Synthesis of Heterocyclic Ring Systems via Intramolecular Diels-Alder Furan Reactions

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Abbreviations

Ac – acetyl

appt – apparent triplet

br - broad

Boc – tertiary butyloxycarbonyl

BOX - bisoxazoline

CbzCl – benzyloxy carbamate

CMD – concerted metallation deprotonation

COSY – correlation spectroscopy

d – doublet

DCC – N,N'dicyclohexylcarbodiimide

DCM – dichloromethane

DMP – Dess-Martin periodinane

DIBAL – diisobutylaluminium hydride

DKR – Dynamic kinetic resolution

DMAP – 4-dimethylaminopyridine

DMB – 2,4-dimethoxybenzyl

DMEDA - *N,N'*-dimethylethylendiamine

DMF – *N,N*-dimethylformamide

DMSO – dimethylsulfoxide

DNBA – 2,4-dinitrobenzoic acid

EDCI – 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

ELF – European Lead Factory

Et_2O – diethyl ether

Et_3N - triethylamine

FT-IR – Fourier transform-infrared

HMBC – heteronuclear multiple bond correlation

HOMO – highest occupied molecular orbital

HRMS-ESI – high resolution mass spectrometry-electron spray ionisation

IMDA – intramolecular Diels-Alder

IMDAF – intramolecular Diels-Alder Furan

IR – infrared

LUMO – lowest unoccupied molecular orbital

m – multiplet

MND – Motor Neurone Disease

mp – melting point

MS – mass spectrometry

NMO - 4-Methylmorpholine N-oxide

NMR – nuclear magnetic resonance

PCC – pyridinium chlorochromate

PD – Parkinson's Disease

Pet ether – petroleum ether 40/60

PMHS – polymethylhydrosiloxane

PPI – proton pump inhibitor

q – quartet

rf – retention factor

QPhos - 1,2,3,4,5-pentaphenyl-1′-(di-*tert*-butylphosphino)ferrocene

s - singlet

S_EAr – aromatic electrophilic substitution

t – triplet

TBAF – tetra-n-butylammonium fluoride

TBAI – tetra-n-butylammonium iodide

TBDPS – *tert*-butyldiphenylsilyl

TBS – *tert*-butyldimethylsilyl

t-Bu – *tert*-butyl

Tf – trifluoromethanesulfonyl

TFA – trifluoroacetic acid

THF – tetrahydrofuran

TLC – thin layer chromatography

TOF – time of flight

1.0 Abstract

Investigations into the use of the intramolecular Diels-Alder furan cycloaddition (IMDAF) reaction for synthesis of complex polycyclic compounds were carried out. Studies towards a synthesis of the core structure of the akuammiline alkaloid picrinine were commenced, in parallel with an investigation into the potential for asymmetric catalysis on model IMDAF substrates. IMDAF cycloadditions of ether and ester-containing substrates were attempted in the presence of Lewis acids and imidazolidinone catalysts. Substrates containing dienophiles bearing two electron-withdrawing groups underwent uncatalysed cyclisation readily, whereas unactivated substrates were unreactive even in the presence of catalysts. Studies were begun towards an alternative approach, where the reversible cycloaddition is coupled to an irreversible asymmetric transformation in a dynamic kinetic resolution process.

Copper-catalysed N-arylation of oxindole with 2-bromofuran delivered a potentially useful intermediate for the picrinine synthesis, containing diene and all necessary tether atoms for the cycloaddition. It was shown that under the reaction conditions, oxidation of the product to the corresponding isatin was a competing side reaction, an important observation for future optimisation of this reaction.

2.0 Introduction

2.1 The intramolecular Diels-Alder reaction

The Diels-Alder reaction is a powerful transformation for the formation of ring structures. In this reaction the HOMO of a conjugated diene (4π component) overlaps with the LUMO of a dienophile (2π component) e.g. an alkene or alkyne. The driving force is the formation of new, energetically favourable σ-bonds. In a normal demand reaction, the diene is electron rich and the dienophile is substituted with electron withdrawing groups to further lower the LUMO and increase orbital overlap. When the dienophile contains electron donating substituents and the diene is electron poor the reverse is true, and the overlap is between the diene LUMO and the dienophile HOMO in the inverse demand Diels-Alder reaction (figure **1**.)

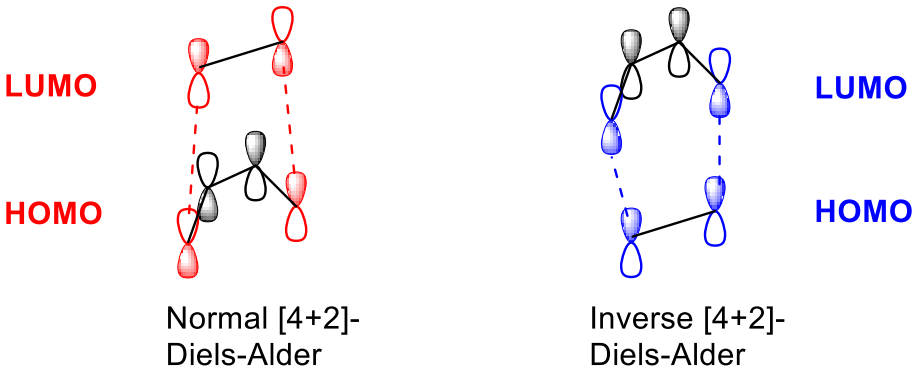
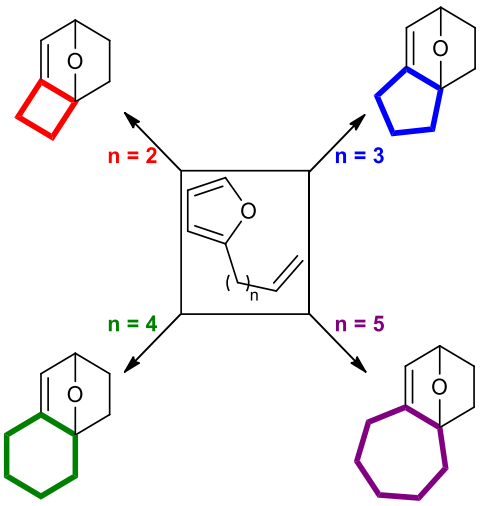


Figure 1

The intramolecular Diels-Alder (IMDA) is especially useful in natural product synthesis because multiple rings and stereocentres can be established simultaneously.[1–6] When a heteroaromatic cyclic diene is used, the Diels-Alder reaction can be utilised to construct heterocyclic rings. However, not all heteroaromatic cyclic compounds can also act as good dienes. Delocalisation of a lone pair of electrons on the oxygen atom of furan makes it an aromatic compound. Furan does have the ability to act as a diene because the high electronegativity of the oxygen atom makes the delocalisation somewhat ineffective, thus if the proposed Diels-Alder reaction is energetically favourable, the aromaticity of furan can be disrupted. This is not true for certain other similar compounds. For example, the sulphur in thiophene is much less electronegative (EN = 2.58 vs 3.44 for oxygen) so delocalisation is more efficient so its disruption has a much higher energy barrier to overcome. Similarly, breaking and reforming the double bonds of benzene is energetically unfavourable because the bonds are well stabilised through resonance – the resonance stabilisation of furan is less than half that of benzene at 67 kJ mol^{-1} vs 150 kJ mol^{-1}.

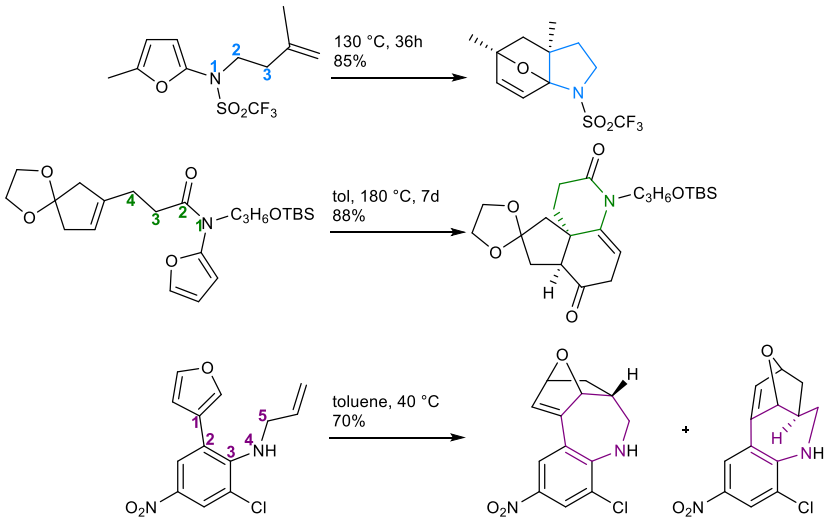
The intramolecular Diels-Alder furan (IMDAF) variant is versatile for its ability to form both stable and easily manipulated cycloadducts. As such, there are a number of variables to consider.

The IMDAF has been used to form rings of between four and seven atoms in size, as seen by the generic examples shown in scheme **1**.[7]



Scheme 1

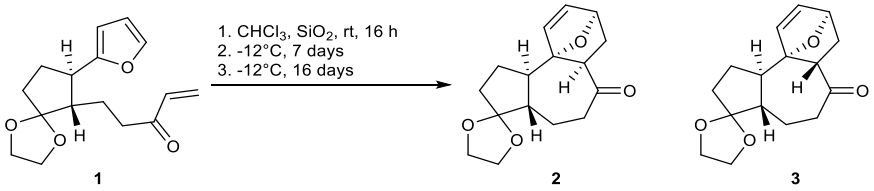
However, it is the substrates where the diene and dienophile are tethered by three or four atoms that are the most successful IMDAF substrates as these form the more thermodynamically stable five- and six- membered rings (scheme **2**).[7] A rare case of the formation of a cycloadduct where a seven-membered ring was formed was reported by Gunderson (scheme **2**)[8] in a 6:1 *endo/exo* diastereomer ratio. The *endo* product was formed in greater yield (59%) and was considerably more thermodynamically stable than its *exo* counterpart.



Scheme 2

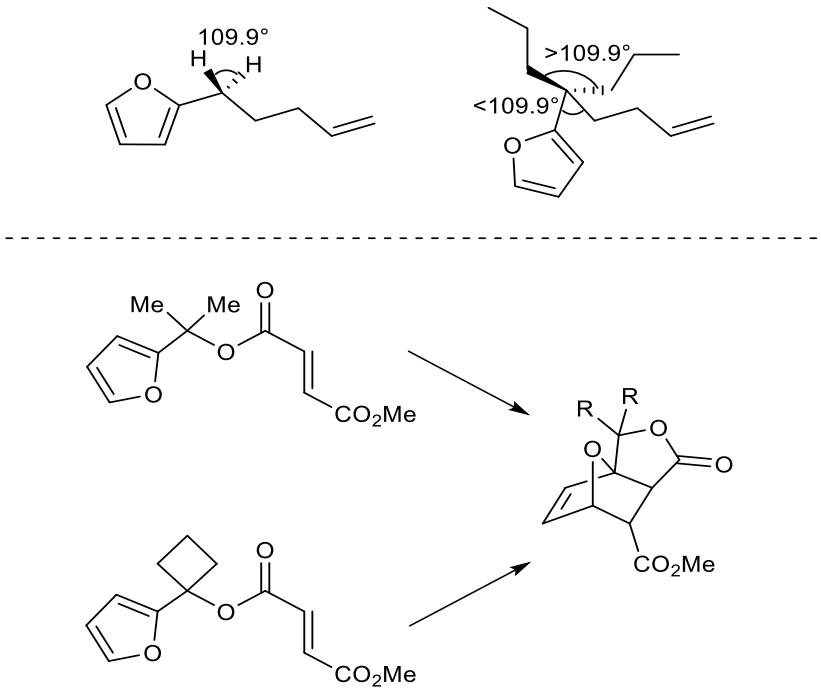
Harwood has extensively studied the formation of seven membered rings through the IMDAF reaction and found that pressures of 5-19 kbar were necessary to form the desired products in most instances.[7,9–12] At atmospheric pressure, if any product formed, both *endo*- and *exo*- seven membered cycloadducts were more labile towards cyclo-reversion than the analogues which formed a 6-atom ring. High pressures were

needed to overcome this observation. It was with some difficulty that a stable product was formed under atmospheric conditions. Stirring **1** in chloroform with 20 mass eq. of silica at room temperature for 16 hours gave a mixture of **1**, **2** and **3** in a 1:2:1 ratio. The major *endo*- component was obtained through crystallisation of the crude mixture after standing at -12 °C for seven days (scheme **3**.) When neat **1** was left to stand at -12 °C for 16 days **3** formed as the major cycloaddition product which did not re-equilibrate.



Scheme 3

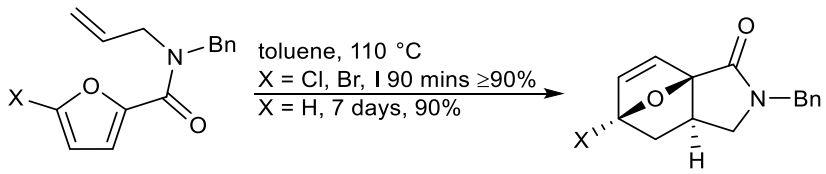
The length and nature of the tether has a significant effect on reactivity of the substrate. A heteroatom in the tether or substituents on a carbon atom can increase reactivity.[7] Several theories have been proposed to support the latter. First, the Thorpe-Ingold effect – an increase in reactivity between two parts of a molecule due to interactions between two geminal substituents. An increase in size of substituents on a tetrahedral centre causes the angle between them to increase due to steric interactions. This decreases the angle between the other two groups, bringing the diene and dienophile closer together so cyclisation is more likely (scheme **4**).



Scheme 4

Jung and Gervay[13] used substituted IMDAF substrates to discount this theory. Following Thorpe-Ingold guidelines, cyclobutyl substituted fumarate substrate, which does not promote angle compression, (scheme **4**) should cyclise at a rate on par with the angle promoting, dimethyl substituted substrate. This was not the case. Instead, dimethyl substitution allowed for a much faster cycloaddition, so they concluded there was another effect at play caused by dialkyl substitution at this central methylene. This could at least in part be the Reactive Rotamer Effect advocated by Bruice and Pandit[14] This describes how the rate of cyclisation increases upon geminal substitution because the repulsion caused by the substituents decreases the number of unprofitable rotamer distributions. Parrill and Dolata[15,16] developed the Facilitated Transition Hypothesis to explain why their rotamer calculations did not correlate with cyclisation rate. The lowest energy substrate conformers are those where substituents on adjacent carbons are staggered rather than eclipsed. In contrast, substituents are relatively eclipsed in the transition state (TS), so bond rotation must take place in order to access the TS from the ground state (GS). The fastest cyclisations will be those where the staggered GS is relatively high energy (destabilised) compared to analogous substrates, and the corresponding TS is lower in energy. Introducing substituents will destabilise both staggered and eclipsed conformations, but the effect is greater for the staggered than eclipsed.[17] The rotational barrier to the TS (and in turn the enthalpy of activation) is accordingly lower for the more substituted substrate. The fastest cyclisations are those where the ground state is destabilised, with substituents staggered along the carbon chain, and the transition state is more stabilised i.e. lower in energy. Bond rotation must occur to reach this lower energy transition state which is aided by substitution.[17] This accounts for the energy of the substrate as an average across all possible conformers, focusing on the transition state as opposed to the starting molecule.

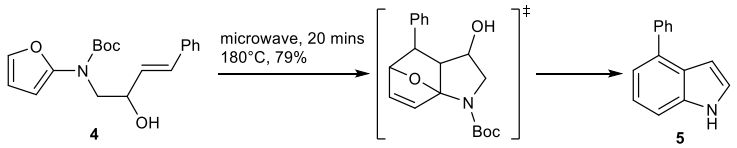
Substituents on the dienophile and the diene also have an effect on reactivity. For example, Padwa found that 5-halo substituted furans underwent IMDA reaction in 90 minutes while the unsubstituted analogue took seven days to go to completion (scheme **5**).[18] Pieniazek and Houk[19] described how halogen substitution on the furan provided higher yields and rates of reaction, including when a Diels-Alder substrate had previously been inert to cycloaddition. The exothermicities of the reactions were increased by 4-9 kcal mol^{-1} and the activation barriers decreased by 2-3 kcal mol^{-1}, indicating halogenation made the reaction more exergonic. These effects were greater when substitution occurred in the 2- rather than the 3- position.



Scheme 5

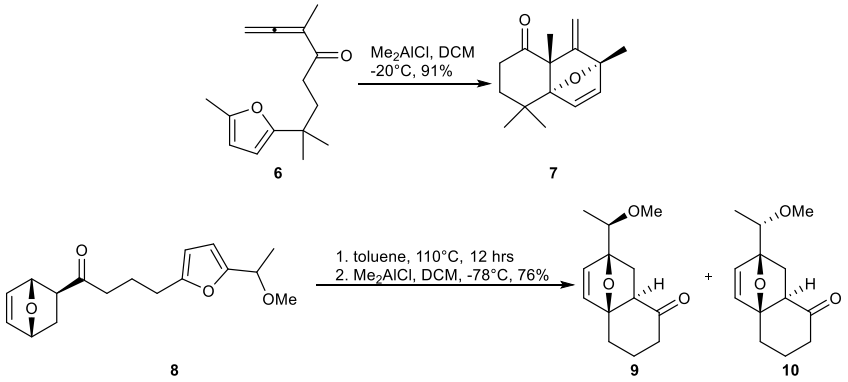
Microwave heating is a useful method to overcome the high energy barrier to the disruption to aromaticity in the IMDAF. It can decrease reaction time and allow

reactions where conventional heating leads only to decomposition products, as demonstrated by Wipf.[20] Refluxing **4** in toluene gave degraded starting material whereas 20 minutes microwave irradiation gave **5** in 79 % yield. The initial [4+2] cycloadduct underwent oxo-bridge ring cleavage, dehydration and aromatisation to give the substituted indole (scheme **6**).



Scheme 6

Lewis acid catalysis can be used both to speed up the IMDAF reaction and to control stereochemistry. Jung used a Lewis acid mediated IMDAF on allenyl ketone **6** (scheme **7**) while investigating the synthesis of AB-ring systems. **7** was formed as the single stereoisomer[21] whereas no thermal equivalent reaction was reported. Chelation of the Lewis acid to the ketone withdraws electron density from the electron rich dienophile, lowering the energy of the LUMO sufficiently for the cycloaddition to occur. Rodrigo[22] reported a retro-Diels-Alder on **8** followed by a Lewis acid catalysed IMDAF which gave a mixture of **9** and **10**.



Scheme 7

Efficient catalytic asymmetric synthesis is vital for many reasons. Manufacturing processes and use of raw materials still contribute to environmental damage if one half of the racemate is wasted. Some compounds, particularly pharmaceuticals, only have one enantiomer which has a therapeutic effect. Certain biological processes distinguish between left and the enantiomer which does not fit into its mechanism may be inactive, harmful or induce side effects when combined with bioactive version. *S*-omeprazole is an effective PPI for the treatment of gastroesophageal reflux disease, but *R*-omeprazole is ineffective. *S*-citalopram is up to 40 times more effective as a selective serotonin reuptake inhibitor than *R*-citalopram, which can in fact reduce the efficacy when administered as a racemate.[23] Both these drugs are examples of 'chiral switch' drugs, where a single enantiomer version replaced the racemate previously prescribed.[24] Thalidomide is a classic example where one enantiomer has a devastating effect. *R*-thalidomide is an effective sedative and treatment for morning

sickness, cancer and leprosy. *S*-thalidomide however is a teratogen which causes limb deformities, internal malformations and even death in the foetus or young child (figure **2**).

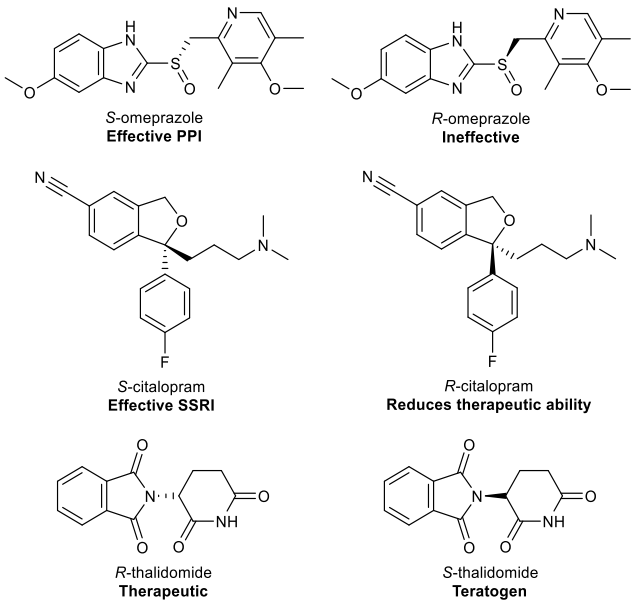


Figure 2

Separation and disposal of the surplus component of a racemate has to be factored into its synthesis. It can be difficult and expensive to separate the eutomer from the distomer as enantiomers have the same physicochemical properties, unlike enantiomers. Chiral HPLC columns are available but are costly so not viable for industry scale manufacture. Classical chiral resolution is appropriate in some instances and involves converting the racemate to diastereoisomer salts which have differing solubilities. For instance, racemic *cis*-sertraline can be resolved by complexing with *R*-mandelic acid. (1*R*, 4*R*)-sertraline.(*R*)-mandelic acid is much more soluble in ethanol than its (1*S*, 4*S*) counterpart, in a ratio of 9:1 (figure **3**).[25] It is (1*S*, 4*S*)-sertraline that is the therapeutic agent.

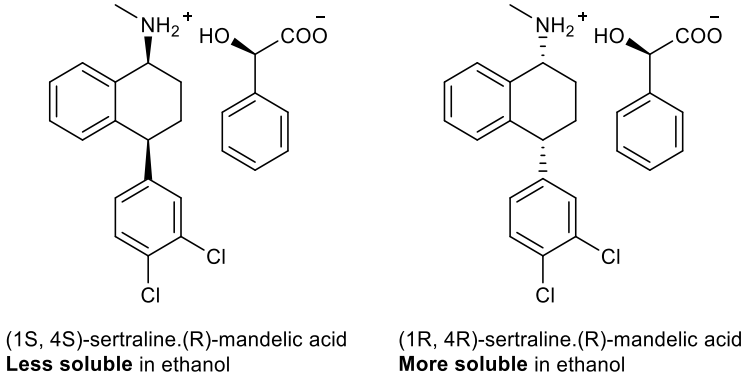
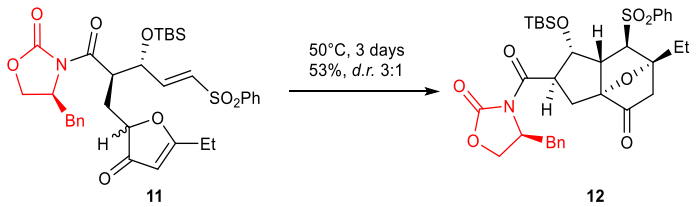


Figure 3

Asymmetric reactions can be beneficial for the synthesis of the lone bioactive enantiomer in order to avoid the necessity of using classical resolution. Chiral

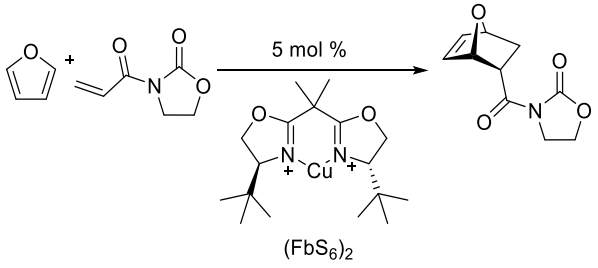
auxiliaries can be an efficient way to do this due to their often (but not always) high yielding attachment and removal. These work by installing one or more chiral centres adjacent to the reaction site. The creation of the new chiral centre proceeds through diastereomeric transition sites to give a mixture of (ideally separable) diastereomeric products. Removal of the auxiliary results in an enantiomerically enriched product. Shair reported the use of an Evans auxiliary[26] (red, scheme **8**) to induce the *endo*-selectivity in an IMDAF.[27] The bulky benzyl group on the oxazolidinone aims to block approach of the dienophile from the top face. Compound **11** converted to **12** as a 3:1 mixture of separable diastereoisomers.



11 **12**

Scheme 8

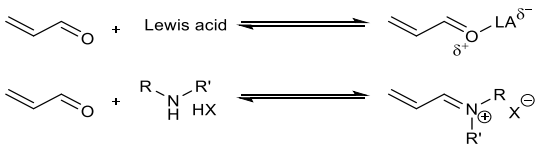
Finally, catalytic asymmetric synthesis whereby diastereomeric catalyst:substrate complexes react through energetically unequal transition states to give an unequal mixture of enantiomeric products, upon removal of the catalyst. In a successful reaction, the lowest energy pathway gives the desired enantiomer. Many examples of catalytic asymmetric synthesis exist. Evans reported an example of an intermolecular Diels-Alder reaction between 3-acryloyloxazolidin-2-one and furan. Using 5 mol % [Cu(*tert*-Bu-box)]$(SbF_6)_2$ as catalyst (scheme **9**) the reaction gave racemic diastereoisomers at standard conditions of -20°C for 24 hours. At -78°C the ratio became 80:20 endo/exo with the endo isomer having 97% *ee*.[28]



Scheme 9

2.2 MacMillan organocatalysis

Although Evans auxiliaries can be recovered and recycled, their attachment and removal require extra steps and stoichiometric amounts are required. The MacMillan group worked extensively[29–33] to develop a new series of organocatalysts which could be used sub-stoichiometrically whilst also controlling the stereochemical outcome of the reaction. MacMillan first considered the LUMO lowering ability and speed of ligand substitution for Lewis acid catalyst turnover. It seemed reasonable that the reversible formation of iminium ions from α,β-unsaturated aldehydes with amine salts might be juxtaposed with the Lewis acid mechanism[32] (scheme **10**.)



Scheme 10

After comparing the Diels-Alder yields between acrolein and cyclopentadiene, amine **17** was found to be the most efficient (99% yield, 93% *ee*) catalyst over *(S)*-Pro-OMe **13** and *(S)*-Abr-OMe **14** and C-2 symmetric **15** and **16** (figure **4**).

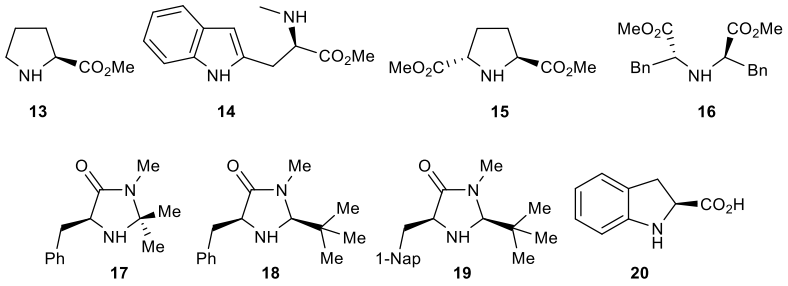
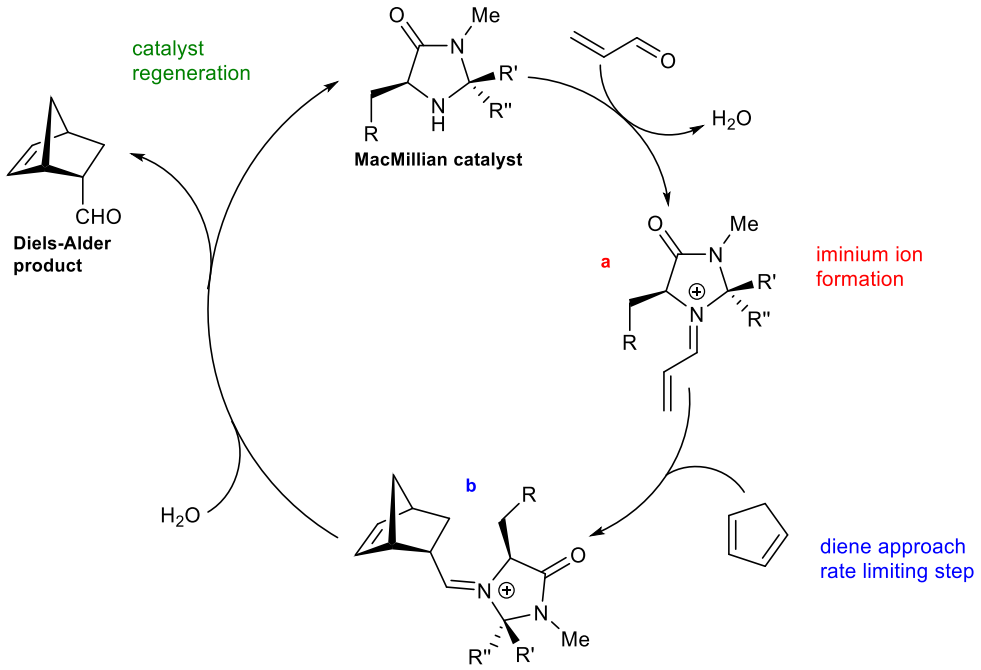


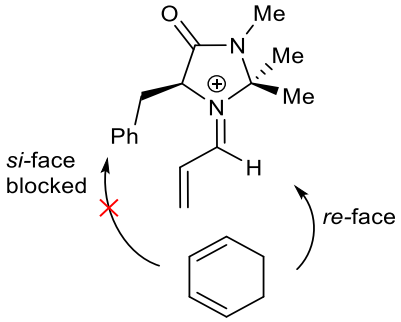
Figure 4

In the mechanistic cycle (scheme **11**) condensation of the aldehyde with the catalyst leads to the iminium species **a**. This activates the dienophile for attack by the diene to give species **b** and hydrolysis of the cycloadduct iminium ion leads to the enantioenriched product. The catalyst is simultaneously regenerated. Approach of the diene component to the iminium ion (i.e. cycloaddition) is the rate limiting step.



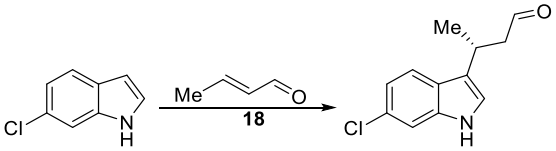
Scheme 11

Using amine **17**, the reaction tolerated both alkyl and aryl groups on the dienophile and diene and could be conducted with wet solvents under aerobic conditions. The high degree of stereocontrol was attributed to the formation of the *(E)*-iminium isomer, thus avoiding steric clash between the gem-dimethyl and vinyl groups, and the catalyst benzyl group shielding the *si*-face forcing diene approach from the *re*-face (scheme **12**.)



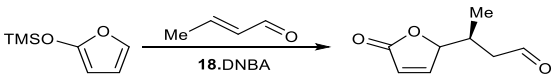
Scheme 12

Second generation catalyst **18** was developed for the Friedel-Crafts alkylation of indoles after **17** gave long reaction times and poor enantioselectivities.[30] Compound **18** gave an increase in efficient iminium ion formation as the *N*-lone pair is no longer eclipsed by the neighbouring substituent. By using a *t*-butyl group in place of the gem dimethyls, steric obstruction is increased between the substituent and the olefin so the *(E)*-iminium ion is formed preferentially. The *re*-face is also better exposed to nucleophilic attack by the indole so it approaches from the *re*-face. Up to 99% *ee* was obtained with catalyst **18** (scheme **13**.)



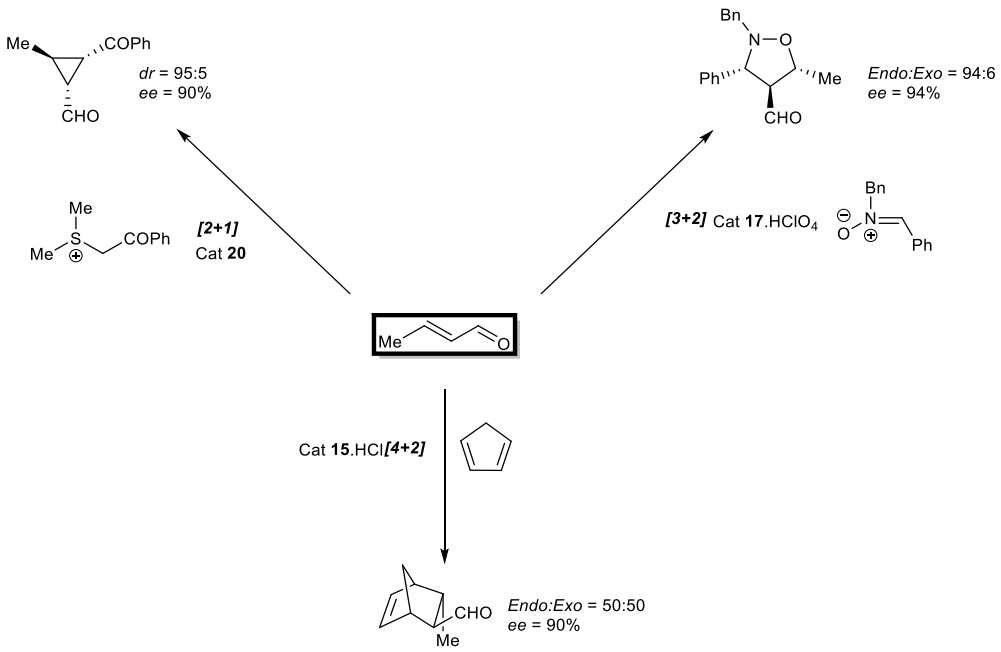
Scheme 13

Catalyst **18** (as the 2,4-dinitrobenzoic acid [DNBA] salt) was also efficiently used to induce the unprecedented 1,4-addition of siloxyfurans to crotonaldehyde (scheme **14**) when Lewis acid catalysis had been used for the analogous 1,2-addition.[34] The *t*-butyl group acted to prevent approach of the nucleophile at the aldehyde carbon for 1,2-addition.



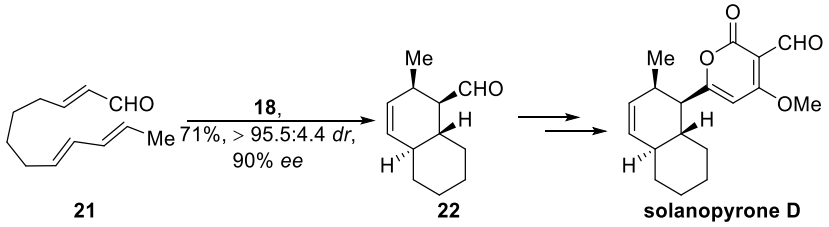
Scheme 14

After developing iminium-activation for in*ter*molecular Diels-Alder reactions, other cycloadditions were explored. Cyclopropanes and isoxaolidinones have also been prepared as summarised in scheme **15**.[32]



Scheme 15

Imidazolidinones **17**, **18** and **19** were also employed as catalysts in IMDA reactions as part of total synthesis sequences.[32] For example, using **18** in a short asymmetric synthesis of solanopyrone D, a natural marine product. Trienal **21** was cyclised to **22** in 71% yield and 90% *ee*. Further manipulations allowed the synthesis of solanopyrone D (scheme **16**) in nine steps compared to the previous synthesis by Hagiwara which involved nineteen steps.[31]



Scheme 16

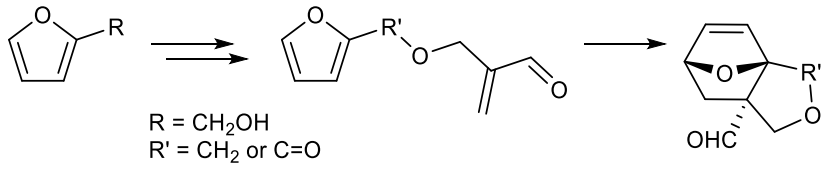
Overall, the choice of catalyst for IMDA largely depends on balancing the ease of formation of the iminium ion species, with any undesired interactions between the dienophile/diene substituents and the blocking groups of the imidazolidinone species. Reversibility of the reaction ought to be kept in mind. Evans also noted that furan is often thought of as a poor diene in Diels-Alder reactions. All this, and there being a lack of catalytic asymmetric IMDAF cycloadditions reported in literature, proposes that any subsequent research may be challenging and fraught with setbacks.

3.0 Results and Discussion

3.1 Novel scaffolds

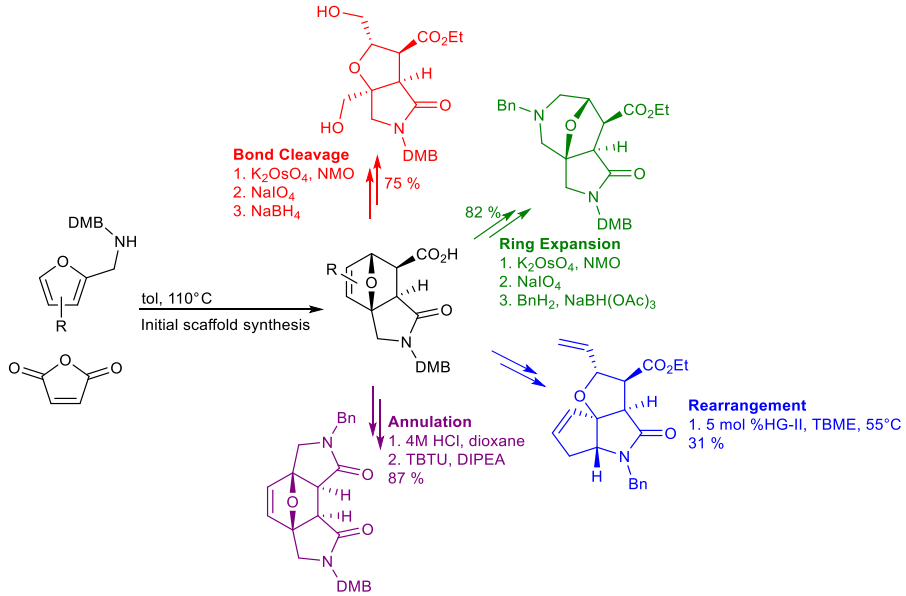
3.1.1 Introduction

An exploration of a wide range of IMDAF cyclisations to produce adaptable scaffolds was begun (scheme **17**). The aim was to provide evidence for the use of imidazolidinone catalysts in an enantioselective IMDAF.



Scheme 17

It was theorised that multiple scaffolds could be developed, building on all the factors noted previously.[35] These could then be manipulated further, providing scope for building them into larger molecules. This synthetic strategy is useful because it leads to compounds which are structurally not too dissimilar to natural products. A core structure with a large scope for further transformation in multiple directions negates the need for stepwise evolution as in biosynthetic pathways. Nelson has published such work inspired by the biosynthesis of diterpenes. The scaffolds were created from substituted furfuryl amines with maleic anhydride, then expanded through a variety of synthetic approaches (scheme **18**).[36] This goes to show the scope of such syntheses if a widely applicable approach can be found. Nelson then went on to use functional group interconversions on the initial scaffolds to demonstrate their use for creating natural product-like structures, although it is worth noting that all of the structures synthesised were racemic.

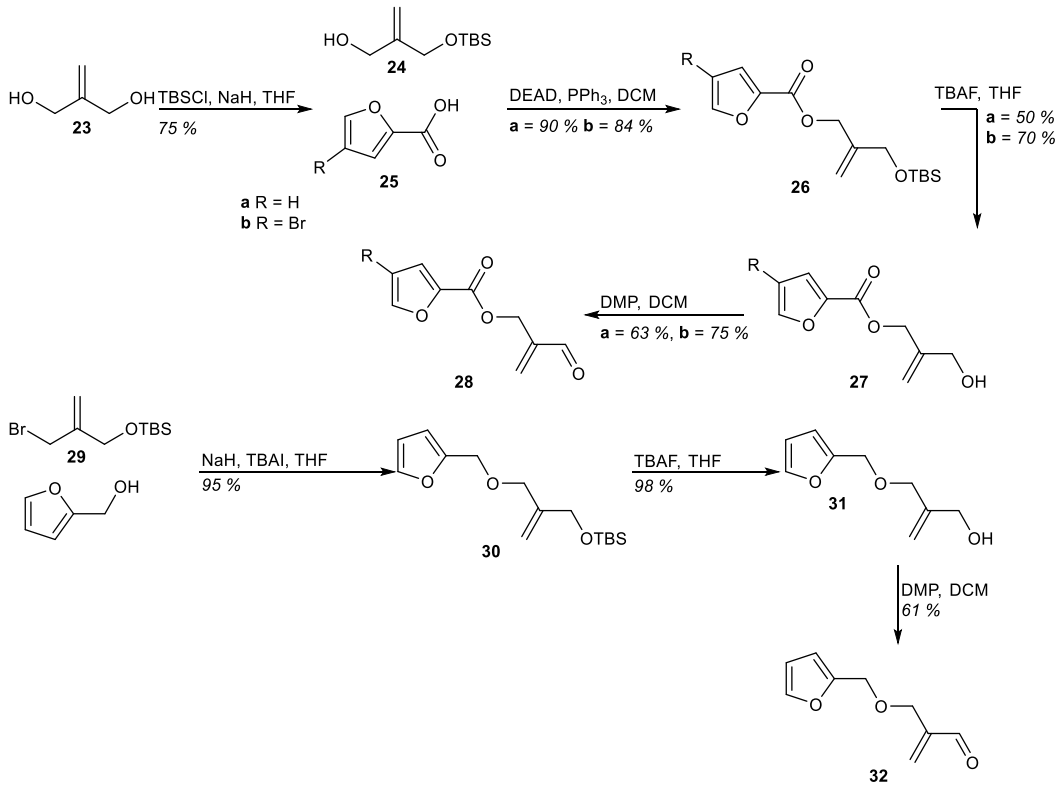


Scheme 18

3.1.2 Synthetic exploration

The aim of these explorations was to target small, relatively simple IMDAF substrates that could be promoted to cyclise by application of MacMillans organocatalysts. By obtaining these enantiomerically enriched scaffolds it was hoped that customisations could be examined, demonstrating the valuable nature of asymmetric catalysis in making potential drug-like molecules.

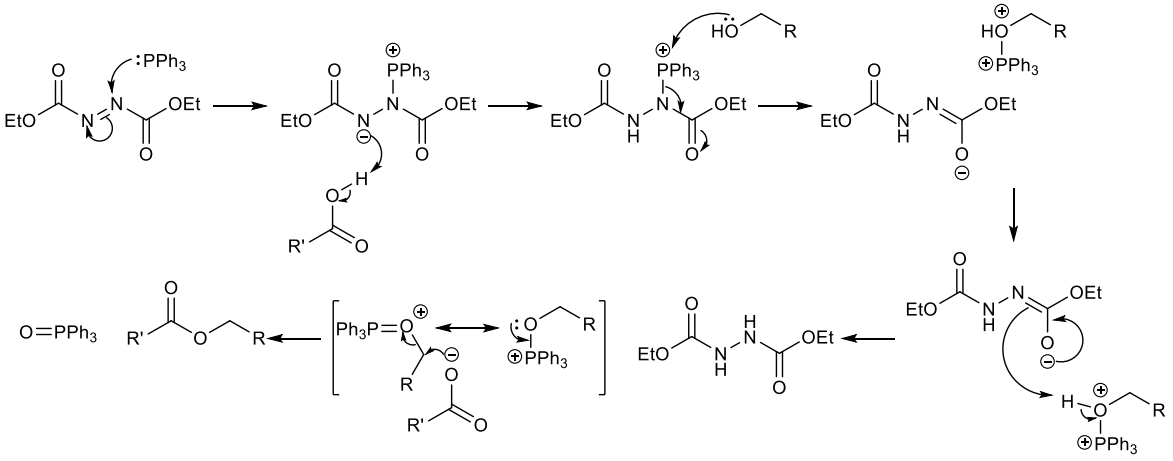
2-Methylene-1,3-propanediol **23** was monoprotected as the TBS-ether **24** using NaH and TBSCl in THF (scheme **19**). This was reacted with 2-furoic acids **25a** and **25b** in a Mitsunobu reaction using DEAD and PPh_3 in DCM. Ester linked **26a** and **26b** were obtained in this way in 90 % and 84 % (0.266g and 2.56g) yield respectively. For ether linked substrate **32**, diol **23** was converted to bromide **68** first using the Appel reaction. An improvement on this method involved forming the bromide via the mesyl protected alcohol. This pathway gave a greater yield (79 % versus 34 %) and a cleaner product. Reaction with furfuryl alcohol in a nucleophilic substitution step then followed. **26a**, **26b** and **30** were all deprotected using TBAF and oxidised using DMP to give **28a**, **28b** and **32**.



Scheme 19

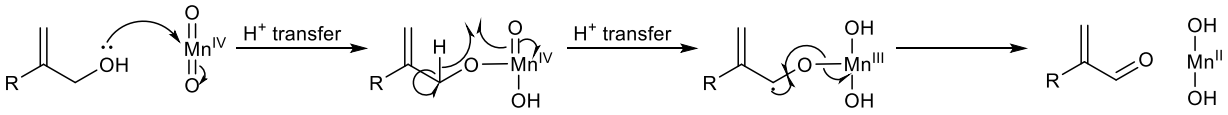
In the mechanism for the Mitsunobu reaction (scheme **20**), the PPh_3 lone pair attacks the DEAD generating a phosphonium intermediate. This zwitterionic species deprotonates the acidic species in the reaction mixture, generating the nucleophile, and the alcohol component attacks the phosphonium ion. The nucleophile then attacks and yields the product and triphenylphosphine oxide, the formation of the stable P=O bond being the driving force in the reaction. The S_N2 attack of the nucleophile makes

the Mitsunobu reaction a useful tool for the inversion of 2° alcohol stereocentres though this is not applicable in this work.



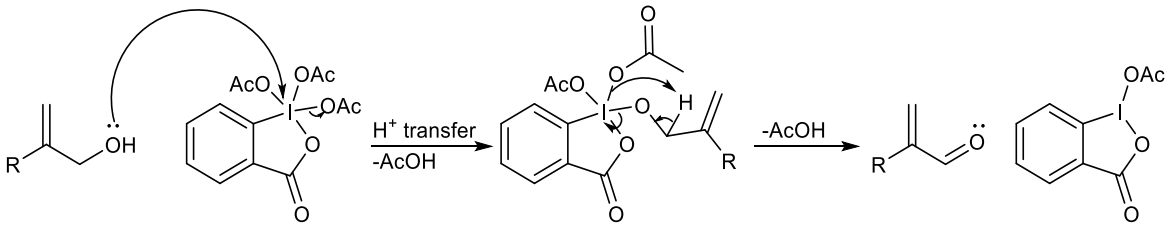
Scheme 20

Oxidation of **27a** to IMDAF substrate **28a** with MnO_2 was attempted. However, exposure to this reagent in DCM for 24 hours at room temperature followed by 24 hours heating at 40 °C only returned starting material. MnO_2 is a selective oxidant for benzylic and allylic alcohols.[37] An initial attack of the alcohol oxygen is followed by a radical pathway thereafter. The Mn-O double bond and an α-C-H bond are both homolytically cleaved, reducing the Mn^{IV} to Mn^{III} and giving a carbon-centred radical stabilised by allylic resonance. The oxidation is completed by the reduction of Mn^{III} to dihydroxylated Mn^{II} and release of the aldehyde (scheme **21**.)



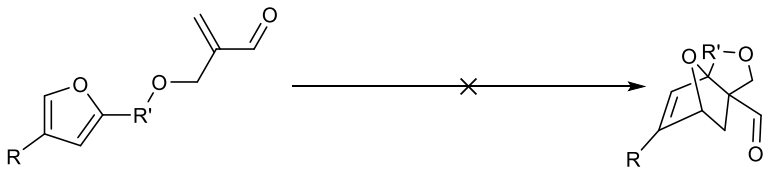
Scheme 21

In place of MnO_2, DMP was used. The mild conditions used involved stirring the alcohol with 1.5 equivalents of DMP at room temperature for 3 hours. A maximum yield of 75 % was obtained after purification. In this mechanism the alcohol oxygen attacks the hypervalent iodine, eliminating acetic acid. A second equivalent of acetic acid is generated when an acetate anion abstracts an α-proton. This simultaneously releases the aldehyde and reduces the I^{V} to I^{III} (scheme **22**.) DMP oxidations occur under mild conditions but the generation of two equivalents of acetic acid will be problematic if the ester linkage proves to be acid labile.



Scheme 22

With substrates **28a**, **28b** and **32** in hand, different conditions were applied in attempts to obtain the cycloadducts either as a racemic or an enantioenriched mixture (scheme **23**). None of these attempts provided a cycloadduct. A mixture of starting material and degradation products were obtained from the use of MacMillan catalysts **17** and **18** as well as from microwave and conventional heating in various solvents. The results are summarised in table **1**. Dimethylaluminium chloride has successfully been used in many IMDAFs[7] but similar conditions here only led to degradation products. It was concluded that the dienophile component of these substrates was not electron deficient enough for an IMDAF to take place under the conditions studied. Furthermore, it was likely that a reactive conformation was not accessible enough, making the chances of reactive orbital overlap very low.

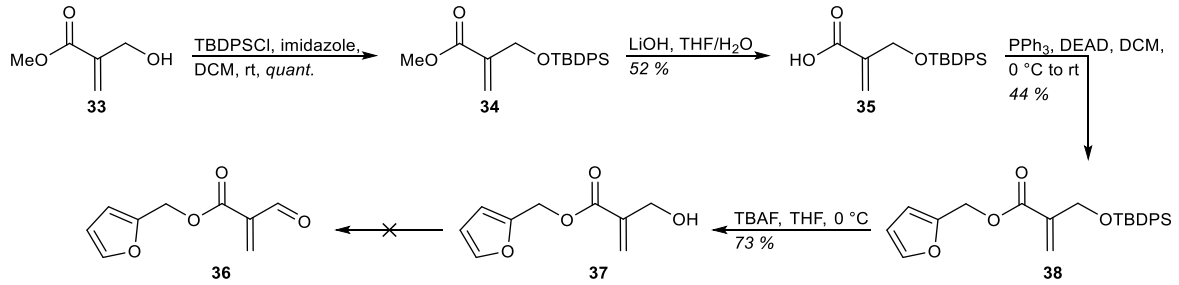


Scheme 23

			Results	
R	**R'**	**Conditions**	**SM returned**	**degradation**
H	C=O	**18**.TFA, MeCN/H_2O, -20 °C – 85 °C, 9 days	✓	✓
		17.HCl, MeCN/H_2O, rt – 85 °C, 72 h	✓	✓
		Microwave, THF, 1 h	✓	
		Toluene, reflux, 90 h	✓	✓
		Me_2AlCl, DCM, -78 °C–rt, 5 h		✓
Br	C=O	**18**.TFA, MeCN/H_2O, rt – 85 °C, 5 days	✓	✓
		17.HCl, MeCN/H_2O, rt – 85 °C, 48 h	✓	✓
		nBuOH, 120 °C, 18 h		✓
		Me_2AlCl, DCM, -78 °C–0 °C, 5 h		✓
H	CH_2	**18**.TFA, MeCN/H_2O, rt – 85 °C, 5 days	✓	✓
		17.HCl, MeCN/H_2O, rt – 85 °C, 72 h		✓
		Toluene, reflux, 90 h	✓	✓
		Me_2AlCl, DCM, -78 °C–0 °C, 2 h		✓

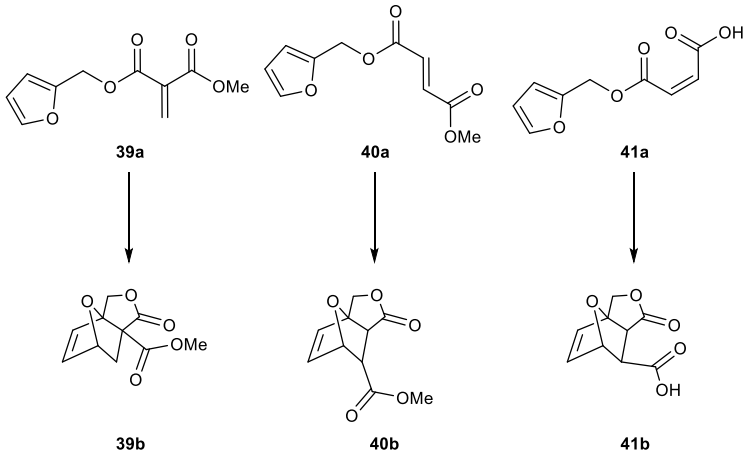
Table 1

With this in mind, IMDAF substrates were designed with a doubly activated dienophile component. Initially compound **38** was targeted (scheme **24**. Hydroxymethyl acrylate **33** was treated with TBDPSCl and imidazole then the methyl ester hydrolysed with aqueous lithium hydroxide to give acid **35**. Mitsunobu and TBAF deprotection reactions as carried out previously gave **37** in 17 % yield over four steps. However, attempts to oxidise **37** to the aldehyde were unsuccessful. **37** proved to be resistant to oxidation by DMP, PCC and MnO_2 as well as prone to degradation at room temperature and above. It is worth noting that despite the additional activation from the carbonyl group, compounds **36** and **37** do not undergo IMDAFs. On the other hand, the analogous amide tethered compounds do spontaneously, reversibly, form a mixture of the cycloadduct and starting material.[38] This can be explained by the amide tethered compounds having a lower energy conformations. The amide moiety dictates that the compound curves around, thus bringing the reactive centres closer together, allowing for easier overlap of orbitals in the diene and dienophile.[39]



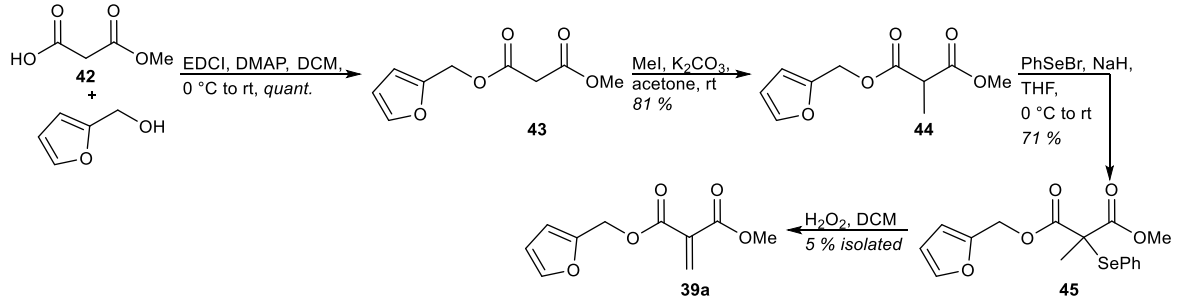
Scheme 24

Three further options for additional electron withdrawing group incorporation were considered in the expectation that the second ester group would provide varying degrees of additional activation, depending on the regioisomer. These options replace the aldehyde with a more stable ester to reduce the chances of degradation. The options considered were the methylene malonate, the fumarate and the maleate (scheme **25**).



Scheme 25

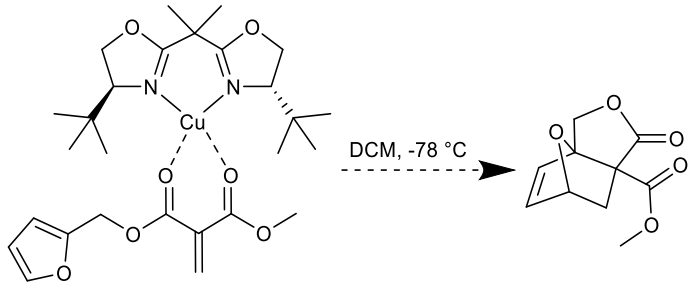
Focus was first directed towards methylene malonate **39a**. **42** was coupled to furfuryl alcohol using EDCI and DMAP (scheme **26**). The crude product was treated with potassium carbonate and iodomethane and **44** was obtained in 81 % yield over two steps. Deprotonation with sodium hydride followed by treatment of the enolate with phenyl selenyl bromide gave selenide **45** in 71 % yield. Methylene malonate **39a** was obtained after oxidation and elimination of the selenide with aqueous hydrogen peroxide.



Scheme 26

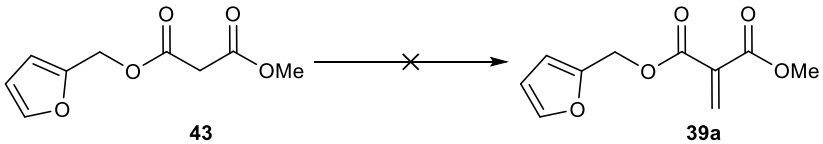
Unfortunately, attempts to purify **39a** led to loss of the compound and the crude product was of poor quality, with no clear evidence of cycloaddition. The physical state of the crude material was a highly coloured, viscous oil which hardened on standing

to an almost glass like material. Nevertheless, conditions for Cu(II) BOX catalysis were examined. It was believed that the electron withdrawing character of the ester carbonyl on either side of the alkene would be enhanced by co-ordination to the bulky Lewis acid (scheme **27**). A successful cycloaddition would potentially furnish cycloadduct **39b** in an enantioenriched form.



Scheme 27

An initial attempt only provided degradation products in place of cycloadduct **39b**. Alternative conditions for the conversion of **43** to **39a** were surveyed (table **2**). Whereas treatment with paraformaldehyde under basic conditions at 80 ºC led to substrate hydrolysis (table **2**, entry 1), under acidic conditions a small amount of cycloadduct **39b** was obtained directly (entry 3). Reaction of **43** with Eschenmoser's salt gave 2:1 adduct **46** following quaternisation and Cope elimination (entry 2).



43 **39a**

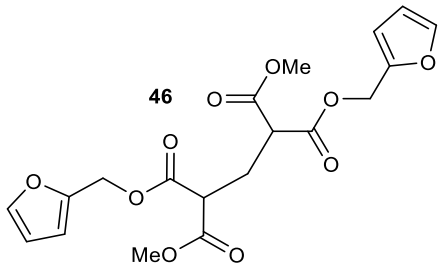
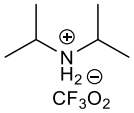
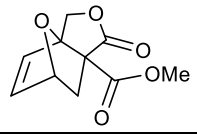
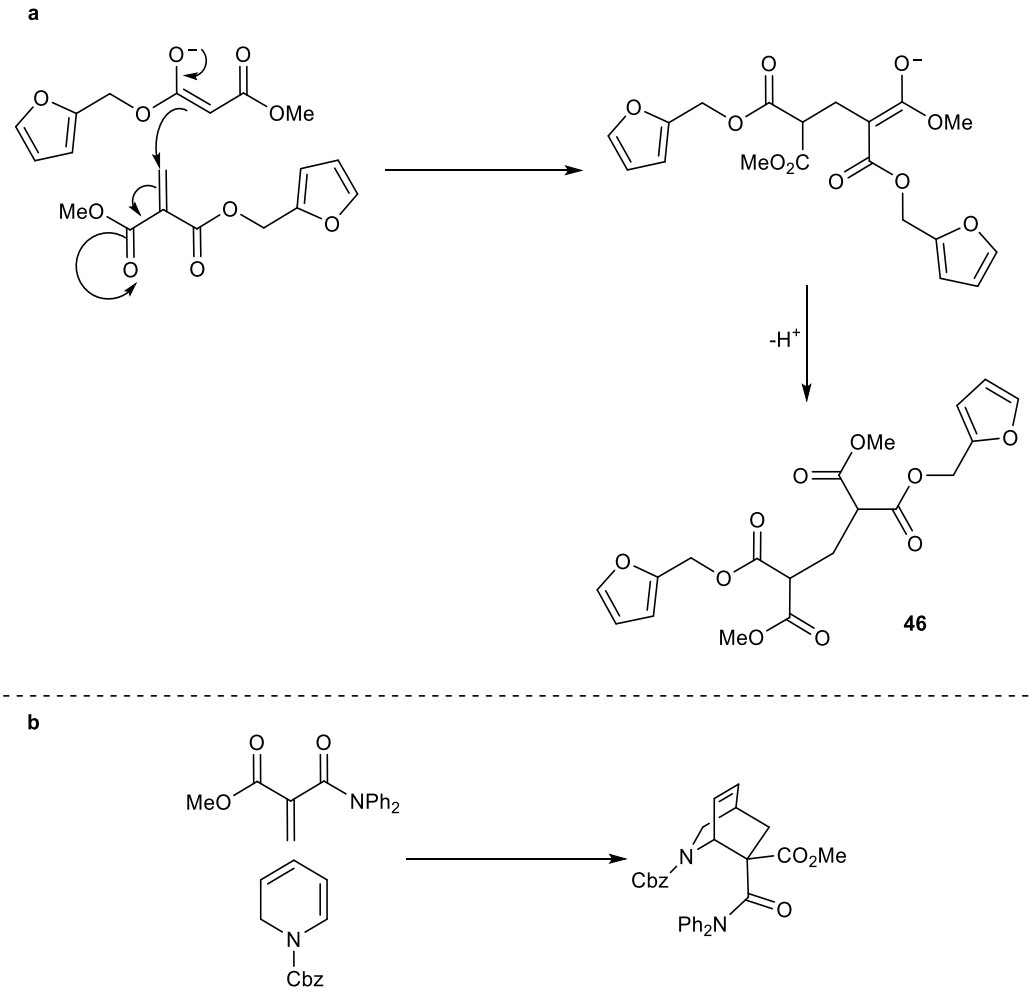
Entry	Conditions	Results
1	Paraformaldehyde, K_2CO_3, TBAI, tol, 80 °C	Starting material hydrolysed to give furfuryl alcohol
2	1. NaH, THF, rt,  2. MeI 3. heat	Step 1 gave the 2:1 adduct **46** 
3	Paraformaldehyde, TFA, THF, 70 °C 	Desired product not obtained. 8 % of cycloadduct isolated 

Table 2

Installation of the methylene group was attempted using paraformaldehyde, potassium carbonate and TBAI in toluene as these conditions were previously successfully used. Only furfuryl alcohol was obtained from this reaction (entry 1), suggesting at least one

of the esters in the molecule are base labile. Eschenmoser's salt is a common methylenating agent so the iodide salt was applied to malonate **39a** but only the 2:1 adduct **46** was obtained (entry 2.)[40] This suggests that the desired **39a** forms but is then captured by the enolate of **39a** (scheme **28a**.)



Scheme 28

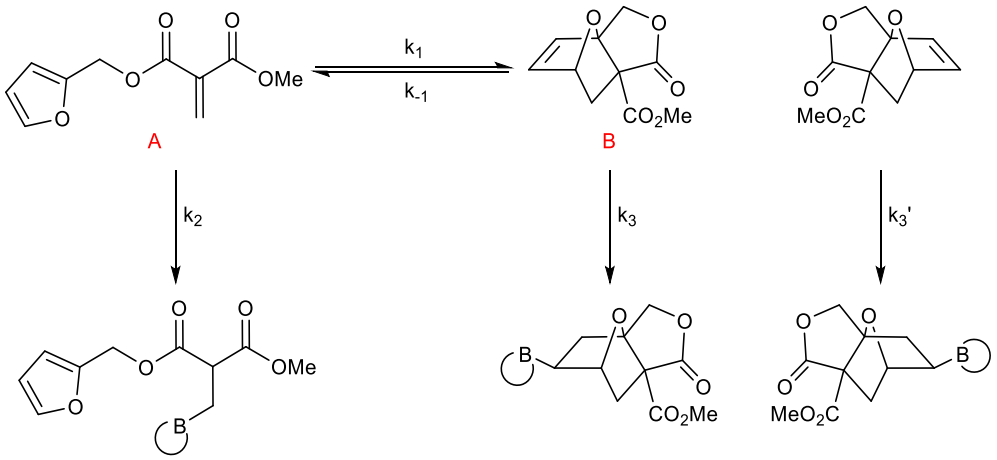
The reaction which gave hope that formation of cycloadduct was possible was a variation of Eschenmoser's methylenation.[41] **45** (1 mmol, 0.2 g), 2 eq. paraformaldehyde, 1 eq. diisopropylammonium 2,2,2-trifluoroacetate as the catalyst and 0.1 eq. TFA as co-catalyst, were refluxed together for 8 hrs. After aqueous work up and chromatographic purification, 8% of **39b** was obtained and none of the target **39a**.

The formation of **39b** is confirmed by several key proton NMR signals. The appearance of two separate signals (4.68 and 4.99 ppm) for 3-*H* and 3-*H'* confirms their non-equivalence. Then there are chemical shifts for 4-*H*, 5-*H* and 6-*H* (6.38, 6.59-6.60 and 5.16-5.17 ppm respectively) consistent with olefin and bridgehead protons. Finally, there are the two signals for the non-equivalent 7-*H* protons which appear at 2.18 ppm (7-*endo*) and 2.51 ppm (7-*exo*). Only 7-*exo* shows coupling to the

bridgehead proton, which is the case for all the compounds made in previous research.[38]

While only a modest yield, it appears to be the only example of an intramolecular cycloaddition involving a methylidene malonate species. Several intermolecular cycloadditions using a malonate dienophile have been published, e.g. scheme **28b**[42], but have stopped short of reporting on the intramolecular counterparts.

As the scope for an asymmetric IMDAF seemed limited, thoughts were directed towards racemic routes where the cycloadducts could be fed into a dynamic kinetic resolution (DKR) approach. This is a method which relies on one enantiomer reacting much faster than the other under the reaction environment (exemplified with a hydroboration in scheme **29**).



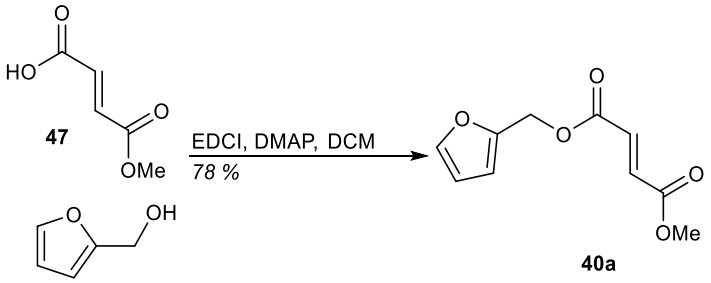
Scheme 29

For this to be effective, a set of conditions must be fulfilled. Firstly, the cycloaddition must be faster than hydroboration of the substrate i.e. $k_1 >> k_2$. The hydroboration has chemoselectivity in that the hydroborating agent reacts much quicker with the cycloadduct than the substrate i.e. $k_3[B] >> k_2[A]$. Hydroboration must also be enantioselective in great preference to the desired enantiomer – $k_3 >> k_{3'}$. Retrocycloaddition needs to much faster than the hydroboration of the undesired enantiomer ($k_{-1} >> k_{3'}$) so that substrate is freed up to cyclise and form more of the desired enantiomer. Finally, rate constants k_1, k_{-1} and k_3 need to be large enough for the reaction is viable, giving a synthetically useful overall rate.

Note that this is an example of the Curtin-Hammett principle – the ratio of two products derived from rapidly interconverting intermediates reflects the relative activation energies of the reactions forming these products, as well as the relative energies of the intermediates.

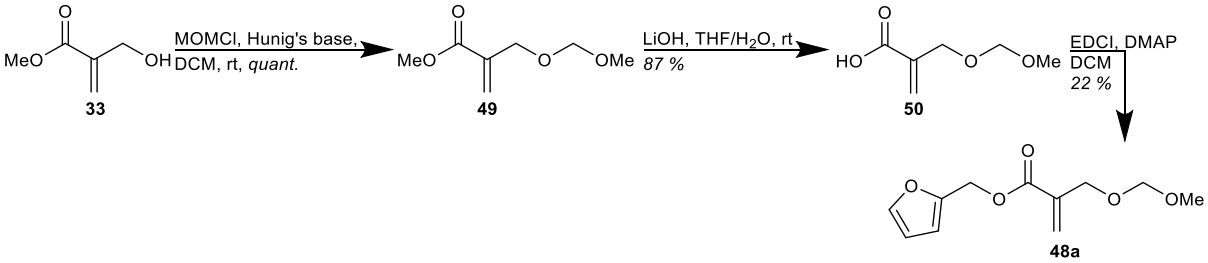
Fumarate isomer **40a** was next approached as it had previously been reported to undergo an IMDAF and was easily prepared (scheme **30**). Treatment of fumarate **47** with 1.5 equivalents each EDCI and DMAP, at room temperature, gave a greater yield

(78 % versus 29 %) and cleaner product than the Mitsunobu conditions used by Jung.[13]



Scheme 30

In conjunction with the divalent Lewis acid catalysts applied to methylene malonate **39a**, MOM-protected substrate **48a** was considered. This was easily synthesised by first protecting hydroxymethyl **33** using MOMCl and Hunig's base (scheme **31**). The methyl ester was then hydrolysed to **50** which was subjected to an EDCI/DMAP coupling with furfuryl alcohol. This quickly led to **48a** and the synthesis only required one purification after the final step.



Scheme 31

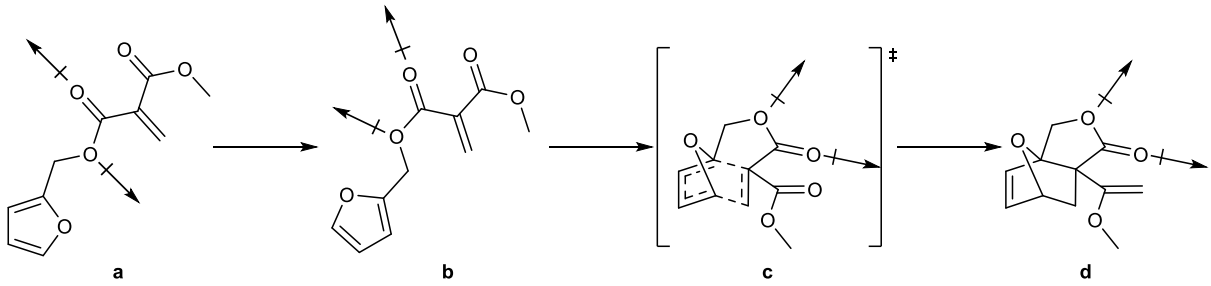
Previous to the application of any Lewis acids to **39a**, **40a** or **48a** some thermal studies were undertaken to gain a comprehension of where the equilibrium lay for the IMDAF of each compound. The results of these are summarised in table **3** below.

		Starting material:cycloadduct					
Starting material	Cycloadduct	$CDCl_3$ 60 °C		MeCN 90 °C		d^6-DMSO 60 °C	
39a	**39b**	24 hr	93:7	24 hr	n/a	23 hr	65:35
		72 hr	88:12	48 hr	65:35		
40a	**40b**	24 hr	98.7:1.3	48 hr	93:7		
		48 hr	98.6:1.4				
		120 hr	98.3:1.7				
48a	**48b**	24 hr	100:0			72 hr	100:0
		48 hr	100:0			+24 hr*	100:0**
		120 hr	100:0			+48 hr*	100:0**
						+72 hr*	100:0**
*100 °C **Evidence of degradation products visible by NMR							

Table 3

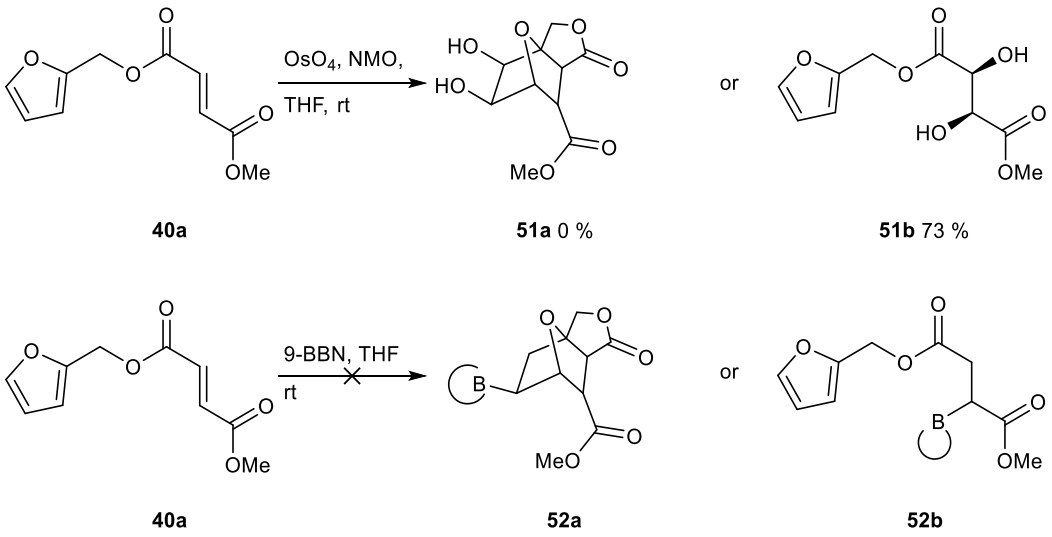
Both methylene malonate **39** and fumarate **40** reach equilibrium faster in more polar solvents. After 72 hours in $CDCl_3$ at 60 °C 12 % of cycloadduct **39b** was present whereas in MeCN the mixture was 35 % after only 48 hours and in DMSO, the same proportion was reached after 24 hours. Based on subsequent data points, this ratio is the equilibrium for this substrate. Fumarate **40a** appeared to be less reactive, reaching 1.3 % cycloadduct after 24 hours heating in $CDCl_3$ and rising to 1.7 % after 120 hours. Again cyclisation was faster in MeCN. A mixture of 6.5 % cycloadduct was obtained after 48 hours and further data points suggested equilibrium had been reached. However, firm conclusions cannot be drawn due to the difference in temperatures used. MOM-protected **48a** appeared to be resistant to cyclisation under comparable conditions and instead degraded when the temperature was increased to 100 °C.

This increase in reactivity with increasing solvent polarity is concordant with data published by Jung. **40a** is the least substituted of the ester tethered furfuryl fumarates studied.[13] An increase in rate of reaction in more polar solvents is explained by the polarity of the transition state of the cycloaddition (scheme **32**). The substrate is more stable in conformation **a** where the dipoles of the ester oxygens are positioned to minimise overall dipole effects i.e. *s-trans*. To bring the reactive groups of the molecule into the correct configuration, rotation about the ester bond must occur. This *s-cis* conformer (**b**) has a larger dipole moment. Hence, the transition state (**c**) is also more polar than the starting material and is therefore better stabilised in more polar solvents.



Scheme 32

IMDAF substrate **40a** was treated with osmium tetroxide and NMO in aqueous THF. It was hoped that the polarity of the mixed solvent would promote the IMDAF[43–45] and the cycloadduct would be dihydroxylated faster than the starting material. It was reasoned that the strained, electron-rich alkene bond in the cycloadduct would be more facile towards dihydroxylation than the electron deficient starting material. This was not the case as none of the dihydroxylated **51a** formed. The only product obtained under the conditions used was **51b** (scheme **33**). This was in line with literature reports describing fast, low temperature dihydroxylations of fumarates in excellent yields.[46–48] A sample of **40a** with approximately 6 % of the corresponding cycloadduct was also subjected to the same conditions. No dihydroxylated product was observed.



40a **51a** 0 % **51b** 73 %

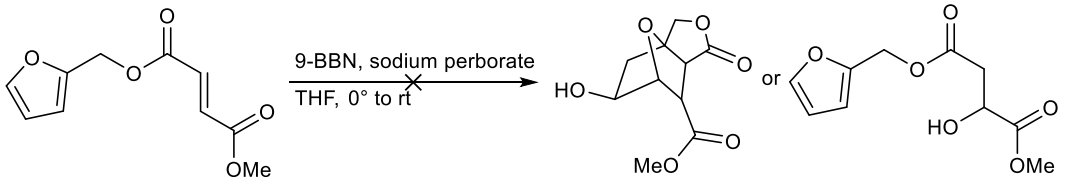
40a **52a** **52b**

Scheme 33

Using the same arguments as for dihydroxylation, hydroboration of **40a** was also attempted using 9-BBN in THF. These conditions proved to be inappropriate for both the desired transformation to form **52a** and the hydroboration of the starting material. The material obtained from the attempts made proved to be a mixture of starting material and degradation product. ^{11}B NMR confirmed that hydroboration had not taken place. Nonetheless **52a** might still be accessible using a different hydroborating reagent. In a review of this class of reactions Brown noted that the organoboranes obtained from 9-BBN are often unstable.[49] Other reagents were found to provide more stable organoboranes including disiamylborane and dicyclohexylborane.[50] These reagents provided the desired alcohol on oxidation of the organoborane without ring opening as was the case with 9-BBN.

The base lability of the ester bonds mean that using the classical oxidation method of basic hydrogen peroxide would destroy the products from the reaction. Indeed, when this method was attempted, only furfuryl alcohol could be obtained. An alternative method using sodium perborate has been described.[51] This reagent has successfully oxidised trialkylboranes, derived from both disiamylborane and dicyclohexylborane as well as others. While still being mildly basic at around pH 9.5, it has been tolerated by a number of functional groups, including esters.

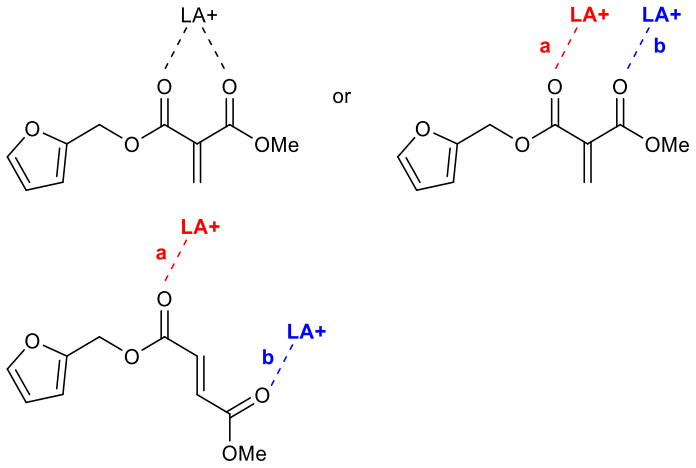
On the basis of this, 9-BBN was applied to **39a** in conjunction with sodium perborate solution. Again, the fumarate substrate proved to be resistant to these conditions and did not produce either the desired cycloadduct **51ai** or the hydroborated fumarate **51bi** (scheme **34**).



39a **51ai** **51bi**

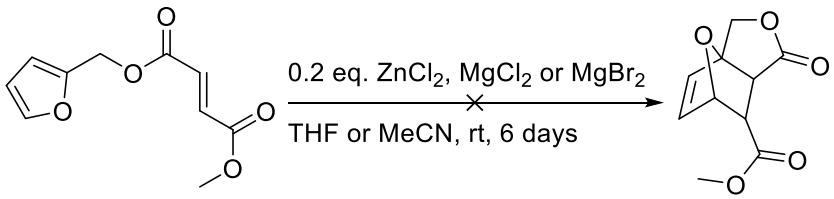
Scheme 34

The slow equilibration of methylene malonate **39a** and fumarate **40a** with their cycloadducts necessitated a method to reach equilibrium faster. Lewis acid catalysis was expected to be of some help. **39a** is a suitable substrate for both mono- and divalent options as the Lewis acid can bind to both the carbonyls at once or one at a time (scheme **35**). Fumarate **40a** has two possible binding sites for monovalent catalysts. Given the remoteness of the furyl group, co-ordination to site **b** is approximately as likely as to site **a**.



Scheme 35

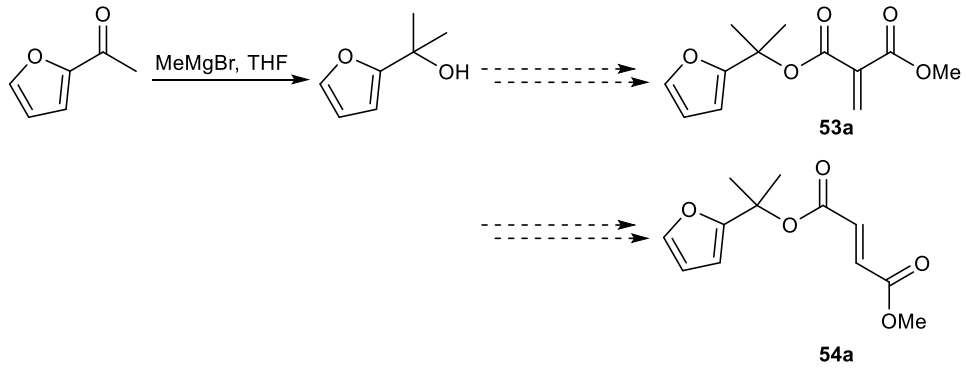
Attention was focussed on fumarate **40a**, the seemingly more stable substrate. 20 mol % of three divalent metal Lewis acids were allowed to stir at room temperature with **40a** and each reaction was monitored by NMR. Two solvents were chosen – THF and MeCN – to see if the IMDAF reaction was sensitive to the polarity of the environment. Unfortunately, even allowing for reaction times of 6 days, neither $ZnCl_2$, $MgCl_2$ nor $MgBr_2$ induced the desired cyclisation (scheme **36**).



Scheme 36

The difficulty of inducing an IMDAF reaction in unsubstituted substrates meant attention was turned to the gem-dimethyl analogues of the above aforementioned substrates. The aim was to overcome the slow IMDAF reaction by designing a more

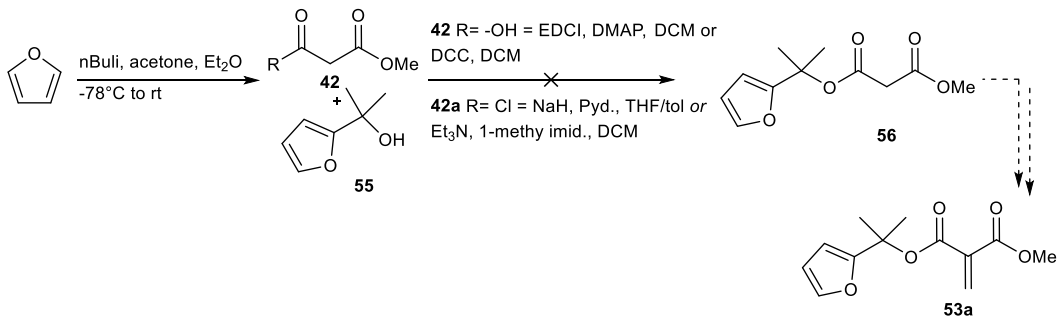
reactive species (e.g. scheme **37**). By using the gem-dimethyl substituted analogues of the species already studied, the equilibrium between precursor and cycloadduct ought to be established much more quickly. More importantly, equilibrium lies in favour of the cycloadduct.



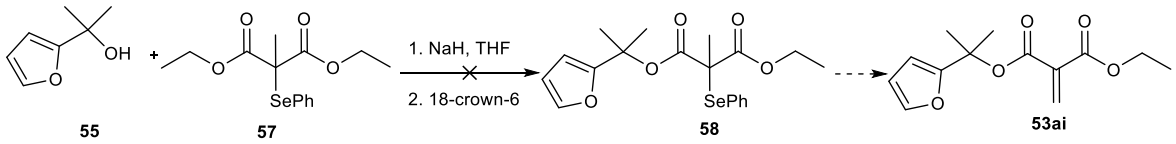
Scheme 37

53a was the first target, with the expectation that a similar route (scheme **38**) to the unsubstituted analogue would be feasible, replacing furfuryl alcohol with the gem-dimethyl equivalent. The first attempt to make 2-furylisopropanol **55** involved reacting 2-acetylfuran with 1.1 eq. of the Grignard reagent methyl magnesium bromide in an umpolung reaction. However, the reaction was unreliable, giving approximately 35% yield which coeluted with the unreacted starting material when column chromatography purification was attempted. Alternatively, treatment of 1.6 eq. of furan with 1.2 e.q. nBuLi followed by the slow addition of acetone gave a consistent crude yield of 80% and the waste products were more easily removed. Furthermore, the crude 2-furylisopropanol was of sufficient quality to progress onto the next stage of the reaction.

The next step of the reaction sequence aimed to couple **42** and 2-furylisopropanol to give gem dimethyl substrate **56**. Initially this was approached the same way as to make **43** but **56** failed to form, even with the addition of further DMAP and increasing the temperature to 45°C. DCC replaced EDCI as the coupling partner to no avail before other conditions were applied with acyl chloride **42a** as an alternative coupling partner. Stirring **42a** with **55** 1.2 eq. NaH and 0.5 eq. pyridine produced no discernible products at any temperatures, nor did stirring with 1.5 eq. triethylamine and 0.2 eq. 1-methyl imidazole as a co-catalyst. Extended reaction times were allowed for each set of conditions but all that could be obtained from the reaction mixture were degradation products. A further attempt to obtain a gem-dimethyl/malonate IMDAF substate using diethyl malonate **57** via a direct displacement reaction (scheme **39**.) However, even the addition of a crown ether after an extended reaction time, was not sufficient to overcome the activation energy for the reaction. Instead, attention was directed towards the fumarate equivalents.

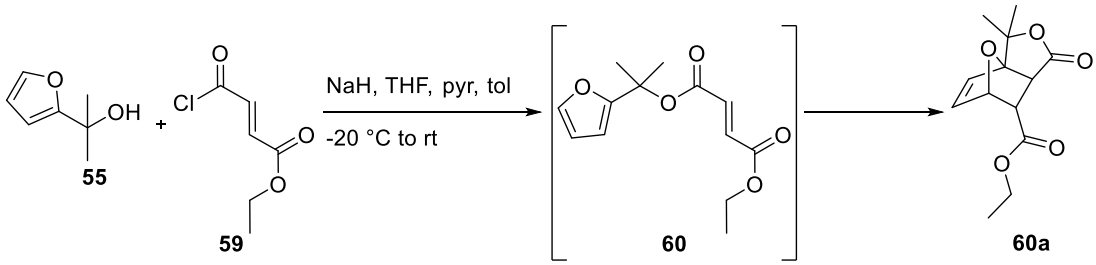


Scheme 38



Scheme 39

The gem-dimethyl/fumarate IMDAF substrates and products proved to be much easier to obtain. A condensation reaction between **55** and **59** using 1.5 eq. NaH and 0.5 eq. pyridine did not produce IMDAF substrate **60** but instead gave the cycloadduct **60a** (scheme **40**) in 44 % yield after purification. No uncyclised product was obtained as is to be expected[52] suggesting **60** is more of an intermediate en route to the more energetically stable **60a**.



Scheme 40

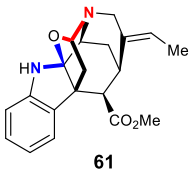
On the basis of this, a variety of conditions were tested on both methyl fumarate **40a** and ethyl fumarate **60a**. 'Hydroboration with 9-BBN or BH_3.THF, followed by oxidative workup with sodium perborate was attempted, but no evidence of reaction could be found. Despite this, the amide analogues were successful in congruent reactions.[38]

3.3 Organocatalytic IMDAF for the synthesis of picrinine – Introduction

In conjunction with these model studies, an application in target synthesis was also pursued. The value of the IMDAF reaction in building heterocyclic rings into complex structures[7] supports the use of this method to contribute to the fused-ring framework of picrinine. Reports on the use of imidazolidinone organocatalysts in IMDAF reactions have not yet been published, but their wide-ranging application suggests it is a viable concept for use in a new total synthesis of picrinine. This would differ from Garg's synthesis[53] by delivering picrinine in an enantioenriched form.

First extracted in 1965,[54] picrinine **61** (figure **5**) is an akuammiline alkaloid found in the plant *Alstonia scholaris*.[55] Its cage-like structure contains a highly functionalised

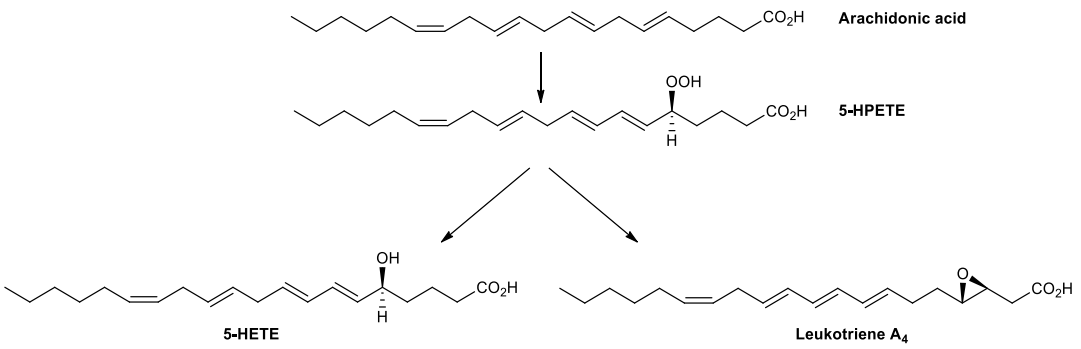
cyclohexane ring at its centre bridged by a [3.3.1]-azabicyclic framework. This framework is connected with a *N,O*-acetal linkage (red) while a second *N,O*-acetal group (blue) links to an indoline component.



61

Figure 5

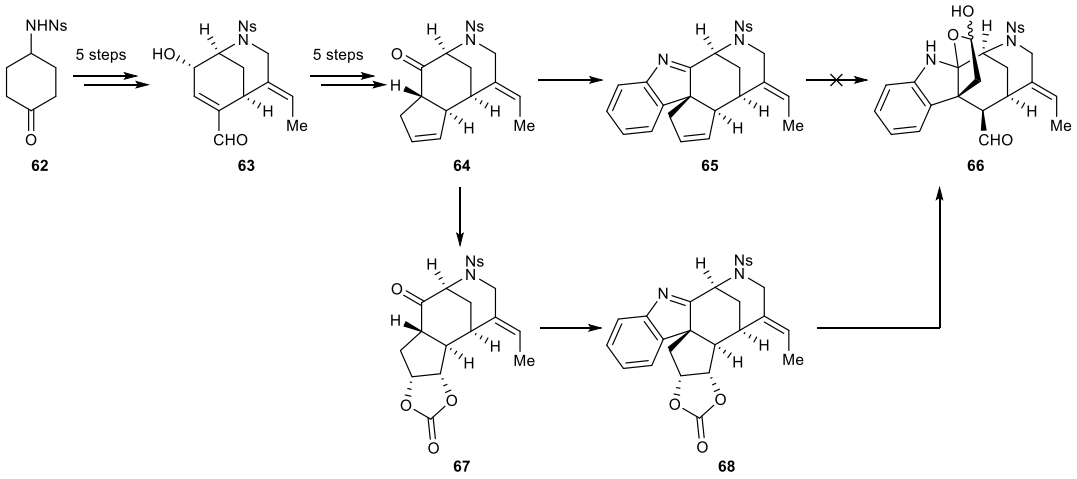
It has shown promise as an antioxidant and anti-inflammatory agent *via* inhibition of the 5-lipoxygenase enzyme. When functioning regularly this enzyme oxidises arachidonic acid to 5-hydroxyperoxyeicosaterenoic acid (5-HPETE) which is metabolised to 5-hydroxy-eicosateraenoic acid (5-HETE) or a variety of leukotrienes e.g. A_4 (scheme **41**).[56]



Scheme 41

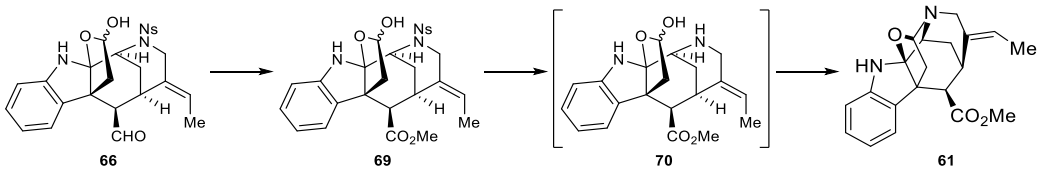
5-HETE and leukotrienes cause inflammation and oxidative stress on the cardiovascular system, particularly in older animals.[56] The effect of this is an increased susceptibility to other stressors which can lead to neurodegeneration.

Garg reported the only total synthesis of picrinine to date.[53] Starting from readily available sulfonamide **62**, enal intermediate **63** was accessed in 5 steps. Synthesis of tricycle **64** was achieved in a further 5 steps, representing the core of the target molecule. To this intermediate was applied the key Fischer indolisation step to give **65**, but failure to cleave the cyclopentene moiety to access **66** led to the conclusion that the newly built indolene was blocking the cyclopentene ring. To circumvent this obstacle, olefin dihydroxylation and protection (**67**) was carried out prior to the Fischer indolisation (**68**). Removal and oxidative cleavage of the cyclic carbonate gave **66**, completing the picrinine scaffold (scheme **42**).



Scheme 42

Oxidation followed by esterification of the aldehyde gave **69**. The remaining two transformations were completed in one step by denosylation to intermediate aminolactol **70** which cyclised in a proximity driven process (scheme **43**.)



Scheme 43

The route is meritorious for its short assembly of the core structure **66**, the key Fischer-indole transformation to construct the complete skeleton and the success of the late stage transformations without disturbing the delicate lactol linkage. However, the final product is racemic but is only the (-)-enantiomer which has displayed bioactive properties.

The structure of picrinine offers a potential application of an asymmetric IMDAF reaction as part of a potential total synthesis. If successful compound **71** (figure **6**) would be the IMDAF substrate. A successful reaction would install the required chiral centre and the structure could be expanded from thereon.

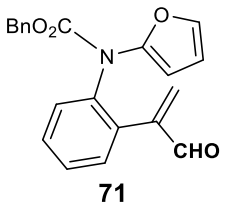
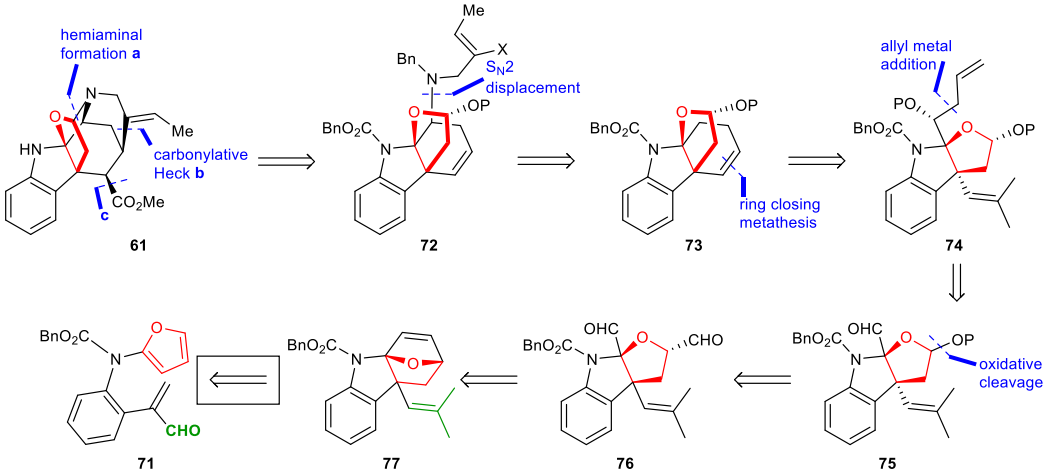


Figure 6

In our alternative retrosynthesis (scheme **44**) disconnection of the cyclohexyl-tetrahydrofuran hemiaminal **a**, the ester and the cyclohexyl-olefin bonds **b** and **c**, simplifies the structure of picrinine to **72**. A carbonylative Heck would install these latter two bonds in the forward sense. **72** can be simplified further to **73** which is envisaged

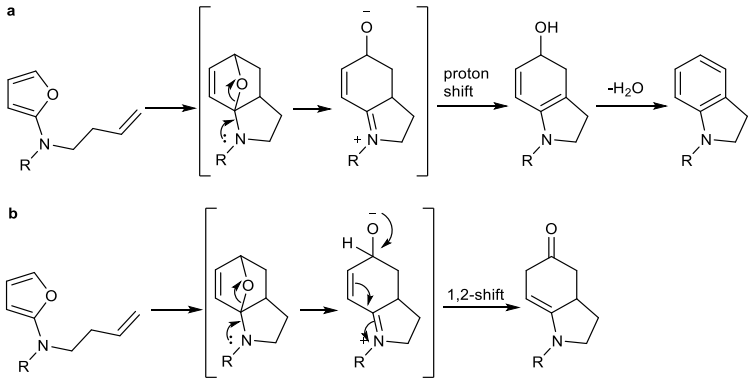
after S_N2 displacement. The cyclohexane ring can be disconnected to **74** and further to **75** which would be available from dialdehyde **76** based on oxidative cleavage of the less hindered tetrahydrofuran aldehyde followed by allyl metal addition to the other aldehyde. **76** would be obtained from cycloadduct **77** while **71** is the IMDAF substrate.



Scheme 44

The amine would be appropriately protected by the Cbz because of its electron withdrawing ability and hence, the nucleophilicity of the nitrogen would be minimised. Cbz is preferential over the Boc group because removal of the latter is by treatment with TFA which may simultaneously cleave the hemiaminal and ester linkages in **61**. Silyl groups are good O-protectors as the O-Si bond is hydrolytically stable under most conditions. Their removal is expedient however with fluoride ions e.g. TBAF. The silicon substituents can be altered to change the lability to suit the reaction conditions as well as to increase the steric encumbrance of neighbouring parts of the molecule.

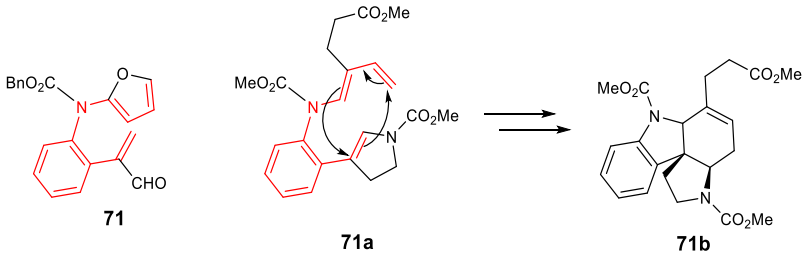
A potential impediment in this IMDAF approach is the fragmentation of the strained oxygen bridged cycloadduct.[2–5,7,57] For example, *N*-assisted ring opening followed by dehydration can lead to aromatisation of the newly formed ring (scheme **45**) or the formation of an unsaturated cyclic ketone.



Scheme 45

These fragmentations occur when high temperatures are used for the IMDAF step thus promoting ring opening. Fortunately, many examples remain where the oxo-

bridge is sustained after cycloaddition.[7,58] The use of a catalyst (e.g. **17** to **19**) should be conducive to lower reaction temperatures. Furthermore, the pendant aldehyde in **61** (green in scheme **45**) should activate the dienophile making the IMDAF more facile. The short tether should not be a limiting factor as the reaction has previously been used to make indolines. Rawal[59] reported one example, and even used a similar arrangement (**71a**) to synthesise indoline **71b** in 99% yield (scheme **46**.)



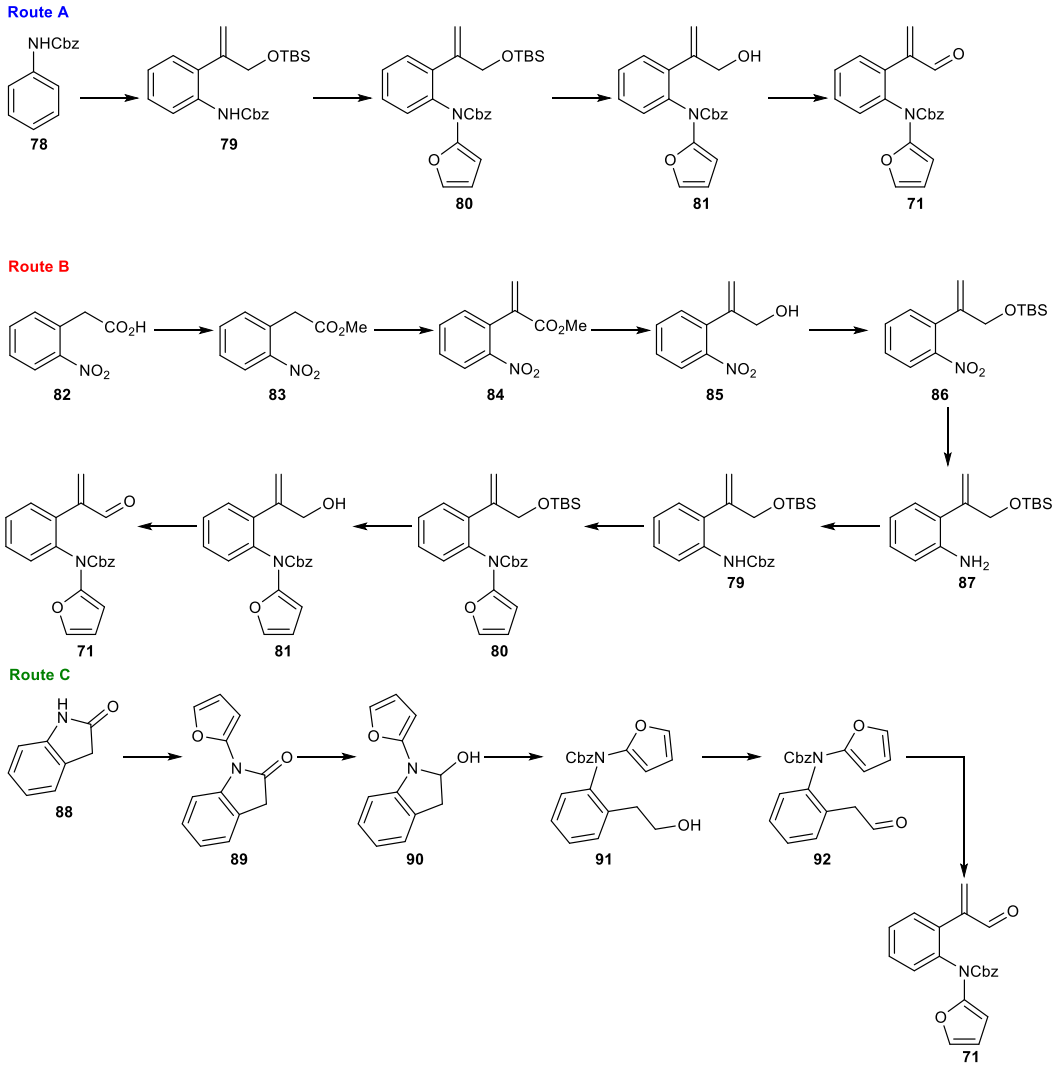
Scheme 46

3.4 Organocatalytic IMDAF for the synthesis of picrinine – Synthetic exploration

Three routes towards cycloaddition substrate were evaluated and are summarised in scheme **47**. Ortho-lithiation of protected aniline **78**, transmetalation to zinc and Negishi coupling with allyl alcohol **93** would give **79** (route A.)[60] The diene could then be installed onto the nitrogen giving **80** and the IMDAF substrate would be available following deprotection and oxidation to the aldehyde **71**.[18]

Route B is based on a previous literature procedure of an aniline derivative reported by Takemoto.[61] It depends on a linear sequence of transformations but negates the need for lithiating reagents. Esterification and methylenation of 2-nitrophenylacetic acid **82** would give **84**, which can be reduced and protected as allyl alcohol **86**. Reduction of the nitro group would give **79** following Cbz-protection of aniline **87** which would be cross coupled with 2-bromofuran to give **80**.[62] Deprotection and oxidation, as before, would give the IMDA substrate **71**.

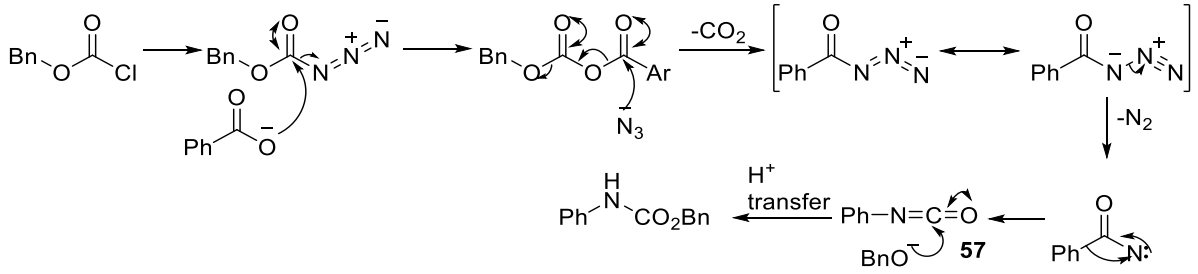
Route C starts from oxindole **88**, forming the N-C bond by copper catalysed coupling with the diene (**89**).[18] Reduction of the lactam to the hemiaminal (**90**) would facilitate ring opening with an *N*-protecting group.[63–66] The alcohol could then be oxidised to the aldehyde **92** and the dienophile installed by methylenation.



Scheme 47

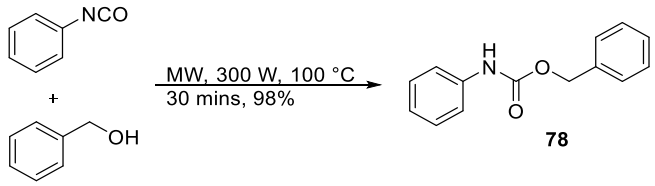
3.4.1 Route A

The first step in route A was to protect the aniline nitrogen. The tertiary butyl carbamate (Boc) group has previously been used to protect aniline[67] and has been successfully employed in IMDA substrates[5] proving it is resistant to cleavage or degradation under these conditions. However, removal of this protecting group is often by treatment with trifluoroacetic acid which may simultaneously cleave the hemiaminal and ester linkages in **61**. Cbz would be a useful protecting group because of its electron withdrawing capability and easy hydrogenative removal. Moreover, it is stable to basic conditions as well as mild acids and oxidising agents. The first method investigated to make **78** was a one-pot method reported by Lebel[68] (scheme **48**). Benzyl chloroformate is converted to the azidoformate. Deprotonated benzoic acid attacks this, eliminating N_3^- while also activating the benzyl carbonyl. The eliminated azide attacks at the activated carbonyl and the species eliminates CO_2 and undergoes Curtius rearrangement to the isocyanate which is trapped by the phenylmethanolate ion.



Scheme 48

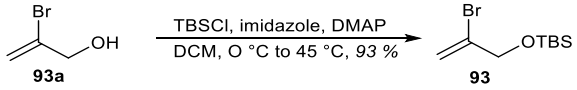
Low yields of the desired product were obtained using this procedure, so efforts were focussed on a more direct method using solvent free microwave heating at 100 °C, 300 W power output for 30 minutes to promote the addition of benzyl alcohol to phenyl isocyanate (1 mol e.q). Reaction temperature was kept at well below the boiling point for both reagents and synthesis of carbamate **78** was completed smoothly using this protocol in 98% yield, 9.35g (scheme **49**).



Scheme 49

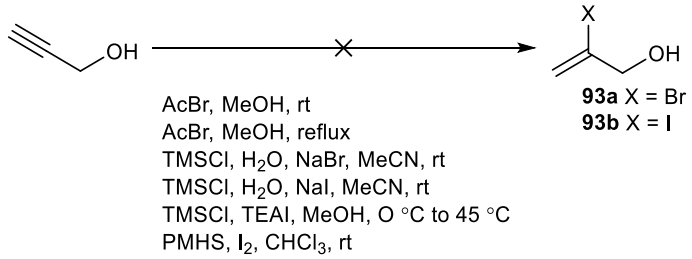
This reaction was inspired by the Curtius rearrangement where during the last steps a nucleophile (often an alcohol) attacks the isocyanate formed *in situ* and a proton is transferred to the nitrogen. By using microwave conditions, the two starting materials were able to be used neat and the desired product obtained cleanly.

The next step was to couple protected allyl alcohol **59** to compound **41** in the *ortho* position. Examination of this began with the protection of 2-bromoallyl alcohol **93a** with TBSCl to form **93**. This was achieved using TBSCl (1.5 eq) and imidazole (1.5 eq.) with DMAP (10 mol %) as a catalyst (scheme **50**) stirred together at 45°C for 5 hours.



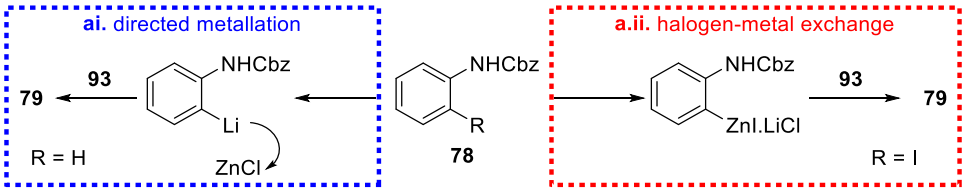
Scheme 50

Several options[69–72] were explored to synthesise **93a** and iodo analogue **93b** from propargyl alcohol (scheme **51**). These attempts involved stirring the reagents in various solvent at temperatures between 0° and reflux. Unfortunately, no isolatable product could be obtained from any of the conditions explored. A minimal amount of 2-iodoallyl alcohol was obtained using the mild conditions of I_2 with PMHS stirred at room temperature but the desired product could not be isolated from the remaining polymer residue, despite successful attempts being reported in literature.

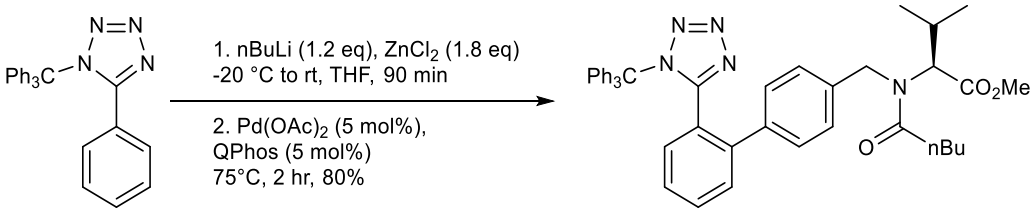


Scheme 51

With both coupling partners in hand, a range of cross-coupling conditions were considered (scheme **52**). N-H deprotonation followed by directed *ortho* lithiation could occur followed by transmetallation to zinc as the precursor for Negishi coupling (route a.i.). Mehta[73] used this method to couple aryl bromides to an arene ring (scheme **53**). Carbamates are good directing groups[74,75] suggesting a similar ortho lithiation could be successful. Furthermore, vinyl halides such as compound **93** are more reactive than aryl halides. ^{t}BuLi would be required as the base because ^{n}BuLi has previously been demonstrated to have insufficient reactivity.[74] If an *ortho*-hydrogen on compound **78** was replaced with an iodine atom, halogen metal exchange could be successful as reported by Knochel[76,77] (route **aii**). Zinc then inserts into the C-I bond followed by coupling to the halide reagent.

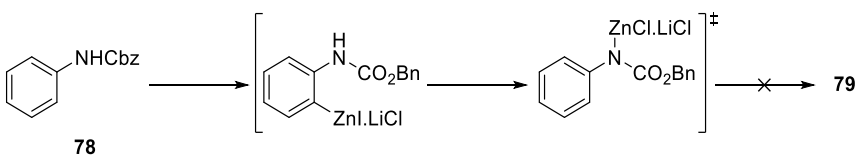


Scheme 52



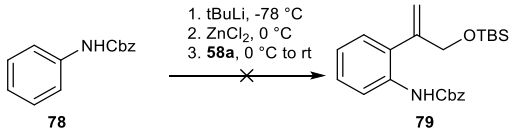
Scheme 53

There is a possibility that the acidic proton on the carbamate nitrogen of **41** could allow rearrangement to the N-metallated compound (scheme **54**). Nonetheless, Knochel described good functional group tolerance so it was a promising starting point for investigations into the desired coupling.



Scheme 54

78 was subjected to the conditions used by Mehta[60,73] using 2.8 eq. ^{t}BuLi and quenched with TBS-ether **93** (scheme **55**) but the desired **79** was not obtained. It was suspected that the carbamate directing group was not efficient enough to promote deprotonation and subsequent coupling. Henceforth, efforts were directed to route B which would build the allyl alcohol onto the aryl unit instead of a direct coupling, thus avoiding the use of pyrophoric reagents.



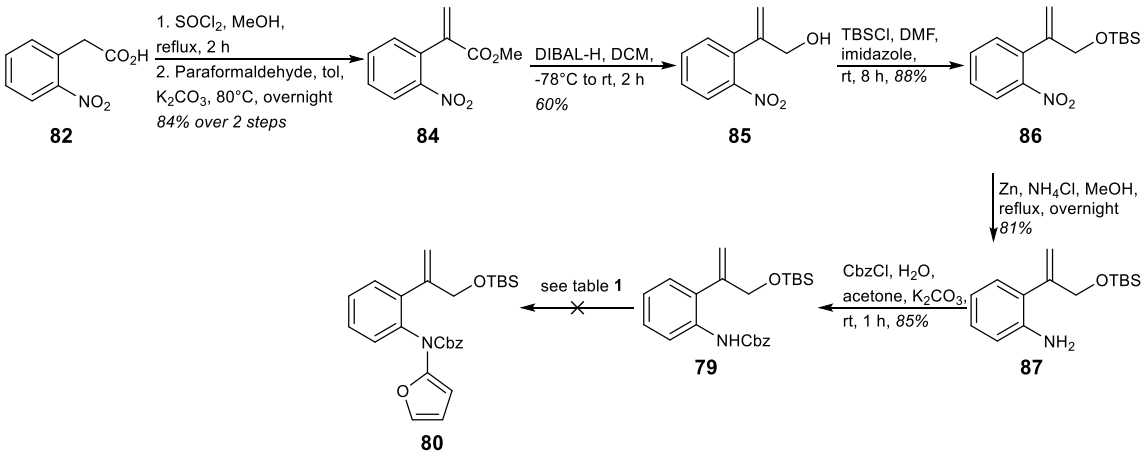
78 79

Scheme 55

3.4.2 Route B

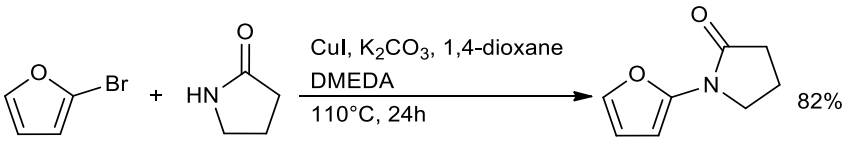
Esterification of 2-nitrophenylacetic acid **82** (scheme **56**) was achieved by refluxing in methanol with thionyl chloride (1 mol eq.). No purification was necessary prior to methylenation. This was achieved by heating with 2.8 e.q. paraformaldehyde and 3 eq. K_2CO_3 at 80°C overnight.[78] This is an improvement on the formalin/methanol/water system used by Takemoto, obtaining a cleaner product (**84**) at a higher yield (84% compared to 31%.)

Treatment of ester **84** with 2.4 eq. DIBAL for 2 hours resulted in alcohol **85** after an aqueous workup. This was then protected as the TBS- derivative (1.2 e.q. TBSCl) aided by 2 eq. as the base-catalyst. The nitro- group of **86** was reduced to the 1°amine using 10 eq. of zinc powder with ammonium chloride in methanol heated at 75°C overnight. Aniline protection of **87** was completed with 1.5 eq. each CbzCl and K_2CO_3 in an aqueous-acetone system at room temperature. The reaction had to be carefully monitored by TLC as reaction times longer than 1 hour resulted in cleavage of the TBS-ether. The choice of base and solvent appears to be of further importance. For example, using triethylamine in DCM, Cbz-protection of **87** did not occur, even with DMAP as a catalyst. Using $NaHCO_3$ as the base allowed the reaction to progress with a similar time and yield, indicating bulky triethylamine caused too much steric hindrance. However, this method required dry THF, the preparation of which was considered time inefficient.



Scheme 56

With protected aniline **79** in hand, copper catalysed coupling to attach the furan dienophile was attempted using conditions developed by Padwa (CuI, DMEDA, K_2CO_3, dioxane, scheme **57**).[62]



Scheme 57

Other solvents and bases used in similar reactions include K_3PO_4, Cs_2CO_3, DMSO and toluene[18,62,79,80] and so a solvent/base screen for the reaction to N-arylate **79** was conducted. None of these attempts were successful in giving desired product **80**. Instead, the products obtained were either starting material, the unprotected aniline **87** or the desilylated aniline **87a** (figure **7** and table **4**.) Although no examples of copper catalysed arylations using Cbz protected substrates have been reported, it has not been specifically noted that the group is incompatible with the reaction conditions.

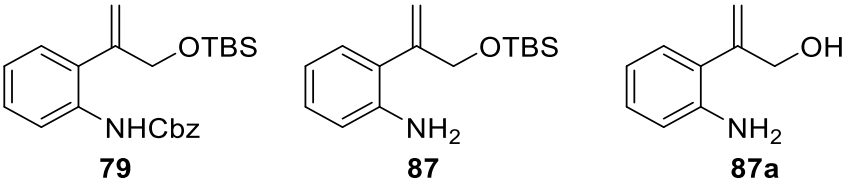
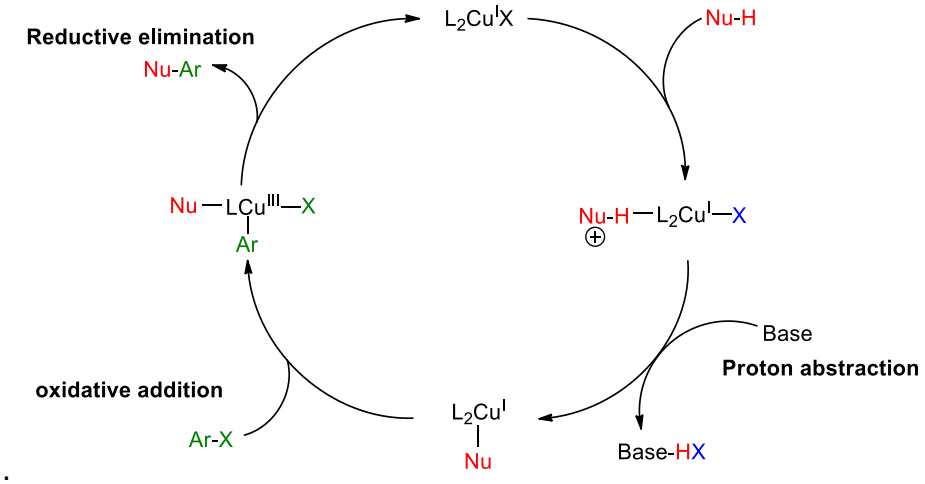


Figure 7

Solvent / Base	Dioxane	DMSO	Toluene
K_2CO_3	**79**	**87** + **87a**	**79**
K_3PO_4	**87**	**87a**	**79** + **87**
Cs_2CO_3	**87**	**87a**	**87**

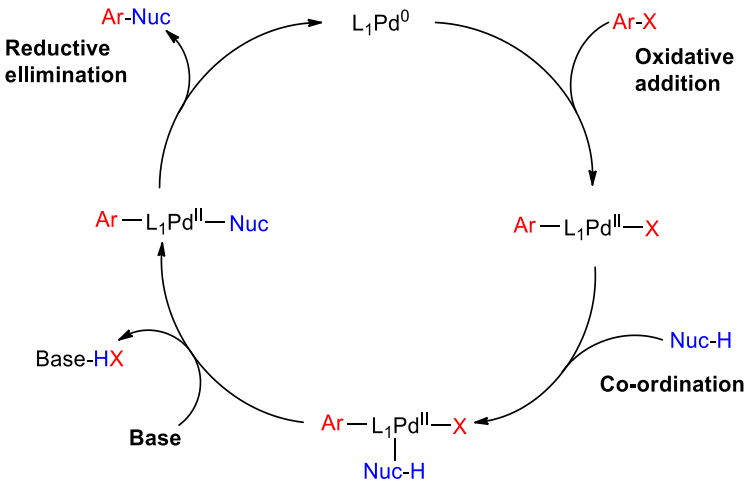
Table 4

In the mechanism for nucleophilic substitution reactions of aryl halides (scheme **58**)[81] the nucleophile co-ordinates to the Cu(I) species first. Base then removes a proton and the counter ion to the copper salt. Oxidative addition of the halide gives a Cu^{III} intermediate then reductive elimination completes the cycle. It has not been fully elucidated which is the rate limiting step in the sequence so it may be true that slow nucleophile co-ordination leads to substrate degradation. Hence it was deduced that deprotection of **79** was more facile than co-ordination to the copper salt. This is likely due to the carbamate nitrogen not being sufficiently nucleophilic.



Scheme 589

This copper mediated process can be contrasted with that for palladium catalysis (scheme **59**) in which analogous steps are differently ordered. The cycle starts with oxidative addition of the aryl halide to the Pd^0 centre which is oxidised to Pd^{II}. The nucleophile co-ordinates to the palladium and the base abstracts HX. Reductive elimination completes the cycle, giving the product and returning the palladium to Pd^0.[81]



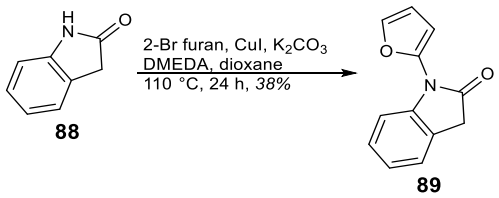
Scheme 59

Palladium catalysed arylations[82–86] of amines and amides have been widely reported so this is merits exploration in the future. Meanwhile, a different route beginning with a more nucleophilic substrate was studied.

3.4.3 Route C

Literature precedent for *N*-arylations of oxindole come from Buchwald and Hudson,[81,87] though no such coupling using a furan moiety has been reported. Conditions reported by Padwa[18,62] for N-arylation of amides (2-bromofuran, 0.1 eq. each of CuI and DMEDA, 4.3 eq. K_2CO_3 and 1.2 eq. oxindole) were applied to compound **88**, all heated at 110°C in a sealed environment for 24 hours. Note that the aryl halide is the limiting reagent in these conditions, while oxindole is in excess. A 38% yield of **89** was obtained (scheme **60**.) The formation of **89** was evidenced by the four oxindole aromatics and 3 furan signals all integrating to one proton each. GC-MS also highlighted the $[M+H]^+$ compound where m/z = 200.0706 $[M+H]^+$.

No other identifiable products could be isolated, and it was assumed that the balance of the material was made up of degradation products. A control study was conducted subjecting 2-bromo furan to the reaction conditions in the absence of oxindole. Neither products or 2-bromofuran were isolated, and it was assumed 2-bromofuran polymerises faster than it can react. In contrast, oxindole was recovered from the study when the reaction conditions were applied without 2-bromofuran.



88 **89**

Scheme 60

With a view to increase the yield the method was studied in greater detail with monitoring by GC-MS analysis. A controlled addition of the 2-bromofuran over eight hours was used and the chromatograms compared over the course of the reaction (figure **8**) with the areas of interest highlighted in figure **9**. The desired compound **89** elutes at 12.18 mins. The compound which elutes at 12.94 mins is believed to be *N*-arylated isatin **94** shown in figure **10**. The proton NMR spectrum of this product contained only aromatic signals. This is to be expected of **94** as the only protons present are situated on the furan and phenyl portions of the molecule. Multiplet signals at approximately 6.6, 6.7, 7.2 and 7.8 ppm suggest the formation of **94** but the integration is not wholly accurate due to impurities that were not removed by the initial column conditions. The proton ortho to the carbonyl would be expected to be deshielded and at a higher shift than the other phenyl protons. Until further confirmation is obtained, it is credible that the signal at 7.8 ppm corresponds to this proton, especially as the signal for the same proton of **89** is more shielded, appearing at 7.26-7.27 ppm. Hence, on the basis of the current NMR data, and the GC-MS

software database, the structure of **94** is believed to be correct. Unfortunately, the product could not be isolated in a pure enough fashion for further GC-MS analysis.

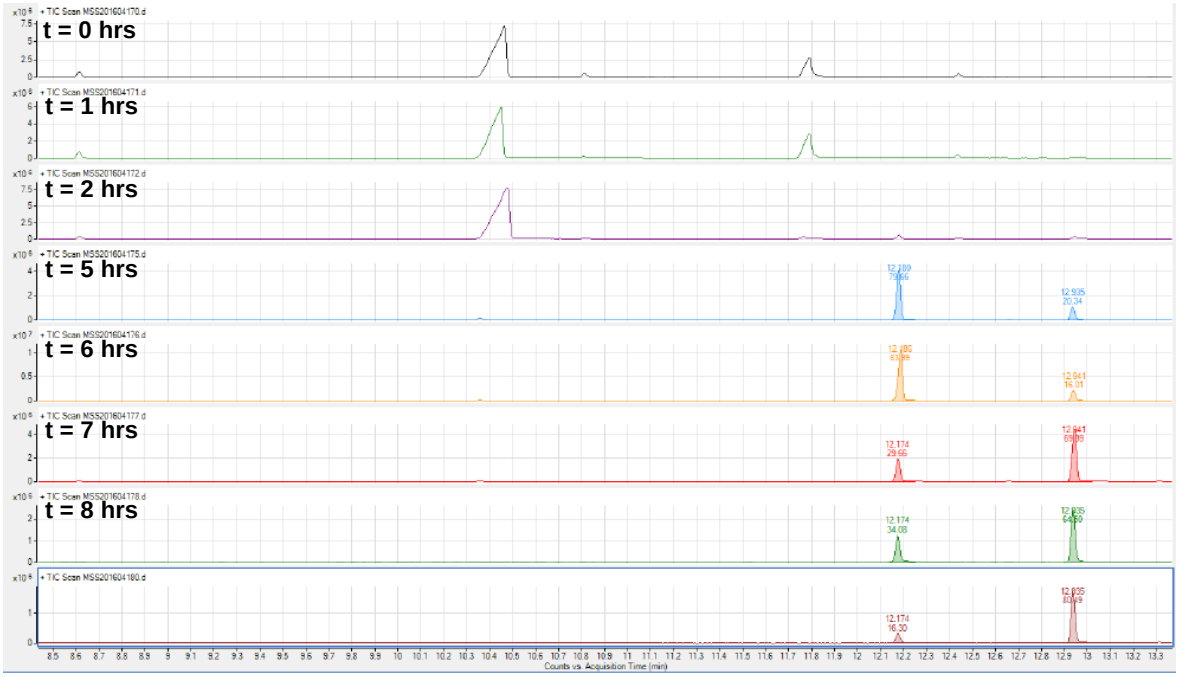


Figure 8

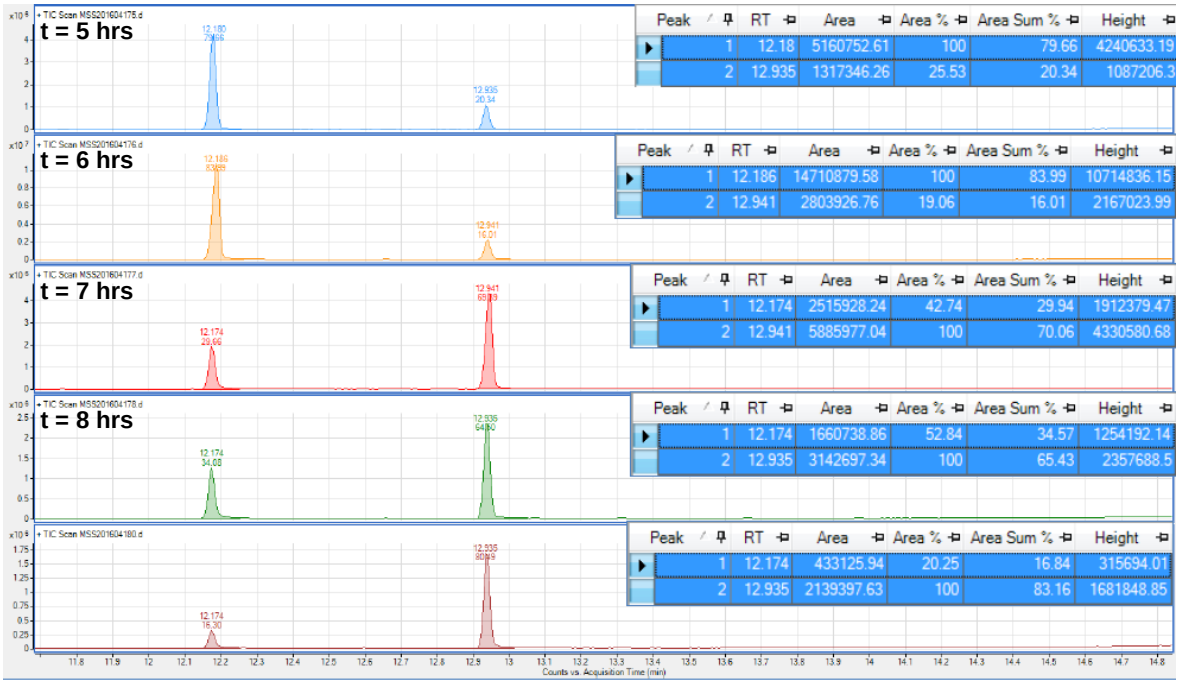
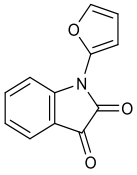


Figure 9

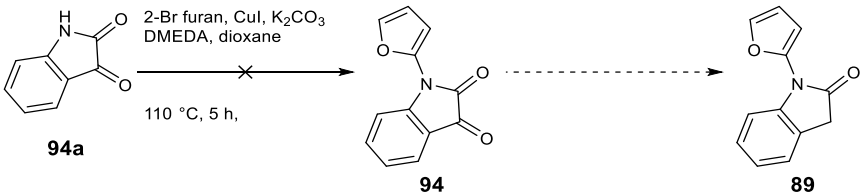


94

Figure 10

At t = 2 hours (chromatogram 3, figure **8**) the desired product had started to form along with an insignificant amount of **94**. By t = 5 hours the majority of oxindole (elution time = 10.4 mins) had been consumed and at t = 6 hours (chromatograms 1 and 2 respectively, figure **9**) the ratio of **89** to **94** was the highest at 5.25:1. The proportional increase of **94** thereafter indicates that the optimal reaction time is 6 hours. Furthermore, the largest increase in proportion of **94** is between t= 6 and t = 7 hours. This suggests there is an induction time for the oxidation to **89** to **94** after which the conversion is rapid. If the theorised structure of **94** is correct, the oxidation may occur due to adventitious oxygen in the system. The use of an argon atmosphere rather than nitrogen may help to reduce the side-reaction, due to its density being greater than that of air.

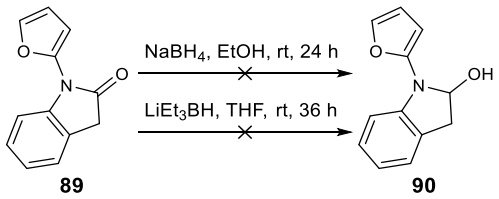
The results of this reaction monitoring warranted further investigation. Isatin was subjected to the same reaction conditions as oxindole (scheme **61**). 2-Bromofuran was reacted with 1.2 eq. of isatin at 110 °C using potassium carbonate as the base and catalytic quantities of copper iodide and DMEDA. The mixture was heated for five hours based on the induction time suggested in the results of the reaction monitoring. Unfortunately, the conditions that were successful for coupling the furan moiety to oxindole proved to be less effective when isatin was the other partner. It was concluded that **94** did not arise from coupling of 2-bromofuran with isatin (formed by oxidation of oxindole). However, the decomposition of **89** parallels the production of **94**, so it would appear that the latter is the product of oxidation of **89**.



94a **94** **89**

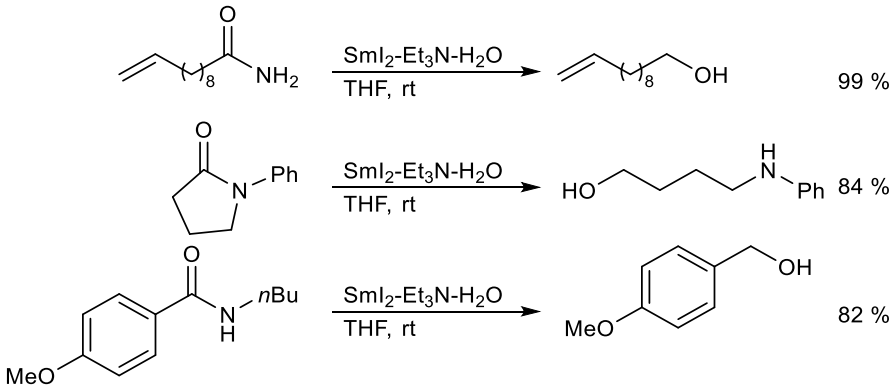
Scheme 61

A brief study was made into the reduction of the lactam in **89** to hemiaminal **90** (scheme **62**.) Sodium borohydride in ethanol[63,88] and superhydride in THF[64] were both tested though no useful products were obtained. Although these methods have previously been successfully applied to β- and γ-lactams,[88] the products resulting from treatment with sodium borohydride could not be identified. Aromatic and alkyl proton NMR signals were evident but could not be assigned to a structure. The use of superhydride only gave degradation products.



Scheme 62

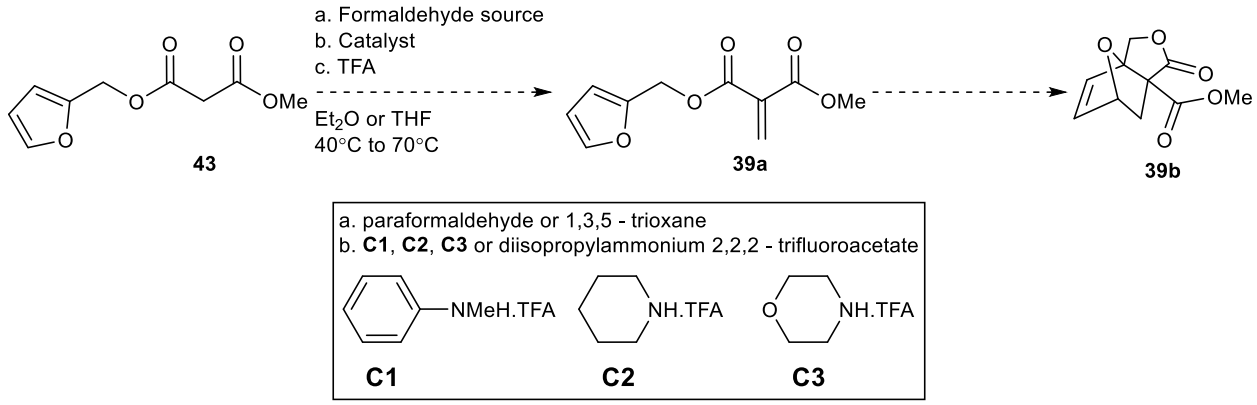
Other options for reducing the lactam in **89** to **90** are suggested in the literature. For example Procter has reported using a SmI_2-amine-water system for the chemoselective reduction of amides to alcohols (scheme **63**).[89] However, these conditions would only serve as a starting point for such investigations as no example of an oxindole lactam was reported. Still, Procter notes that there is a wide substrate scope for the mild conditions studied.



Scheme 63

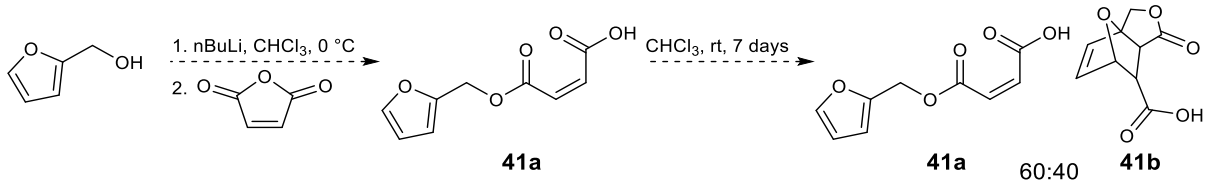
3.4 Future work

The novelty of cycloadduct **39b** prompts the optimisation of the condensation-cycloaddition that precedes it. Connell[90] studied a range of ammonium based catalysts for methylenation and found that along with diisopropylammonium 2,2,2-trifluoroacetae, catalysts **C1** to **C3** led to high yields. If a suitable catalyst, in the ideal stoichiometry, can be found, a lower reaction temperature may be advantageous in preventing degradation and may allow for isolation of **39a** prior to cycloaddition. A controlled addition of the formaldehyde source (whether this be paraformaldehyde or the alternative 1,3,5-trioxane) may reduce unwanted side reactions, for example, if 1 eq. was added to the reaction mixture every hour instead of 2 eq. every 2 hours. These considerations are summarised in scheme **64**.



Scheme 64

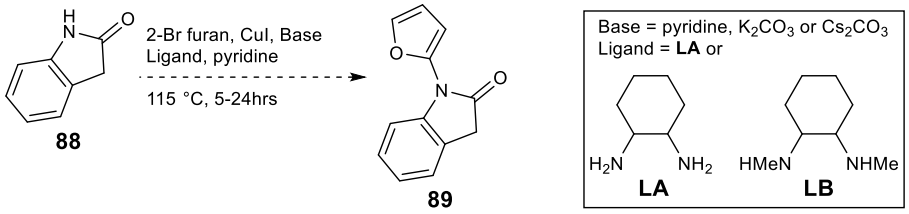
To complete the picture of the reactivity of these ester-linked substrates maleate isomer **41a** will also be studied. It has been reported that upon treatment with nBuLi, furfuryl alcohol reacts with maleic anhydride to give **41a**. Upon prolonged reaction in $CHCl_3$ at room temperature, a 60:40 mixture of the starting material and cycloadduct **41b** is obtainable (scheme **65**).[91] Interestingly, if diethyl ether is used as the reaction solvent, formation of the intermolecular Diels-Alder product is favoured.



Scheme 65

The other key reaction that requires optimisation is the copper mediated cross coupling shown in scheme **61**, in order to prevent oxidation to isatin derivative **94**. As previously mentioned, exclusion of oxygen will be key here. As well as an argon atmosphere, a different solvent could be used. Pyridine is a possible alternative as it has a high boiling point as well as a lower oxygen solubility than dioxane which was previously used.[92] It is a good ligand for copper so there will be an equilibrium between various Cu-ligand. Pyridine may not be basic enough to act as the base in the reaction, but it has successfully been used in combination with Cs_2CO_3 in aryl halide coupling reactions.[93]

The ligand in the reaction could be varied as well as the solvent. Ligands based on an ethylenediamine (e.g. DMEDA as previously used) or cyclohexanediamine structure (e.g. **LA** and **LB**, shown in the summary in scheme **66** below) in particular provide the desired product in similar reactions.[94] Mono substitution at the amine, especially in the case of methylation, provides the highest reaction rates. Further substitution hinders reactivity and where the amine centre is left unsubstituted, unwanted N-arylation is likely to occur.


2-Br furan, CuI, Base
Ligand, pyridine
115 °C, 5-24hrs
88
89
Base = pyridine, K_2CO_3 or Cs_2CO_3
Ligand = **LA** or
H_2N
NH_2
HMeN
NHMe
LA
LB

Scheme 66

4.0 Conclusion

Three routes to an IMDAF substrate towards the synthesis of (-)-picrinine have been described. The key step in one route was an *ortho*-lithiation of a Cbz-protected aniline while a second was beneficial in that linear manipulations replaced the need for lithiating reagents. Both of these routes were unsuccessful. The third route is more promising. Copper mediated coupling between oxindole and 2-bromofuran was successful, and with further optimisation could form the basis of a viable route to IMDAF substrates relevant to the synthesis of picrinine.

Studies were began into the synthesis of a wider range of model IMDAF substrates. A range of aldehyde-bearing substrates were prepared to investigate the scope for asymmetric organocatalysis using chiral imidizolidinones. After attempts to induce an asymmetric IMDAF using these catalysts were unsuccessful, the activation of the dienophile was increased by using a di-ester substituted alkene. A new strategy was introduced to use DKR to obtain a single enantiomer from a racemic mixture of cycloadducts.

5.0 Experimental

5.1 General methods

All chemicals were supplied by Sigma Aldrich, Tokyo Chemical Industry, Acros and Fisher Scientific and were used as received. DMF, MeCN, THF and toluene were purchased anhydrous. MeOH and DCM were distilled from calcium sulfate. THF was dried and distilled over sodium wire/benzophenone. All experiments were performed in flame or oven dried glassware under a protective atmosphere of nitrogen.

All column chromatography was performed using Fisher silica gel, 60 Å pore size, 230-400 mesh, 40-63 μm. All TLC analysis was performed using silica gel on Merck aluminium TLC silica gel plates, with visualisation by fluorescence quenching using 254 nm light or staining with potassium permanganate solution.

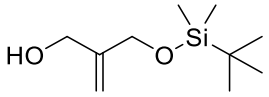
Nuclear magnetic resonance (NMR) data were acquired using a Bruker Avance 400 MHz spectrometer. Chemical shifts (δ_H) for hydrogen are expressed in parts per million (ppm) relative to tetramethylsilane (0.0 ppm). Chemical shifts for carbon (δ_C) are reported in parts per million relative to the carbon resonances of the residual solvent peak. Carbon resonances were assigned by correlation with hydrogen resonance using HSQC and HMBC spectra. Coupling constants (J) are expressed in Hz and rounded to the nearest 0.1 Hz.

All Fourier transform infra-red (FTIR) data acquired as thin films using a Thermo Electron Corporation Nicolet 380 FTIR with Smart Orbit diamond window instrument with wavenumbers (ν_{max}) being reported in cm^{-1}.

MS data exploiting electrospray ionisation in the positive mode (ESI+) was acquired using an Agilent 6210 TOF spectrometer with direct injection.

5.2 Synthesis of compounds

2-(((Tertbutyldimethylsilyl)oxy)methyl)prop-2-en-1-ol **24**[95]



NaH (0.80 g, 20 mmol) was added to a flask and the majority of the oil removed by washing with THF. 50 mL dry THF was added to the flask and cooled. At 0°C 2-methylenepropane-1,3-diol (1.63 mL, 20 mmol) was added dropwise. The mixture was brought to room temperature and allowed to stir for 50 mins. TBSCl (3.01 g, 20 mmol) was added in one batch then the mixture was allowed to stir overnight under N_2. The reaction was quenched with H_2O then extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo*.

The crude product was purified by silica gel column chromatography (15% EtOAc in hex) and the desired product was obtained as a colourless oil in 57% yield (2.31 g, 11.40 mmol).

^{1}H NMR (400 MHz): δ_H 0.09 (s, 6H, Si(C(CH$_3$)$_3$(C*H$_3$*)$_2$)), 0.91 (s, 9H, Si(C(C*H$_3$*)$_3$(CH$_3$)$_2$), 1.96 (t, J = 6.1 Hz, 1H, *OH*), 4.18 (d, J = 6.0 Hz, 2H, C*H$_2$*OH), 4.25 (s, 2H, C*H$_2$*OTBS), 5.09 (d, J = 7.0 Hz, 2H, CC*H$_2$*)

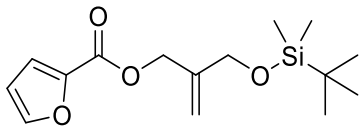
^{13}C NMR (100 MHz): δC -5.4 (*C*H$_3$, Si(*C*H$_3$)$_2$C(CH$_3$)$_3$), 18.3 (*C*, Si(CH$_3$)$_2$*C*(CH$_3$)$_3$), 25.9 (*C*H$_3$, Si(CH$_3$)$_2$C(*C*H$_3$)$_3$), 64.8 (*C*H$_2$, *C*H$_2$OH), 65.2 (*C*H$_2$,*C*H$_2$OTBS), 111.2 (*C*H$_2$, C*C*H$_2$), 147.4 (*C*, *C*CH$_2$)

MS: HRMS-ESI calculated for C$_{10}$H$_{12}$O$_2$Si m/z = 202.1389, found m/z = 203.1462 [M+H]$^+$ and 225.1283 [M+Na]$^+$

IR: υ (OH) 3353.9 cm^{-1}

R_f = 0.07 (15% EtOAc in hexane)

2-(((Tertbutyldimethylsilyl)oxy)methyl)allyl furan-2-carboxylate **26a**[96]



Furoic acid (1 mmol, 112 mg), PPh$_3$ (1.1 mmol, 289 mg) and 2-(((tertbutyldimethylsilyl)oxy)methyl)prop-2-en-1-ol **24** (1.1 mmol, 223 mg) were added to a flask followed by 10 mL dry DCM. DEAD (1.1 mmol, 0.2 mL) was then added dropwise at 0 °C over a few minutes and the reaction was left to stir at room temperature under an atmosphere of N_2 for 22 hours. The mixture was washed with sat. aq. NaHCO$_3$, then water, dried over Na$_2$SO$_4$ and the solvent removed *in vacuo*. The crude product was subjected to silica gel column chromatography using fine silica gel (4→8% EtOAc/Hex) and the desired product was obtained as a yellow oil in 90 % yield (0.266 g).

^{1}H NMR (400 MHz): δ_H 0.08 (s, 6H, Si(C(CH$_3$)$_3$(C*H$_3$*)$_2$)), 0.91 (s, 9H, Si(C(C*H$_3$*)$_3$(CH$_3$)$_2$), 4.23 (d, J = 6.0 Hz, 2H, C*H$_2$*OTBS), 4.82 (s, 2H, C*H$_2$*O(CO)), 5.22 (s, 1H, CC*H*H'), 5.29 (s, 1H, CCH*H'*), 6.51-6.53 (m, 1H, 4-Ar*H*), 7.19 (d, J = 3.4 Hz, 1H, 3-Ar*H*), 7.59 (d, J = 1.6, 1H, 5-Ar*H*)

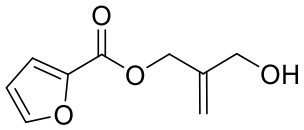
^{13}C NMR (100 MHz): δC -5.4 (*C*H$_3$, Si(*C*H$_3$)$_2$C(CH$_3$)$_3$), 18.4 (*C*, Si(CH$_3$)$_2$*C*(CH$_3$)$_3$), 28.9 (*C*H$_3$, Si(CH$_3$)$_2$C(*C*H$_3$)$_3$), 63.8 (*C*H$_2$, *C*H$_2$OTBS), 64.9 (*C*H$_2$, *C*H$_2$O(CO)), 111.8 (*C*H, 4-Ar*C*), 113.5 (*C*H$_2$, C*C*H$_2$), 118.0 (*C*H, 3-Ar*C*), 142.9 (*C*, *C*CH$_2$), 144.6 (*C*, 2-Ar*C*), 146.4 (*C*H, 5-Ar*C*), 158.4 (*C*, *C*O)

MS: HRMS-ESI calculated for C$_{15}$H$_{24}$O$_4$Si m/z = 296.1449, found m/z = 297.1521 [M+H]$^+$ and m/z = 319.1344 [M+Na]$^+$

IR: υ (CO) 1720.9 cm^{-1}

R_f = 0.13 (4% EtOAc in hex)

2-(Hydroxymethyl)allyl furan-2-carboxylate **27a**



2-(((Tertbutyldimethylsilyl)oxy)methyl)allyl furan-2-carboxylate **26a** (0.9 mmol, 266 mg) was dissolved in dry THF (5 mL) and TBAF (1.8 mmol, 1.8 mL, 1M in THF) added dropwise at 0°C. The solution was allowed to stir at room temperature under an atmosphere of nitrogen for 2.5 hours and was then quenched with water and extracted with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude product was subjected to silica gel column chromatography (20% EtOAc in hexane) and the desired product was obtained as a yellow oil in 50% yield (0.081 g, 0.45 mmol).

^{1}H NMR (400 MHz): δ_H 1.86 (t, J = 6.2 Hz, 1H, CH_2O*H*), 4.22 (d, J = 6.0 Hz, 2H, C*H*$_2$OH), 4.89 (s, 2H, C*H*$_2$O(CO)), 5.30 (d, 2H, CC*H*$_2$), 6.53 (dd, J_a = 1.7, J_b= 3.5, 1H, 4-Ar*H*), 7.22 (dd, J_a = 0.4, J_b= 3.5, 1H, 3-Ar*H*), 7.60 (d, J = 0.9, 1H, 5-Ar*H*)

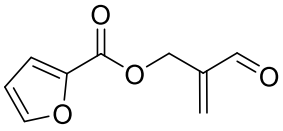
^{13}C NMR (100 MHz): 63.8 (*C*H_2, *C*H_2OH), 65.1 (*C*H_2, *C*H_2O(CO)), 112.0, (*C*H, 4-Ar*C*), 115.1 (*C*H_2, C*C*H_2), 118.4 (*C*H, 3-Ar*C*), 143.0 (*C*, *C*CH_2), 144.3 (*C*, 2-Ar*C*), 146.6 (*C*H, 5-Ar*C*), 158.6 (*C*, *C*O)

MS: HRMS-ESI calculated for $C_9H_{10}O_4$ m/z = 182.0577, found m/z = 183.0650 $[M+H]^+$ and m/z = 205.0469 $[M+Na]^+$

IR: υ (CO) 1635.4 cm^{-1}, υ (OH) 3150.0 cm^{-1}

R_f = 0.09 (20% EtOAc in hex)

2-Formylallyl furan-2-carboxylate **28a**



2-(Hydroxymethyl)allyl furan-2-carboxylate **27a** (0.44 mmol, 81 mg) and DMP (0.66 mmol, 283 mg) were added to a flask followed by 3 mL dry DCM. The reaction was allowed to stir under an atmosphere of N_2 for three hours. The reaction was quenched with sat. aq. $NaHCO_3$ then extracted with DCM. The combined organic extracts were washed with water, dried over Na_2SO_4 then the solvent removed *in vacuo*. The crude product was subjected to silica gel column chromatography (10 % EtOAc/hex) and the desired product was obtained as a white solid in 63 % yield (0.050 g, 0.28 mmol).

^{1}H NMR (400 MHz): δ_H 5.06 (t, J = 1.2, 2H, C*H*$_2$O(CO)), 6.26 (s, 1H, CC*H*H'), 6.55 (t, J = 1.4 Hz, 1H, CCH*H'*), 6.53 (dd, J_a = 1.7, J_b= 3.5, 1H, 4-Ar*H*), 7.23 (d, J = 3.5, 1H, 3-Ar*H*), 7.61 (d, J = 0.9 Hz, 1H, 5-Ar*H*), 9.64 (s, 1H, C*H*O)

^{13}C NMR (100 MHz): δC 60.3 (*C*H$_2$, *C*H$_2$O(CO)), 112.0, (*C*H, 4-Ar*C*), 118.5 (*C*H, 3-Ar*C*), 135.0 (*C*H$_2$, C*C*H$_2$), 143.3 (*C*, *C*CH$_2$), 144.4 (*C*, 2-Ar*C*), 146.9 (*C*H, 5-Ar*C*), 159.6 (*C*, *C*O), 192.4 (*C*H, *C*HO)

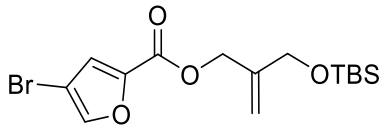
MS: HRMS-ESI calculated for $C_9H_8O_4$ m/z = 180.0422, found m/z = 181.0495 $[M+H]^+$ and m/z = 203.0313 $[M+Na]^+$

IR: υ (C=*C*-*H*) 3129.4 and 3114.3 cm^{-1}, υ (*C*-*H*O) 2925.9 and 2852.0 cm^{-1}, υ (CO) 1720.4 cm^{-1}, υ (C=*CH$_2$*) 1673.6 cm^{-1}

R_f = 0.22 (10% EtOAc in hex)

Mp: 73-74 °C

2-(((Tertbutyldimethylsilyl)oxy)methyl)allyl 4-bromofuran-2-carboxylate **26b**[96]



4-Bromofuran-2-carboxylic acid (8.08 mmol, 1.54 g), PPh_3 (8.89 mmol, 2.33 g) and 2-(((tert-butyldimethylsilyl)oxy)methyl)prop-2-en-1-ol (8.89 mmol, 1.80 g) were added to a flask followed by 70 mL dry DCM. DEAD (8.89 mmol) was then added dropwise at 0°C over a few minutes and the reaction was left to stir at room temperature under an atmosphere of N_2 for 22 hours. The mixture was washed with sat. aq. $NaHCO_3$, then water, dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography using fine silica gel (2 % EtOAc/petrol). The desired product was obtained as a yellow oil in 84% yield (2.56 g, 6.79 mmol).

^{1}H NMR (400 MHz): δ_H 0.08 (s, 6H, Si(C(CH$_3$)$_3$(C*H$_3$*)$_2$)), 0.91 (s, 9H, Si(C(C*H$_3$*)$_3$(CH$_3$)$_2$), 4.21 (s, 2H, C*H$_2$*OSi(C(CH$_3$)$_3$(C*H$_3$*)$_2$)), 4.82 (s, 2H, C(O)OC*H$_2$*C(CH$_2$)), 5.21 (s, 1H, C(C*H*H')), 5.29 (s, 1H, C(CH*H'*)), 7.19 (s, 1H, 3-Ar*H*), 7.58 (s, 1H, 5-Ar*H*)

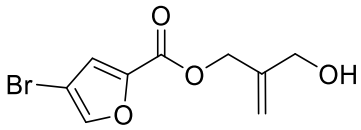
^{13}C NMR (100 MHz): δ_C -5.4 (*C*H$_3$, Si(C(*C*H$_3$)$_3$(CH$_3$)$_2$), 18.3 (*C*, Si(*C*(CH$_3$)$_3$(CH$_3$)$_2$)), 25.9 (*C*H$_3$, Si(C(CH$_3$)$_3$(CH$_3$)$_2$)), 63.8 (*C*H$_2$, *C*H$_2$OSi(C(CH$_3$)$_3$(CH$_3$)$_2$)), 65.3 (*C*H$_2$, C(O)O*C*H$_2$C(CH$_2$)), 113.8 (*C*H$_2$, C(*C*H$_2$)), 120.4 (*C*H, 5-Ar-*C*), 142.6 (*C*, *C*(CH$_2$)), 144.5 (*C*H, 3-Ar*C*), 150.0 (*C*, 4-Ar*C*), 157.5 (*C*, *C*(O))

MS: HRMS-ESI calculated for $C_{15}H_{24}O_4Si$ m/z = 374.0549, found m/z = 375.0622 $[M+H]^+$

IR: υ (CO) 1727.4 cm^{-1}

R_f = 0.17 (2% EtOAc in petrol)

2-(Hydroxymethyl)allyl 4-bromofuran-2-carboxylate **27b**



2-(((Tert-butyldimethylsilyl)oxy)methyl)allyl 4-bromofuran-2-carboxylate (6.55 mmol, 2.46 g) was dissolved in dry THF (23 mL) and TBAF (13.10 mmol, 13.1 mL) added dropwise at 0°C. The solution was allowed to stir at this temperature under an atmosphere of nitrogen for 1 hour and then the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (10 → 40 % EtOAc in petrol) to give the desired product as a pale yellow oil in 70 % yield (1.20 g, 4.59 mmol).

^{1}H NMR (400 MHz): δ_H 1.82 (t, J = 5.7 Hz, 1H, CO*H*), 4.21 (d, J = 3.4 Hz, 2H, C*H*$_2$OH), 4.88 (s, 2H, C(O)OC*H*$_2$C(CH$_2$)), 5.27 (q, J_a = 1.1 Hz, J_b = 2.0 Hz, 1H, C(C*H*H')), 5.32 (s, 1H, CCH*H'*), 7.22 (d, J = 0.7 Hz, 1H, 5-Ar*H*), 7.59 (d, J = 0.8 Hz, 1H, 3-Ar-H)

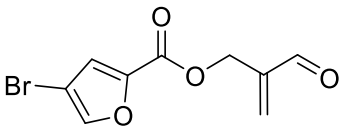
^{13}C NMR (100 MHz): δC 63.7 (*C*H$_2$, *C*H$_2$OH), 65.4 (*C*H$_2$, C(O)O*C*H$_2$C(CH$_2$)), 101.4 (*C*, 2-ArC), 115.3 (*C*H$_2$, C(*C*H$_2$)), 120.7 (*C*H, 5-Ar-*C*), 142.7 (*C*, *C*(CH$_2$)), 144.7 (*C*H, 3-Ar*C*), 144.8 (*C*, 4-Ar-*C*), 157.6 (*C*, *C*(O))

MS: HRMS-ESI calculated for $C_9H_{12}O_3$ m/z = 259.9684, found m/z = 260.9752 $[M+H]^+$ and 282.9578 $[M+Na]^+$

IR: υ (OH) 3391.6 cm^{-1}, υ (CO) 1716.5 cm^{-1},

R_f = 0.17 (10% EtOAc in petrol)

2-Formylallyl 4-bromofuran-2-carboxylate **28b**



2-(Hydroxymethyl)allyl 4-bromofuran-2-carboxylate (4.40 mmol, 1.15 g) was dissolved in 20 mL dry DCM and DMP (6.60 mmol, 2.80 g) was added at 0 °C. The reaction was allowed to stir under an atmosphere of argon at this temperature for three hours. The reaction was quenched with sat. aq. $NaHCO_3$ then extracted with DCM. The combined organic extracts were washed with brine, dried over Na_2SO_4 then the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (10 → 15 % EtOAc/petrol) to give the desired product as a white solid in 75 % yield (0.86 g, 3.30 mmol).

^{1}H NMR (400 MHz): δ_H 5.05 (appt, J = 1.2, 2H, C*H*$_2$O(CO)), 6.27 (t, J = 1.0, 1H, CC*H*H'), 6.54 (t, J = 1.4 Hz, 1H, CCH*H*'), 7.23 (d, J = 0.7, 1H, 3-Ar*H*), 7.60 (d, J = 8, 1H, 3-Ar*H*), 9.63 (s, 1H, C*H*O)

^{13}C NMR (100 MHz): δC 60.6 (*C*H$_2$, *C*H$_2$O(CO)), 101.39, (*C*, 2-Ar*C*), 120.9 (*C*H, 5-Ar*C*), 135.3 (*C*H$_2$, C(*C*H$_2$)), 144.0 (*C*, *C*(CH$_2$)), 144.5 (*C*, 4-Ar*C*), 144.8 (*C*H, 3-Ar*C*), 157.1 (*C*, *C*O), 192.2 (*C*H, *C*HO)

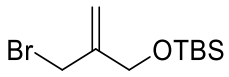
MS: HRMS-ESI calculated for $C_9H_{10}O_3$ m/z = 257.8522, found m/z = 258.9597 [M+H$^+$] and 280.9414 [M+Na$^+$]

IR: υ (C=O) 1715.8 cm^{-1}, υ (CHO) 1687.6 cm^{-1}

MP: 90 – 92 °C

R_f = 0.16 (10 % EtOAc in petrol)

((2(Bromomethyl)allyl)oxy)(tertbutyl)dimethylsilane **29**[97]



2(((Tertbutyldimethylsilyl)oxy)methyl)prop-2-en-1-ol (16.2 mmol, 3.28 g) was dissolved in dry THF (35 mL), cooled to -20 °C then trimethylamine (32.4 mmol, 4.5 mL) and MsCl (22.3 mmol, 1.89 mL) were added. The mixture was stirred at -20 °C for 1.5 hours then warmed to 0 °C and LiBr (4 M, 4.8 mL) added dropwise. A further 4.8 mL LiBr was added after 2 hrs then after a further 1 hr stirring under an atmosphere of argon the reaction was quenched with sat. aq. $NaHCO_3$ and extracted with ether. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (petrol) to give the desired product as a pale yellow oil in 79 % yield (3.39 g, 11.3 mmol).

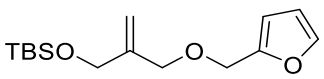
^{1}H NMR (400 MHz): δ_H 0.10 (s, 6H, Si(*CH$_3$*)$_2$C(CH$_3$)$_3$), 0.92 (s, 9H, Si(CH$_3$)$_2$C(*CH$_3$*)$_3$), 4.01 (s, 2H, *CH$_2$*Br), 4.27 (t, J = 1.4, 2H, *CH$_2$*OSi), 5.23-5.24 (m, 2H, C*CH$_2$*)

^{13}C NMR (100 MHz): δC -5.4 (*C*H$_3$, Si(CH$_3$)$_2$C(*C*H$_3$)$_3$), 18.3 (*C*, Si(CH$_3$)$_2$*C*(CH$_3$)$_3$), 25.9 (*C*H$_3$, Si(CH$_3$)$_2$C(*C*H$_3$)$_3$), 32.8 (*C*H$_2$, *C*H$_2$Br), 63.5 (*C*, *C*H$_2$OSi), 114.8 (*C*H$_2$, C*C*H$_2$), 144.8 (*C*, *C*CH$_2$)s

IR: υ (C=*C*-*H*) 2954.4, 2928.6 and 2856.4 cm^{-1}

Rf = 0.4 (petrol)

Tert-butyl((2-((furan-2-ylmethoxy)methyl)allyl)oxy)dimethylsilane **30**[98]



A solution of furfuryl alcohol (12.1 mmol, 1 mL) in THF (16 mL) was slowly added to a suspension of NaH (24.2 mmol, 0.97 g) and TBAI (1.20 mmol, 0.48 g) in THF (18 mL) at 0 °C under an atmosphere of Ar, followed by 40 min stirring. ((2(bromomethyl)allyl)oxy)(tertbutyl)dimethylsilane (12.4 mmol, 3.30 g) in THF (8 mL) was then added, and the mixture was stirred for one hour under an atmosphere of argon. The reaction was quenched with water and extracted with ether. The combined organic phases were washed with brine, dried with $MgSO_4$ and the solvent removed *in vacuo.* The crude product was purified by silica gel column chromatography (1 % EtOAc/petrol) to give the desired product in 95 % yield (3.26 g, 11.50 mmol).

^{1}H NMR (400 MHz): δ_H 0.07 (s, 6H, Si(C(CH_3)$_3$(C*H*$_3$)$_2$)), 0.91 (s, 9H, Si(C(C*H*$_3$)$_3$(CH_3)$_2$), 4.02 (s, 2H, O*CH*$_2$CCH_2), 4.17 (s, 2H, C*CH*$_2$OSi(C(CH_3)$_3$(CH_3)$_2$), 4.43 (s, 2H, CH_2O*CH*$_2$C), 5.12 (s, 1H, CC*H*H'), 5.24 (s, 1H, CCH*H'*), 6.30-6.31 (m, 1H, 3-Ar*H*), 6.33-6.34 (m, 1H, 4-Ar*H*), 7.40-7.41 (m, 1H, 5-Ar*H*)

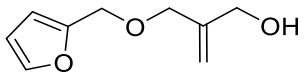
^{13}C NMR (100 MHz): δC -5.4 (*C*H_3, Si(*C*H_3)$_2$C(CH_3)$_3$), 18.30 (*C*, Si(CH_3)$_2$*C*(CH_3)$_3$), 25.9 (*C*H_3, Si(CH_3)$_2$C(*C*H_3)$_3$), 63.6 (*C*H_2, O*C*H_2-ArC), 63.8 (*C*H_2, C*C*H_2OSi(CH_3)$_2$C(CH_3)$_3$), 70.6 (*C*H_2, CH_2O*C*H_2C), 109.3 (*C*H, 3-Ar*C*), 110.2 (*C*H, 4-Ar*C*), 112.2 (*C*, C(*C*H_2)), 142.78 (*C*H, 5-Ar*C*), 144.9 (*C*, *C*(CH_2)), 151.80 (*C*, 2-Ar*C*).

MS: HRMS-ESI calculated for $C_{15}H_{24}O_4Si$ m/z = 296.14, found m/z = 297.15 $[M+H]^+$ and m/z = 319.13 $[M+Na]^+$

IR: υ (CO) 1720.9 cm^{-1}

Rf (1% EtOAc/hex) = 0.44

2-((Furan-2-ylmethoxy)methyl)prop-2-en-1-ol **31**



Tert-butyl((2-((furan-2-ylmethoxy)methyl)allyl)oxy)dimethylsilane (11.6 mmol, 3.26 g) was dissolved in dry THF (40 mL) and TBAF (23.1 mmol, 23.1 mL) added dropwise at 0 °C. The solution was allowed to stir at 0°C under an atmosphere of argon for 1 hour and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (15% EtOAc in petrol) to give the desired product as a pale yellow oil in 98 % yield (1.92 g, 11.3 mmol).

^{1}H NMR (400 MHz): δ_H 1.86 (t, J = 5.8 Hz, 1H, CO*H*), 4.09 (s, 2H, CH_2OC*H*$_2$C(CH_2)), 4.19 (2, J = 5.1 Hz, 1H, C*H*$_2$OH), 4.46 (s, 2H, C*H*$_2$OCH_2C(CH_2)), 5.15 (s, 1H, CC*H*H'), 5.21 (s, 1H, CCH*H'*), 6.31-6.32 (m, 1H, 4-Ar*H*), 6.35-6.36 (m, 1H, 5-Ar-H), 7.41-7.42 (m,1H, 3-ArH)

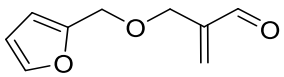
^{13}C NMR (100 MHz): δC 64.0 (*C*H_2, *C*H_2OCH_2C(CH_2)), 64.6, (*C*H_2, *C*H_2OH), 71.5 (*C*H_2, CH_2O*C*H_2C(CH_2)), 109.5 (*C*H, 4-Ar*C*), 110.3 (*C*H, 5-Ar-*C*), 113.9 (*C*H_2, C*C*H_2), 142.9 (*C*H, 3-Ar*C*), 144.8 (*C*, *C*CH_2), 151.5 (*C*, 2-Ar*C*)

MS: HRMS-ESI calculated for $C_9H_{12}O_3$ m/z = 168.0786, found m/z = 191.0679 $[M+Na]^+$

IR: υ (OH) 3363.8 cm^{-1}

R_f = 0.1 (15% EtOAc in petrol)

2-((Furan-2-ylmethoxy)methyl)acrylaldehyde **32**



2-((Furan-2-ylmethoxy)methyl)prop-2-en-1-ol (11.5 mmol, 1.94 g) and DMP (17.3 mmol, 7.35 g) were added to a flask followed by 50 mL dry DCM. The reaction was allowed to stir under an atmosphere of N_2 for three hours. The reaction was quenched with sat. aq. $NaHCO_3$ then extracted with DCM. The combined organic extracts were washed with water twice, dried over Na_2SO_4 then the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (3→6 % EtOAc/hex) to give the desired product as a clear oil in 61 % yield (1.19 g, 7.02 mmol).

^{1}H NMR (400 MHz): δ_H 4.24 (t, J = 1.6, 2H, C*H*$_2$C(CH$_2$)), 4.52 (s, 2H, C*H*$_2$OCH$_2$C(CH$_2$)), 6.15 (dd, J_a = 1.4 Hz, J_b = 2.3, 1H, CC*H*H'), 6.35 (d, 2H, J = 1.4, 3-Ar*H*, 4-Ar*H*), 6.55-6.56 (m, 1H, CCH*H'*), 7.42 (t, J = 1.4, 1H, 5-Ar*H*), 9.58 (s, 1H, C*H*O)

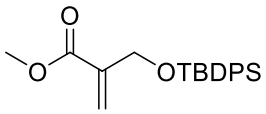
^{13}C NMR (100 MHz): δC 64.9 (*C*H$_2$, O*C*H$_2$C(CH$_2$)), 65.6 (*C*H$_2$, *C*H$_2$OCH$_2$C(CH$_2$)), 109.7 (*C*H, 3-Ar*C*), 110.3 (*C*H, 4-Ar*C*), 134.3 (*C*H$_2$, C*C*H$_2$)), 143.0 (*C*H, 5-Ar*C*), 146.5 (*C*, *C*(CH$_2$)), 151.3 (*C*, 2-Ar*C*), 193.4 (*C*H, *C*HO)

MS: HRMS-ESI calculated for $C_9H_{10}O_3$ m/z = 166.0631, found m/z = 189.0523 $[M+Na^+]$

IR: υ (C=O) 1684.5 cm^{-1}

R_f = 0.20 (3 % EtOAc in hex)

Methyl 2-(((tert-butyldiphenylsilyl)oxy)methyl)acrylate **34**[99]



Imidazole (40.6 mmol, 2.76 g) was dissolved in dry DCM (120 mL) and methyl 2-(hydroxymethyl)acrylate (36.9 mmol, 3.8 mL) added. TBDPSCl (40.6 mmol, 10.6 mL) was added over 5 minutes at 0 °C and the mixture was allowed to stir at room temperature for 1 hr 50 minutes under an atmosphere of argon. The reaction was quenched at 0 °C with water and extracted with EtOAc. The combined organic phases were washed with brine, dried over MgSO4, filtered, and concentrated *in vacuo*. The

crude product was progressed without purification. Quantitative yield (13.1 g, 36.9 mmol) was assumed.

^{1}H NMR (400 MHz): δ_H 1.08 (s, 9H, C(C*H*$_3$)$_3$), 3.69 (s, 3H, C*H*$_3$O(CO)), 4.24 (s, 2H, C*H*$_2$OTBDPS), 6.12 (dd, J_a = 2.0 Hz, J_b = 4.0 Hz, 1H, CC*H*H'), 6.34 (dd, J_a = 1.8 Hz, J_b = 3.7 Hz, 1H, CCH*H'*), 7.67-6.68 (m, 4H, Ar*H*), 7.40-7.41 (m, 6H, Ar*H*)

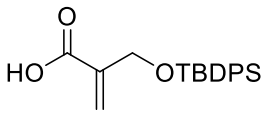
^{13}C NMR (100 MHz): δC 19.3 (*C*, *C*(CH$_3$)$_3$), 26.8 (*C*H$_3$, C(*C*H$_3$)$_3$), 51.7 (*C*H$_3$, O*C*H$_3$), 62.2 (*C*H$_2$, *C*H$_2$OTBDPS), 124.1 (*C*H$_2$. C(*C*H$_2$)), 127.8 (*C*H, 2,3,5,6-Ar*C*), 129.8 (*C*H, 4-Ar*C*), 133.2 (*C*, 1-Ar*C*), 135.5 (*C*H, 2,3,5,6-Ar*C*), 139.4 (*C*, *C*(CH$_2$), 166.3 (*C*, *C*(CO))

MS: HRMS-ESI calculated for $C_{21}H_{26}O_3Si$ m/z = 354.1651, found m/z = 377.1543 [M+Na$^+$]

IR: υ (C=O) 1715.5 cm^{-1}

R_f = 0.19 (2 % EtOAc in petrol)

2-(((Tertbutyldiphenylsilyl)oxy)methyl)acrylic acid **35**[100]



Methyl 2-(((tertbutyldiphenylsilyl)oxy)methyl)acrylate (36.9 mmol, 13.1 g) was dissolved in THF/H2O (v/v = 1/1, 195 mL) and aq. LiOH (4.6 N, 38.8 mL) was added. The mixture was stirred at room temperature for overnight. The reaction was acidified (pH = 1.0) with 1.0 N aq. HCl and extracted with diethyl ether. The organic layer was dried over anhydrous Na2SO4, filtered and concentrated *in vacuo*. The crude product was recrystallised from 1:10 Et$_2$O/Hexane to give the pure product as clear crystals in 52 % yield (6.36 g, 19.2 mmol).

^{1}H NMR (400 MHz): δ_H 1.08 (s, 9H, C(C*H*$_3$)$_3$), 3.69 (s, 3H, C*H*$_3$O(CO)), 4.24 (s, 2H, C*H*$_2$OTBDPS), 6.12 (dd, J_a = 2.0 Hz, J_b = 4.0 Hz, 1H, CC*H*H'), 6.34 (dd, J_a = 1.8 Hz, J_b = 3.7 Hz, 1H, CCH*H'*), 7.66-7.67 (m, 4H, Ar*H*), 7.40-7.41 (m, 6H, Ar*H*)

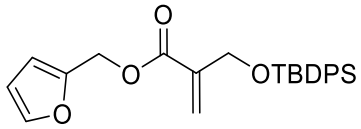
^{13}C NMR (100 MHz): δC 19.3 (*C*, *C*(CH$_3$)$_3$), 26.8 (*C*H$_3$, C(*C*H$_3$)$_3$), 51.7 (*C*H$_3$, O*C*H$_3$), 62.2 (*C*H$_2$, *C*H$_2$OTBDPS), 124.1 (*C*H$_2$. C(*C*H$_2$)), 127.8 (*C*H, 2,3,5,6-Ar*C*), 129.8 (*C*H, 4-Ar*C*), 133.2 (*C*, 1-Ar*C*), 135.5 (*C*H, 2,3,5,6-Ar*C*), 139.3 (*C*, *C*(CH$_2$), 166.3 (*C*, *C*(CO))

MS: HRMS-ESI calculated for $C_{20}H_{24}O_3Si$ m/z = 340.1494, found m/z = 339.1420 [M-H$^-$]

Mp = 125-126 °C

R_f = 0.19 (2 % EtOAc in petrol)

Furan-2-ylmethyl 2-(((tert-butyldiphenylsilyl)oxy)methyl)acrylate **36**[96]



2-(((tert-butyldiphenylsilyl)oxy)methyl)acrylic acid (11.3 mmol, 3.85 g), PPh_3 (12.4 mmol, 3.26 g) and furfuryl alcohol (12.4 mmol, 1.1 mL) were added to a flask followed by 100 mL dry DCM. DEAD (8.89 mmol, 2 mL) was then added dropwise at 0 °C over a few minutes and the reaction was left to stir at room temperature under an atmosphere of argon for 1 hour. The mixture was quenched with sat. aq. $NaHCO_3$, extracted with DCM, dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (2 % EtOAc/petrol). The desired compound was obtained as a yellow oil in 44 % yield (2.1 g, 4.97 mmol).

^{1}H NMR (400 MHz): δ_H 1.06 (s, 9H, C(C*H*$_3$)$_3$), 4.42 (s, 2H, C*H*$_2$OTBDPS), 5.10 (s, 2H, C*H*$_2$OC(O)), 6.12 (dd, J_a = 2.1 Hz, J_b = 4.0 Hz, 1H, CC*H*H'), 6.34 (m, 2H, CCH*H'* and 4-Ar*H*), 6.38 (d, J = 3.2 Hz, 1H, 3-Ar*H*), 7.39-7.40 (m, 7H, 5-Ar*H* and Ph-Ar*H*), 7.65-7.66 (m, 4H, Ph-Ar*H*)

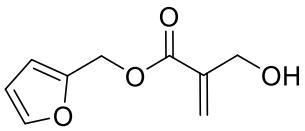
^{13}C NMR (100 MHz): δC 19.3 (*C*, *C*(CH$_3$)$_3$), 26.8 (*C*H$_3$, C(*C*H$_3$)$_3$), 58.1 (*C*H$_2$, *C*H$_2$OC(O)), 62.2 (*C*H$_2$, *C*H$_2$OTBDPS), 110.5 (*C*H, 4-Ar*C*), 110.7 (*C*H, 3-Ar*C*), 124.7 (*C*H$_2$. C(*C*H$_2$)), 127.8 (*C*H, 2,3,5,6-PhAr*C*), 129.8 (*C*H, 4-PhAr*C*), 133.2 (*C*, 1-PhAr*C*), 135.5 (*C*H, 2,3,5,6-PhAr*C*), 139.2 (*C*, *C*(CH$_2$), 143.2 (*C*H, 5-Ar*C*), 149.4 (*C*, 2-Ar*C*), 165.4 (*C*, *C*(CO))

MS: HRMS-ESI calculated for $C_{25}H_{28}O_4Si$ m/z = 443.1648, found m/z = 420.1757 $[M+Na]^+$

IR: υ (CO) 1715.3 cm^{-1}

R_f = 0.23 (2% EtOAc in petrol)

Furan-2-ylmethyl 2-(hydroxymethyl)acrylate **37**



Furan-2-ylmethyl 2-(((tert-butyldiphenylsilyl)oxy)methyl)acrylate (4.99 mmol, 2.1 g) was dissolved in 35 mL dry THF and then TBAF (7.49 mmol, 7.5 mL) was added dropwise at 0 °C. The mixture was allowed to stir at this temperature under an atmosphere of argon for 1 hour. The reaction was quenched with brine and extracted with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. The crude product was subjected to silica

gel column chromatography (ethyl acetate/petrol, 3 % → 30 % EtOAc). The desired product was obtained as a pale yellow oil in 73 % yield (0.67 g, 3.64 mmol).

^{1}H NMR (400 MHz): δ_H 2.23 (br s, 1H, O*H*), 4.34 (s, 2H, C*H*$_2$OH), 5.18 (s, 2H, C*H*$_2$OC(O)), 5.86 (dd, J_a = 1.4 Hz, J_b = 2.6 Hz, 1H, CC*H*H'), 6.29 (s, 1H, CCH*H'*), 6.36-6.37 (m, H, 3-Ar*H*), 6.44 (d, J = 3.2 Hz, 1H, 4-Ar*H*), 7.43-7.44 (m, 1H, 5-Ar*H*)

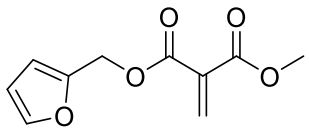
^{13}C NMR (100 MHz): δC 58.4 (*C*H$_2$, *C*H$_2$OC(O)), 62.6 (*C*H$_2$, *C*H$_2$OH), 110.6 (*C*H, 3-Ar*C*), 110.9 (*C*H, 4-Ar*C*), 126.5 (*C*H$_2$. C(*C*H$_2$)), 139.1 (*C*, *C*(CH$_2$), 143.4 (*C*H, 5-Ar*C*), 149.1 (*C*, 2-Ar*C*), 165.9 (*C*, *C*(CO))

MS: HRMS-ESI calculated for $C_9H_{10}O_4$ m/z = 182.0579, found m/z = 206.0473 $[M+Na]^+$

IR: υ (OH) 3399.3 cm^{-1}, υ (CO) 1709.9 cm^{-1}

R_f = 0.3 (20% EtOAc in petrol)

1-(Furan-2-ylmethyl) 3-methyl 2-methylenemalonate **39a**[101]



1-(Furan-2-ylmethyl) 3-methyl 2-methyl-2-(phenylselanyl)malonate (1 mmol, 0.4 g) was dissolved in DCM (27 mL) and H_2O_2 (30 % in water, 5.6 mL) added dropwise at 0°C. The reaction was allowed to stir at this temperature for 35 minutes under an atmosphere of argon. Water was added to dissolve the white precipitate and the aqueous layer was extracted with DCM. The combined organic layers were dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. The desired product was obtained in the crude form as a yellow oil in 92 % yield (0.21 g, 0.92 mmol). Subjecting the crude product to silica gel column chromatography led to significant loss of the product. The desired compound eluted in 10 % EtOAc/petrol and was obtained as a clear oil in 5 % yield (90 mg, 0.05 mmol).

^{1}H NMR (400 MHz): δ_H 3.82 (s, 3H, OC*H*$_3$), 5.21 (s, 2 H, C*H*$_2$OC(O)), 6.37-6.38 (m, 1H, 4-Ar*H*), 6.46 (d, J = 3.2 Hz, 1 H, 3-Ar*H*), 6.58 (s, 1H, C(C*H*H')), 6.58 (s, 1H, C(CH*H'*)), 7.43-7.44 (m, 1H, 5-Ar*H*)

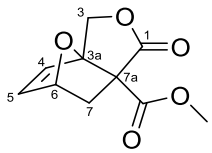
^{13}C NMR (100 MHz): δC 52.5 (*C*H$_3$, O*C*H$_3$), 58.9 (*C*H$_2$, *C*H$_2$OC(O)), 110.6 (*C*H, 4-Ar*C*), 111.1 (*C*H, 3-Ar*C*), 134.0 (*C*, *C*(CH$_2$)), 135.6 (*C*H$_2$, C(*C*H$_2$)), 143.5 (*C*H, 5-Ar*C*), 148.9 (*C*, 2-Ar*C*), 163.4 (*C*, CH$_2$O*C*(O)), 164.1 (*C*, CH*C*(O)OCH$_3$)

MS: HRMS-ESI calculated for $C_{10}H_{10}O_5$ m/z = 210.0528, found m/z = 233.0419 $[M+Na]^+$

IR: υ (CO) 1731.4 cm^{-1}

R_f = 0.29 (20 % EtOAc/petrol)

Methyl (3aR,6R)-1-oxo-6,7-dihydro-3H-3a,6-epoxyisobenzofuran-7a(1H)-carboxylate **39b**[41]



Furan-2-ylmethyl methyl malonate (1.01 mmol, 0.2 g), paraformaldehyde (2.02 mmol, 0.061 g) and diisopropylammonium 2,2,2-trifluoroacetate (1.01 mmol, 0.21 g) were dissolved in dry THF and TFA (0.10 mmol, 78 µL) was added. The mixture was stirred at reflux for 2 h under an atmosphere of argon. After 2 hours a second 2 eq. of paraformaldehyde was added. The reaction was then allowed to stir at reflux for a further 6 hrs under an atmosphere of argon. The reaction was allowed to cool then the solvent was removed *in vacuo*. The residue was dissolved in ether and washed twice with 2M HCl. The aqueous layer was extracted with ether and the combined organic layers dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography using 10 $\rightarrow$ 20 % EtOAc/petrol as the eluent. The major component was identified as **39b** and was obtained as an oil in 8 % yield (0.018 g, 0.08 mmol) which contained unidentifiable impurities. Further column chromatography failed to remove the impurities from **39b** as determined by ^{1}H NMR spectroscopy.

^{1}H NMR (400 MHz): δ_H 2.18 (d, J = 12.1 Hz, 1H, 7-*endo*), 2.51 (dd, J_a = 4.7 Hz, J_b = 7-*exo*), 3.75 (s, 3H, OC*H*$_3$), 4.68 (d, J = 10.5 Hz, 1H, 3-*H*), 4.99 (d, J = 10.5 Hz, 1H, 3-*H'*), 5.16-5.17 (m, 1H, 6-*H*), 6.38 (d, J = 5.8 Hz, 1H, 4-*H*), 6.59-6.60 (m, 1H, 5-*H*)

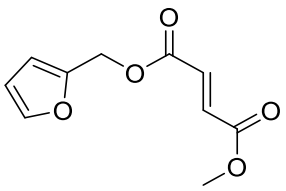
^{13}C NMR (100 MHz): δC 34.5 (*C*H$_2$, 7-*C*) 53.4 (*C*H$_3$, O*C*H$_3$), 69.2 (*C*H$_2$, 3-*C*), 79.9 (*C*H, 6-*C*), 95.5 (*C*, 7a-*C*), 130.1 (*C*H, 4-*C*), 139.2 (*C*H, 5-*C*), 143.5 (*C*, 3a-*C*), 167.1 (*C*, 1-*C*), 172.6 (*C*, *C*(O)OCH$_3$)

MS: HRMS-ESI calculated for $C_{10}H_{10}O_5$ m/z = 210.0528, found m/z = 233.0421 $[M+Na]^+$

IR: υ (CO) 1739.4 cm^{-1} and υ (CO) 1780.1 cm^{-1}

R_f = 0.08 (25% EtOAc in petrol)

Furan-2-ylmethyl methyl fumarate **40a**[13,102]



Monomethyl fumarate (40 mmol, 5.20 g) and DMAP (60 mmol, 7.33 g) were dissolved in dry DCM (80 mL) and furfuryl alcohol (40 mmol, 3.5 mL) was added at 0 °C. EDCI (60 mmol, 11.5 g) was added to the reaction mixture portion wise over a period of 5 minutes. The mixture was allowed to warm to room temperature and was stirred for 3 hours. The resultant mixture was diluted with DCM and washed successively with 2 x 1 M $KHSO_4$ and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo.* The crude product was subjected to silica gel column chromatography (20 % EtOAc/petrol) and the desired product was obtained in 78 % yield (6.57 g, 31.2 mmol).

^{1}H NMR (400 MHz): δ_H 3.80 (s, 3H, OC*H*$_3$), 5.19 (s, 2H, C*H*$_2$OC(O)CH$_2$C(O)), 6.38 (dd, J_a = 1.9, J_b = 3.0, 1H, 4-Ar*H*), 6.46 (d, J = 3.2, 1H, 3-Ar*H*), 6.88 (s, 2H, C(O)C*H*=C*H*C(O)), 7.44 (d, J = 1.2 Hz, 1H, 5-Ar*H*)

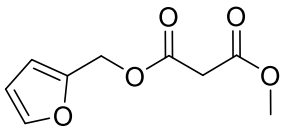
^{13}C NMR (100 MHz): 52.3 (*C*H$_3$, O*C*H$_3$), 58.8 (*C*H$_2$, *C*H$_2$OC(O)CH$_2$C(O)), 110.7 (*C*H, 4-Ar*C*), 111.2 (*C*H, 3-Ar*C*), 133.3 (*C*H, C(O)*C*H=CHC(O)), 133.8 (CH, C(O)CH=*C*HC(O)), 143.5 (*C*H, 5-Ar*C*), 148.8 (*C*, 2-Ar*C*), 164.5 (*C*, *C*(O)CH=CHC(O)), 165.3 (*C*, C(O)CH=CH*C*(O))

MS: HRMS-ESI calculated for $C_9H_{10}O_5$ m/z = 210.0528, found m/z = 233.042 $[M+Na]^+$

IR: υ (CO) 1719.2 cm^{-1}

R_f = 0.44 (20 % EtOAc in petrol)

Furan-2-ylmethyl methyl malonate **43**[102]



Monomethyl malonate (47.8 mmol, 5 mL) and DMAP (71.6 mmol, 8.75g) were dissolved in dry DCM (120 mL) and furfuryl alcohol (47.8 mmol, 4.2 mL) was added at 0 °C. EDCI (71.6 mmol, 13.69 g) was added portion wise over a period of 5 minutes. The reaction mixture was then allowed to warm to room temperature and was stirred for 2.5 hours. The resultant mixture was diluted with DCM and washed successively with 2 x 1 M $KHSO_4$ and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo.* The crude product was obtained as a crude yellow oil in 89 % yield (8.42 g, 42.5 mmol) and was progressed without purification.

^{1}H NMR (400 MHz): δ_H 3.42 (s, 2H, C(O)C*H*$_2$C(O)), 3.74 (s, 3H, OC*H*$_3$), 5.14 (s, 2H, C*H*$_2$OC(O)CH$_2$C(O)), 6.36-7.37 (m, 1H, 3-Ar*H*), 6.44 (d, J = 3.2 Hz, 1H, 4-Ar*H*), 7.42-7.43 (m, 1H, 5-Ar*H*)

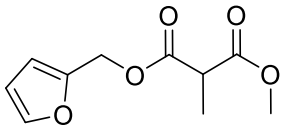
^{13}C NMR (100 MHz): 41.2 (*C*H$_2$, C(O)*C*H$_2$C(O)), 52.6 (*C*H$_3$, O*C*H$_3$), 59.0 (*C*H$_2$, *C*H$_2$OC(O)CH$_2$C(O)), 110.7 (*C*H, 3-Ar*C*), 111.2 (*C*H, 4-Ar*C*), 143.5 (*C*H, 5-Ar*C*), 148.8 (*C*, 2-Ar*C*), 166.2 (*C*, *C*(O)CH$_2$C(O)OCH$_3$), 166.8 (*C*, C(O)CH$_2$*C*(O)OCH$_3$)

MS: HRMS-ESI calculated for $C_9H_{10}O_5$ m/z = 198.0529, found m/z = 221.042 $[M+Na]^+$

IR: υ (CO) 1731.0 cm^{-1}

R_f = 0.45 (20 % EtOAc in petrol)

1-(Furan-2-ylmethyl) 3-methyl 2-methylenemalonate **44**[101]



Potassium carbonate (50.9 mmol, 7.03 g) and furan-2-ylmethyl methyl malonate (42.3 mmol, 8.4 g) were suspended in 45 mL dry acetone and stirred at room temperature for 5 minutes. Methyl iodide (50.9 mmol, 3.16 mL) was added dropwise and the reaction was allowed to stir at room temperature under an atmosphere of argon overnight (approx. 18 hours). The mixture was then filtered through celite and the solvent removed *in vacuo*. The crude product was subjected to silica gel column chromatography (5 →10 % EtOAc/petrol) and the desired product was obtained as a pale yellow oil in 81 % yield (7.27 g, 34.3 mmol).

^{1}H NMR (400 MHz): δ_H 1.43 (d, J = 7.3 Hz, 3H, CHC*H*$_3$), 3.48 (q, J = 7.3 Hz, 1 H, C*H*CH$_3$), 3.71 (s, 3H, OC*H*$_3$), 5.13 (dd, J_a = 13.1 Hz, J_b = 21.4 Hz, 2 H, C*H*$_2$OC(O)), 6.36-6.37 (m, 1H, 4-Ar*H*), 6.43 (d, J = 3.2 Hz, 1 H, 3-Ar*H*), 7.24 (d, J = 1.2 Hz, 1 H, 5-Ar*H*)

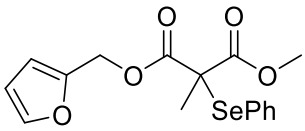
^{13}C NMR (100 MHz): δC 13.6 (*C*H$_3$, CH*C*H$_3$), 45.9 (*C*H, *C*HCH$_3$), 52.5 (*C*H$_3$, O*C*H$_3$), 58.9 (*C*H$_2$, *C*H$_2$OC(O)), 110.6 (*C*H, 4-Ar*C*), 110.9 (*C*H, 3-Ar*C*), 143.4 (*C*H, 5-Ar*C*), 149.0 (*C*, 2-Ar*C*), 169.8 (*C*, CH$_2$O*C*(O)), 170.3 (*C*, CH*C*(O)OCH$_3$)

MS: HRMS-ESI calculated for $C_{10}H_{12}O_5$ m/z = 212.0683, found m/z = 235.0574 $[M+Na]^+$

IR: υ (CO) 1730.9 cm^{-1}

R_f = 0.39 (20 % EtOAc in petrol)

1-(Furan-2-ylmethyl) 3-methyl 2-methyl-2-(phenylselanyl)malonate **45**[101]



Sodium hydride (55.0 mmol, 2.2 g) was added to a flask followed by 100 mL THF, and cooled to 0 °C. 1-(Furan-2-ylmethyl) 3-methyl 2-methylenemalonate (36.7 mmol, 7.27 g) in 14.6 mL THF was added slowly dropwise. After gas evolution had ceased (approximately 5 minutes) a solution of PhSeBr (40.4 mmol, 9.53 g) in 28 mL THF was

added quickly in one portion and a yellow suspension formed. The reaction was allowed to stir at room temperature under an atmosphere of argon for 1 hour and was then diluted with Et_2O and quenched with sat. aq. $NaHCO_3$. The organic layer was separated and washed twice with sat. aq. Na_2SO_3, three times with H_2O, dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. The crude material was subjected to silica gel column chromatography (5 % EtOAc/petrol) and the desired compound was obtained as a yellow oil in 71 % yield (9.68 g, 26.1 mmol).

^{1}H NMR (400 MHz): δ_H 1.67 (s, 3H, CC*H*$_3$), 3.69 (s, 3H, OC*H*$_3$), 5.12 (s, 2 H, C*H*$_2$OC(O)), 6.37-6.38 (m, 1H, 4-Furan*H*), 6.43 (d, J = 3.1 Hz, 1 H, 3-Furan*H*), 7.27-7.31 (m, 2H, 2,2'-Ph*H*), 7.54-7.56 (m, 2H, 3,3'-Ph*H*), 7.40-7.40 (m, 1H, 4-Ph*H*), 7.43-7.43 (m, 1H, 5-Ar*H*)

^{13}C NMR (100 MHz): δC 22.5 (*C*H$_3$, C*C*H$_3$), 53.1 (*C*H$_3$, O*C*H$_3$), 59.5 (*C*H$_2$, *C*H$_2$OC(O)), 110.6 (*C*H, 4-Furan*C*), 111.2 (*C*H, 3-Furan*C*), 126.3 (*C*, 1-Ph*C*), 128.9 (*C*H, 2,2'-Ph*C*), 129.8 (*C*H, 4-Ph*C*), 138.2 (*C*H, 3,3'-Ph*C*), 143.4 (*C*H, 5-Furan*C*), 148.8 (*C*, 2-Furan*C*), 169.6 (*C*, CH$_2$O*C*(O)), 170.1 (*C*, CH*C*(O)OCH$_3$)

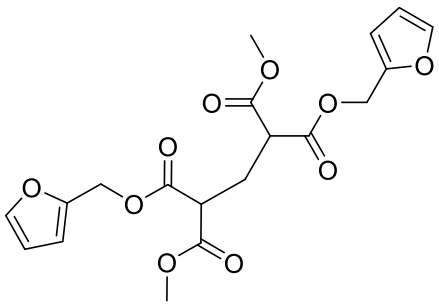
MS: HRMS-ESI calculated for $C_{16}H_{16}O_5Se$ m/z = 362.0197, found m/z = 363.0270 $[M+H]^+$,

m/z = 385.0120 $[M+Na]^+$

IR: υ (CO) 1724.7 cm^{-1}

R_f = 0.08 (4 % EtOAc in petrol)

1-(Furan-2-ylmethyl) 3-methyl 2-methylenemalonate dimer **46**[40]



Sodium hydride (1.43 mmol, 0.057 g) was added to a flask followed by 1.5 mL dry THF and cooled to 0 °C. Furan-2-ylmethyl methyl malonate (1.31 mmol, 0.260 g) was dissolved in 1 mL dry THF and added to the flask. The mixture was allowed to stir for 1 hour under an atmosphere of argon. Eschenmoser's salt (3.25 mmol, 0.601 g) was then added and the reaction allowed to stir under an atmosphere of argon for a further hour at 0 °C. The reaction was acidified to pH 1 with 2 M HCl and extracted with EtOAc. The aqueous layer was made basic with saturated aq. $NaHCO_3$ and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. The crude product was subjected to silica gel column

chromatography (10 → 20 % EtOAc/petrol) and **x** was identified as the only isolatable product as a yellow solid in 34 % yield (90 mg, 0.22 mmol).

^{1}H NMR (400 MHz): δ_H 2.45-2.50 (m, 2H, CHC*H*$_2$CH), 3.51 (t, J = 7.5 Hz, 2H, 2x C*H*), 3.69 (d, J = 3.4 Hz, 6H, 2x OC*H*$_3$), 5.08-5.16 (m, 4H, 2x C*H*$_2$OC(O)), 6.35-6.36 (m, 2H, 2x 4-Ar*H*), 6.41-6.42 (m, 2H, 2x 3-Ar*H*), 7.41 (m, 2H, 2x 5-Ar*H*)

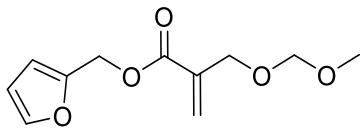
^{13}C NMR (100 MHz): δC 27.3 (*C*H$_2$, CH*C*H$_2$CH), 49.0 (*C*H, 2x *C*H), 52.8 (*C*H$_3$, 2x (O*C*H$_3$), 59.1 (*C*H$_2$, 2x *C*H$_2$OC(O)), 110.6 (*C*H, 2x 4-Ar*C*), 111.1 (*C*H, 2x 3-Ar*C*), 143.4 (*C*H, 2x 5-Ar*C*), 148.7 (*C*, 2-Ar*C*), 168.1 (*C*, O*C*(O)CH), 168.7 (*C*, CH*C*(O)OCH$_3$)

MS: HRMS-ESI calculated for $C_{19}H_{20}O_{10}$ m/z = 408.1058, found m/z = 426.1396 $[M+NH_4]^+$

IR: υ (CO) 1731.9 cm^{-1}

R_f = 0.15 (20 % EtOAc in petrol)

Furan-2-ylmethyl 2-((methoxymethoxy)methyl)acrylate **48a**[102]



2-((Methoxymethoxy)methyl)acrylic acid (33.5 mmol, 4.9 g) and DMAP (50.3 mmol, 6.14 g) were dissolved in dry DCM (80 mL) and furfuryl alcohol (33.5 mmol, 2.9 mL) was added at 0 °C). EDCI (50.3 mmol, 9.61 g) was added to the reaction mixture portion wise over a period of 5 minutes. The mixture was allowed to warm to room temperature and was stirred for 2.5 hours under an atmosphere of argon. The resultant mixture was diluted with DCM and washed successively with 2 x 1 M $KHSO_4$ and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo.* The crude product was subjected to silica gel column chromatography and the desired product was obtained as a pale yellow oil in 22 % yield (1.73 g, 7.37 mmol).

^{1}H NMR (400 MHz): δ_H 3.36 (s, 3H, OC*H*$_3$), 4.28 (s, 2H, C*H*$_2$OCH$_2$OCH$_3$), 4.67 (s, 2H, CH$_2$OC*H*$_2$OCH$_3$), 5.16 (s, 2H, C*H*$_2$OC(O)C(CH$_2$), 5.91 (d, J = 1.4 Hz, 1H, C(C*H*H')), 6.34-6.35 (m, 1H, 4-Ar*H*), 6.36-6.37 (m, 1H, C(CH*H*')), 6.44 (d, J = 3.3 Hz, 1H, 3-Ar*H*), 7.43-7.44 (m, 1H, 5-Ar*H*)

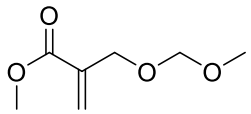
^{13}C NMR (100 MHz): 55.4 (*C*H$_3$, O*C*H$_3$), 58.3 (*C*H$_2$, *C*H$_2$OC(O)C(CH$_2$)), 96.0 (*C*H$_2$, CH$_2$O*C*H$_2$OCH$_3$), 110.6 (*C*H, 4-Ar*C*), 110.8 (*C*H, 3-Ar*C*), 126.9 (*C*H$_2$, C(*C*H$_2$)), 136.86 (*C*, *C*(CH$_2$)), 143.3 (*C*H, 5-Ar*C*), 149.3 (*C*, 2-Ar*C*), 165.4 (*C*, *C*(O)C(CH$_2$)

MS: HRMS-ESI calculated for $C_{11}H_{14}O_5$ m/z = 198.0529, found m/z = 221.042 $[M+Na]^+$

IR: υ (CO) 1716.3 cm^{-1}

R_f = 0.14 (5 % EtOAc in petrol)

Methyl 2-((methoxymethoxymethyl)acrylate **49**[103]



Methyl 2-(hydroxymethyl)acrylate (38.9 mmol, 4 mL) was dissolved in dry DCM (38 mL) and cooled to 0 °C. Hunig's base (235 mmol, 41 mL) and MOMCl (156 mmol, 11.8 mL) were added and the reaction was allowed to stir at room temperature for 1 hour 30 mins. The reaction was quenched with 2 M HCl (25 mL). The mixture was diluted with water and then extracted with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. The desired product was obtained as yellow oil in assumed quant. yield (6.40 g, 38.9 mmol) and was progressed into the next reaction without purification.

^{1}H NMR (400 MHz): δ_H 3.39 (s, 3H, $CH_2OCH_2OC\mathit{H_3}$), 3.79 (s, 3H, C(O)$OC\mathit{H_3}$), 4.29 (s, 2H, $CH_2OC\mathit{H_2}OCH_3$), 4.69 (s, 2H, $C\mathit{H_2}OCH_2OCH_3$), 5.90-5.91 (m, 1H, C(C*H*H')), 6.31-6.32 (m, 1H, C(CH*H'*))

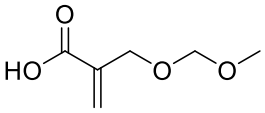
^{13}C NMR (100 MHz): 51.9 ($\mathit{C}H_3$, C(O)$\mathit{C}H_3$), 55.3 ($\mathit{C}H_3$, $CH_2OCH_2O\mathit{C}H_3$), 65.7 ($\mathit{C}H_2$, $CH_2O\mathit{C}H_2OCH_3$), 96.0 ($\mathit{C}H_3$, $\mathit{C}H_2OCH_2OCH_3$), 126.4 ($\mathit{C}H_2$, C($\mathit{C}H_2$)), 137.0 (*C*H, *C*(CH_2)), 166.3 (*C*, *C*(O))

MS: HRMS-ESI calculated for $C_7H_{12}O_4$ m/z = 198.0529, found m/z = 221.042 $[M+Na]^+$

IR: υ (CO) 1719.4 cm^{-1}

R_f = 0.74 (33 % EtOAc in hexane)

2-((Methoxymethoxy)methyl)acrylic acid **50**[100]



A solution of methyl 2-((methoxymethoxymethyl)acrylate (38.8 mmol, 6.40 g) in THF/H2O (v/v = 1/1, 205 mL) was treated with aq. LiOH (4.6 M, 40.77 mL). The mixture was stirred at room temperature overnight. The reaction was acidified at 0 °C (pH = 2) with 2 M aq. HCl and extracted with diethyl ether. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The desired crude product was obtained as a light yellow oil in 87 % yield (4.97 g, 33.8 mmol). No purification was carried out and was instead progressed into the next reaction.

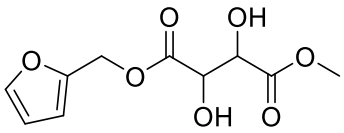
^{1}H NMR (400 MHz): δ_H 3.40 (s, 3H, $CH_2OCH_2OC\mathit{H_3}$), 4.29 (s, 2H, $CH_2OC\mathit{H_2}OCH_3$), 4.70 (s, 2H, $C\mathit{H_2}OCH_2OCH_3$), 6.02 (d, J = 1.5 Hz, 1H, C(C*H*H')), 6.46 (d, J = 1.1 Hz, 1H, C(CH*H'*))

^{13}C NMR (100 MHz): 55.5 (*C*H_3, $CH_2OCH_2OCH_3$), 65.3 (*C*H_2, $CH_2OCH_2OCH_3$), 96.0 (*C*H_2, $CH_2OCH_2OCH_3$), 128.8 (*C*H_2, C(*C*H_2)), 136.5 (*C*H, *C*(CH_2)), 171.0 (*C*, *C*(O))

MS: HRMS-ESI calculated for $C_6H_{10}O_4Si$ m/z = 146.0584, found m/z = 169.047 $[M+Na]^+$

IR: υ (C=O) 1697.3 cm^{-1}, υ(OH) 2889.5 cm^{-1}

1-(Furan-2-ylmethyl) 4-methyl 2,3-dihydroxysuccinate **51b**[104]



Furan-2-ylmethyl methyl fumarate (1 mmol, 0.21 g) was dissolved in THF (1 mL) and NMO (0.44 mL, 50 % in H_2O) was added. Osmium tetroxide (0.38 mL, 2.5 % in tBuOH) was then added and the reaction was allowed to stir under an atmosphere of argon for 2 hours at room temperature. The reaction was quenched with the slow addition of a 20 % aq. solution of $NaHSO_4$. Water was added and the aqueous layer was extracted with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. The crude product was obtained as a brown oil in 73 % yield (0.178 g, 0.73 mmol) which was not purified or progressed any further.

^{1}H NMR (400 MHz): δ_H 3.29 (br s, 2H, CH(O*H*)CH(O*H*)), 3.84 (s, 3H, OC*H*$_3$), 4.57 (d, J = 2.7, 2H, C*H*(OH)C*H*(OH)), 5.16 (d, J = 13.0, 1H, C*H*H'OC(O)), 5.30 (d, J = 13.2, 1H, CH*H'*OC(O)), 6.34 (dd, J_a = 1.9, J_b = 3.1, 1H, 4-Ar*H*), 6.47 (d, J = 3.2, 1H, 3-Ar*H*), 7.44-7.44 (m, 1H, 5-Ar*H*)

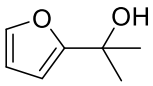
^{13}C NMR (100 MHz): 53.2 (*C*H_3, O*C*H_3), 59.7 (*C*H_2, *C*H_2OC(O)), 72.0 (*C*H, *C*H(OH)CH(OH)), 72.1 (*C*H, CH(OH)*C*H(OH)), 110.7 (*C*H, 4-Ar*C*), 111.5 (*C*H, 3-Ar*C*), 143.7 (*C*H, 5-Ar*C*), 148.3 (*C*, 2-Ar*C*), 171.2 (*C*, *C*(O)CH(OH)CH(OH)C(O)), 171.9 (*C*, C(O)CH(OH)CH(OH)*C*(O))

MS: HRMS-ESI calculated for $C_{10}H_{12}O_7$ m/z = 244.0583, found m/z = 262.092 $[M+NH_4]^+$ and m/z = 267.047 $[M+Na]^+$

IR: υ (OH) 3485.8 cm^{-1}, υ (CO) 1736.2 cm^{-1}

R_f = 0.05 (20 % EtOAc in petrol)

2-(Furan-2-yl)propan-2-ol **55**[105]



Dry Et_2O (200 mL) was added to a flask followed by freshly distilled furan (2.32 mL, 64 mmol). The solution was cooled to 0 °C and *n*-BuLi (19.2 mL, 2.5 M in hexanes) was added slowly. The mixture was stirred at this temperature under an atmosphere of argon for 1 hour and then cooled to -78 °C. Dry acetone (2.92 mL, 40 mmol) was added slowly and the mixture was allowed to slowly come to room temperature over 20 hours. The reaction was quenched with the addition of sat. aq. NH_4Cl followed by brine. The aqueous phase was extracted with EtOAc and the combined organic phases dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude product was obtained as a yellow oil in 80 % yield (4.03 g, 51.2 mmol) and was used directly in the next reaction without further purification.

^{1}H NMR (400 MHz): δ_H 1.59 (s, 6H, C(C*H*$_3$)$_2$), 2.48 (s, 1H, O*H*), 6.19 (d, J = 3.2, 1H, 3-Ar*H*), 6.30 (dd, J_a = 1.8, J_b = 3.2, 1H, 4-Ar*H*), 7.35 (d, J = 0.9, 1H, 5-Ar*H*)

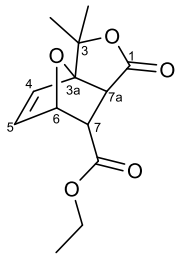
^{13}C NMR (100 MHz): 28.7 (*C*H$_3$, C(*C*H$_3$)$_2$), 68.8 (*C*, *C*(CH$_3$)$_2$), 103.6 (*C*H, 3-Ar*C*), 110.0 (*C*H, 4-Ar*C*), 141.52 (*C*H, 5-Ar*C*), 160. (*C*, 2-Ar*C*)

MS: HRMS-ESI calculated for $C_9H_{10}O_5$ m/z = 126.0681, found m/z = 109.0647 [M-H_2O+H]$^+$

IR: υ (OH) 3412.9 cm^{-1}

R_f = 0.17 (20 % EtOAc in hexane)

Ethyl (3aR,6S)-3,3-dimethyl-1-oxo-1,6,7,7a-tetrahydro-3H-3a,6-epoxyisobenzofuran-7-carboxylate **60a**[13]



Sodium hydride (0.738 g, 18.5 mmol, 60 % in mineral oil) was washed with dry THF then suspended in 95 mL dry THF. 2-(Furan-2-yl)propan-2-ol (1.94 g, 15.4 mmol) was dissolved in 20 mL dry THF and then slowly added. The mixture was allowed to stir at room temperature under an atmosphere of argon for 1 hour (minimum 30 mins) and then the solvent removed *in vacuo*. The mixture was redissolved in 95 mL dry toluene, cooled to -20 °C and pyridine added. Ethyl (E)-4-chloro-4-oxobut-2-enoate (30.76 mmol, 5 g) was dissolved in 20 mL dry toluene and added dropwise. The ice bath was removed and the mixture allowed to stir at room temperature under an atmosphere of

argon overnight. The crude mixture was filtered through celite and the solvent removed *in vacuo*. The crude material was then washed six times with sat. aq. $NaHCO_3$ followed by brine, dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude material was subjected to silica gel column chromatography (EtOAc/DCM, 0→5 %). The cycloadduct of the desired compound coeluted with remaining acid chloride so the collected fractions were washed with $NaHCO_3$ three times, once again with brine, dried and the solvent removed *in vacuo*. The cycloadduct was obtained as a brown solid in 44 % yield (1.70 g, 6.77 mmol).

^{1}H NMR (400 MHz): δ_H 1.27 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 1.48 (s, 3H, 3-C((C*H*$_3$)(CH_3)'), 1.66 (s, 3H, 3-C((CH_3)(C*H*$_3$)'), 3.20 (d, J = 3.3 Hz, 1H, 7a-*H*), 3.59 (dd, Ja = 3.3 Hz, Jb = 4.9 Hz, 1H, 7-*H*), 4.14 (q, 2H, O C*H*$_2$$CH_3$), 5.32 (dd, Ja = 1.5 Hz, Jb = 4.9 Hz, 1H, 6-*H*), 6.38 (dd, Ja = 1.6 Hz, Jb = 5.8 Hz, 1H, 5-*H*), 6.56 (d, J = 5.8 Hz, 1H, 4-*H*)

^{13}C NMR (125 MHz): δC 14.2 (*C*H_3, OCH_2*C*H_3), 21.6 (*C*H_3, 3-C((*C*H_3)(CH_3)'), 25.1 (*C*H_3, 3-C((CH_3)(*C*H_3)'), 48.8 (*C*H, 7-*C*), 49.8 (*C*H, 7a-*C*), 61.5 (*C*H_2, O*C*$H_2$$CH_3$), 80.6 (*C*H, 6-*C*), 83.3 (*C*, 3-*C*), 97.7 (*C*, 3a-*C*), 133.0 (*C*H, 4-*C*), 135.92 (*C*H, 5-*C*), 169.8 (*C*, *C*(O)OCH_3), 174.0 (*C*, 1-*C*)

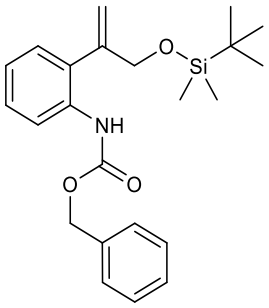
MS: HRMS-ESI calculated for $C_{13}H_{16}O_4$ m/z = 252.1012, found m/z = 253.1086 $[M+H]^+$

IR: pendant υ (CO) 1731.4 cm^{-1}, lactone υ (CO) 1770.6 cm^{-1}

R_f = 0.08 (10% EtOAc/petrol)

mp = 98-99 °C

Benzyl (2-(3-((tert-butyldimethylsilyl)oxy)prop-1-en-2-yl)phenyl)carbamate **79**[106]



Acetone (75 mL) and water (75 mL) were added to 2-(3-((tert-butyldimethylsilyl)oxy)prop-1-en-2-yl)aniline **86** (3.91 g, 14.9 mmol) then K_2CO_3 (2.05 g, 14.9 mmol) and CbzCl (3.2 mL, 22.3 mmol) added. The mixture was stirred under an atmosphere of N_2 at room temperature for 1 hour then water added and extracted with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (Hex/EtOAc 98:2) to give the product as a colourless oil in 85% yield (5.05 g, 12.7mmol).

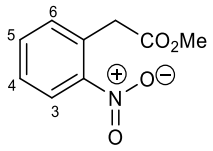
^{1}H NMR (400 MHz): δ_H 0.02 (s, 6H, Si(C*H*$_3$)$_2$C(CH$_3$)$_3$), 0.87 (s, 9H, Si(CH$_3$)$_2$C(C*H*$_3$)$_3$), 4.24 (s, 2H, C*H*$_2$OSi(CH$_3$)$_2$C(CH$_3$)$_3$), 5.14 (dd, J_a = 1.3 Hz, J_b = 2.6 Hz, 1H, C*H*H'), 5.18 (s, 2H, CO$_2$C*H*$_2$Ph), 5.59 (dd, J_a = 1.7 Hz, J_b = 3.4 Hz, 1H, CH*H'*), 7.04-7.05 (m, 2H, Ar*H*), 7.35-7.36 (m, 6H, Ar*H*), 7.52 (br s, 1H, N*H*)

^{13}C NMR (100 MHz): δ_C -5.5 (*C*H$_3$, Si(*C*H$_3$)$_2$C(CH$_3$)$_3$), 18.4 (*C*, Si(CH$_3$)$_2$*C*(CH$_3$)$_3$), 25.9 (*C*H$_3$, Si(CH$_3$)$_2$C(*C*H$_3$)$_3$), 66.8 (*C*H$_2$, *C*H$_2$OTBS), 67.0 (*C*H$_2$, CO$_2$*C*H$_2$Ph), 116.6 (*C*H$_2$, C*C*H$_2$), 119.5 (*C*, Ar*C*), 122.9 (*C*, Ar*C*), 128.2 (*C*, Ar*C*), 128.4 (*C*, Ar*C*), 128.4 (*C*, Ar*C*), 128.5 (*C*, Ar*C*), 128.7 (*C*, Ar*C*), 130.3 (*C*, *C*CH$_2$), 135.5 (*C*, 2-Ar*C*), 136.2 (*C*, 1'-Ar*C*), 145.8 (*C*, 1-Ar*C*), 153.5 (C, (*C*O)OBn)

MS: HRMS-ESI calculated for $C_{23}H_{31}NO_3Si$ m/z = 397.2075, found m/z = 398.2148 $[M+H]^+$ and m/z = 420.1965 $[M+Na]^+$

R_f = 0.19 (EtOAc/pet ether 4:1)

Methyl 2-(2-nitrophenyl)acetate **83**[61]

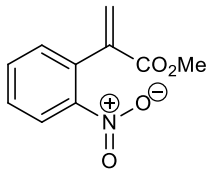


2-Nitrophenylacetic acid (10.0g, 55.2 mmol) was dissolved in dry MeOH (55 mL) and $SOCl_2$ (4.1 mL, 55.2 mmol) added. The reaction mixture was heated at reflux under an atmosphere of N_2 for 2 hours. The reaction was cooled to room temperature and the solvent removed in vacuo. Saturated $NaHCO_3$ was added to the oily residue and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. The crude product was obtained in a 98% yield (10.5 g, 54.0 mmol). The yellow oil was progressed to compound **84** without further purification.

^{1}H NMR (400 MHz): δ_H 3.72 (s, 3H,CO$_2$C*H*$_3$), 4.04 (s, 2H, C*H*$_2$CO$_2$CH$_3$), 7.36-7.37 (m, 1H, 6-Ar*H*), 7.48-7.49 (m, 1H, 5-Ar*H*) 7.61 (td, J_a = 1.2 Hz, J_b = 7.5 Hz, 1H, 4-Ar*H*), 8.13 (dd, J_a = 0.9 Hz, J_b = 8.2 Hz, 1H, 3-Ar*H*)

R_f = 0.28 (EtOAc/pet ether 4:1)

Methyl 2-(2-nitrophenyl)acrylate **84**[61]



Methyl 2-(2-nitrophenyl)acetate **83** (10.5 g, 54.0 mmol) was dissolved in toluene (55 mL). Paraformaldehyde (4.53 g, 151 mmol), TBAI (0.797 g, 2.16 mmol) and K_2CO_3

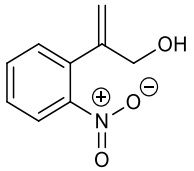
(22.4 g, 162 mmol) were added and the mixture was stirred at 80 °C overnight. The reaction was cooled to room temperature and water added. The aqueous layer was extracted with toluene and the combined organic fractions were washed with brine, dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude product was obtained as a dark yellow oil in a yield of 84% (9.39 g, 45.4 mmol) and was not purified further.

^{1}H NMR (400 MHz): δ_H 3.73 (s, 3H, CO_2CH_3), 5.88 (s, 1H, C*H*H'), 6.55 (s, 1H, CH*H'*), 7.40 (dd, J_a = 1.4 Hz, J_b = 7.6 Hz, 1H, 6-Ar*H*), 7.54 (td, J_a = 1.5 Hz, J_b = 6.7 Hz, 1H, 5-Ar*H*), 7.66 (td, J_a = 1.2 Hz, J_b = 7.5 Hz, 1H, 4-Ar*H*), 8.13 (dd, J_a = 1.0 Hz, J_b = 8.2 Hz, 1H, 3-Ar*H*)

^{13}C NMR (100 MHz): δ_C 52.3 (CH_3, CO_2CH_3)), 124.6 (*C*H, 3-Ar*C*), 127.6 (CH_2, CCH_2), 129.4 (*C*, 5-Ar*C*), 132.1 (*C*, *C*CH_2) 133.0 (*C*H, 6-Ar*C*), 133.7 (*C*H, 4-Ar*C*), 139.8 (*C*, 1-Ar*C*), 147.9 (*C*, 2-Ar*C*), 165.3 (*C*, *C*O(OCH_3))

R_f = 0.25 (EtOAc/hexane 9:1)

2-(2-Nitrophenyl)prop-2-en-1-ol **85**[78]



Methyl 2-(2-nitrophenyl)acrylate **84** (9.38 g, 45.3 mmol) was dissolved in dry DCM (150 mL) and DIBAL-H (109 mL, 1M in hexanes) was added slowly over 1 hour at -78 °C. The reaction was stirred at -78 °C under an atmosphere of N_2 for 2 hours and then allowed to warm to room temperature. Saturated NaOAc was added then the mixture transferred to a flask containing 75 mL saturated NH_4Cl and 350 mL EtOAc and the contents allowed to stir for approximately 1 hour until a gel formed. The mixture was filtered through celite, dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude product was subjected to silica gel column chromatography (10 → 35 % EtOAc/Hex) and the desired product was obtained as a pale yellow oil in 60 % yield (4.84 g, 27.2 mmol).

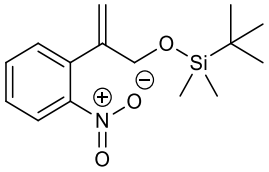
^{1}H NMR (400 MHz): δ_H 1.90 (br s, 1H, O*H*), 4.42 (s, 2H, CH_2OH), 5.10 (s, 1H, C*H*H'), 5.47 (s, 1H, CH*H'*), 7.36 (dd, J_a = 0.9 Hz, J_b = 7.3 Hz, 1H, 6-Ar*H*), 7.46-7.47 (m, 1H, 5-Ar*H*) 7.60 (td, J_a = 0.9 Hz, J_b = 7.6 Hz, 1H, 4-Ar*H*), 7.94-7.95 (m, 1H, 3-Ar*H*)

^{13}C NMR (100 MHz): δ_C 66.0 (CH_2, CH_2OH), 114.7 (CH_2, CCH_2), 124.30 (*C*H, 3-Ar*C*), 128.6 (*C*, 5-Ar*C*), 131.3 (*C*, 6-Ar*C*), 132.9 (*C*, 4-Ar*C*), 135.5 (*C*, *C*CH_2), 146.5 (*C*, 1-Ar*C*), 148.7 (*C*, 2-Ar*C*)

IR: υ (OH) 3360.7 cm^{-1}

R_f = 0.18 (EtOAc/hex 1:4)

Tert-butyldimethyl((2-(2-nitrophenyl)allyl)oxy)silane **86**[61]



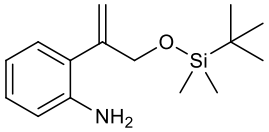
2-(2-Nitrophenyl)prop-2-en-1-ol **85** (4.83 g, 27.1 mmol) was dissolved in dry DMF (46 mL) and TBSCl (4.89 g, 32.5 mmol) and imidazole (3.68 g, 54.1 mmol) added at room temperature. The reaction was allowed to stir at room temperature under an atmosphere of N_2 for 5 hours and then was quenched with water. The aqueous layer was extracted with Et_2O and the combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (Hex/EtOAc, 95:5) to obtain the product as a yellow oil in 88% yield (6.95 g, 23.8 mmol).

^{1}H NMR (400 MHz): δ_H 0.04 (s, 6H, Si(C*H*$_3$)$_2$C(CH$_3$)$_3$), 0.87 (s, 9H, Si(CH$_3$)$_2$C(C*H*$_3$)$_3$), 4.41 (s, 2H, C*H*$_2$OSi(CH$_3$)$_2$C(CH$_3$)$_3$), 5.05 (dd, J_a = 1.5 Hz, J_b = 3.0 Hz, 1H, C*H*H'), 5.43 (dd, J_a = 1.8 Hz, J_b = 3.2 Hz, 1H, CH*H'*), 7.33 (dd, J_a = 1.2 Hz, J_b = 7.6 Hz, 1H, 6-Ar*H*), 7.43-7.44 (m, 1H, 5-Ar*H*), 7.56 (td, J_a = 1.2 Hz, J_b = 7.5 Hz, 1H, 4-Ar*H*), 7.91 (dd, J_a= 0.9 Hz, J_b = 8.17 Hz, 1H, 3-Ar*H*)

^{13}C NMR (100 MHz): δ_C -5.5 (*C*H$_3$, Si(*C*H$_3$)$_2$C(CH$_3$)$_3$), 18.3 (*C*, Si(CH$_3$)$_2$*C*(CH$_3$)$_3$), 25.8 (*C*H$_3$, Si(CH$_3$)$_2$C(*C*H$_3$)$_3$), 65.5 (*C*H$_2$, *C*H$_2$OTBS), 113.3 (*C*H$_2$, C*C*H$_2$), 124.0 (*C*H, 3-Ar*C*), 128.3 (*C*, 5-Ar*C*), 132.0 (*C*, 6-Ar*C*), 132.5 (*C*, 4-Ar*C*), 135.6 (*C*, *C*CH$_2$), 146.4 (*C*, 1-Ar*C*), 148.7 (*C*, 2-Ar*C*)

R_f = 0.43 (Hex/EtOAc 95:5)

2-(3-((Tert-butyldimethylsilyl)oxy)prop-1-en-2-yl)aniline **87**[61]



Tert-butyldimethyl((2-(2-nitrophenyl)allyl)oxy)silane **86** (6.95g, 23.7 mmol) was dissolved in dry MeOH (220 mL) and NH_4Cl (12.7g, 237 mmol) and zinc (15.5g 237 mmol) added. The mixture was stirred at 75 °C overnight under an atmosphere of N_2 then cooled to room temperature and filtered through celite. The filtrate was concentrated *in vacuo*, water added then extracted with DCM. The combined organic layers were dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. The crude product was subjected to silica gel column chromatography (Hex/EtOAc 95:5) to give the product as a colourless oil in 75% yield (4.68 g, 17.8 mmol).

^{1}H NMR (400 MHz): δ_H 0.09 (s, 6H, Si(C*H*$_3$)$_2$C(CH$_3$)$_3$), 0.93 (s, 9H, Si(CH$_3$)$_2$C(C*H*$_3$)$_3$), 3.87 (br s, 2H, N*H*$_2$), 4.28 (br s, 2H, C*H*$_2$OSi(CH$_3$)$_2$C(CH$_3$)$_3$), 5.19 (dd, J_a = 2.0 Hz, J_b

= 3.8 Hz, 1H, C*H*H'), 5.60 (dd, J_a = 2.1 Hz, J_b = 4.1 Hz, 1H, CH*H'*), 6.74-6.75 (m, 2H, 5-*Ar*H, 6-Ar*H*), 6.96 (dd, J_a = 1.2 Hz, J_b = 7.4 Hz, 1H, 4-Ar*H*), 7.08-7.09 (m, 1H, 3-Ar*H*)

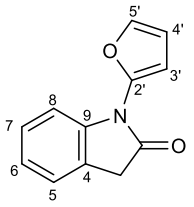
^{13}C NMR (100 MHz): δ_C -5.4 (*C*H_3, Si(*C*H_3)$_2$C(CH_3)$_3$), 18.4 (*C*, Si(CH_3)$_2$*C*(CH_3)$_3$), 26.0 (*C*H_3, Si(CH_3)$_2$C(*C*H_3)$_3$), 65.5 (*C*H_2, *C*H_2OTBS), 113.5 (*C*H_2, C*C*H_2), 115.4 (*C*H, 5-Ar*C*), 118.0 (*C*, 6-Ar*C*), 125.9 (*C*, *C*CH$_2$), 128.4 (*C*, 3-Ar*C*), 129.0 (*C*, 4-Ar*C*), 143.80 (*C*, 2-Ar*C*), 146.6 (*C*, 1-Ar*C*)

MS: HRMS-ESI calculated for $C_{15}H_{25}NOSi$ m/z = 263.1708, found m/z = 264.1780 $[M+H]^+$

IR: υ (NH) 3366.2 cm^{-1}

R_f = 0.23 (Hex/EtOAc 95:5)

1-(Furan-2-yl)indolin-2-one **89**[18]



Oxindole (0.240g, 1.80 mmol), CuI (0.03g, 0.15 mmol) and K_2CO_3 (0.89g, 6.45 mmol) were added to a microwave tube under a flow of N_2. DMEDA (0.015 mL, 0.15 mmol), 2-bromofuran (0.13 mL, 1.50 mmol) and dry dioxane (4.5 mL) were then added and the tube was back filled three times with N_2. The seal was removed and the tube capped then the mixture heated at 110°C with stirring for 24 hours then allowed to cool to room temperature. The mixture was filtered through celite, washed with DCM and the solvent removed *in vacuo*. The crude product was subjected to silica gel column chromatography (100% DCM). The desired product was obtained as a pale yellow oil in 38% yield (0.113 g, 0.57 mmol).

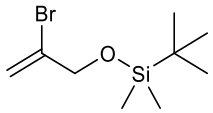
^{1}H NMR (400 MHz): 3.70 (s, 2H, COC*H*$_2$), 6.45-6.46 (m, 1H, 3'-Ar*H*), 6.55 (dd, J_a = 2.1, J_b = 3.2, 1H, 4'-Ar*H*), 7.01 (d, J = 7.9 Hz, 1H, 8-Ar*H*), 7.11 (t, J = 7.4 Hz, 1H, 7-Ar*H*), 7.26-7.27 (m, 2H, 5-Ar*H*, 6-Ar*H*), 7.41-7.41 (m, 1H, 5'-Ar*H*)

^{13}C NMR (100 MHz): δ_C 35.8 (*C*H$_2$, CO*C*H$_2$), 103.6 (*C*H, 3'-Ar*C*), 110.4 (*C*H, 8-Ar*C*), 111.4 (*C*H, 4'-Ar*C*), 123.4 (*C*, 9-Ar*C*), 123.6 (*C*H, 7'-Ar*C*), 124.6 (*C*H, 6-Ar*C*), 128.1 (*C*H, 5-Ar*C*), 139.9 (*C*H, 5'-Ar*C*), 141.6 (*C*, 2'-Ar*C*), 143.7 (*C*, 4-Ar*C*), 173.9 (*C*, *C*O)

MS: HRMS-ESI calculated for $C_{12}H_9NO_2$ m/z = 199.0634, found m/z = 200.0706 $[M+H]^+$ and 222.0526 $[M+Na]^+$

R_f = 0.21 (DCM)

((2-Bromoallyl)oxy)(tert-butyl)dimethylsilane **93**[107]



2-Bromoallyl alcohol (3 mL, 36.5 mmol), DMAP (0.450g, 3.65 mmol) and imidazole (3.74 g, 54.6 mmol) were dissolved in dry DCM (120 mL) at 0°C under an atmosphere of N_2. TBSCl (8.27 g, 54.8 mmol) was added and the mixture was left to stir at room temperature for 5 hours. The reaction was quenched with water and the aqueous layer extracted with DCM. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. The crude product was purified by silica gel chromatography (hexane) to give the product as a colourless oil in 87% yield (8.05 g, 31.8 mmol).

^{1}H NMR (400 MHz): δ_H 0.10 (s, 6H, Si(C(CH$_3$)$_3$(C*H$_3$*)$_2$)), 0.92 (s, 9H, Si(C(C*H$_3$*)$_3$(CH$_3$)$_2$), 4.21 (t, J = 1.5 Hz, 2H, TBSO-*CH$_2$*), 5.53 (dd, J_a = 1.7 Hz, J_b = 3.2 Hz, 1H, BrCC*H*H'), 5.96 (dd, J_a = 1.9 Hz, J_b = 3.7 Hz, 1H, BrCCH*H'*)

^{13}C NMR (100 MHz): δ_C -5.4 (*C*H$_3$, Si(C(CH$_3$)$_3$(*C*H$_3$)$_2$)), 18.3 (*C*, Si(*C*(CH$_3$)$_3$(CH$_3$)$_2$)), 25.8 (*C*H$_3$, Si(C(*C*H$_3$)$_3$(CH$_3$)$_2$)), 67.4 (*C*H$_2$, TBSO-*C*H$_2$), 114.7 (*C*H$_2$, BrC*C*H$_2$), 131.8 (*C*, Br*C*CH$_2$)

IR: alkyl υ (CH) 2929.1 cm^{-1}

R_f = 0.30 (Hex)

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