NEW SYNTHETIC METHODS TO ACCESS NON-CODED AMINO ACIDS

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ABSTRACT

α-Amino acids are a ubiquitous class of compounds which are vital to the existence of all life on earth. In addition to providing the building blocks of life's machinery, they are increasingly finding use as starting materials for total syntheses, as ligands in chiral catalysis or as novel pharmaceutically active compounds in their own right. As such, the development of new synthetic methods to access existing α-amino acids, as well as previously unknown amino acids is of significant importance.

The introduction contained in the first part of this report aims to provide a general overview of the catalytic methods currently used to prepare α-amino acids, as well as to highlight a notable class of α-amino acids called the kainoids, with specific attention directed to covering previous total synthesis routes to access (-)-α-kainic acid.

The work described in the second part of this report was based on the extension of methodology developed by Shaw, and focuses on attempts to develop catalytic, diastereoselective aldol reaction methodology with azido hydroxamic acid-containing substrates in order to prepare diastereomerically pure α-amino acids.

The third and final section of this report discusses the preparation of substituted tetrahydropyridinium ylide precursors and their subsequent rearrangement in the presence of neutrally-generated benzyne is explored. The selectivity observed when asymmetric arynes are generated as reactive species was also investigated. Finally, the successful expansion of this methodology to acyclic substrates is also discussed.

TABLE OF CONTENTS

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"We choose to go to the moon in this decade and do the other things, not because they are easy, but because they are hard" – John F. Kennedy, 12th September 1962

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Last but not least, I would like to say thankyou to my parents and family who have provided me with both support and encouragement at every point up until now. Without them, I wouldn't be where I am today.

ABBREVIATIONS

Ac	Acetyl
Aq	Aqueous
Ar	Aryl
COD	Cyclooctadiene
DBU	1,8-Diazabicycloundec-7-ene
DCM	Dichloromethane
DIPAMP	Ethane-1,2-diylbis[(2-methoxyphenyl)phenylphosphane]
DMF	Dimethylformamide
DMAP	4,4-Dimethylaminopyridine
DMSO	Dimethylsulfoxide
DSC	Differential scanning calorimetry
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
NMR	Nuclear magnetic resonance
TGA	Thermogravimetric analysis
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
VAPOL	2,2′-Diphenyl-(4-biphenanthrol)

INTRODUCTION

Amino Acids

Amino acids are a class of compounds which are vital to the existence of all life on earth, and contain both amino and carboxylic acid functional groups. It is possible to classify an amino acid by considering its structure; where the amino group is bound to the same carbon as the carboxylic acid, the α-carbon, it is called an α-amino acid. In β-amino acids the amino group is bound to the β-carbon (Figure 1). To date, there are in excess of 500 known amino acids, each of which possesses a unique side-chain.[1]

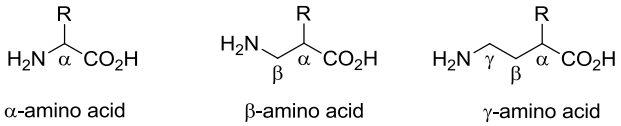


Figure 1 - Structural classification of amino acids

The 22 most commonly encountered naturally occurring amino acids are all L-stereoisomers, and are responsible for the construction of proteins (proteinogenic). Twenty of these proteinogenic amino acids are coded for directly by triplet codons found in the genetic code, and as such are referred to as coding amino acids. The two non-coding proteinogenic amino acids pyrrolysine (22) and selenocysteine (11) are incorporated into proteins by distinct post-translational biosynthetic mechanisms.

Proteinogenic amino acids are condensed together to form a peptide linkage in a process called translation. Peptides that are between 3 and 10 residues in length are called oligopeptides while peptides longer than 10 residues in length are referred to as polypeptides. Polypeptide chains with a molecular weight greater than 10,000 mass units are considered to be proteins.[2]

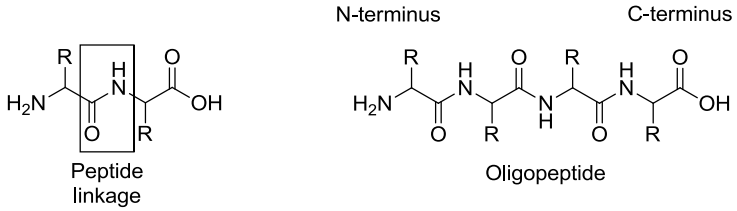


Figure 2 - Schematic of peptide bonding.

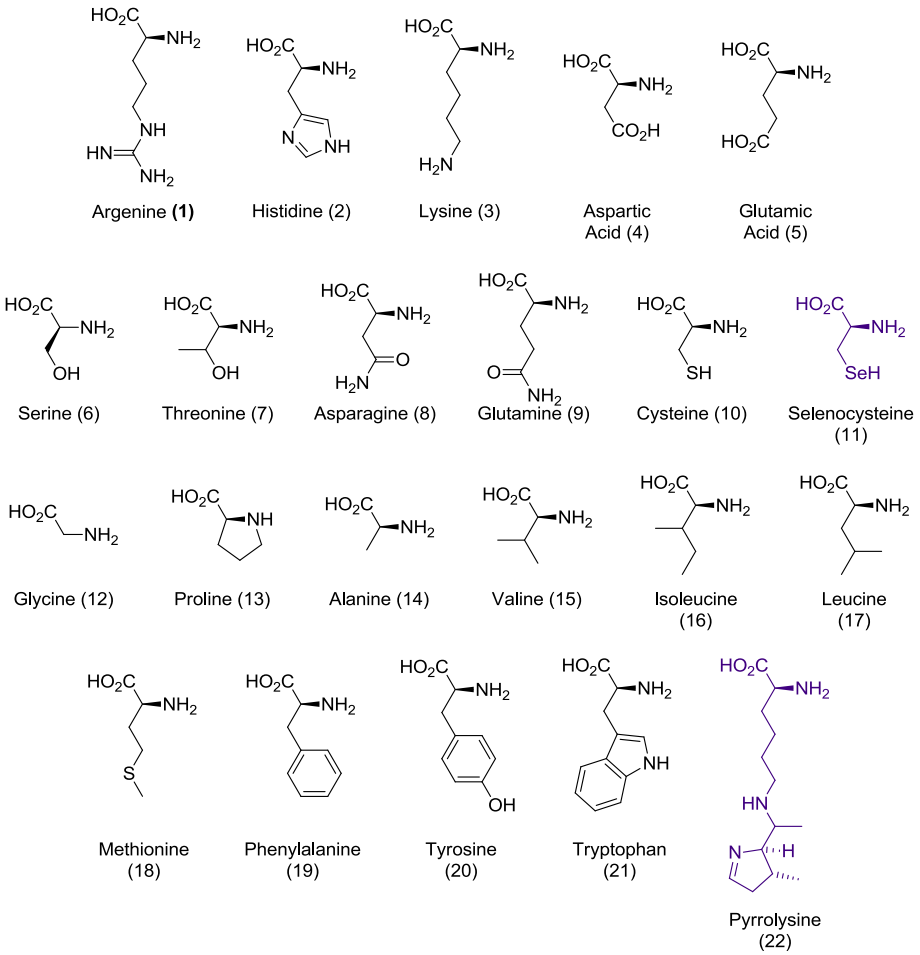


Figure 3 - The 22 proteinogenic amino acids of the human body.

Coding amino acids also fulfil a variety of critical roles within the body which are unrelated to protein formation. For example, glutamic acid (5) (as its glutamate ion) is the primary excitatory neurotransmitter in the brain,[3] while glycine (12) is an important substrate in the synthesis of porphyrins used in red blood cells.[4]

Adittionally, both proteinogenic and non-proteinogenic amino acids are frequently employed as chiral catalysts or as chiral pool building blocks for total synthesis and ligand design.[5]

Synthesis of amino acids

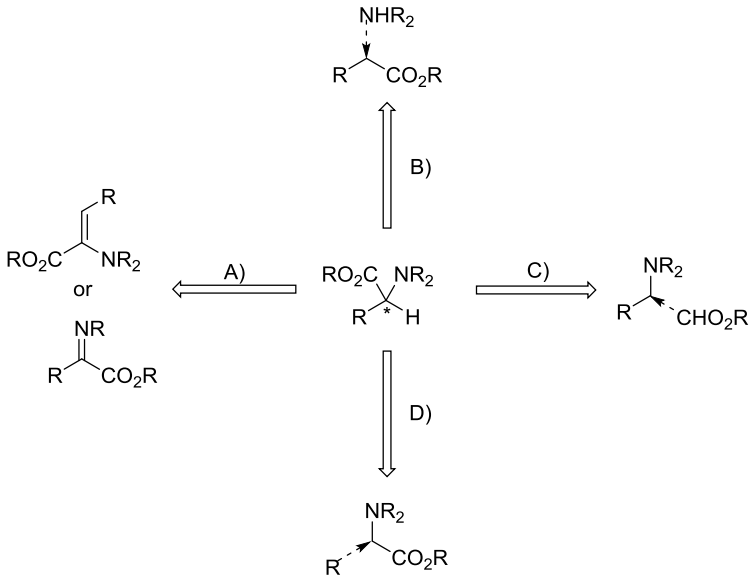
Prior to the early 1980's, the most commonly employed methods of synthesising α-amino acids were based on chemical and enzymatic methodology.

Over the next 20 years, the diastereoselective synthesis of α-amino acids became more popular, relying on chiral templates based on chiral pool α-amino acids.

In the last 15 years, catalytic enantioselective methods have seen a large growth in popularity due to their versatility compared to traditional methods.[6]

Catalytic Enantioselective Synthesis of Amino Acids

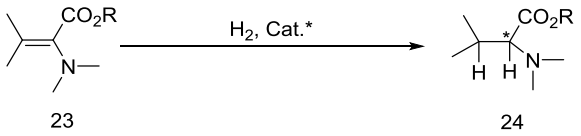
There are four approaches to prepare α-amino acids in a catalytic manner (Scheme 1): A) enantioselective introduction of the α-hydrogen, B) enantioselective introduction of the α-amino group, C) enantioselective introduction of the α-side chain and D) enantioselective introduction of the carboxy group.[7]



Scheme 1 – General overview of catalytic asymmetric synthesis of amino acids.

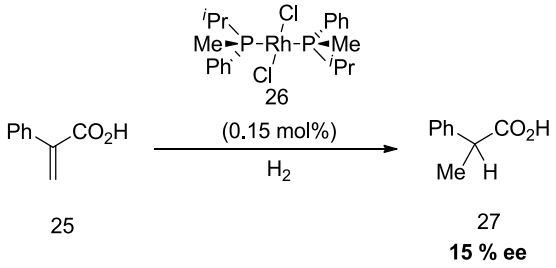
A) Enantioselective Introduction of the α-Hydrogen

There are a number of approaches by which it is possible to introduce α-hydrogens into α-amino acids asymmetrically. The most common method is the enantioselective hydrogenation of the C=C double bond of an α,β-didehydro-α-amino acid derivative (23) (Scheme 2). Due to the low catalyst loading, the minimal amounts of solvent required, the clean nature of the reducing agent and the reliability of the process, this has led to asymmetric hydrogenation becoming a key step in a considerable number of industrial processes.



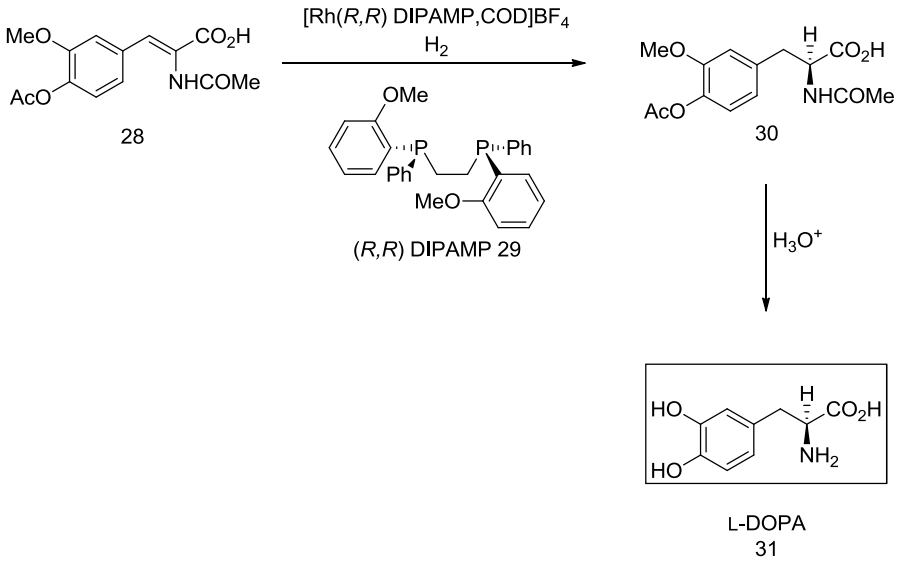
Scheme 2 – General scheme for the catalytic hydrogenation of α,β-didehydro-α-amino acid.

Knowles and Sabacky reported the first catalyst for asymmetric hydrogenation (Scheme 3), employing chiral phosphine ligands with a rhodium catalyst to achieve a modest 15 % enantiomeric excess.[8]



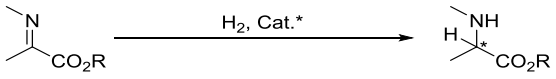
Scheme 3 - Early application of asymmetric hydrogenation.

The first notable application of this chemistry to asymmetric amino acid synthesis was the industrial synthesis of L-Dopa (31) using chiral DIPAMP-[Rh] complex (29), for which Knowles and Sabacki shared the 2001 Nobel prize in Chemistry.[9]



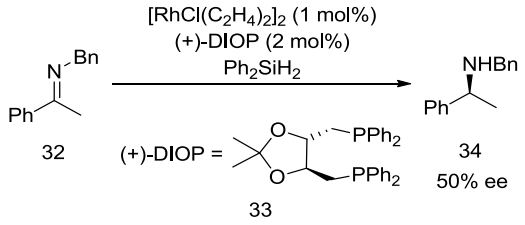
Scheme 4 - Key asymmetric hydrogenation in the preparation of L-DOPA.

Similarly, the asymmetric reduction of imines is an attractive route towards preparing enantiomerically enriched α-amino acids (Scheme 5).



Scheme 5 – General scheme for the asymmetric hydrogenation of α-imino-esters.

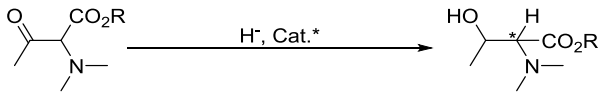
The earliest example of catalytic asymmetric reduction of this type was reported by Kagan *et. al.*, who prepared N-(α-methylbenzylidene)benzylamine (34) in 50% ee using rhodium catalysis with chiral diphosphine ligand (33) (Scheme 6).[10]



Scheme 6 - Early asymmetric reduction of imines.

While it is possible to efficiently hydrogenate simple aliphatic and aromatic aldimines enantioselectively, the hydrogenation of acyclic α-imino esters represents a considerable challenge.[11] This difficulty has resulted in the methodology for accessing α-amino acids by reduction of a C=N bond remaining primitive, especially when compared to the reduction of C=C and C=O bonds.

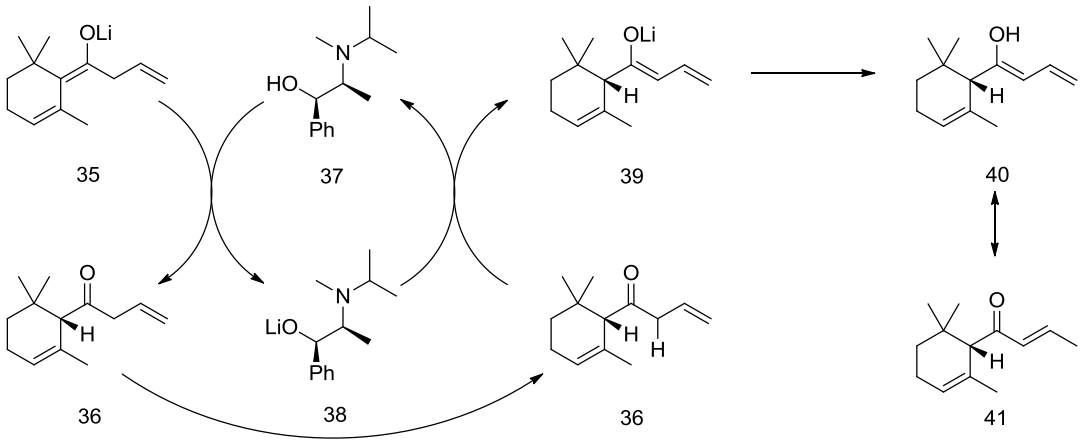
Finally, the enantioselective protonation and reduction of an enolate using a chiral protonating agent represents an attractive approach in accessing chiral amino acids (Scheme 7).



Scheme 7 – General scheme for the asymmetric protonation and reduction of an enolate.

The principle of de-racemisation by using asymmetric protonating agents was first proposed by Duhamel in 1977.[12]

Fehr *et. al.* applied this approach to prepare (S)-α-damascone (Scheme 8).[13] They found that the chiral protonation of lithium enolate (35) with chiral aminoalcohol (37) proceeded by autocatalysis, as the resulting Li-aminoalkoxide deprotonates the newly formed ketone, forming the desired unsaturated alcohol and regenerating the protonating agent on work-up. Using this method, it was possible to prepare (*s*)-α-damascone (41) in 86% yield with 93% ee.

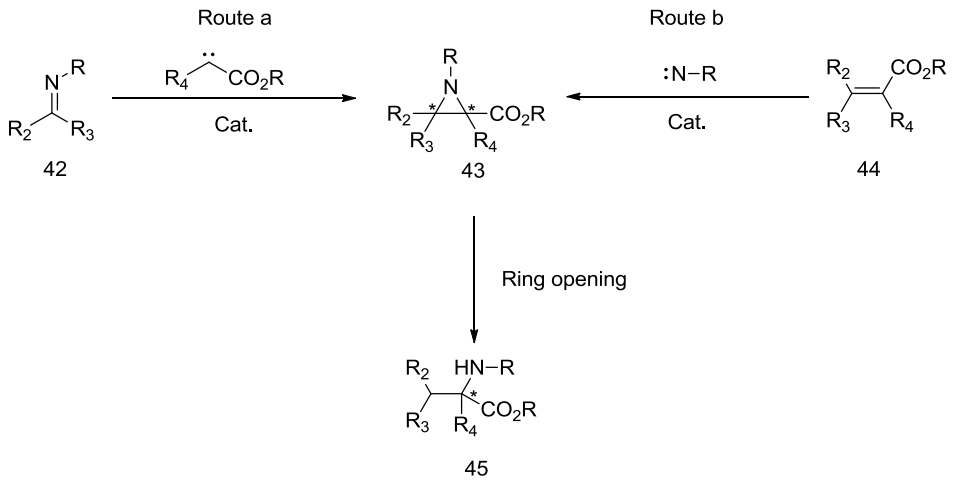


Scheme 8 - Asymmetric protonation applied to the preparation of (s)-α-damascone.

B) Enantioselective Introduction of the α-Amino Group

There are three approaches to introduce the amino group in an enantioselective manner. The first is to generate a chiral aziridine (43), which can be prepared catalytically by using either a carbene (route a) or nitrene (route b) species. The resulting aziridine can then be subjected to ring-opening in order to furnish the desired α-amino acid (Scheme 9).

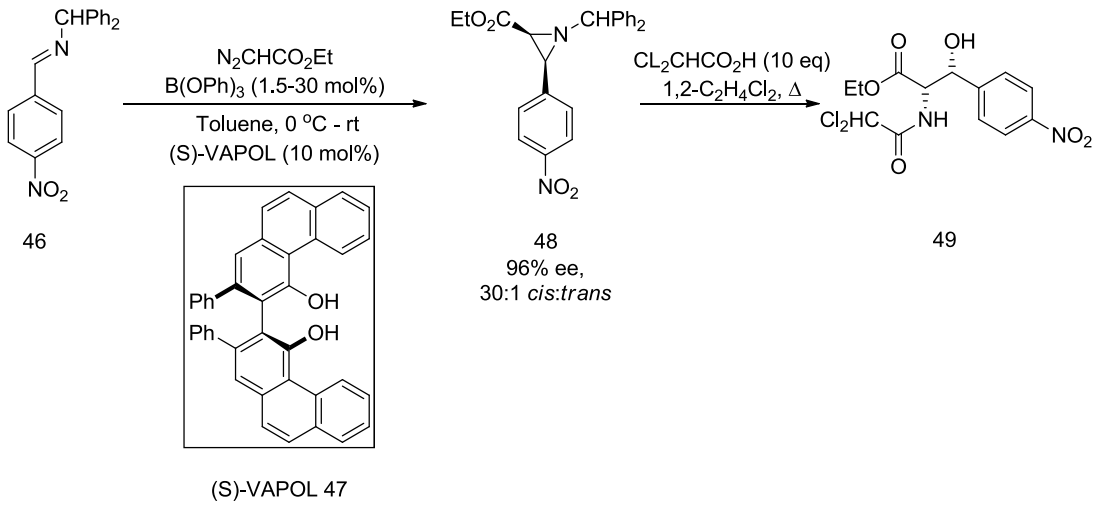
The development of methods to make optically active aziridines has proven to be more challenging when compared to catalytic asymmetric epoxidation processes.[14]



Scheme 9 – General scheme for catalytic asymmetric aziridination.

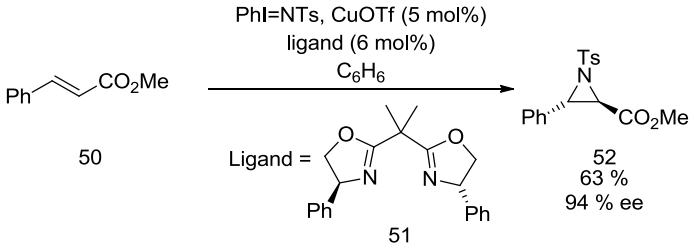
An example of chiral catalytic aziridination by addition of imines to carbene intermediates was demonstrated in the preparation of (-)-chloramphenicol (Scheme 10) by Wulff *et. al.*[15] Using a catalyst generated from triphenylborate and (S)-VAPOL (47) they prepared aziridine (48) from the benzhydryl imine of 4-nitrobenzaldehyde in a highly enantio and

diastereoselective manner, which could subsequently be subjected to ring-opening to yield protected amino acid (49) in 80 % yield as a single diastereoisomer.



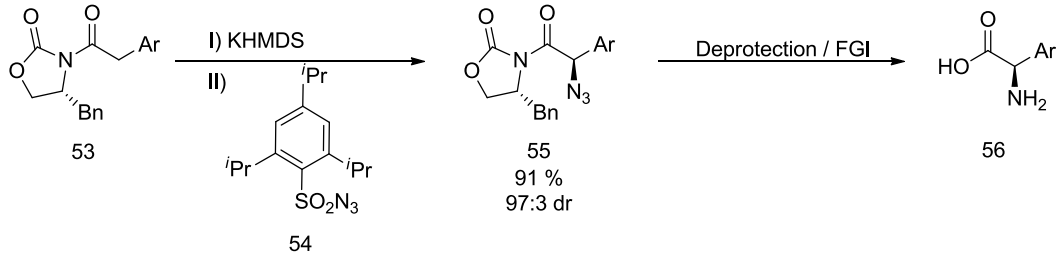
Scheme 10 - Catalytic asymmetric aziridination of an imine with a carbene species.

The aziridination of olefins using nitrenes is exemplified by Evans *et. al.* who developed a procedure using 4,4'-disubstituted bis(oxazolines) with a copper catalyst.[16] Treating methyl-cinnamate ester (50) with (*N*-(*p*-toluenesulfonyl)imino)phenyliodinane (PhI=NTs) in the presence of copper triflate and chiral 4,4'-disubstituted bix(oxazoline) (51) resulted in the formation of a chiral aziridine (52) in 63% yield with 94% ee (Scheme 11).



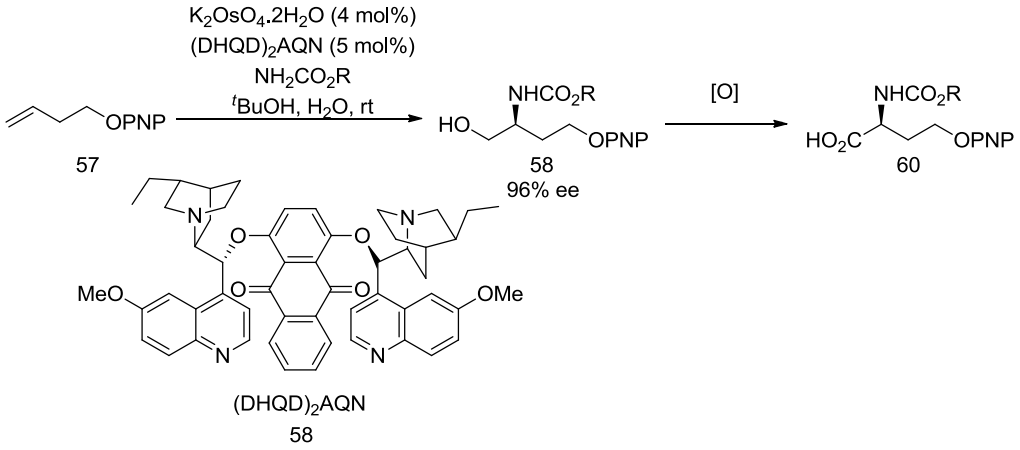
Scheme 11 – Catalytic asymmetric aziridination of an olefin with a nitrene species.

The amination of enolates using electrophilic nitrogenated reagents such as trisyl azide (54) represent an attractive method to access chiral α-amino acids (Scheme 12).[17,18]



Scheme 12 - Electrophilic amination of an enolate with trisylazide.

Finally, Sharpless has demonstrated it is possible to carry out aminohydroxylation using alkylimido osmium complexes.[19] An example of this chemistry being applied to the synthesis of α-amino acids involves the enantioselective aminohydroxylation of terminal alkene (57), which gives rise to protected β-aminoalcohol (59) which is subsequently oxidised to give protected α-amino acid (60) (Scheme 13).[20]

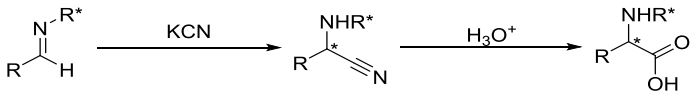


Scheme 13 - Enantioselective catalytic aminohydroxylation.

C) Enantioselective Introduction of the Carboxy Group

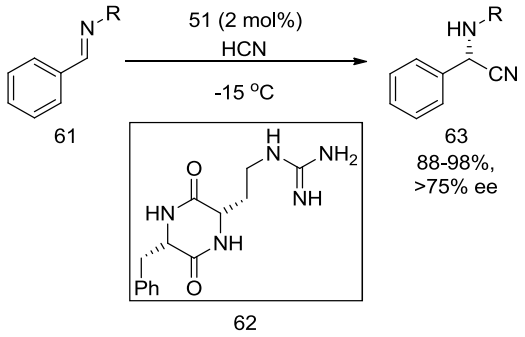
The enantioselective addition of cyanide to imines represents an elegant route by which to introduce a masked carboxylic acid.

The development of an asymmetric Strecker-type reaction has allowed for the efficient synthesis of α-amino acids. This approach has proven to be an attractive method for accessing important chiral arylglycines, with a number of enantioselective examples reported using optically active amines in the place of ammonia to serve as chiral auxilliaries (Scheme 14).[21]



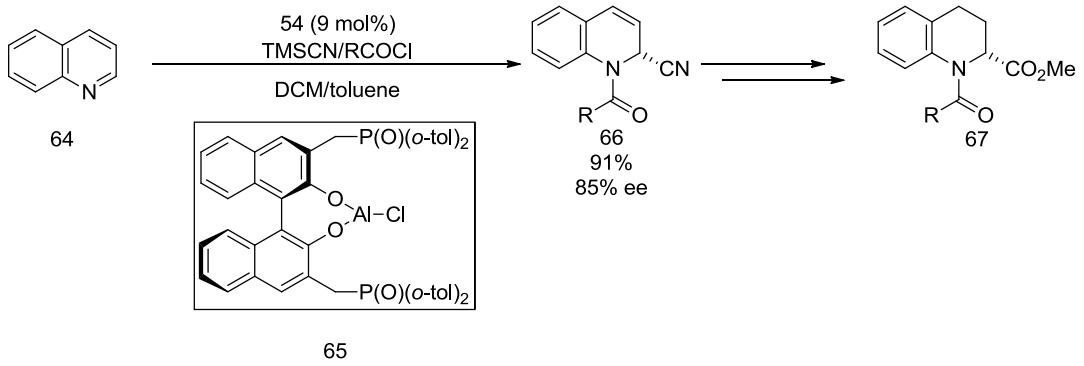
Scheme 14 – Asymmetric Strecker reaction with chiral amine auxilliary.

The first catalytic asymmetric Strecker-type reaction was reported by Lipton *et. al.* who employed a cyclic, chiral dipeptide (61) as an organocatalyst with HCN (Scheme 15).[22]



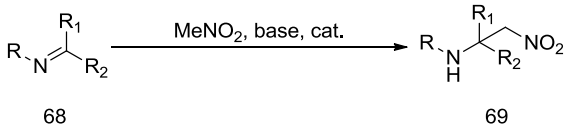
Scheme 15 – Asymmetric Strecker reaction with chiral catalyst.

Additionally, the addition of cyanide to substituted quinoline and isoquinoline derivatives *via* Reissert-type reactions have recently been demonstrated by Shibisaki *et. al.*, who used bifunctional chiral aluminium catalyst (65) to prepare chiral tetrahydroquinoline-2-carboxylate compounds (67) (Scheme 16).[23]



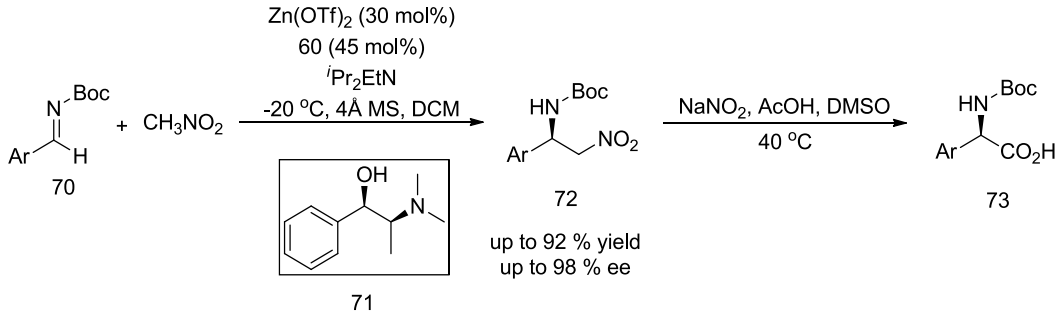
Scheme 16 – Reissert-type reaction with chiral, bifunctional catalyst.

Finally, it is possible to apply the nitro-Mannich/aza-Henry-type reaction in an enantioselective manner to prepare enantiomerically enriched 1,2-nitroamine adducts (69) which can be converted easily to α-amino acids (Scheme 17).



Scheme 17 – General reaction scheme for nitro-Mannich/aza-Henry type reaction

Palomo *et. al.* reported a zinc-catalysed example of the nitro-Mannich reaction, using (-)-*N*-methylephedrine (71) as a ligand to impart stereocontrol in the product (Scheme 18).[24]

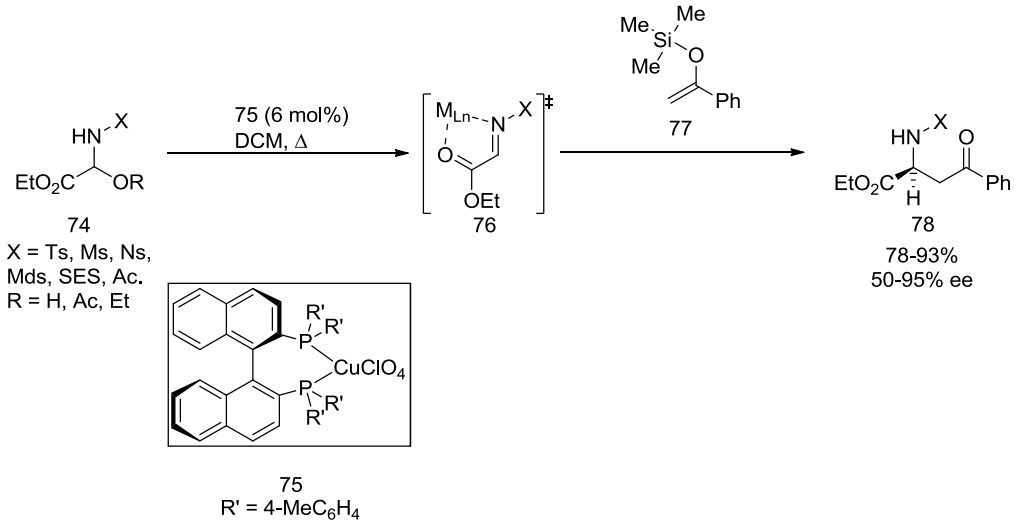


Scheme 18 - Asymmetric nitro-Mannich reaction.

D) Enantioselective Introduction of the α-Side Chain

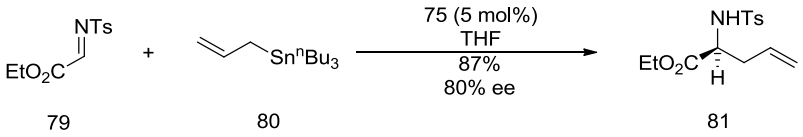
There are a diverse range of methods by which it is possible to asymmetrically introduce the α-side chain of an α-amino acid, which can be broadly grouped into two categories; nucleophilic alkylations of α-imino esters and enantioselective cycloaddition reactions.

Lectka's group demonstrated the introduction of allylic side-chains into α-amino acid derivatives by treating α-imino esters with allyl silanes such as (77), using a chiral $Cu^{(I)}$-based Lewis acid (64) to catalyse the formation of the reactive imine. It is believed that subsequent coordination of this Lewis acid with both the imine nitrogen and carbonyl oxygen is what dictates the stereochemical outcome of the reaction (Scheme 19).[25]



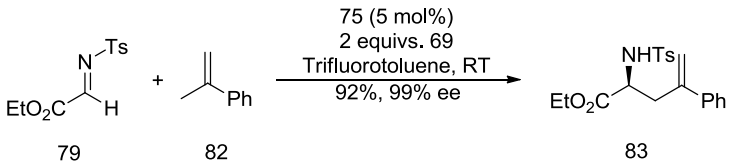
Scheme 19 – Lewis acid-catalysed allylation with allyl silane

Work carried out independently by Jørgensen's group also showed that it was possible to use this catalyst (75) to carry out allyl alkylation with allyl stannanes (Scheme 20).[26]

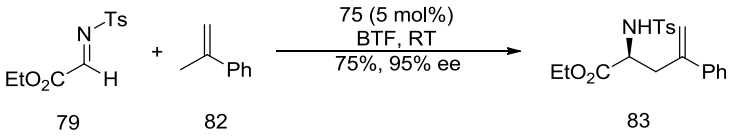


Scheme 20 - Lewis acid-catalysed allylation with allyl stannane.

Both Lectka's[27] and Jørgensen's[28] groups simultaneously applied the use of catalyst (75) to carrying out the alkenylation of *N*-tosylamine (79) using the ene reaction. While both groups carried out the reaction under different conditions (Lectka used 5 mol% of catalyst (75) with 2 equivalents of alkene (82) in trifluorotoluene (Scheme 21); Jørgensen used 5 mol% of catalyst (75) and one equivalent of alkene (82) in THF (Scheme 22)), they obtained similar results. (92 %, 99% ee and 75 %, 95 % ee, respectively)

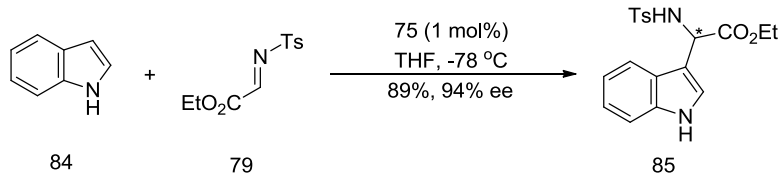


Scheme 21 - Ene reaction catalysed by 75 – Lectka's conditions.



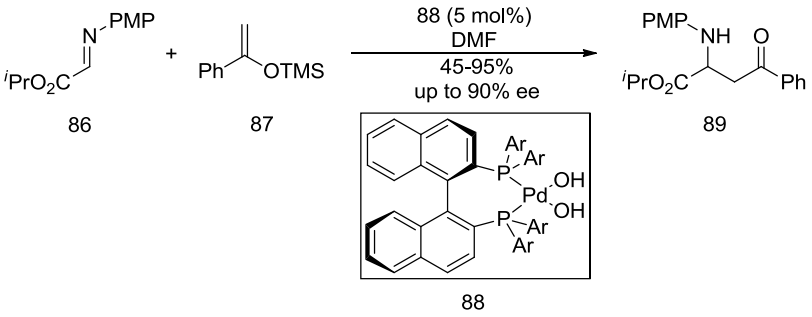
Scheme 22 - Ene reaction catalysed by 75 - Jørgensen's conditions.

The enantioselective aryl-transfer to imines by direct asymmetric addition of electron-rich aromatic species *via* the aza-Friedel-Crafts reaction allows for the synthesis of optically active α-aryl-α-amino acids with relative ease. Johannsen reported that when exposed to indole in the presence of catalyst 75, tosyl imine (79) readily undergoes an aza-Friedel-Crafts reaction to form protected α-amino acid (85) (Scheme 23).[29]



Scheme 23 - Asymmetric aza-Friedel-Crafts reaction to form α-aryl-α-amino acids.

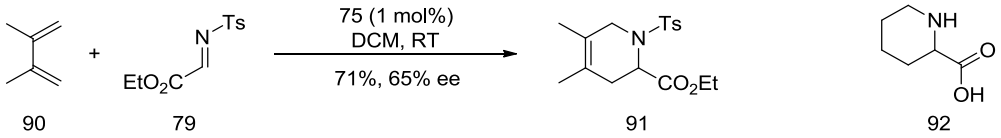
It is also possible to employ Mannich-type reactions in order to introduce functionality into the α-position of α-imino esters. Sodeoka's group described the catalytic alkylation of α-imino ester (86) with enol silyl ether (87) using palladium catalyst (88) (Scheme 24).[30]



Scheme 24 - Asymmetric Mannich-like α-alkylation of α-imine esters.

The aza-Diels-Alder reaction is one of the most useful transformations for the preparation of nitrogen-containing heterocycles. When applied to the synthesis of enantiomerically enriched α-amino acids, the aza-Diels-Alder reaction can be used to access bicyclic α-amino acids and substituted derivatives of the pipecolic acid family (92). In either case, α-imino esters are preferred over 2-azadienes as dienophiles.[31]

Jørgensen found that reacting *N*-tosyl-α-imino ester (79) with diene (90) in the presence of substoichiometric amounts of chiral Lewis acid (75) afforded cyclic α-amino acid (91).[32]

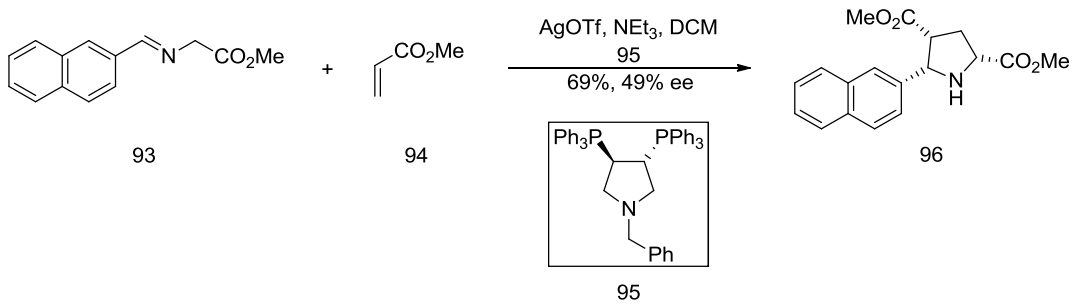


Scheme 25 - aza-Diels-Alder reaction to access cyclic α-amino acids.

The reaction of azomethine ylides with electrophilic alkenes by 1,3-dipolar cycloaddition reaction is a powerful method to access polysubstituted proline derivatives in a stereoselective manner from relatively simple starting materials.[33]

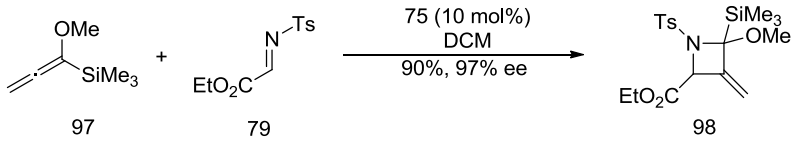
It is reported that the most effective Lewis acids for the cycloaddition of metallo-azomethine ylides are $Ag^{(I)}$ salts, with short reaction times and high yields generally observed.[34]

One of the first examples of stereoselective $Ag^{(I)}$-catalysed cycloaddition reactions of azomethine ylides used a chiral bisphosphine ligand (95) (Scheme 26).[35]



Scheme 26 – 1,3-dipolar addition of an azomethine ylide to a conjugated ester.

Finally, [2 + 2] cycloadditions between either alkenes or allenes and α-imino esters provide access to 2-azetidinecarboxylic acid derivatives. Akiyama *et. al.* developed enantioselective methodology for the conversion of α-imino ester (79) to azetidinecarboxylic acid (98) in the presence of 1-methoxyallenyltrimethylsilane (97) and chiral lewis acid (75) (Scheme 27).[36]



Scheme 27 – Lewis acid-catalysed [2 + 2] cycloaddition of an allene to an α-imino ester.

Kainoids

The kainoids are a class of non-coded amino acids, of which (-)-α-kainic acid (99), also known as digenic acid, is the parent compound (Figure 4). Kainic acid was first isolated in 1953 from a species of Japanese seaweed called *Digenea simplex*. Other members of this class of compounds include (+)-allokainic acid (100) and (-)-domoic acid (101), which have been isolated from species of marine algae.

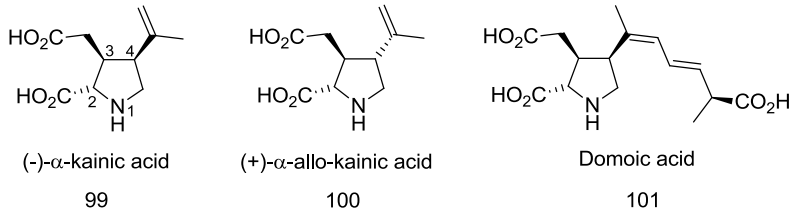
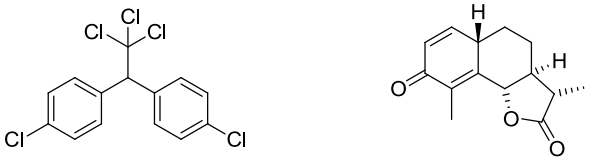


Figure 4 - Examples of kainoids.

The compounds of this class all exhibit strong insecticidal, anti-helmintic (anti-intestinal worm) and neuroexcitatory properties. For example, domoic acid is 14 times more potent as an insecticide than DDT (102), while kainic acid has been shown to be 10 times more potent than santonin (103) at killing intestinal worms, without exhibiting toxicity or disturbances to vision which are commonly encountered with santonin.[37]



DDT

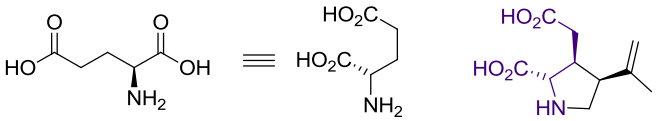
102

Santonin

103

Figure 5 – Structures of DDT (102) and Santonin (103).

The neuroexcitatory activity of these compounds is thought to stem from the structural similarities they show to glutamic acid (Figure 6), and are thought to act *via* the glutamergic receptors.



5

Kainic Acid

99

Figure 6 - Comparison of (-)-α-kainic acid (99) to glutamic acid (5).

The insecticidal activity of these compounds has been demonstrated to stem from the nature of the C4 side-chain. Additionally, their *anti*-helmintic activity had been shown to be dependent on the *cis*-stereochemistry of the C3 and C4 chains – allokainic acid (100) and other kainoids with *trans*-geometry at these positions have very weak anti-helmintic activity.[38]

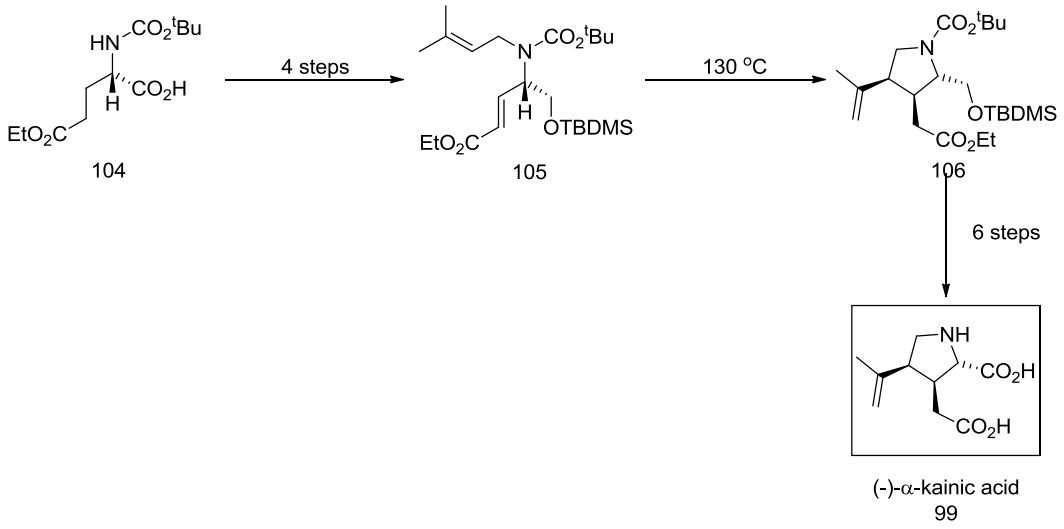
The strong neuoroexcitatory properties of these compounds also mean that they are commonly used as biological probes. A number of studies have shown that they are able to selectively block neuronal processes, targeting the glutamergic system in both vertebrates and invertebrates and resulting in the specific death of neurons in the brain. Injection of kainoids leads to neuronal degredation which mimics the symptoms of neuronal diseases such as epilepsy and Huntington's disease, as well as acting as a good model for the neuronal cell loss commonly associated with senile dementia.[39]

Synthetic routes towards kainic acid

Oppolzer's enantioselective total synthesis

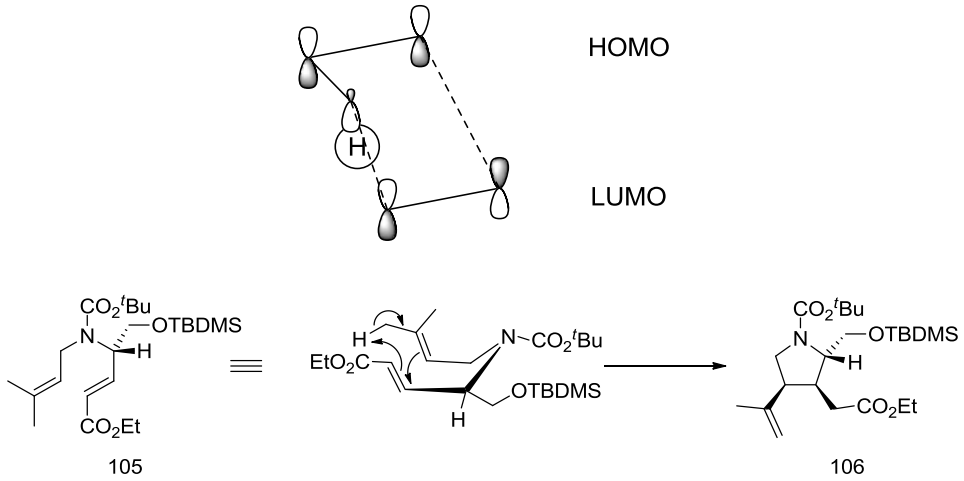
Oppolzer reported the first enantioselective total synthesis of (-)-α-kainic acid in 1982. Construction of the pyrrolidine core was carried out by making the bond between the C3 and C4 position, which was achieved using an intramolecular ene-reaction.[40]

The *tert*-butyl carbamate-protected (+)-5-ethyl glutamate starting material (104) was subjected to diborane reduction, protection and *N*-prenylation. Conjugation of the saturated ester was accomplished by introducing a selenophenol group which was oxidised to the selenoxide and subjected to elimination to furnish the α,β-unsaturated ester (105) (Scheme 28).



Scheme 28 - Oppolzer's total synthesis of (-)-α-kainic acid.

The ene-reaction was accomplished by heating a 5 % solution of the diene in a sealed tube at 130 °C in toluene for 40 hours to furnish the desired pyrrolidine product (106) in 75% yield. The stereochemistry of the product can be explained by considering the molecular orbitals involved in the ene-reaction (Scheme 29).



Scheme 29 - Mechanism of key ene-reaction.

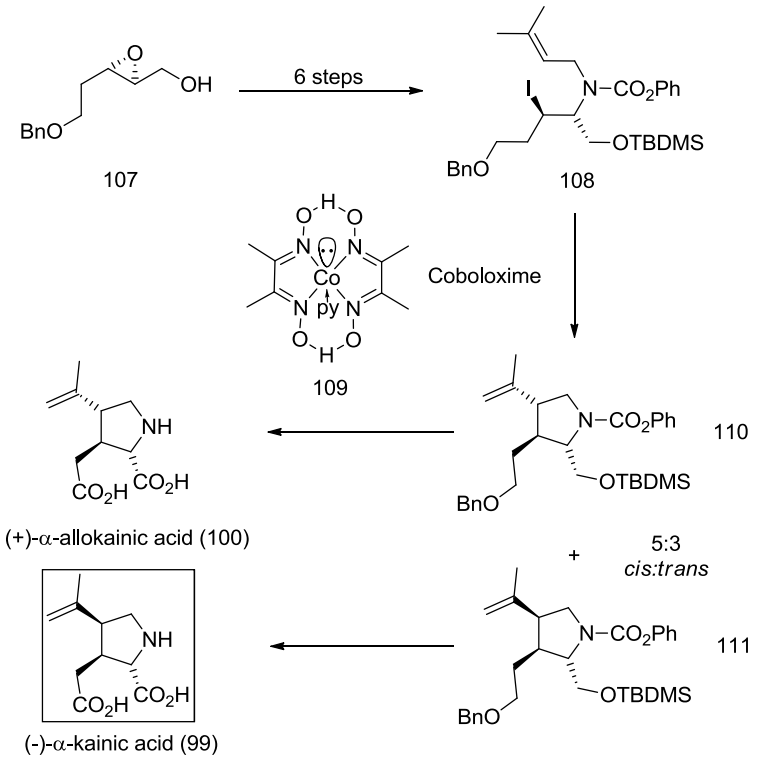
With the pyrrolidine core in place with the desired stereochemistry, the final steps of the synthesis were to carry out deprotections to furnish (-)-α-kainic acid (99) in 5% overall yield over 14 steps.

Baldwins total synthesis[41]

Baldwin's total synthesis, reported in 1987, relies on a cobalt-mediated cyclisation to simultaneously form the C3-C4 bond of the pyrrolidine ring and to introduce the double bond into the C4-side chain.

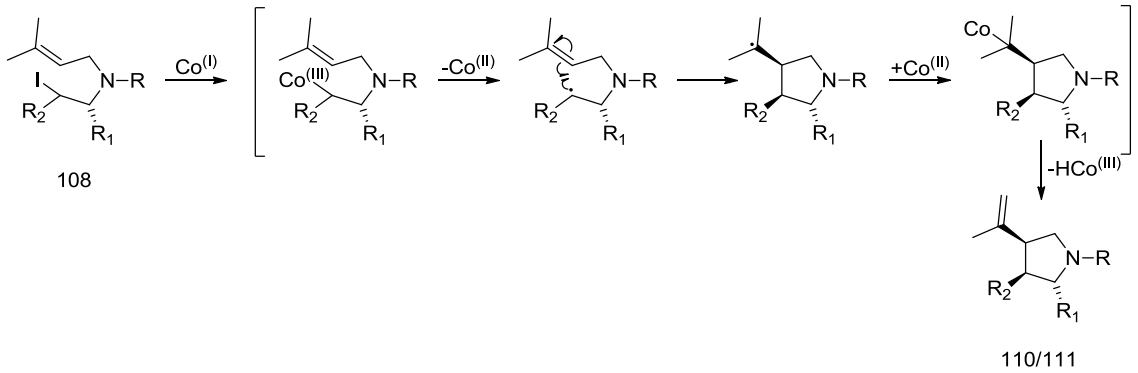
The key acyclic intermediate was prepared by treatment of epoxide (107), prepared by Sharpless asymmetric epoxidation, successively with 1-isocyanato-3-methylbut-2-ene, sodium hydride and sodium hydroxide. The resulting secondary amine was protected as a carbamate, the primary alcohol was selectively converted to the silyl ether and the secondary alcohol was converted to iodide (108) with inversion of stereochemistry.

The cyclisation was achieved by treating intermediate (108) with cobaloxime$^{(I)}$ (109), which was generated *in situ* by reducing chlorocobaloxime$^{(III)}$ with sodium borohydride.[42] A mixture of separable isomers was obtained, with a preference for the *cis*-isomer in a 5:3 ratio. Both isomers were deprotected and had their oxidation states adjusted separately to give (-)-α-kainic acid and (+)-α-allokainic acid.



Scheme 30- Baldwin's total synthesis of (-)-α-kainic acid.

The key step in this synthesis is the cobalt-mediated radical cyclisation (Scheme 31 - *Mechanism of Co-mediated radical cyclisation*). The supernucleophilic Co(I) centre displaces the iodide then undergoes homolytic bond cleavage to furnish a radical species. After cyclisation, the resulting tertiary radical is trapped by the cobalt species which undergoes β-hydride elimination to emplace the double bond required in the C-4 side chain.



Scheme 31 - Mechanism of Co-mediated radical cyclisation.

Knight's total synthesis[43]

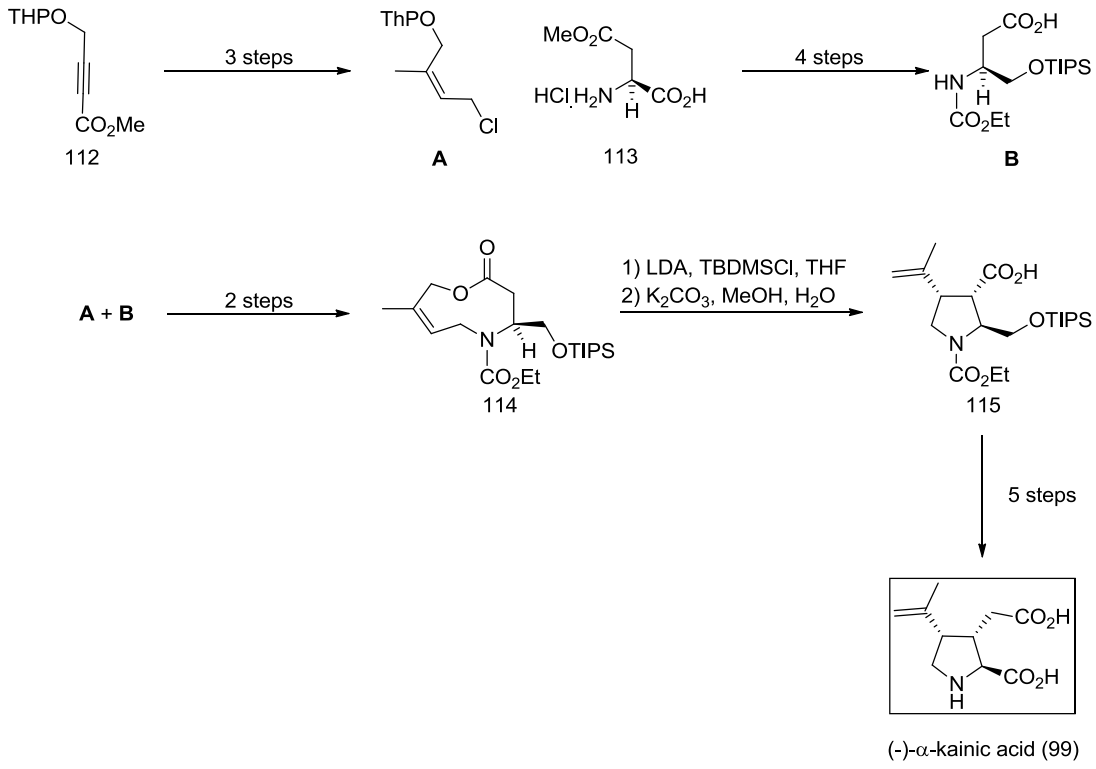
Knight developed a synthesis relying on the stereocontrolled enolate Claisen-rearrangement of a 9-membered azolactone in order to form the C3-C4 bond with the desired *cis*-stereochemistry.

The key lactone intermediate (114) was prepared by coupling together two fragments; fragment A was prepared in 3 steps from tetrahydropyran-protected prop-2-ynyl methyl ester (112); fragment B was prepared in 4 steps from the hydrochloride salt of β-methyl-L-aspartic acid (113).

The two fragments were joined by treating fragment **B** successively with 2 equivalents of ^{n}BuLi followed by fragment **A**. Deprotection of the tetrahydropyran group and subsequent lactonisation was carried out to give key intermediate (114).

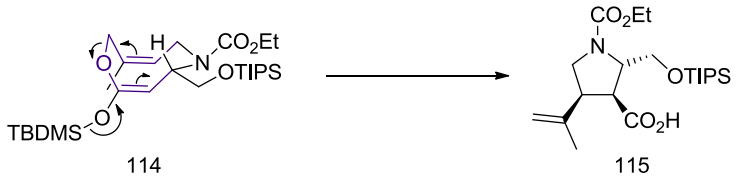
The Claisen rearrangement was carried out according to the 'pre-mix' method of Ireland and Norbeck, where the lactone is converted to a trapped enolate by treatment with LDA and TBDMSCl at -100 °C. On allowing the reaction to warm to room temperature, rearrangement occurs to furnish the pyrolidine ring with the desired stereochemistry.

The synthesis was completed by manipulating the side chains of the pyrrolidine; homologation using the Arndt-Eistert reaction, deprotection of the TIPS group, subsequent oxidation and hydrolysis of the methyl ester furnished (-)-α-kainic acid (99) with an overall yield of 0.65 % over 16 steps .



Scheme 32 - Knight's synthesis of (-)-α-kainic acid.

The key transformation of this synthesis is the Claisen rearrangement, which proceeds through a boat-like transition state to afford the *cis*-stereochemistry observed in the product. The high diastereomeric purity is partly attributed to the pseudoequatorial nature of the silyl-protected alcohol.



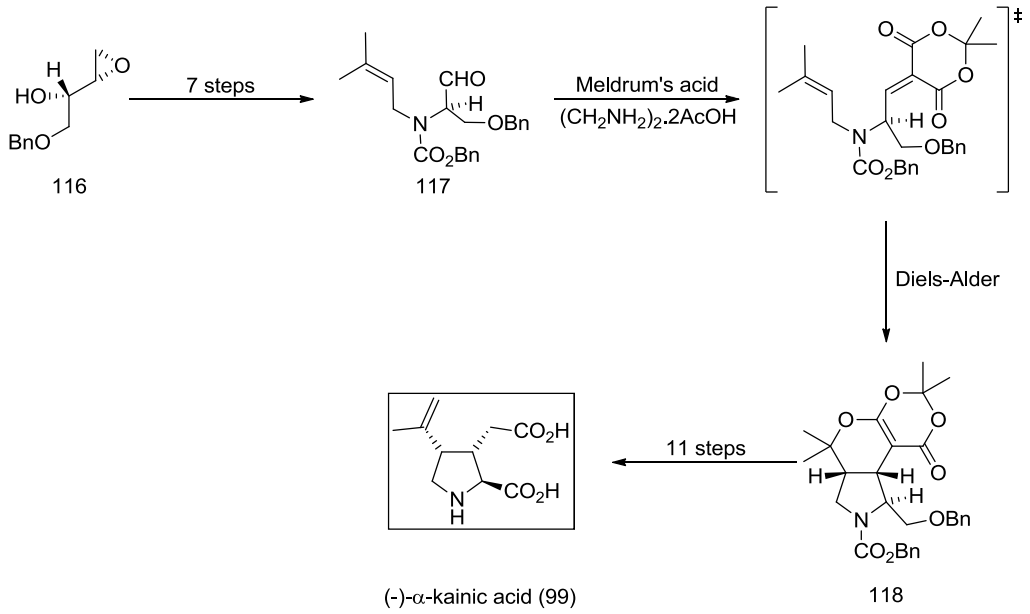
Scheme 33 - Key Claisen rearrangement mechanism.

Takano's synthesis[44]

Takano and co-workers developed a route to kainic acid utilising an intramolecular hetero-Diels-Alder reaction to make the C3-C4 bond with control over the stereochemistry.

Starting from epoxy alcohol (116) derived from dimethyl L-tartrate, the key disubstituted glyceraldehyde intermediate (117) was prepared in 7 steps.

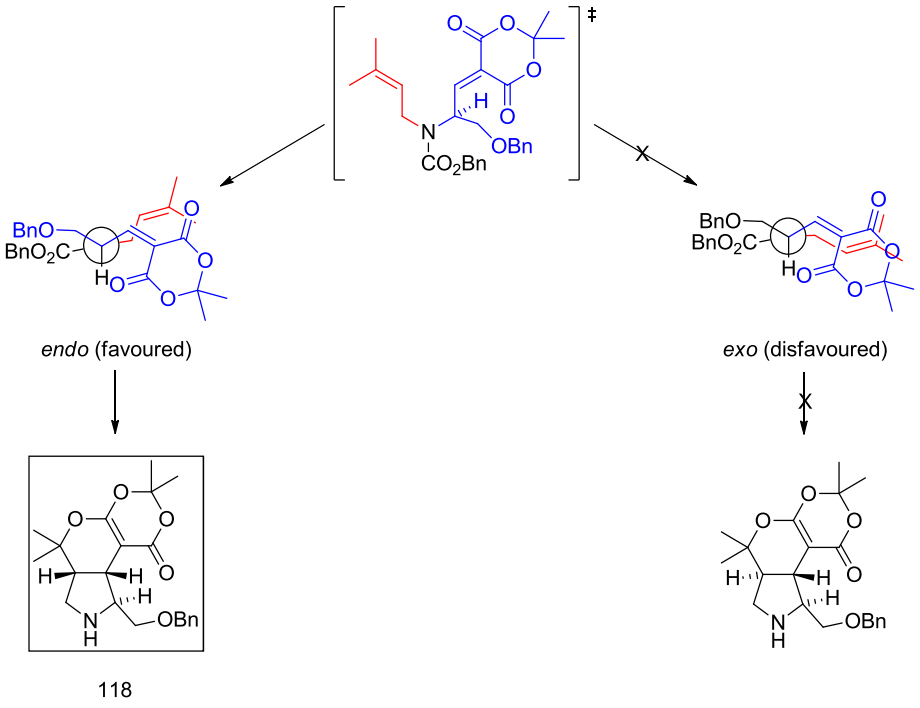
When treated with Meldrum's acid, the compound underwent a Diels-Alder cycloaddition to yield tricyclic product (118) as a single diastereoisomer, which was converted to (-)-α-kainic acid (99) in 11 steps, with an overall yield of 2.9 % over 19 steps.



Scheme 34 - Takano's total synthesis of (-)-α-kainic acid.

The key intramolecular Diels-Alder reaction occurs spontaneously on warming to room temperature, furnishing the desired tricyclic product with the correct facial selectivity. This

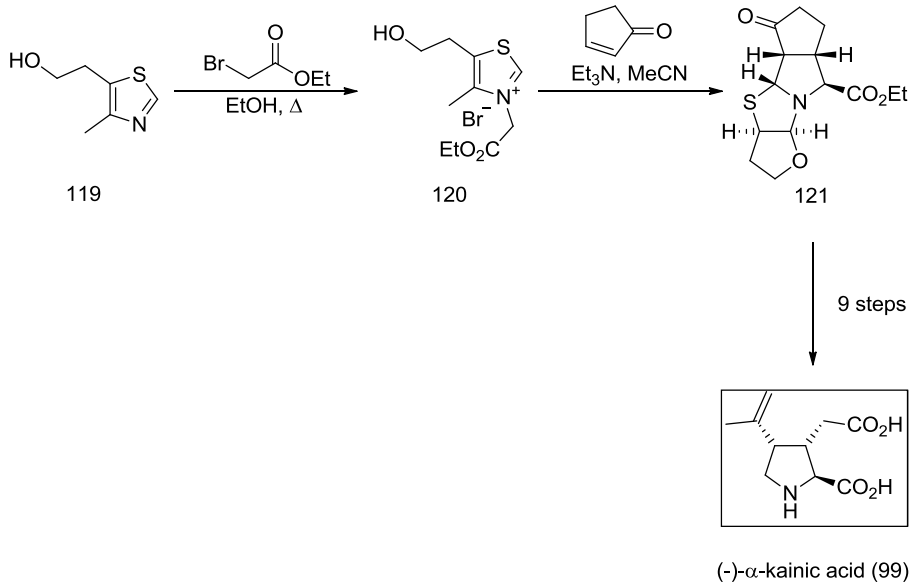
selectivity is achieved due to the planar sp^2-like nature of the carbamate nitrogen, which only allows for efficient [2π + 4π] overlap to occur in the *endo* transition state.



Scheme 35 - Transition states of key intramolecular Diels-Alder reaction.

Monn's synthesis[45]

Monn's synthesis approaches the formation of the pyrrolidine core by forming the C2-C3 and C4-C5 bonds simultaneously *via* an intermolecular [3+2] cycloaddition between a thiazolium ylide and 2-cyclopentenone.



Scheme 36 - Monn's total synthesis of (-)-α-kainic acid.

Ylide precursor (120) was prepared by alkylating substituted thiazole (119) with ethyl bromoacetate. The resulting salt was treated with trimethylamine in the presence of 2-cyclopentenone to furnish the tetracylic compound (121) as a 6.8:1 mixture of diastereoisomers.

While these isomers were separable, it was deemed unnecessary since the 3-thiotetrahyrofuranal portions of the ring system were to be excised by reductive cleavage in the following steps. Tetracyclic intermediate (121) was converted to (-)-α-kainic acid (99) in 9 steps.

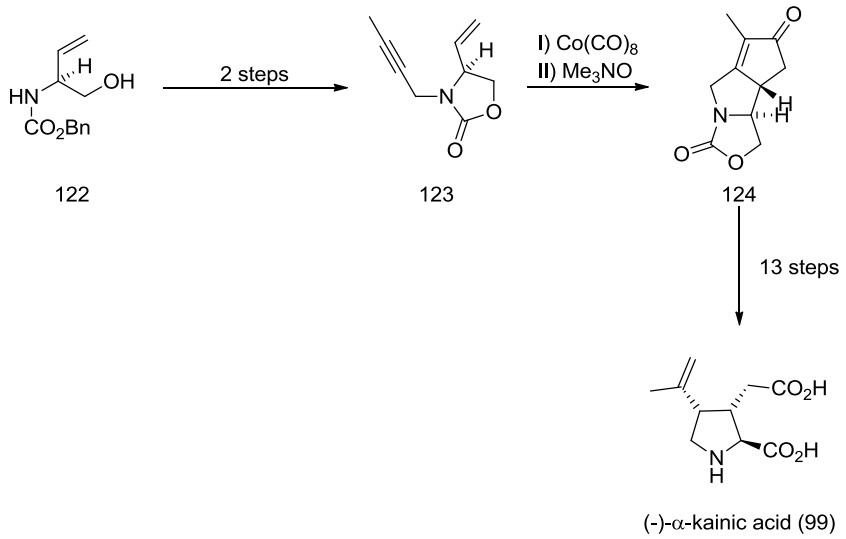
The stereocontrol observed in the cycloaddition is presumed to arise from the thiazolium ylide, which can exist in two conformations. It is believed that the thiazolium ylide approaches the 2-cyclopentenone ring from above, causing the *trans*-geometry observed at the C2 and C3 positions while simultaneously forcing the C3 and C4 positions to adopt *cis*-geometry.

An additional benefit of this approach is that the stereochemical requirements of the conformationally restricted 3-azabicyclo[3.3.0] octane nucleus prevents epimerisation of the C4-centre, forcing it to retain *cis*-geometry with respect to C3.

Yoo's synthesis[46]

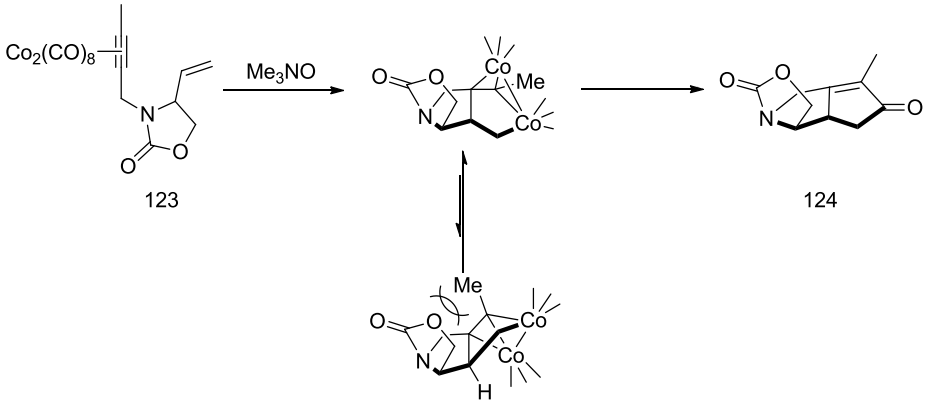
Yoo's synthesis employed a Pauson-Khand reaction to form the C3-C4 pyrrolidine bond, using an oxazolidinone ring to both protect the amine and alcohol functionality and direct the stereoselectivity of the product.

The Pauson-Khand substrate (123) was derived in two steps from a glutamic acid-based substrate, and was treated with $Co(CO)_8$ to furnish tricyclic compound (124) as a single diastereoisomer with the desired configuration. Conversion of this compound to (-)-α-kainic acid was achieved in 13 steps.



Scheme 37 - Yoo's total synthesis of (-)-α-kainic acid.

The stereocontrol observed in the key Pauson-Khand transformation arises from steric interactions between the oxazolidinone and methyl groups, illustrated in (Scheme 38).



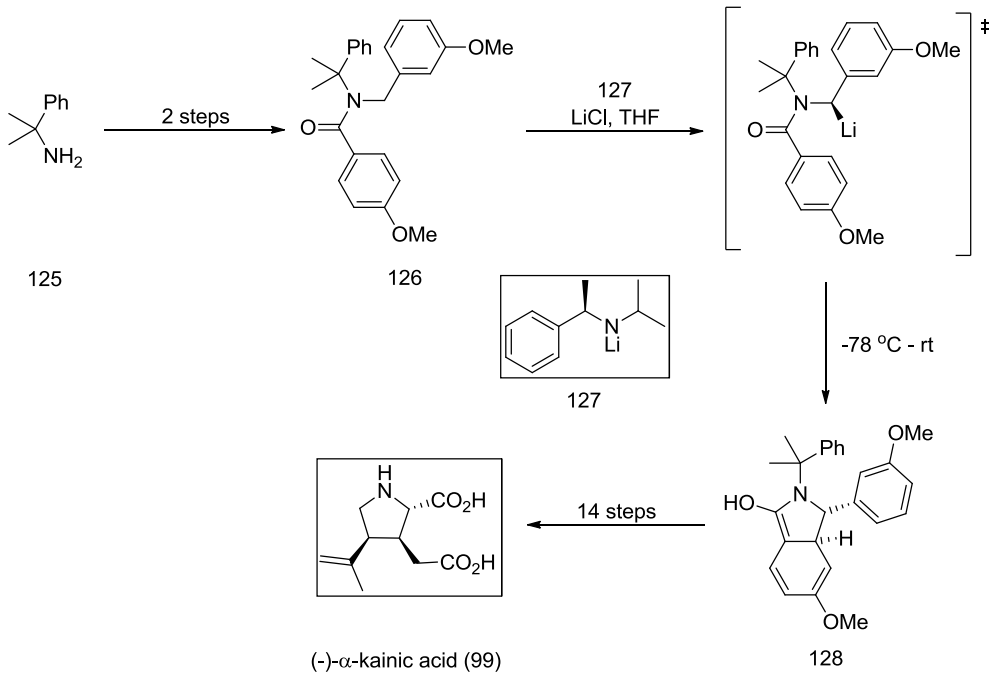
Scheme 38 - Geometry of Pauson-Khand reaction.

Clayden's synthesis[47]

Clayden's synthesis forms the C2-C3 bond of the kainoid pyrrolidine ring, and relies on the use of a chiral lithium amide to carry out an asymmetric deprotonation to effect an asymmetric, dearomatising cyclisation.

The substrate for this cyclisation (126) was prepared in two steps from cumylamine (125).

Cyclisation was carried out by treating a mixture of the substrate and the chiral amine salt (127) with 2 equivalents of ^{n}BuLi at –78 °C then allowing the mixture to warm to ambient temperature to promote the asymmetric deprotonation and subsequent cyclisation to form an enolate. After aqueous workup, the desired enone (128) was converted to (-)-α-kainic acid in a further 14 steps, with an overall yield of 11.1 % over 16 steps.



Scheme 39 - Clayden's total synthesis of (-)-α-kainic acid.

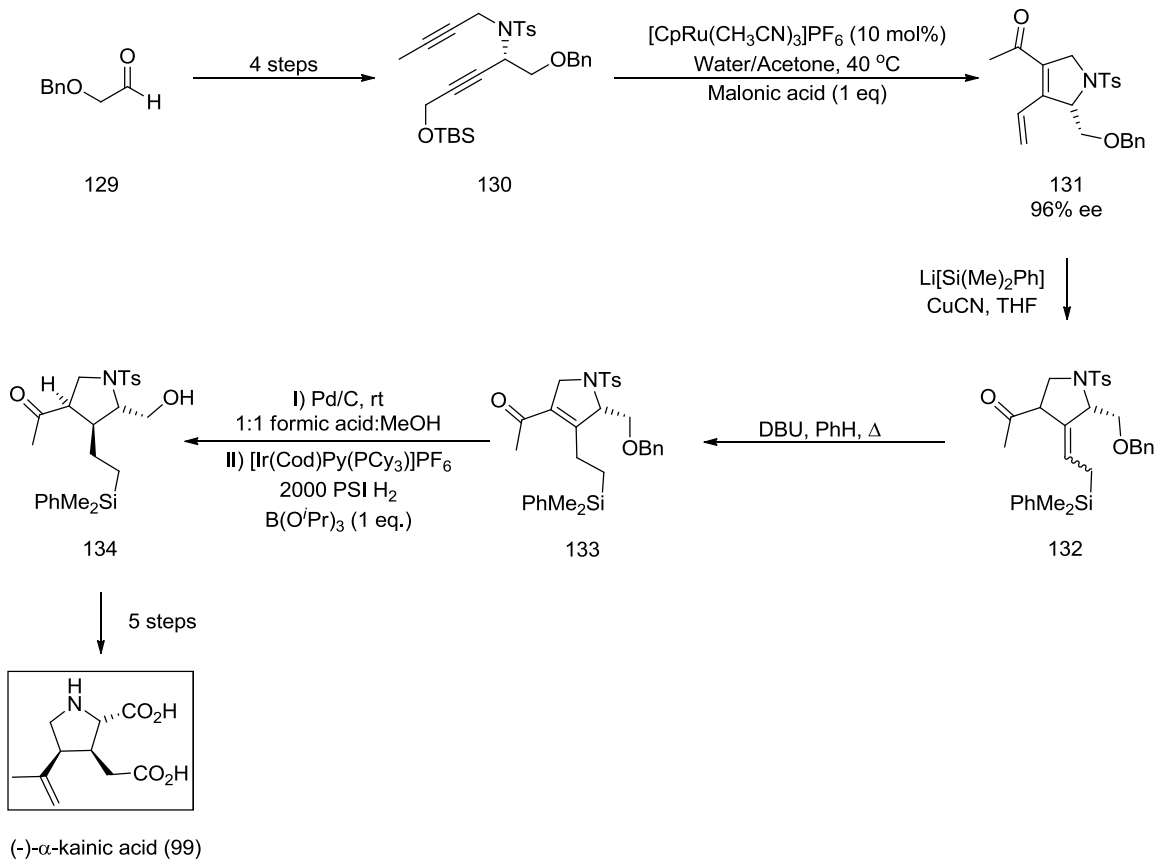
Trost's synthesis[48]

Trost's total synthesis uses a ruthenium-catalysed alkyne-propargyl alcohol addition to form the C3-C4 bond, with the definition of the C3 and C4 stereocentres carried out in a later asymmetric hydrogenation.

The substrate for the cycloisomerisation, diyne (130) was prepared in 4 steps from commercially available aldehyde (129).

The cyclisation was carried out using $[CpRu(CH_3CN)_3]PF_6$ as a catalyst in aqueous acetone, which also deprotects the unhindered silyl ether *in situ* to yield compound (131). 1,6-Addition of dimethylphenylsilyl cuprate at 0 °C and subsequent isomerisation with DBU in refluxing benzene led to the formation of (133). In order for efficient hydrogenation to take place it was necessary to deprotect the primary alcohol prior to treatment with Crabtree's catalyst to yield (134).

With the desired stereocentres in place, (-)-α-kainic acid was accessed in a further 5 steps, with an overall yield of 15 % over 14 steps.

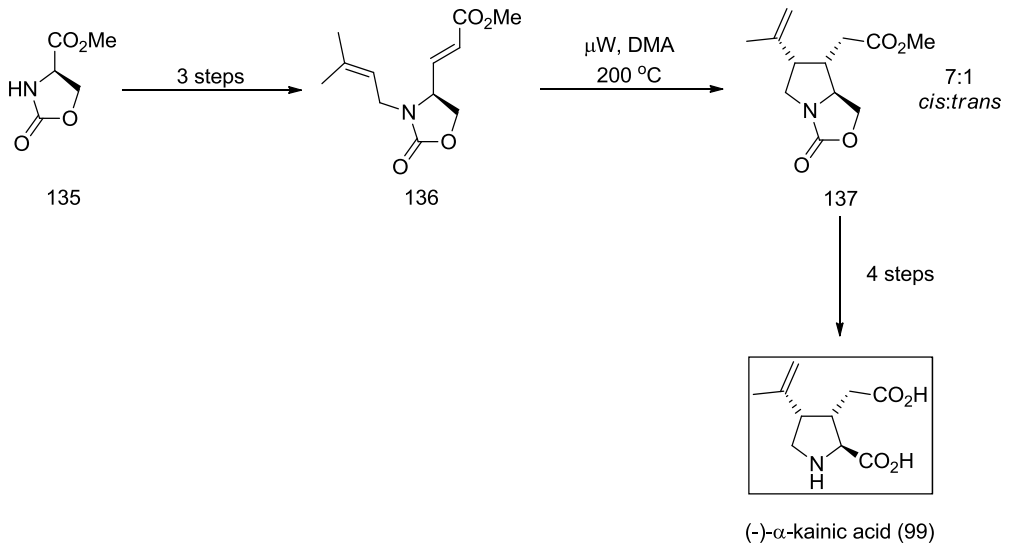


Scheme 40 - Trost's total synthesis of (-)-α-kainic acid.

Parson's synthesis[49]

Parson's total synthesis of (-)-α-kainic acid relies on an intramolecular ene-reaction accelerated by microwave irradiation to form the C3-C4 bond of the pyrrolidine ring.

The substrate (136) for the ene-reaction was prepared 3 steps starting from cyclic oxazolidinone ester (135) derived from D-serine hydrochloride. The ene-reaction was carried out by subjecting compound (136) to microwave heating in diethylaniline at 200 °C to yield the pyrrolidine core (137) in a 7:1 diastereomeric ratio. Both diasteroisomers were carried through another 4 steps to yield (-)-α-kainic acid.



Scheme 41 - Parsons's total synthesis of (-)-α-kainic acid.

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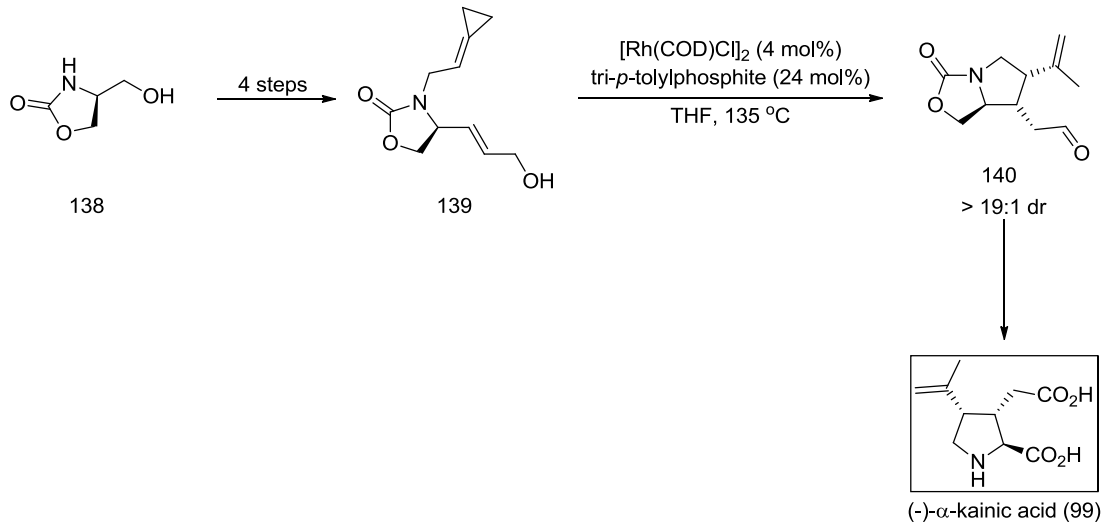
Evans' synthesis[50]

Evan's synthesis of (-)-α-kainic acid uses a diastereoselective rhodium-catalysed ene-cycloisomerisation to build the pyrrolidine ring at the C3-C4 bond.

Starting from commercially available amino alcohol (138), the substrate for cyclisation was constructed in 3 steps. This alkenylidinenecyclopropane (139) was treated with $[Rh(cod)cl]_2$ and tri-*p*-tolyl phosphite in supercritical THF to afford the cyclisation with a diastereomeric ratio of greater that 19:1. The product (140) was then converted to (-)-α-kainic acid in a further 4 steps, with an overall yield of 17 % over 8 steps.



Scheme 42 - Evan's total synthesis of (-)-α-kainic acid.

To date, in excess of 70 total syntheses of kainic acid have been published; however, despite the abundance of syntheses, the cost per kilogram of kainic acid remains in excess of £13 million.[51] This indicates that a definitive route capable of delivering the product on an industrial-scale has yet to be developed, and means that the development of synthetic methods to prepare (-)-α-kainic acid remains a pertinent and non-trivial challenge to both academia and industry.

Aims

It is the overarching aim of this project to develop new methodology for the preparation of non-coded amino acids, with a view to accessing new routes to novel compounds as well as existing synthetic targets such as the kainoids.

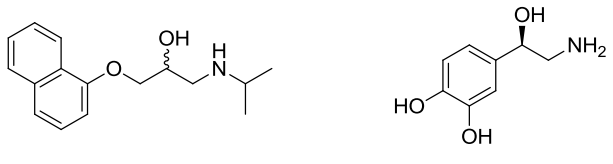
DEVELOPING STEREOSELECTIVE ALDOL METHODS TO PREPARE AZIDOALCOHOLS

2-Aminoalcohols

It has been demonstrated that α-amino acids can be prepared in a stereoselective manner by simply oxidising 2-aminoalcohols **(**Scheme 13**)**.

Chiral 2-aminoalcohols can also be used as building blocks in the construction of natural products, as seen in Yoo's synthesis of kainic acid **(**Scheme 37**)** where a heavily substituted 2-aminoalcohol **(122)** is used as a starting material.

Additionally, 2-aminoalcohols are a common structural motif in biologically active compounds.

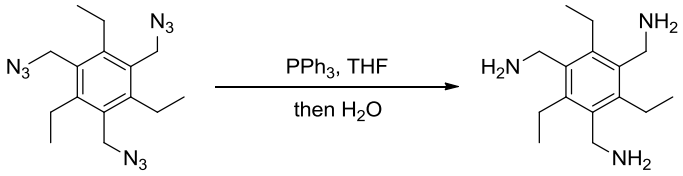


Propanolol
141

Norepinephrine
142

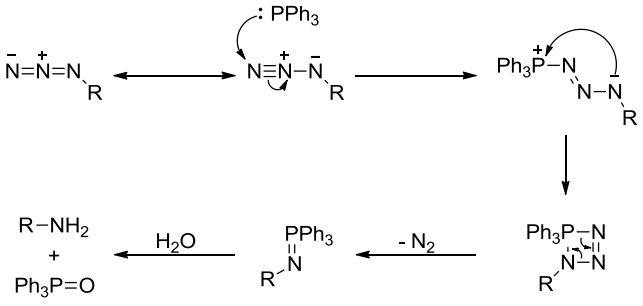
Figure 7 - Examples of α,β-aminoalcohols.

It is common during synthesis of such compounds for the amine functionality to be masked as an azide, which can easily be converted to the desired amine using the Staudinger reaction (Scheme 43).[52]



143 144

Scheme 43 - Conversion of azide functional group using the Staudinger reaction.



Scheme 44 - Mechanism of the Staudinger reaction.

1,2-Azidoalcohols can also be considered as bioorthogonal chemical reporters, defined as "non-native, non-perturbing chemical handles that can be modified in living systems through highly selective reactions with exogenously delivered probes." Effectively, this means that azidoalcohols are also biologically active in their own right.[53]

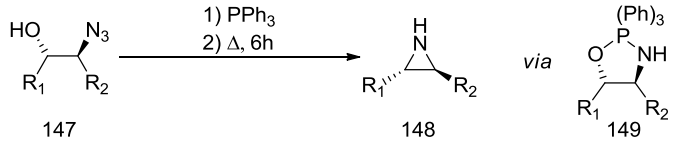
For example, Zidovodine (145) is a potent inhibitor of reverse transcriptase,[54] while azidomorphine (146) has been shown to be 40 times more potent than morphine with a reduced addiction liability.[55]

145
Zidovudine

146
Azidomorphine

Figure 8- Examples of biologically active azidoalcohols.

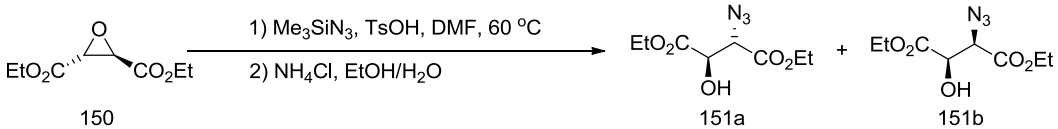
Azidoalcohols can also be converted to aziridines by treatment with triphenylphosphine under reflux conditions (Scheme 45).[56]



147 148 149

Scheme 45 – Aziridnation of azidoalcohol.

1,2-Azidoalcohols can be prepared by a variety of methods, the most common approach being by ring opening of an epoxide with azide ion. This methodology was adopted by Zwanenburg and co-workers for preparing precursors for the synthesis of aziridine carboxylic acids (Scheme 46).[57]



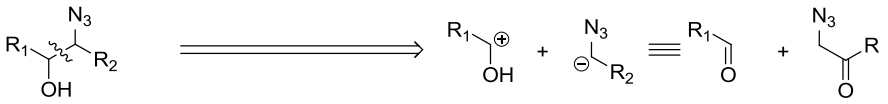
150 151a 151b

Scheme 46 – Formation of α,β-aminoalcohols by ring opening of an epoxide.

This approach is limited however by a number of factors. While it is possible to influence the resulting stereochemistry of the ring opened product by controlling the geometry of the starting material, the formation of a mixture of diastereoisomers is possible. Additionally, the

conditions required for the ring opening may preclude certain substrates susceptible to nucleophilic attack.

A proposed alternative route towards preparing azidoalcohols can be imagined by disconnection across the C-C bond. This approach gives synthons which correspond to the aldol reaction.

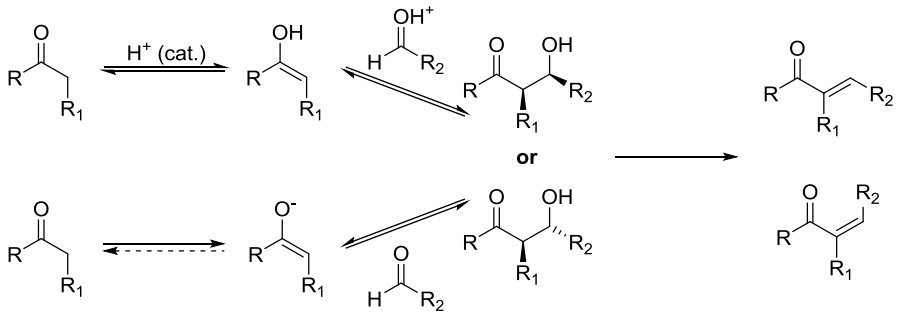


Scheme 47 - Proposed retrosynthetic pathway.

The Aldol Reaction

The aldol reaction involves the coupling of two carbonyl compounds, at least one of which is enolisable. The reaction proceeds by formation of an enolate which reacts with the other carbonyl, forming a C-C bond.

Early examples carried out under either acidic or basic conditions yielded an uncontrolled mixture of stereo and regioisomers (Scheme 48). Additionally, a range of side products arising from self-condensation, polycondensation and elimination can also arise. This lack of control meant for a long time the aldol reaction was considered to be of little interest synthetically.

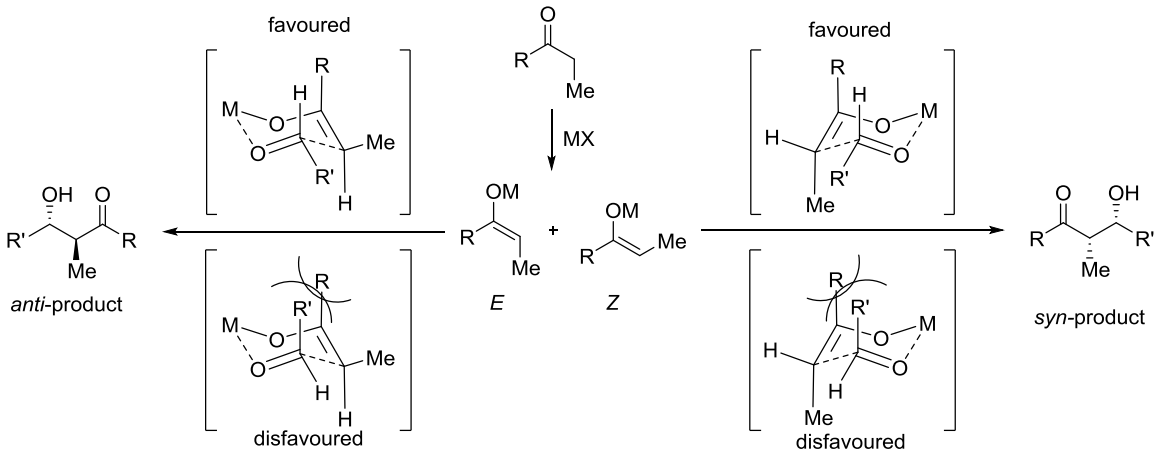


Scheme 48 - Mechanism of acid- and base-catalysed aldol reaction.

Progress in the preparation of strong bases led to a renewed interest in the aldol reaction. It was discovered that under certain conditions, treating an enolisable compound with a suitably strong base leads to the quantitative formation of its enolate. Subsequent addition of an electrophile to this preformed enolate leads to the formation of the product with improved diastereomeric control. The development of this methodology transformed the reaction into a powerful, synthetically useful technique.[58]

The diastereoselectivity of the reaction with preformed enolates can be rationalised by application of the Zimmerman-Traxler model (Scheme 49).[59]

The reaction proceeds *via* a 6-membered transition state, which occupies a chair conformation. In forming this transition state, the electrophile can approach in one of two orientations; one which places the R group in a pseudo-equatorial position, and another which places it in an pseudo-axial position. Of the two approaches, it is most favourable for the R group to occupy the pseudo-equatorial position, as it is lower in energy and also avoids unfavourable steric interactions arising from 1,3-axial interactions.



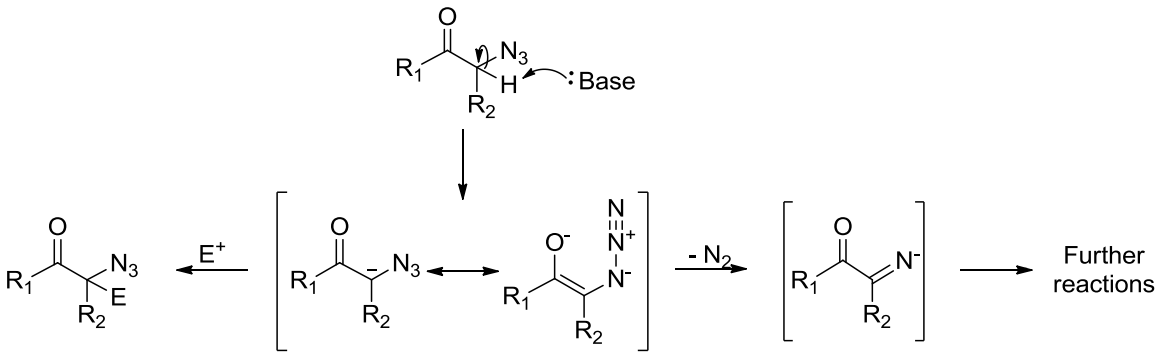
Scheme 49 - The diastereoselectivity of the aldol reaction with preformed enolates is determined by the Zimmerman-Traxler model.

As the R group will adopt the pseudo-equatorial position preferentially, the diastereomeric outcome will be dictated by the stereochemistry of the enolate. Thus, a *Z*-enolate will primarily give the *syn*-product, while the *E*-enolate will predominantly give the *anti*-diastereoisomer.

Preformed enolates can be easily prepared in a highly regio and stereoselective manner, with Li, B and Ti enolates, and Si enol ethers being the most commonly employed synthetically.[60]

Aldol reaction to form azidoalcohols

Under basic conditions, α-azidoketones with α-hydrogens readily undergo the loss of N_2 to form α-imino ketones, which can undergo further reactions (Scheme 50).[61]

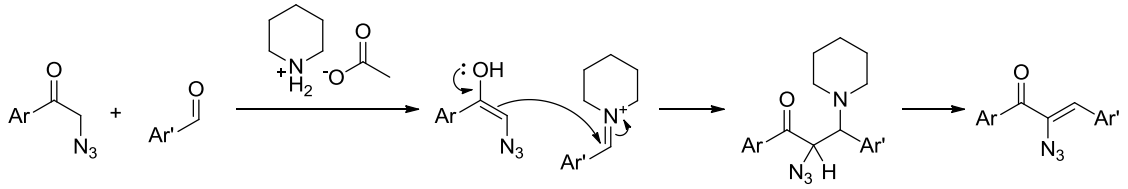


Scheme 50 – Mechanism of deprotonation and further reactions of α-azidoketones.

Although the deprotonation of α-azidoketones has seen limited use in the preparation of α-amino cyclic- and heterocyclic enones, in substrates lacking β-hydrogens, the resulting α-imino ketone is of little synthetic value.

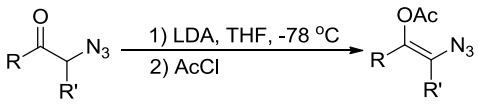
To extrude N_2, it is assumed that two discrete anions are formed sequentially. It was theorised that these intermediates could potentially act as nucleophiles, which could open up a route towards accessing substituted α-azides.[62]

Early work by Hemetsberger and Knittel demonstrated that phenacyl azides could be condensed with aromatic aldehydes catalytically in the presence of piperidinium acetate to furnish azidocinnamates (Scheme 51).[63]



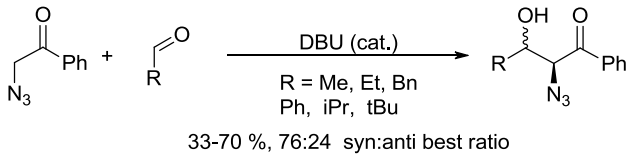
Scheme 51 - Condensation of phenacyl azides with aromatic aldehydes.

Another early example involved the trapping of phenacyl azide-derived Li enolates with acetic anhydrides and other acyl chlorides at -78 °C to furnish *O*-acylated vinyl azides (Scheme 52).[64]



Scheme 52 - Trapping Li enolates of phenacyl azides.

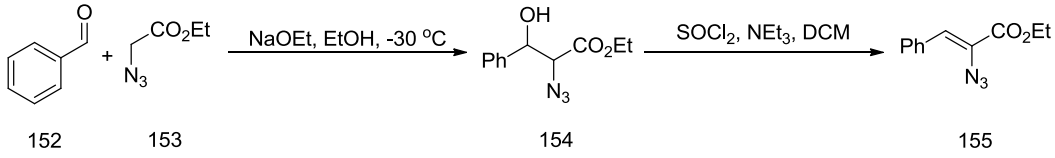
More recently, the formation of α,β-azidoalcohols were reported by Patonay and Hoffman. Phenacyl azide was treated with sub-stoichiometric amounts of DBU in the presence of a range of aldehydes, with diastereomeric ratios up to 76:24 *syn*:*anti* achieved (Scheme 53).[62]



Scheme 53 – Aldol reaction of phenacyl azide with substoichiometric DBU.

Another recent example was reported by Murukami *et. al.* while preparing azidocinnamate esters as part of an investigation into the Hemetsberger-Knittel reaction, where the group isolated a stable azidoalcohol thought to be an intermediate in the reaction.[65]

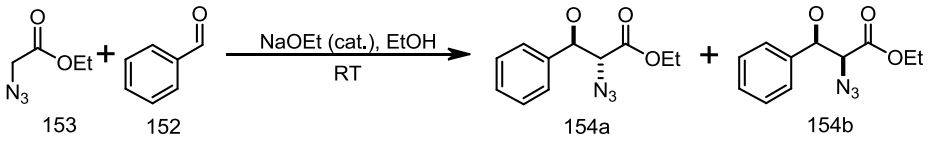
Murukami's group reported that the azidoalcohol (154) is formed preferentially at low (-30 ^{o}C) temperatures when following Knittel's conditions,[65] and that this intermediate is readily converted to azidocinnamate (155) when treated with thionyl chloride under basic conditions (Scheme 54).



Scheme 54 – Low-temperature formation of azidoalcohol.

Previous work within the Sweeney group has focused on developing the methodology of the Murukami group's procedure, with the aim of converting the resulting azidoalcohols into substituted aziridines. Work carried out by Shaw[69] demonstrated the use of substoichiometric amounts of base affords only the desired azidoalcohols (154a) and (154b) regardless of the temperature of the reaction, in stark contrast to the previously reported results (Table 1).

Table 1

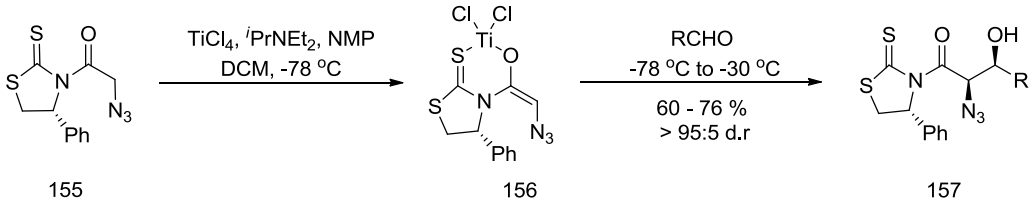


Conditions	R	Yield/%	Syn:anti
NaOEt, EtOH, rt	Et	46	2.5:1
NaO^{t}Bu, ^{t}BuOH, rt	^{t}Bu	56	2.5:1
LiHMDS (2 eq) THF, -78 ^{o}C to rt, 48 h	^{t}Bu	20	4.4:1
NaHMDS (2 eq) THF, -78 ^{o}C	Et	27	3.4:1
LDA, THF, -78 ^{o}C to rt, 72 h	Et	0	-

Despite successfully extending the methodology, the diastereomeric ratio observed in the products remained low. The highest ratio reported as 4.4:1 *syn*:*anti*. Unfortunately, although the use of strong base which gave a better diastereomeric ratio, a diminished yield was observed due to a retroaldol process taking place.

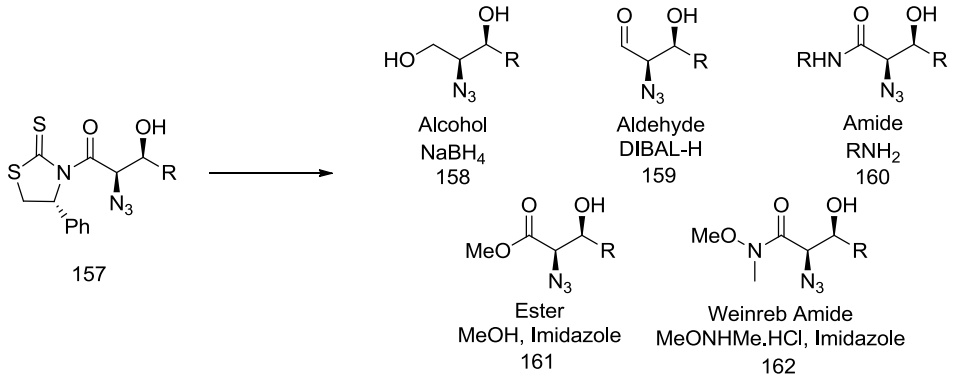
One approach to combat the issue of low diastereoselectivity in a reaction is to employ a chiral auxiliary to favour one diastereoisomer over the other. It has been reported that an Evans chiral auxiliary has successfully been used to prepare diastereomerically enriched azidoalcohols (Scheme 55).[66]

Treatment of the thiazolidinethione-containing substrate (155) with $TiCl_4$ at low temperature gives rise to a stable, isolatable Ti-coordinated intermediate (156) which, when treated with an electrophile reacts to furnish the azidoalcohol product (157) with a diastereomeric ratio of >95:5 *anti*:*syn*.



Scheme 55 - Diastereomeric azidoaldol reaction using chiral auxilliary.

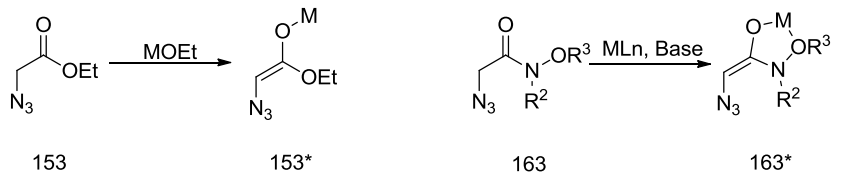
In addition to the observed diastereoselectivity, this approach has the added benefit that the thiazolidinone auxiliary readily undergoes cleavage and can easily be converted to a variety of other functional groups (Scheme 56).



Scheme 56 - Functional group exchange of chiral auxilliary.

Aims

The aim of the work described in this chapter is to develop methodology for the preparation of chiral 2-azidoalcohols using the aldol reaction. It was proposed that by employing the metal-chelating properties of the hydroxamic acid functional group, it may be able to achieve high diastereoselectivity while remaining atom efficient and synthetically versatile (Scheme 57)



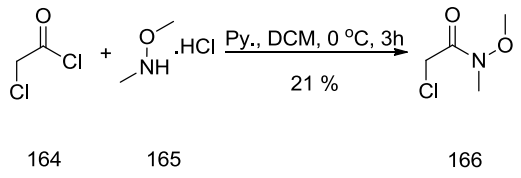
Scheme 57 - Proposed hydroxamic acid chelating group.

It was believed the strong binding affinity of the hydroxamic acid would lead to a stablised complex, which would drastically lower the pKa of the α-hydrogens to favour the formation of an enolate and potentially enable the reaction to be carried out in a catalytic manner. Should this be the case, it would allow for the use of a chiral catalyst in order to influence diastereoselectivity. Alternatively, if the hydroxamic acid functional group possesses chirality, it could act as a novel chiral auxiliary.[67]

Preparation of Azido hydroxamic acid substrate

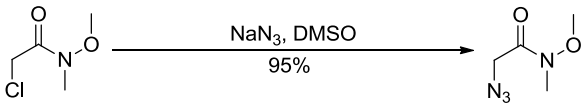
Investigation was begun by preparing a simple azidohydroxamic acid substrate with which to screen reaction conditions.

It was decided to prepare a substrate containing Weinreb amide (166). This was achieved by first treating a cooled suspension of dimethyl hydroxylamine hydrochloride (165) with pyridine in DCM followed by the slow addition of chloroacetyl chloride (164), giving a yield of (166) of 21 % (Scheme 58).[68]



Scheme 58 - Preparation of azidohydroxamic acid precursor.

The resulting compound was then converted to the corresponding azide (163) in quantitative yield by treatment with sodium azide in DMSO (Scheme 59).[69]



166 163

Scheme 59 - Formation of azide substrate.

With this substrate in hand, the immediate priority was to assess the safety aspects associated with low molecular weight compounds containing such a large proportion of heteroatoms. After subjecting it to thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC), it was demonstrated the compound was thermally stable, undergoing a slow, controlled loss of mass consistent with the thermal decomposition of an organic compound (Figure 9).

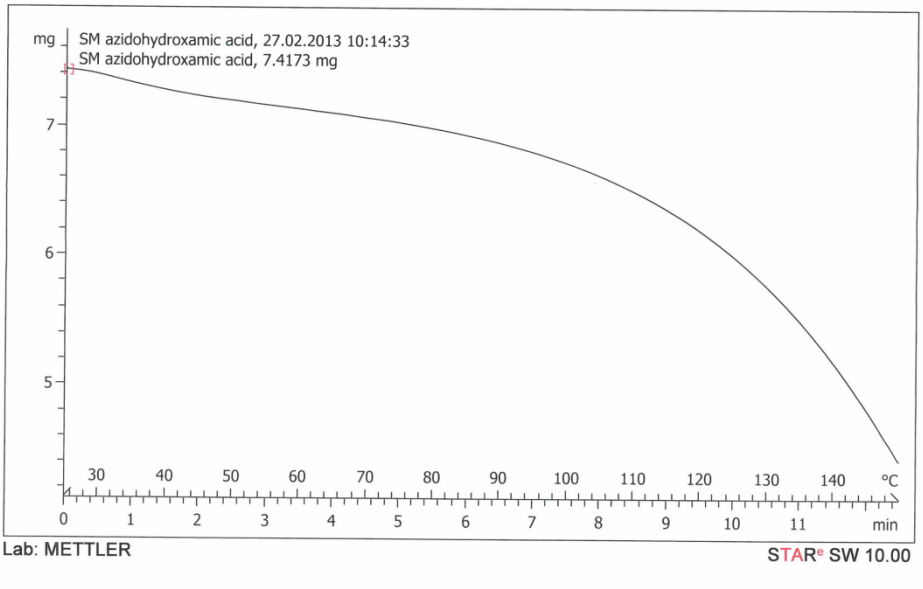
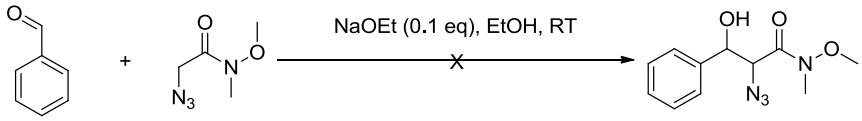


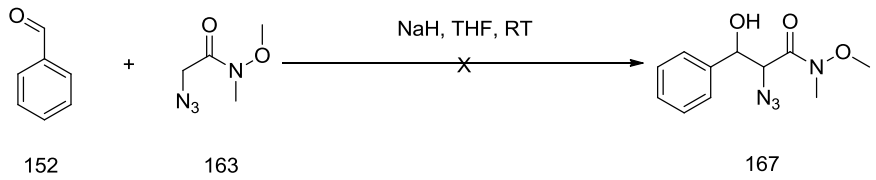
Figure 9 - TGA Spectrum for compound (163).

Satisfied by the safety of the azidohydroxamic acid substrate (163), attention was directed towards investigating its reactivity in the aldol reaction. The compound was subjected to the aldol reaction conditions reported previously by Shaw.[70]



Scheme 60 - attempted aldol reaction under Shaw's conditions.

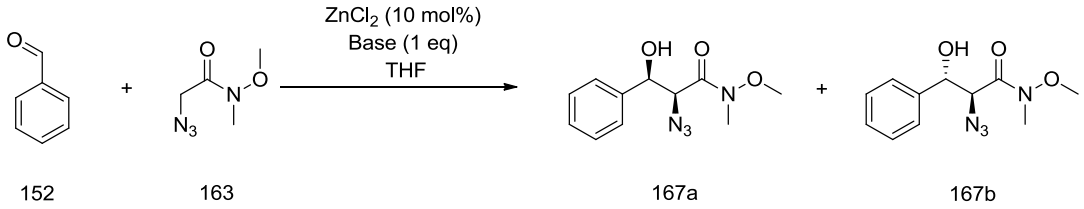
Unfortunately, under these conditions no formation of the desired product was observed, and only the starting materials were returned. Repeating the reaction with a stronger base, sodium hydride, again failed to furnish the desired product.



Scheme 61 - Attempted aldol reaction with sodium hydride.

It was believed that deprotonation was not taking place due to the hydroxamic acid functional group raising the pKa of the adjacent protons. In order to determine whether this was the case, a range of organic, non-nucleophilic bases were screened along with the addition of a Lewis acid additive, in this case zinc chloride in 10 mol% amounts (Table 2). It was believed that the addition of the Lewis acid would coordinate to and lower the pKa to allow deprotonation to occur.

Table 2 - Results from screen of bases.



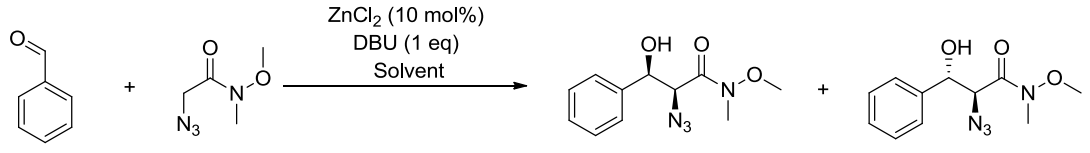
Base	Conversion (%)*	syn:anti
NEt_3	0	-
DMAP	0	-
DIPEA	0	-
Pyridine	0	-
DBU	89	2.2:1
NBu_3	0	-
NMM	0	-
TMEDA	0	-

**Calculated from ^{1}H NMR*

The desired coupling product was formed when using DBU as a base, favouring the *syn* product (167a). In all other cases, only starting materials were recovered.

The next priority in this investigation was to determine whether or not the Lewis acid additive was participating in the reaction mechanism. The reaction was run both with and without catalyst simultaneously in a range of solvents (Table 3).

Table 3 - Results of solvent screen.



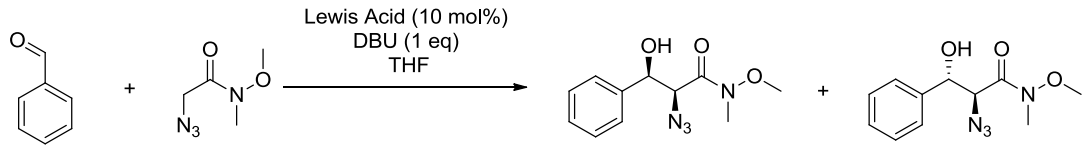
152 163 167a 167b

Solvent	Catalyst	Conversion (%)*	syn:anti
THF	$ZnCl_2$	87	2:1
	None	88	2.1:1
DCM	$ZnCl_2$	78	2.2:1
	None	83	2.2:1
EtOAc	$ZnCl_2$	70	2.3:1
	None	85	1:1
MeOH	$ZnCl_2$	0	-
	None	0	-
MeCN	$ZnCl_2$	79	2.7:1
	None	83	2.7:1

**Calculated from ^1H NMR*

Of the solvents surveyed, acetonitrile gave the best diastereomeric ratio by a small margin, while in methanol no reaction was observed. Unfortunately, these results showed no effect of the proposed catalyst. Additionally, there was no significant difference in the diastereomeric ratio when comparing the results from reactions run with and without catalyst. These results suggested the substrate was not coordinating to the Lewis acid. In an attempt to confirm this and to determine whether this was due to the nature of the substrate or the chelator, a range of Lewis acids were screened (Table 4).

Table 4 - Results of Lewis acid screening.



152 163 167a 167b

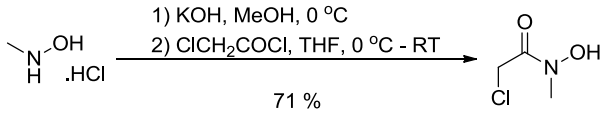
Catalyst	Conversion (%)*	syn:anti
$ZnCl_2$	85	2:1
$FeCl_3$	35	2.1:1
$MgCl_2$	40	2.1:1
$CuCl_2$	44	1.8:1
KCl	43	2.2:1
$CdCl_2$	34	2.1

**Calculated from ^{1}H NMR*

These results showed $ZnCl_2$ gave the best conversion in this reaction and there was no significant change in the diastereomeric ratio observed by varying the Lewis acid. It was hypothesised the methyl group was discouraging coordination, which is supported by the observation that in the presence of $FeCl_3$ no colour change was observed, which is contrary to literature reports of solutions of $FeCl_3$ undergoing 'spectacular colour changes' in the presence of hydroxamic acids.[71]

It was decided to investigate this hypothesis by preparing the analogous compound without substitution on the oxygen and repeating the reaction.

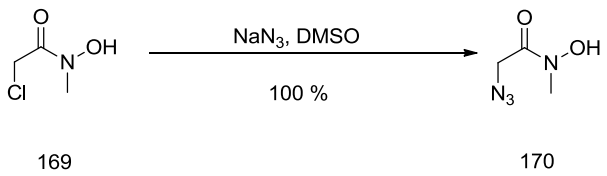
This was accomplished by following a similar protocol as before. It was found that under previous conditions the reaction was sluggish, requiring slight modification to proceed satisfactorily. Under these modified conditions the desired compound (169) was isolated in 71 % yield as pale orange needles (Scheme 62).[72]



168 169

Scheme 62 - Preparation of analagous azidohydroxamic acid precursor.

This was then converted to the corresponding azidohydroxamic acid (170) in the same manner as before (Scheme 63).



169 170

Scheme 63 - Preparation of azidohydroxamic acid substrate.

Again, concerns were raised about the safety of this compound, so it was subjected to TGA and DSC analyses as before to ascertain its thermal stability (Figure 10).

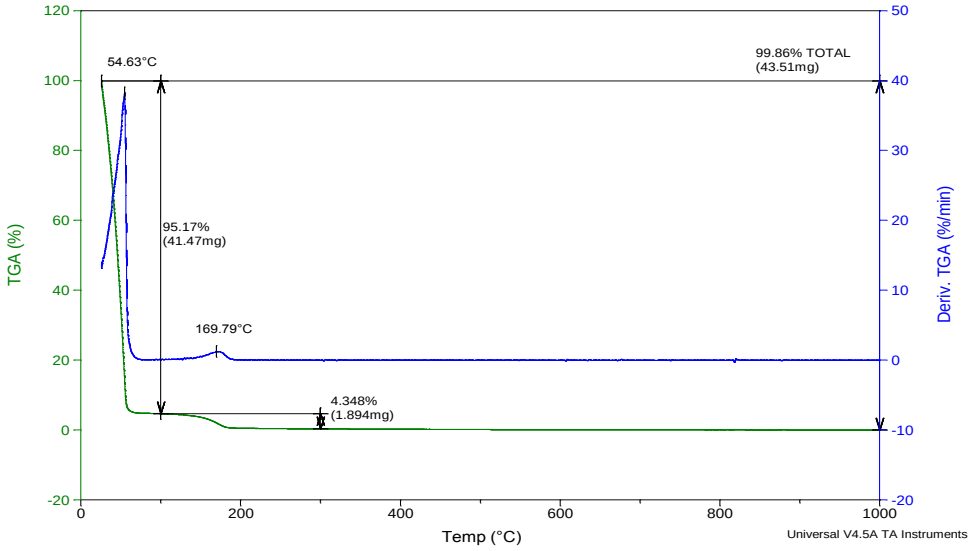


Figure 10 - TGA and DSC spectra for compound (170).

Satisfied the substrate would not spontaneously decompose, the compound was subjected to a simple experiment to determine whether or not it was capable of coordination. A small amount of the compound (170) was dissolved in diethyl ether and a few drops of ferric chloride solution in diethyl ether were added, resulting in an immediate and dramatic colour change from yellow to cherry red (Figure 11).

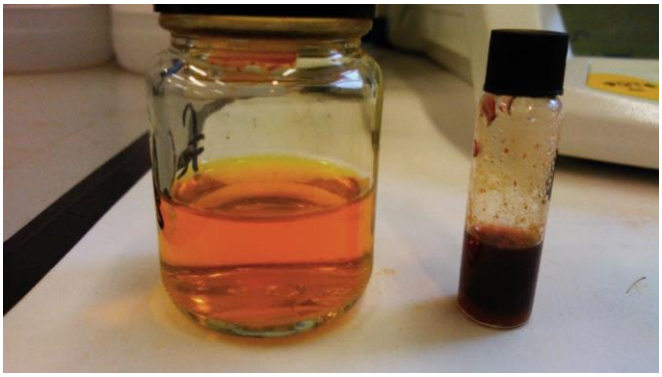
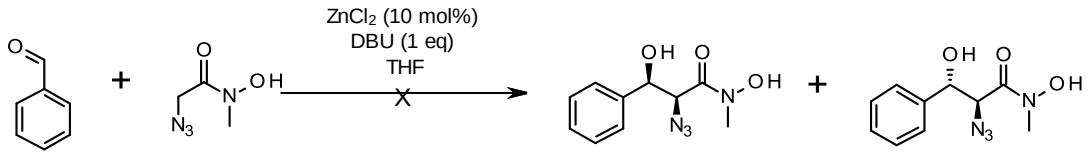


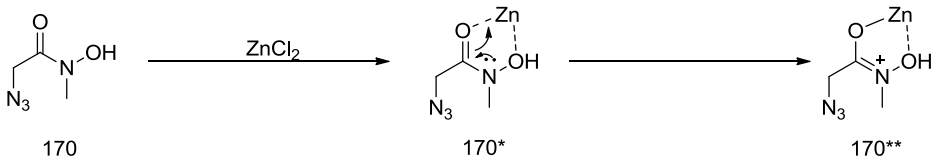
Figure 11 - Colour change observed upon treating an ethereal solution of $FeCl_3$ with compound (170).

Having confirmed that coordination was occurring with the new substrate it was then subjected to the coupling conditions reported previously.



Scheme 64.

Unfortunately, under these conditions no formation of the desired product was observed. It is believed that the addition of the Lewis acid to compound (170) forms chelated complex (170*) as predicted, however the resulting complex favours the formation of an imine species (170**), which is unreactive under the conditions employed in this study (Scheme 65).



Scheme 65 - Proposed formation of imine intermediate.

Conclusions and Future work

In conclusion, although the scope is currently limited to the reaction of a single example of an azidohydroxamic acid with benzaldehyde, methodology has been developed for a novel route to access α,β-aminoalcohols. Future work in this area will be directed towards further screening of reaction conditions for compound (170). Once this has been achieved, efforts will be focused on improving the diastereomeric ratio observed in the product, either through the use of a chiral lewis acid or by introducing a chiral directing group into the hydroxamic acid functional group.

METAL- AND BASE-FREE [2,3]-SIGMATROPIC REARRANGEMENT OF AMMONIUM YLIDES

As outlined in chapter 1, there are a number of methods reported in the literature for the preparation of α-amino acids. More specifically, the large number of syntheses of kainic acid and the related kainoids demonstrate there is significant interest in the preparation of functionalised pyrrolidine cores.

Additionally, functionalised pyrrolidine cores are also popular targets for active pharmaceuticals. A number of compounds based around a pyrrolidine core can be found in the patent literature (Figure 12), representing a number of novel compounds with the potential to treat diseases such as Alzheimer's and other neurodegenerative diseases.[73,74,75]

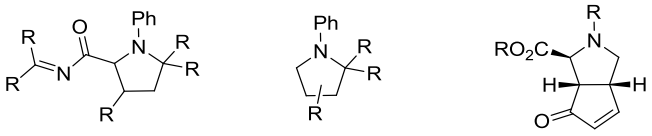
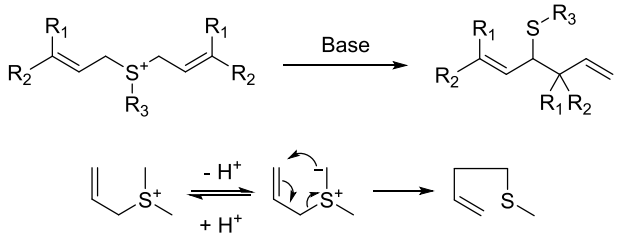


Figure 12 - Examples of substituted pyrrolidines found in patent literature.

It is believed that the development of methodology exploiting the [2,3]-sigmatropic rearrangement of tetrahydropyridine compounds could represent an attractive route towards accessing such compounds.

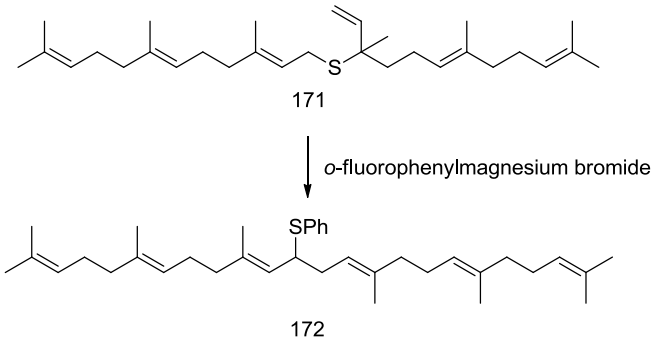
Previous work

The [2,3]-sigmatropic rearrangement of vinylsulfonium ylides was first reported by Baldwin in 1968 while investigating the mechanism for squalene synthase as part of the biosynthesis of squalene. Baldwin proposed this rearrangement proceeds by "a ready 6-electron" process.[76] In the paper that followed, he raionalised that the reaction is driven by the conversion of the formally tetravalent sulfonium ylide to a divalent state (Scheme 66).[77]



Scheme 66 - [2,3]-sigmatropic rearrangement of vinylsulfonium ylides.

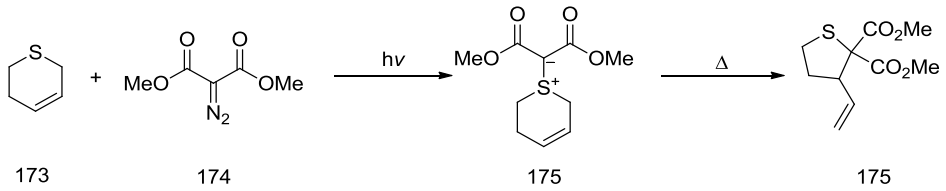
Later work by Ollis provided further evidence for this rearrangement process, generating an ylide by exposing allyl sulphide (171) to benzyne to effect the rearrangement to form squalene (172) (Scheme 67)[78]



Scheme 67 - Ollis' synthesis of squalene.

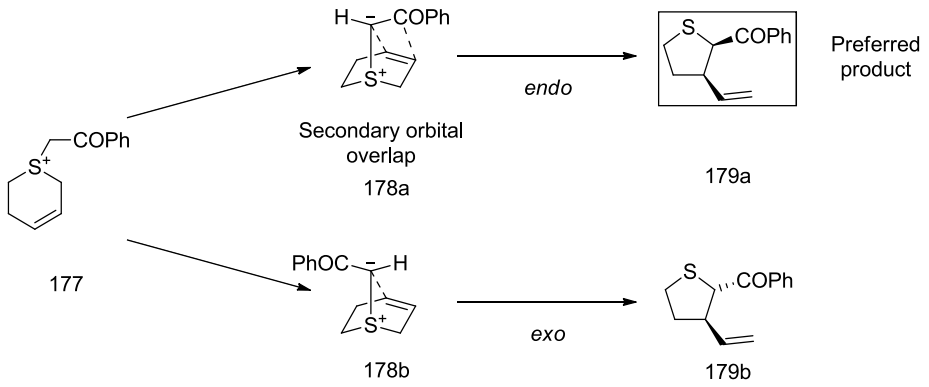
Rearrangement of cyclic substrates

The first example of such a rearrangement taking place with cyclic allyl substrates was documented by Ando in 1972, while investigating the photolytic decomposition of dimethyl diazomalonate (174). It was reported that when dihydrothiopyran (173) was subjected to irradiation in the precence of dimethyldiazomalonate, ylide intermediate (175) was formed which was easily isolated from solution. It was found that this intermediate only underwent rearrangement at elevated temperature, in contrast to other examples where rearrangement proceeded at room temperature (Scheme 68).[79]



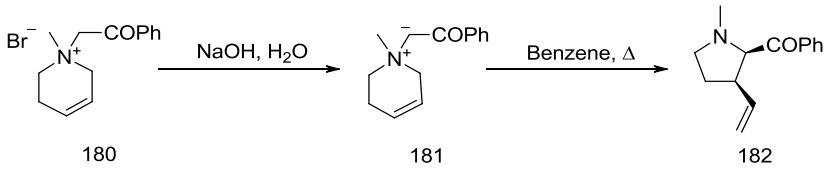
Scheme 68 - Generation and rearrangement of a cyclic sulfonium ylide.

Methodology for the low temperature rearrangement of a cyclic phenacyl sulfonium ylide (177) was developed by Ollis in 1981. The reactive ylide for this process (178) was generated *via* a two-step process by alkylation of the dihydrothiopyran substrate and subsequent treatment with base. It was reported that *cis*-diastereoisomer (179a) was favoured in a ratio of 25:1 *cis*:*trans*, which was rationalised by considering the secondary orbital overlap in the reactive intermediate (Scheme 69).



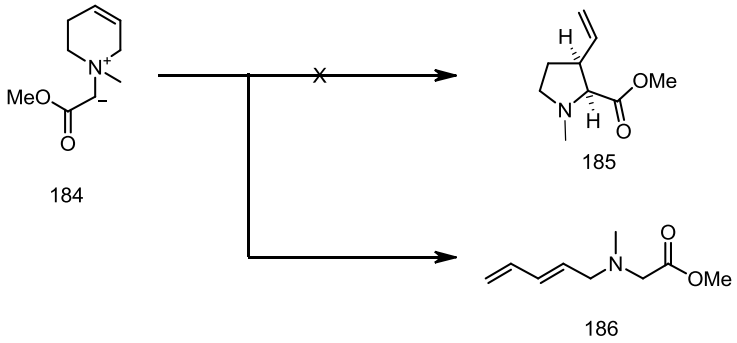
Scheme 69 - secondary orbital overlap observed in the rearrangement of cyclic phenacyl sulfonium ylides.

Ollis also reported that cyclic ammonium allyl ylides could also be generated and reacted under these conditions (Scheme 70). It was noted that the *cis*-rearrangement product was formed exclusively under these conditions, indicating that the rearrangement proceeds only through the *endo* transition state.[80]



Scheme 70 - rearrangement of cyclic ammonium ylides.

Later work by Stevenson and co-workers attempted to extend this methodology to the rearrangement of ylide substrates stabilised by ester groups, instead of rearrangement occurring, only a side product arising from an elimination pathway was isolated (186, Scheme 71).[81]

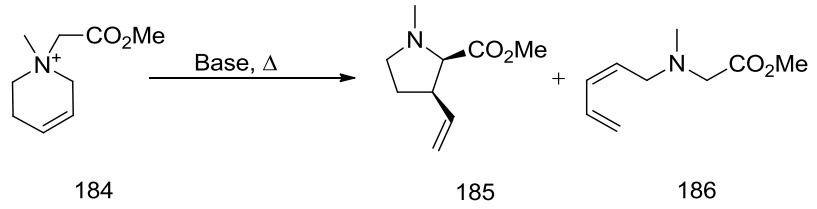


Scheme 71 - Unexpected ring-opening observed in ester-stabilised cyclic ammonium ylides.

Tavassoli's work

The rearrangement of ester stabilised ylides was later reinvestigated by Tavassoli, who prepared a range of substrates bearing an *N*-substituted methyl acetate group (184). After

screening a range of reaction conditions he reported forming a mixture of the *cis*-pyrrolidine (185) rearrangement product and the diene arising from elimination (186) as reported by Stevenson (Scheme 72).



184 185 186

Scheme 72 - Rearrangement and elimination products reported by Tavassoli.

This work demonstrated that the nature of the solvent plays a crucial role in determining the outcome of the reaction. It was found that protic solvents favoured elimination preferentially while ethereal solvents favoured rearrangement (Table 5).[82]

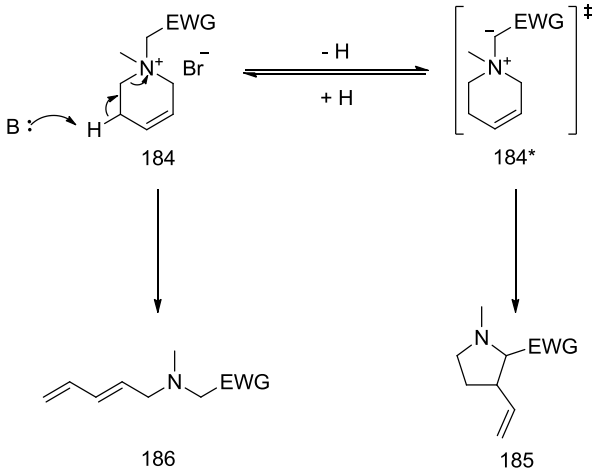
Table 5 – Screen of reaction conditions carried out by Tavassoli.

Solvent	**Base**	**Temp.**	**Yield 185 (%)**	**Yield 186 (%)**
THF	NaH	Ambient	NR	NR
THF	DBU	Ambient	NR	NR
MeOH	NaOMe	Ambient	0	63
THF	LDA	Reflux	20	8
THF	NaH	Reflux	50	8
DME	NaH	Reflux	58	5
Dioxane	NaH	Reflux	54	6
Toluene	NaH	Reflux	0	11

It was also noted that the formation of the rearrangement product (185) is only observed when the reaction is heated above room temperature.

It was proposed that this pattern of reactivity arises from the nature of the reaction manifold; Under protic conditions ylide intermediate (184*) is formed in a reversible process, while base-induced elimination is irreversible, causing the reaction to follow the elimination pathway. Under ethereal conditions the formation of the ylide is irreversible, which precludes

the elimination pathway, only allowing for the formation of the rearrangement product (Scheme 73).



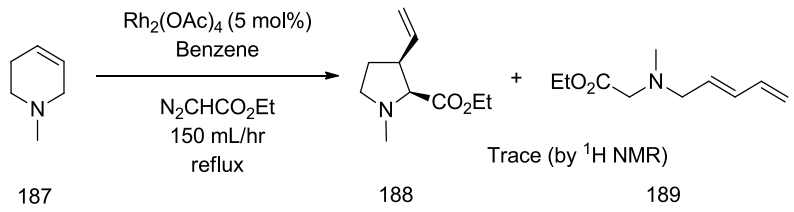
Scheme 73 - Reaction manifold for rearrangement process.

The continued presence of elimination product (186) observed under optimised conditions has been attributed to nature of ylide precursor salt (184). Although it is a trivial matter to prepare and purify the salts, they are highly deliquescent in nature so require careful handling and lengthy drying prior to carrying out the reaction. It is thought that adventitious moisture from the environment allows for the reprotonation of the reactive ylide in aprotic solvents, leading to the formation of small amounts of the elimination product.[83]

The continued formation of the undesired elimination side product led to a need to develop an alternative method to generate ylides required for this reaction.

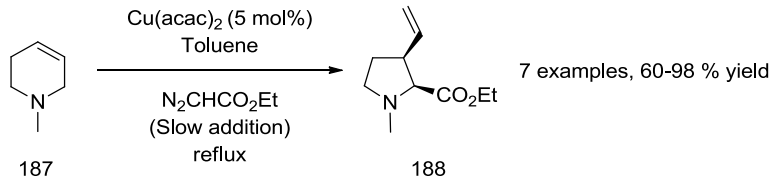
Workman's Work

Workman carried out an investigation into the feasibility of generating the desired ylide intermediates under a catalytic protocol in order to shut down the elimination pathway of the reaction manifold. Using conditions similar to those detailed by Doyle and co-workers (Scheme 74),[84] he reported that traces of both the rearrangement (188) and elimination products (189) could be identified by ^{1}H NMR from the crude reaction mixture, demonstrating that the catalytic approach is a valid one.



Scheme 74 - Catalytic one-pot preparation and rearrangement process.

After optimisation of the conditions for this process, it was determined that the reaction is most efficient when using a copper-based catalyst (Scheme 75).[85]



Scheme 75 - Optimised rearrangement conditions.

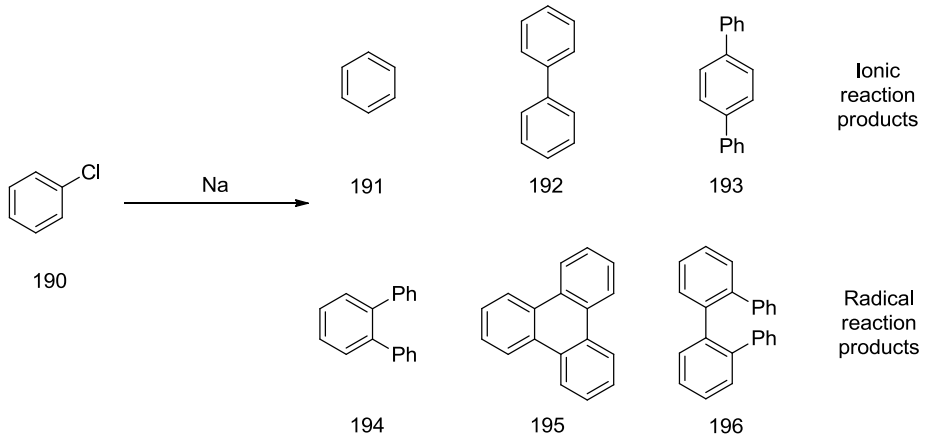
With optimised conditions in hand, a range of substituted tetrahydropyridines were then prepared and subjected to rearrangement.

While this route is attractive due to its one-pot approach, it still suffered from the need to run the reaction at elevated temperature, the requirement of a metal catalyst and the need to prepare substrates containing diazo functionality.

Benzyne as a Reactive Intermediate

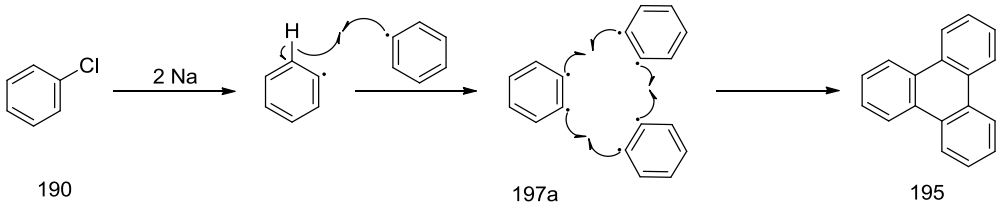
Discovery and Structural Determination of Benzyne

Benzyne is a highly reactive intermediate first reported in 1927 by Bachmann and Clarke while investigating the Wurtz-Fittig reaction of sodium in boiling chlorobenzene.[86] They reported that the reaction produces benzene (191), biphenyl (192) and traces of *p*-diphenylbenzene (193), the formation of which can be explained by an ionic reaction mechanism. However, they also reported the formation of significant amounts of *o*-diphenylbenzene (194), triphenylene (195) and *o,o'*-diphenylbiphenyl (196), whose formation could not be explained by an ionic reaction mechanism (Scheme 76).



Scheme 76 - Products observed from the Wurtz-Fittig reaction of o-chlorobenzene.

They suggested that the formation of the latter three products, especially triphenylene could only occur by a radical mechanism (Scheme 77), where the reactive intermediate, dubbed 'free phenylene' was the biradical species (197a).



Scheme 77 - Proposed radical mechanism for formation of triphenylene.

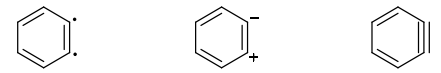
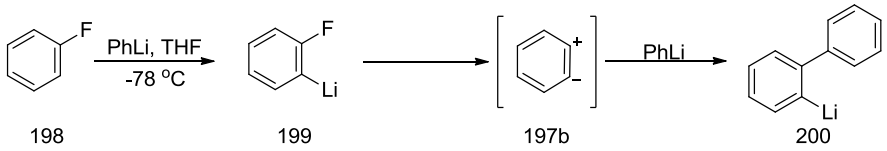


Figure 13 - proposed structures of benzyne.

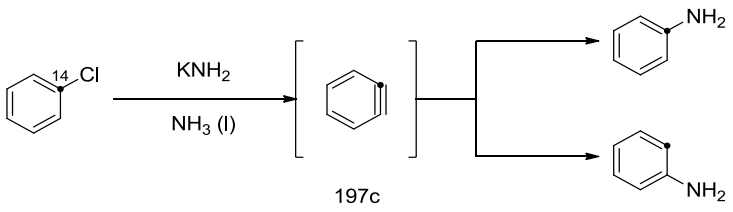
Work by carried out by Wittig and his students in 1942 provided compelling experimental evidence for a zwitterionic intermediate (197b). While investigating the formation of biphenyl by reacting phenyllithium with halobenzenes, it was discovered that the reaction proceeded fastest with fluorobenzene, in contrast to the difficulty usually encountered when trying to directly displace fluoride *via* nucleophilic aromatic substitution reactions (Scheme 78). In order to explain this reactivity, they invoked a dipolar form of benzyne (197b).[87]



Scheme 78 - Reaction of phenyllithium with fluorobenzene.

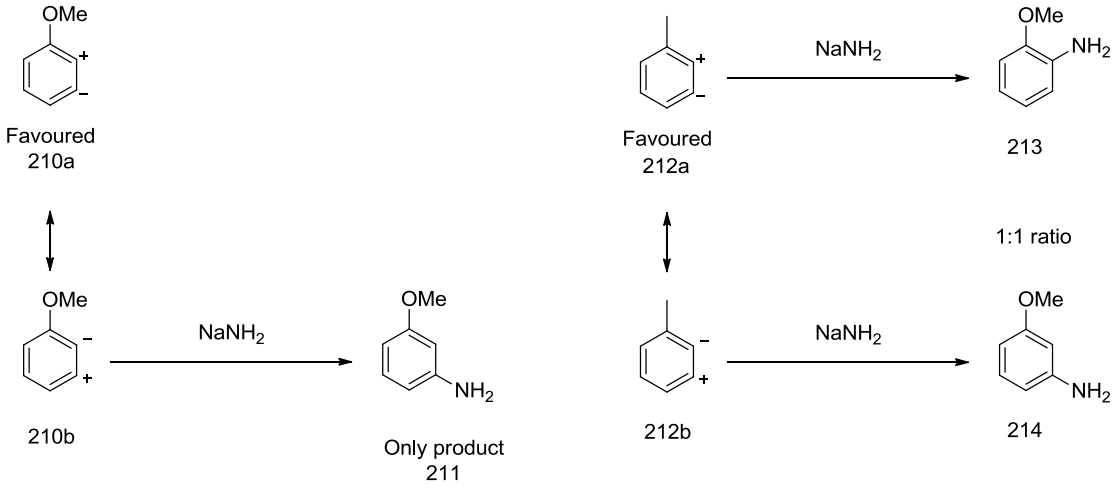
They reasoned the structure of the product and the use of strong base in the reaction implies the presence of a carbanion, while its reactivity towards nucleophiles implies the presence of a carbocation. Taking these two implications together lends credence to the presence of a zwitterion.

In 1953, Roberts and co-workers reported the classic ^{14}C labelling experiment (Scheme 79) in which they investigated the rearrangement observed in the amination of non-activated aryl halides. They reported that the rearrangement proceeds through a symmetrical, electronically neutral intermediate (197c), the structure of which is now accepted to be the correct structure of benzyne.[88]



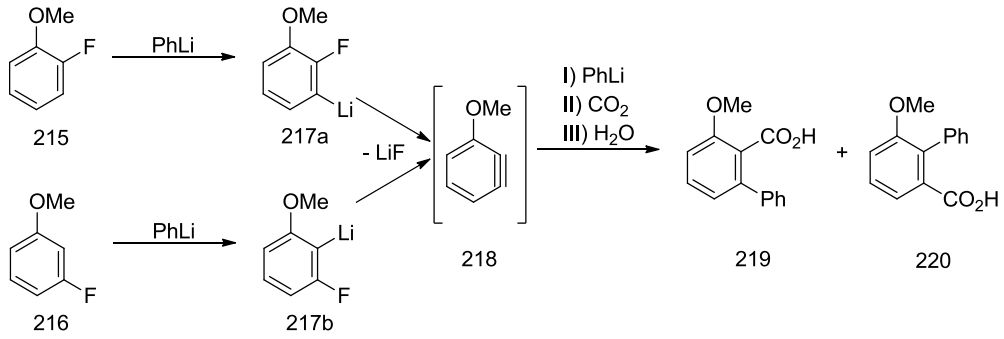
Scheme 79 - ^{14}C labelling experiment for amination of aryl halides.

Roberts *et al.* also demonstrated that with substituted arynes, the zwitterionic structure fails to explain the regioselectivity observed in the product, stating “The pattern of the rearrangements shows a considerable disregard for the influences governing the usual aromatic substitutions.” (Scheme 80). In both cases, the products isolated from the reaction did not correspond to the predicted products.



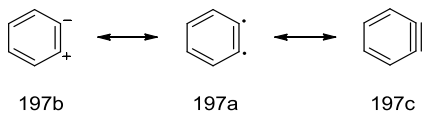
Scheme 80 - Substitution pattern observed for nucleophilic attack of substituted benzynes.

Further evidence for the neutral, aryne structure of benzyne was reported by Huisgen and Rist in 1954, who reported that an identical mixture of carboxylic acids is obtained when *o*- and *m*-fluoroanisole are treated with phenyllithium and subsequently carboxylated with CO_2 (Scheme 81).[89]



Scheme 81 - Further evidence for the neutral aryne structure of benzyne.

The application of the concept of resonance has been applied to the structure of benzyne.[90] Luttringhaus and Schubert proposed that it was possible for resonance to occur between the three forms of benzyne (Scheme 82).



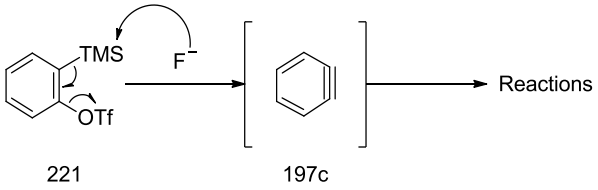
Scheme 82 - Resonance of the three forms of benzyne.

A detailed computational study carried out by Radom *et. al.* in 1986 proposed that the triple-bonded structure (197c) predominates, but that benzyne still possesses significant radical character.[91]

Aside from these structural investigations, the scope of its applications towards syntheses has been limited due to the harsh conditions required for its generation, typically either strong base or elevated temperature.[92]

The development of milder methods of generating benzyne has led to a renewed interest in the intermediate, allowing for more detailed exploration of its reactivity to take place.

It was reported by Kobayashi in 1983 that by treating 2-trimethylsilylphenyltriflate (221) with a source of fluoride, typically TBAF or KF/18-crown-6, it is possible to generate benzyne under almost neutral conditions (Scheme 83).[93]



Scheme 83 - Generation of benzyne under mild conditions.

Aims

The aim of the work described in this chapter is to investigate the possibility of carrying out the rearrangement of tetrahydropyridine substrates similar to those investigated previously by Workman and Tavassoli, using the benzyne rearrangement chemistry demonstrated by Ollis in the rearrangement of squalene (Scheme 67).

It is proposed that an arylative-rearrangement can be effected by generating benzene under the mild conditions reported by Kobayashi, eliminating the need to use harsh conditions or transition metal catalysts.

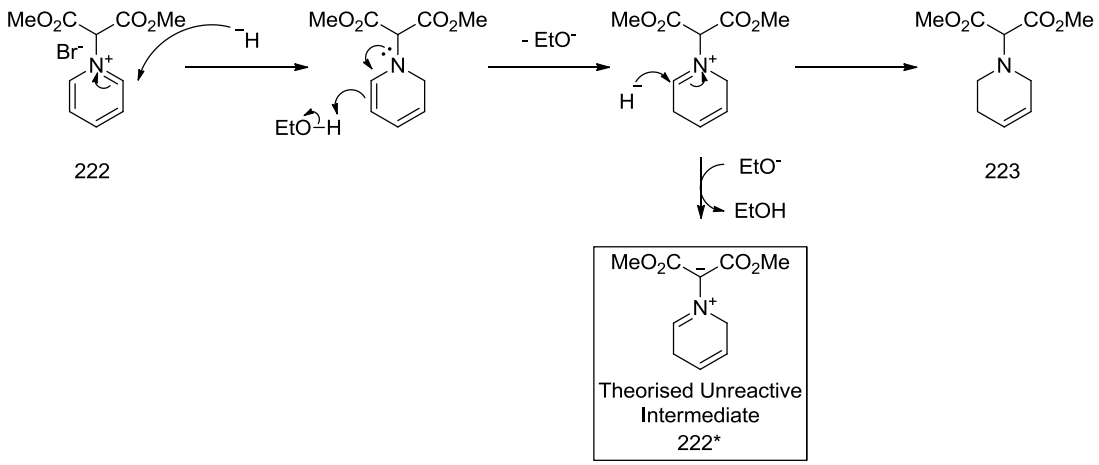
Once the validity of this approach has been determined, the scope of the reaction will be probed with a range of substituted tetrahydropyridines and asymmetrically substituted arynes.

Finally, investigation into the extension of this methodology will be carried out to determine the possibility of effecting rearrangement in acyclic substrates, with the aim of preparing amino acid derivatives.

Rearrangement of Dimethylmalonate-*N*-substituted Tetrahydropyridines

Preparation of Tetrahydropyridine substrates

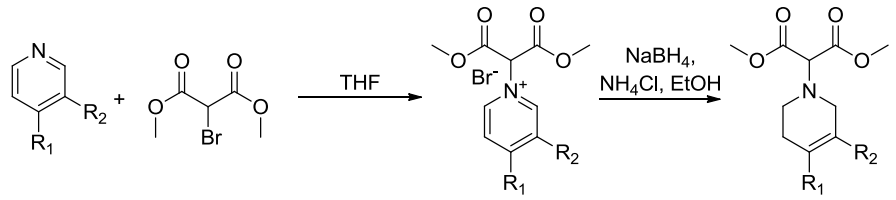
The tetrahydropyridine substrates were prepared by alkylating the desired pyridine with dimethylbromomalonate and reducing the resulting salt subsequently with sodium borohydride. Modification of standard literature conditions was required in order to ensure acceptable yields of the desired tetrahydropyridine (Scheme 84).



Scheme 84 - Mechanism for reduction of pyridinium salts.

Under standard reaction conditions an equivalent of ethoxide is formed over the course of the reaction. It is theorised that this leads to the abstraction of the acidic malonate α-proton to form an ylide (222*), which is unreactive under the reaction conditions and results in reduced yields. In order to prevent the formation of this ylide, an excess of ammonium chloride was added to the reaction mixture.

Table 6 - Summary of results for preparation of tetrahydropyridine substrates.



224 225 222 223

Entry	R_1	R_2	Yield (%)
a	H	H	43
b	Me	H	47
c	Et	H	53
d	Ph	H	16
e	CO_2Et	H	16
f	H	Me	40
g	H	Et	42 (28)*
h	H	Ph	13
i	H	CO_2Et	15
j	Me	Me	29

*yield in parentheses indicates yield of side product 226

The formation of the desired tetrahydropyridine substrates is confirmed by a number of factors.

Firstly, a comparison of the ^{1}H NMR spectra of the pyridinium salt and tetrahydropyridine product shows the disappearance of the signals in the aromatic region of the spectrum, with the corresponding appearance of peaks upfield which are confirmed by DEPT135 experiments to be CH_2 groups. Additionally, the appearance of a complex multiplet around δ 5.6 indicates the presence of the expected alkene protons (Figure 14).

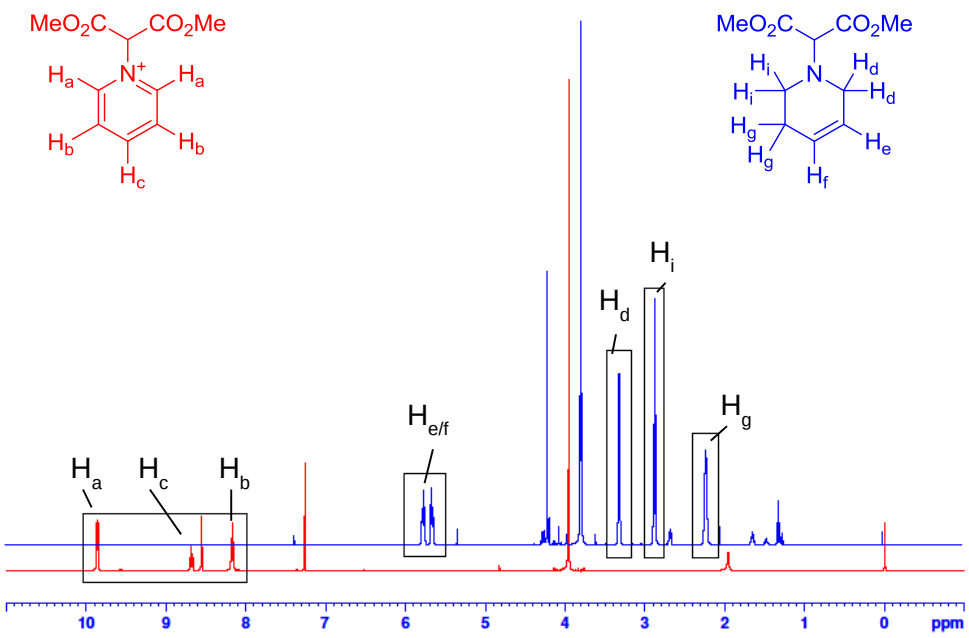
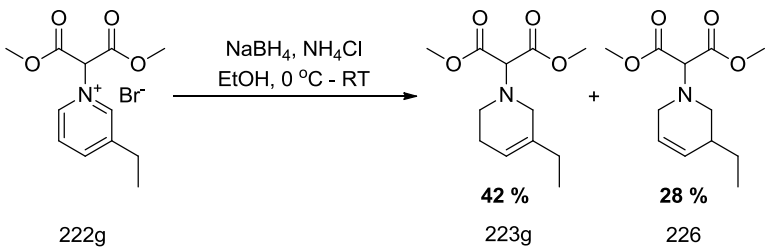


Figure 14 - Comparsion of ^{1}H NMR spectra of pyridinium salt starting material (red) with tetrahydropyridine product (blue).

Similarly, the aromatic signals in the ^{13}C NMR spectrum of the pyridinium salt are not observed in the spectrum for the tetrahydropyridine product.

Finally, the mass of the expected product is consistent with the mass calculated by mass spectrometry.

The reduction of 222g led to the formation of unexpected product 226, which was isolated in 28 % yield and was determined to be an isomer of the expected product. This product is believed to be a kinetic product, in contrast to the other examples which formed only the thermodynamic product.



Scheme 85- Unexpected product isolated from reduction of 222g.

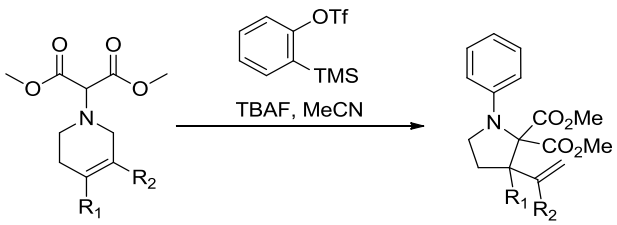
Rearrangement to substituted pyrrolidines

With a number of tetrahydropyridine substrates in hand, investigation of their rearrangement in the presence of benzyne was begun. The reactive benzyne species was generated according to the protocol reported by Kobayashi *et. al*. ,[93] treating compound (221) with a source of F^-. 1M TBAF solution was selected as the fluoride source due to the ease of manipulation, and because it allows for controlled rate of addition, limiting the rate of formation of the intermediate and minimising the formation of dimerisation side-products.

An excess of both the tetrahydropyridine substrate (223) (1.1 eq) and fluoride source (1.5 eq) were used in order to ensure that the benzyne precursor underwent complete conversion to the reactive benzyne species.

Under these conditions, tetrahydropyridines (223a-j) reacted as expected, generating substituted pyrrolidines at room temperature as outlined in (Table 7).

Table 7 - Summary of rearrangement results.



223 227

Entry	R_1	R_2	Yield (%)
a	H	H	99
b	Me	H	84
c	Et	H	97
d	Ph	H	83
e	CO_2Et	H	57
f	H	Me	67
g	H	Et	49
h	H	Ph	93
i	H	CO_2Et	37
j	Me	Me	95

The rearrangement of the tetrahydropyridine substrates to the desired pyrrolidine is confirmed by a number of factors.

Firstly, the appearance of peaks in the aromatic region of the spectrum demonstrate the presence of the *N*-phenyl group, while the shift in the alkane region and the absence of one of the CH_2 environments demonstrates the rearrangement of the 6-membered ring to a five-membered ring. Additionally, the absence of the singlet at δ 4.1 indicates loss of the proton situated between the ester groups. Finally, the pair of multiplets at δ 5.6 observed in the tetrahydropyridine substrate, which correspond to the protons of the alkene, are absent in the rearranged product. They are replaced by a double double doublet at δ 5.9, which corresponds to the newly-formed vinylic proton, and a pair of doublets around δ 5.2 which correspond to the two terminal protons of the newly-formed alkene (Figure 15).

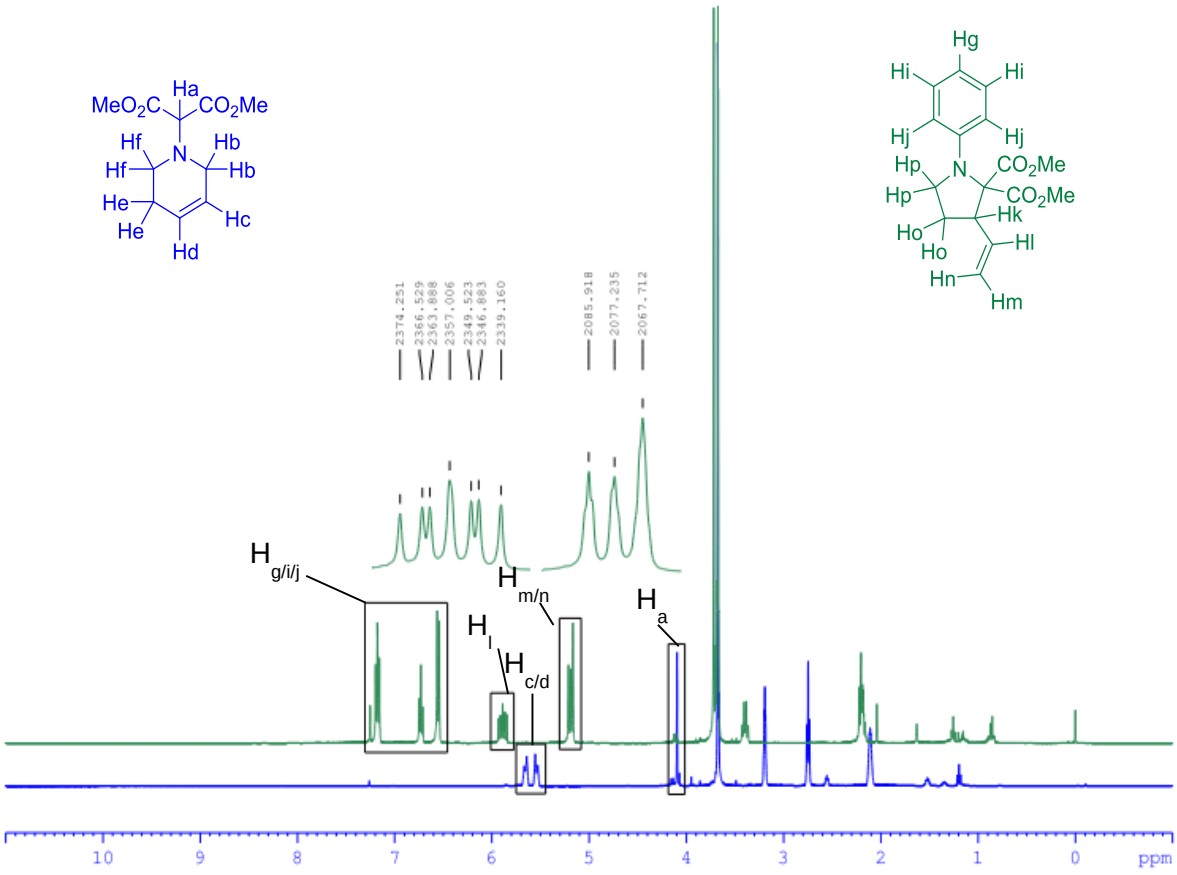


Figure 15 - Comparsion of ^{1}H NMR spectra of tetrahydropyridine starting material (blue) with rearrangement product (green).

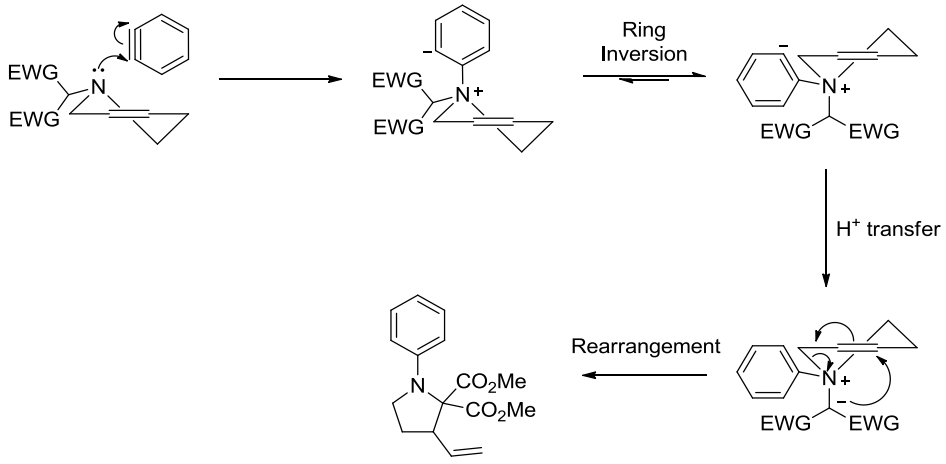
This evidence is reinforced by considering the coupling constants of these new peaks. The double double doublet at δ 5.9 has *J* values of 17.6, 9.8 and 7 Hz respectively, which correspond to the *trans*- and *cis*-couplings with the terminal alkene protons and the C3-proton respectively, and are matched by the *J*-values of the two doublets at δ 5.2 (Figure 15).

Similarly, the ^{13}C spectrum of the rearrangement product shows the appearance of the aromatic group.

Finally, the mass of the expected product is consistent with the mass determined by mass spectrometry.

Mechanism

The mechanism proposed for this reaction involves initial trapping of the benzyne intermediate by the lone pair of the nitrogen. The resulting tetrahydropyridinium intermediate then undergoes ring flip inversion, placing the bulkier aromatic ring in the more stable equatorial position. Proton transfer then occurs to generate the reactive ylide intermediate which then undergoes 5-*endo*-*trig* rearrangement (Scheme 86).



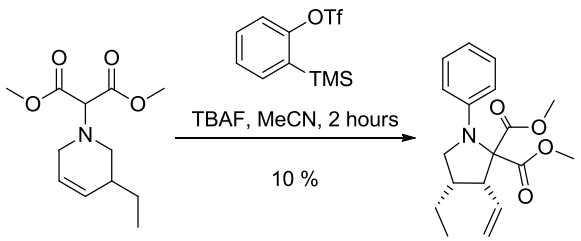
Scheme 86 - Proposed mechanism for rearrangement.

Under equilibrium conditions, the tetrahydropyridine substrate occupies a half-chair conformation, placing the most bulky group, in this example the dimethylmalonate group, in the equatorial position.[94] In order for rearrangement to occur, the reactive group needs to be in the axial position where it can reach the π-system in order to react.

It is believed that the presence of this bulky phenyl group is the reason why this rearrangement takes place at ambient temperature, while the examples reported by Tavassoli, which contain a significantly less bulky methyl group, required elevated temperature to react. It is believed that the phenyl group sits preferentially in the equatorial position, forcing the malonate group into the axial position where it can react.

Diastereoselectivity

When subjected to rearrangement conditions, compound 226 (the kinetic product isolated from the reduction of 222g) rearrangement occurred to give product (228) as expected. Unexpectedly however, only *cis*-configuration was observed in the product (Scheme 87).



226 228

Scheme 87 – Rearrangement of (226) to give cis-product (228).

The ^{1}H and COSY NMR spectra of this compound are shown in *Figure 16*, and show the aromatic and vinylic proton environments consistent with compound (227a) (Figure 15, green spectrum). Using the COSY spectrum, it is possible to identify the C-3 proton (H_d in Figure 16) in order to calculate the ^{3}J values, which can be compared to those calculated using the Karplus equation.

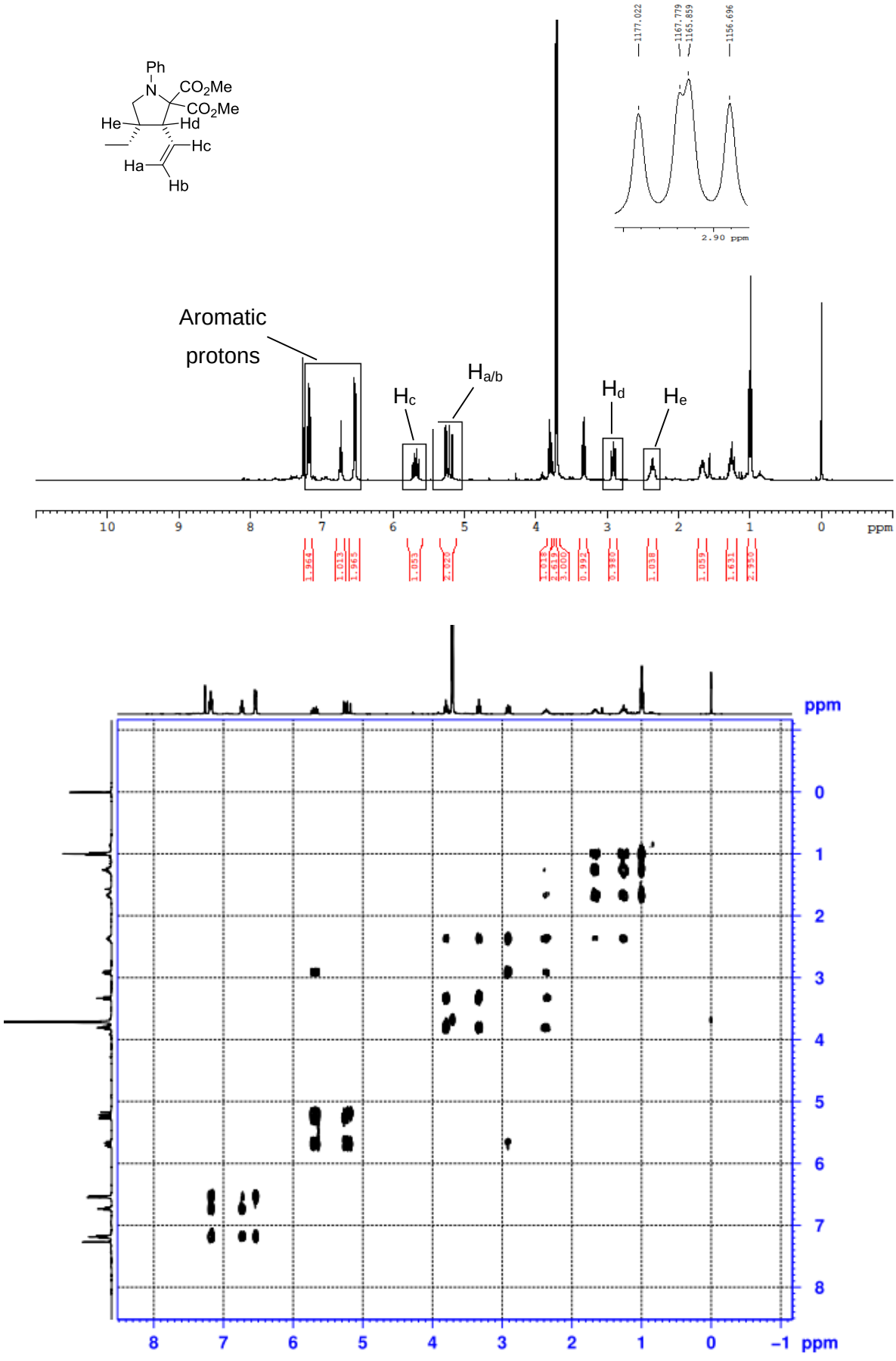
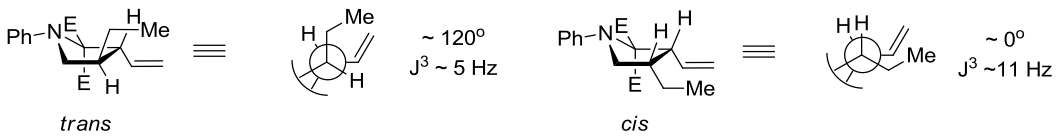


Figure 16 - ^{1}H and COSY spectra of compound (228).

According to the Karplus equation, the vicinal ^3J values for *cis* vs *trans* protons are predicted to be 11 and 5 Hz respectively (Scheme 88).[95]

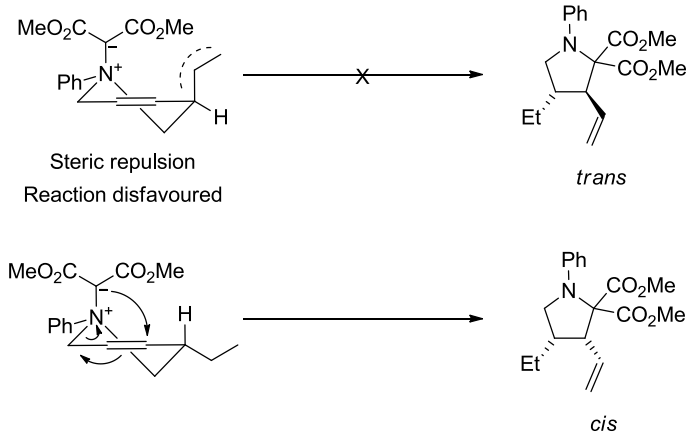


Scheme 88 - Predicted ^3J values for cis and trans isomers.

^3J values for C3 position of 11.2 and 9.2 Hz observed experimentally, which confirms that the product has *cis*-configuration.

It is possible to explain this observed diastereoselectivity by considering the structure of the quaternary tetrahydropyridinium intermediate (Scheme 89).

In the course of generating the reactive tetrahydropyridinium ylide, it is possible to form two diastereoisomers; one where the ethyl chain sits in an axial position, and another where the ethyl chain is in an equatorial position. It is proposed that in the case of, the steric effect of having the ethyl substituent in the axial position makes it unfavourable for the reactive group to approach, preventing rearrangement from taking place and therefore preventing the formation of the *trans*-product.



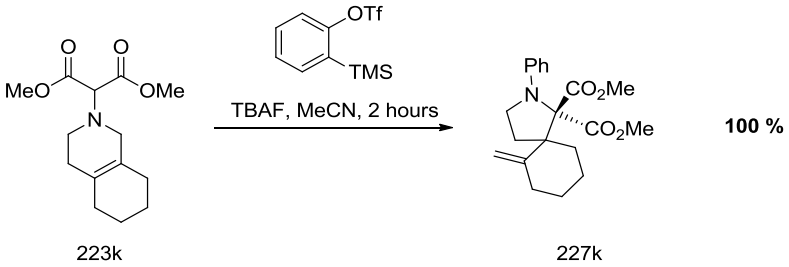
Scheme 89 - Mechanism for formation of cis-isomer of (228).

Where the ethyl substituent is in the equatorial position, there is no such steric interaction, allowing the rearrangement to readily take place to form the *cis*-product (228).

More complex tetrahydropyridine substrates

Having demonstrated that the rearrangement proceeds cleanly and efficiently with simple substrates, it was decided to prepare more structurally complex systems to subject to rearrangement conditions.

A bicyclic, hexahydroisoquinoline compound (223k) was prepared according to the previous procedure and, when subjected to the rearrangement conditions, rearranged to furnish a spirocyclic pyrrolidine (227k) in excellent yield (Scheme 90). Of particular note in the ^{1}H NMR are the pair of singlets around δ 5 which correspond to the isolated alkene protons (*Figure 17*).



Scheme 90 - Rearrangement of hexahyroisoquinoline compound (223k) to spirocyclic pyrrolidine (227k).

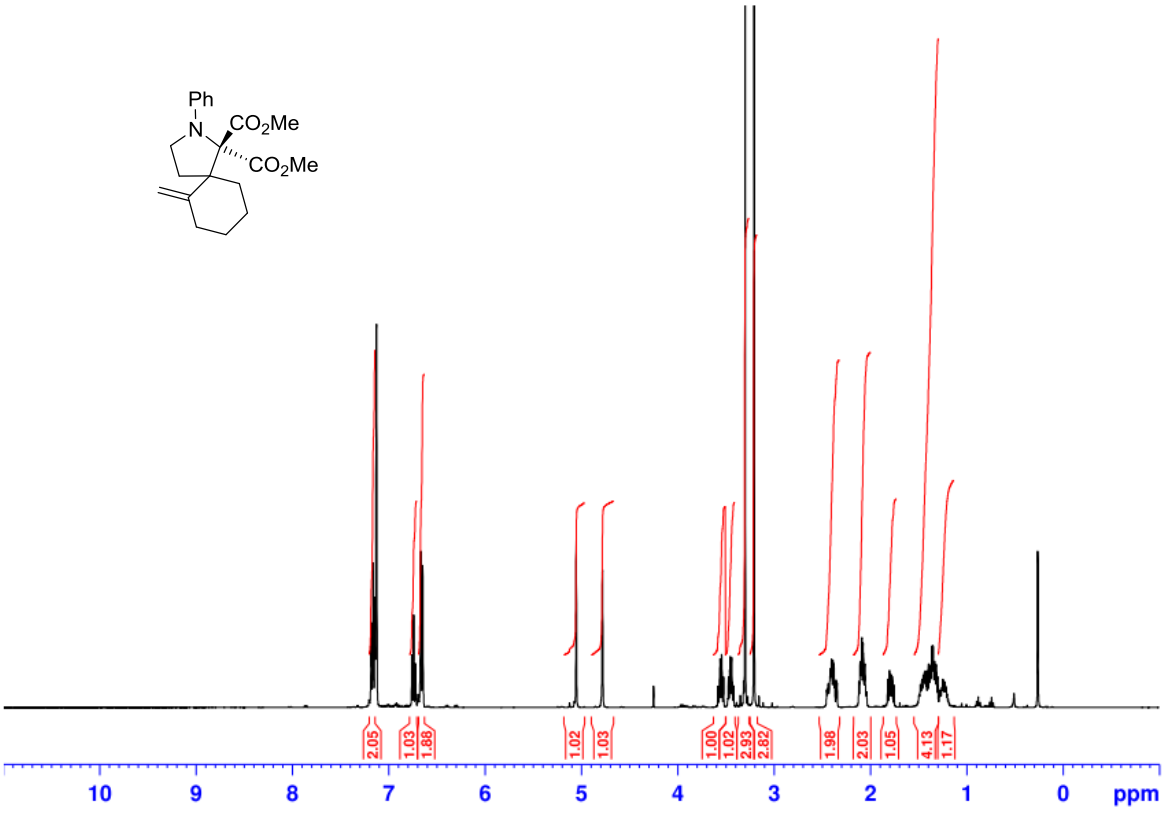
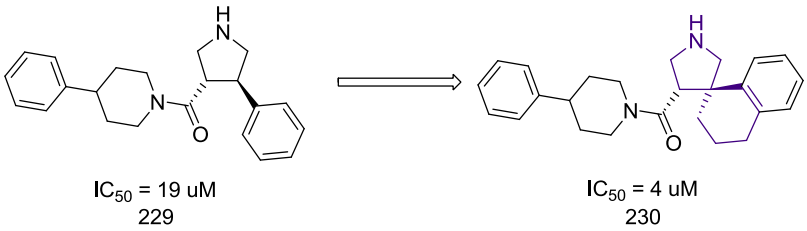


Figure 17 - ^{1}H NMR of compound (227k).

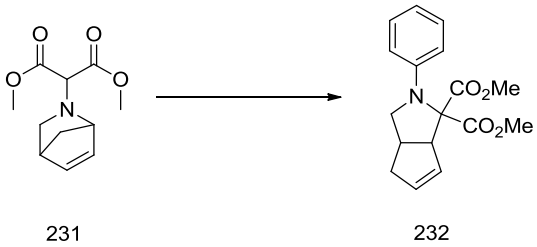
This particular rearrangement is particularly interesting due to the spirocyclic nature of the product as there are very few methods of generating spirocyclic pyrrolidines in the literature. Generally, spirocyclic compounds are regarded as a biologically privileged class of compounds, as evidenced by a recent paper by Stachel *et. al.* who prepared a potent BACE inhibitor containing a spirocyclic pyrrolidine moiety (Scheme 91).[96]



Scheme 91 - Spirocyclic pyrrolidine-based BACE inhibitor.

While optimising a lead-candidate drug (229), a 10-fold increase in binding potency and a 5-fold decrease in the IC_{50} of the candidate drug was effected by introducing the 6-membered spirocycle (230). Stachel remarks that “Spirocyclisation leads to enhanced potency”, and that the ring restricts the inhibitor into its bioactive conformation.

In addition to preparing spiro ring systems, it is believed that treating an azanorbornene-based substrate with benzyne should furnish a 5,5-fused ring system (Scheme 92).



Scheme 92 - Proposed rearrangement of an azanorbornene system.

It is believed that this represents an attractive route to accessing these systems, which are currently showing promise in the patent literature as anti-Alzheimer’s drugs (Figure 18)[75]

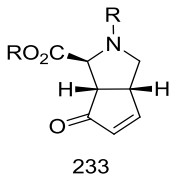
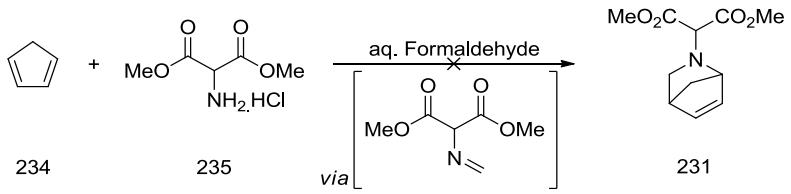


Figure 18- Literature example of a potential anti-Alzheimer's drug.

The synthesis of compound (231) was attempted according to Grieco’s method,[97] preparing an imine *in situ* by treating the hydrochloride salt of desired amine with aqueous formaldehyde in order to facilitate an aza-Diels-Alder reaction upon addition of freshly prepared cyclopentadiene. Initially, the reaction was carried out with dimethylaminomalonate hydrochloride (235) in an effort to prepare the desired substituted norbornene compound (231) directly.

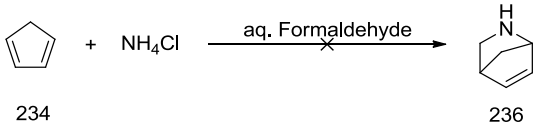


Scheme 93 - Attempted synthesis of an azanorbornene substrate.

On workup however, effervescence was observed, and after extraction and solvent removal a black tar was obtained. ^{1}H NMR analysis of this substance showed peaks indicating the presence of an azanorbornene ring, however the characteristic peaks expected for the N-dimethylmalonate group were absent. It is believed that the effervescence observed on work up indicated that the desired product had undergone decarboxylation after treatment with sodium hydroxide during the work up.

The reaction was repeated and the reaction worked up, omitting the base-treatment step to yield a similar black tar, however ^{1}H NMR indicated the presence of the product. TLC analysis of the crude mixture failed to identify a suitable solvent system to allow for chromatographic separation. Bulb-to-bulb distillation was attempted, however the product was heavily contaminated with dicyclopentadiene and another, unknown compound thought to arise from a retro-Diels-Alder process. In light of these difficulties encountered, this route was abandoned.

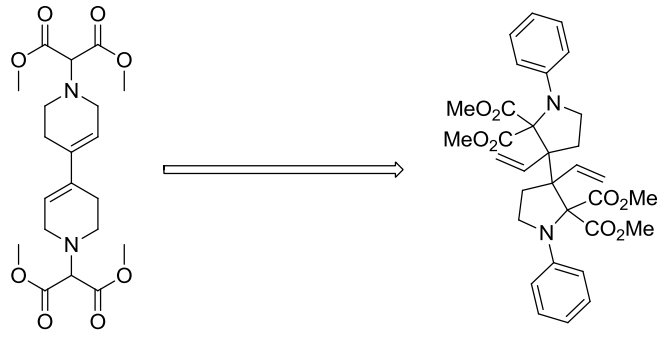
The reaction was repeated, this time in a solution of saturated ammonium hydrochloride in order to furnish azanorbornene as the hydrochloride salt of (186), which would then be alkylated with dimethylbromomalonate.



Scheme 94 - Attempted synthesis of an unsubstituted azanorbornene substrate.

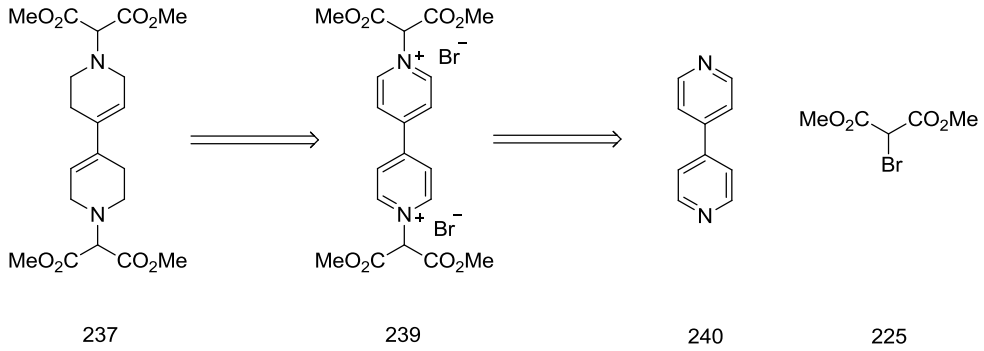
Unfortunately the presence of compound (236) was not observed in the crude reaction mixture.

Another bicyclic compound of interest is illustrated in (Scheme 95). It was proposed that treating 4,4-bistetrahydropyridine dimer (237) with 2 equivalents of benzyne would cause it to undergo double rearrangement to give an unusual 3,3-bispyrrolidine structure (238). It is believed that such compounds have potent biological properties



Scheme 95 - Proposed rearrangement of a bis-tetrahydrpyridine substrate.

It was proposed that it would be possible to access bis-tetrahydropyridine (237) using the same chemistry employed previously.

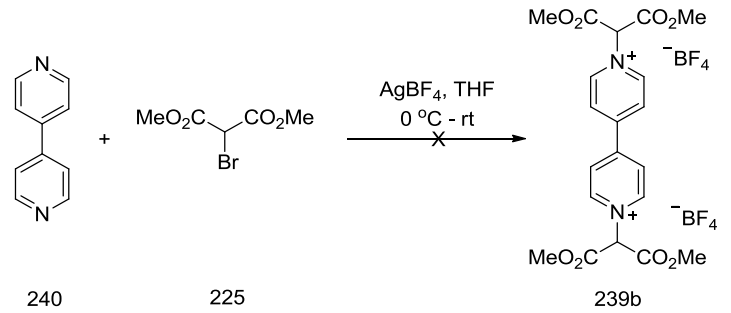


Scheme 96 - Proposed route to access bistetrahydropyridine substrate.

Unfortunately, treatment of 4,4-bipyridine (240) with 2 equivalents of dimethylbromomalonate (225) failed to yield the desired bispyridinium salt, yielding a brick red solid with a ^{1}H NMR inconsistent with the dialkylated product.

Subjecting the reaction to more forcing conditions yielded a deep purple/black solid with a ^{1}H NMR consistent with the desired product, however the isolated solid was deliquescent in nature, and further attempts at purification led to decomposition of the product.

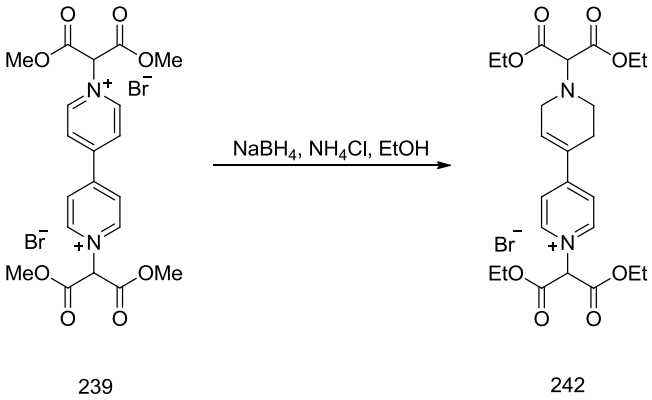
In an attempt to facilitate easier purification and modify the deliquescent properties of the compound, work was undertaken to prepare a salt with an alternative counterion. In order to accomplish this, dimethylbromomalonate was treated with $AgBF_4$ prior to addition to a solution of 4,4-bipyridine. Unfortunately, formation of the desired product was not observed.



Scheme 97 - Attempted synthesis of (188) with BF_4 counterions.

It was decided instead to attempt the reduction step without purification of the bispyridinium salt, taking additional measures in an effort to prevent decomposition. The reaction was repeated and allowed to reflux overnight, in a flask modified to exclude light. The solid bispyridinium salt was isolated by filtration and was rapidly dried under reduced pressure in order to minimise the effect of its deliquescence. The salt was immediately subjected to the reduction conditions stated previously, albeit for a longer reaction time (24 hours) and with a second addition of sodium borohydride and ammonium chloride added after 20 hours.

^{1}H analysis of the crude reaction mixture failed to show the presence of desired bis-tetrahydropyridine (237), however peaks consistent with compound (242) were observed, suggesting that only one end of the bis-pyridnium ring system has been reduced and that the ester groups have undergone interconversion.



Scheme 98 - Proposed product from reduction of (239).

It is believed that it may be possible to access compound (237) in a stepwise manner, reducing both pyridinium rings sequentially.

Rearrangement with other aryne precursors.

With the fundamental rearrangement with benzyne demonstrated to be viable, work was then carried out to investigate the reactivity of a range of substituted aryne precursors. It was

decided to carry out screening using a range of precursors commercially available from TCI in order to determine their reactivity towards this rearrangement process.

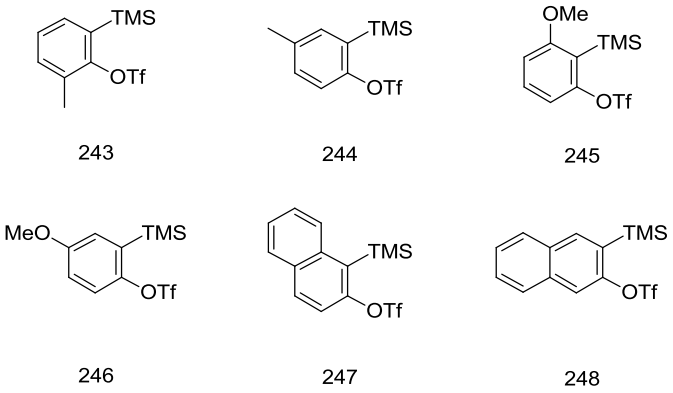


Figure 19 - Assymetric aryne precursors commercially available from TCI.

Predicting the reactivity of unsymmetrical arynes

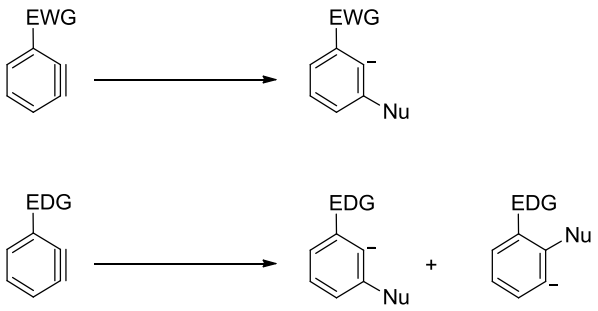
Unlike nucleophilic attack of benzyne, nucleophilic attack on unsymmetrical substituted arynes has the potential to yield two products, as the nucleophile can attack at either end of the aryne triple bond.

There are three models which have been proposed to explain the regioselectivity observed experimentally; the electronic model, the steric model and the aryne distortion model.

The simplest model is that of the steric model, which states that the position at which nucleophilic attack occurs is dictated by steric repulsion arising from adjacent groups.

In the electronic model, it is believed that substituents on the ring influence either by polarising the triple bond or stabilising or destabilising the negative charge formed in the transition state, either of which can influence the site of preferred nucleophilic attack.

Under this model, electron withdrawing substituents in the 3-position display a significant degree of regiocontrol, favouring *meta* addition as the developing negative charge in this position experiences greater stabilisation (Scheme 99). Nucleophilic attack of arynes bearing electron donating substituents in the 3-position are generally not as selective, as the stabilisation of the developing negative charge in the *meta*-position is offset by steric factors. Unless the substituent is strongly electon donating, a mixture of *ortho*- and *meta*-substitution is observed in the product.[98]



Scheme 99 - Selectivity observed for 3-substituted arynes.

Under this model, the degree of selectivity is also related to the nature of the nucleophile. Stronger nucleophiles are less selective.[99]

Finally, the aryne distortion model states that the geometry of the aryne intermediate is the determining factor of the regiochemical outcome of nucleophilic attack.

This theory states that by considering the difference between the bending distortion inherent in the aryne and the distortion energy – defined as the energy required to distort the indolyne and nucleophile reagents into their transition state geometries – required to reach the transition state geometry energy, it is possible to both explain and predict the regioselectivity observed experimentally.

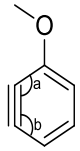
More simply, nucleophilic addition to unsymmetrical arynes is favoured at the position which requires the minimum geometric and energetic change to the transition state structure. Typically, this is at the carbon with the greatest internal angle.

Computational studies of aryne precursors

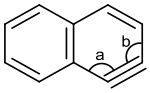
In order to predict the reactivity for each of the aryne precursors, it was necessary to generate optimised structures for each aryne intermediate. This was achieved using the NWChem[100] software package to carry out DFT computations at the B3LYP/6-311G* level of theory.

Initial efforts were directed towards ensuring it was possible to generate optimised structures that were consistent with those reported by the Garg group.[101] Therefore, 12,-naphthyne and 3-methoxybenzyne were first modelled and compared to the structures reported in the literature (Table 8).

Table 8 – Comparison of computationally calculated angles and energies of 4-methoxybenzyne and 3-naphthyne with literature values.[101]



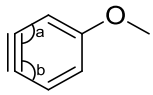
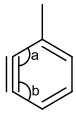
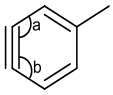
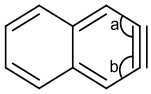
	Computed	Literature
A	119.91	119
B	134.44	135
Energy	-345.5244	-345.4388



	Computed	Literature
α	127.31	127.8
β	127.95	127.8
Energy	-384.6428	-384.5556

Satisfied that it was possible to generate optimised structures with the required accuracy, the remaining aryne substrates were modelled in the same manner (Table 9).

Table 9 - Calculated angles and energies for substituted arynes.

	α	128.15
	β	126.16
	Energy	-345.5143
	α	128.24
	β	127.21
	Energy	-270.2939
	α	127.73
	β	126.19
	Energy	-270.2902
	α	127.97
	β	127.97
	Energy	-384.6382

Applying the aryne distortion model to these results, it is now possible to predict which position it is most favourable for nucleophilic attack to occur, indicated in (Figure 20) by an arrow. Garg reports that a difference of ~ 3 ° between angles α and β is required in order to observe a 'useful' difference in selectivity. This means that a mixture of isomers should be expected in most cases.

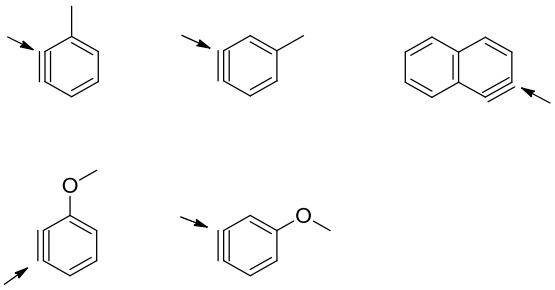
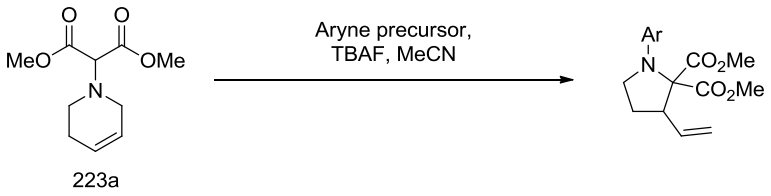


Figure 20 - Predicted sites of nucleophilic attack.

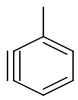
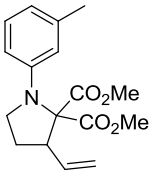
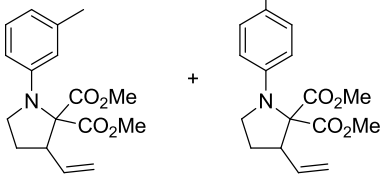
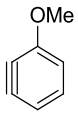
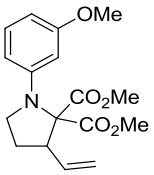
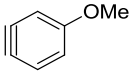
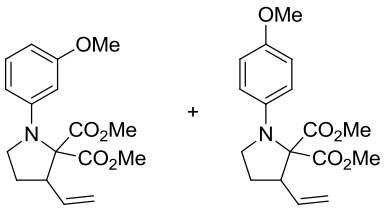
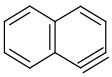
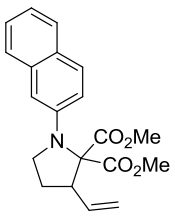
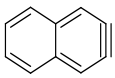
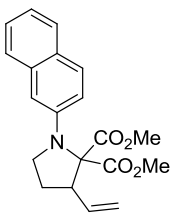
Results from reaction with unsymmetrical aryne precursors

With these predictions in hand, the previously prepared tetrahydropyridine was resubjected to the previous rearrangement conditions in the presence of the unsymmetrical, commercially available aryne precursors discussed above (Table 10).

Table 10 - Summary of rearrangement of unsymmetrical arynes with unsubstituted tetrahydropyridine substrate.



223a

Entry	Aryne	Product(s)	Ratio	Yield
249			-	75 %
250		 **A** **B**	55:45	81 %
251			-	77 %
252		 **A** **B**	55:45	65 %
253			-	52 %
254			-	45 %

In all examples the rearrangement proceeded as expected in yields between 45 – 81 %. While these yields are generally lower than for that of the reaction with unsubstituted benzyne, it is important to note that the reaction conditions are unoptimised for these new arynes.

The low yields encountered for both of the naphthyne examples (253 and 254) were accompanied by the presence of an unknown impurity observed in the crude ^{1}H NMR of the reaction mixtures (Figure 21). While it was possible to isolate this impurity by column chromatography, detailed NMR and MS analysis have failed to elucidate its exact structure.

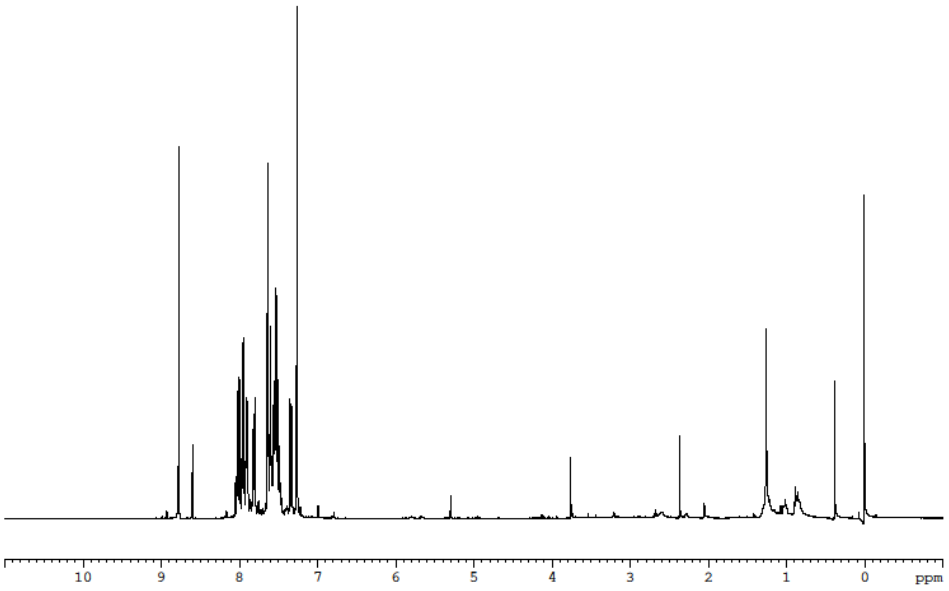
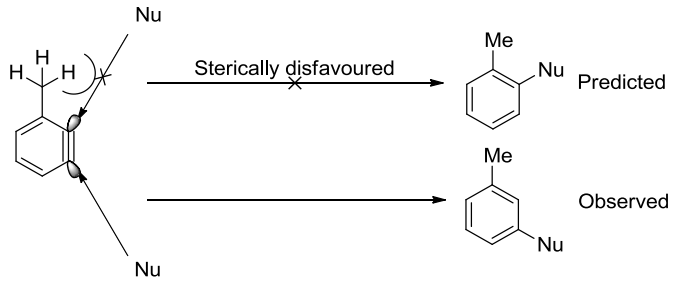


Figure 21 – ^{1}H NMR of side product arising from reactions with naphthyne.

Whether the reactive naphthyne species is dimerising, being intercepted or is simply sluggish to react due to its electron-rich nature, it is believed that this side product is the fate of the naphthyne intermediate, and that this side-reaction is the reason behind the diminished yields observed.

With regards to the regioselectivity of the products, in almost all examples the observed regioselectivity follows the predictions made using the aryne distortion model. However, in the case of entry (249), the regioselectivity observed in the product is opposite to that which was predicted using the aryne distortion model.

The computationally generated intermediate for 3-methylbenzyne shows that the position with the greatest flattening is the C2-position, which is where the predicted geometry of the intermediate formed from nucleophilic attack is most like that of the aryne intermediate. This means that the *o*-methyl product should be formed preferentially; instead, only the *m*-methyl product is observed.



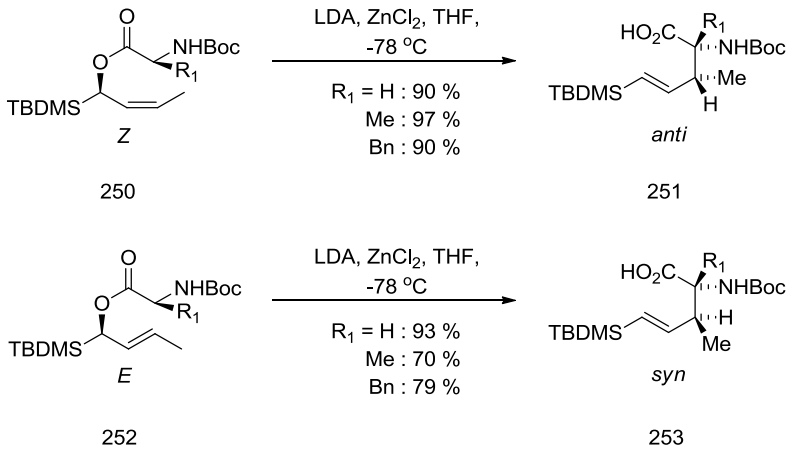
Scheme 100 - Rationalisation for observed substitution.

It is believed that this reversed selectivity is due to the methyl group in the 3-position, as the preferred angle of attack lies close to the plane of the triple bond. If the approaching nucleophile is bulky, as is the case in this example, then the additional steric repulsion prevents attack at the 2-position.

Arylative Rearrangement of Allyl Sarcosine Ethyl Esters

There are only a few examples in the literature regarding sigmatropic rearrangements being used to introduce an allyl group to the α-position of an amino acid,

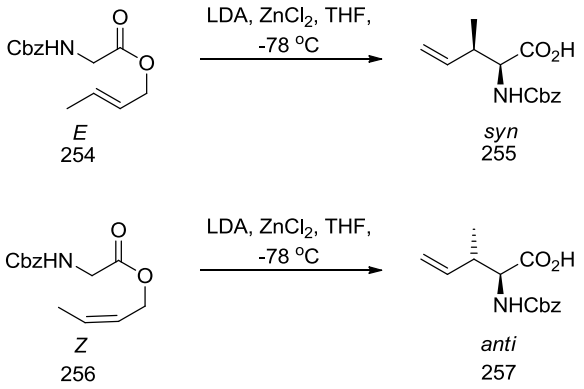
Sakaguchi and Ohfune *et. al*. reported carrying out the ester-enolate Claisen rearrangement of α-acyloxytrialkyl silanes, with transfer of chirality from the starting material (Scheme 101).[102]



Scheme 101 - Ester-enolate Claisen rearrangement to form α-allyl amino acid.

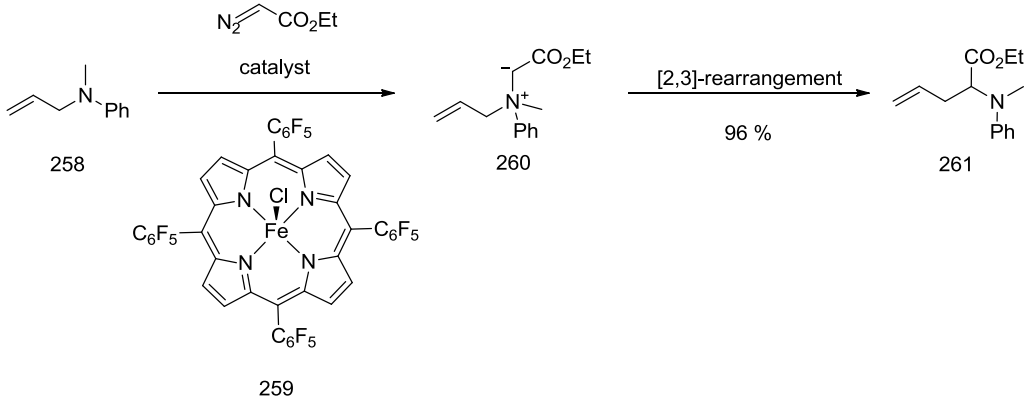
They reported that *Z*-substituted examples rearrange to furnish a single *anti*-diastereoisomer, while the *E*-substituted example furnishes a single *syn*-diastereoisomer.

More recently, Morimoto *et. al*. also reported carrying out a chelate-enolate Claisen rearrangement in order to access a key intermediate in their synthesis and stereochemical determination of 2-amino-3-cyclopropyl butanoic acid (Scheme 102).[103]



Scheme 102 - Chelate-enolate Claisen rearrangement to form α-allyl amino acid.

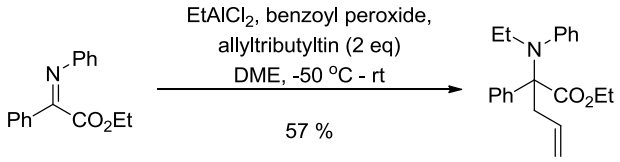
α-allyl amino acids can also be generated by treating a tertiary allyl amine with ethyl diazoacetate in the presence of a catalyst in order to generate a reactive carbene species which undergoes addition and subsequent rearrangement. This approach is similar to the work carried out by Workman previously for the rearrangement of tetrahydropyridines (Scheme 103).[104] This approach has also been carried out previously in a stepwise manner.[105]



Scheme 103 - Catalytic generation of reactive carbene species and subsequent rearrangement to form α-allyl amino acid.

Alternatively, it has been demonstrated that tandem *N*-alkylation-*C*-allylation of α-imino esters can be carried out in order to prepare α-allyl amino acids. Shimizu and Niwa reported

that treating an α-amino ester with diethylaluminium chloride, benzoyl peroxide and allyltributyltin results in double nucleophilic addition across the imine bond (Scheme 104).[106]



262 263

Scheme 104 - Tandem N-alkylation-C¬-allylation of α-imino esters to form α-allyl amino acids.

Although the literature shows that there are approaches to preparing α-allyl amino acids, there are a number of issues associated with each method. With the Claisen rearrangements shown in Scheme 101 and Scheme 102, there is the requirement for the use of strong base, while the catalytic methodology shown in Scheme 103 requires the use of an expensive[107] porphyrin-based transition-metal catalyst, requiring a relatively high mass of catalyst even under low catalyst loading. Finally, the tandem *N*-alkylation-*C*-allylation methodology shown in Scheme 104 requires the use of poisonous aluminium- and tin-based compounds, making it unsuitable for use on a large scale.

Aims

It is the aim of this section of work to investigate the possibility of taking the aryne-induced rearrangement methodology demonstrated on cyclic substrates and attempt to extend it to acyclic substrates, in order to prepare α-allyl amino acids.

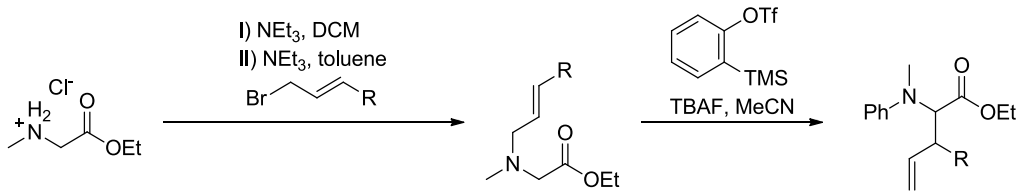
Rearrangement of *N*-allyl sarcosine ethyl ester

It was decided that a suitable substrate to carry out this investigation could be prepared from sarcosine (*N*-methyl glycine) (264).

The substrates were prepared by basifying sarcosine ethyl ester hydrochloride and treating the resulting solution with the desired substituted allyl bromide in the presence of base.

The prepared substrates were then treated with benzyne according to the procedure developed previously (Table 11).

Table 11 - Summary of N-methyl-N-allylsarcosine ethyl ester rearrangement.



264 265 266

Entry	R	Yield (%)	d.r
a	H	86	n/a
b	Me	99	n/a*
c	Ph	90	5:1

**Diastereoisomers present, but ratio not determinable by ^1H NMR*

All three examples underwent [2,3]-sigmatropic rearrangement as expected in good to excellent yield. The formation of the desired product is confirmed by ^1H NMR, as detailed in (Figure 22).

This spectrum is also consistent with that reported by Aviv and Gross (see supporting information of reference 104, page S18).

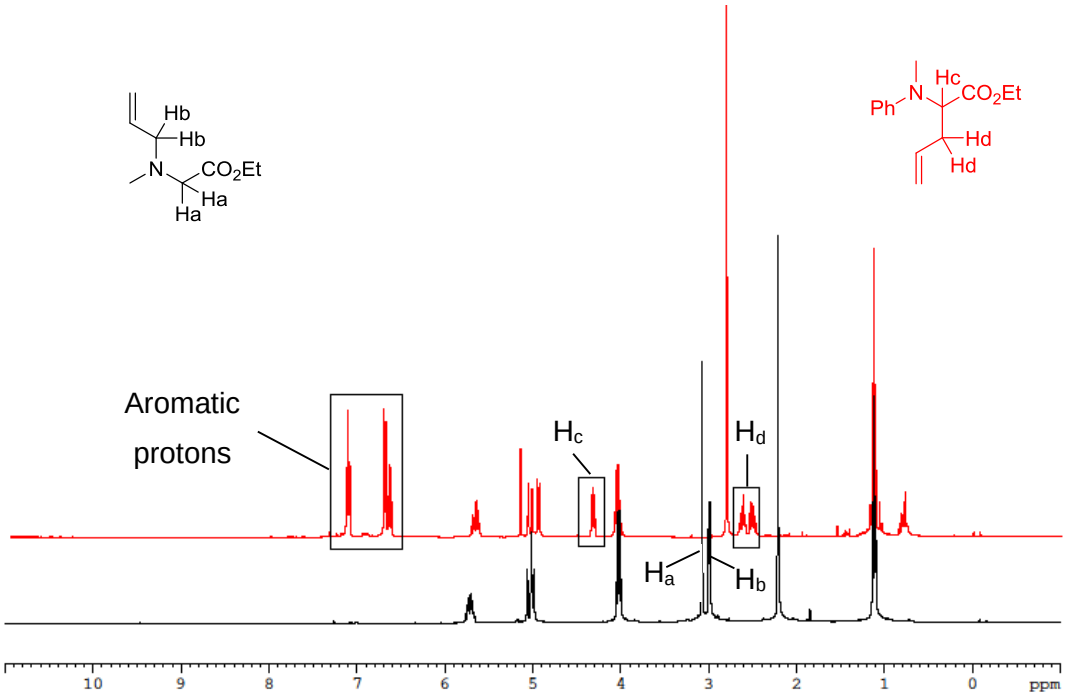


Figure 22 - Comparison of allyl sarcosine ethyl ester starting material (black) and rearrangement product (red).

Additionally, the mass of the expected product is consistent with the mass determined by mass spectrometry.

With the rearrangements products arising from substituted substrates (265b) and (265c), it is possible to observe shouldering on certain peaks, indicating the presence of diastereoisomers.

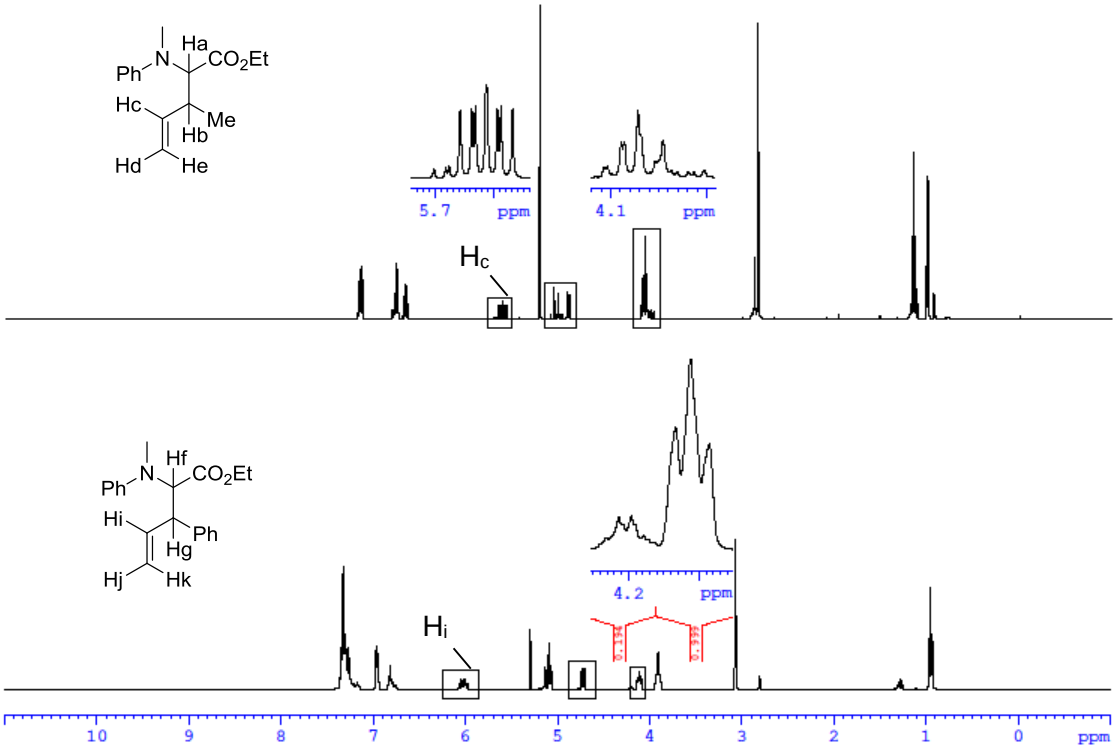


Figure 23 - Shouldering of peaks observed in the spectra of 265b (top) and 265c (bottom).

In the case of compound (265b) it was not possible to determine the diastereomeric ratio by ^{1}H NMR spectroscopy, however for (265c) it was possible to calculate a diastereomeric ratio of approximately 5:1 using the signal from the C-3 proton. Without further information it was not possible to assign whether the *syn- or anti*-diastereoisomer was predominant.

Conclusion

In conclusion, it has been demonstrated that it is possible to carry out a metal- and base-free arylative rearrangement of cyclic and acyclic substrates using arynes generated under mild conditions, and that the reaction is tolerant of a variety of functional groups.

It has been shown that this rearrangement is able to produce complex substituted pyrrolidine rings in good yields in as little as three steps, with the ability to form spirocyclic rings and control diastereoselectivity.

With further refinement in the synthesis of tetrahydropyridine rearrangement precursors it should be possible to generate fused bicyclic ring systems and generate novel bis-pyrrolidine compounds using this methodology.

Investigation into the extension of this methodology to asymmetric arynes has further demonstrated the synthetic utility of this rearrangement, enabling the ability to introduce functionality onto the aryl group. These studies have also shown that it is possible to predict the outcome of the product computationally by applying the aryne distortion model.

Finally, it has been demonstrated that it is possible to carry out the rearrangement of acyclic substrates using this methodology in order to introduce functionality into the α-position of N-methyl amino acids in two steps with high yield with a degree of diastereoselectivity,

Further work in this area will proceed across a number of areas. Firstly, a more in depth investigation of the mechanism of this reaction is to be carried out in tandem with detailed computational studies of the transition state.

Secondly, the work concerning the formation of bicyclic- and *bis*-pyrroles will be completed.

Thirdly, the preparation and rearrangement of substrates bearing synthetically useful handles, such as halides, as well as the synthesis and reaction of halide-bearing arynes in order to explore the ability to further functionalise the pyrrolidine cores generated by this reaction.

Finally, as a number of the compounds generated by this reaction are similar in structure to known biologically active compounds and are novel in nature, studies will be carried out to assess their biological activity and determine whether or not it is fruitful to explore further structural modifications.

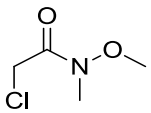
EXPERIMENTAL

Unless otherwise stated, all reactions were carried out under an inert atmosphere of dried nitrogen, in glassware which had been oven-dried. Reagents were purchased from Sigma-Aldrich, Acros, Alfa Aesar, Fisher Scientific, TCI UK or Lancaster Research Chemicals and were not purified except where stated. Solvents were purchased anhydrous and stored over molecular sieves, or distilled under nitrogen from an appropriate drying agent in accordance with the procedures of Perrin and Armarego.[108] THF and diethyl ether were distilled from sodium benzophenone ketyl radical while DCM, acetonitrile and DMSO were distilled from calcium hydride. Thin layer chromatography was performed on aluminium sheets coated with Merck silica gel 60 F254 with visualisation using potassium permanganate solution, vanillin solution and/or scrutinised under 254 nm UV light. Column chromatography was performed using Silica 60 (35-70 microns) supplied by Fisher unless otherwise stated.

Nuclear magnetic resonance (NMR) spectroscopy was performed on a Bruker Avance 400 NMR spectrometer (^{1}H NMR at 400 MHz, ^{13}C NMR at 100 MHz) with the appropriate deuterated solvent. Chemical shifts in 1H NMR spectra are expressed as ppm downfield from TMS and in 13C NMR, are relative to internal standard, and reported as singlet (s), doublet (d), triplet (t), quartet (q) and combinations thereof, or multiplet (m). Coupling constants (*J*) are quoted in Hz and are averaged between coupling partners and rounded to the nearest 0.2 Hz. Mass spectrometry was performed using a Bruker MicroTOF-Q instrument with electrospray ionisation in the positive mode. FT-IR data was acquired using Thermo Electron Corporation Nicolet 380 FTIR with Smart Orbit diamond window instrument with wavenumbers being reported in cm^{-1}. All melting points were obtained using a Stuart SMP10 melting point instrument and are uncorrected.

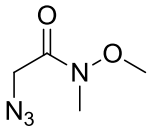
Preparation of Azidohydroxamic Acids

(166) 2-Chloro-*N*-methoxy-*N*-methylacetamide[109]



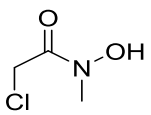
To a cooled (0 °C) solution of *N*,*O*-dimethylhydroxylamine hydrochloride (0.98 g, 10 mmol) and pyridine (1.78 mL, 22 mmol) in chloroform (25 mL) was added dropwise chloroacetyl chloride (0.8 mL, 10 mmol). Upon complete addition, the reaction was allowed to stir for 3 hours at 0 °C. The mixture was then washed with water (3 x 20 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to yield a pale yellow oil. The crude oil was subjected to bulb-to-bulb distillation (150 °C, 15 mbar) to yield colourless needles (0.237 g, 21 %); **Mp** 39-40 °C; **^{1}H NMR ($CDCl_3$)** δ 4.50 (s, 2H, $ClC\underline{H}_2CO$), 3.78 (s, 3H, $CO(NC\underline{H}_3)OCH_3$), 3.23 (s, 3H, $CO(NCH_3)OC\underline{H}_3$); **^{13}C NMR ($CDCl_3$)** δ 167.4 (Q, $\underline{C}$=O), 61.6 ($O\underline{C}H_3$), 40.9 (CH_2, $\underline{C}H_2Cl$), 32.5 ($N\underline{C}H_3$); **FTIR (neat)** ν_{MAX} 1662.3 (C=O); **GC-MS m/z:** $(M+H)^+$ calcd for $C_4H_8NO_2Cl$, 138.0316; found 138.0315.

(163) 2-Azido-N-methoxy-N-methylacetamide[69]



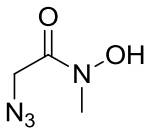
To a solution of **(166)** 2-chloro-N-methoxy-N-methylacetamide (145) (0.69 g, 5 mmol) in DMSO (40 mL) was added carefully sodium azide (0.65 g, 10 mmol). The reaction was allowed to stir overnight at room temperature, after which time water (40 mL) was added dropwise. The resulting mixture was extracted with ethyl acetate (3 x 20 mL) and the combined organic layers washed with water (40 mL). The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure to yield a pale yellow oil (0.688 g, 95 %); **^{1}H NMR ($CDCl_3$)** δ 4.06 (s, 2H, $N_3C\underline{H}_2CO$), 3.71 (s, 3H, $CO(NC\underline{H}_3)OCH_3$), 3.22 (s, 3H, $CO(NCH_3)OC\underline{H}_3$); **^{13}C NMR ($CDCl_3$)** δ 168.7 (Q, $\underline{C}$=O), 61.5 ($O\underline{C}H_3$), 49.8 ($N_3\underline{C}H_2$), 32.3 ($N\underline{C}H_3$); **FTIR (neat)** ν_{MAX} 2101.3 (N_3), 1671.2 (C=O);

(169) 2-Chloro-N-methyl-N-hydroxyacetamide[110]



Cooled (0 ^{o}C) solutions of N-methylhydroxylamine hydrochloride (1.84 g, 22 mmol) in MeOH (25 mL) and potassium hydroxide (1.12 g, 20 mmol) in MeOH (25 mL) were mixed and allowed to stir at 0 ^{o}C for 5 minutes. Chloroacetyl chloride (0.80 mL, 10 mmol) in THF (25 mL) was added dropwise to this mixture over half an hour and upon complete addition, the reaction was allowed to stir for a further half hour at 0 ^{o}C, then at room temperature for another 2 hours. The mixture was then concentrated under reduced pressure and the residue was treated with saturated NaCl solution (20 mL). The resulting solution was then extracted with ethyl acetate (3 x 50 mL), the organic layers were combined, dried over magnesium sulphate, filtered and concentrated under reduced pressure to yield an orange oil which solidified upon standing. The crude solid was recrystallised from chloroform, using hexane as a co-solvent to yield pale orange needles (0.862 g, 71 %) **mp** 62-64 ^{o}C; **^{1}H NMR ($CDCl_3$)** δ 4.38 and 4.10 (s, 2H, $ClC\underline{H}_2CO$), 3.46 and 3.30 (s, 3H, $NC\underline{H}_3$); **^{13}C NMR ($CDCl_3$)** δ 167.8 (Q, $\underline{C}$=O), 41.5 (CH_2, $\underline{C}H_2Cl$), 36.7 ($N\underline{C}H_3$); **FTIR (neat)** ν_{MAX} 1660.7 (C=O).

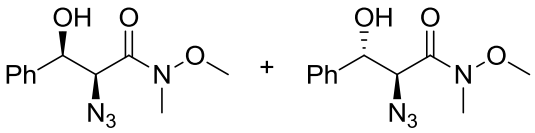
(170) 2-Azido-N-methyl-N-hydroxyacetamide[69]



To a solution of **(169)** 2-chloro-N-methyl-N-hydroxyacetamide (149) (47.5 mg, 0.38 mmol) in DMSO (5 mL) was added carefully sodium azide (20 mg, 0.38 mmol). The mixture was allowed to stir overnight at room temperature, after which time water (5 mL) was added slowly. The resulting mixture was then extracted with ethyl acetate (2 x 20 mL), the combined organic layers washed with water (20 mL), dried over sodium sulphate, passed through a silica plug and concentrated under reduced pressure to yield a pale yellow oil, which turned cherry red in an aqueous solution of $FeCl_3$ (50.2 mg, 100 %). **^{1}H NMR ($CDCl_3$)** δ 4.06 (s, 2H, $N_3C\underline{H}_2CO$), 3.71 (s, 3H, $NC\underline{H}_3$); **^{13}C NMR ($CDCl_3$)** δ 168.7 (Q, $\underline{C}$=O), 49.8 ($N_3\underline{C}H_2CO$), 32.3 ($N\underline{C}H_3$); **FTIR (neat)** ν_{MAX} 3176.5 (OH), 2101.9 (N_3), 1632.3 (C=O); **m/z (ES^{+})** calculated for $C_3H_7ClNO_2$ [M + H^{+}]; 124.0160, found 124.0159.

Aldol Reaction Screening of AzidoHydroxamic Acids Substrates

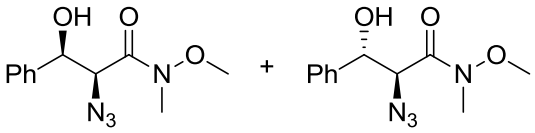
Screen of Non-nucleophilic bases



To a solution of benzaldehyde (0.035 mL, 0.35 mmol), zinc chloride (0.035 mmol) and 2-Chloro-N-methoxy-N-methylacetamide (0.35 mmol, 0.050 g) in THF (5 mL) was added 1 mL of a solution of the appropriate base in 10 mL of THF (0.35 mmol, see table below). The mixture was allowed to stir overnight at room temperature after which time it was concentrated under reduced pressure and subjected to analysis by NMR.

Entry	Base	Amount in 10 mL THF	Conversion	*Syn:anti* ratio
1	Triethylamine	0.49 mL	0	-
2	DMAP	0.42 g	0	-
3	DIPEA	0.61 mL	0	-
4	Pyridine	0.28 mL	0	-
5	DBU	0.53 mL	89 %	2.2:1
6	Tributylamine	0.83 mL	0	-
7	NMM	0.38 mL	0	-
8	TMEDA	0.52 mL	0	-

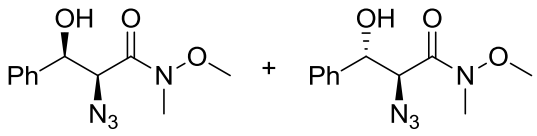
Screen of Solvents



To a solution of benzaldehyde (0.35 mmol, 0.035 mL), zinc chloride (0.035 mmol) and 2-chloro-N-methoxy-N-methylacetamide (0.35 mmol, 0.050 g) in the solvent (5 mL) was added 1 mL of a solution of DBU in 10 mL of the solvent (0.35 mmol, 0.53 mL). The mixture was allowed to stir overnight at room temperature after which time it was concentrated under reduced pressure and subjected to analysis by NMR.

Entry	Solvent	$ZnCl_2$ catalyst	Conversion	*Syn:anti* ratio
1	THF	X	87	2:1
2	THF	-	88	2.1:1
3	DCM	X	78	2.2:1
4	DCM	-	83	2.2:1
5	EtOAc	X	70	2.3:1
6	EtOAc	-	85	1:1
7	MeOH	X	0	-
8	MeOH	-	0	-
9	MeCN	X	79	2.7:1
10	MeCN	-	83	2.7:1

Screen of Metal Chlorides



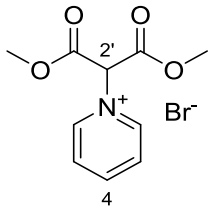
To a solution of benzaldehyde (0.35 mmol, 0.035 mL), the metal chloride catalyst (0.035 mmol) and 2-Chloro-N-methoxy-N-methylacetamide (0.35 mmol, 0.050 g) in the THF (5 mL) was added 1 mL of a solution of DBU in 10 mL of THF (0.35 mmol, 0.53 mL). The mixture was allowed to stir overnight at room temperature after which time it was concentrated under reduced pressure and subjected to analysis by NMR.

Entry	Catalyst	Conversion	*Syn:anti* ratio
1	$ZnCl_2$	85	2:1
2	$FeCl_3$	35	2.1:1
3	$MgCl_2$	40	2.1:1
4	$CuCl_2$	44	1.8:1
5	KCl	43	2.2:1
6	$CdCl_2$	34	2.1

General Procedure for the Preparation of Pyridinium Salts

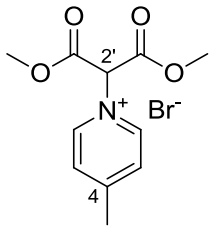
Dimethylmalonyl bromide (2.0 mL, 15 mmol) and the substituted pyridine (15 mmol) were allowed to stir at room temperature in THF (10 mL) for 18 hours, after which time the resulting precipitate was collected by filtration, washed with Et_2O and allowed to dry under vacuum.

(222a) 1-(1,3-Dimethoxy-1,3-dioxopropan-2-yl)pyridin-1-ium Bromide[111]



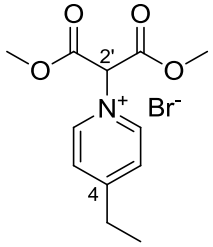
Prepared from pyridine (1.21 mL, 15 mmol) according to the general procedure above to yield a colourless solid (1.52 g, 35 %); **mp:** 118 ºC (decomp.) (lit. = 137-138 ºC); **^{1}H NMR ($CDCl_3$)** δ_H 9.86 (d, *J* = 7.0, 2H, C2-H), 8.68 (t, *J* = 7.0, 1H, C4-H), 8.56 (s, 1H, C2'-H), 8.17 (t, *J* = 7.0, 2H, C3-H), 3.95 (s, 6H, OCH_3); **^{13}C NMR ($CDCl_3$)** δ_C 163.2 (Q, C=O), 147.4 (C4), 147.0 (C2), 127.6 (C3), 71.0 (C2'), 55.1 (OCH_3); ν_{max} **(ATR, cm^{-1})** 1734 (C=O); **m/z (ES$^+$)** calculated for $C_{10}H_{12}NO_4$ $[M - Br]^+$; 210.0761, found 210.0750 (-7.62 ppm).

(222b) 1-(1,3-Dimethoxy-1,3-dioxopropan-2-yl)-4-methylpyridin-1-ium Bromide



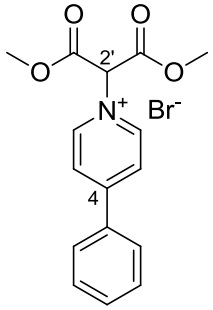
Prepared from 4-methylpyridine (1.78 mL, 15 mmol) according to the general procedure above to yield a light brown solid (4.47 g, 89 %); **mp:** 112 ºC (decomp.); **^{1}H NMR ($CDCl_3$)** δ_H 9.65 (d, *J* = 6.6, 2H, C3-H), 8.44 (s, 1H, C2'-H), 7.91 (d, *J* = 6.6, 2H, C3-H), 3.94 (s, 6H, OCH_3), 2.77 (s, 3H, C4-CH_3); **^{13}C NMR ($CDCl_3$)** δ_C 163.4 (Q, C=O), 161.7 (Q, C4), 145.7 (C2), 127.9 (C3), 70.2 (C2'), 54.9 (OCH_3), 22.7 (C4-CH_3); ν_{max} **(ATR, cm^{-1})** 1741 (C=O); **m/z (ES$^+$)** calculated for $C_{11}H_{14}NO_4$ $[M - Br]^+$; 224.0293, found 224.0916 (-3.12 ppm).

(222c) 1-(1,3-Dimethoxy-1,3-dioxopropan-2-yl)-4-ethylpyridin-1-ium Bromide



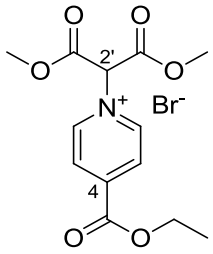
Prepared from 4-ethylpyridine (1.61 mL, 15 mmol) according to the general procedure above to yield a pale orange solid (2.94 g, 62 %); **mp:** 97-99 ºC (decomp.); **^{1}H NMR ($CDCl_3$)** δ_H 9.71 (d, *J* = 6.8, 2H, C2-H), 8.52 (s, 1H, C2'-H), 7.87 (d, *J* = 6.8, 2H, C3-H), 3.95 (s, 6H, OCH_3), 3.03 (q, *J* = 7.6, 2H, C4-CH_2CH_3), 1.41 (t, *J* = 7.6, 3H, C4-CH_2CH_3); **^{13}C NMR ($CDCl_3$)** δ_C 166.8 (Q, C=O), 163.5 (Q, C4), 146.0 (C2), 126.5 (C3), 70.1 (C2'), 55.0 (OCH_3), 29.3 (CH_2, CH_2CH_3), 13.1 (C4-CH_2CH_3); ν_{max} **(ATR, cm^{-1})** 1736 (C=O); **m/z (ES$^+$)** calculated for $C_{12}H_{16}NO_4$ $[M - Br]^+$; 238.1074, found 238.1073 (-0.42 ppm).

(222d) (1-(1,3-Dimethoxy-1,3-dioxopropan-2-yl)-4-phenylpyridin-1-ium Bromide



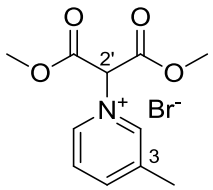
Prepared from 4-phenylpyridine (2.14 g, 15 mmol) according to the general procedure above to yield a colourless solid (2.95 g, 54 %); **mp:** 133 ºC (decomp.); **^{1}H NMR ($CDCl_3$)** δ_H 9.84 (d, *J* = 7.0, 2H, C3-H), 8.52 (s, 1H, C2'-H), 8.24 (d, *J* = 7.0, 2H, C2-H), 7.84 (d, *J* = 6.6, 2H, Ar-H), 7.69-7.62 (m, 3H, Ar-H), 3.96 (s, 6H, OCH_3); **^{13}C NMR ($CDCl_3$)** δ_C 163.5 (Q, C=O), 156.5 (Q, C4), 146.5 (C3), 133.3 (Q, Ar-C), 133.2 (Ar-C), 130.2 (Ar-C) 128.0 (Ar-C), 123.9 (C2), 70.1 (C2'), 55.0 (OCH_3); ν_{max} **(ATR, cm^{-1})** 1739 (C=O); **m/z (ES$^+$)** calculated for $C_{16}H_{16}NO_4$ $[M - Br]^+$; 286.1074, found 286.1079 (1.75 ppm).

(222e) 1-(1,3-Dimethoxy-1,3-dioxopropan-2-yl)-4-(ethoxycarbonyl)pyridin-1-ium Bromide



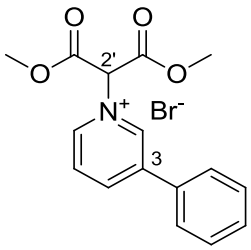
Prepared from ethylisonicotinate (2.14 g, 15 mmol), according to the general procedure above. The reaction mixture was concentrated under reduced pressure then allowed to stand overnight. The resulting solid was washed with ether and THF and dried under vacuum to yield a pale yellow solid (2.32 g, 42 %); **mp:** 155 ºC (decomp.); **^{1}H NMR ($CDCl_3$)** δ_H 10.12 (d, *J* = 6.8, 2H, C2-H), 8.61 (s, 1H, C2'-H), 8.58 (d, *J* = 6.8, 2H, C3-H), 4.54 (q *J* = 7.2, 2H, OCH_2CH_3), 3.95 (s, 6H, OCH_3), 1.46 (t, *J* = 7.2, 3H, OCH_2CH_3); **^{13}C NMR ($CDCl_3$)** δ_C 162.7 (Q, C=O), 161.0 (Q, CO_2Et), 148.5 (C3), 146.2 (Q, C4), 126.7 (C2), 71.3 (C2'), 64.0 (CH_2, OCH_2CH_3), 55.2 (OCH_3), 14.0 (OCH_2CH_3); ν_{max} **(ATR, cm^{-1})** 1761 (C=O), 1730 (C=O); **m/z (ES$^+$)** calculated for $C_{13}H_{16}NO_6$ $[M - Br]^+$; 282.0978, found 282.0976 (-0.71 ppm).

(222f) 1-(1,3-Dimethoxy-1,3-dioxopropan-2-yl)-3-methylpyridin-1-ium Bromide



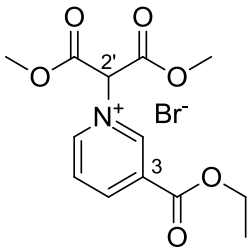
Prepared from 3-methylpyridine (1.78 mL, 15 mmol) according to the general procedure above to yield a pale yellow solid (3.41 g, 75 %); **mp:** 136 ºC (decomp.); **^{1}H NMR ($CDCl_3$)** δ_H 9.72 (s, 1H, C2-H), 9.67 (d, *J* = 7.2, 1H, C6-H), 8.49 (s, 1H, C2'-H), 8.45 (d, *J* = 7.2, 1H, C4-H), 8.05 (t, *J* = 7.2, 1H, C5-H), 3.95 (s, 6H, OCH_3), 2.69 (s, 3H, C3-CH_3); **^{13}C NMR ($CDCl_3$)** δ_C 163.3 (Q, C=O), 147.8 (CH, C4), 146.1 (CH, C2), 144.0 (CH, C6), 139.0 (Q, C3), 126.9 (CH, C5), 70.7 (CH, C2'), 55.0 (CH_3, OCH_3), 18.8 (CH_3, C3-CH_3); ν_{max} **(ATR, cm^{-1})** 1738 (C=O); **m/z (ES$^+$)** calculated for $C_{11}H_{14}NO_4$ $[M - Br]^+$; 224.0923, found 224.0918 (-2.23 ppm).

(222h) 1-(1,3-Dimethoxy-1,3-dioxopropan-2-yl)-3-phenylpyridin-1-ium Bromide



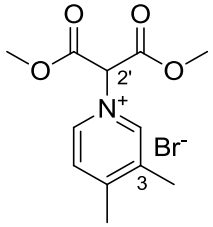
Prepared from 3-phenylpyridine (1.78 mL, 15 mmol) according to the general procedure above to yield a colourless solid (4.03 g, 74 %); **mp:** 119 ºC (decomp.); **^{1}H NMR (CDCl$_3$)** δ_H 10.06 (s, 1H, C2'-H), 9.76 (d, *J* = 6.2, 1H, C6-H), 8.80 (d, *J* = 8.2, 1H, C4-H), 8.73 (s, 1H, C2-H), 8.21 (dd, *J* = 8.2, 6.2, 1H, C5-H), 7.84 (d, *J* = 80, 2H, Ar-H), 7.60-7.53 (m, 3H, Ar-H), 3.96 (s, 6H, OCH$_3$); **^{13}C NMR (CDCl$_3$)** δ_C 163.4 (Q, C=O), 144.6 (C4), 144.5 (C2'), 144.4 (C6), 141.1 (Q, C3), 132.2 (Q, Ar-C), 130.9 (Ar-C), 130.0 (Ar-C), 127.6 (Ar-C), 127.5 (C5), 71.0 (C2), 55.1 (OCH$_3$); ν_{max} **(ATR, cm^{-1})** 1736 (C=O); **m/z (ES$^+$)** calculated for $C_{16}H_{16}NO_4$ [M - Br]$^+$; 286.1074, found 286.1078 (1.39 ppm).

(222i) 1-(1,3-Dimethoxy-1,3-dioxopropan-2-yl)-3-(ethoxycarbonyl)pyridin-1-ium Bromide



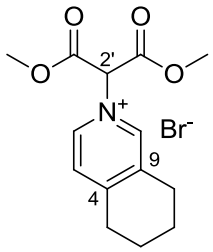
Prepared from ethylnicotinate (2.04 mL, 15 mmol), according to the general procedure above. The reaction mixture was concentrated under reduced pressure then allowed to stand overnight. The resulting solid was washed with ether and THF and dried under vacuum to yield a pale yellow solid (2.93 g, 54 %); **mp:** 120 ºC (decomp.); **^{1}H NMR (CDCl$_3$)** δ_H 10.67 (br s, 1H, C2-H), 9.87 (s, 1H, C2'-H), 9.13 (d, *J* = 8.0, 1H, C4-H), 8.81 (br s, 1H, C2-H), 8.37 (br s, 1H, C5-H), 4.56 (q, *J* = 7.2, 2H, OCH$_2$CH$_3$), 3.99 (s, 6H, OCH$_3$), 1.50 (t, *J* = 7.2, 3H, OCH$_2$CH$_3$); **^{13}C NMR (CDCl$_3$)** δ_C 162.9 (Q, C=O), 160.6 (Q, CO$_2$Et), 150.4 (C6), 147.7 (C4), 147.1 (C2), 130.2 (Q, C3), 127.9 (C5), 71.1 (C1'), 63.8 (CH$_2$, CH$_2$CH$_3$), 55.3 (OCH$_3$), 14.2 (CH$_2$CH$_3$); ν_{max} **(ATR, cm^{-1})** 1759 (C=O), 1738 (C=O); **m/z (ES$^+$)** calculated for $C_{13}H_{16}NO_4$ [M - Br]$^+$; 282.0978, found 282.0972 (-2.13 ppm).

(222j) 1-(1,3-Dimethoxy-1,3-dioxopropan-2-yl)-3,4-dimethylpyridin-1-ium Bromide



Prepared from 3,4-dimethylmethylpyridine (1.68 mL, 15 mmol) according to the general procedure above to yield a light brown solid (3.50 g, 74 %); **mp:** 126 ºC (decomp.); **^{1}H NMR ($CDCl_3$)** δ_H 9.55 (s, 1H, C2-H), 9.40 (d, *J* = 6.4, 1H, C6-H), 8.27 (s, 1H, C2'-H), 7.84 (d, *J* = 6.4, 1H, C5-H), 3.89 (s, 6H, OCH_3), 2.61 (s, 3H, C3-CH_3), 2.51 (s, 3H, C4-CH_3); **^{13}C NMR ($CDCl_3$)** δ_C 163.5 (Q, C=O), 160.6 (Q, C4), 144.7 (C2), 143.3 (C6), 137.7 (Q, C3), 127.9 (C5), 70.1 (C2'), 54.9 (OCH_3), 20.9 (C3-CH_3, 17.2 (C4-CH_3); ν_{max} **(ATR, cm^{-1})** 1741 (C=O); **m/z (ES$^+$)** calculated for $C_{12}H_{16}NO_4$ $[M - Br]^+$; 238.1074, found 238.1072 (-0.84 ppm).

(222k) 2-(1,3-Dimethoxy-1,3-dioxopropan-2-yl)-5,6,7,8-tetrahydroisoquinolin-2-ium Bromide

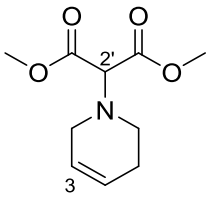


Prepared from 5,6,7,8-tetrahydroisoquinoline (1.94 mL, 15 mmol) according to the general procedure above to yield a pale brown solid (4.38 g, 85 %); **mp:** 115 ºC (decomp.); **^{1}H NMR ($CDCl_3$)** δ_H 9.59 (s, 1H, C2'-H), 9.36 (d, *J* = 6.4, 1H, C10-H), 8.38 (s, 1H, C1-H), 7.71 (d, *J* = 6.4, 1H, C3-H), 3.94 (s, 6H, OCH_3), 3.08-3.03 (m, 4H, C5-H_2, C8-H_2), 1.95 (t, *J* = 3, 4H, C6-H_2, C7-H_2); **^{13}C NMR ($CDCl_3$)** δ_C 163.6 (Q, C=O), 160.7 (Q, C4), 145.5 (C10), 142.1 (C2), 138.2 (Q, C9), 127.0 (C3), 70.0 (C2'), 54.8 (OCH_3), 30.0 (CH_2, C8), 26.4 (CH_2, C5), 20.94 (CH_2, C7), 20.90 (CH_2, C6); ν_{max} **(ATR, cm^{-1})** 1740 (C=O); **m/z (ES$^+$)** calculated for $C_{14}H_{18}NO_4$ $[M - Br]^+$; 264.1230, found 264.1233 (1.14 ppm).

General Procedure for the Preparation of Substituted Tetrahydropyridines

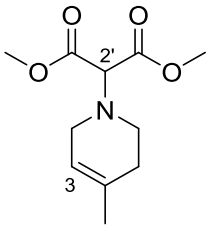
To a cooled (0 ºC) vigorously stirred solution of the pyridinium salt (3.39 mmol) and ammonium chloride (0.26 g, 4.84 mmol) in ethanol (40 mL) was added sodium borohydride (0.50 g, 13.04 mmol) in a single portion. The mixture was allowed to stir for 15 minutes, after which time it was allowed to warm to room temperature and allowed to stir for a further two hours. The reaction was then quenched by the addition of water (150 mL) and extracted with DCM (250 mL). The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure to yield a crude oil which was then subjected to flash column chromatography to yield the title compound.

(223a) Dimethyl 2-(5,6-tetrahydropyridin-1(2H)-yl)malonate



Prepared from **(222a)** 1-(1,3-dimethoxy-1,3-dioxopropan-2-yl)pyridin-1-ium Bromide (0.75 g, 3.39 mmol) according to the general procedure above. The resulting crude oil was subjected to column chromatography (20 % ethyl acetate in petroleum ether) to yield a pale yellow oil (0.31 g, 43 %) $\mathbf{R_f}$ 0.08 (10 % ethyl acetate in petroleum ether); **^{1}H NMR ($CDCl_3$)** δ_H 5.79-7.73 (m, 1H, C3-H), 5.67-5.62 (m, 1H, C4-H), 4.20 (s, 1H, C2'-H), 3.78 (s, 6H, OCH_3), 3.30 (m, 2H, C2-H_2), 2.85 (t, *J* = 5.6, 2H, C6-H_2), 2.21 (m, 2H, C5-H_2); **^{13}C NMR ($CDCl_3$)** δ_C 167.3 (Q, C=O), 125.0 (C3), 124.8 (C4), 70.2 (C2'), 52.2 (OCH_3), 49.4 (CH_2, C2), 46.7 (CH_2, C6), 26.4 (CH_2, C5); ν_{max} **(ATR, cm^{-1})** 1731 (C=O); **m/z (ES$^+$)** calculated for $C_{10}H_{16}NO_4$ [M + H]$^+$; 214.1074, found 214.1070 (-1.87 ppm).

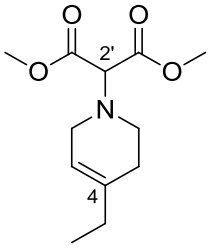
(223b) Dimethyl 2-(4-methyl-5,6-tetrahydropyridin-1(2H)-yl)malonate



Prepared from **(222b)** 1-(1,3-dimethoxy-1,3-dioxopropan-2-yl)-4-methylpyridin-1-ium bromide (1.03 g, 3.39 mmol) according to the general procedure above. The resulting crude oil was subjected to column chromatography (20 % ethyl acetate in petroleum ether) to yield

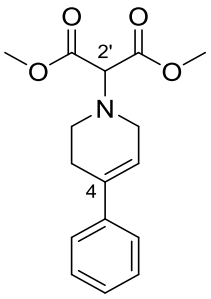
a pale yellow oil (0.36 g, 47 %); **R_f**: 0.11 (10 % ethyl acetate in petroleum ether);**^{1}H NMR ($CDCl_3$)** δ_H 5.17 (br s, 1H, C3-H), 4.01 (s, 1H, C2'-H), 3.59 (s, 6H, OCH_3), 3.06 (br s, 2H, C2-H_2), 2.67 (t, *J* = 5.8, 2H, C6-H_2), 1.94 (br s, 2H, C3-H_2), 1.50 (s, 3H, C4-CH_3); **^{13}C NMR ($CDCl_3$)** δ_C 167.4 (Q, C=O), 132.2 (Q, C4), 118.6 (C3), 69.9 (C2'), 51.9 (OCH_3), 49.2 (CH_2, C2), 46.7 (CH_2, C6), 30.9 (CH_2, C3), 22.7 (C4-CH_3); ; ν_{max} **(ATR, cm^{-1})** 1731 (C=O); **m/z (E S$^+$)** calculated for $C_{11}H_{17}NO_4$ $[M + H]^+$; 228.1232, found 228.1232 (0 ppm).

(223c) Dimethyl 2-(4-ethyl-5,6-tetrahydropyridin-1(2H)-yl)malonate



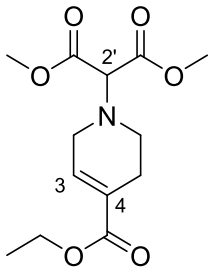
Prepared from **(222c)** 1-(1,3-dimethoxy-1,3-dioxopropan-2-yl)-4-ethylpyridin-1-ium bromide (1.12 g, 3.39 mmol). The resulting crude oil was subjected to column chromatography (20 % ethyl acetate in petroleum ether) to yield a pale yellow oil (0.43 g, 53 %); **R_f** 0.18 (10 % ethyl acetate in petroleum ether); **^{1}H NMR ($CDCl_3$)** δ_H 5.14 (br s, 1H, C3-H), 4.01 (s, 1H, C2'-H), 3.59 (s, 6H, OCH_3), 3.08 (br s, 2H, C2-H_2), 2.66 (t, *J* = 5.6, 2H, C6-H_2), 1.95 (br s, 2H, C5-H_2), 1.80 (q, *J* = 7.4, 2H, C4-CH_2CH_3), 0.82 (t, J = 7.4, 2H, C4-CH_2CH_3); **^{13}C NMR ($CDCl_3$)** δ_C 167.4 (Q, C=O), 137.6 (Q, C4), 116.8 (C3), 69.9 (C2'), 51.9 (OCH_3), 49.3 (CH_2, C1), 46.7 (CH_2, C6), 29.4 (CH_2, C5), 29.3 (CH_2, C4-CH_2CH_3), 11.6 (C4-CH_2CH_3); ν_{max} **(ATR, cm^{-1})** 1732 (C=O); **m/z (ES$^+$)** calculated for $C_{12}H_{20}NO_4$ $[M + H]^+$; 242.1387, found 242.1387 (0 ppm).

(223d) Dimethyl 2-(4-phenyl-5,6-tetrahydropyridin-1(2H)-yl)malonate



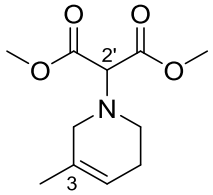
Prepared from **(222d)** 1-(1,3-dimethoxy-1,3-dioxopropan-2-yl)-4-phenylpyridin-1-ium bromide (1.23 g, 3.39 mmol) according to the general procedure above. The resulting crude oil was subjected to column chromatography (20% ethyl acetate in petroleum ether) to yield a yellow oil (0.157 g, 16 %); **R_f** 0.09 (10 % ethyl acetate in petroleum ether); **^{1}H NMR ($CDCl_3$)** δ_H 7.38 – 7.22 (m, 5H, Ar-H), 6.02 (s, 1H, C3-H), 4.27 (s, 1H, C2'-H), 3.80 (s, 6H, OCH_3), 3.50 (br s, 2H, C2-H_2), 3.02 (t, *J* = 5.6, 2H, C6-H_2), 2.02 (br s, 2H, C5-H_2); **^{13}C NMR ($CDCl_3$)** δ_C 167.6 (Q, C=O), 140.8 (Q, Ar-C), 135.1 (Q, C4), 128.3 (Ar-C), 127.0 (Ar-C), 124.9 (Ar-C), 121.3 (C3), 70.0 (C2'), 52.4 (OCH_3), 49.8 (CH_2, C2), 47.0 (CH_2, C6), 28.4 (CH_2, C5); ν_{max} **(ATR, cm^{-1})** 1738.9 (C=O); **m/z (ES$^+$)** calculated for $C_{16}H_{20}NO_4$ [M+H$^+$]; 290.1387, found 290.1373 (-4.83 ppm).

(223e) Dimethyl 2-(4-(ethoxycarbonyl)-5,6-tetrahydropyridin-1(2H)-yl)malonate



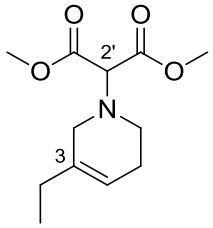
Prepared from **(222e)** 1-(1,3-dimethoxy-1,3-dioxopropan-2-yl)-4-(ethoxycarbonyl)pyridin-1-ium bromide (1.22 g) according to the general procedure above. The resulting crude oil was subjected to column chromatography (20 % ethyl acetate in petroleum ether) to yield a yellow oil (0.152 g, 16 %); **R_f:** 0.12 (10 % ethyl acetate in petroleum ether)**; ^{1}H NMR ($CDCl_3$)** δ_H 6.74 (br s, 1H, C3-H), 4.12 (s, 1H, C2'-H), 4.09-4.05 (m, 2H, OCH_2CH_3), 3.65 (s, 6H, OCH_3), 3.39 (br s, 2H, C1-H_2), 2.77 (br t, *J* = 5.0, 2H, C6-H_2), 2.32 (br s, 2H, C5-H_2), 1.15 (br t, *J* = 5, 3H, OCH_2CH_3); **^{13}C NMR ($CDCl_3$)** δ_C 167.3 (Q, C=O), 166.3 (Q, C=O), 135.9 (C3), 128.6 (Q, C4), 69.4 (C2'), 60.3 (CH_2, OCH_2CH_3), 52.2 (OCH_3), 49.0 (CH_2, C1), 46.5 (CH_2, C6), 25.5 (CH_2, C5), 14.1 (OCH_2CH_3); ν_{max} **(ATR, cm^{-1})**; 1732 (C=O), 1708 (C=O); **m/z (ES$^+$)** calculated for $C_{13}H_{20}NO_6$ [M + H]$^+$; 285.1212, found 285.1210 (-0.70 ppm).

(223f) Dimethyl 2-(3-methyl-5,6-tetrahydropyridin-1(2H)-yl)malonate



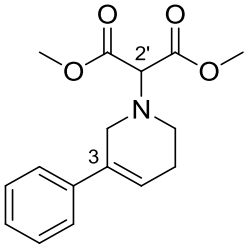
Prepared from **(222f)** 1-(1,3-dimethoxy-1,3-dioxopropan-2-yl)-3-methylpyridin-1-ium bromide (1.03 g, 3.39 mmol) according to the general procedure above. The resulting crude oil was subjected to column chromatography (20 % ethyl acetate in petroleum ether) to yield a a pale yellow oil (0.308 g, 40 %) **R_f:** 0.11 (10 % ethyl acetate in petroleum ether; **^{1}H NMR ($CDCl_3$)** δ_H 5.45 (br s, 1H, C4-H), 4.21 (s, 1H, C2'-H), 3.78 (s, 6H, OCH_3), 3.16 (br s, 2H, C2-H_2), 2.79 (t, *J* = 5.6, 2H, C6-H_2), 2.17 (br s, 2H, C5-H_2), 1.63 (br s, 3H, C3-CH_3); **^{13}C NMR ($CDCl_3$)** δ_C 167.6 (Q, C=O), 131.8 (Q, C3), 119.3 (C4), 70.1 (C2'), 53.4 (CH_2, C2), 52.2 (OCH_3), 46.5 (CH_2, C6), 26.1 (CH_2, C5), 20.8 (C3-CH_3); ν_{max} **(ATR, cm^{-1})** 1731 (C=O); **m/z (ES$^+$)** calculated for $C_{11}H_{17}NO_4$ [M]; 228.1230, found 228.1239 (3.95 ppm).

(223g) Dimethyl 2-(3-ethyl-5,6-tetrahydropyridin-1(2H)-yl)malonate



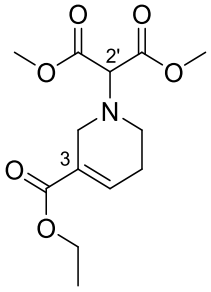
Prepared from **(222g)** 1-(1,3-dimethoxy-1,3-dioxopropan-2-yl)-3-ethylpyridin-1-ium bromide (1.07 g, 3.39 mmol) according to the general procedure above. The resulting crude oil was subjected to flash column chromatography (20 % ethyl acetate in petroleum ether) to yield a pale yellow oil (0.34 g, 42 %); **R_f** 0.18 (10 % ethyl acetate in petroleum ether); **^{1}H NMR ($CDCl_3$)** δ_H 5.46 (br s, 1H, C4-H), 4.21 (s, 1H, C2'-H), 3.78 (s, 6H, OCH_3), 3.18 (br s, 2H, C2-H_2), 2.80 (t, *J* = 5.8, 2H, C6-H_2), 2.18 (br s, 2H, C5-H_2), 1.94 (q, *J* = 7.4, 2H, C3-CH_2CH_3), 1.00 (t, *J* = 7.4, 3H, C3-CH_2CH_3); **^{13}C NMR ($CDCl_3$)** δ_C 167.6 (Q, C=O), 137.3 (Q, C3), 117.4 (C4), 70.1 (C2'), 52.4 (CH_2, C2), 52.1 (OCH_3), 46.8 (CH_2, C6), 27.6 (CH_2, C5), 26.0 (CH_2, C3-CH_2CH_3), 12.0 (C3-CH_2CH_3);

(223h) Dimethyl 2-(3-phenyl-5,6-tetrahydropyridin-1(2H)-yl)malonate



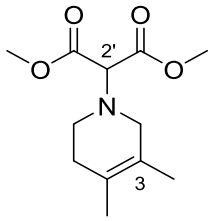
Prepared from **(222h)** 1-(1,3-dimethoxy-1,3-dioxopropan-2-yl)-3-phenylpyridin-1-ium bromide (1.24 g, 3.39 mmol) according to the general procedure above. The resulting crude oil was subjected to column chromatography (20% ethyl acetate in petroleum ether) to yield a yellow oil (0.132 g, 13 %); **R_f** 0.15 (10 % ethyl acetate in petroleum ether); **^{1}H NMR (CDCl$_3$)** δ_H 7.38 – 7.22 (m, 5H, Ar-H), 6.02 (s, 1H, C4-H), 4.27 (s, 1H, C2'-H), 3.80 (s, 6H, OCH$_3$), 3.48 (br s, 2H, C2-H$_2$), 3.02 (t, *J* = 5.6, 2H, C6-H$_2$), 2.62 (br s, 2H, C5-H$_2$); **^{13}C NMR (CDCl$_3$)** δ_C 167.6 (Q, C=O), 139.7 (Q, Ar-C), 135.2 (Q, C3), 128.3 (Ar-C), 127.1 (Ar-C), 125.0 (Ar-C), 122.4 (C4), 70.2 (C2'), 52.3 (CH_2, C1), 51.4 (OCH3), 46.4 (CH_2, C6), 26.7 (CH_2, C5); ν_{max} **(ATR, cm^{-1})** 1731 (C=O); **m/z (ES$^+$)** calculated for $C_{16}H_{20}NO_4$ $[M + H]^+$; 290.1387, found 290.1390 (1.03 ppm).

(223i) Dimethyl 2-(3-(ethoxycarbonyl)-5,6-tetrahydropyridin-1(2H)-yl)malonate



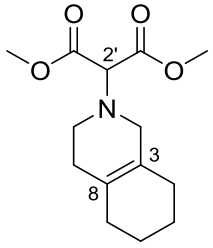
Prepared from **(222i)** 1-(1,3-dimethoxy-1,3-dioxopropan-2-yl)-3-(ethoxycarbonyl)pyridin-1-ium bromide (1.22 g) according to the general procedure above. The resulting crude oil was subjected to column chromatography (20 % ethyl acetate in petroleum ether) to yield a red oil (0.184 g, 19 %); **^{1}H NMR (C$_6$D$_6$)** δ_H 6.94-6.91 (m, 1H, C4-H), 4.10 (s, 1H, C2'-H), 3.96 (1, *J* = 7.0, 2H, OCH$_2$CH$_3$), 3.77 (br s, 2H, C2-H$_2$), 3.23 (s, 6H, OCH$_3$), 2.83 (t, *J* = 5.4, 2H, C5-H$_2$), 2.00-1.95 (m, 2H, C6-H$_2$), 0.91 (t, *J* = 7.0, 3H, OCH$_2$CH$_3$); **^{13}C NMR (C$_6$D$_6$)** δ_C 167.3 (Q, C=O), 165.0 (Q, C=O), 137.3 (C4), 129.4 (Q, C3), 69.5 (C2'), 59.9 (CH_2, OCH$_2$CH$_3$), 51.2 (OCH$_3$), 49.0 (CH_2, C2), 45.2 (CH_2, C6), 26.8 (CH_2, C5), 13.9 (OCH$_2$CH$_3$); ν_{max} **(ATR, cm^{-1});** 1736 (C=O), 1700 (C=O); **m/z (ES$^+$)** calculated for $C_{13}H_{20}NO_6$ $[M + H]^+$; 285.1212, found 285.1213 (0.35 ppm).

(223j) Dimethyl 2-(3,4-dimethyl-5,6-tetrahydropyridin-1(2H)-yl)malonate



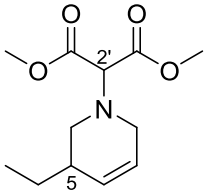
Prepared from **(222j)** 1-(1,3-dimethoxy-1,3-dioxopropan-2-yl)-3,4-dimethylpyridin-1-ium bromide (1.08 g) according to the general procedure above. The resulting crude oil was subjected to column chromatography (20 % ethyl acetate in petroleum ether) to yield a yellow oil (0.241 g, 29 %) $\mathbf{R_f}$: 0.21 (10 % ethyl acetate in petroleum ether); **^{1}H NMR ($CDCl_3$)** δ_H 4.19 (s, 1H, C2'-H), 3.78 (s, 3H, OCH_3), 3.12 (br s, 2H, C2-H_2), 2.81 (t, *J* = 4.6, 2H, C5-H_2), 2.11 (br s, 2H, C6-H_2), 1.62 (s, 3H, C4-CH_3), 1.57 (s, 3H, C3-CH_3); **^{13}C NMR ($CDCl_3$)** δ_C 167.5 (Q, C=O), 124.3 (Q, C4), 123.4 (Q, C3), 70.0 (C2'), 54.3 (CH_2, C2), 52.1 (OCH_3), 47.3 (CH_2, C5), 32.1 (CH_2, C6), 18.2 (C4-CH_3), 16.3 (C3-CH_3); ν_{max} **(ATR, cm^{-1})** 1733 (C=O); **m/z (ES$^+$)** calculated for $C_{12}H_{20}NO_4$ $[M + H]^+$; 242.1387, found 242.1372 (-6.19 ppm).

(223k) Dimethyl 2-(3,4,5,6,7,8-hexahydroisoquinolin-2(1H)-yl)malonate



Prepared from **(222k)** 2-(1,3-dimethoxy-1,3-dioxopropan-2-yl)-5,6,7,8-tetrahydroisoquinolin-2-ium bromide (1.17 g) according to the general procedure above. The resulting crude oil was subjected to column chromatography (20 % ethyl acetate in petroleum ether) to yield an orange oil (yield, 0.567 g, 63 %); $\mathbf{R_f}$ 0.35 (10 % ethyl acetate in petroleum ether); **^{1}H NMR ($CDCl_3$)** δ_H 4.19 (s, 1H, C2'-H), 3.78 (s, 6H, 2 x OCH_3), 3.08 (br s, 2H, C2-H_2), 2.82 (t, *J* = 5.8, 2H, C9-H_2), 2.06 (br s, 2H, C10-H_2), 1.85 (br s, 2H, C5-H_2, C6-H_2), 1.80 (br s, 2H, C5-H_2, C6-H_2) 1.58-1.55 (br s, 4H, C4-H_2, C7-H_2); **^{13}C NMR ($CDCl_3$)** δ_C 147.7 (Q, C=O), 126.7 (Q, C3), 126.1 (Q, C8), 70.3 (CH, C2'), 53.5 (CH_2, C2), 52.3 (CH_3, 2 x OCH_3), 47.3 (CH_2, C10), 30.9 (CH_2, C9), 29.4 (CH_2, C7), 27.5 (CH_2, C4), 22.7 (CH_2, C6), 22.6 (CH_2, C5); ν_{max} **(ATR, cm^{-1})**; 1731 (C=O); **m/z (ES$^+$)** calculated for $C_{14}H_{22}NO_4$ $[M + H]$; 268.1543, found 268.1546 (1.12).

(226) Dimethyl 2-(3-ethyl-3,6-dihydropyridin-1(2H)-yl)malonate

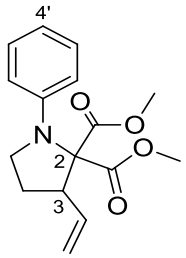


Prepared from **(222g)** 1-(1,3-dimethoxy-1,3-dioxopropan-2-yl)-3-ethylpyridin-1-ium bromide (1.07 g, 3.39 mmol) according to the general procedure above. The resulting crude oil was subjected to flash column chromatography (20 % ethyl acetate in petroleum ether) to yield a pale yellow oil (0.23 g, 28 %); **R_f** 0.22 (10 % ethyl acetate in petroleum ether); **^{1}H NMR ($CDCl_3$)** δ_H 5.66 (m, 2H, C3-H, C4-H), 4.20 (s, 1H, C2'-H), 3.78 (s, 6H, OCH_3), 3.27 (br s, 2H, C2-H_2), 3.61-2.96 (m, 1H, C6-H_2), 2.47 (dd, *J* = 11.0, 7.6, 1H, C6-H_2), 2.24 (br s, 1H, C5-H), 1.41-1.33 (m, 2H, CH_2CH_3), 0.93 (t, J = 7.6, 3H, CH_2CH_3); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C 167.6 (Q, C=O), 129.9 (C3), 124.3 (C4), 71.3 (C2'), 52.0 (OCH_3), 51.9 (CH_2, C6), 49.7 (CH_2, C2), 38.2 (C5), 27.5 (CH_2, CH_2CH_3), 11.4 (CH_2CH_3).

General Procedure for the Arylative Rearrangement of Tetrahydropyridines

To a stirred solution of the tetrahydropyridine (0.49 mmol) and 2-trimethylsilylphenyl triflate (0.08 mL, 0.33 mmol) in dry acetonitrile (10 mL) was added dropwise over two hours TBAF (1M sln. in THF, 0.94 mL, 0.94 mmol). After complete addition, the mixture was passed through a silica plug and washed with ethyl acetate (2 x 25 mL). The resulting solution was concentrated under reduced pressure to yield a crude oil which was subjected to flash column chromatography to yield the title compound.

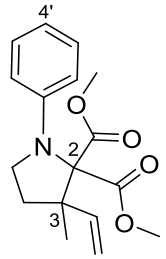
(227a) Dimethyl 1-phenyl-3-ethenylpyrrolidine-2,2-dicarboxylate



Prepared from **(223a)** dimethyl 2-(5,6-tetrahydropyridin-1(2H)-yl)malonate (0.104 g, 0.49 mmol) according to the general procedure above. The resulting crude oil was subjected to flash column chromatography (10% ethyl acetate in petroleum ether) to yield a yellow oil

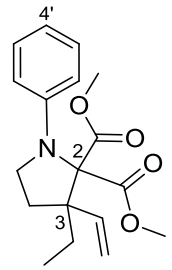
(0.090 g, 94 %); **R_f:** 0.15 (10 % ethyl acetate in petroleum ether); **^{1}H NMR ($CDCl_3$)** δ_H 7.18 (t, *J* = 7.6, 2H, C3'-H), 6.73 (t, *J* = 7.6, 1H, C4'-H), 6.55 (d, *J* = 7.6, 2H, C2'-H), 5.89 (ddd, *J* = 17.6, 9.8, 7.0, 1H, CH=CH_2), 5.19 (d, *J* = 17.6, 1H, CH=CH_2), 5.18 (d, *J* = 9.8, 1H, CH=CH_2), 3.72 (s, 3H, OCH_3), 3.70-3.67 (m, 5H, C5-H_2, OCH_3), 3.43-3.37 (m, 1H, C3-H), 2.22-2.16 (m, 2H, C4-H_2); **^{13}C NMR ($CDCl_3$)** δ_C 170.1 (Q, C=O), 169.1 (Q, C=O), 145.5 (Q, C1'), 134.5 (CH=CH2), 128.7 (C5), 118.1 (CH_2, CH=CH2), 117.5 (C4'), 113.4 (C2'), 75.8 (Q, C2), 54.0 (C3), 52.8 (OCH_3), 52.4 (OCH_3), 49.2 (CH_2, C5), 28.6 (CH_2, C4); ν_{max} **(ATR, cm^{-1})** 1728 (C=O), 1600 (C=C), 1505 (Ar C-C); **m/z (ES^+)** calculated for $C_{16}H_{20}NO_4$ $[M + H]^+$; 290.1387, found 290.1381 (-2.06 ppm).

(227b) Dimethyl 1-phenyl-3-methyl-3-ethenylpyrrolidine-2,2-dicarboxylate



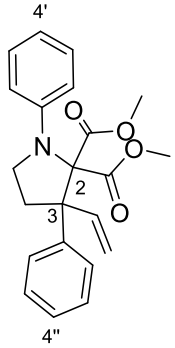
Prepared from **(223b)** dimethyl 2-(4-methyl-5,6-tetrahydropyridin-1(2H)-yl)malonate (0.111 g, 0.49 mmol) according to the general procedure above. The resulting crude oil was subjected to flash column chromatography (10% ethyl acetate in petroleum ether) to yield a pale yellow oil (0.084 g, 84 %); **R_f:** 0.26 (10 % ethyl acetate in petroleum ether); **^{1}H NMR ($CDCl_3$)** δ_H 7.16 (t, *J* = 7.6, 2H, C3'-H), 6.72 (d, *J* = 7.6, 2H, C4'-H), 6.46 (t, *J* = 7.6, 2H, C2'-H), 6.11 (dd, *J* = 17.4, 10.8, 1H, CH=CH_2), 5.15 (d, *J* = 17.4, 1H, CH=CH_2), 5.13 (d, *J* = 10.8, 1H, CH=CH_2), 3.77 (t, *J* = 6.8, 2H, C5-H_2), 3.72 (s, 3H, OCH_3), 3.62 (s, 3H, OCH_3), 2.37 (t, *J* = 6.8, 1H, C4-H_2), 2.05-2.00 (m, 1H, C4-H_2), 1.27 (s, 3H, C3-CH_3); **^{13}C NMR ($CDCl_3$)** δ_C 169.24 (Q, C=O), 169.20 (Q, C=O), 146.5 (Q, C1'), 140.2 (CH=CH2), 128.6 (C3'), 117.4 (C4'), 114.4 (CH_2, CH=CH2), 113.5 (C2'), 79.5 (Q, C2), 53.4 (Q, C3), 52.4 (OCH_3), 52.3 (OCH_3), 49.4 (CH_2, C5), 34.6 (CH_2, C4), 22.0 (C3-CH_3); ν_{max} **(ATR, cm^{-1})** 1739 (C=O), 1599 (C=), 1505 (Ar C=C); **m/z (ES^+)** calculated for $C_{17}H_{22}NO_4$ $[M + H]^+$; 304.1543, found 304.1544 (0.33 ppm).

(227c) Dimethyl 1-phenyl-3-ethyl-3-ethenylpyrrolidine-2,2-dicarboxylate



Prepared from **(223c)** dimethyl 2-(4-ethyl-5,6-tetrahydropyridin-1(2H)-yl)malonate (0.118 g, 0.49 mmol) according to the general procedure above. The resulting crude oil was subjected to flash column chromatography (10% ethyl acetate in petroleum ether) to yield a yellow oil (0.102 g, 97 %); **R_f:** 0.24 (10 % ethyl acetate in petroleum ether); **^{1}H NMR (C_6D_6)** δ_H 7.16 (t, *J* = 7.8, 2H, C3'-H), 6.72 (t, *J* = 7.8, 1H, C4'-H), 6.44 (d, *J* = 7.8, 2H, C2'-H), 5.95 (dd, *J* = 17.6, 11.0, 1H, CH=CH_2), 5.26 (d, *J* = 11.0, 1H, CH=CH_2), 5.13 (d, *J* = 17.6, 1H, CH=CH_2), 3.77-3.71 (m, 5H, C5-H_2, OCH_3), 3.61 (s, 3H, OCH_3), 2.45-2.38 (m, 1H, C4-H_2), 2.11-2.05 (m, 1H, C4-H_2), 1.62-1.57 (q, *J* = 7.4, 2H, C$H_2$$CH_3$), 0.65 (t , *J* = 7.4, 3H, CH_2CH_3); **^{13}C NMR (C_6D_6)** δ_C 168.9 (Q, C=O), 168.4 (Q, C=O), 147.1 (Q, C1'), 138.5 (CH=CH_2), 128.5 (C3'), 117.4 (C4'), 115.7 (CH_2, CH=CH_2), 113.9 (C2'), 80.5 (Q, C2), 57.5 (Q, C3), 51.5 (OCH_3), 51.3 (OCH_3), 49.3 (CH_2, C5), 27.4 (CH_2, C4), 26.2 (CH_2, $CH_2$$CH_3$), 8.5 ($CH_2CH_3$); **(ATR, cm^{-1})** 1737 (C=O), 1568 (C=C); **m/z (ES^+)** calculated for $C_{18}H_{23}NO_4Na$ $[M + Na]^+$; 340.1525, found 340.1513 (-3.53 ppm).

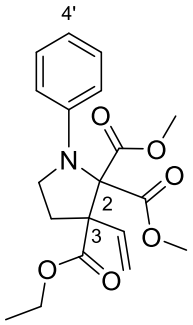
(227d) Dimethyl 1,3-diphenyl-3-ethenylpyrrolidine-2,2-dicarboxylate



Prepared from **(223d)** dimethyl 2-(4-phenyl-5,6-tetrahydropyridin-1(2H)-yl)malonate (0.142 g, 0.49 mmol). The resulting crude oil was subjected to flash column chromatography (10% ethyl acetate in petroleum ether) to yield a yellow oil (0.100 g, 83 %); **R_f:** 0.27 (10 % ethyl acetate in petroleum ether); **^{1}H NMR ($CDCl_3$)** δ_H 7.54 (d, *J* = 7.4, 2H, C2''-H), 7.33 (t, *J* = 7.4, 2H, C3''-H), 7.29-7.23 (m, 3H, C4''-H, C3'-H), 6.82(t, *J* = 7.4, C4'-H), 6.69-6.62 (m,

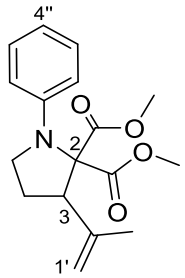
3H, C<u>H</u>=CH2, C2'-<u>H</u>), 5.43 d, *J* = 10.8, 1H, CH=C<u>H</u>$_2$), 5.22 (d, *J* = 17.6, 1H, CH=C<u>H</u>$_2$), 4.09 (m, 1H, C5-<u>H</u>$_2$), 3.82 (m, 1H, C5-<u>H</u>$_2$), 3.67 (s, 3H, OC<u>H</u>$_3$), 3.30 (s, 3H, OC<u>H</u>$_3$), 2.96-2.89 (m, 1H, C4-<u>H</u>$_2$), 2.26-2.20 (m, 1H, C4-<u>H</u>$_2$); **^{13}C NMR (CDCl$_3$)** δ_C 170.0 (Q, <u>C</u>=O), 168.6 (Q, <u>C</u>=O), 146.5 (Q, <u>C</u>1''), 143.0 (Q, <u>C</u>1'), 139.7 (<u>C</u>H=CH$_2$), 128.5 (<u>C</u>3'), 128.1 (<u>C</u>3''), 127.0 (C2''), 126.8 (<u>C</u>4''), 117.8 (<u>C</u>4'), 116.4 (CH$_2$, CH=<u>C</u>H$_2$), 114.2 (<u>C</u>2'), 80.8 (Q, <u>C</u>2), 61.3 (Q, <u>C</u>3), 52.6 (O<u>C</u>H$_3$), 50.4 (O<u>C</u>H$_3$), 50.4 (CH$_2$, <u>C</u>5), 33.2 (CH$_2$, <u>C</u>4); ν_{max} **(ATR, cm^{-1})** 1734 (C=O), 1598 (C=C); **m/z (ES$^+$)** calculated for $C_{22}H_{24}NO_4$ [M + H]$^+$; 366.1700, found 366.1687 (-3.55 ppm).

(227e) 3-Ethyl 2,2-dimethyl 1-phenyl-3-ethenylpyrrolidine-2,2,3-tricarboxylate



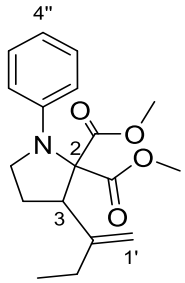
Prepared from **(223e)** dimethyl 2-(4-(ethoxycarbonyl)-5,6-tetrahydropyridin-1(2H)-yl)malonate (140 mg) according to the general procedure above. The resulting crude oil was subjected to flash column chromatography (10% ethyl acetate in petroleum ether) to yield a pale yellow oil (0.068 g, 57 %); **R$_f$** 0.24 (10 % ethyl acetate in petroleum ether); **^{1}H NMR (CDCl$_3$)** δ_H 7.19 (t, *J* = 8.0, 2H, C3'-<u>H</u>), 6.76 (t, *J* = 8.0, 1H, C4'-<u>H</u>), 6.58 (d, *J* = 8.0, 2H, C2'-<u>H</u>), 6.35 (dd, *J* = 17.6, 11.0, 1H, C<u>H</u>=CH$_2$), 5.32 (d, *J* = 17.6, 1H, CH=C<u>H</u>$_2$), 5.29 (d, *J* = 11.0, 1H, CH=C<u>H</u>$_2$), 4.20 (q, *J* = 7.2, 2H, OC<u>H</u>$_2$CH$_3$), 3.87 (t, *J* = 7.2, 1H, C5-<u>H</u>$_2$), 3.74 (s, 3H, OCH$_3$), 3.67 (s, 3H, OC<u>H</u>$_3$), 2.68-2.59 (m, 2H, C4-<u>H</u>$_2$), 2.45-2.39 (m, 1H, C5-<u>H</u>$_2$), 1.28 (t, *J* = 7.2, 3H, OCH$_2$C<u>H</u>$_3$); **^{13}C NMR (CDCl$_3$)** δ_C 169.7 (Q, <u>C</u>=O), 168.6 (Q, <u>C</u>=O), 166.3 (Q, <u>C</u>=O), 145.0 (Q, <u>C</u>1'), 138.5 (<u>C</u>H-CH$_2$), 128.8 (<u>C</u>3'), 125.1 (<u>C</u>4'), 117.9 (<u>C</u>2'), 113.5 (CH$_2$, CH=<u>C</u>H$_2$), 94.2 (Q, <u>C</u>2) 61.1 (O<u>C</u>H$_2$CH$_3$), 52.6 (O<u>C</u>H$_3$), 52.2 (O<u>C</u>H$_3$), 50.0 (Q, <u>C</u>3), 48.4 (<u>C</u>5), 27.3 (<u>C</u>4), 15.1 (OCH$_2$<u>C</u>H$_3$); ν_{max} **(ATR, cm^{-1})** 1765 (C=O), 1727 (C=O), 1709 (C=O), 1628 (C=C), 1600 (Ar-C-C);

(227f) Dimethyl 1-phenyl-3-(prop-1-en-2-yl)pyrrolidine-2,2-dicarboxylate



Prepared from **(223f)** dimethyl 2-(3-methyl-5,6-tetrahydropyridin-1(2H)-yl)malonate (0.111 g, 0.49 mmol) according to the general procedure above. The resulting crude oil was subjected to flash column chromatography (10% ethyl acetate in petroleum ether) to yield a pale yellow oil (0.073 g, 73 %); **R_f:** 0.12 (10 % ethylacetate in pet ether); **^{1}H NMR ($CDCl_3$)** δ_H 7.17 (t, *J* = 6.2, 2H, C3''-H), 6.73 (t, *J* = 6.2, 1H, C4''-H), 6.55 (d, *J* = 6.2, 2H, C2''-H), 4.94 (s, 1H, C1'-H_2), 4.84 (s, 1H, C1'-H_2), 3.75-3.65 (m, 8H, C5-H_2, 2 x OCH_3), 3.55 (q, *J* = 4.8, 1H, C4-H_2), 2.28-2.20 (m, 1H, C4-H_2), 2.14-2.09 (m, 1H, C3-H), 1.80 (s, 3H, C3'-H_3); **^{13}C NMR ($CDCl_3$)** δ_C 170.8 (Q, C=O), 168.7 (Q, C=O), 145.7 (Q, C1''), 142.1 (Q, C2'), 128.8 (C3''), 117.6 (C4''), 113.4 (CH_2, C1'), 113.2 (C2''), 75.9 (Q, C2), 56.7 (C3), 52.7 (OCH_3), 52.2 (OCH_3), 49.0 (CH_2, C5), 27.2 (CH_2, C4), 22.7 (C3'); ν_{max} **(ATR, cm^{-1})**; 1731 (C=O), 1599 (C=C), 1506 (Ar C=C) **m/z (ES$^+$)** calculated for $C_{17}H_{22}NO_4$ $[M + H]^+$; 304.1543, found 304.1543 (0 ppm).

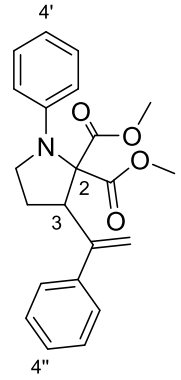
(227g) Dimethyl 1-phenyl-3-(but-1-en-2-yl)pyrrolidine-2,2-dicarboxylate



Prepared from **(223g)** dimethyl 2-(4-ethyl-5,6-tetrahydropyridin-1(2H)-yl)malonate (0.118 g, 0.49 mmol) according to the general procedure above. The resulting crude oil was subjected to flash column chromatography (10% ethyl acetate in petroleum ether) to yield a yellow oil (0.051 g, 49 %); **R_f:** 0.20 (10 % ethyl acetate in petroleum ether); **^{1}H NMR (C_6D_6)** δ_H 7.17-7.13 (m, 2H, C3''-H), 6.73-6.71 (m, 3H, C4''-H, C2''-H), 4.84 (s, 1H, C1'-H_2), 4.82 (s, 1H, C1'-H_2), 3.58 (t, *J* = 6.0, 1H, C3-H), 3.39-3.33 (m, 2H, C5-H_2), 3.28 (s, 3H, OCH_3), 3.21 (s, 3H, OCH_3), 2.29-2.19 (m, 1H, C4-H_2), 2.12-1.94 (m, 2H, C3'-H_2), 1.69-1.63 (m, 1H, C4-

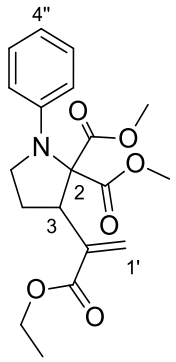
$\underline{H}_2$), 0.94 (t, *J* = 7.4, 3H, C4'-$\underline{H}_3$); **NMR (C_6D_6)** δ_C 170.3 (Q, $\underline{C}$=O), 168.1 (Q, $\underline{C}$=O), 148.2 (Q, $\underline{C}$2'), 145.6 (Q, $\underline{C}$1''), 128.8 ($\underline{C}$3''), 117.7 ($\underline{C}$4''), 113.6 ($\underline{C}$2''), 109.9 (CH_2, $\underline{C}$1'), 76.0 (Q, $\underline{C}$2), 55.1 ($\underline{C}$3), 51.9 (O$\underline{C}H_3$), 51.4 (O$\underline{C}H_3$), 49.9 (CH_2, $\underline{C}$5), 28.7 (CH_2, $\underline{C}$3'), 27.2 (CH_2, $\underline{C}$4), 11.9 ($\underline{C}$4'); **(ATR, cm^{-1})** 1737 (C=O), 1599 (C=C), 1505 (Ar C=C)**; m/z (ES^+)** calculated for $C_{18}H_{24}NO_4$ $[M + H]^+$; 318.1700, found 318.1699 (-0.31 ppm).

(227h) Dimethyl 1-Phenyl-3-(1-phenylethenyl)pyrrolidine-2,2-dicarboxylate



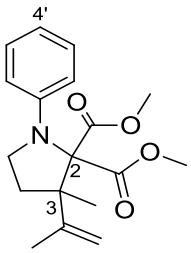
Prepared from **(223h)** dimethyl 2-(3-phenyl-5,6-tetrahydropyridin-1(2H)-yl)malonate (0.142 g, 0.49 mmol). The resulting crude oil was subjected to flash column chromatography (10% ethyl acetate in petroleum ether) to yield a yellow oil (0.070 g, 58 %); $\mathbf{R_f}$ 0.18 (10 % Ethyl acetate in petroleum ether); **^{1}H NMR ($CDCl_3$)** δ_H 7.35-7.26 (m, 5H, 5 x Ar''-$\underline{H}$), 7.17 (t, *J* = 7.8, 2H, C3'-$\underline{H}$), 6.73 (t, *J* = 7.8, 1H, C4'-$\underline{H}$), 6.52 (d, J = 7.8, 2H, C2'-$\underline{H}$), 5.33 (s, 1H, C=C$\underline{H}_2$), 5.20 (s, 1H, C=C$\underline{H}_2$), 4.18 (dd, *J* = 10.6, 6.8, 1H, C3-$\underline{H}$), 3.81 (apparent q, *J* = 8.2, 1H, C5-$\underline{H}_2$), 3.73 (dt, *J* = 8.0, 2.8, 1H, C5-$\underline{H}_2$), 3.66 (s, 3H, OC$\underline{H}_3$), 3.31 (s, 3H, OC$\underline{H}_3$), 2.40-2.33 (m, 2H, C4-$\underline{H}_2$); **^{13}C NMR ($CDCl_3$)** δ_C 170.1 (Q, $\underline{C}$=O), 168.4 (Q, $\underline{C}$=O), 146.5 (Q, $\underline{C}$=CH_2), 145.4 (Q, $\underline{C}$1'), 141.8 (Q, $\underline{C}$1''), 128.8 ($\underline{C}$3'), 128.1 ($\underline{C}$3''), 127.7 ($\underline{C}$4''), 127.1 ($\underline{C}$2''), 117.6 ($\underline{C}$4'), 115.5 (CH_2, C=$\underline{C}H_2$), 113.1 ($\underline{C}$2'), 76.2 (Q, $\underline{C}$2), 54.2 ($\underline{C}$3), 52.5 (O$\underline{C}H_3$), 52.1 (O$\underline{C}H_3$), 48.9 (CH_2, $\underline{C}$5), 29.0 (CH_2, $\underline{C}$4); ν_{max} **(ATR, cm^{-1})** 1731 (C=O), 1599 (C=C), 1505 (Ar-C-C); **m/z (ES^+)** calculated for $C_{22}H_{24}NO_4$ $[M + H]^+$; 366.1700, found 366.1693 (-1.91 ppm).

(227i) Dimethyl 3-(3-ethoxy-3-oxoprop-1-en-2-yl)-1-phenylpyrrolidine-2,2-dicarboxylate



Prepared from **(223i)** dimethyl 2-(3-(ethoxycarbonyl)-5,6-tetrahydropyridin-1(2H)-yl)malonate (0.140 g, 0.49 mmol) according to the general procedure above. The resulting crude oil was subjected to flash column chromatography (10% ethyl acetate in petroleum ether) to yield a pale yellow oil (0.044 g, 37 %); **R_f** 0.22 (10 % ethyl acetate in petroleum ether); **^{1}H NMR ($CDCl_3$)** δ_H 7.17 (t, *J* = 7.8, 2H, C3''-H), 6.74 (t, *J* = 7.8, 1H, C4''-H), 6.55 (t, *J* = 7.8, 2H, C2''-H), 6.33 (s, 1H, C1'-H_2), 5.63 (s, 1H, C1'-H_2), 4.30-4.23 (m, 1H, C3-H), 4.22-4.16 (m, 2H, OCH_2CH_3), 3.70-3.66 (m, 2H, C5-H_2), 3.65 (s, 3H, OCH_3), 3.62 (s, 3H, OCH_3), 2.31-2.20 (m, 1H, C4-H_2), 2.14-2.08 (m, 1H, C4-H_2), 1.32 (t, *J* = 7.2, 3H, OCH_2CH_3); **^{13}C NMR ($CDCl_3$)** δ_C 169.7 (Q, C=O), 168.7 (Q, C=O), 166.3 (Q, C=O), 145.0 (Q, C1''), 138.5 (Q, C2'), 128.8 (C3''), 125.1 (CH_2, C1'), 117.9 (C4''), 113.5 (C2''), 76.0 (Q, C2), 61.1 (CH_2, OCH_2CH_3), 52.6 (OCH_3), 52.2 (OCH_3), 50.0 (C3), 48.4 (CH_2, C5), 27.3 (CH_2, C4), 14.1 (OCH_2CH_3); ν_{max} **(ATR, cm^{-1})** 1760 (C=O), 1724 (C=O), 1713 (C=O), 1633 (C=C), 1599 (Ar-C-C);

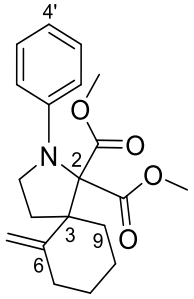
(227j) Dimethyl 3-methyl-1-phenyl-3-(prop-1-en-2-yl)pyrrolidine-2,2-dicarboxylate



Prepared from **(223j)** dimethyl 2-(3,4-dimethyl-5,6-dihydropyridin-1(2H)-yl)malonate (118 mg) according to the general procedure above. The resulting crude oil was subjected to flash column chromatography (10% ethyl acetate in petroleum ether) to yield a yellow oil (0.100 g, 95 %); **Rf:** 0.20 (10 % ethyl acetate in petroleum ether); **^{1}H NMR ($CDCl_3$)** δ_H 7.16 (t, *J* = 7.6, 2H, C3'-H), 6.71 (t, *J* = 7.6, 1H, C4'-H), 6.43 (d, *J* = 7.6, 2H, C2'-H), 5.00 (s, 1H,

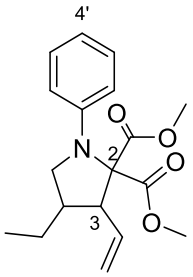
C=C$\underline{H}_2$), 4.94 (s, 1H, C=C$\underline{H}_2$), 3.78-3.75 (m, 1H, C5-$\underline{H}_2$), 3.68 (apparent q, *J* = 8.0, 1H, C5-$\underline{H}_2$), 3.64 (s, 3H, OC$\underline{H}_3$), 3.61 (s, 3H, OC$\underline{H}_3$), 2.57-2.52 (m, 1H, C4-$\underline{H}_2$), 1.95-1.92 (m, 1H, C4-$\underline{H}_2$), 1.91 (s, 3H, C$\underline{H}_3$), 1.32 (s, 3H, C3-C$\underline{H}_3$); **^{13}C NMR ($CDCl_3$)** δ_C 169.7 (Q, $\underline{C}$=O), 169.0 (Q, $\underline{C}$=O), 147.5 (Q, $\underline{C}$=CH_2), 146.3 (Q, $\underline{C}$1'), 128.7 ($\underline{C}$3'), 117.2 ($\underline{C}$4'), 113.6 (CH_2, C=$\underline{C}H_2$), 113.1 ($\underline{C}$2'), 79.7 (Q, $\underline{C}$2), 56.1 (Q, $\underline{C}$3), 52.3 (O$\underline{C}H_3$), 52.2 (O$\underline{C}H_3$), 49.2 (CH_2, $\underline{C}$5), 35.3 (CH_2, $\underline{C}$4), 23.6 (C3-$\underline{C}H_3$), 21.2 ($\underline{C}H_3$)**; ν_{max} (ATR, cm^{-1})** 1724.8 (C=O), 1598.5 (C=C) 1505.3 (Ar-C=C); **m/z (ES$^+$)** calculated for $C_{18}H_{24}NO_4$ $[M + H]^+$; 318.1700, found 318.1695 (-1.57 ppm).

(227k) Dimethyl 6-methylene-2-phenyl-2-azaspiro[4.5]decane-1,1-dicarboxylate



Prepared from **(223k)** dimethyl 2-(3,4,5,6,7,8-hexahydroisoquinolin-2(1H)-yl)malonate (0.130 g) according to the general procedure above. The resulting crude oil was subjected to flash column chromatography (10% ethyl acetate in petroleum ether) to yield a yellow oil (0.113 g, 100 %); **R_f** 0.29 (10 % ethyl acetate in petroleum ether); **^{1}H NMR (C_6D_6)** δ_H 7.16 (t, *J* = 7.8, 2H, C4'-$\underline{H}$), 6.74 (t, *J* = 7.8, 1H, C3'-$\underline{H}$), 6.66 (d, *J* = 7.8, 2H, C2'-H), 5.06 (s, 1H, C6=C$\underline{H}_2$), 4.78 (s, 1H, C6=C$\underline{H}_2$), 3.55 (apparent q, *J* = 7.6, 1H, C5-$\underline{H}$), 3.46 (ddd, *J* = 8.2, 8.2, 5.2, 1H, C5-$\underline{H}$), 3.30 (s, 3H, OC$\underline{H}_3$), 3.21 (s, 3H, OC$\underline{H}_3$), 2.45-2.35 (m, 2H, C7-$\underline{H}$, C10-$\underline{H}$), 2.12-2.04 (m, 2H, C7-$\underline{H}$, C4-$\underline{H}$), 1.82-1.76 (m,1H, C4-$\underline{H}$), 1.58-1.30 (m, 4H, 2 x C8-$\underline{H}$, C9-$\underline{H}$, C10-$\underline{H}$), 1.28-1.20 (m, 1H, C9-$\underline{H}$); **^{13}C NMR (C_6D_6)** δ_C 170.0 (Q, $\underline{C}$=O), 168.7 (Q, $\underline{C}$=O, 148.9 (Q, $\underline{C}$6), 147.1 (Q, $\underline{C}$1'), 128.4 ($\underline{C}$3'), 117.4 ($\underline{C}$4'), 114.1 ($\underline{C}$2'), 109.9 (CH_2, C6=$\underline{C}H_2$), 79.6 (Q, $\underline{C}$1), 56.9 (Q, $\underline{C}$5), 51.6 (OCH_3), 51.3 (O$\underline{C}H_3$), 49.4 (CH_2, $\underline{C}$3), 34.2 (CH_2, $\underline{C}$4), 34.1 (CH_2, $\underline{C}$7), 34.0 (CH_2, $\underline{C}$8), 26.1 (CH_2, $\underline{C}$10), 22.1 (CH_2, $\underline{C}$9); **ν_{max} (ATR, cm^{-1})** 1761 (C=O), 1597 (C=C), 1504 (Ar-C=C); **m/z (ES$^+$)** calculated for $C_{20}H_{26}NO_4$ [M + H]; 344.1856, found 344.1861.

(228) Dimethyl 4-ethyl-1-phenyl-3-ethenylpyrrolidine-2,2-dicarboxylate



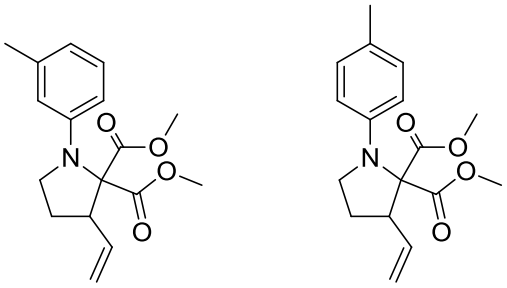
Prepared from **(226)** dimethyl 2-(5-ethyl-5,6-tetrahydropyridin-1(2H)-yl)malonate (0.111 g, 0.49 mmol) according to the general procedure above. The resulting crude oil was subjected to column chromatography (10% ethyl acetate in pet ether) to yield a yellow oil (0.010 g, 10 %); $\mathbf{R_f}$ 0.21 (10 % ethyl acetate in petroleum ether); **^{1}H NMR ($CDCl_3$)** δ_H 7.18 (t, *J* = 7.8, 2H, C3'-H), 6.73 (t, *J* = 7.8, 1H, C4'-H), 6.54 (d, *J* = 7.8, 2H, C2'-H), 5.69 (apparent dt, *J* = 17.0, 9.2, 1H, CH=CH_2), 5.26 (d, *J* = 9.2, 1H, CH=CH_2), 5.20 (d, *J* = 17.0, 1H, CH=CH_2), 3.81 (t, *J* = 8.8, 1H, C5-H_2), 3.72 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.33 (t, *J* = 8.8, 1H, C5-H_2), 2.92 (dd, *J* = 11.2, 9.2, 1H, C3-H), 2.42-2.32 (m, 1H, C4-H), 1.72-1.62 (m, 1H, C4-C$H_2$$CH_3$), 1.31-1.20 (m, 1H, C4-C$H_2$$CH_3$), 1.00 (t, *J* = 7.4, C4-CH_2CH_3); **NMR (C_6D_6)** δ_C 169.9 (Q, C=O), 169.3 (Q, C=O), 145.3 (Q, C1'), 133.6 (CH=CH_2), 128.8 (C3), 120.3 (CH_2, CH=CH_2), 117.4 (C4'), 113.0 (C2'), 60.3 (C3), 55.0 (CH_2, C5), 52.7 (OCH_3), 52.4 (OCH_3), 42.1 (C4), 24.7 (CH_2, C4-$CH_2$$CH_3$), 12.5 (C4-$CH_2CH_3$); **(ATR, cm^{-1})** 1757 (C=O), 1599 (C=C), 1507 (Ar C=C)**; m/z (ES$^+$)** calculated for $C_{18}H_{24}NO_4$ $[M + H]^+$; 318.1700, found 318.1697 (-0.94 ppm).

General Procedure for the Arylative Rearrangement of Substiuted Tetrahydropyridine With Asymmetric Substituted Aryne precursors

To a stirred solution of dimethyl 2-(5,6-tetrahydropyridin-1(2H)-yl)malonate (0.104 g, 0.49 mmol) and the substituted aryne precursor (0.33 mmol) in dry acetonitrile (10 mL) was added dropwise over two hours TBAF (1M sln. in THF, 0.94 mL, 0.94 mmol). After complete addition, the mixture was passed through a silica plug and washed with ethyl acetate (2 x 25 mL). The resulting solution was concentrated under reduced pressure to yield a crude oil which was subjected to flash column chromatography to yield the title compound.

(250A) Dimethyl 1-(3-methylphenyl)-3-ethenylpyrrolidine-2,2-dicarboxylate

(250B) Dimethyl 1-(4-methylphenyl)-3-ethenylpyrrolidine-2,2-dicarboxylate

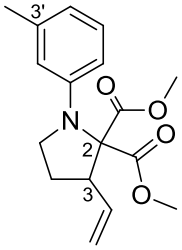


Prepared from **(223a)** dimethyl 2-(5,6-dihydropyridin-1(2H)-yl)malonate (0.104 g) and **(224)** 2-trimethylsilyl-4-methylphenyltrifluoromethylsulfonate (0.09 mL) according to the general procedure above. The resulting crude oil was subjected to flash column chromatography (10% ethyl acetate in petroleum ether) to yield a yellow oil (0.081 g, 81 %) (55:45 ratio *m*:*p*); **Rf:** 0.16 (10 % ethyl acetate in petroleum ether); **m/z (ES$^+$)** calculated for $C_{17}H_{21}NO_4$ $[M+H]^+$; 304.1543, found 304.1552 (2.96 ppm);

m: **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H 7.05 (t, *J* = 7.8, 1H, C5'-H), 6.56 (d, *J* = 7.8, 1H, C4'-H), 6.39 (s, 1H, C2'-H), 6.34 (d, *J* = 7.8, 1H, C6'-H), 5.89 (ddd, *J* = 17.2, 10.2, 7.2, 1H, CH=CH_2), 5.20 (d, *J* = 10.2, 1H, CH=CH_2), 5.16 (d, *J* = 17.4, 1H, CH=CH_2), 3.72 (s, 3H, OCH_3), 3.70 (m, 2H, C5-H_2), 3.67 (s, 3H, OCH_3), 3.38 (apparent q, *J* = 7.2, 1H, C3-H), 2.28 (s, 3H, C3'-CH_3), 2.19 (t, *J* = 7.2, 2H, C4-H_2); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C 170.2 (Q, C=O), 169.2 (Q, C=O), 145.5 (Q, C1'), 138.5 (Q, C3'), 134.5 (CH=CH2), 128.6 (C5'), 118.5 (C4'), 118.1 (CH_2, CH=CH_2), 113.9 (C2'), 110.5 (C6'), 75.8 (Q, C2), 54.1 (C3), 52.8 (OCH_3), 52.4 (OCH_3), 49.3 (CH_2, C5), 28.6 (CH_2, C4), 21.9 (C3'-CH_3);

p: **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H 6.99 (d, *J* = 9.0, 2H, C3'-H), 6.48 (d, *J* = 9.0, 2H, C2'-H), 5.89 (ddd, *J* = 17.2, 10.2, 7.2, 1H, CH=CH_2), 5.20 (d, *J* = 10.2, 1H, CH=CH_2), 5.16 (d, *J* = 17.4, 1H, CH=CH_2), 3.72 (s, 3H, OCH_3), 3.70 (m, 2H, C5-H_2), 3.67 (s, 3H, OCH_3), 3.38 (apparent q, *J* = 7.2, 1H, C3-H), 2.23 (s, 3H, C3'-CH_3), 2.19 (t, *J* = 7.2, 2H, C4-H_2); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C 170.2 (Q, C=O), 169.2 (Q, C=O), 145.5 (Q, C1'), 138.5 (Q, C3'), 134.5 (CH=CH_2),129.4 (C2'), 118.1 (CH_2, CH=CH_2), 113.3 (C3'), 75.8 (Q, C2), 54.1 (C3), 52.8 (OCH_3), 52.4 (OCH_3), 49.3 (CH_2, C5), 28.6 (CH_2, C4), 20.5 (C3'-CH_3);

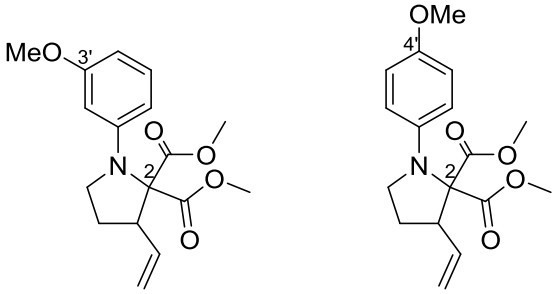
(250A) Dimethyl 1-(3-methylphenyl)-3-ethenylpyrrolidine-2,2-dicarboxylate



Prepared from **(223a)** dimethyl 2-(5,6-dihydropyridin-1(2H)-yl)malonate (0.104 g) and **(243)** 2-trimethylsilyl-6-methylphenyltrifluoromethylsulfonate (0.09 mL) according to the general procedure above. The resulting crude oil was subjected to flash column chromatography (10% ethyl acetate in petroleum ether) to yield a yellow oil (0.075 g, 75 %); **Rf:** 0.16 (10 % ethyl acetate in petroleum ether); NMR spectra and mass are consistent with those previously reported.

(252A) Dimethyl 1-(3-methoxyphenyl)-3-ethenylpyrrolidine-2,2-dicarboxylate

(252B) Dimethyl 1-(4-methoxyphenyl)-3-ethenylpyrrolidine-2,2-dicarboxylate



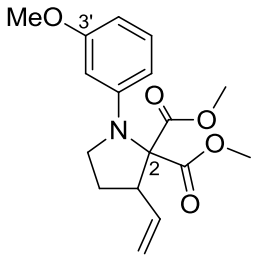
Prepared from **(223a)** dimethyl 2-(5,6-dihydropyridin-1(2H)-yl)malonate (0.104 g) and **(246)** 4-methoxyl-2-trimethylsilylphenyltrifluoromethylsulfonate (0.09 mL) according to the general procedure above. The resulting crude oil was subjected to flash column chromatography (10% ethyl acetate in petroleum ether) to yield inseparable isomers as an oil (0.065 g, 65 %) (45:55 ratio *m*:*p*); **Rf:** 0.13 (10% ethyl acetate in petroleum ether); **m/z (ES+)** calculated for $C_{18}H_{23}NO_5$ [M + H^+]; 320.1492, found 320.1491 (0.38 ppm);

m: **^{1}H NMR ($CDCl_3$)** δ 7.07 (t, *J* = 8.2, 1H, C5'-H), 6.31 (d, *J* = 8.2, 1H, C6'-H), 6.15-6.13 (m, 2H, C2'-H, C4'-H), 5.88 (ddd, *J* = 17.4, 9.8, 7.6, 1H, CH=CH_2), 5.21-5.15 (m, 2H, CH=CH_2), 3.74 (s, 3H, CO_2CH_3), 3.71 (s, 3H, OCH_3), 3.70-3.61 (m, 2H, C5-H), 3.68 (s, 3H, CO_2CH_3), 3.45-3.35 (m, 1H, C3-H), 2.22-2.16 (m, 2H, C4-H); **^{13}C NMR ($CDCl_3$)** δ_C 170.2 (Q, C=O), 169.4 (Q, C=O), 160.3 (Q, C3'), 146.9 (Q, C1'), 134.8 (CH=CH_2), 129.4 (C5') 118.1 (CH_2,

CH=CH$_2$), 106.4 (C4'), 102.6 (C6'), 99.9 (C2'), 76.3 (Q, C2), 55.7 (OCH$_3$), 54.1 (C3), 52.8 (OCH$_3$), 52.4 (OCH$_3$), 49.7 (CH$_2$, C5), 28.7(CH$_2$, C4).

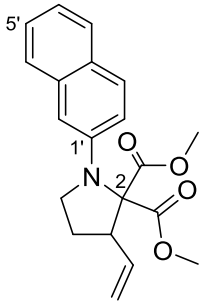
p: **^{1}H NMR (CDCl$_3$)** δ 6.78 (d, *J* = 9.0, 2H, C3'-H) 6.54 (d, *J* = 9.0, 2H, C2'-H) 5.88 (ddd, *J* = 17.4, 9.8, 7.6, 1H, CH=CH$_2$), 5.21-5.15 (m, 2H, CH=CH$_2$), 3.75 (s, 3H, OCH$_3$), 3.74 (s, 3H, CO$_2$CH$_3$), 3.70-3.61 (m, 2H, C5-H), 3.68 (s, 3H, CO$_2$CH$_3$), 3.45-3.35 (m, 1H, C3-H), 2.22-2.16 (m, 2H, C4-H); **^{13}C NMR (CDCl$_3$)** δ_C 170.1 (Q, C=O), 169.0 (Q, C=O), 151.9 (Q, C4'), 139.9 (Q, C1'), 134.4 (CH=CH$_2$), 117.9 (CH$_2$, CH=CH$_2$), 114.6 (C2'), 114.3 (C3'), 75.8 (Q, C2), 55.1 (OCH$_3$), 53.8 (C3), 52.7 (OCH$_3$), 52.3 (OCH$_3$), 49.3 (CH$_2$, C5), 28.6 (CH$_2$, C4).

(252A) Dimethyl 1-(3-methoxyphenyl)-3-ethenylpyrrolidine-2,2-dicarboxylate



Prepared from **(223a)** dimethyl 2-(5,6-dihydropyridin-1(2H)-yl)malonate (0.104 g) and **(245)** 2-methoxy-6-(trimethylsilyl)phenyl trifluoromethanesulfonate (0.09 mL) according to the general procedure above. The resulting crude oil was subjected to flash column chromatography (5% ethyl acetate in petroleum ether) to yield a colourless oil (0.077 g, 77 %); **Rf:** 0.11 (10 % ethyl acetate in petroleum ether); NMR spectra and mass are consistent with those previously reported.

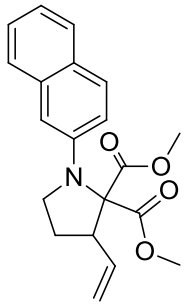
(253) Dimethyl 1-(Naphthalen-2-yl)-3-ethenylpyrrolidine-2,2-dicarboxylate



Prepared from **(223a)** dimethyl 2-(5,6-dihydropyridin-1(2H)-yl)malonate (0.104 g, 0.49 mmol) and **(247)** 1-trimethylsilyl-2-naphthyltrifluoromethylsulfonate (0.09 mL, 0.33 mmol) according to the general procedure above. The resulting crude oil was subjected to

flash column chromatography (10% ethyl acetate in petroleum ether) to yield a yellow oil (0.058 g, 52 %); **^{1}H NMR ($CDCl_3$)** δ_H 7.67 (d, *J* = 8.6, 1H, (C4'-H), 7.63 (d, *J* = 8.6, 2H, C9'-H, C10'-H), 7.35 (t, *J* = 8.6 Hz, 1H, C5'-H), 7.20 (t, *J* = 8.6, 1H, C6'-H), 6.89 (d, J = 8.6, 1H, C7'-H), 6.84 (s, 1H, C2'-H), 5.93 (ddd, *J* = 17.2, 10.2, 7.8, 1H, CH=CH_2), 5.22 (d, *J* = 17.2, 1H, CH=CH_2), 5.20 (d, *J* = 10.2, 1H, CH=CH_2), 3.83-3.77 (m, 2H, C5-H_2), 3.72 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.46 (apparent q, J = 7.8, 1H, C3-H), 2.27-2.21 (m, 2H, C4-H_2), **^{13}C NMR ($CDCl_3$)** δ_C 170.1 (Q, C=O), 169.2 (Q, C=O), 143.5 (Q, C1'), 134.7 (Q, C3'), 134.5 (CH=CH_2), 128.2 (C9'), 127.4 (C4'), 127.1 (Q, C8'), 126.3 (C10'), 126.1 (C5'), 122.3 (C6'), 118.1 (CH_2, CH=CH_2), 116.3 (C7'), 107.5 (C2'), 76.0 (Q, C2), 54.1 (C3), 52.8 (OCH_3), 52.4 (OCH_3), 49.5 (CH_2, C5), 28.6 (C4); **m/z (ES$^+$)** calculated for $C_{20}H_{21}NO_4$ [M + H$^+$]; 340.1543, found 340.1545 (0.68 ppm).

(253) Dimethyl 1-(Naphthalen-2-yl)-3-ethenylpyrrolidine-2,2-dicarboxylate

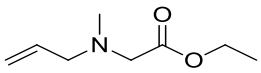


Prepared from **(223a)** dimethyl 2-(5,6-dihydropyridin-1(2H)-yl)malonate (0.104 g) and **(248)** 3-trimethylsilyl-2-naphthyltrifluoromethylsulfonate (0.09 mL) according to the general procedure above. The resulting crude oil was subjected to flash column chromatography (10% ethyl acetate in petroleum ether) to yield a yellow oil (0.045 g, 40 %); NMR spectra and mass are consistent with those previously reported.

General Procedure for Preparation of Substituted N-allyl Sarcosine Ethyl Esters

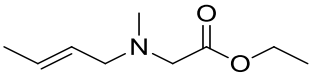
To a vigorously stirred suspension of sarcosine ethyl ester hydrochloride (1.69 g, 11.03 mmol) in DCM (25 mL) was added triethylamine (3.6 mL, 25.89 mmol). After formation of a colourless precipitate, toluene (55 mL), the stated allyl bromide (13.5 mmol) and triethylamine (2.05 mL, 14.7 mmol) were added sequentially and the mixture was heated to reflux for 4 hours. After allowing to cool, the reaction mixture was washed with water (100 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to yield the a crude oil, which was subjected to column chromatography to yield the title compound.

(265a) Ethyl 2-(allyl(methyl)amino)acetate



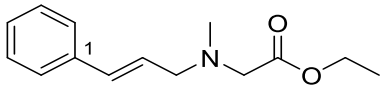
Prepared from allyl bromide (1.16 mL, 13.5 mmol) according to the general procedure above. The resulting crude oil was subjected to flash column chromatography (20% ethyl acetate in petroleum ether) to yield a pale yellow oil (0.65 g, 38 %); **R_f**: 0.08 (10 % ethyl acetate in petroleum ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H 5.79 (ddt, *J* = 17.4, 10.4, 6.6, 1H, N-CH_2C<u>H</u>=CH_2), 5.14 (d, *J* = 17.4, 1H, N-CH_2CH=C<u>H</u>$_2$), 5.08 (d, *J* = 10.4, 1H, N-CH_2CH=C<u>H</u>$_2$), 4.10 (q, *J* = 7.2, 2H, OC<u>H</u>$_2$$CH_3$), 3.15 (s, 2H, NC<u>H</u>$_2$$CO_2$Et), 3.06 (d, *J* = 6.6, 2H, N-C<u>H</u>$_2$CH=CH_2), 2.29 (s, 3H, N-C<u>H</u>$_3$), 1.19 (t, *J* = 7.2, 3H, OCH_2C<u>H</u>$_3$); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C 170.7 (Q, C=O), 135.0 (NCH_2<u>C</u>H=CH_2), 118.1 (CH_2, NCH_2CH=<u>C</u>H_2) , 60.3 (CH_2, N<u>C</u>H_2C=O), 60.1 (CH_2, O<u>C</u>$H_2$$CH_3$), 57.4 ($CH_2$, N<u>C</u>$H_2$CH=$CH_2$), 42.2 (N<u>C</u>$H_3$), 14.1 ($OCH_2$<u>C</u>$H_3$); ν_{max} **(ATR, cm^{-1})**; 1732 (C=O); **m/z (ES$^+$)** calculated for $C_8H_{16}NO_2$ $[M + H]^+$; 158.1176, found 158.1169 (-4.43 ppm).

(265b) (*E*)-Ethyl 2-(but-2-en-1-yl(methyl)amino)acetate



Prepared from crotyl bromide (1.39 mL, 13.5 mmol) according to the general procedure above. The resulting crude oil was subjected to flash column chromatography (20% ethyl acetate in petroleum ether) to yield a pale brown oil (0.46 g, 27 %), 1:4 *cis:trans*; **R_f:** 0.13 (10 % ethyl acetate in petroleum ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H 5.52 (m, 2H, 2 x C<u>H</u>=C<u>H</u>), 4.14 (q, *J* = 7.0, 2H, OC<u>H</u>$_2$$CH_3$), 3.17 (s, 2H, NC<u>H</u>$_2$C=O), 3.01 (d, *J* = 6.5 Hz, 2H, NC<u>H</u>$_2$CH=CH), 2.30 (s, 3H, NC<u>H</u>$_3$), 1.65 (d, *J* = 6.0, 3H, CH=CHC<u>H</u>$_3$), 1.24 (t, *J* = 7.0, 3H, OCH_2C<u>H</u>$_3$); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C 171.1 (Q, <u>C</u>=O), 129.5 (<u>C</u>=C), 127.7 (C=<u>C</u>), 60.4 (CH_2, O<u>C</u>$H_2$$CH_3$), 59.5 ($CH_2$, N<u>C</u>$H_2$CH=CH), 57.6 ($CH_2$, N<u>C</u>$H_2$C=O), 42.5 (N<u>C</u>$H_3$), 17.8 (CH=CH<u>C</u>$H_3$), 14.2 ($OCH_2$<u>C</u>$H_3$); ν_{max} (ATR, cm^{-1}) 1738 (C=O);

(265c) Ethyl 2-(cinnamyl(methyl)amino)acetate

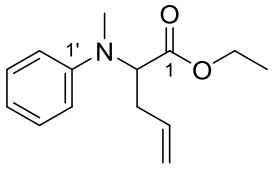


Prepared from cinnamyl bromide (1.99 mL, 13.5 mmol) according to the general procedure above. The resulting crude oil was subjected to flash column chromatography (20% ethyl acetate in petroleum ether) to yield a pale yellow oil (1.20 g, 47 %); **R_f**: 0.05 (10 % ethyl acetate in petroleum ether); **^{1}H NMR (400 MHz, CDCl3)** δ_H 7.13 (d, *J* = 7.0, 2H, C2-H), 7.04 (t, *J* = 7.0, 2H, C3-H), 6.96 (t, *J* = 7.0, 1H, C4-H), 6.28 (br d, *J* = 15.8, 1H, N-CH_2CH=CH), 6.05 (dt, *J* = 15.8, 7.0, 1H, N-CH_2CH=CH), 3.90 (q, *J* = 7.0, 2H, OCH_2CH_3), 3.03 (t, *J* = 7, N-CH_2CH=CH), 3.01 (s, 2H, NCH_2CO_2Et), 2.16 (s, 3H, N-CH_3), 0.98 (t, *J* = 7, 3H, OCH_2CH_3); **ν_{max}** (ATR, cm^{-1}) 1731 (C=O);

General Procedure for the Arylative Rearrangement of Substituted N-allyl Sarcosine Esters

To a solution of the stated allyl amine (0.49 mmol) and 2-trimethylsilylphenyl triflate (0.33 mmol, 0.08 mL) in dry acetonitrile (10 mL) was added dropwise over two hours TBAF (1M sln. in THF, 0.94 mmol, 0.94 mL). After complete addition, the mixture was passed through a silica plug and washed with ethyl acetate (2 x 25 mL). The resulting solution was concentrated under reduced pressure to yield a crude oil which was subjected to flash column chromatography to yield the title compound.

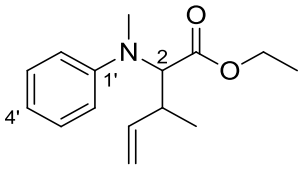
(266a) Ethyl 2-(methyl(phenyl)amino)pent-4-enoate



Prepared from **(265a)** ethyl 2-(allyl(methyl)amino)acetate (0.077 g, 0.49 mmol) according to the general procedure above. The resulting crude oil was subjected to flash column chromatography (10% ethyl acetate in petroleum ether) to yield a colourless oil (0.066 g, 86 %); **R_f**: 0.37 (10 % ethyl acetate in petroleum ether); **^{1}H NMR (CDCl3)** δ_H 7.15 (t, *J* = 7.8, 2H, C3'-H), 6.73 (d, *J* = 7.8, C2'-H), 6.67 (t, *J* = 7.8, C4'-H), 5.69 (tdd, *J* = 17.0, 10.2, 6.8, 1H, C4-H), 5.07 (d, *J* = 17.0, 1H, C4=CH_2), 4.97 (d, *J* = 10.2, 1H, C4=CH_2), 4.35 (t, *J* = 7.6, 1H, C2-H), 4.11-4.03 (m, 2H, OCH_2CH_3), 2.82 (s, 3H, N-CH_3), 2.68-2.61 (m, 1H, C3-H_2), 2.56-2.48 (m, 1H, C3-H_2), 1.14 (t, *J* = 7.2, 3H, OCH_2CH_3); **^{13}C NMR ($CDCl_3$)** δ_C 172.2 (Q, C=O), 150.1 (Q, C1'), 134.3 (C4), 129.2 (C3'), 117.65 (C4'), 117.63 (CH_2, C4=CH_2), 113.5 (C2'), 61.7 (C2), 60.8 (CH_2, OCH_2CH_3), 34.2 (CH_2, C3), 32.9 (N-CH_3), 14.3 (OCH_2CH_3); ν_{max}

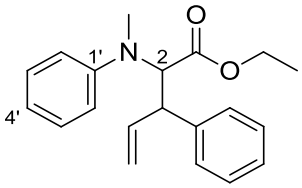
(ATR, cm^{-1}); 1729 (C=O), 1597 (C=C), 1503 (Ar-C-C); **m/z (ES$^+$)** calculated for $C_{14}H_{20}NO_2$ $[M + H]^+$; 234.1489, found 234.1487 (0.85 ppm).

(266b) Ethyl 3-methyl-2-(methyl(phenyl)amino)pent-4-enoate



Prepared from **(265b)** (*E*)-Ethyl 2-(but-2-en-1-yl(methyl)amino)acetate (0.084 g, 0.49 mmol) according to the general procedure. The resulting crude oil was subjected to preparative TLC (5% ethyl acetate in petroleum ether) to yield a colourless oil (0.081 g, 99 %); **Rf**: 0.45 (10 % ethyl acetate in petroleum ether); **^{1}H NMR (400 MHz, CDCl3)** δ_H 7.15 (t, *J* = 7.8, 2H, C3'-H), 6.76 (d, *J* = 7.8, 2H, C2'-H), 6.66 (t, *J* = 7.8, 1H, C4'-H), 5.61 (ddd, *J* = 17.2, 10.2, 7.6, 1H, C4-H), 5.03 (d, *J* = 17.2, 1H, C4=CH_2), 4.90 (d, *J* = 10.2, 1H, C4=CH_2), 4.09 (q, *J* = 7.4, 2H, OCH_2CH$_3$), 4.06-4.04 (m, 1H, C2-H), 2.93-2.88 (m, 1H, C3-H), 2.84 (s, 3H, NCH_3), 1.15 (t, *J* = 7.4, 3H, OCH$_2$CH_3), 1.00 (d, *J* = 6.6, 3H, C3-CH_3); **^{13}C NMR (100 MHz, CDCl$_3$)** δ_C 171.3 (Q, C=O), 150.2 (Q, C1'), 140.2 (C4), 129.2 (C3'), 117.4 (C4'), 115.2 (CH_2, C4=CH_2), 113.5 (C2'), 66.4 (C2), 60.6 (CH_2, OCH_2CH$_3$), 38.0 (C3), 32.6 (NCH_3), 17.7 (C3-CH_3), 14.3 (OCH$_2$CH_3); ν_{max} **(ATR, cm^{-1})** 1729 (C=O), 1598 (C=C), 1503 (Ar-C-C); **m/z (ES$^+$)** calculated for $C_{15}H_{22}NO_2$ $[M + H]^+$; 248.1645, found 248.1643 (0.81 ppm).

(266c) Ethyl 2-(methyl(phenyl)amino)-3-phenylpent-4-enoate



Prepared from **(265c)** ethyl 2-(cinnamyl(methyl)amino)acetate (0.114 g, 0.49 mmol) according to the general procedure above. The resulting crude oil was subjected to preparative TLC (5% ethyl acetate in petroleum ether) to yield a colourless oil (0.0919 g, 90 %). **R$_f$**: 0.39 (10 % ethyl acetate in petroleum ether); **^{1}H NMR (400 MHz, CDCl$_3$)** δ_H 7.35-7.26 (m, 7H, 5 x Ar-H, 2 x C3'-H), 6.96 (d, *J* = 7.6, 2H, C2'-H), 6.82 (t, *J* = 7.6, 1H, C4'-H), 6.02 (ddd, *J* = 16.8, 9.2, 8.8, 1H, C4-H), 5.11 (d, *J* = 16.8, 1H, C4=CH_2), 5.08 (d, *J* = 9.2, 1H, C4=CH_2), 4.72 (d, *J* = 11, 1H, C2-H), 4.11 (dd, *J* = 8.8, 11, 1H, C3-H), 3.91 (q, *J* = 7, 2H, OCH_2CH$_3$), 3.07 (s, 3H, N-CH_3), 0.95 (t, *J* = 7, 3H, OCH$_2$CH_3); **^{13}C NMR (100 MHz, CDCl$_3$)** δ_C 170.4 (Q, C=O), 150.4 (Q, C1'), 140.1 (Q, C3-ArC), 138.1 (C4), 129.2 (C3-ArC), 128.7

(C3-Ar<u>C</u>), 128.6 (C3-Ar<u>C</u>), 127.1 (<u>C</u>2'), 117.8 (<u>C</u>4'), 117.0 (CH_2, C4=<u>C</u>H_2), 113.7 (C3'), 65.8 (<u>C</u>2), 60.4 (CH_2, O<u>C</u>H_2CH_3), 50.3 (<u>C</u>3), 32.3 (N<u>C</u>H_3), 14.0 (OCH_2<u>C</u>H_3); ν_{max} **(ATR, cm^{-1})** 1730 (C=O), 1597 (C=C), 1503 (Ar-C-C); **m/z (ES$^+$)** calculated for $C_{20}H_{24}NO_2$ $[M + H]^+$; 310.1802, found 310.1797 (-1.61 ppm).

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