LRMS (CI [M+H]⁺): m/z 230 (100%), 162 (30%), 67 (15%); HRMS (ES, $[M+H]^+$): (EI) found m/z 230.1297, (C₁₃H₁₆N₃O⁺) requires m/z 230.1228; ¹H NMR (400MHz, CDCl₃) δ : 7.92 (1H, br s), (2H, d, J = 7 Hz), 7.44 (1H, t, J = 7 Hz), 7.36 (2H, t, J = 7 Hz), 7.05 (1H, br s), 6.96 (1H, br s), 4.06 (2H, t, J = 7 Hz),3.91 (2H, m), 3.43 (2H, aparant q, J = 6 Hz); ¹³C NMR (100MHz, CDCl₃) δ : 168.1, 138.2, 135.2, 130.4, 129.0, 128.5, 126.5, 118.3, 52.1, 40.7, 38.2.

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