SUBSTITUTION EFFECTS IN INTRAMOLECULAR FURAN CYCLOADDITIONS

Robert Lammie Rae

Submitted for the degree of Doctor of Philosophy

Heriot-Watt University

Institute of Chemical Sciences
School of Engineering and Physical Sciences

March 2014

The copyright in this thesis is owned by the author. Any quotation from the thesis or use of any of the information contained in it must acknowledge this thesis as the source of the quotation or information.

ABSTRACT

The intramolecular Diels-Alder reaction of furan (IMDAF) provides a high degree of structural complexity in one step. However, reaction reversibility issues and the lower reactivity of furan in comparison to non-aromatic dienes prevent more widespread use of furan as a diene component in such reactions. Initial efforts to develop a new mode of organocatalysis which we hoped would facilitate IMDAF reaction was unfortunately unsuccessful, thus alternative means of IMDAF facilitation were investigated.

For the first time, a comprehensive synthetic and computational study of the effect of halogen substitution on the IMDAF reaction has been undertaken. We have successfully demonstrated that halogenation of the furan moiety facilitates the IMDAF reaction (displaying increased reactivity to the non-halogenated analogue, regardless of halogen position), whereas dienophile halogenation hinders it. Additionally, careful selection of the position of the halogen on the furan can somewhat overcome the detrimental effect of having a halogen on the dienophile leading to highly functionalised cycloadducts with potential for further modification.

Computational data produced by Martin Paterson and Justyna McKinlay support the idea that frontier molecular orbital effects cannot explain the experimental observations and we thus believe that the reactions are controlled by the interplay of three factors: positive charge stabilisation in the transition state and product, steric effects and a dipolar interaction term identified by the high level calculations.

Finally, we have briefly demonstrated that nitro groups on the furan moiety also facilitate the IMDAF reaction whereas acyl groups appear to hinder the reaction.

STEREOCHEMICAL ABSTRACT

Any chiral compounds included in this thesis are racemic in nature. However, for clarity, such mixtures are schematically represented by drawings of only one of the enantiomers.

ACKNOWLEDGEMENTS

Firstly and foremost, I would like to thank my supervisor, Dr. Magnus Bebbington, for all his support and encouragement throughout my studies. Without his enthusiasm and ideas, this thesis would not have been possible and I would not have managed so well without him.

I would also like to thank Prof. Martin Paterson and Justyna McKinlay for kindly producing the computational data that accompanies the experimental work.

I also extend my thanks to Dr. Dave Ellis for NMR spectroscopy, as well as discussions regarding some NMR data. I would also like to thank the NMSCC in Swansea for mass spectrometry data, Heriot-Watt University for the opportunity to conduct a PhD and the EPSRC for funding this research.

My time in the lab was made much more enjoyable by the presence of Mari, Anita, Lorna and Tom, so I thank each of them not only for their friendships, but for the numerous, interesting conversations over the years in addition to the many, many laughs. Additionally, I would like to thank the various project students over the years as well as the Lee group (particularly Paul), who also made my time here more enjoyable.

I would also like to thank Don Sutherland, whose enthusiasm for the subject in addition to his brilliance at teaching inspired me all those years ago to pursue a career in chemistry.

I am not certain I would have made it this far if it were not for my friends, so I extend my thanks to all of them for their continued support throughout the years, with particular thanks going to Fraser, Ross, Colin, Steven and Scott.

Finally, I would especially like to thank my parents, my grandfather and Allan for all their encouragement and support, and Nicolle for her much needed patience and encouragement throughout the final years of my PhD. Without all of them the completion of this thesis would have seemed an extremely daunting task.

ACADEMIC REGISTRY
Research Thesis Submission

Name*:*	ROBERT LAMMIE RAE		
School/PGI:	EPS/CHEMISTRY		
Version: *(i.e. First, Resubmission, Final)*	FINAL	Degree Sought (Award **and** Subject area)	PhD CHEMISTRY

Declaration

In accordance with the appropriate regulations I hereby submit my thesis and I declare that:

1) the thesis embodies the results of my own work and has been composed by myself
2) where appropriate, I have made acknowledgement of the work of others and have made reference to work carried out in collaboration with other persons
3) the thesis is the correct version of the thesis for submission and is the same version as any electronic versions submitted*.
4) my thesis for the award referred to, deposited in the Heriot-Watt University Library, should be made available for loan or photocopying and be available via the Institutional Repository, subject to such conditions as the Librarian may require
5) I understand that as a student of the University I am required to abide by the Regulations of the University and to conform to its discipline.

* *Please note that it is the responsibility of the candidate to ensure that the correct version of the thesis is submitted.*

Signature of Candidate*:*		Date:	

Submission

Submitted By *(name in capitals):*	ROBERT LAMMIE RAE
Signature of Individual Submitting:	
Date Submitted:	

For Completion in the Student Service Centre (SSC)

Received in the SSC by *(name in capitals):*			
Method of Submission *(Handed in to SSC; posted through internal/external mail):*			
*E-thesis Submitted (**mandatory for final theses)***			
Signature:		Date:	

CONTENTS

ABBREVIATIONS

AAO	Acetalisation Assisted Organocatalysis
AO	Atomic Orbital
Boc	*Tert*-Butyloxycarbonyl
$(Boc)_2O$	Di-*tert*-butyl dicarbonate
CBS	Complete Basis Set
DCE	Dichloroethane
DCM	Dichloromethane
DFT	Density Functional Theory
DMAD	Dimethyl Acetylenedicarboxylate
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
Et_2O	Diethyl Ether
EtOAc	Ethyl Acetate
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDG	Electron Donating Group
EWG	Electron Withdrawing Group
FMO	Frontier Molecular Orbital
GC	Gas Chromatography
H-G II	Hoveyda-Grubbs 2nd Generation Catalyst
HOBt	Hydroxybenzotriazole
HOMO	Highest Occupied Molecular Orbital
HMPT	Hexamethylphosphorus Triamide
HWE	Horner-Wadsworth-Emmons
IMDA	Intramolecular Diels-Alder
IMDAF	Intramolecular Diels-Alder of Furan
LDA	Lithium Diisopropylamide
LUMO	Lowest Unoccupied Molecular Orbital
MFA	*N*-methylformanilide
MIDA	*N*-methyliminodiacetic Acid
MO	Molecular Orbital
n-BuLi	*n*-Butyl Lithium
$NaBH(OAc)_3$	Sodium Triacetoxyborohydride
NBS	*N*-bromosuccinimide

NFSI	*N*-fluorobenzenesulfonimide
NMR	Nuclear Magnetic Resonance
PCC	Pyridinium Chlorochromate
PPTS	Pyridinium *p*-Toluenesulfonate
RCM	Ring Closing Metathesis
ROM	Ring Opening Metathesis
S_EAr	Electrophilic Aromatic Substitution
TBAF	Tetrabutylammonium Fluoride
TBDMS	*Tert*-Butyldimethylsilyl
TFAA	Trifluoroacetic Anhydride
THF	Tetrahydrofuran
THP	Tetrahydropyranyl
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
XPhos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

1. INTRODUCTION

1. INTRODUCTION

1.1 FURAN

Furan (**1**) is a versatile organic building block; an aromatic, heterocyclic, 5-membered ring comprising four sp^2 hybridised carbon atoms (each bonded to a single hydrogen) and a single sp^2 hybridised oxygen atom giving rise to a molecular formula of C_4H_4O.[1,2] Donation of an oxygen lone-pair to the 6π system gives rise to the aforementioned sp^2 hybridisation of oxygen as well as providing the means to maintain the required planarity of the molecule in order to retain its aromaticity (*Fig. 1*). It is a clear and colourless liquid at room temperature and is relatively volatile, with a melting point of -85.6 °C (188 K) and a boiling point of 31.3 °C (304 K).

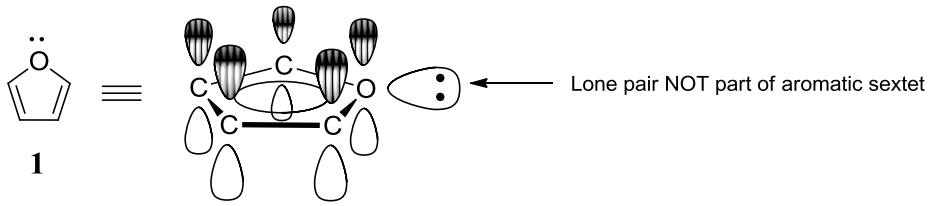


Fig. 1: The structure of furan, complete with 3D orbital representation (H atoms, O and C sp^2 bonding orbitals omitted for clarity).

Furan is isoelectronic with the cyclopentadienyl anion and pyrrole, but is electrically neutral due to the higher nuclear charge of oxygen. Another consequence due to the presence of oxygen is the loss of radial symmetry within the molecule. Examination of the mesomeric resonance forms of furan reveal that it has one form with no charge separation (**1**) accompanied by two equivalent forms (**2** & **5**, **3** & **4**) where there is charge separation (*Fig. 2*). This indicates π electron density drifting away from the oxygen atom with a partial positive charge present on it, with partial negative charges on the carbon atoms of the system.

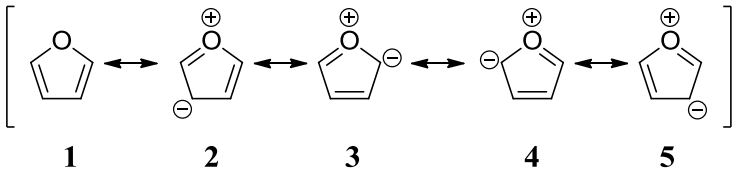


Fig. 2: Mesomeric resonance forms of furan.

The resonance contributions are not equal, with the order of contribution being **1** > **2** & **5** > **3** & **4**. A reflection of these contributions can be seen when examining the bond lengths within furan, where the shortest bond lengths are either between carbon and oxygen, or between C2 and C3 of the ring (consistent with more π character in these bonds as predicted by the order of importance of the resonance forms - *Fig. 3*).[2]

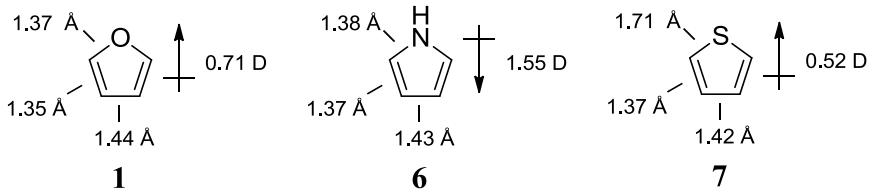


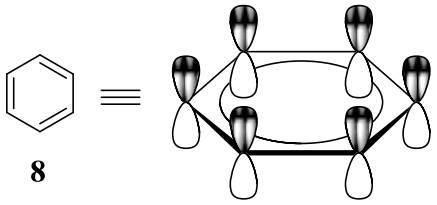
Fig. 3: Bond lengths and dipole moments of the mono-heteroatom, 5-membered heterocycles and their dipole moments.

As is also depicted above, the dipole moments of furan and thiophene are directed towards the heteroatom, whereas in pyrrole is is directed towards the ring system. This is a consequence of furan and thiophene each possessing a lone pair on the heteroatom (which is orthogonal to the ring system) - something that pyrrole lacks. Additionally, the greater heteroatom-carbon bond length seen in thiophene is due to the larger bonding radius of sulfur due to it being a period 3 element.

As seen above, furan is structurally similar to its 5-membered heterocyclic analogues, pyrrole (**6**) and thiophene (**7**); the difference for the latter being that sulfur takes the place of oxygen, while the former has nitrogen instead, which structurally deviates a little further due to having a bonded proton to the heteroatom instead of a lone pair (*Fig. 3*).

The greater dipole moment of pyrrole intrinsically means that intermolecular forces will be stronger between pyrrole molecules than for furan or thiophene, which helps to rationalise why the melting and boiling points of pyrrole are relatively high in comparison to either furan or thiophene. Additionally, the NH present in pyrrole (as opposed to the lone pair found in furan and thiophene) results in intermolecular hydrogen bonding where the ring system is acting as the H-acceptor - this would also explain why it has a higher melting and boiling point.

Of course, all 3 heterocyclic species share a structural similarity to benzene (**8**) given that they all contain six electrons within the aromatic π cloud. The obvious difference being that in benzene, each π electron originates from a single sp^2 carbon atom and as such is a 6-membered aromatic system with the molecular formula C_6H_6 (*Fig. 4*).



8

Fig. 4: The structure of benzene, complete with 3D orbital representation.

Given the electronic similarities between benzene and the three aforementioned heterocycles, it is not surprising that they display similar chemistry. Incidentally, the heterocycles are *more* electron rich than benzene due to the fact they each have six π-electrons spread over only five atoms instead of six. Additionally, the degree of aromaticity of each of the three heterocycles is not equal. This can be rationalised by once again examining the electronegativity values of each of the heteroatoms. Oxygen, being the most electronegative of the three, binds the lone pair that contributes to the π-cloud of furan more tightly to the nucleus than the nitrogen of pyrrole, and even more so than the sulfur of thiophene. As a result, the lone pair is less able to contribute to the aromaticity of the molecule. Thus, it follows that thiophene actually possesses the most aromatic character, followed by pyrrole and finally furan. The aromatic stabilisation energies of each heterocycle in comparison to benzene accentuates these differences in aromaticity (benzene: 152 kJ mol^{-1}, thiophene: 121 kJ mol^{-1}, pyrrole: 92 kJ mol^{-1}, furan 67 kJ mol^{-1}),[3] the ultimate conclusion being that furan has a stabilisation energy less

than half of that of benzene. The aromaticity of thiophene is further bolstered due to the heteroatom-carbon bond length mentioned previously. The increased bond length somewhat alleviates angle strain in comparison to furan and pyrrole, resulting in increased stability.

Another description for the π-system of furan lies in molecular orbital (MO) theory.[4] Here, a linear combination of atomic orbitals (LCAO) gives rise to the construction of a set of MOs. As previously discussed, each atom of the ring is sp^2 hybridised and these sp^2 orbitals give rise to the σ–bonds (and thus, σ-MOs) of furan. The $2p_z$ AO of each atom contribute to the π-MOs of furan. A schematic drawing of the contributions of the $2p_z$ AOs to the MOs of furan is shown in *Fig. 5*, with a view from the z-axis (note that the orbital co-efficients for each MO are not scaled).

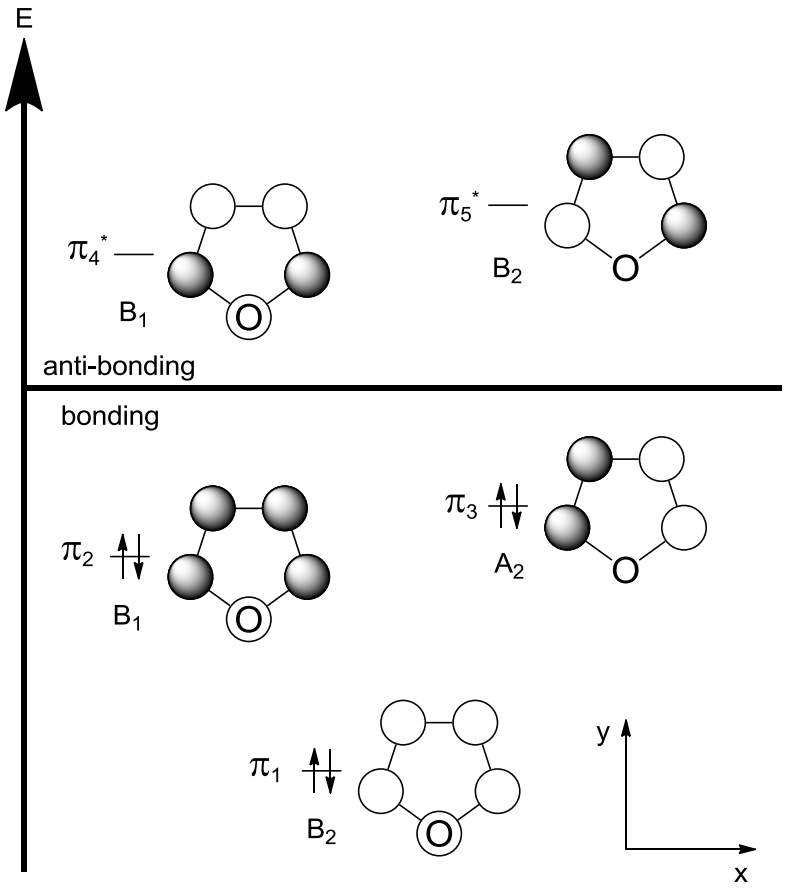


Fig. 5: Schematic drawing of the $2p_z$ AO contributions to the π-MOs of furan complete with symmetry labels (energy differences not to scale).

As can be seen above, the occupied bonding orbitals are π_1 to π_3, with the ground state π-MO being π_1 and the HOMO being π_3, which is *not* degenerate to π_2 (which is in contrast to benzene where π_2 and π_3 *are* degenerate). Likewise, the unoccupied anti-bonding orbitals, π_4 and π_5, are also non-degenerate (again in contrast to benzene), with π_4 being the LUMO.

Heterocycles are more susceptible towards typical reactions of benzene such as S_EAr due to being more 'electron rich' or 'π-excessive'. Additionally, the order of reactivity towards S_EAr of the heterocycles is as follows: pyrrole > furan > thiophene.[1] In recent years with advances in theoretical chemistry, computational calculations have been demonstrated to concur with the observed orders of both aromaticity and reactivity.[5]

1.2 REACTIONS OF FURAN

1.2.1 ELECTROPHILIC AROMATIC SUBSTITUTION

Regarding both the order of reactivity towards S_EAr and the preferred position for electrophilic substitution in the heterocycles, examination of the intermediates for both the 2- and 3-substitution products allows us to rationalise the fact that 2-substitution is favoured (*Fig. 6*).

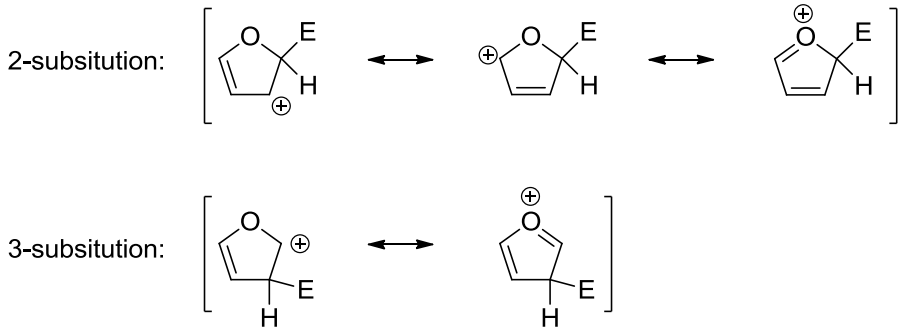


Fig. 6: Intermediates and corresponding resonance forms for 2-substitution and 3-substitution products of furan.

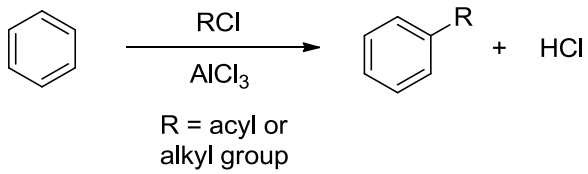
As can be seen above, the positive charge can be more effectively delocalised in the intermediate giving rise to the 2-substitution product than that giving rise to 3-

substitution product. Thus, preference for substitution in the 2-position is to be expected and indeed is generally observed.

Additionally, the ability of each heteroatom to contribute towards the stabilisation of these intermediates rationalises the orders of reactivity towards S_EAr. As detailed earlier, the lone pair of the N atom in pyrrole is most able to contribute mesomerically to the ring system and thus stabilise the reaction intermediates and thus is the most reactive of the three heterocycles. Thiophene is the least capable of contributing its lone pair to the stabilisation of the intermediates due to its lone pair being in a larger orbital and as such is the least reactive of the three heterocycles towards S_EAr.

1.2.1.1 Friedel-Crafts Reaction

The Friedel-Crafts reaction is a synthetically useful and well studied example of S_EAr that allows the acylation or alkylation of aromatic systems, developed in the later stages of the 19th century by Friedel and Crafts.[6,7] The reaction usually employs an alkyl or acyl halide and an appropriate Lewis acid (such as $AlCl_3$), which generates either a carbocation in the case of the former or an acylium ion for that of the latter *via* halide abstraction. The generated electrophile then reacts with the aromatic substrate by S_EAr to afford the desired product (*Scheme 1*).

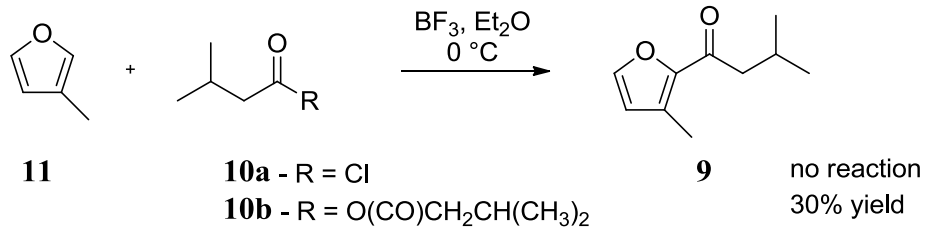


Scheme 1: General reaction scheme for the Friedel-Crafts reaction involving benzene and RCl with $AlCl_3$ as a Lewis Acid promoter, for example.

Although alkyl and acyl halides are usually employed, the generation of a suitable electrophile is the overarching goal of the Friedel-Crafts methodology. The reaction can also be employed where an alkene is the substrate in place of an aromatic species.[8]

An example of furan undergoing this type of reaction can be seen in the studies conducted by Finan and Fothergill.[9] In their efforts to synthesise Elsholtzia ketone (**9**),

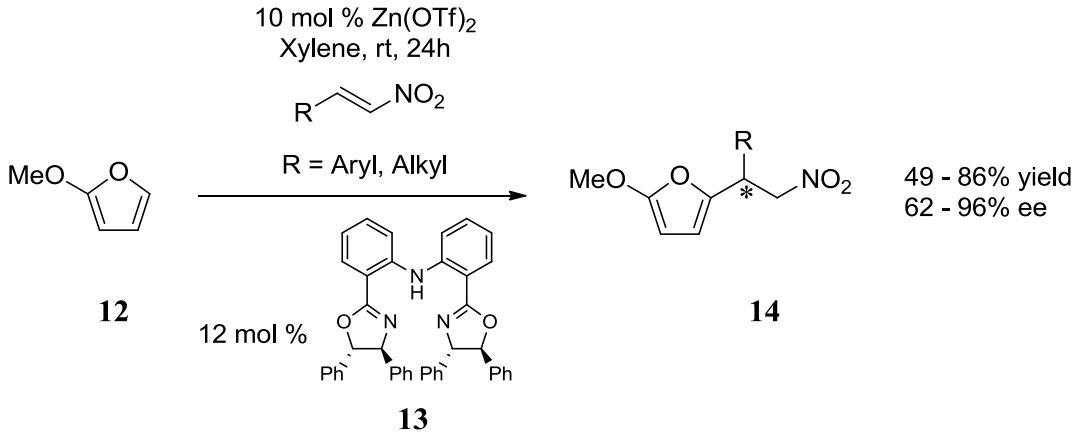
they initially employed isovaleryl chloride (**10a**) and reacted this with boron trifluoride (BF_3), in order to acylate 3-methylfuran (**11** - *Scheme 2*). However, they discovered that no reaction occurred with the acyl chloride and that with use of the corresponding anhydride instead, **10b**, a modest 30% yield was achieved.



Scheme 2: The attempted syntheses of **9** *utilising both* **10a** *and* **10b**, *with only the latter succeeding.*

Finan and Fothergill observed similar reactivity differences upon conducting test reactions on standard furan and 2-methylfuran. This probably indicates that BF_3 more efficiently abstracts isovalerate than it does chloride to generate the desired electrophile. The reasoning for this likely to be the affinity boron has for oxygen, although the authors do not address this difference in reactivity specifically. As a note, $AlCl_3$ is generally avoided as the Lewis acid in Friedel-Crafts reactions involving furans as it is known to promote polymerisation. Furthermore, due to the increased reactivity of furan towards S_EAr, weaker Lewis acids (such as BF_3 seen above) can be successfully employed.

Relatively recently, Friedel-Crafts methodology has also been employed asymmetrically in alkylations to afford enantioenriched products.[10] In this example, Hu *et al.* reacted 2-methoxyfuran (**12**) (which was peculiarly found to be the only suitable substrate, despite various other electron rich furans being tested) with various nitroalkenes under the catalysis of **13**-$Zn(OTf)_2$ complexes to afford 2,5-disubstituted products **14** (*Scheme 3*).



*Scheme 3: General reaction scheme for the asymmetric Friedel-Crafts alkylation of 2-methoxyfuran (**12**).*

The authors' most prominent result was recorded when R was 3,4-dimethoxyphenyl, affording the product in 86% yield and 96% ee in favour of the *S*-configuration at the carbon β to the nitro group. The rationalisation of the stereochemical outcome can be viewed in *Fig. 7* (*vide infra*) where the proposed transition state of the reaction is visualised.

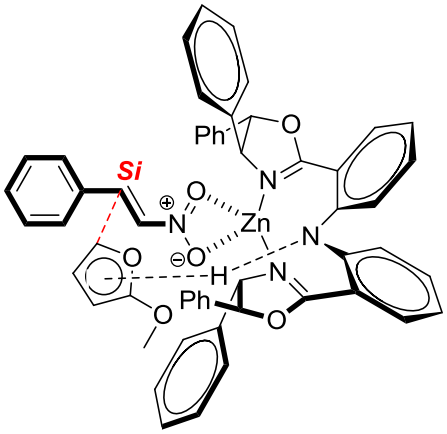
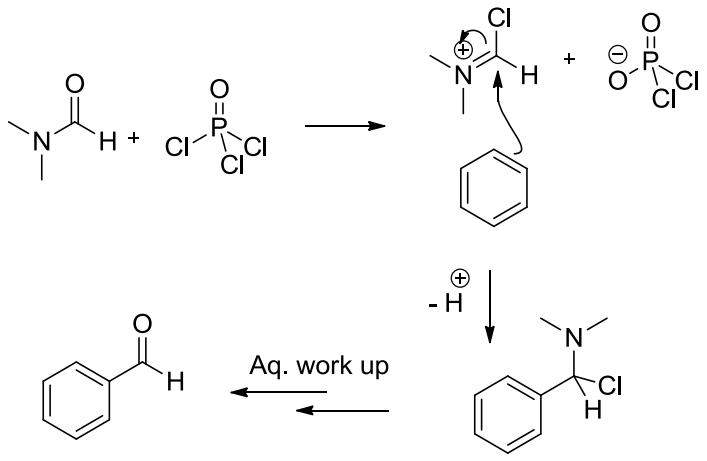


Fig. 7: The proposed transition state for the Friedel-Crafts alkylation detailed in the work by Hu et al.

As can be seen, the catalyst is believed to be working in a bifunctional mode with Zn(II) acting as a Lewis acid to activate the nitrostyrene substrate while the NH group acts as a H-bond donor *via* an NH-π interaction. This directs the attack of **12** from the *si* face which gives rise to the *S*-products.

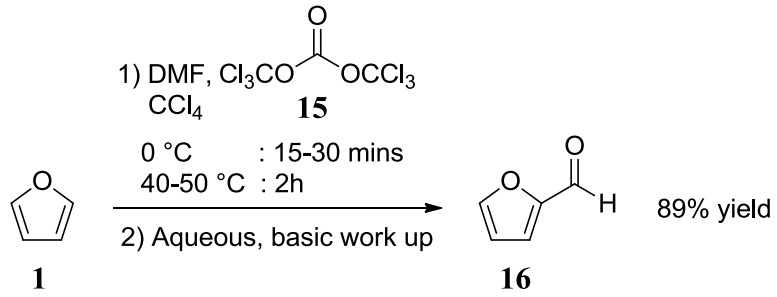
1.2.1.2 Vilsmeier-Haack Formylation

The Vilsmeier-Haack formylation reaction involves an S_EAr reaction between a suitable carbon nucleophile and a halomethylene-iminium salt, first established in 1927 by the authors whom the reaction is named after.[11] Classically, the reaction involves the employment of phosphorus oxychloride ($POCl_3$) and DMF or MFA to generate the aforementioned salt, which then reacts with the substrate to afford the corresponding product (*Scheme 4*). Phosgene has also been used in place of ($POCl_3$).



Scheme 4: General reaction scheme for Vilsmeier-Haack formylation.

A recent example of the Vilsmeier-Haack methodology being conducted on furan has been reported by Shan and co-workers.[12] The authors successfully achieved furan formylation under very mild Vilsmeier-Haack conditions in impressive yield to afford furfural (**16 -** *Scheme 5*).

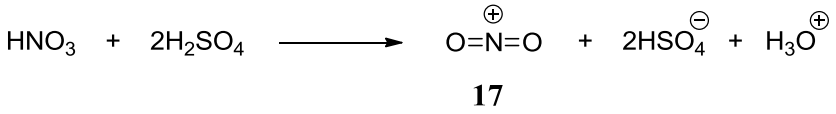


Scheme 5: Conditions for the modified Vilsmeier-Haack formylation of furan.

The subtle but elegant difference from traditional Vilsmeier-Haack conditions lies with the employment of the more environmentally friendly bis(trichloromethyl) carbonate (**15**), in place of either $POCl_3$ or phosgene - both of which are rather unpleasant compounds to work with (particularly the latter). Use of **15** also provides other benefits in the form of being convenient to store and transport as it is a stable solid, unlike the conventional reactants.

1.2.1.3 Nitration

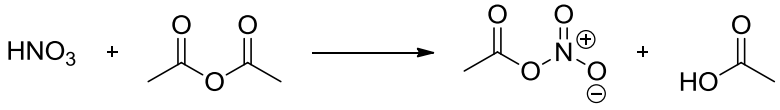
Nitration is another substitution reaction that is essentially characteristic of aromatic compounds.[13] It is a process classically achieved by combination of concentrated nitric and sulfuric acid in order to generate the reactive nitronium ion (**17**), which is a reactive electrophile (*Scheme 6*).



Scheme 6: Formation of **17**, *the nitronium ion, from concentrated nitric and sulfuric acid.*

The nitronium ion then reacts with the corresponding nucleophile to give the desired product. In the case of furan, however, it is desirable to nitrate *via* alternative means due to the susceptibility of furan to undergo polymerisation in the presence of concentrated sulfuric acid.

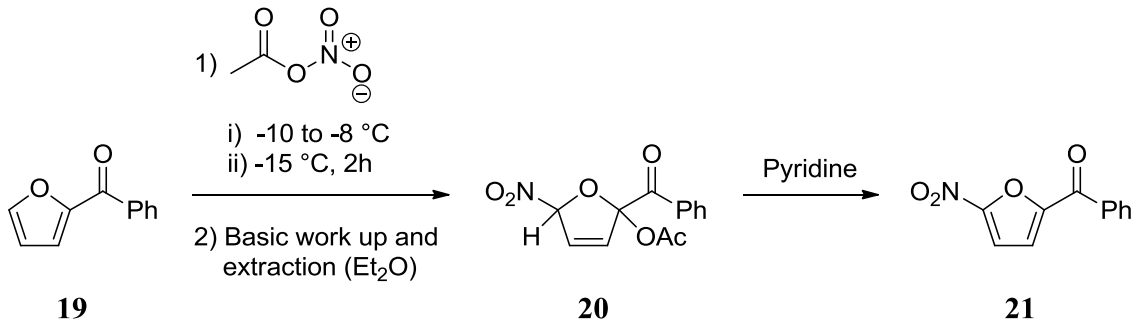
With due consideration to this, a different methodology for introducing the nitro functionality must be employed instead so as to avoid the presence of concentrated sulfuric acid. This is typically in the form of acetyl nitrate (**18**) as demonstrated by Gilman and Young.[13] Acetyl nitrate itself is generated *in situ via* combination of acetic anhydride and concentrated nitric acid (*Scheme 7*).



18

Scheme 7: Formation of acetyl nitrate by reaction of nitric acid and acetic anhydride.

Gilman and Young successfully nitrated 2-furylphenyl ketone (**19**) *via* this methodology in moderate yield (*Scheme 8*). A particularly interesting feature of this reaction is that nitration does not occur on the phenyl moiety of **19** at all, highlighting the increased reactivity of furan in comparison to benzene towards S_EAr. Another feature to note when employing this methodology is the use of pyridine in order to complete the reaction. The use of pyridine as a mild base is a necessity due to the formation of addition product **20** (*Scheme 8*), which is the result of an initial addition reaction between the substrate and acetyl nitrate. Pyridine facilitates the elimination of acetic acid from this intermediate, restoring the aromaticity of the system upon formation of the final product **21** (*Scheme 8*).

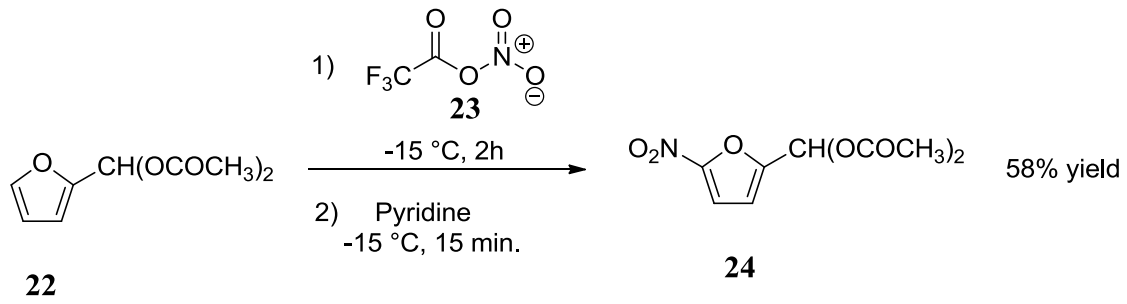


19 **20** **21**

51% yield

Scheme 8: Formation of **21** *via nitration of* **19***, including the addition intermediate* **20**.

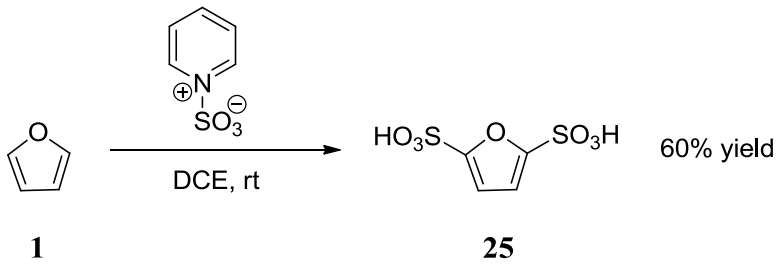
In more recent times, it has been demonstrated that the requirement of temporarily isolating addition intermediates analogous to **20** can be circumvented by slightly modifying the reaction.[14] Katritzky and co-workers discovered that by replacing acetic anhydride with TFAA (which affords nitrating agent **23**), not only could isolation of the addition intermediates be avoided, but reaction yields were also much improved (*Scheme 9*). For example, upon formation of **24**, a yield of 58% was recorded in one step. In comparison, in the literature, attempts to synthesise the same compound *via* the acetyl nitrate methodology afforded yields of 15-43% over two steps.[15]



Scheme 9: Nitration of **22**, *leading directly to* **24**.

1.2.1.4 Sulfonation

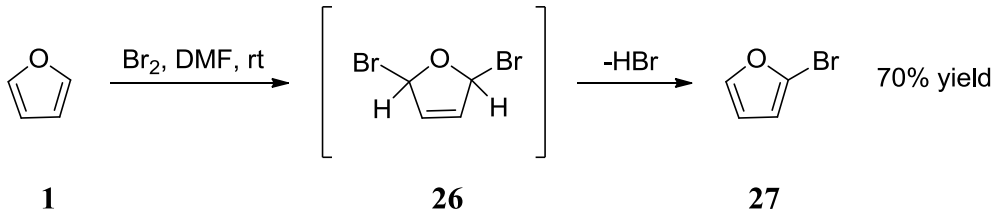
Analogously to the case of nitration, conventional methods of sulfonation are not applicable to furan due to aforementioned sensitivity towards concentrated sulfuric acid. However, the pyridine-sulfur trioxide complex can be employed to successfully transform furan (**1**) into the 2,5-disubstituted product (**25**) seen below (*Scheme 10*).[16]



Scheme 10: Sulfonation of furan employing pyridine-sulfur-trioxide complex.

1.2.1.5 Halogenation

Another classic case of furan reactivity is that with elemental halogens. Furan is known to react vigorously with bromine and chlorine at room temperature to afford poly-halogenated products, although no reactivity is displayed towards iodine.[17] A simple example of bromination has been reported by Brandsma *et al*., in which furan (**1**) was treated with elemental bromine in DMF at room temperature (*Scheme 11*).[18]

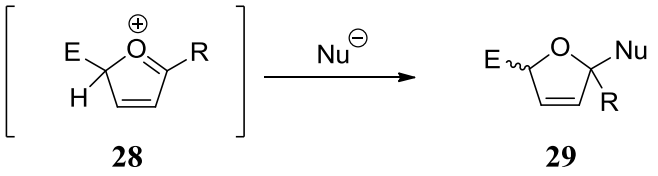


Scheme 11: Reaction pathway giving rise to 2-bromofuran **27**.

In a manner somewhat similar to the nitration reaction involving acetyl nitrate (*vide supra*), an addition intermediate, **26**, is formed during this reaction which, *via* elimination of HBr then affords the mono-substituted furan. However, the authors noted that dibromination was possible if **27** was treated with excess bromine. The appearance of **26** has been confirmed in subsequent NMR studies.[19]

1.2.2 ADDITION REACTIONS

As seen earlier (*vide supra*), addition products are possible intemediates in substitution reactions of furans. Mechanistically, this is an indication that there is a tendency in certain circumstances for the cationic intermediate of the reaction (**28**) to be intercepted by a nucleophile and afford an addition product (**29**) rather than lose a proton (*Scheme 12*). Indeed, this kind of reactivity is a general feature of furan chemistry.

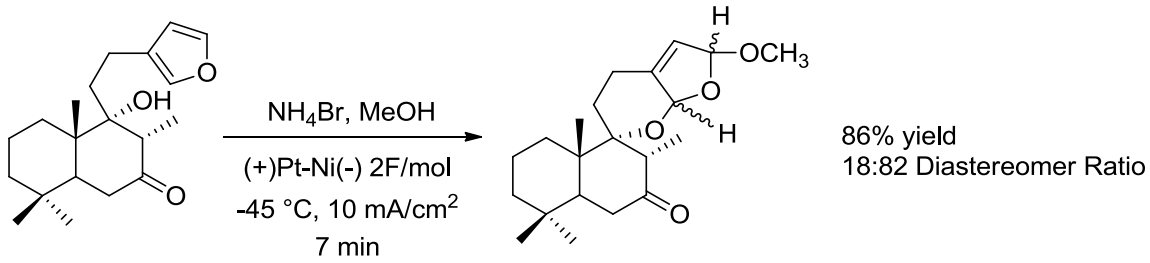


28 **29**

Scheme 12: An example of a general furan addition product **29***, formed when the cation intermediate* **28** *is in the presence of a sufficient nucleophile.*

The foundation for this tendency towards addition products can be traced to the fact furan is not as aromatic as pyrrole (which does not so easily undergo addition reactions). As a result, furan has less of a thermodynamic driving force to restore aromaticity from its adducts and as such more readily undergoes addition reactions of this nature in comparison to pyrrole. Indeed, work elsewhere in the literature has purposely involved isolating these nitro/acetate addition products.[20]

In a different methodology, the more facile reactivity of furan towards addition has been exploited by Frontana-Uribe and co-workers.[21] Unlike with the addition processes already seen (*vide supra*), the method of addition in this example was achieved *via* electro-oxidation of the substrate, hispanolone (**30**), to diastereomeric derivatives of structure **31** (*Scheme 13*). The electrochemical cell featured a platinum anode and nickel cathode.



30 **31**

Scheme 13: Transformation of **30** *into diastereomeric, electro-oxidation products* **31***, involving intramolecular addition of the hydroxyl functionality.*

The conditions listed in *Scheme 13* were those that gave the maximum isolated yield of the diastereomeric mixture. The diastereoisomers themselves were then separated *via* medium pressure chromatography and recrystallisation. The oxidation takes place *via* the mechanism presented in *Fig. 8*, which generates a stoichiometric amount of Br_2 - a necessity in order for oxidation to occur.

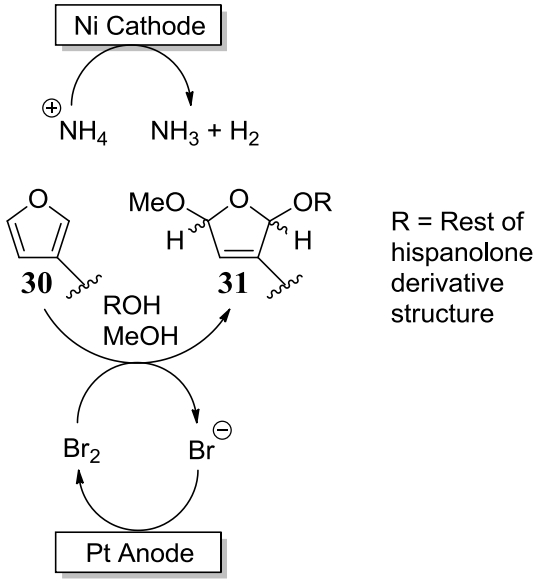
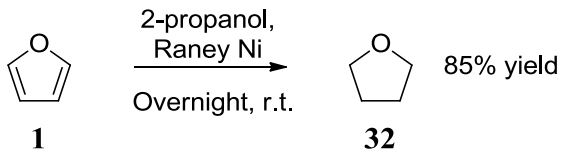


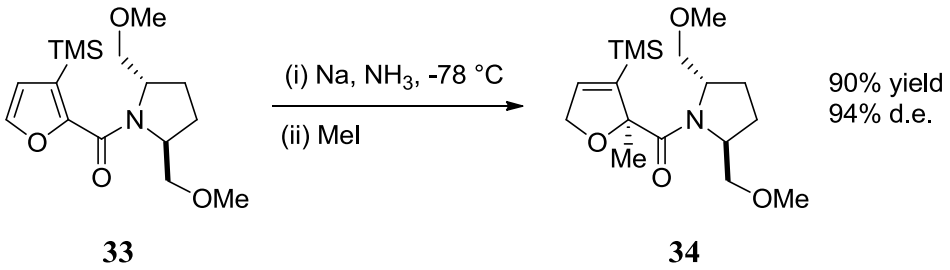
Fig. 8: Visualisation of the electro-oxidation indicating electrodes, with bromine as the oxidant, in order to afford the addition products of structure **31**.

A classic example of addition reactivity in furan can be seen in the form of total reduction to THF (**32**), as demonstrated by Srivastava *et al.*.[22] The group demonstrated facile conditions (notably in the absence of high pressure) for the reductive process employing 2-propanol as the reducing agent and Raney Ni as the catalyst (*Scheme 14*).



Scheme 14: A simple representation of the transformation of furan into THF via catalytic hydrogenation.

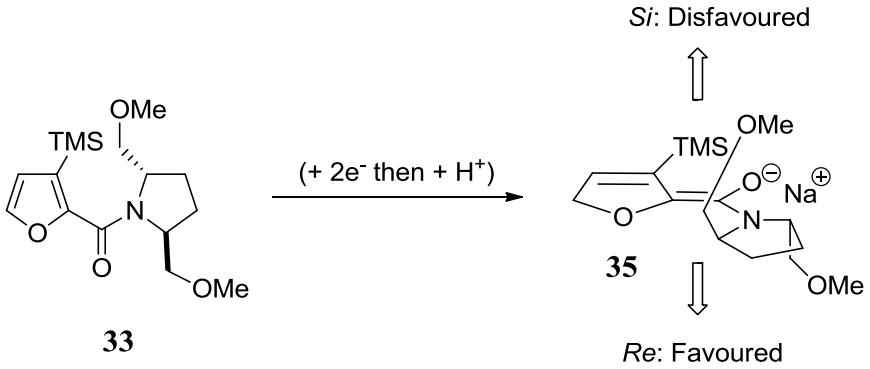
A more exotic example of furan reduction has been elegantly demonstrated by Donohoe and co-workers. A set of stereoselective Birch reductive alkylations were carried out on 3-silyl-2-furoic acid derivatives **33**.[23] The most successful of these involved methylation (*Scheme 15*), although high diastereomeric excesses were observed even in the examples where a lower yield was recorded. Indeed, Donohoe *et al.* have achieved similar results on the 3-methyl analogue of **33** (where the methyl group is in place of the TMS moiety),[24] however, difficulty in removal of the 3-methyl group prompted them to investigate the same chemistry on **33** (where the choice can be made to remove the TMS moiety). The presence of a 3-substituent on the furan in these reactions is essential to achieving good yields and selectivity.



33 **34**

Scheme 15: Stereoselective Birch reductive methylation of **33**.

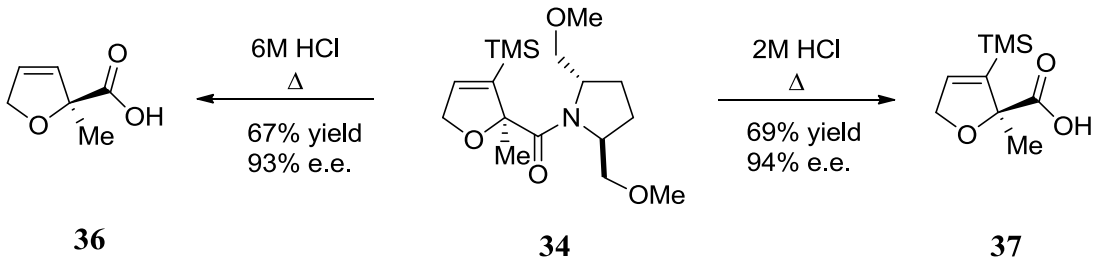
A high degree of *Re* face stereoselectivity was observed in all cases. The possible rationalisation for this selectivity is visualised below (*Scheme 16*). The authors speculated that the *trans* enolate geometry of intermediate **35** (required for this mechanistic proposal to be valid) is favoured firstly by steric considerations but also commented on the possibility of an attractive O-Si interaction.



33

Scheme 16: Formation of the reactive trans enolate, which offers an explanation for the source of the observed stereselectivity.

As discussed previously, upon formation of the Birch reduced amide, the authors identified that the TMS group could be either removed, or retained for further functionalisation upon ultimate formation of furoic acids **36** and **37** respectively (*Scheme 17*). Removal of the TMS group was achieved concomitantly with the hydrolysis of the bis(hydroxymethyl)pyrroline amide under harsh acidic conditions. Alternatively, selective hydrolysis of the amide group was achieved in milder acidic conditions.



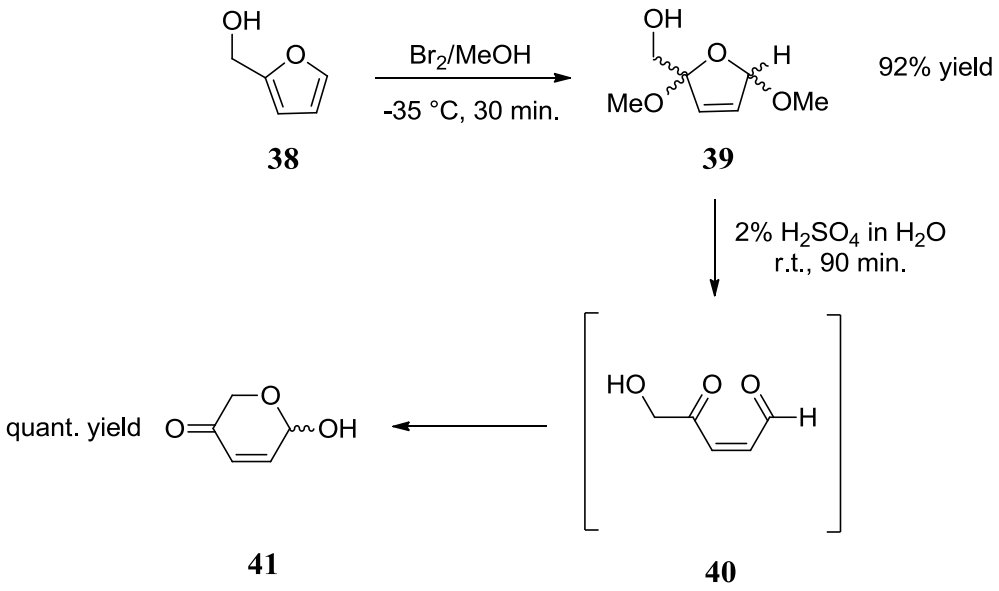
36 **34** **37**

Scheme 17: Eventual formation of furoic acids.

1.2.3 RING OPENING REACTIONS

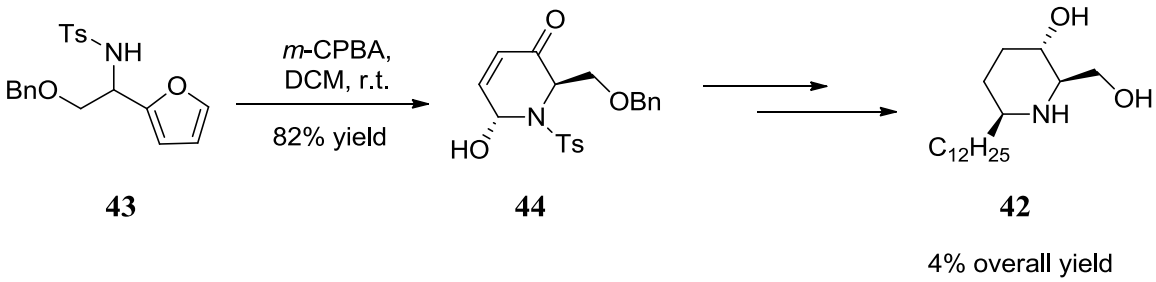
Another form of reactivity exhibited by furans is that of ring-opening reactions. One such example of this reactivity is displayed in the Achmatowicz reaction,[25] which ultimately results in the formation of dihydropyrans from furan derivatives. This is the initial step in the reversal of chemistry established in the earlier part of the 19th century by Döbereiner, who observed the formation of furfural (**16**) upon heating xylose in the presence of MnO_2 and H_2SO_4.[26]

Achmatowicz and co-workers achieved the dihydropyran formations by initially treating the furan substrate, which in the example shown is furfuryl alcohol (**38**) with Br_2 and MeOH to afford addition intermediate **39** (*Scheme 18*). Subsequent acidification of **39** resulted in a ring-opening of the furan structure to afford the non-isolated dicarbonyl compound **40**, which underwent cyclisation to afford compound **41**. The authors proposed that additional synthetic steps performed on **41** (and appropriate analogues) would provide a general approach to the total synthesis of monosaccharides.



Scheme 18: Formation of compound **41** *from* **38** *via the Achmatowicz procedure.*

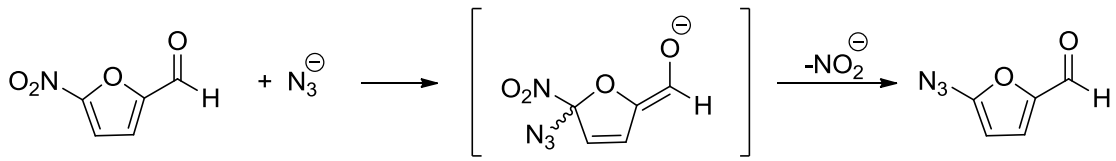
More modern adaptations of the Achmatowicz reaction have involved the use of *m*-CPBA to conduct the ring-opening step directly from the starting furan substrate, an example of which was demonstrated as the key step by Yang *et al.* in the total synthesis of (+)-desoxoprosophylline (**42** - *Scheme 19*).[27] Treatment of furfuryl amine derivative **43** under such conditions afforded dihydropyridone **44**, which was subsequently converted to **42** in several steps.



Scheme 19: Achmatowicz reaction as the key step in the synthesis of (+)-desoxoprosophylline **42**.

1.2.4 NUCLEOPHILIC AROMATIC SUBSTITUTION

Although electrophilic substitution is more common for furan, under certain reaction conditions and on certain substrates, nucleophilic aromatic substitution can also be achieved. Typically, the substrate involved bears electron-withdrawing substituents that can be displaced by appropriate nucleophiles as demonstrated below (*Scheme 20*). Here, an azide nucleophile has displaced the nitro moiety of 5-nitro-2-furaldehyde (**45**) *via* elimination of addition intermediate **46** to afford **47**.[28]

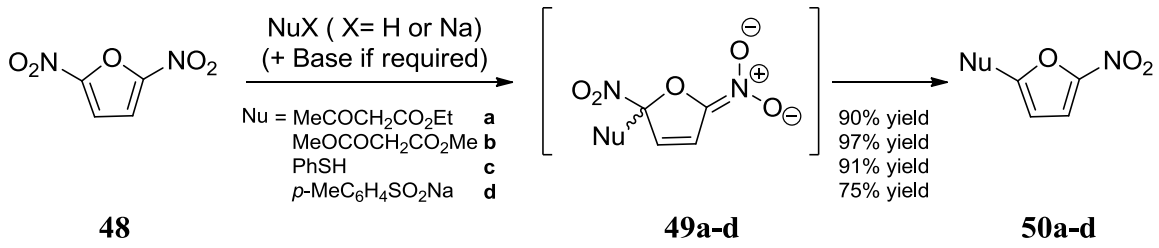


45 **46** **47**

Scheme 20: Formation of **47** *from* **45** *via nitrite elimination of nucleophilic addition intermediate* **46**.

The addition-elimination pathway for nucleophilic substitution (S_NAr) seen above is ubiquitous for reactions of this nature, with kinetic experiments verifying the formation of the addition intermediates, or Meisenheimer complexes as they are known.[29]

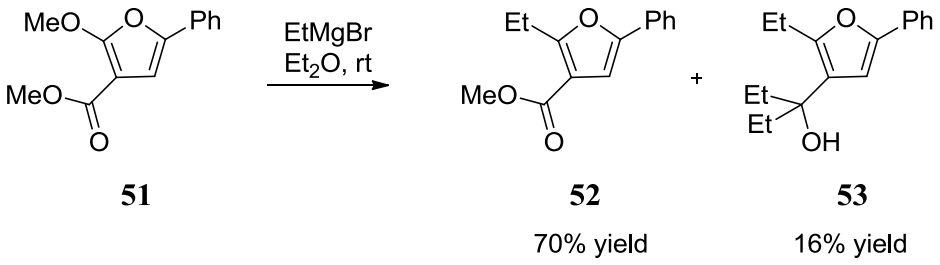
Padwa and Waterson fairly recently investigated the scope and synthetic utility of S_NAr reactions of furan using 2,5-dinitrofuran (**48**).[30] They discovered that they could use a mixture of hard and soft nucleophiles to displace one of the nitro groups, with all reactions presumably going through a Meisenheimer complex (**49a-d**), which after undergoing elimination afforded the 2-substituted product **50a-d** (*Scheme 21*).



Scheme 21: The addition of various nucleophiles to **48**.

Impressive yields were obtained for each nucleophile used, highlighting the broad scope of various nucleophiles that can be employed in S_NAr reactions.

In a rather peculiar example of S_NAr, a study in the literature has revealed nucleophilic substitution of a 2-methoxy group by Grignard reagents in substrates featuring a 3-methoxycarbonyl functionality.[31] The authors demonstrated that upon treatment of substrate **51** with EtMgBr under standard conditions, a product mixture of **52** and **53** was afforded, **52** being the major product (*Scheme 22*).

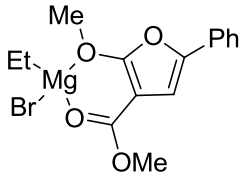


Scheme 22: Transformation of **51** *into* **52** *and* **53** *under Grignard conditions.*

On initial examination, somewhat surprisingly, no evidence was found for a product where methoxy substitution had not occurred. Product **52** was the dominant product where only the methoxy moiety had been substituted by ethyl, while **53** is the expected Grignard product from reaction with the ester.

Interestingly, the authors established that exposing the 4- and 5-methoxycarbonyl-2-methoxy analogues of **51** to the same reaction conditions resulted in no substitution of the methoxy moiety and the only products were that of addition to the

ester group. The explanation for this can be attributed to the magnesium forming a strong complex (**54**) with the vicinal carbonyl and methoxy functionalities (only possible in 3-methoxycarbonyl-2-methoxy furans) in accordance with Meyer's hypothesis (*Fig. 9*).[32] The ethyl nucleophile attacks the 2-position which ultimately results in elimination of the methoxy group to afford the 2-substituted product.



54

Fig. 9: The proposed Mg-substrate complex.

The authors carried out a series of reactions on substrates analogous to **51**, with various Grignard reagents as well as different substituents in the 5-position of the substrate, recording isolated yields of the 2-substituted products between 12% and 80% depending on these variables. Of particular note was that upon replacing the 3-methoxycarbonyl functionality with a methyl ketone, substitution of the methoxy moiety *still* occurred at the 2-position, although due to the increased reactivity of ketones, addition predominated over substitution.

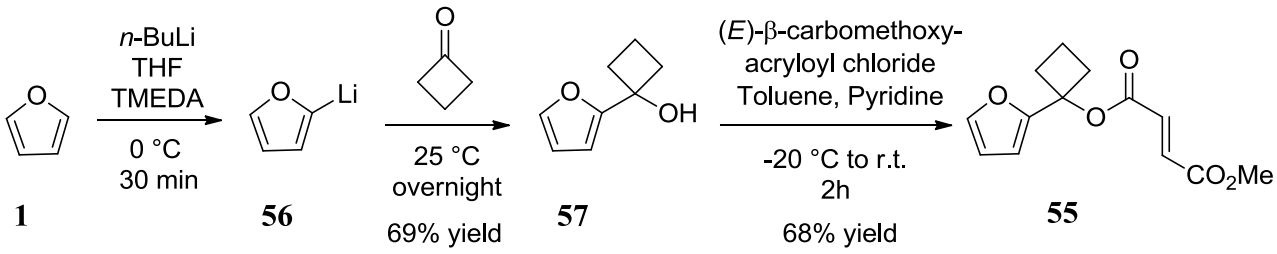
1.2.5 GENERATION OF ORGANOMETALLICS FROM FURAN

The example above involves an organometallic nucleophile reacting with furan. However, a broadly employed approach for incorporating furan rings into other moieties is to conduct organometallic chemistry on the furan itself. The resulting metallated species have been shown to participate in a wide range of reactions primarily involving nucleophilic addition and metal-catalyzed cross-coupling reactions.[33]

1.2.5.1 Lithiates

Direct deprotonation of furan conventionally takes place at the 2-position (or 5-position if the 2-position is already substituted), due to the increased acidity of these protons. Conventionally, this is achieved by employing alkyl lithium reagents such as *n*-BuLi (with or without TMEDA, which increases the reactivity of said alkyl lithiums) or lithium amide bases such as LDA.[33,34]

A simple example of such lithiation chemistry in action has been demonstrated by Jung and Gervay.[35] In their efforts towards synthesising a range of 2-furfuryl methyl fumarates of structure **55** for Diels-Alder reaction studies, they first had to synthesise key precursor alcohol **57** (*Scheme 23*). They accomplished this by lithiating furan (**1**) under conventional conditions and reacting the lithiated species **56** (without isolation) with the corresponding ketone to afford the desired substrate. The example displayed uses cyclobutanone as the electrophile to afford the product **57**, however, an array of other ketones were also employed under slightly varied reaction conditions to afford analogous products.

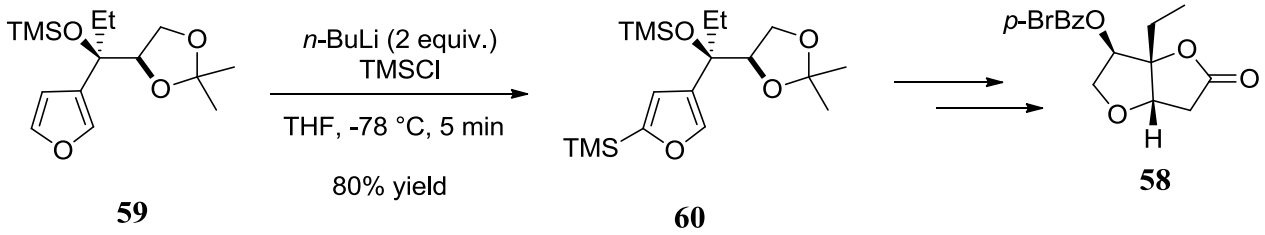


Scheme 23: Formation of **55** *from key precursor* **57**, *itself formed via reaction of cyclobutanone with lithiated furan* **56**.

Note that in this case, TMEDA was added in order to facilitate the lithiation process. Another general fact is that low temperatures are often required for lithiation procedures in order to limit undesired side reactions, such as the reaction of *n*-BuLi with THF.[36]

This methodology has been employed in synthetic routes towards more complex structures, including efforts towards natural product synthesis as demonstrated by Lee and Wong.[37] On the route towards compound **58**, a potential core skeleton of the

platarkone family of natural products, intermediate **59** was subjected to lithiation in order to produce silylated compound **60** (*Scheme 24*).

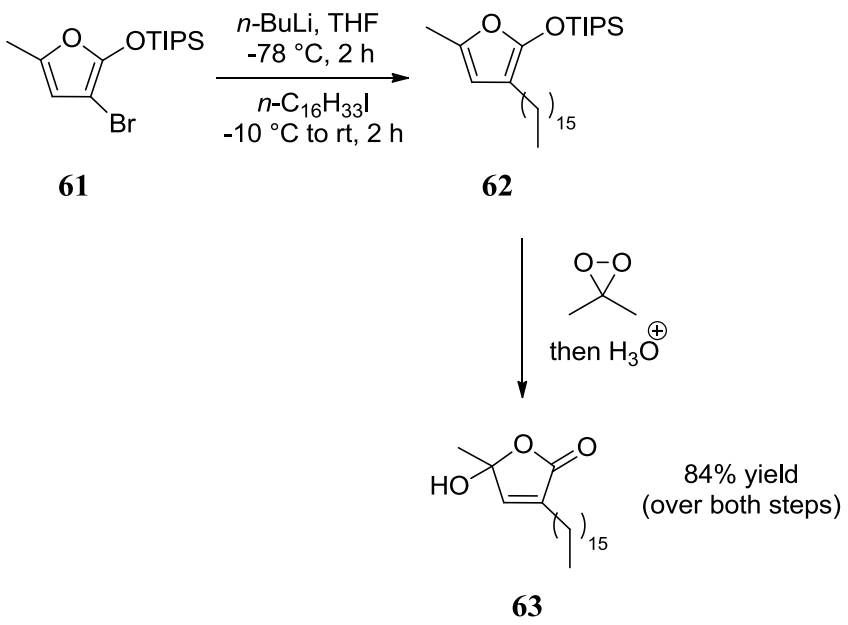


Scheme 24: Synthesis of 5-silylated intermediate **60***, which was transformed in several steps to* **58**.

The authors demonstrated that silylation of **59** proceeded regioselectively at the sterically less hindered 5-position as intended. Compound **60** was then eventually transformed into the key lactone in several further steps.

Another method for achieving furan lithiation is by lithium-halogen exchange (pertinent to I>Br>Cl but *not* F), which is a widely applicable reaction that occurs much faster than lithium-hydrogen exchange detailed above.[38]

Lithiation of the less acidic 3-position in furan is usually achieved *via* this approach (which can also be employed to generate 2-lithiated furans) as demonstrated in by Boukouvalas and Loach.[39] The authors conducted facile lithium-bromine exchange on substrate **61** in order to react it with 1-iodohexadecane in order to generate the 2,3,5-trisubstituted furan **62**, the immediate precursor to the target gorgonian lipid **63** (*Scheme 25*).



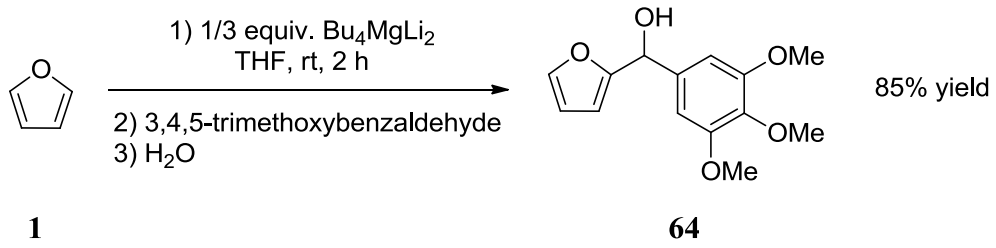
Scheme 25: Lithium-halogen exchange on **61** *and with reaction with n-$C_{16}H_{33}I$ affords intermediate* **62**, *which is then transformed into desired gorgonian lipid* **63**.

Treatment of intermediate **62** with dimethyldioxirane followed by acidic work-up afforded the desired product **63** in good yield over the two steps.

1.2.5.2 Magnesiates

In an effort to avoid undesirable side reactions that may occur due to the high reactivity and nucleophilicity of lithium bases, alternative methodologies involving the magnesiation of furan have been developed. These can often be conducted at higher temperatures than the corresponding lithiations, even at ambient temperature in certain cases.[33]

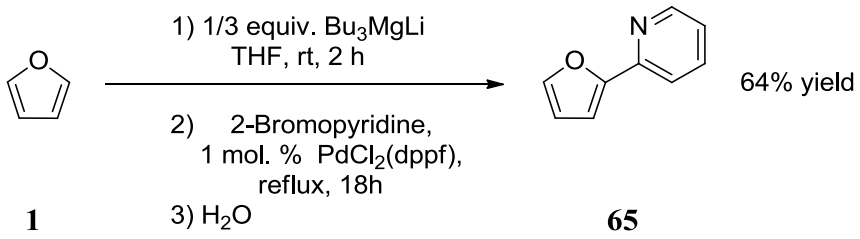
Deprotonation at the 2-position of furan can be achieved *via* the use of lithium-magnesiates under relatively mild conditions in comparison to lithiation, as demonstrated by Mongin *et al.* as recently as 2005.[40] They examined the power of two magnesiating reagents, Bu_3MgLi and Bu_4MgLi_2, finding the hgher order species to be the most effective. For example, furan (**1**) was transformed into alcohol **64** *via* this methodology upon treatment with Bu_4MgLi_2 in impressive yield (*Scheme 26*).



1 **64**

Scheme 26: Magnesiation of furan and subsequent quenching with 3,4,5-trimethoxybenzaldehyde to afford alcohol **64**.

Monitoring of the magnesiation process confirmed that over a two hour time period, 95% deprotonation had occurred. It was also ascertained that quenching with the electrophiles involved was very rapid. As can be seen above, the reaction was carried out at room temperature, highlighting an advantage of this methodology over conventional proton abstraction. Another advantage over lithiation chemistry was the ability of furan magnesiates to undergo cross-coupling reactions without the requirement for their conversion to organozinc, organotin or organoboron derivatives. The evidence for this was revealed in the Kumada-type cross coupling reaction between the magnesiate of furan and 2-bromopyridine to afford **65** (*Scheme 27*).

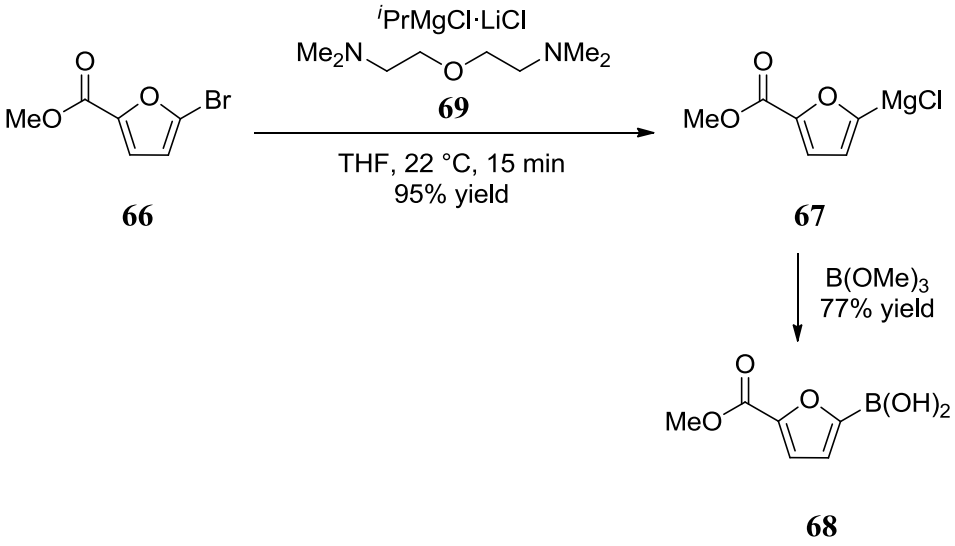


1 **65**

Scheme 27: Magnesiation of furan followed by cross-coupling with 2-bromopyridine to afford **65**.

In addition to the furan magnesiates exemplified above, the generation of Grignard reagents has also been successfully achieved on bromofurans.[41] Wang and co-workers discovered that, among other aromatic substrates, methyl 5-bromofuran-2-carboxylate (**66**) underwent magnesium-halide exchange with ^{i}PrMgCl·LiCl to afford Grignard

reagent **67**, which was subsequently reacted with trimethylborate to afford boronic acid **68** in good yield (*Scheme 28*).

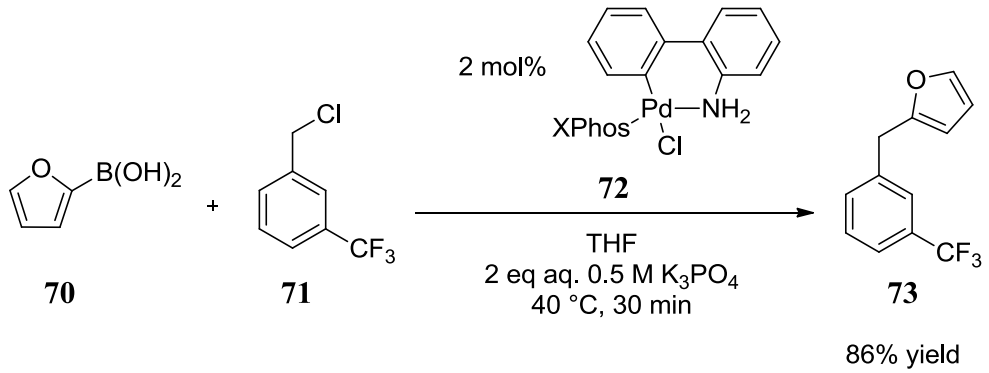


Scheme 28: Formation of **68** *via boronation of Grignard reagent* **67**, *derived from* **66**.

An interesting feature of this Grignard methodology is that the 2-carboxylate functionality remains intact throughout the procedure. This is attributed to the presence of diamine **69**, which chelates to Mg in a tridentate fashion, thus lowering the reactivity of the Grignard reagent. This lower reactivity results in more chemoselective reactivity of the Grignard reagents with trimethylborate. This fact is highlighted by the greatly reduced yields when the reaction is attempted in the absence of **69**, where the first step drops to 57% and the boronation to 28%.

1.2.5.3 Boronates

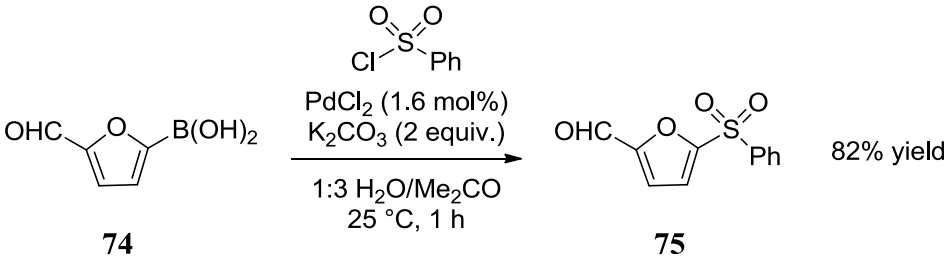
Furanboronic acids themselves also have synthetic utility, particularly in cross-coupling reactions.[33] This has been demonstrated by Buchwald and co-workers, when they successfully coupled a range of aryl boronic acids with an assortment of aryl and benzyl halides.[42] In the case of a furan-based substrate, 2-furanboronic acid (**70**) was coupled with 3-(trifluoromethyl)benzyl chloride (**71**) in the presence of XPhos pre-catalyst **72** to afford **73** (*Scheme 29*).



Scheme 29: Successful Suzuki-Miyaura cross-coupling of **70** *and* **71** *to afford* **73**.

K_3PO_4 is responsible for generating the active XPhos-Pd(0) catalyst from **72**, but it was also chosen due to the sensitivity of free boronic acids towards bases. K_3PO_4 not only very rapidly reacts with the pre-catalyst, but also reacts very slowly with the boronic acid substrate so as to limit protodeboronation and thus overall facilitates the formation of **73**. As a final note, sp^2-sp^2 coupling was successfully conducted with furanboronic acids in addition to the sp^2-sp^3 coupling demonstrated above.

Furanboronic acids have not only been demonstrated to be useful in carbon-carbon coupling, but also with carbon-heteroatom bond formation.[43] Reaction of furanboronic acid **74** with phenylsulfonyl chloride in the presence of $PdCl_2$ and K_2CO_3 yielded sulfone **75** in good yield (*Scheme 30*). Of particular note are the mild reaction conditions and the absence of SO_2 extrusion to afford biaryl compounds. This is in contrast to similar work involving the coupling of sulfonyl chlorides with organostannanes, where such extrusion was recorded in conjunction with generally harsher reaction conditons.[44]



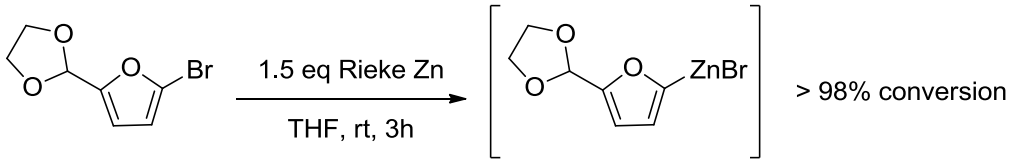
Scheme 30: Coupling of phenylsulfonyl chloride and **74** *to afford* **75** *under the catalysis of $PdCl_2$ in mild conditions.*

In addition to the use of furanboronic acids for coupling purposes as seen above, other boronate functionalities have also been employed such as trifluoroboronates and MIDA boronates.[45,46]

1.2.5.4 Zincates

Another common metallation seen in furan chemistry is that of zinc to form organozinc derivatives, which due to a more covalent carbon–metal bond, are less reactive than the organomagnesium and organolithium compounds discussed earlier.[47] Thus, zincates are soft nucleophiles and are commonly employed for cross-coupling reactions.

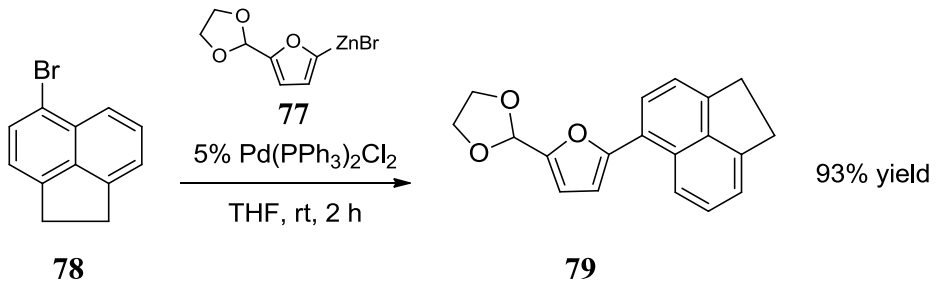
Rieke and Kim have demonstrated the synthetic utility of furan zincates in the formation of a variety of 5-substituted furan derivatives.[48] Generation of the organozinc reagent **77** was achieved by treatment of the corresponding halide **76** with activated Rieke zinc[49] at ambient temperature (*Scheme 31*).



76 **77**

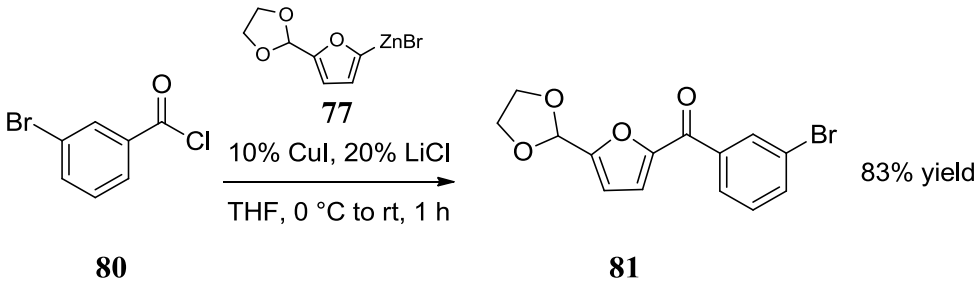
Scheme 31: Formation of reactive zincate **77** *from* **76** *using Rieke zinc*.

The quantification of the zinc insertion was verified by subsequent iodination and analysis by GC and established to be greater than 98% conversion. Zincate **77** was then reacted in a Pd cross-coupling reaction with a variety of substrates, one highlight of which was the reaction of **77** with aryl halide **78** to afford product **79** (*Scheme 32*).



Scheme 32: Cross-coupling of **77** *with* **78** *under Pd catalyzed conditions.*

Additionally, the zincate could be used in cross coupling reactions on hydroxy and amino aryl halides. Cu catalyzed coupling to various acyl chlorides was also reported, an example of which is visualised in *Scheme 33*, where **77** and **80** were succesfully coupled to afford **81**.

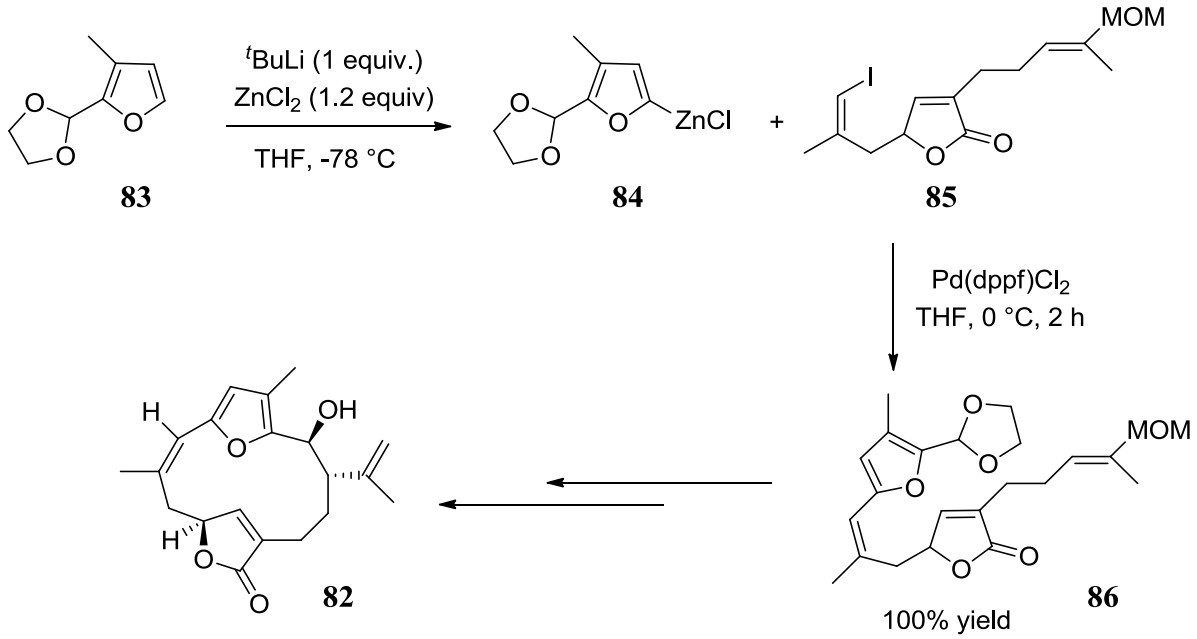


Scheme 33: Copper mediated catalysis for the coupling of acyl chlorides and zincates.

Note that due to the reaction now being mediated by copper, no reaction occurs at the aryl bromide. Of particular note in this study were the mild reaction conditions used for every example, accentuating a key benefit of this organozinc methodology.

A highlight in furan zincate chemistry has been displayed in natural product synthesis, where it plays a key role in the total synthesis of (±)-bipinnatin J (**82** - *Scheme 34*).[50] The crucial step was a palladium-mediated Negishi cross-coupling protocol reaction between organozinc reagent **84** (generated from **83**) and compound **85** to afford **86**, a key precursor in the synthesis of macrocycle **82**. The organozinc species itself was obtained *via* deprotonation and transmetallation. An impressive feature of

this reaction is no doubt the quantitative yield of **86** under relatively mild conditions, further bringing to light the advantages of this organozinc chemistry.



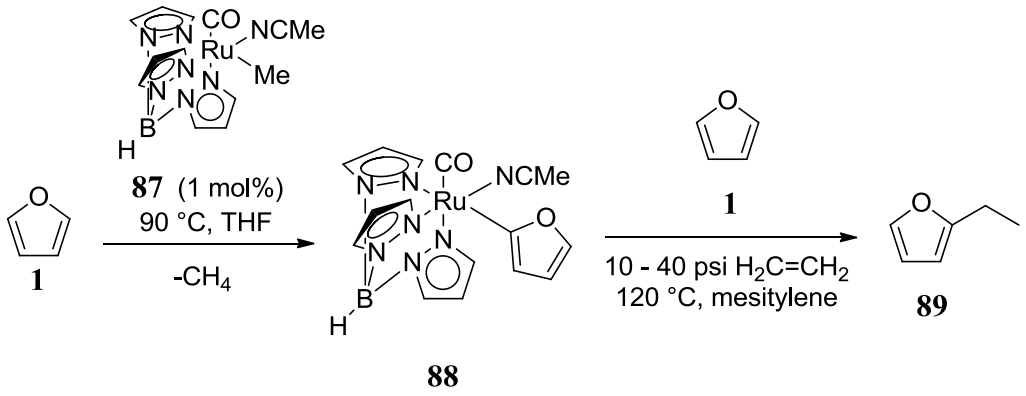
Scheme 34: Synthetic strategy utilising zincate **84** *towards key intermediate* **86**, *which was subsequently transformed into* **82**.

1.2.6 *C-H* ACTIVATION

The above metallation procedures all involve the creation of a stoichiometric quantity of reactive furan species *via* formation of carbon-metal bonds. However, the direct functionalisation of *C-H* bonds (*C-H* activation) under stoichiometric *and* catalytic conditions have also been developed in recent decades.[51] Relatively recently, this methodology has been employed to functionalise furan moieties, such as that demonstrated by Pittard *et al.* when alkylation of furan was succesfully achieved.[52]

The authors recorded that reaction of Ru(II) catalyst **87** with furan (**1**) in a pressure vessel resulted in formation of complex **88** with concomitant loss of methane (*Scheme 35*). Evidence for formation of **88** was gathered by various spectroscopic techniques which suggested the regioselective formation of it in a near quantitative yield. The generated active complex was then exposed to an atmosphere of ethylene

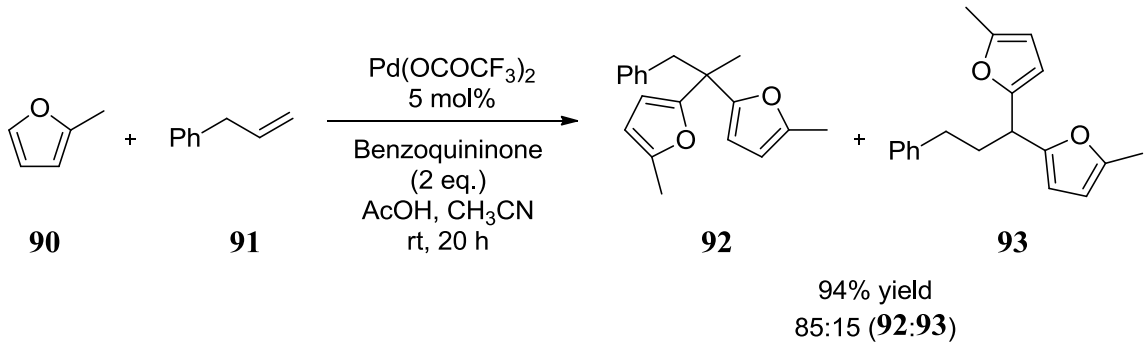
gas in the presence of more furan to afford 2-ethylfuran (**89** - *Scheme 35*). The products were determined by gas chromatography and it was established that higher pressures of ethylene resulted in greater turnover rates, with a pressure of 40 psi displaying 17 turnovers.



Scheme 35: CH activation of furan via reaction with **87** *to ultimately afford 2-ethylfuran* (**89**) *after exposure of active complex* **88** *to ethylene.*

Product quantities were determined *via* gas chromatography analysis using integrated areas of 2-ethylfuran versus an internal standard (decane), although no products were actually isolated. Despite this, the transformation demonstrates the feasibility of Ru(II)-mediated olefin hydroarylation using furan in *C-H* activation methodology.

Another example of *C-H* activation on furans was demonstrated by Le Bras and co-workers in 2008.[53] The striking feature of this work was that the unanticipated bis-addition of 2-methylfuran (**90**) to an assortment of allyl arenes and styrenes was achieved, as highlighted in *Scheme 36* (*vide infra*) with allyl benzene (**91**).

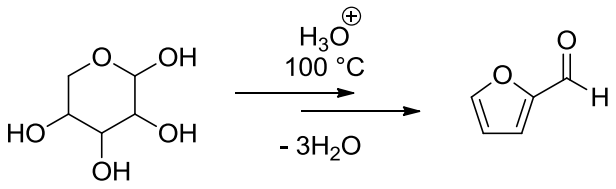


Scheme 36: C-H activation of **90** *by Pd(OCOCF$_3$), ultimately affording* **92** *and* **93**.

Of note in this particular reaction is that the presence of acetonitrile as a co-solvent was a necessity for the bis-additions to occur - a requirement the authors identified upon trying to establish optimum reaction conditions for mono-addition, which is not observed when acetonitrile is present. Benzoquinone was used to prevent undesired isomerisation of the allyl arenes to the corresponding methyl styrenes. Finally, the choice of catalyst not only affected the yield of the reactions, but also the product ratios. $Pd(OCOCF_3)_2$ was found to afford higher yields in comparison to $Pd(OAc)_2$ and also favoured the most substituted product (**92**, in the above example as opposed to **93**). As with the previously discussed *C-H* activation methodology, only the 2-position of furan was activated.

1.3 FURAN SYNTHESES

As is evident from its vast array of reactions, syntheses and sources of furan itself are highly important. Furfural (**16**) is an agricultural by-product manufactured from xylose (**94** - obtained from pentosans; polysaccharides extracted from many plants such as corn cobs) and, as such, is readily available (*Scheme 37*).[54] Acid catalysis promotes a multi-step process which involves the loss of three mole equivalents of water from xylose to afford **16** in excellent yield.



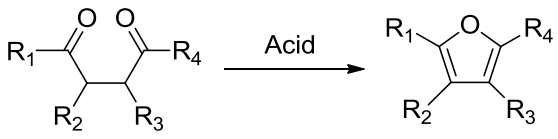
94 **16**

Scheme 37: The production of furfural (**16**) *from xylose* (**94**) *via acid-catalyzed dehydration.*

Furan can, in turn, be produced from **16** *via* vapour-phase decarbonylation and can be oxidised, reduced or further substituted to afford several other simple furans.[2]

1.3.1 PAAL-KNORR SYNTHESIS

The cyclisation of 1,4-dicarbonyl compounds is both a classical and the most widely employed approach to furans, first described independently in 1884 by Paal and Knorr.[55,56] This reaction involves the (protic or Lewis) acid-catalyzed cyclisation of the 1,4-dicarbonyl compound **95** to afford the furan **96** as visualised in *Scheme 38* (*vide infra*). Catalysts such as sulfuric acid, phosphorus(V) oxide, zinc chloride and Amberlyst® have all been employed successfully.



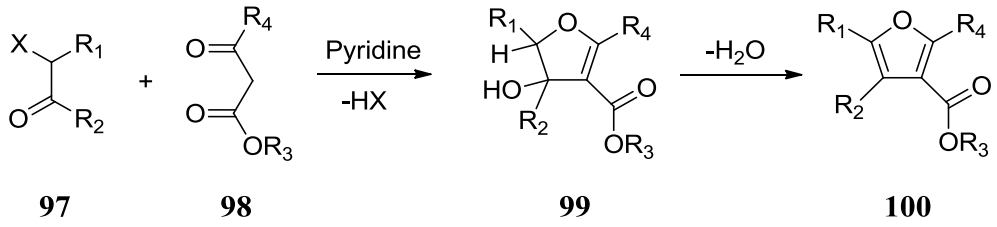
95 **96**

Scheme 38: General scheme for the Paal-Knorr furan synthesis involving acid-catalyzed cyclisation of a 1,4-dicarbonyl compound.

Due to the increase in methods of 1,4-dione syntheses over recent years,[57] the synthetic utility of the Paal-Knorr reaction has further expanded.

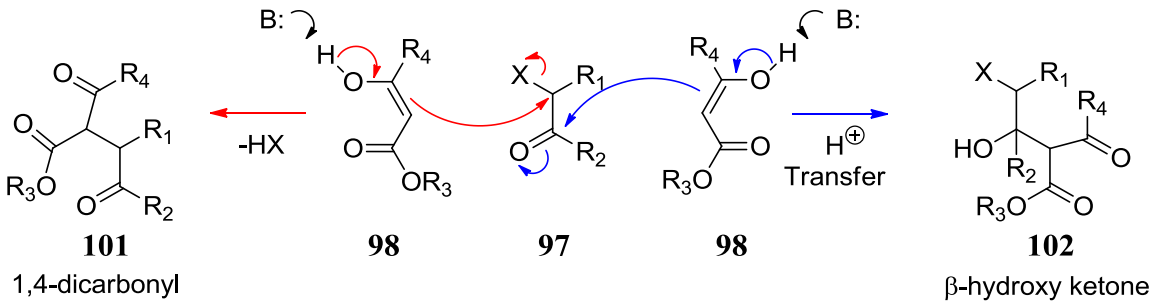
1.3.2 FEIST-BENARY SYNTHESIS

Also a classical synthesis of furans, the Feist-Benary reaction involves an initial aldol condensation at the carbonyl carbon of an α-haloketone (**97**), followed by intramolecular displacement of the halide by an enolate oxygen.[58,59] Elimination of water from intermediate **99** then affords the furan product (**100** - *Scheme 39*). Classically, pyridine is the amine used to catalyze the process.



Scheme 39: The Feist-Benary furan synthesis.

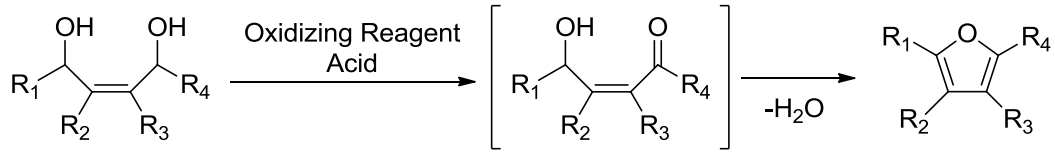
An important note for the Feist-Benary reaction is the distinction between an initial aldol condensation on the α-haloketone to give **102**, as opposed to an initial alkylation *via* displacement of the α-halide to give **101** (*Scheme 40*). This would result firstly in the formation of a 1,4-dicarbonyl species of structure **101** (and not the β-hydroxy ketone of structure **102**), which can then be subjected to ring closure conditions as in the Paal-Knorr synthesis to afford a furan product. Thus, greater reactivity of the carbonyl group in **97** is required to ensure that the reaction proceeds through the Feist-Benary sequence.



*Scheme 40: Different reactive pathways for enol **98** and haloketone **97**. The blue arrows indicate the initial mechanistic pathway required for the Feist-Benary sequence.*

1.3.3 DIOL OXIDATION-CYCLISATION

Another effective route to furans involves the oxidation of appropriate diol-containing alkenes (**103**) with subsequent ring closure. An oxidising agent results in the formation of a 4-hydroxy-enal/-enone of structure **104** which then undergoes cyclisation with the elimination of water to afford the furan product (**105** - *Scheme 41*).

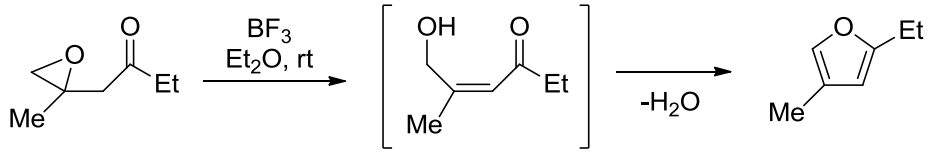


103 **104** **105**

Scheme 41: Furan formation via oxidation-cyclisation of the corresponding diol.

Examination of the furan precursor above reveals four carbons with two degrees of unsaturation. An oxygen is also present at a terminus of a 5-atom sequence including the carbon atoms. These are features that are common to a range of furan syntheses of which this is the simplest example.

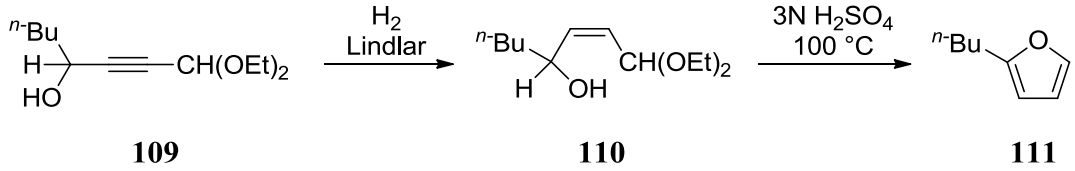
A slightly more elaborate reaction involves ring opening of an epoxide moiety (compound **106**) with concomitant alkene formation to afford precursor **107**, which then undergoes ring closure to afford the product **108** due to it meeting the 4-hydroxy-enone criteria mentioned above (*Scheme 42*).[60,61]



106 **107** **108**

Scheme 42: Furan formation from initial epoxide via treatment with BF_3.

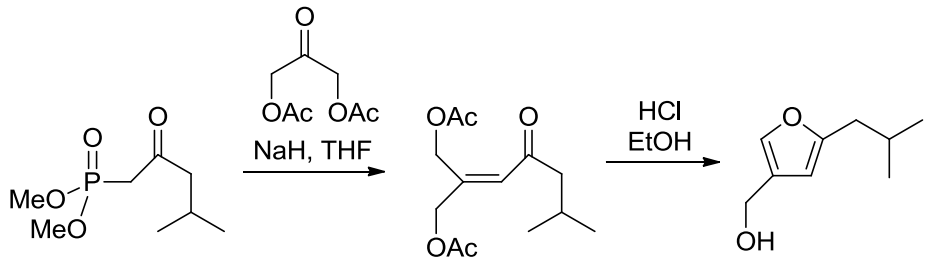
Another suitable furan precursor can be generated by reduction of alkynyl acetal **109**, which is then cyclised in acidic conditions.[62] Reduction of the alkyne moiety under Lindlar conditions afforded requisite alkene **110**, acid treatment of which then exposed the aldehyde. This, in turn, underwent intramolecular cyclisation with the alcohol functionality to afford desired furan **111** (*Scheme 43*).



109 **110** **111**

Scheme 43: Partial reduction of an alkyne, followed by acid treatment to allow cyclisation to the furan product.

The Horner-Wadsworth-Emmons reaction has also been used to afford a precursor to an intermediate suitable for cyclisation.[63] Treatment of diacetate product **113** (derived from **112**) with acid resulted in exposing the alcohol functionalities and thus cyclisation could occur to afford the furfuryl alcohol product (**114** - *Scheme 44*).

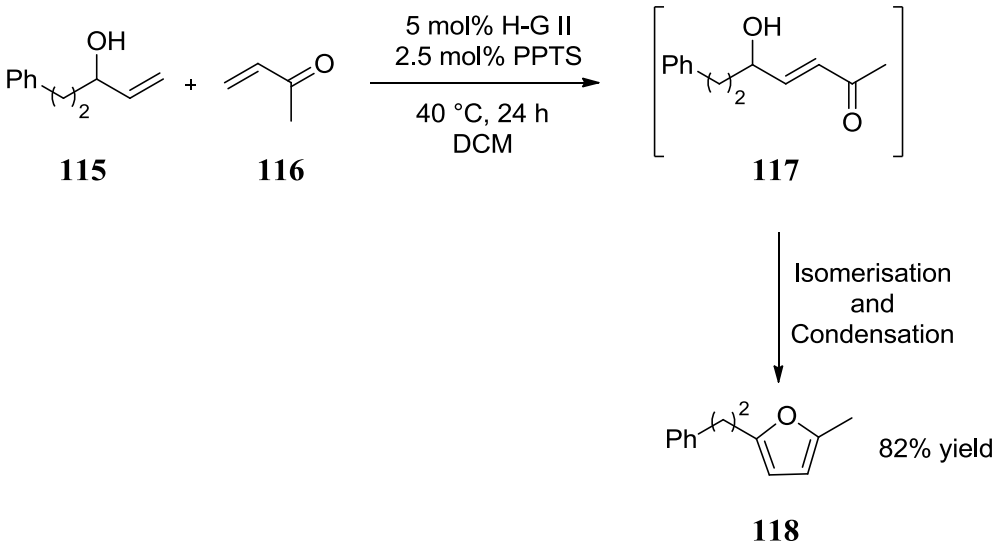


112 **113** **114**

Scheme 44: HWE methodology to afford a diacetate intermediate which when treated with acid affords the furan product.

A recent and rather elegant example of furan synthesis involves the use of olefin cross-metathesis to generate suitable furan precursors.[64] For example, alcohol **115** was reacted with **116** in the presence of H-G II and PPTS to afford cross-metathesis product

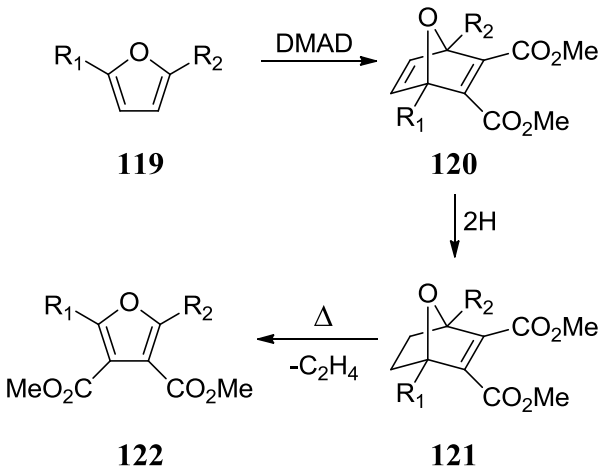
117 (*Scheme 45*). Subsequent isomerisation and ring-closure of intermediate **117** then afforded furan **118** in impressive yield.



Scheme 45: Furan formation from a precursor synthesised via cross-metathesis.

1.3.4 FROM DIELS-ALDER REACTIONS

Exploitation of the Diels-Alder reaction of furan (see later) and DMAD affords another method of furan preparation.[65] An initial Diels-Alder reaction between a furan species (**119**) and DMAD afforded a 7-oxanorbornadiene intermediate (**120**) which was then hydrogenated across the more easily reduced alkene moiety (disubstituted rather than tetrasubstituted). Thermally induced retro cycloaddition of the hydrogenated adduct (**121**) resulted in the extrusion of ethylene to afford a 3,4-diester furan product (**122**), which still held the same 2,5-substitution pattern as the initial furan (*Scheme 46*).



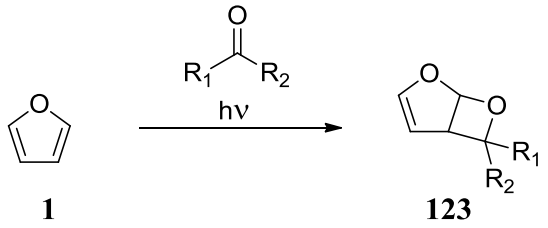
Scheme 46: Forward and retro Diels-Alder processes leading to furan 3,4-dicarboxylates (**122**).

1.4 FURAN IN DIELS-ALDER REACTIONS

Furan can participate in several different cycloaddition processes, the most important of which is the Diels-Alder reaction (as seen above in both the forward and retro reactions). Furan is well known for acting as the 4π component (diene) in this reaction and has been extensively studied for decades - it was even included in the initial studies by Diels and Alder over 80 years ago.[66] As a note, furan is more reactive in such processes than the other 5-membered, aromatic heterocycles due to being the least aromatic of the three.

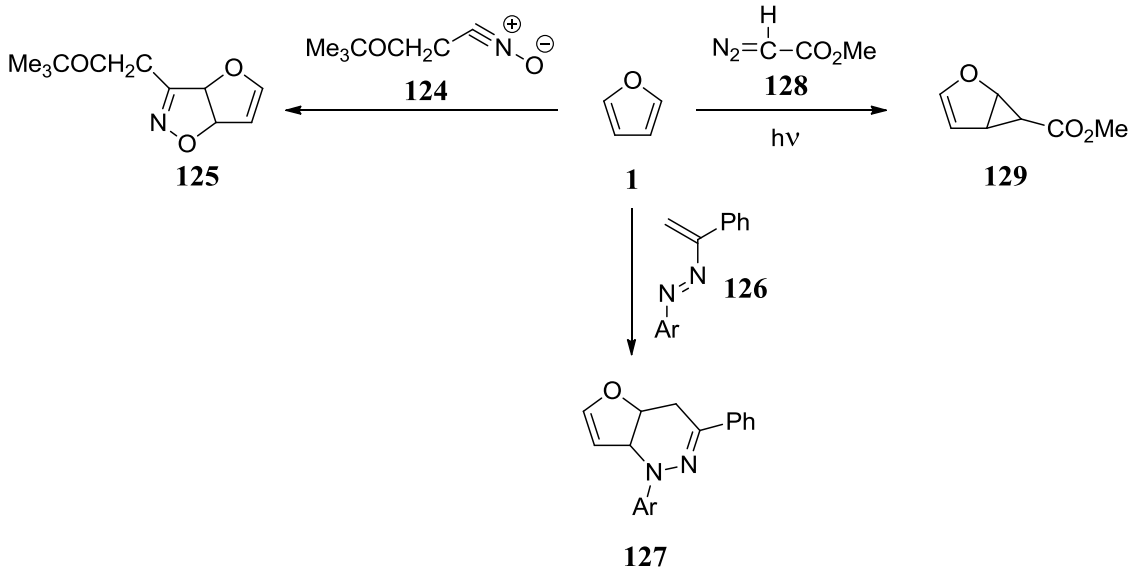
1.4.1 AS A DIENOPHILE AND IN DIPOLAR ADDITIONS

As well as the Diels-Alder reaction, there are examples of furan participating in other cycloaddition reactions, including those where furan is not acting as a diene. An example of such behaviour can be seen in photochemical [2π + 2π] cycloaddition reactions, such as the remarkably regioselective Paterno-Buchi reaction between furan (**1**) and ketones or aldehydes to form adducts of structure **123** (*Scheme 47*).[67]



Scheme 47: Photochemical [2π+2π] cycloaddition to afford oxetano-dihydrofurans (**123**).

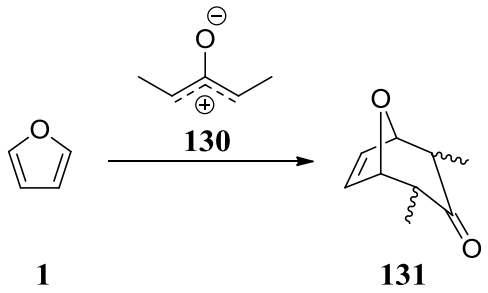
Various other examples where furan (**1**) behaves as a 2π component in cycloaddition reactions have also been observed (*Scheme 48*). For example, reactions with 1,3-dipoles, such as nitrile oxide **124**, afford fused dihydroisoxazoles akin to **125**[68] and addition to azo olefins, such as **126**, afford fused pyridazine derivatives (**127**).[69] Additionally, cyclopropane derivatives such as **129** can also be obtained *via* addition to carbenes obtained from the corresponding di-azo compounds like **128**.[70]



Scheme 48: Furan as a 2π component in cycloadditions.

Another example of cycloaddition reactivity is that of dipolar [4π + 3π] additions with oxyallyl cations.[71] These reactive cations (**130**), generated from α,α'-dibromoketones

(*via* treatment with NaI/Cu in this example), react with furan (**1**) to afford the corresponding bicyclic adducts (**131** - *Scheme 49*).



Scheme 49: Cycloaddition of furan (**1**) *to an oxallyl cation* (**130**).

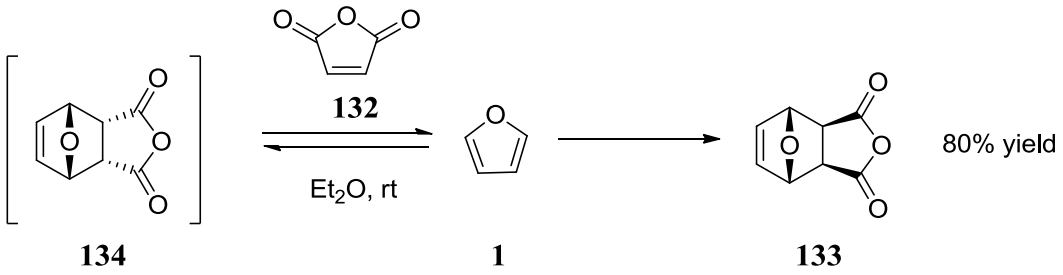
1.4.2 IN [4π+2π] CYCLOADDITIONS

As indicated earlier, however, the most important role for furan in cycloadditions is acting as the diene component in the Diels-Alder reaction. As such, a multitude of synthetic applications have been developed over the decades for said chemistry.[72,73] In general, furans participate in concerted, pericyclic [4π + 2π] cycloadditions with a variety of activated dienophiles such as alkenes, alkynes, allenes and benzynes. Typically, the HOMO of furan reacts with the LUMO of the dienophile (although not always). The proclivity of furans to participate in these reactions is a feature they hold despite their aromaticity and thus lower expected reactivity towards the Diels-Alder reaction in comparison to non-aromatic dienes.

Although furans are capable of reacting with simple dienophiles, they typically display enhanced reactivity towards dienes containing EWG's.[72,73] Lewis acids such as $AlCl_3$ have also been demonstrated to facilitate the reaction by lowering the energy of the dienophile LUMO.[74] The main drawback to the Diels-Alder process with furans is the reversible nature of the reaction. However, as seen previously in reactions with DMAD, this reversibility can sometimes be exploited in the synthetic chemists favour. There are two main categories for furan Diels-Alder chemistry: *inter*molecular and *intra*molecular processes.

1.4.2.1 Intermolecular Processes

The classic example with regards to the intermolecular Diels-Alder reaction of furan is the reaction with maleic anhydride (**132** - *Scheme 50*), which occurs readily at room temperature (or even below).[66]



Scheme 50: Reaction between furan and maleic anhydride, initially forming the endo-adduct but ultimately affording the exo- adduct.

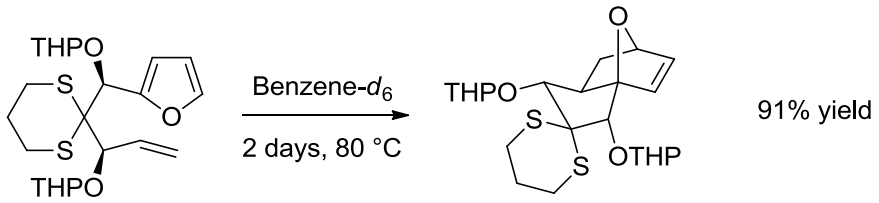
The *exo*-adduct **133** is the recovered product of this reaction which seems contrary to the *endo* rule. However, NMR studies have verified that the *endo*-adduct **134** does indeed initially form but this then converts to its *exo* isomer, *via* retroaddition followed by readdition in the alternative orientation.[75] The implication of this is that **133** is thermodynamically more stable, i.e. the thermodynamic product, whereas **134**, being more rapidly formed, is the kinetic product.

1.4.2.2 Intramolecular Processes

By having a reactive enough dienophile on a tether of appropriate length, furans can easily participate in IMDA reactions to afford even more complex polycyclic compounds. Analogously to intermolecular Diels-Alder reaction involving furan, the IMDA reactions also have a broad scope with respect to both the furan and dienophile, but additionally the nature of the tether has a profound effect on reactivity.

An example of IMDA chemistry in action has been demonstrated by Sternbach and co-workers.[76] Heating of THP protected diol **135** for 2 days resulted in the exclusive production (determined *via* NMR) of adduct **136** (*Scheme 51*). This outcome was identified to be dominated by the THPO group at C8 (initially the THPO moiety closest to the alkene in **135**) having a strong preference for adopting a pseudo-equatorial

position. Another noteworthy point for this reaction is the excellent yield obtained, particularly given that the terminal alkene dienophile is unactivated.

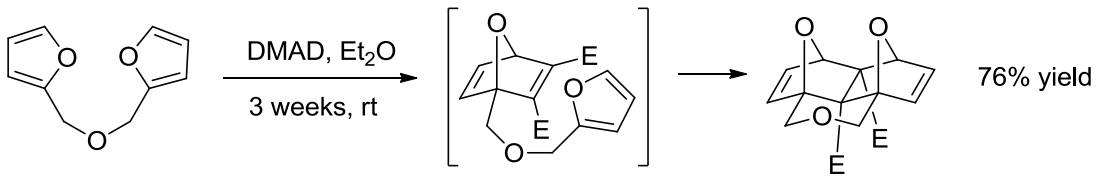


135 **136**

Scheme 51: Exclusive formation of **136** *upon heating substrate* **135**.

A rather exciting example which combines both intermolecular and intramolecular DA reactions has been elegantly demonstrated by Lautens and Fillions.[77] The authors prepared a series of complex adducts *via* tandem 'pincer' DA reactions involving DMAD and a bis-diene substrate - a furan which is linked *via* the 2 position to another furan by a 3 atom tether (also to its 2-position). An example of this is displayed in *Scheme 52* (*vide infra*).

The initial reaction was an intermolecular one between a furan of **137** and DMAD to afford intermediate **138** (not isolated), this was then succeeded by an IMDA reaction between the newly formed adduct and the remaining furan functionality to afford **139** exclusively. Visualisation of the reaction process demonstrates why the term 'pincer' has been adopted to describe this methodology. Overall, this approach is both a regio- and stereo- controlled method towards polyheterocyclic ring systems.

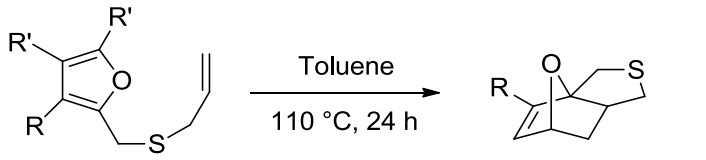


137 **138** **139**

Scheme 52: Tandem 'pincer' [4π + 2π] cycloaddition reactions between **137** *and DMAD, via* **138** *to produce adduct* **139**.

1.4.2.3 Substituent Effects on IMDAF Reactions

As with intermolecular processes, substituents on the furan can also influence IMDA reactions. In addition to classical rate-changing substituents such as EDGs on the furan moiety and EWGs on the dienophile which alter the energies of the FMOs of each, more subtle substituent effects have been demonstrated for IMDA reactions involving furan. For example, it has been established that increased substitution of the furan results in enhanced reactivity and, in particular, substitution at the C3 position (of a C2 tether substituted furan) has the greatest effect.[78] Klein demonstrated that the yield was improved when the 3-substituent of **140** was changed from hydrogen to a methyl group (*Scheme 53*). The rationale offered for this observation is the relief in steric strain between the tether and the bulkier 3-substituent upon formation of the corresponding adduct **141**, where this eclipsing interaction becomes slightly skewed.



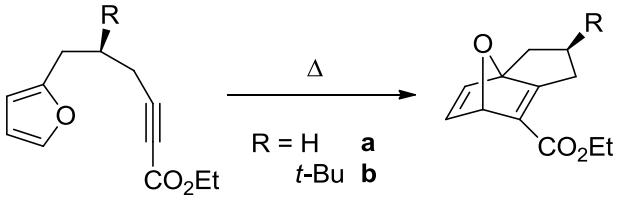
140a	R = H, R' = H	**141a**	23% yield
140b	R = Me, R' = H	**141b**	77% yield
140c	R = Br, R' = H	**141c**	83% yield
140d	R = Me, R' = Me	**141d**	92% yield

Scheme 53: IMDA reaction yields influenced by the size of the 3-substituent.

Klein also demonstrated that when bromine is present as the 3-substituent a yield of 83% is recorded, despite the fact that one might predict a more sluggish reaction in comparison to the methyl analogue on electronic grounds. This is important as it proves that any electronic contribution from the substituent is not significant in these cases. In support of steric relief driving the reaction forward, Klein also noted that substrate **141d** (which is tri-substituted with methyl groups in addition to the C2 tether) produced the highest yield. Obviously, in this case, eclipsing interactions are being relieved on both sides of the furan moiety.

Interestingly, in addition to substituents on the furan ring and dienophile contributing towards IMDA processes, substituents on the tether itself can also have a

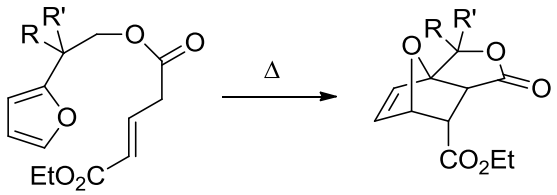
profound effect on the reaction. One of these rate-accelerating effects is known as the '*t*-butyl effect', which is demonstrated below (*Scheme 54*).[79] The presence of *t*-butyl as the R group on **142** instead of hydrogen resulted in a 60-fold increase in reactivity in the production of the corresponding adduct **143**. Indeed, this increase in reactivity was found to be proportional to the steric bulk of R.



142a-b **143a-b**

Scheme 54: The 't-butyl effect', where the formation of **143b** *was 60 times faster than that of* **143a** *due to the presence of t-Bu as the R group.*

Phenomena related to the above effect are known as the '*gem*-dialkyl' and '*gem*-dialkoxy' effects. These both refer to rate acceleration effects observed in substrates that have a *gem*-disubstitution on the tether. Jung and Gervay have demonstrated and studied the *gem*-dialkyl effect on systems of type **144** for the production of **145** (*Scheme 55*).[80] A selection of alkyl substituents of varying bulk were installed for the R and R' groups including methyl, ethyl, vinyl and allyl groups and each demonstrated enhanced rates in comparison to the unsubstituted system.



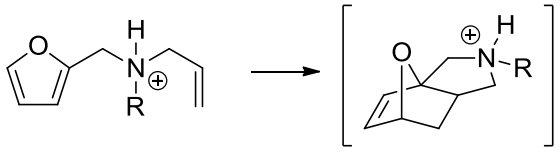
144 **145**

Scheme 55: Transformations of substrates of type **144** *into adducts* **145**, *analyzing the gem-dialkyl effect.*

The reason for such effects is the subject of much debate, with various explanations being put forward to rationalise the observations. Classically, the *gem*-dialkyl and *gem*-dialkoxy effects have been attributed to the Thorpe-Ingold effect,[81] which postulates that upon increasing substituent bulk, the angle between the diene and dienophile is compressed, thus accelerating the reaction as the reactants are in closer proximity.

In evidence against this, in the report produced by Jung and Gervay above, the authors calculated that enthalpic contributions and *not* entropic contributions were lowering the free energy of the reaction, thus eliminating this angle compression as the major source of rate enhancement. Rather, they postulated that the more substituted systems result in enriched populations of reactive rotamers in the ground state, facilitating the IMDA reaction. However, evidence has also been produced that argues against the findings of Jung and Gervay, where theoretical chemistry suggests an overall lowering of the free energy of reaction as opposed to the 'reactive rotamer' theory.[82]

Other more subtle tether substitution effects also have also been observed in IMDA chemistry, for example the transformation of **146** into intermediate adduct **147** was found only to be possible when the tether nitrogen was protonated (*Scheme 56*).[83] This was presumably due to conformational changes of the tether upon nitrogen protonation.



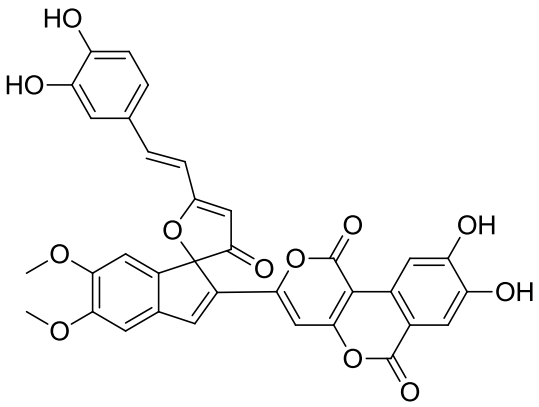
146 **147**

Scheme 56: IMDA only made possible via protonation of the tether nitrogen atom.

1.4.3 IN TARGET SYNTHESIS

Given the structural diversity that the Diels-Alder reaction can provide in one step, it is not surprising that it has been widely used in target synthesis. Phelligridin G (**148** - *Fig. 10*) is a fungal extract from the *Phellinus igniarius* species that exhibits moderately selective cytotoxicity against colon and ovarian cancer lines.[84] As such, phelligridin G and its derivatives are synthetically attractive targets due to their potential for use in

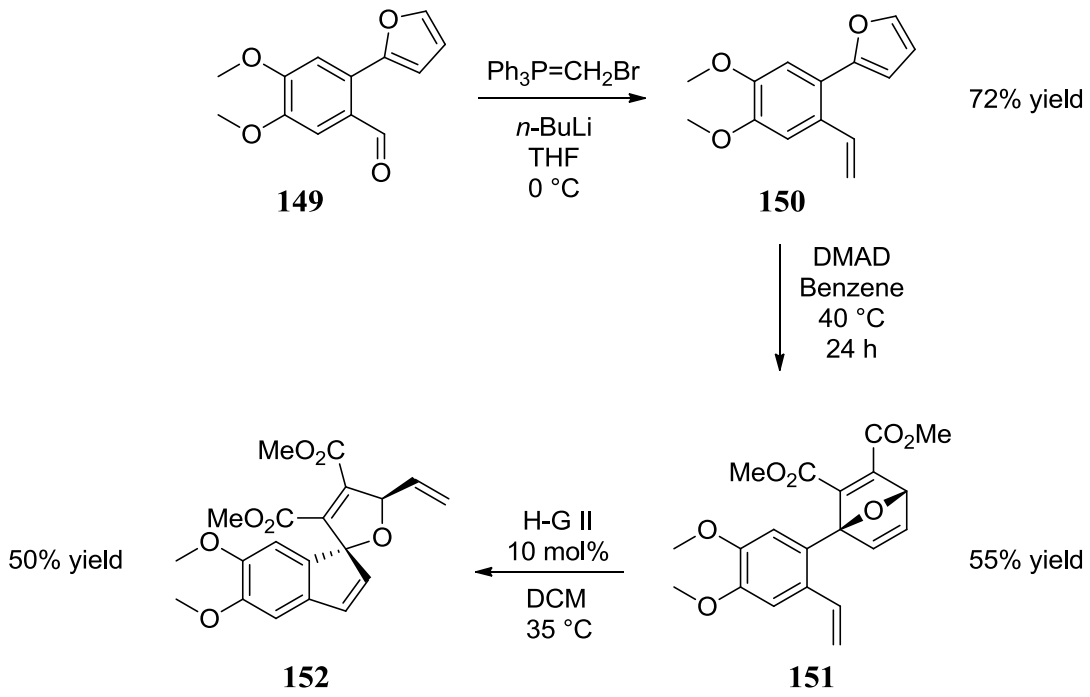
anti-cancer treatments. Furthermore, it possesses a spirofused-furanone core which presents a synthetic challenge.



148

Fig. 10: Phelligridin G, containing a spirofused-furanone core.

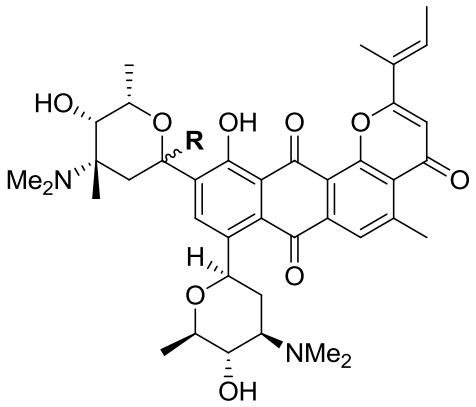
The challenge to assemble a suitable core for an approach to phelligridin G and its derivatives was undertaken by Cooper and Wright, who developed a simple intermolecular Diels-Alder strategy followed by metathesis based reorganisation to achieve this goal.[85] The authors conducted a Wittig reaction on compound **149** (synthesised *via* coupling of the furan boronic acid with the corresponding aryl bromide) to afford the Diels-Alder substrate **150** (*Scheme 57*). The adduct **151** was then synthesised *via* reaction of **150** with DMAD, which was subsequently exposed to ROM/RCM conditions under H-G II catalysis to yield **152**.



Scheme 57: Synthesis of potential phelligridin G precursor **152***, harnessing an intermolecular Diels-Alder process as one of the key synthetic steps.*

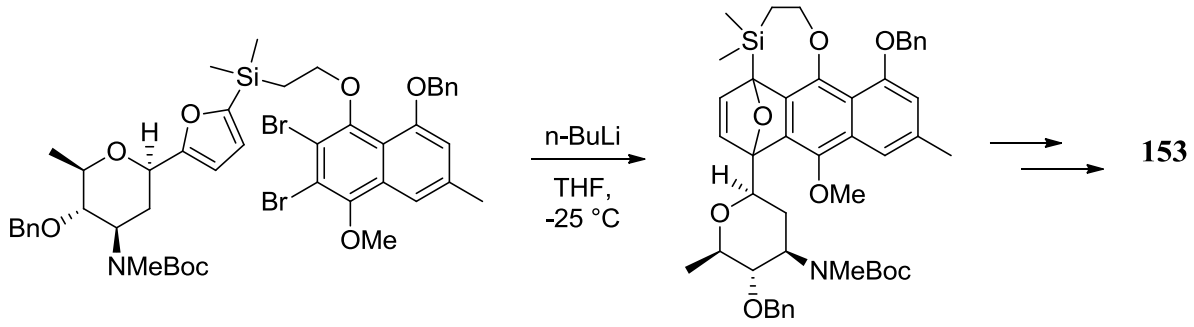
Something of particular note, with reference to the conversion of **150** into the adduct **151**, is that aryl substituted furans are often reluctant to participate in Diels-Alder processes due to the intrinsic loss of extended π-conjugation. For the same reason, any adduct that does form often has the propensity to easily undergo retroaddition to the starting materials.[86] This is the reason proposed by the authors for the modest yield of cycloadduct **151** obtained. Nevertheless, the complex precursor **152** was still obtained *via* this challenging Diels-Alder process followed by insightful 'domino' metathesis. Efforts towards the total synthesis of phelligridin G and its derivatives are currently ongoing based on this strategy.

Isokidamycin (**153**) is a *C*-arylglycoside antibiotic which is an isomer of kidamycin (**154**), another *C*-arylglycoside antibiotic and natural product obtained from *Streptomyces phae-overticillatus* (*Fig. 11*). Recently, Martin *et al.* have developed a synthetic strategy towards **153**, of which the key step involves an IMDA reaction of intermediate **155** between the furan moiety and the *in situ* generated naphthyne (*Scheme 58*).[87] This process proved to be highly efficient and was achieved in excellent yield.



Isokidamycin (**153**) **R** = ◄H
Kidamycin (**154**) **R** = ····H

Fig. 11: The structures of isokidamycin **153** *and kidamycin* **154**.



155 **156**

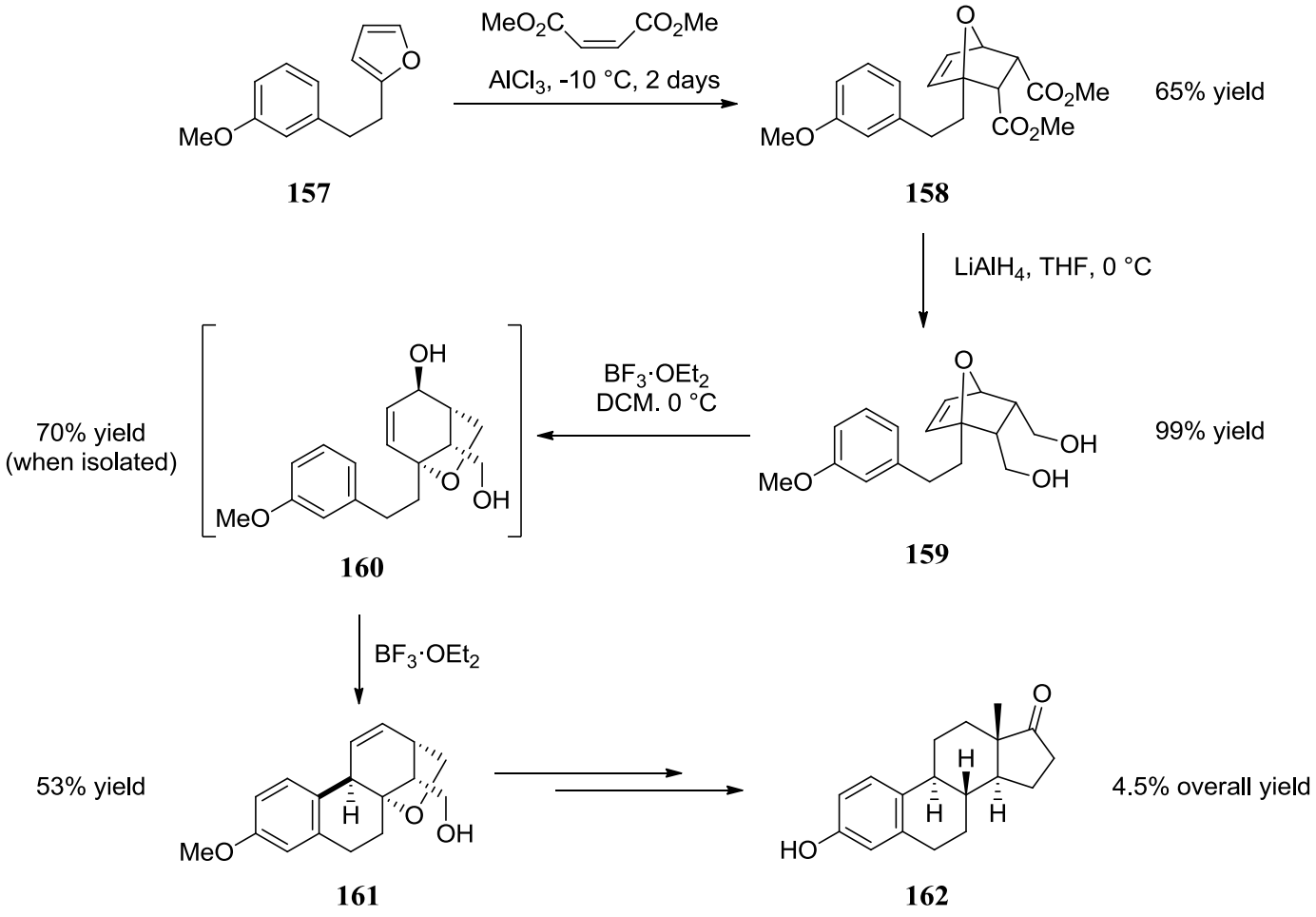
92% yield

Scheme 58: The key synthetic step involving an IMDA between the furan moiety and an in situ generated naphthyne functionality.

The IMDA substrate **155** itself was prepared in a multitude of steps involving the coupling of a naphthol unit with a protected amino glycosyl furan (both of which also requiring their own synthesis) *via* Mitsunobu etherification. The IMDA adduct and key intermediate **156** was subsequently taken on in several more steps, one of which involved an *O*→*C*-glycoside rearrangement, to eventually afford isokidamycin (**153**). This is the first total synthesis of this antibiotic. Incidentally, the same group employed similar Diels-Alder chemistry to produce other major *C*-aryl glycoside antibiotics several years earlier.[88]

1.4.4 UNDER CATALYTIC CONDITIONS

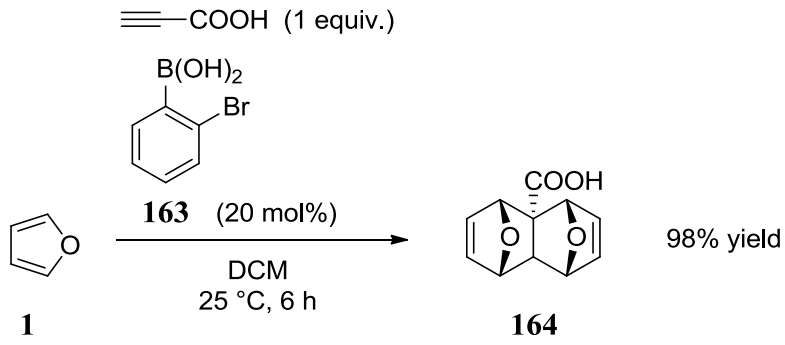
Some examples of furan Diels-Alder reactivity under catalytic conditions have been employed in target synthesis. An example of such chemistry is demonstrated in the reaction between furan **157** and dimethyl maleate to afford **158**, a process which was catalyzed by $AlCl_3$ under solvent-free conditions (*Scheme 59*).[89] Although the *exo*-adduct was also produced in, it was the minor product (17% yield) and was easily separable from the desired *endo*-adduct **158**. This step was key in the synthesis of (±)-estrone (**162**), a prominent female sex hormone.



Scheme 59: $AlCl_3$ catalyzed Diels-Alder reaction to product key intermediate **158**, *which was ultimately converted to (±)-estrone* (**162**).

The crucial steps immediately following formation of **158** are also included above to clarify the fate of the oxa-norbornene ring in this synthetic route, as well as highlighting how both cyclohexane rings were incorporated into the structure. Reduction of **158** afforded diol **159**, the oxa-bridge of which was opened by a cyclisation process aided by the presence of the Lewis acid $BF_3 \cdot OEt_2$ to afford intermediate **160**. The same Lewis acid then facilitated the carbocyclisation of **160** to afford **161**, which was then transformed *via* several additional steps into **162**.

Zheng and Hall have demonstrated furan participating in Diels-Alder reactions under more elaborate catalytic conditions.[90] In this case, a boronic acid (**163** - *Scheme 60*) was used to catalyse Diels-Alder reactions between various diene substrates and propiolic acid. When furan (**1**) was employed as the diene, the authors noted that the product was polyheterocycle **164**; the product of the initial adduct reacting with excess furan (*Scheme 58*).



Scheme 60: Formation of Diels-Alder adduct upon reacting furan (**1**) *with propiolic acid under the catalysis of* **163**.

Remarkably, the authors reported the exclusive formation of the one isomer of **164** in a near-quantitative yield. The authors also demonstrated that in the absence of **163**, evidence for only trace amounts of the adduct were observed which highlights the activation power of the catalyst.

The mode of activation proposed is most likely that of lowering the LUMO energy of the propiolic acid as visualised in *Fig. 12*. The boronic acid couples with propiolic acid with concomitant dehydration, this has a LUMO-lowering effect on the propiolic acid and thus facilitates the Diels-Alder process.

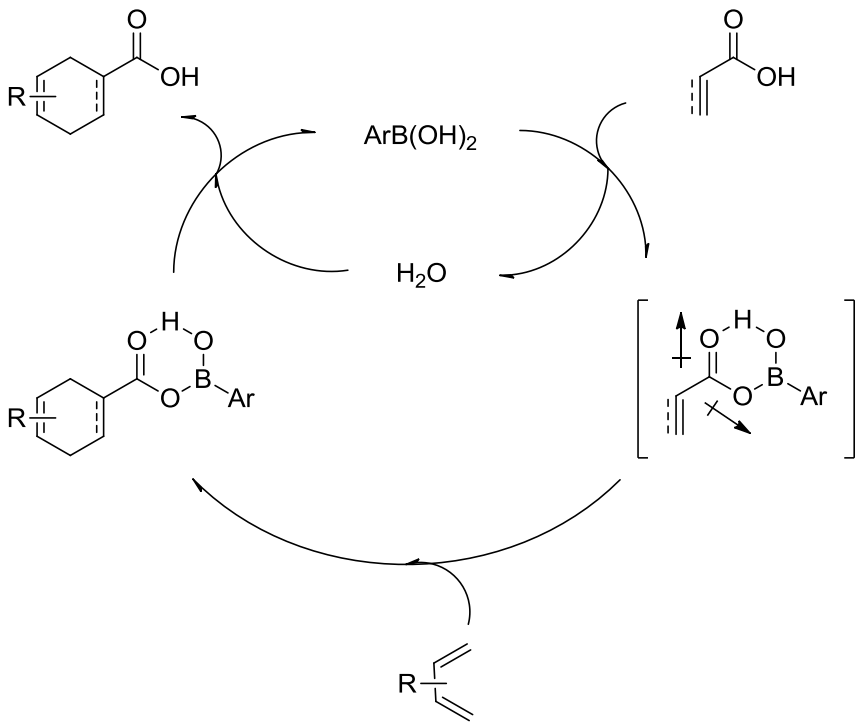


Fig. 12: Proposed general catalytic cycle under boronic acid catalyzed conditions.

With regards to furan, presumably after the initial Diels-Alder reaction has occurred, another cycloaddition immediately follows to afford **164** before the boronic acid/carboxylic acid complex is hydrolysed.

In any event, this catalytic process is impressive and adds to the large body of work that has successfully been conducted on furan moieties, in addition to the other methodologies presented above. Indeed, the synthetic versatility of furan in general is self evident, but of particular interest are the IMDA reactions of furan due to the high degree of structural complexity they can achieve in one step. If one could develop general catalytic means of facilitating the IMDA reaction of furan, it is not hard to imagine the synthetic power that such a methodology could potentially offer synthetic chemists.

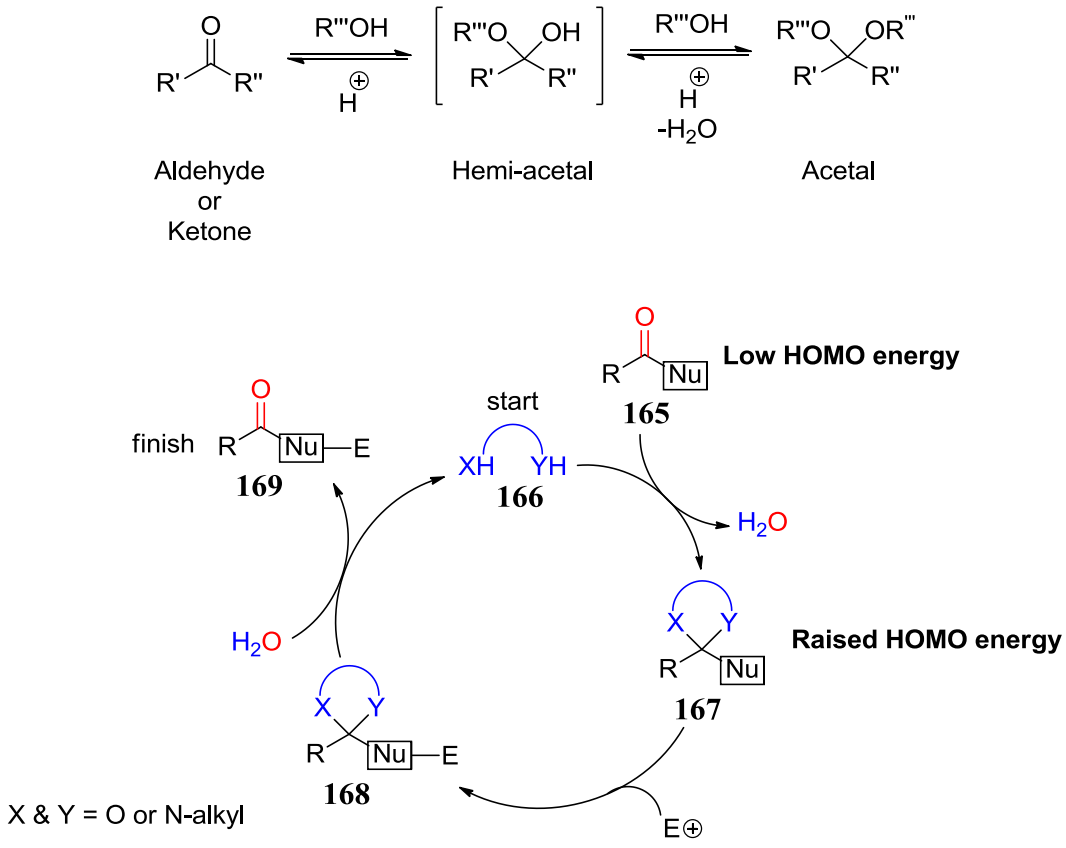
2. ACETALISATION-ASSISTED ORGANOCATALYSIS

2. ACETALISATION ASSISTED ORGANOCATALYSIS

2.1 INTRODUCTION

Our first attempt to catalytically facilitate the IMDA reaction of furans was envisaged to be *via* a novel mode of activation; acetalisation-assisted organocatalysis (AAO).

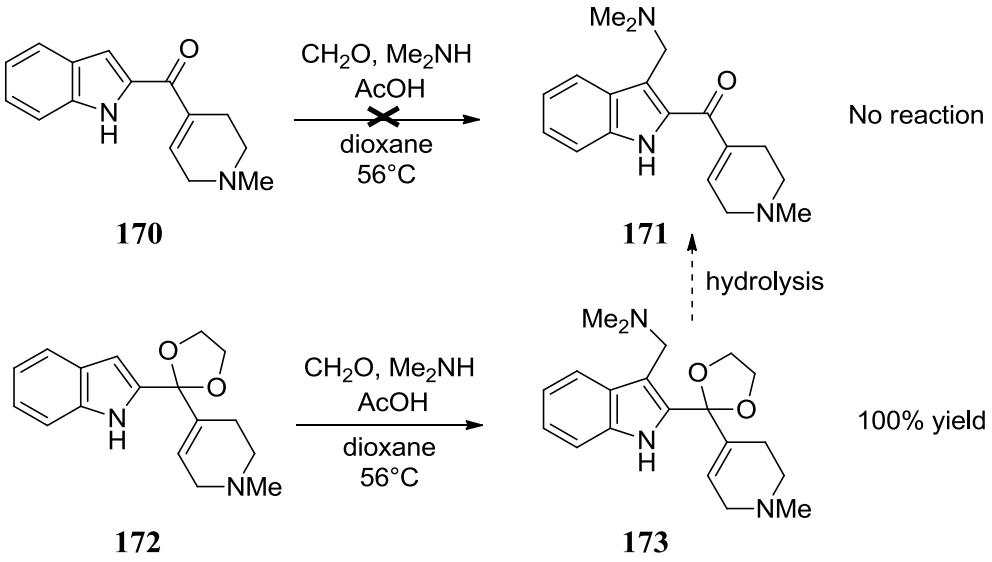
A requirement of an organocatalytic process is that the catalyst can reversibly bind with the substrate in order to turn over the catalytic cycle. As such, it was hypothesised that the reversible formation of acetals, aminals or *N,O*-acetals could be exploited to develop this new mode of organocatalysis. The formation of acetals classically involves the initial transformation of an aldehyde or ketone into a hemi-acetal intermediate *via* reaction with an alcohol under acidic conditions. Elimination of water followed by further attack of the alcohol present then affords the acetal product (*Scheme 61*). Both the formation of the hemi-acetal and acetal are reversible. The synthesis of aminals or *N,O*-acetals occurs in an analogous fashion with amines or amino alcohols respectively.



Scheme 61: Reversible formation of acetals via an hemi-acetal intermediate, as well as the generalised catalytic cycle for AAO.

The theory behind AAO is relatively simple; the postulate being that acetals, aminals or *N,O*-acetals will have raised HOMO energies in comparison to the corresponding carbonyl substrate from which they are derived. As a result of this alteration to the HOMO energy, a nominally deactivated pro-nucleophilic substrate will now be activated towards reaction with an electrophilic partner. In a generalised catalytic cycle (*Scheme 61*), an acylated pro-nucleophile **165** will react with organocatalyst **166** to afford the activated intermediate **167** (an acetal, aminal, or *N,O*-acetals depending on **166**). This activated species will then be able to undergo reaction with an electrophilic partner to produce **168**, which when hydrolysed will afford the product **169** while simultaneously regenerating the catalyst **166**.

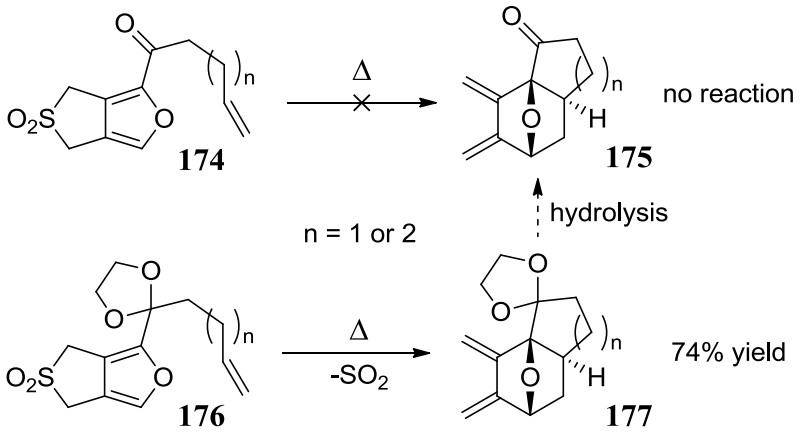
Evidence for this mode of activation is already present in the literature. In 1979, Martinez and Joule identified that conjugated acylindole **170** was unreactive towards the Mannich reaction required to give dimethylamine **171**.[91] However, the corresponding ketal **172** reacted quantitatively under the same conditions to produce the Mannich product **173**, which was then hydrolysed to obtain **171** (*Scheme 62*).



Scheme 62: Evidence for activation by acetalisation discovered by Martinez and Joule.

Further evidence for this mode of activation has been identified through the work of Takayama *et al.*, who demonstrated that in order for the intramolecular Diels-Alder

reaction of furan **174** (*Scheme 63*) to proceed and produce **175**, the ketone functionality must be acetalised.[92] Heating of **176**, the corresponding ketal of **174**, resulted in the formation of tricyclic ether **177**, hydrolysis of which afforded **175**.



Scheme 63: Further evidence for activation by acetalisation demonstrated by Takayama et al.

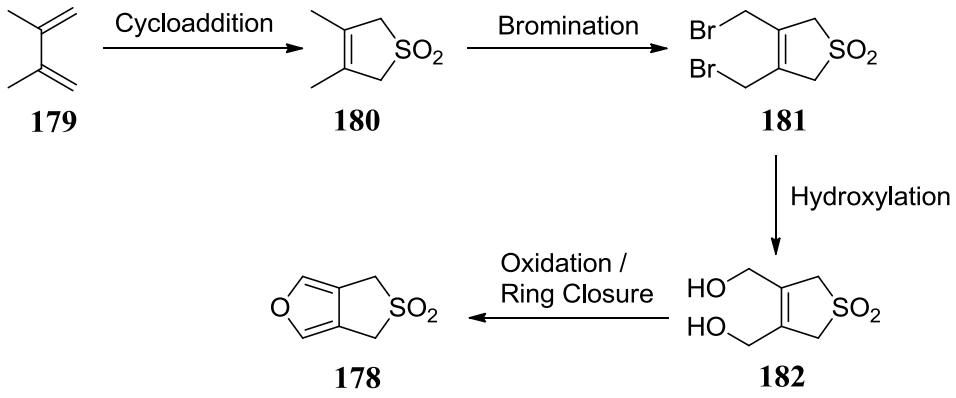
Given the success demonstrated by Joule and Takayama, our initial efforts were concentrated on proving the concept that acetalisation facilitates the reactivity of the substrates. Thus, given the importance of the Diels-Alder reaction to organic chemists, the preparation of Takayama type compounds (**174**) was prioritised at the beginning of our studies. We envisaged that once compounds of this nature were obtained, IMDA reactions would be attempted on both the acetal-protected and deprotected compounds to ascertain the effect of raising the HOMO energy.

If successful, more advanced catalytic studies would be conducted to establish the principle of AAO. Furthermore, research into the development of chiral catalysts that could be used for asymmetric induction could be undertaken.

2.2 RESULTS AND DISCUSSION

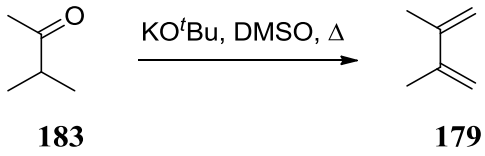
Our initial efforts were directed at the synthesis of furan **178**, a key building block for production of the Takayama compounds detailed above. Shown below is the approach taken by Takayama *et al*. for the synthesis of **178** (*Scheme 64*). We decided to follow

this apparently straightforward route to **178** in order to study its use as a synthon for IMDA substrates.[93]



Scheme 64: Outlining the envisaged synthetic route to afford key furan **126**.

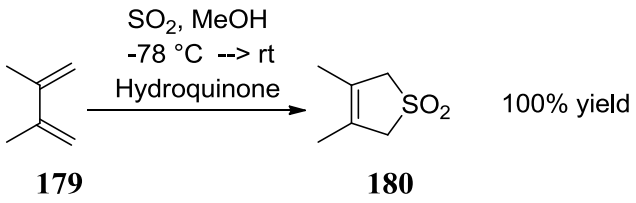
Although commercially available, it was deemed to be cost-effective if diene **179** could be readily synthesised from inexpensive ketone **183**. The procedure consisted of reacting **183** with DMSO in the presence of KO^{t}Bu at 130-140 °C to afford **179** (*Scheme 65*).[94] The product would then be isolated by distillation.



Scheme 65: Attempted synthesis of **179** *from* **183**.

Although analysis of the crude product mixture *via* ^{1}H NMR confirmed the presence of **179**, its isolation *via* distillation proved to be arduous due to the boiling point of the product being similar to both that of the starting material and of ^{t}BuOH (a by-product of the reaction resulting from deprotonation of DMSO). Due to this difficulty, it was decided to abandon the reaction in favour of purchasing commercial **179**.

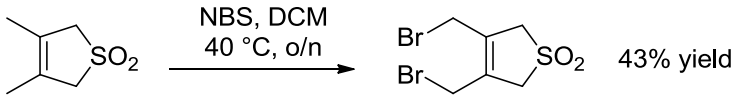
The diene **179** was thus converted into sulfone **180** in quantitative yield *via* cheletropic cycloaddition with SO_2 following the same procedure used by Takayama and co-workers (*Scheme 66*).[93]



179 **180**

Scheme 66: Synthesis of **180** *from* **179** *involving a cheletropic cycloaddition.*

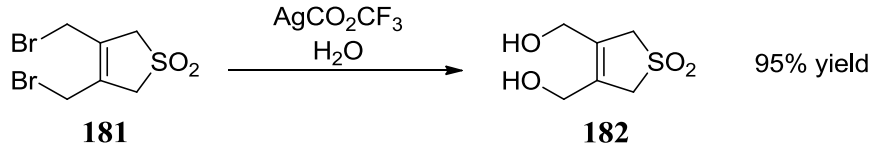
Free radical chemistry provided the means to afford dibromide **181**, using NBS as the source of bromine radicals.[93] Refluxing a mixture of **180** and NBS in DCM at reflux afforded the crude product mixture, from which **181** was isolated *via* recrystallisation from DCM and light petroleum (*Scheme 67*).



180 **181**

Scheme 67: Generation of dibromide **181** *from* **180** *via treatment with NBS.*

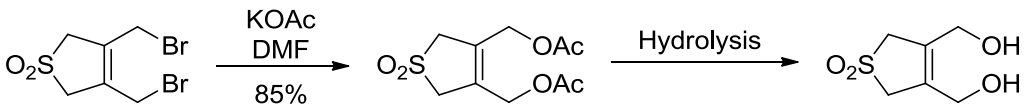
On attempting to synthesise diol **182**, Takayama *et al.* utilised silver trifluoroacetate ($AgCO_2CF_3$). The corresponding bis-trifluoroacetate formed *via* reaction of $AgCO_2CF_3$ with **181** was easily hydrolysed to afford the product - a procedure that we too ultimately adopted (*Scheme 68*).



181 **182**

Scheme 68: Synthesis of diol **182** *from* **181** *via reaction with $AgCO_2CF_3$ and subsequent hydrolysis.*

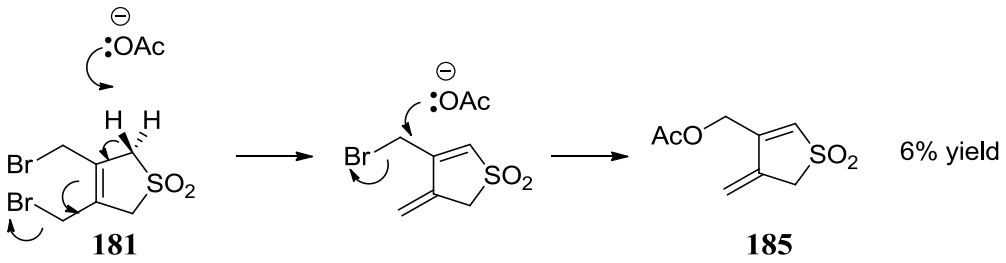
Preceding this eventual synthesis, however, we had explored numerous other ways of synthesising **182** in the interest of cost-effectiveness. We initially envisaged that hydrolysis of diacetate **184** (formed from **181**) could afford the desired diol **182** without recourse to the relatively expensive $AgCO_2CF_3$ (*Scheme 69*).



181 **184** **182**

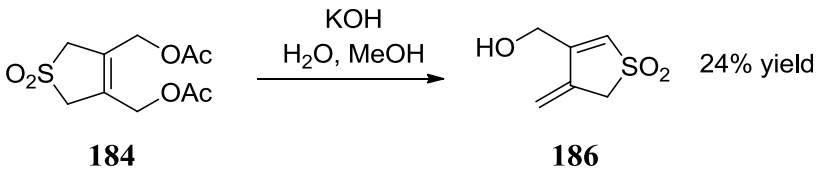
Scheme 69: Envisaged route towards diol **182** *from diacetate intermediate* **184**.

Diacetate **184** was obtained from **181** using a literature procedure involving *in-situ* generation of KOAc.[95] However, **184** was not the exclusive product of this reaction. Analysis of the ^{1}H NMR spectrum led us to believe that the elimination product **185** had also formed, which we imagined was the result of deprotonation of the acidic protons α to the sulfur atom (*Scheme 70*). However, this by-product was separable from **184** *via* flash chromatography and a maximum isolated yield of 85% of **184** was recorded on one occasion. It was also observed that a bizarre polymerisation process occurred at larger reaction scales (generating a substance either rubber or cellophane-like in appearance depending on how it aggregated), making it an unviable process for mass-production.



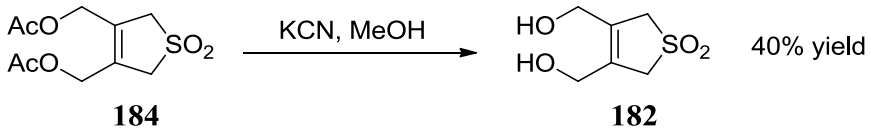
Scheme 70: Mechanism showing the postulated alternative reaction pathway responsible for generating elimination by-product **185**.

The acidity of the α-protons mentioned above also seemed to impair the production of the desired diol **182** from the diacetate **184** under several conditions. Reaction of **184** under standard basic ester hydrolysis conditions with KOH exclusively afforded the elimination product **186** (*Scheme 71*), which we believe is formed in an analogous matter to **185**, save that hydroxide is now the base/nucleophile and the diacetate now the initial substrate.



Scheme 71: Elimination product from several deacylation methodologies attempted on **184**.

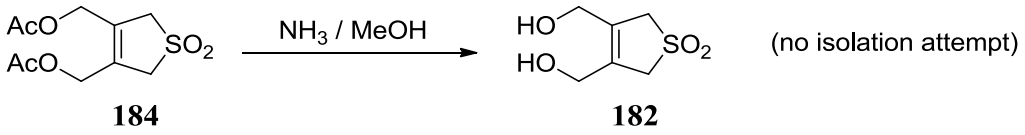
In order to remove (or at least reduce) the potential for undesired eliminations of this nature, we experimented with other conditions that involved different nucleophiles which were less basic than hydroxide. An effort involving the employment of catalytic KCN in methanol was trialled, but despite formation of some diol, the elimination product was still present, thus reducing yields (*Scheme 72*).[96]



184 **182**

Scheme 72: Catalytic KCN mediated hydrolysis of **132**.

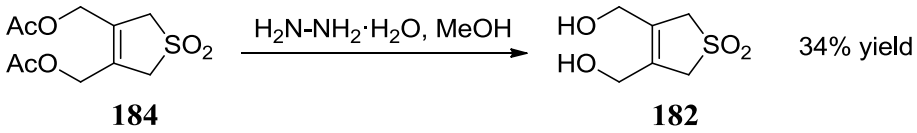
Additionally, methanolic ammonia was employed in order to try and mildly cleave the acetate functionalities (*Scheme 73*).[97] However, this too resulted in the elimination by-product despite forming some diol **182** (which was not isolated as a result), highlighting the particular acidity of the aforementioned α-protons in that even ammonia can facilitate the elimination mechanism.



184 **182**

Scheme 73: Deacylation attempt utilising methanolic ammonia.

Hydrazine provided a promising alternative not only to the conventional basic hydrolysis, but also to both alternative methods described above.[98] To our satisfaction, addition of hydrazine to a solution of **184** in methanol at room temperature afforded **182** with no sign of competing elimination (*Scheme 74*).



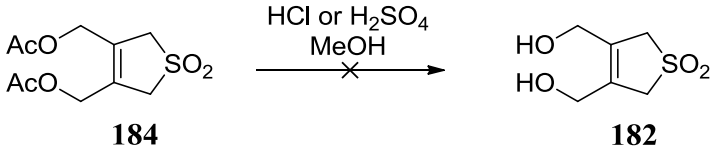
184 **182**

Scheme 74: Deacylation attempt employing hydrazine.

However, the hydrazone by-product formed unfortunately co-eluted with the product as was discovered on attempted various purifications *via* flash chromatography. Recrystallisation also proved unsuccessful, perhaps in part due to the fact that the

hydrazone impurity was produced twice in number to that of **182**. Purification *via* precipitation of **182** from DCM eventually allowed us to isolate some product, however, a poor yield was recorded.

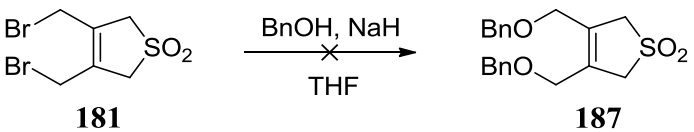
Due to the difficulties being encountered with the use of even mildly basic reagents, our attentions turned to acid-mediated hydrolysis in the hope that it might provide a viable pathway to **182**. The initial attempt was conducted utilising hydrochloric acid (HCl) in MeOH (*Scheme 75*), but instead of the desired diol, an unidentified by-product was formed where the symmetry of the compound had been destroyed according to ^{1}H NMR. Surmising that the mildly nucleophilic nature of the chloride anion present might have a role to play in the construction of this by-product, a re-attempt was made employing sulfuric acid (H_2SO_4 – *Scheme 75*) but to our surprise the same unidentified product was indicated again by ^{1}H NMR. As a result, this approach was discontinued in favour of searching for other methods.



184 **182**

Scheme 75: Attempt at acid mediated hydrolysis of **184** *to afford* **182**.

Hypothetically, **182** could also be afforded by catalytic hydrogenolysis of the corresponding dibenzyl compound **187**. Due to the double bond present being fully substituted, it was postulated that mild catalytic conditions would not saturate the compound. To test this postulate, the attempted synthesis of **187** was conducted on **181** utilising Williamson's etherification methodology (*Scheme 76*).[99]

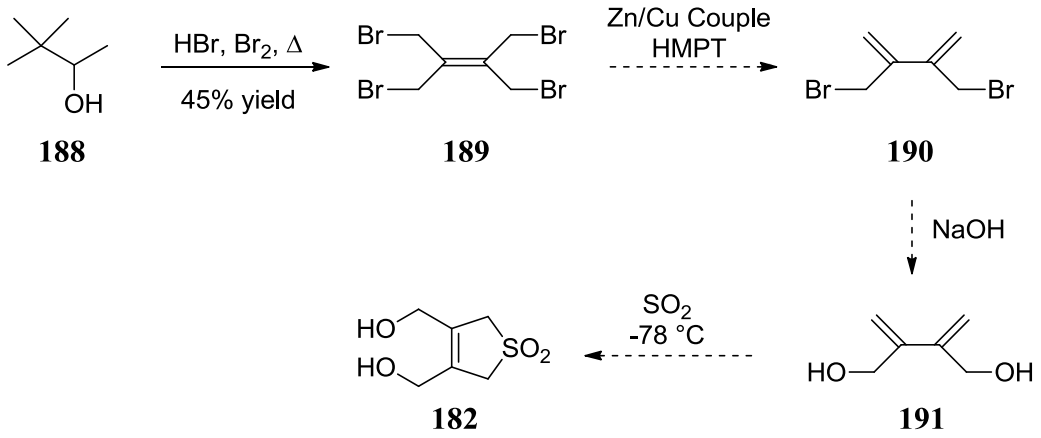


181 **187**

Scheme 76: Failed attempt to generate dibenzyloxy species **187**.

Despite the greatest care to add solvated **181** in a dropwise manner to the reaction mixture, so as to avoid undesirable side-reactions, the elimination process described previously appeared to be largely occuring *via* analysis of the crude ^{1}H NMR data and thus this route was also abandoned.

Due to the troublesome nature of generating diol **182** *via* the Takayam route, an alternative strategy was also conducted involving a different approach (*Scheme 77*). It involved installing the diol functionality prior to performing the cycloaddition which affords the desired dihydrothiophene moiety, which would afford compound **191**. We postulated that this would circumvent any issues we were having with unwanted eliminations and other side reactions relating to the hydrolysis attempts on diacetate **184**.



188 **189** **190** **191** **182**

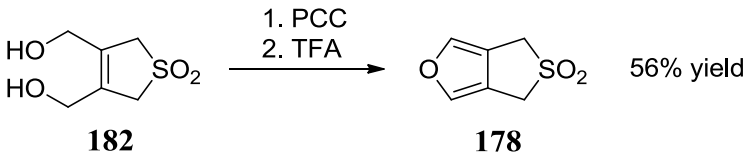
Scheme 77: Alternative route towards diol **182**.

Thus, treatment of pinacolyl alcohol (**188**) with HBr and Br_2 at 50°C resulted in bromination and afforded tetrakis(bromomethyl)ethylene (**189**) in modest yield.[100] The next step involved elimination of bromine utilising HMPT and Zn/Cu couple,[101] with the metal couple being synthesised prior to the reaction.[102] However, difficulties encountered upon purifying **190** led to abandonment of this route in favour of the existing methodologies although they were less less than ideal.

Due to the combined failures and limited successes displayed above, it was decided to purchase the AgO_2CCF_3 salt mentioned previously. Thus, direct conversion

of **181** to **182** was achieved under the same conditions as described by Takayama and co-workers (*Scheme 68* - p. 59), although not in the quantitative yield the authors report.

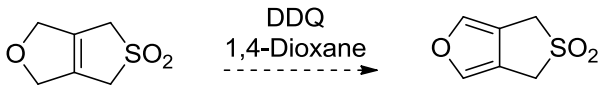
After obtaining sufficient quantities of **182** (a culmination of the various methods above), conversion to the furan **178** was achieved by employing PCC in the presence of TFA (*Scheme 78*).[93] The acid was added a short time after the PCC so as to enter the reaction mixture when only one of the alcohol groups present on **182** had been oxidised to the aldehyde. This resulted in acid-mediated ring closure of the intermediate and afforded **178** in modest yield.



182 **178**

Scheme 78: *Oxidative ring closure of* **182** *to afford key furan* **178**.

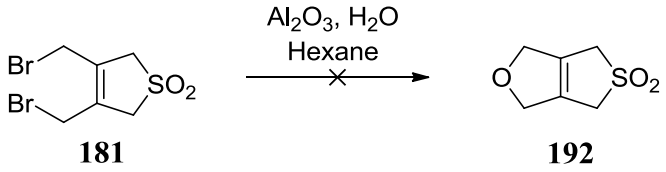
In an attempt to improve on this yield, an alternative strategy was devised to afford **178**. We surmised that oxidation of dihydrofuran **192** by employment of DDQ would result in the formation of the desired furan (*Scheme 79*).[103]



192 **178**

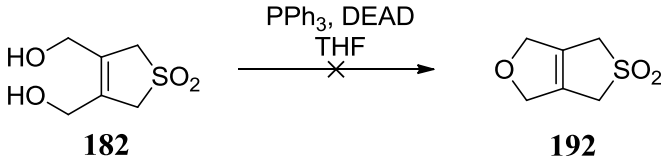
Scheme 79: Envisaged oxidation of **192** *to* **178**.

Two attempts were made to prepare the required starting material **192**. Firstly, reaction of **181** with aluminium oxide (Al_2O_3) and water was attempted (*Scheme 80*).[104] However, no trace of the product could be found upon work up and thus this methodology was abandoned. Additionally, an intramolecular Mitsunobu reaction was conducted on diol **182** to try to afford **192** (*Scheme 81*).[105] Unfortunately, however, unreacted starting material was observed in the crude NMR spectra.



181 **192**

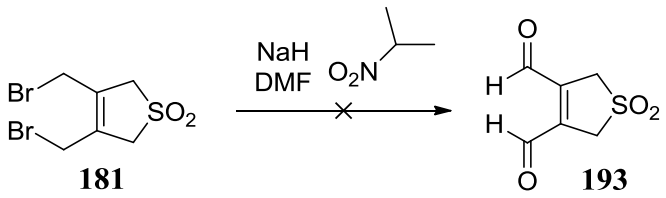
Scheme 80: Failed direct syntheses of **192** *from* **181**.



182 **192**

Scheme 81: Unsuccessful Mitsunobu reaction on **182**.

A final potential route investigated to afford furan **178** was envisaged to proceed *via* the reduction of dialdehyde **193** by one equivalent of a reducing agent, followed by acid-mediated ring closure to afford the desired product. As such, an attempt was made to synthesise **193** by reacting dibromide **181** with 2-nitropropane and sodium hydride in a modified Hass procedure (*Scheme 82*).[106]

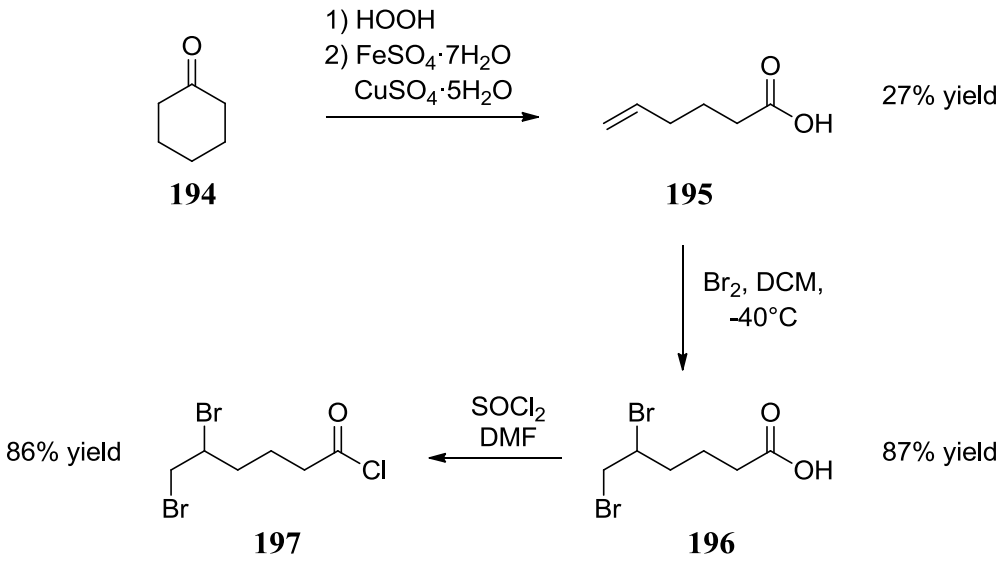


181 **193**

Scheme 82: Unsuccessful modified Hass procedure towards **193**.

To our disappointment, however, no product could be isolated. Thus, further investigations into an alternative route to **178** were dismissed as a whole in favour of the previously established oxidative ring closure. A sufficient quantity of **178** was thus obtained *via* the method depicted in *Scheme 78* (p. 64) from diol **182**.

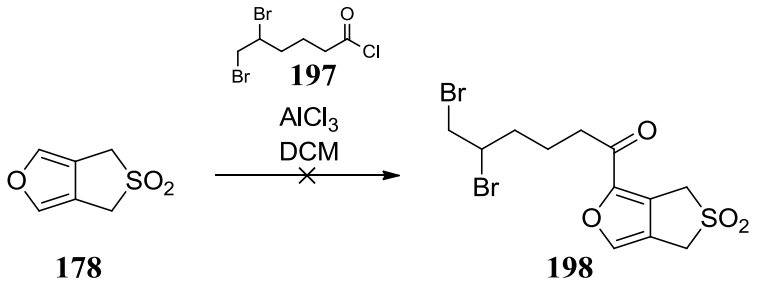
Attaching a suitable tether to afford a Takayama-like substrate was our next priority and thus we embarked on transforming cyclohexanone (**194**) into acyl chloride **197** in three steps (*Scheme 83*).



Scheme 83: Synthesis of desired acyl chloride **197** *from* **194** *in several steps.*

Oxidative ring opening of **194** afforded hex-1-enoic acid (**195**) in modest yield, but large quantities of inexpensive starting materials were employed to counter this shortcoming.[107] Bromination of **195** afforded protected alkene **196** (done so to avoid any potential, unwanted side reactions upon subjection to Friedel-Crafts conditions later),[108] which was subsequently chlorinated under standard conditions to afford the desired acyl chloride **197**.

However, upon attempting to acylate furan **178** with **197** under classic Friedel-Crafts conditions, isolation of the desired IMDA substrate precursor **198** was unattainable despite several attempts (*Scheme 84*). Additionally, the reaction was attempted with the acyl chloride derived from hex-1-enoic acid (**195**), but this also failed to afford the substrate.



Scheme 84: Attempted synthesis of IMDA substrate precursor **198**.

2.3 SUMMARY

Given the lack of success with regard to our intentions of investigating AAO, the decision was made to switch our focus to another mode of substrate activation for the IMDA reactions of furans, where we anticipated that the syntheses of appropriate substrates would be more facile. This method of activation pertains to what we refer to as the 'halogen effect' and will be discussed in more detail in the next chapter.

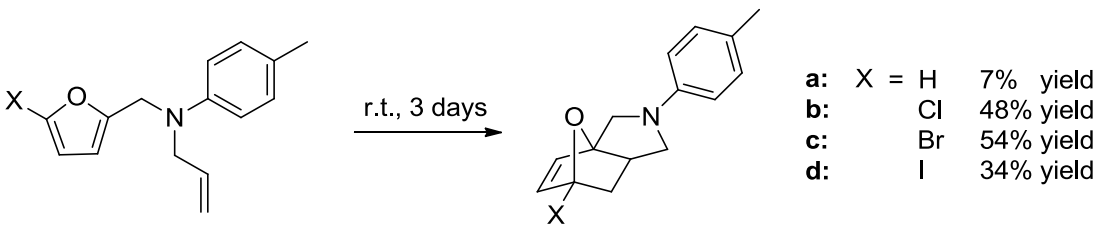
3. THE HALOGEN EFFECT

3. THE HALOGEN EFFECT

3.1. INTRODUCTION

As with the acetalisation effect which was our basis for investigating AAO, there is also precedence in the literature for the facilitation of IMDAF reactions *via* the halogen effect - where the presence of a halogen promotes the reaction when compared to the non-halogenated substrate. Although no longer catalytic in nature, we still found these findings to be intriguing enough to merit further study, given that halogenation of the furan moiety appears to make a previously arduous transformation more facile.

The effect of halogen substitution on IMDAF reactions was first examined in 1987 by Klepo and Jakopcic, where they demonstrated that halogen substitution (among other substituents) facilitated the IMDA reaction of furfuryl allylamines **199** to their corresponding adducts **200** (*Scheme 85*).[109]



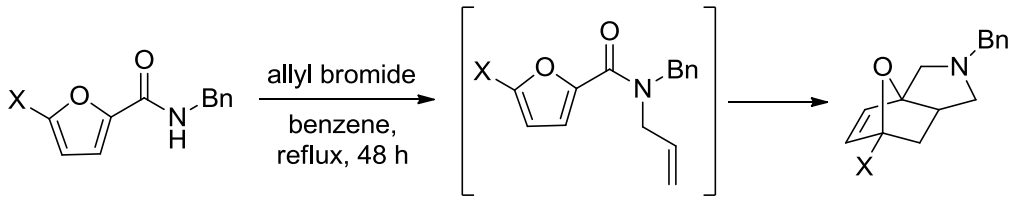
199a-d **200a-d**

Scheme 85: The first evidence for IMDAF.

The authors demonstrated that yields were substantially improved when the 5-substituent (X) was a halogen in comparison to the non-substituted species. Note that the stereochemistry of the adducts are always consistent with the preferred *exo* orientation of the 5-carbon tether in the IMDAF cycloaddition reaction and is analogous to that reported for all related furanyl systems possessing short (3-5 atom) tethers.[110]

However, it was not until both the experimental and theoretical work conducted by Padwa and Houk that the effect of halogen substitution on furan Diels-Alder processes became clearer.[111,112] Padwa and co-workers prepared, from amines **201**, closely related analogues (**202**) of the substrates investigated by Klepo and Jakopcic and

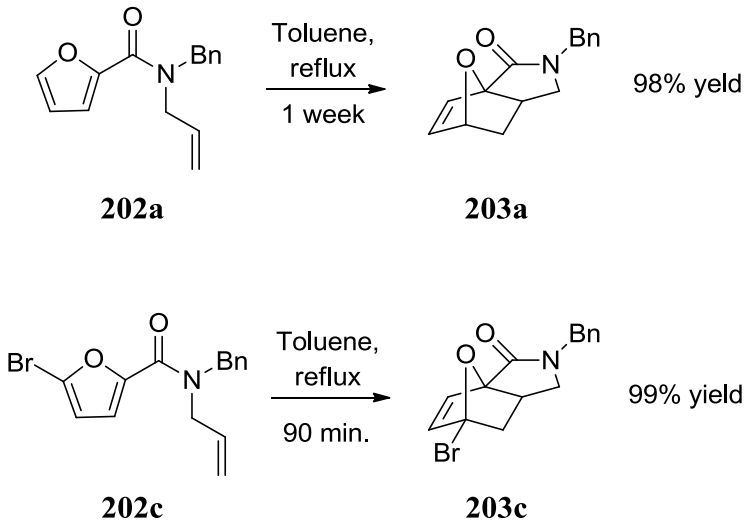
identified a significant rate enhancement of IMDAF reactions when a halogen substituent was present at the 5-position (*Scheme 86*). Although the substrates were taken on to the adducts *in situ* (*Scheme 86*), Padwa and co-workers also heated isolated samples of **202a** and **202c** at reflux and measured the time for reaction completion (*Scheme 87*). They observed that the activation by the bromine substituent was dramatic, in that transformation of substrate **202c** to adduct **203c** was complete in just 90 minutes. This is in stark contrast to the non-substituted analogue, **202a**, which took one week to complete its transformation to adduct **203a**.



201a-d **202a-d** **203a-d**

a: X = H 42% yield
b: Cl 92% yield
c: Br 100% yield
d: I 94% yield

Scheme 86: Yields of adducts **203a-d** *obtained after 48 hours following one-pot N-allylations and intramolecular cycloadditions of secondary amides* **201a-d**.



202a **203a**

202c **203c**

Scheme 87: Demonstration of the halogen effect on IMDAF reactions of isolated substrates being converted to their adducts.

As is evident from these results, halogen substitution appears to have a profound effect on the IMDA reaction of furan systems. However, the reason for these rate and yield enhancements were in need of elucidation, a proposal for which was offered by Houk and Pieniazek.[112] It was calculated, *via* high-accuracy CBS–QB3 methods, that halogenation (F, Cl and Br) of furan at the 2-position increases the exergonicity of the Diels-Alder processes by 4-9 kcal/mol accompanied by a small decrease in activation barriers (2-3 kcal/mol), which intrinsically creates a larger barrier to the retro-Diels-Alder process. These changes are depicted below, where the theoretical intermolecular Diels-Alder reaction involving ethylene and furan is compared with that of ethylene and 2-chlorofuran (*Fig. 13*).

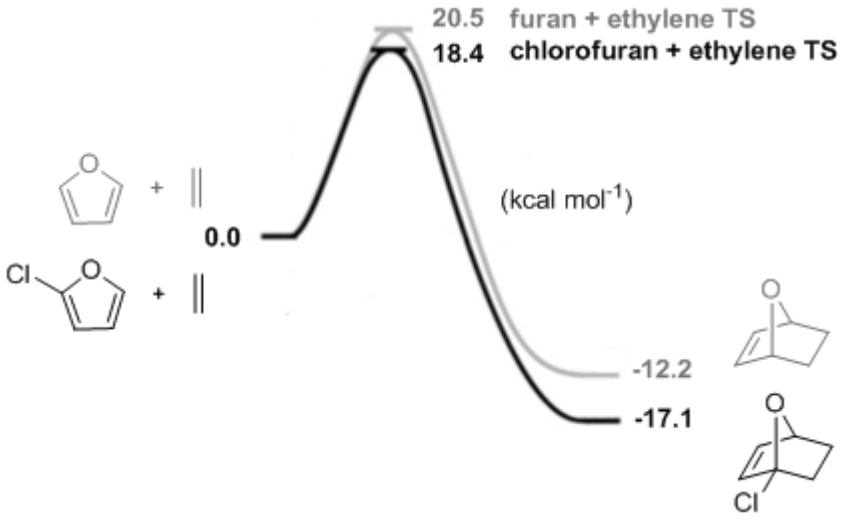
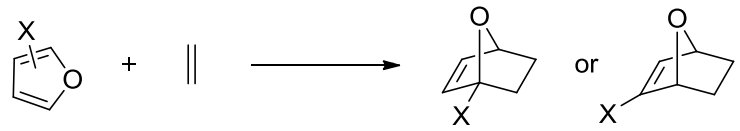


Fig. 13: The calculated halogen effect on the DA reaction of furan and ethylene.

For 2-substitution, this halogen effect was actually calculated to be greatest for fluorine, followed by chlorine and bromine which were both found to be approximately equal in terms of the change in activation energy (*Fig. 14*). Fluorine was calculated to decrease further the activation energy ($\Delta H^{\ddagger}$) by 1.2-1.3 kcal/mol and substantially further increase exergonicity (ΔH_r) by 3.7-3.8 kcal/mol in comparison to bromine and chlorine.

Additionally, halogen substitution at the 3-position was also calculated to facilitate the process almost as much as 2-substitution, albeit in this case fluorine was theoretically a poorer activator than chlorine and bromine which were again calculated to have effects of similar magnitude on $\Delta H^{\ddagger}$ and ΔH_r.



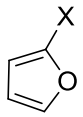
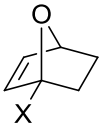
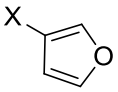
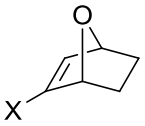
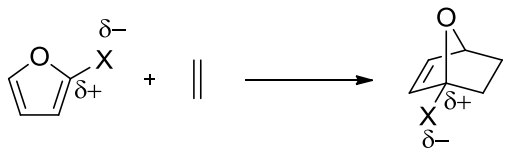
X		$\Delta H^{\ddagger}$ (kcal mol^{-1})		ΔH_r (kcal mol^{-1})
H		20.5		-12.2
Br		18.3		-17.2
Cl		18.4		-17.1
F		17.1		-20.9
H		20.5		-12.2
Br		18.0		-16.0
Cl		18.1		-16.0
F		18.6		-16.2

Fig. 14: CBS–QB3 calculated activation and reaction enthalpies for the reactions of furan along with 2- and 3- halogenated furans with ethene.

The origin of this increased rate of cycloaddition for the halo-substituted furans when compared to non-substituted examples was unclear. Until Houk's work, FMO theory would predict that EDG's on the diene will facilitate a normal-demand Diels-Alder reaction. However, predicting the electronic effect of a halo group is complicated by their concomitant σ-withdrawing and weak π-donating nature.

Houk offers an explanation for the effect of a halogen in the 2-position of furan, where electronic effects were identified to be most profound (*Fig. 14 - vide supra*). The rationale offered is that greater stabilisation of the partial positive charge at the 2-carbon is present in both the transition state and the cycloadduct than in the corresponding starting material due to the change in hybridisation from sp^2 to sp^3 (*Scheme 88*). This allowed for better hyperconjugative stabilisation.

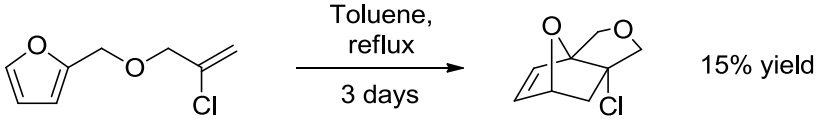


Scheme 88: Charge stabilisation at C-2.

Although this explanation indeed sounds plausible, no such explanation was extended towards 3-halogenation, where the sp^2 hybridisation remains throughout the reaction. However, one could argue that in the case of 3-halogenation, the same hyperconjugative stabilisation of the halogen to the bridgehead carbon could be effected through allylic means.

When it comes to intramolecular Diels-Alder processes of furans with a tether at the 2-position, similar decreases in activation barriers and increases in exothermicities were calculated. Additionally, with respect to 3-halogenation specifically within the amide tether systems that Padwa employed, a conformational destabilisation of the starting material was predicted where repulsion between the amide oxygen and the halogen atom disrupts conjugation. A result of this perturbation is more facile cycloaddition, in addition to the electronic effects exerted by the halogen itself.

In addition to work in the literature detailing halogenation effects on the diene (furan) component of IMDAF reactions, limited work has also been conducted on IMDAF reactions where the dienophile moiety holds a halogen. Karaarslan and Demircan have demonstrated that with both *N*-Boc tether and ethereal tether substrates, adduct formation can be successful with a halogen present on the alkene moiety. [113] As an example of this which is pertinent to discussion later on in this chapter, the authors reported formation of adduct **205** from the corresponding substrate **204** (*Scheme 89*).



204 **205**

Scheme 89: Formation of adduct **205** *from chloro-alkene substrate* **204**.

Unfortunately, however, the authors did not attempt the above conversion (or indeed any conversion involving a halo-alkene substrate) with the non-halogenated analogues and, as such, no conclusions could be drawn about the effect (if any) that halogen substitution of the dienophile has on the Diels-Alder process of reactions involving furan.

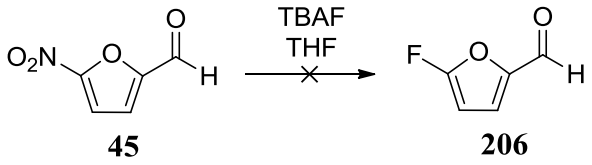
Taking all of the above into consideration, it is clear that there are unresolved issues with respect to the halogen effect on IMDAF reactions (although appreciable progress has already been made in understanding some of these effects). Namely, there is no explanation as to why 4-substitution still facilitates the IMDAF reaction and it is yet to be established what effect (if any) halogenation of the dienophile component has on the reaction.

3.2 RESULTS AND DISCUSSION

Our initial intentions were to synthesise suitable non-halogenated substrates that could undergo an IMDA reaction and thereafter investigate these processes on halo-alkene variants. Another goal was to produce α-fluoro-furans and investigate whether or not there is any agreement between experimental findings and the theoretical predictions made by Houk (as has been observed for the cases of chlorine and bromine). There are no such investigations in the literature.

3.2.1 FLUORINATION ATTEMPTS

Procedures in the literature regarding the α-fluorination of furans tend to lack generality and occur in low yields.[114] As such, we embarked on attempting to fluorinate a range of furan substrates that could potentially be taken on towards an IMDAF substrate *via* attachment of a suitable tether. Our initial efforts towards these compounds were focused on nucleophilic displacement of the nitro group in 5-nitro-2-furaldehyde (**45**) with TBAF as the source of F^- (*Scheme 90*).[115] However, this reaction failed to produce any product (**206** - which conceivably has several possibilities for the attachment of a tether at the aldehyde functionality), under both conventional and microwave conditions.

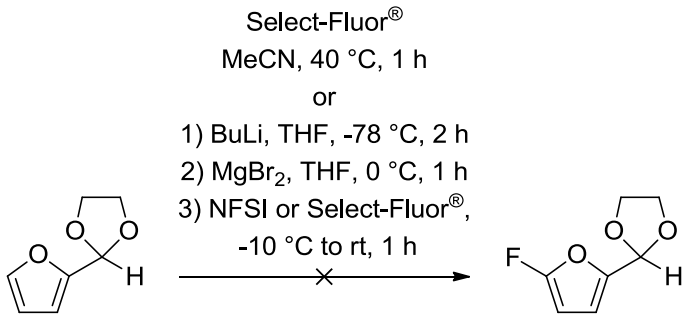


45 **206**

Scheme 90: Attempt to fluorinate **45** *via employment of TBAF.*

Efforts were then concentrated on fluorinating **207**, the acetal of furfural derived from reaction with ethylene glycol (*Scheme 91*). Initially, several reactions were carried out on the diethyl acetal analogue of **207**, but it was discovered that the acetal functionality in the diethyl compound was unstable. The cyclic acetal **207** offers improved stability.

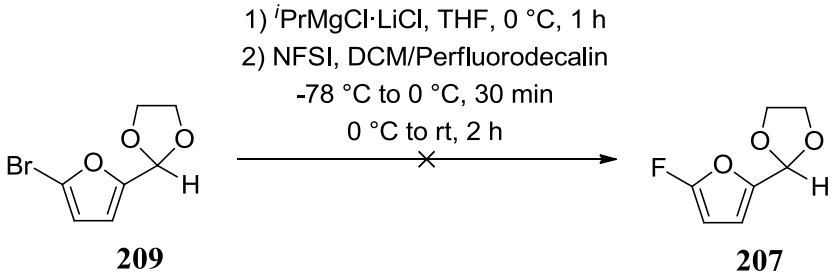
Firstly, **207** was heated in the presence of Select-Fluor® to ascertain whether or not any reaction would take place to form the fluorinated furan **208** (*Scheme 91*).[116] No evidence was found for fluorination under these conditions and so we decided to next explore the generation of a Grignard reagent *in situ*. This was attempted by treating **207** firstly with BuLi, followed by $MgBr_2$ to invoke transmetallation (*Scheme 91*). NFSI (*N*-fluorobenzenesulfonimide) was then added. However, no evidence for fluorination could be found due to the amount of decomposition. The same reaction was conducted employing Select-Fluor® instead of NFSI, but this too resulted in only decomposition.



207 **208**

Scheme 91: Attempts to fluorinate acetal **207**.

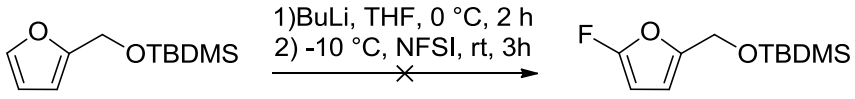
Continuing with the Grignard methodology, an attempt was made to produce the Grignard directly from **209**, the 2-bromo analogue of **207**, using ^{i}PrMgCl·LiCl (*Scheme 92*).[117] Subsequent treatment of this with NFSI in a 4:1 solvent combination of DCM and perfluorodecalin was conducted, but this too was unsuccessful.



209 **207**

Scheme 92: Alternative Grignard methodology which also failed to produce **207**.

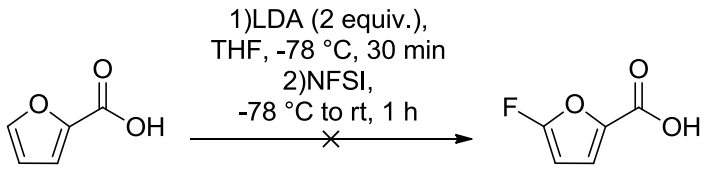
As an alternative route to fluorination, an investigation was carried out to ascertain if TBDMS-protected furfuryl alcohol **210** was amenable to fluorination *via* treatment with BuLi and NFSI (*Scheme 93*).[118] This was carried out in the event that electronic effects of the acetal functionality were perhaps hindering the previous transformations. Disappointingly, however, decomposition was again observed utilising this methodology.



210 **211**

Scheme 93: Attempted fluorination of TBDMS protected **210**.

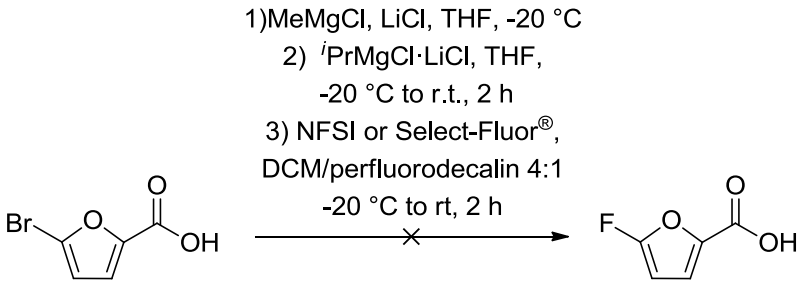
Another failed attempt towards generating a fluorinated furan involved the reaction of 2-furoic acid (**212**, which also has several possibilities for the attachment of a dienophile) with two equivalents of LDA ,[119] followed by treatment with NFSI (*Scheme 94*).



212 **213**

Scheme 94: Attempted fluorination of 2-fuoric acid (**212**).

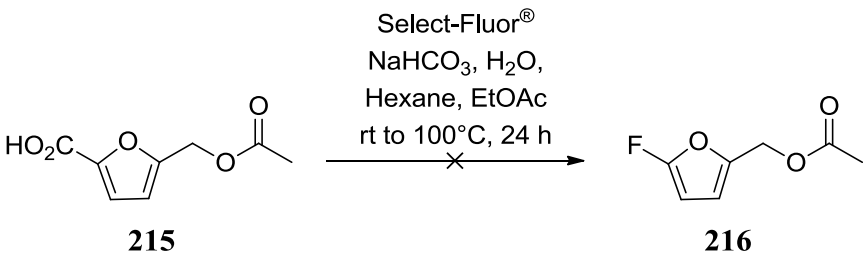
Further perseverance with Grignard chemistry was undertaken. In this instance, 5-bromo-2-furoic acid (**214**) was treated with MeMgCl in the presence of LiCl (*Scheme 95*).[120] After deprotonation of the acid moiety was complete, ^{i}PrMgCl·LiCl was introduced to generate the Grignard reagent. Introduction of NFSI or Select-Fluor® in the DCM/perfluorodecalin solvent mixture, described earlier, was tried but no product was afforded in either case.



214 **213**

Scheme 95: Recent efforts to transform **214** *into* **213** *via Grignard chemistry.*

As a final attempt to fluorinate a furan substrate, a fluoro-decarboxylation was attempted on furoic acid **215** (derived from oxidation of the corresponding aldehyde)[121] employing Select-Fluor® (*Scheme 96*).[122] However, much to our disappointment, the corresponding fluorofuran **216** was not observed despite a number of attempts at elevated temperature.



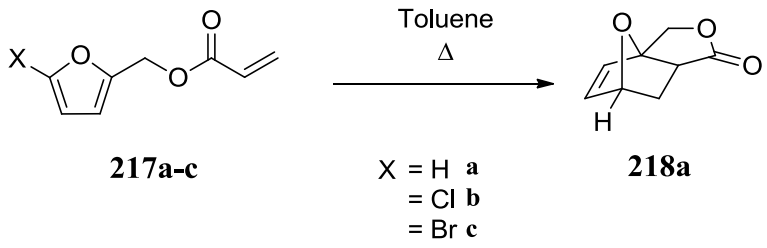
215 **216**

Scheme 96: Fluoro-decarboxylation attempt on acid **215**.

3.2.2 SUBSTRATE AND ADDUCT SYNTHESES

3.2.2.1 Ester and Ether-Tethered Substrates and Adducts

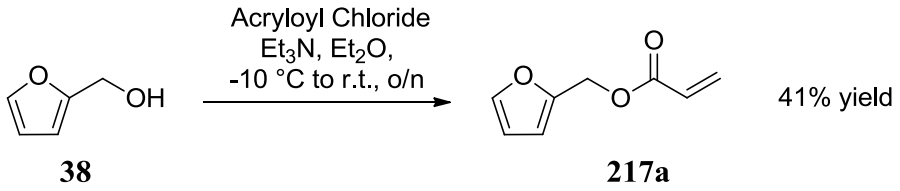
Due to the lack of success in synthesising fluorofurans, our focus switched to obtaining appropriate bromine/chlorine containing IMDAF substrates instead. Our initial efforts were conducted towards the synthesis of substrate **217a** and its halogenated counterparts (**217b-c**) so as to conduct studies on the intramolecular Diels-Alder reaction of these substrates (*Scheme 97*). The reason for selecting this particular tether was because **217a** is already known not to form its adduct (**218a**) upon heating.[112]



217a-c X = H **a** = Cl **b** = Br **c** **218a**

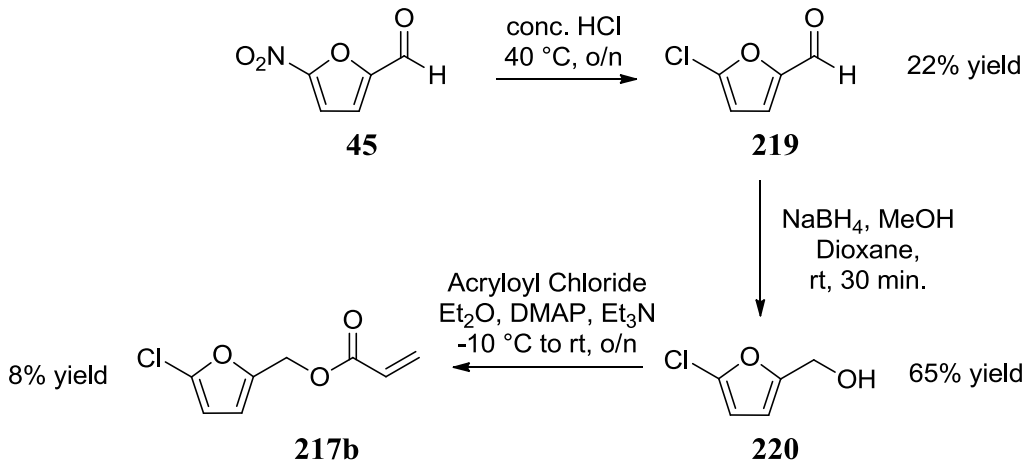
Scheme 97: Initial targets for studies of the effect of halogenation on the IMDAF reaction to give tricyclic lactones.

The proposed synthetic route to non-halogenated furan **217a** was simple. Treatment of commercially available furfuryl alcohol (**38**) with acryloyl chloride resulted in formation of **217a** in modest yield (*Scheme 98*).[123]



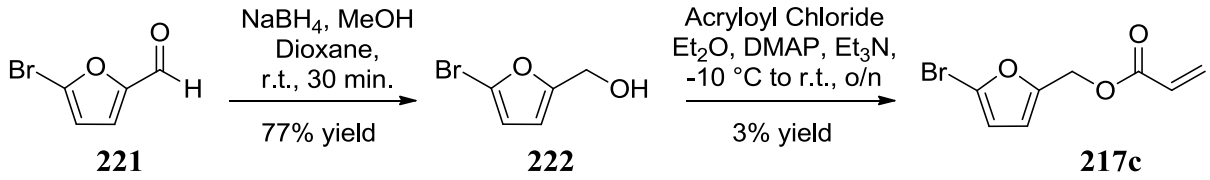
Scheme 98: Preparation of non-halogenated substrate **217a**.

Syntheses of the chlorinated and brominated substrates (**217b** and **217c** respectively) were also achieved, albeit with impurities (*vide infra*). Preparation of the chlorinated compound began by treating commercially available 5-nitro-2-furaldehyde (**45**) with concentrated HCl (*Scheme 99*).[124] This unusual reaction, involving nucleophilic substitution of nitrite, afforded **219** in a 22% yield. From here, $NaBH_4$ reduction of the aldehyde resulted in formation of alcohol **220**.[125] Transformation into the desired substrate **217b** was then achieved under the same conditions as for formation of **217a**, using acryloyl chloride.[126] The final step occurred in poor yield, a factor which was attributed to the instability of alcohol **220**, unlike its non-halogenated analogue **38**.



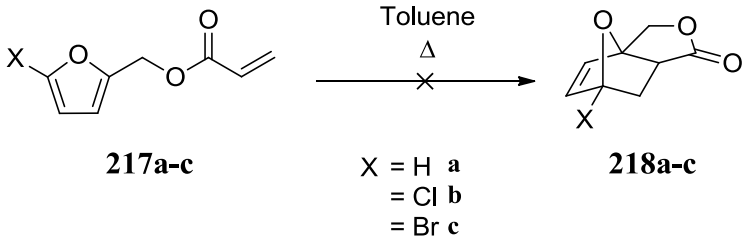
Scheme 99: Synthetic route to chlorinated substrate **217b**.

Brominated substrate **217c** was prepared along similar lines, beginning with commercially available **221** (*Scheme 100*). Treatment of this with $NaBH_4$ resulted in the corresponding alcohol **222**, which in turn was converted into **217c** with acryloyl chloride which, like the chlorinated analogue, also proceeded in poor yield. The low yield in this case is again likely due to the instability of **222**. Further to our disappointment, purification of both **217b** and **217c** proved to be ineffective and thus pure samples were never obtained.



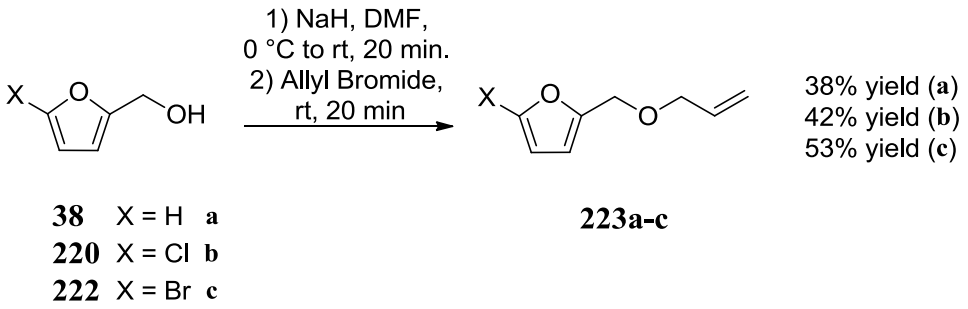
Scheme 100: Synthetic route to brominated substrate **217c**.

Despite the contamination of substrates **217b** and **217c**, it was decided to attempt the IMDA reaction on both compounds to try and afford their corresponding adducts, **218b** and **218c** respectively (*Scheme 101*). Non-halogenated substrate **217a** was also heated and, as expected, failed to form any adduct (**218a**). Unfortunately, however, no evidence for transformation of the chlorinated analogues was seen either, despite raising the reaction temperature to reflux.



Scheme 101: Attempt to find evidence for cycloaddition via the IMDAF reaction of halogenated substrates **217b** *and* **217c**.

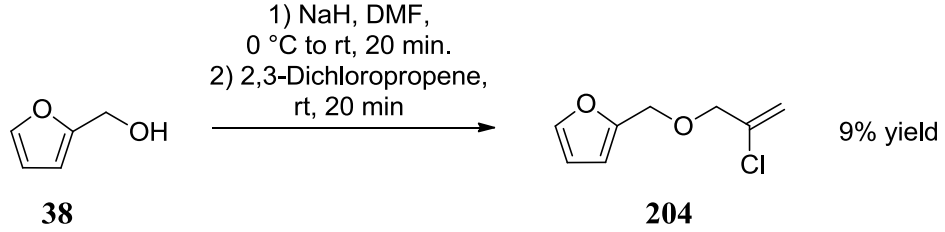
In conjunction with the ester-tethered substrates of structure **217**, efforts to synthesise the analogous ether-tether substrates **223a-c** were also undertaken. These were afforded *via* Williamson etherification of the corresponding alcohols (synthesised as previously described) with allyl bromide (*Scheme 102*).[127]



Scheme 102: Preparation of ether substrates **223a-c** *in moderate yield.*

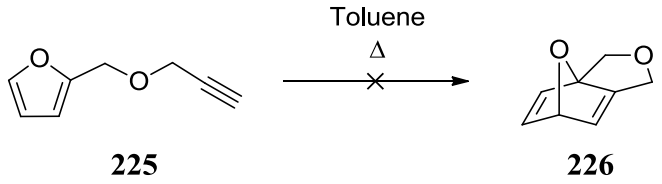
However, upon heating these substrates, decomposition occurred. Evidence for formation of the non-halogenated adduct of **223a** (**224a** - *vide infra*) could be seen with a 17% conversion in the ^{1}H NMR spectrum, but a pure sample was not isolated. Evidence for cycloadducts of the halogenated substrates **223b** and **223c** was difficult to ascertain due to the extent of decomposition upon heating, thus, no firm conclusions could be drawn about the effects of furan halogenation on IMDAF for these systems.

However, in addition to our attempts to investigate halogen substitution of the furan moiety on systems of type **223**, we also conducted a control experiment by reproducing substrate **204** - the chloro-alkene substrate reported by Karaarslan and Demircan. Synthesis of **204** was achieved *via* the same route as the ethers above, except that 2,3-dichloropropene was used for the alkylation instead of allyl bromide (*Scheme 103*).



Scheme 103: Formation of substrate **204**.

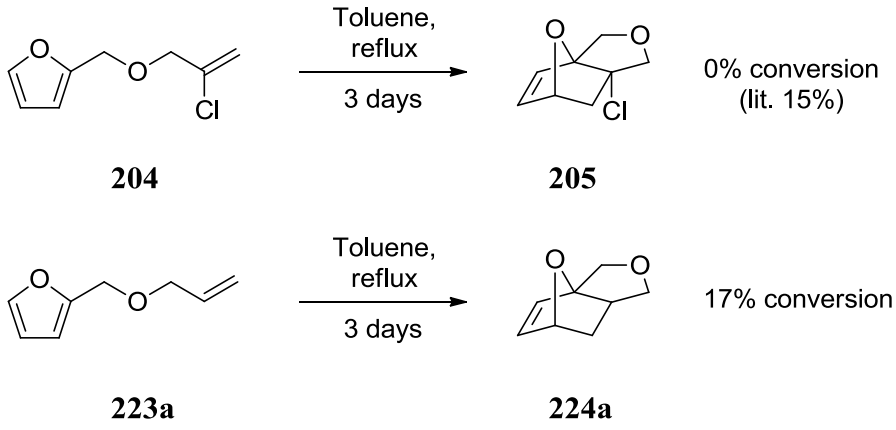
The poor yield for formation of **204** was initially puzzling until closer inspection of the ^{1}H NMR data, where it was identified that the alkyne **225** had also formed (*Scheme 104*). Curious as to how it would perform in an IMDAF reaction, we thus heated **225**. However, no sign of cycloadduct **226** could be detected (*Scheme 104*). This was not to our surprise given the highly strained nature of adduct **226**.



225 **226**

Scheme 104: Attempted IMDAF reaction of alkyne substrate **225**.

Our first result of interest arose at this stage when we attempted the IMDAF reaction on substrate **204** for ourselves. To recap, Karaarslan and Demircan did not attempt any cycloaddition reaction on the non-halogenated analogue of **204** (**223a**), but reported a 15% conversion of **204** to the adduct **205** after 3 days. However, upon attempting the same conversion with **204**, on no occasion did we observe any evidence for cycloadduct formation despite numerous attempts (*Scheme 105*). We also identified that decomposition occured in a similar fashion to the other ether-tethered substrates discussed previously.



204 **205**

223a **224a**

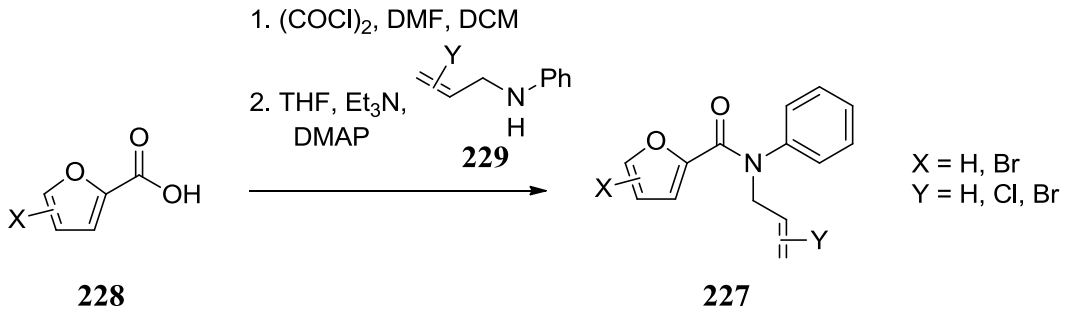
Scheme 105: Attempted IMDAF of **204** *and* **223a**.

3.2.2.2 Amide-Tethered Substrates and Adducts

Given the contradictory results we obtained compared to Karaarslan and Demircan, it was obvious that we needed to test this phenomenon on another class of IMDAF substrate so as to ascertain whether or not the retardation we observed on the haloalkene substrate **204** was an isolated event. Furthermore, the decomposition issues experienced made it desirable to identify a more stable class of IMDAF substrate in any event, so we turned our attention to synthesising amide-tether substrates closely related to those studied by Padwa.

As such we initially embarked upon synthesising substrates of structure **227** (*Scheme 106*), *via* standard methods by combining the appropriate furoic acids (**228**) and corresponding *N*-allyl anilines (**229**).[111] Note that these structures deviate from those of Padwa and co-workers in that they possess an *N*-phenyl group rather than *N*-benzyl.

We envisaged producing substrates where atom X would either be hydrogen or bromine (bromine was chosen due to both the commercial availability and the ease of syntheses of bromofuroic acids, *vide infra*) and Y would either be hydrogen, chlorine or bromine (chlorine was chosen in the majority of cases because the three isomeric *N*-chloroallyl anilines were readily prepared from commercially available chloroallyl chlorides, *vide infra*).

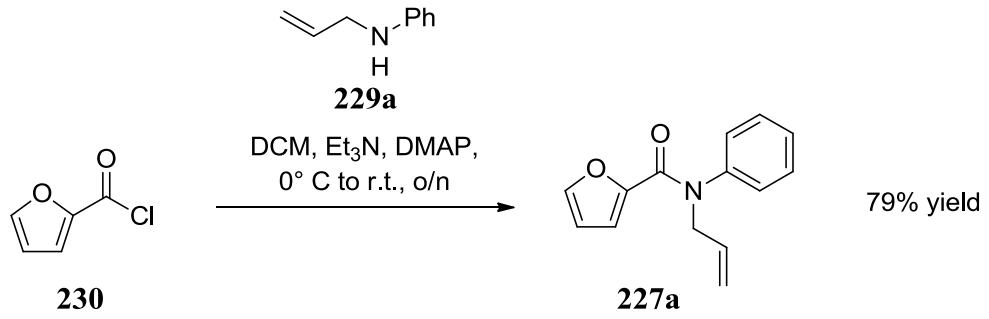


Scheme 106: Production of substrates via combination of various furoic acids and corresponding N-allyl anilines.

The system where both X and Y were hydrogen (**227a**), would act as a control for IMDAF reactivity and offer a reference point for comparison of the various halogenated

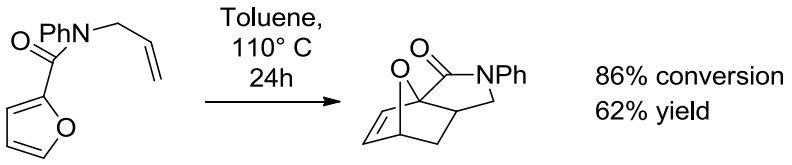
analogues. All combinations of possible halogen substitution within these substrates were envisaged, i.e. all pairings of 2-,3- and 4-bromo furans along with *E*-, *Z*- and 2-haloalkene moieties. Furthermore, these systems of structure **227** were henceforth designated as 'inverse demand' systems, owing to the electron withdrawing amide functionality attached directly to the furan. As a note, the nomenclature adopted of 'inverse' and 'normal' (*vide infra*) demand systems is purely based on the different orientation of the amide oxygen of the compounds and is *not* an indication of the HOMO-LUMO orbital interactions taking place.

The non-halogenated substrate **227a** was the first compound in this series which we attempted to generate *via* combination of commercially available starting materials 2-furoyl chloride (**230**) and *N*-allyl aniline (**229a** - *Scheme 107*). Amide **227a** was afforded in good yield and was easily isolable *via* flash chromatography.



Scheme 107: Successful synthesis and isolation of non-halogenated 'inverse demand' substrate **227a**.

Due to the successful acquisition of pure **227a**, generation of the cycloadduct **231a** was subsequently attempted (*Scheme 108*). To our gratification, a relatively clean reaction was observed and isolation of cycloadduct **231a** was achieved after 24 hours of heating in toluene at reflux, recording an 86% conversion and a 62% yield.

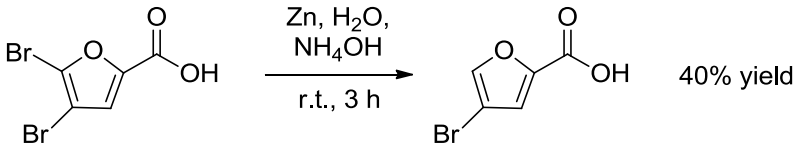


227a **231a**

Scheme 108: Successful formation and isolation of **231a** *via IMDAF reaction of substrate* **227a**.

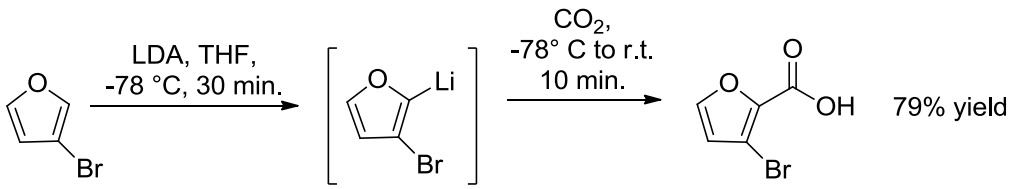
Successful IMDAF reaction of **227a** and isolation of the corresponding adduct prompted us to confirm that we would observe the same activation upon halogen substitution of the furan moiety as reported by Padwa. As such, the three isomeric bromo-2-furoic acids (**214** and **228a-b** - *vide infra*) were required. 5-Bromo-2-furoic acid (**214**) was commercially available, however, 4- and 3-bromo-2-furoic acid, **228a** and **228b** both required synthesis.

Compound **228a** was synthesised *via* zinc-mediated reduction of 4,5-dibromo-2-furoic acid (**232**) in the presence of ammonium hydroxide solution and was achieved in modest yield (*Scheme 109*).[128] Acid **228b** was synthesised by carboxylation of lithiated species **234** (generated *via* treatment of **233** with LDA) using solid CO_2 (*Scheme 110*).[129] Subsequent acidification gave the desired acid **228b**.



232 **228a**

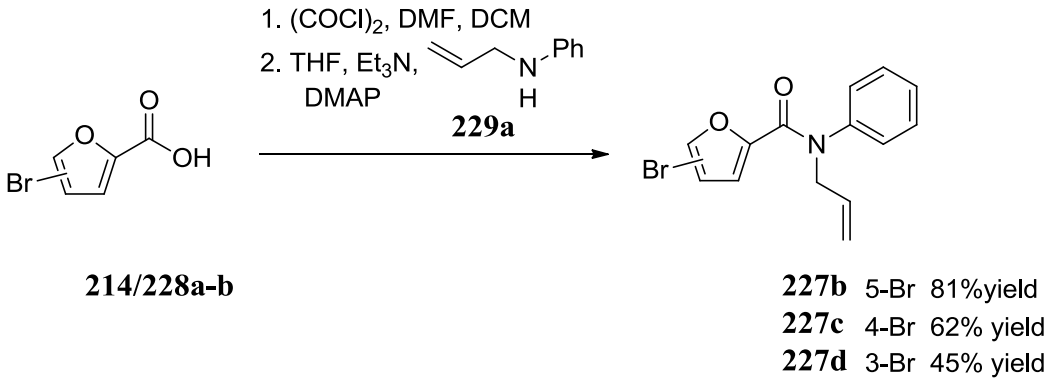
Scheme 109: Generation of acid **228a**.



232 **234** **228b**

Scheme 110: Generation of acid **228b**.

Amidation was thus achieved for all three acids under slightly modified conditions compared to those employed by Padwa and co-workers (*Scheme 111*). Conversions to the corresponding acyl chlorides were first conducted (without isolation) followed by subsequent reaction with commercially available *N*-allyl aniline (**229a**). Like the non-halogenated analogue **227a**, isolation of the corresponding IMDAF substrates was straightforward.



Scheme 111: Synthesis of bromofuran 'inverse demand' substrates.

In agreement with the observations of Houk, heating of **227b-d** in toluene resulted in more facile formation of the corresponding adducts - greater conversions and yields were recorded for the bromofuran substrates than for the case of the non-halogenated analogue **227a**. For comparison, a tabulation of these results is detailed below, including the conversion of **227a** into **231a** (*Fig. 15*). As can be seen, after a 24 h period, no starting material was detectable for any IMDAF reaction containing a bromofuran substrate, indicating that halogenation of the furan moiety has a profound effect on reactivity regardless of where the halogen is located on the furan.

A quantitative recovery was achieved for adduct **231b**, whereas **231c** and **231d** required purification due to some decomposition accompanying the reaction, however, superior yields were still recorded for these compounds in comparison to non-halogenated adduct **231a**. Additionally, the rate of reaction was demonstrated to be greater for these reactions. This was highlighted by the fact that after one hour at reflux, the conversion of **227a** to **231a** was 19%, which was in stark contrast to the conversion of **227b** to **231b**, identified to be 63% by ^{1}H NMR analysis.

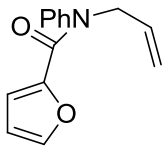
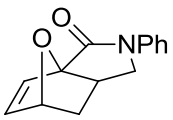
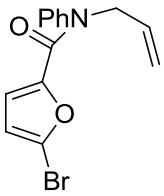
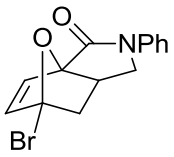
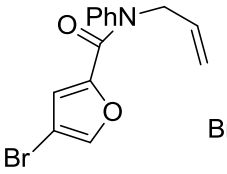
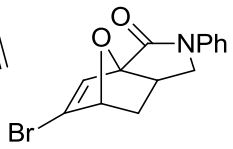
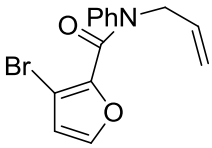
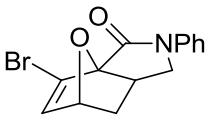
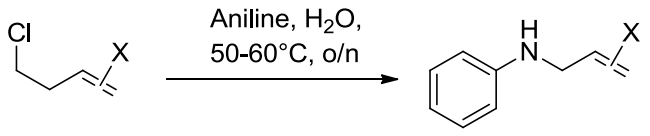
Precursor	Cycloadduct	Time/h	Ratio Adduct:S.M.	Yield %
 **227a**	 **231a**	24	86:14	62
 **227b**	 **231b**	24	100:0	100
 **227c**	 **231c**	24	100:0	77
 **227d**	 **231d**	24	100:0	77

Fig. 15: Summary of IMDAF results for substrates **227a-d**, *all reactions conducted in toluene at reflux.*

The success with the conversions of substrates **227a-d** also prompted us to investigate whether or not we would observe the same retardation upon halogen substitution of the *alkene* moiety as we previously saw in the case of substrate **204** (*Scheme 105* - p. 82). In order to probe suitable substrates of this nature, we first of all needed to obtain the appropriate halogenated *N*-allyl anilines.

Hence, *N*-chloroallyl anilines **229b-d**, that covered all possible isomers with respect to chlorine substitution, were furnished *via* combination of the corresponding chloroallyl chloride (**235a-c**, 2-chloro, *Z*-chloro and *E*-chloro respectively) and aniline (*Scheme 112*).[130] Although modest yielding due to undesired di-alkylation of aniline,

relatively large quantities of the starting materials could be employed to ensure the production of gram quantitites of the targets. Additionally, *N*-2-bromoallyl aniline **229e** was also generated in this manner in order to try and establish any differences arising from the presence of different halogens on the alkene moiety of the IMDAF substrate.

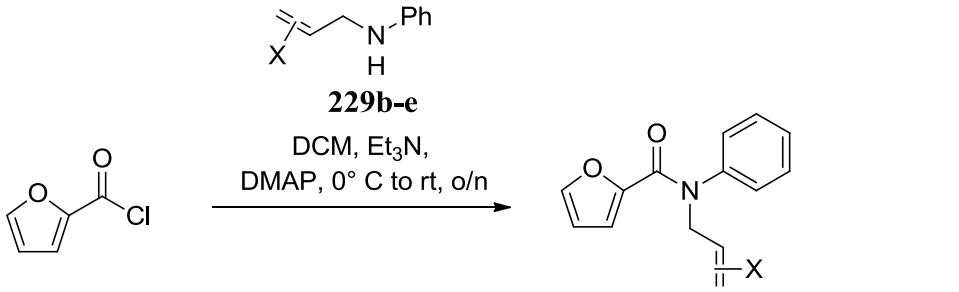


235a-c X = 2-Cl, *Z*-Cl, *E*-Cl
235d X = 2-Br

229b X = 2-Cl 33% yield
229c X = *Z*-Cl 37% yield
229d X = *E*-Cl 29% yield
229e X = 2-Br 42% yield

Scheme 112: Successful synthetic strategy towards desired N-haloallyl anilines **229b-e**.

Once in possession of the above *N*-haloallyl anilines, they were then reacted with furoyl chloride in a fashion identical to the production of non-halogenated inverse demand substrate **227a**, as depicted in *Scheme 113*. Once again, isolation of the pure substrates was achieved with moderate to good yields attained.



230

227e X = 2-Cl 76% yield
227f X = *Z*-Cl 61% yield
227g X = *E*-Cl 54% yield
227h X = 2-Br 72% yield

Scheme 113: Synthesis of N-haloallyl substrates **227e-h**.

Upon subjecting the *N*-haloallyl substrates to the IMDAF conditions, it was ascertained that our previous observation was not a unique occurrence. In fact, halogenation of the alkene moiety of these IMDAF substrates appears to retard the forward reaction in comparison to the parent non-halogenated system - regardless of where the halogen is located (*Fig. 16*).

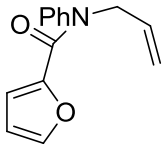
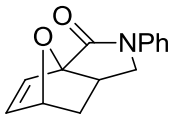
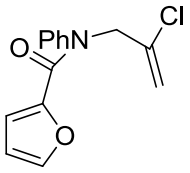
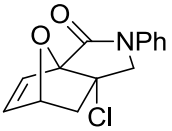
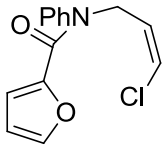
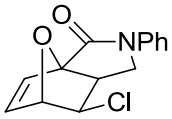
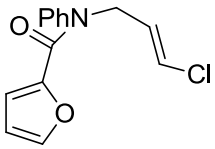
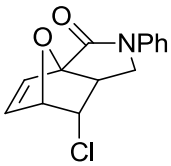
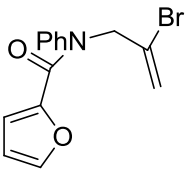
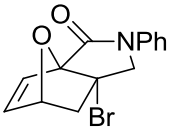
Precursor	Cycloadduct	Time/h	Ratio Adduct:S.M.	Yield %
 **227a**	 **231a**	24	86:14	62
 **227e**	 **231e**	24	40:60	27
 **227f**	 **231f**	24	12:88	7
 **227g**	 **231g**	24	63:37	28
 **227h**	 **231h**	24	50:50	44

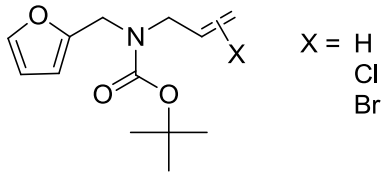
Fig. 16: Summary of IMDAF results for substrates **225e-h**, *all reactions conducted in toluene at reflux.*

We identified that some decomposition accompanies these transformations and as such we compared conversions between **227a** and **227e** after only 3 hours, using a known quanitity of cyclohexane as an internal NMR standard. Our results verified that the observed retardation was in fact genuine as no decomposition was detected after a shorter time-frame. The non-halogenated substrate had a 37% conversion to the adduct, whereas only 16% of **227e** had converted to its adduct in the same time frame.

With respect to the chloro compounds in this class of substrate, it was demonstrated that having the chlorine in a *cis* configuration on the alkene moiety had the most profoundly detrimental effect on the forward reaction whereas the *trans* species was the least so. This was somewhat surprising given that the corresponding adduct of the *Z*-chloroallyl substrate intrinisically bears the chlorine in the normally more hindered face of the tricyclic adduct. Indeed, this feature was consistent with all IMDAF reactions studied (*vide infra*).

Additionally, due to firstly conducting the transformation of **227e** into **231e**, we initially suspected that steric hindrance may have been the primary cause of this detrimental effect, particularly in this case as it involves the generation of a quaternary carbon centre. However, the results from converting **227f** and **227g** into their corresponding adducts cast doubt on this, hence the synthesis of bromo substrate **227h**. If steric effects were truly the primary source of the observed retardation, then we suspected that the conversion of substrate **227h** would inevitably be more difficult than that of **227e**. However, much to our surprise, not only did we identify bromo substitution as being no worse than chlorine substitution, it was in fact marginally less hindering to the process (although still detrimental compared to no halogen).

Given that we consistently observed IMDAF retardation upon dienophile halogenation, a further check was conducted to investigate the generality of this effect. To achieve this we embarked on synthesising *N*-Boc systems of structure **236**, which are a class of IMDAF substrates already investigated by Karaarslan and Demircan (*Fig. 17*). However, as with the ether-tethered substrate **204** (*Scheme 105* - p. 82), no comparison was made of their findings to the non halogenated species, which is something we wished to address.



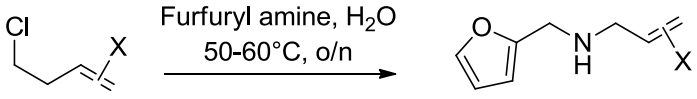
236

Fig. 17: General structure of N-Boc substrates.

As such, syntheses of five substrates analogous **227e-h**, as well as a non-halogenated variant was undertaken. The syntheses of non-halogenated amine **237a** as well as the appropriate secondary, *N*-chloroallyl amines (**237b-e**) was therefore required in the first instance. Non-halogenated amine **237a** was afforded by reacting allyl amine with furfural (**16**) in a reductive amination procedure (*Scheme 114*).[131] The *N*-chloroallyl amines were synthesised *via* adoption of the same methodology developed previously, but where aniline was replaced by furfuryl amine (*Scheme 114*).

16 **237a**

Scheme 114: Preparation of non-halogenated amine **237a**.



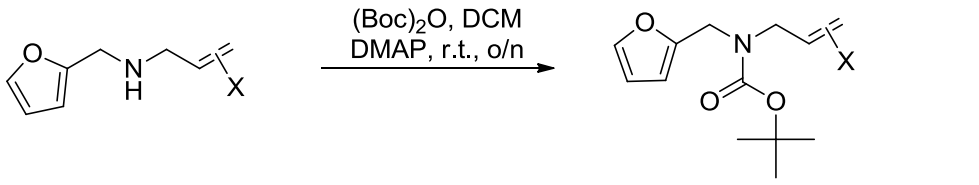
235a-c X = 2-Cl, *Z*-Cl, *E*-Cl
235d X = 2-Br

237b X = 2-Cl 28% yield
237c X = *Z*-Cl 32% yield
237d X = *E*-Cl 41% yield
237e X = 2-Br 50% yield

Scheme 115: Preparation of N-chloroallyl furfuryl amines **235b-e**.

Although the yields obtained for amines **237a-e** were moderate at best, large quantities of starting materials were also employed here to overcome this shortcoming.

Once the amines were in our possession, they were each reacted with $(Boc)_2O$ to afford the desired class of IMDAF substrates **236a-e** (*Scheme 116*). To our satisfaction, moderate to good yields were obtained for each substrate. Additionally, as excess $(Boc)_2O$ was the only impurity come the end of the reactions, a facile procedure simplified purification which involved removing the excess $(Boc)_2O$ *via* reaction with imidazole and subsequent mild acid rinsing.[132]



237a-e

236a X = H 64% yield
236b X = 2-Cl 84% yield
236c X = *Z*-Cl 88% yield
236d X = *E*-Cl 61% yield
236e X = 2-Br 81% yield

Scheme 116: Preparation of N-Boc IMDAF substrates **236a-e**.

The new set of substrates obtained were in due course heated to reflux in toluene to afford the corresponding adducts, **238a-e** (*Fig. 18*). Once again, we observed that halogen substitution on the alkene moiety most certainly did not exhibit any beneficial effect on the IMDAF reaction, but in most cases quite the opposite. Furthermore, it appears that the same trend of reactivity with respect to chlorine position on the dienophile functionality is being observed, i.e. having chlorine in a *cis* orientation has the most profoundly detrimental effect whereas *trans* is the least. Interestingly, having chlorine in a *trans* orientation appears to have little to no effect on reactivity in comparison to the non-halogenated substrate in this class of IMDAF substrates.

Furthermore, we once more observed that steric influences are not the exclusive cause of this retardation effect, as the 2-bromoallyl adduct **238e** was produced in greater

yield and conversion than the analogous 2-chloroallyl adduct **238b**. This will be discussed further, later in the chapter.

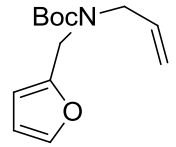
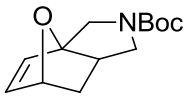
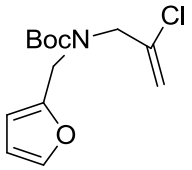
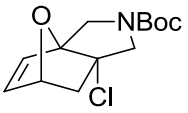
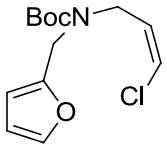
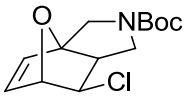
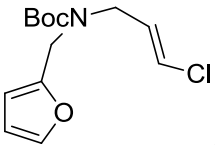
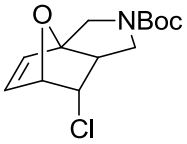
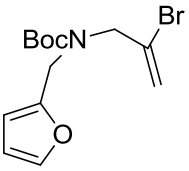
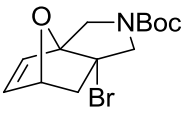
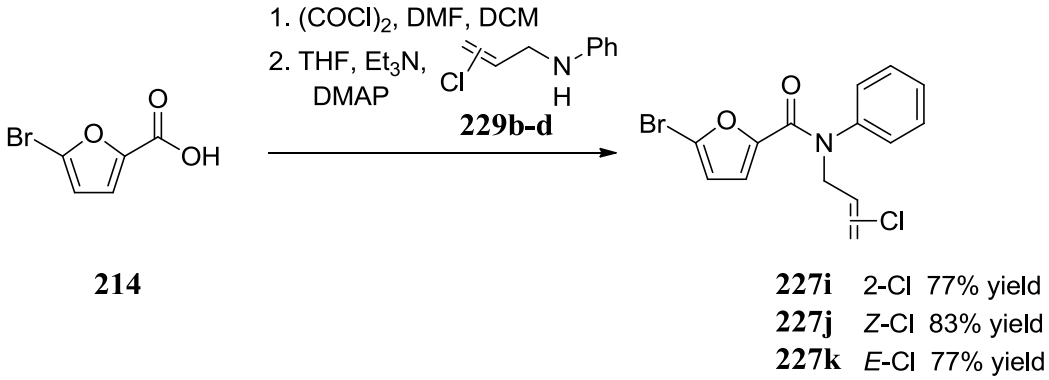
Precursor	Cycloadduct	Time/h	Ratio Adduct:S.M.	Yield %
 **236a**	 **238a**	24	54:46	46
 **236b**	 **238b**	24	31:69	15
 **236c**	 **238c**	24	11:89	7
 **236d**	 **238d**	96	53:47	31
 **236e**	 **238e**	24	48:52	28

Fig. 18: Summary of IMDAF results for substrates **236a-e**, *all reactions conducted in toluene at reflux.*

Having now demonstrated, with two separate (although related) classes of IMDAF substrates, that alkene halogenation is detrimental to the process, whereas halogenation of the furan moiety has the opposite effect, we were now interested to ascertain the effect of combining these two substitutions.

As such, we initially embarked upon producing a series of three IMDAF substrates derived from combination of 5-bromo-2-furoic acid (**214**) with the various *N*-chloroallyl anilines **229b-d**. This was accomplished employing the same synthetic strategy utilised to the previous bromofuran substrates, which furnished di-halogenated IMDAF substrates **227i-k** in good yields (*Scheme 117*).



214

227i 2-Cl 77% yield
227j *Z*-Cl 83% yield
227k *E*-Cl 77% yield

Scheme 117: Syntheses of 5-bromofuran, N-chloroallyl substrates **227i-k**.

Subsequently, substrates **227j-k** were then subjected to the IMDAF conditions employed thus far (*Fig. 19*). In comparison to the parent 5-bromofuran system **227b** (included in *Fig. 19*), the conversions and yields were not quite as impressive (particularly for the conversion of **227j** into **231j** - *vide infra*). However, it was evident that the retardation effect induced by the presence of a halogen on the dienophile could be overcome to a large extent by having a halogen present on the diene functionality. This was true at least for substrates **227i** and **227k** where a drastic improvement in comparison to substrates **227e** and **227g** was observed, affording di-halogenated adducts **231i** and **231k** in similarly high conversions and yields.

The shorter time-frame for the conversion of **227k** into its adduct is a reflection of the fact that this system was more prone to decomposition at longer reaction times. This decomposition was not unique to this system, however (*vide infra*).

In the case of substrate **227j**, the results were very similar to that of the analogous mono-halogenated substrate **227f** (where the furan halogen is absent). However, we attributed this to the heavy steric impact that would become present *via* a gauche interaction between the two halogen atoms in adduct **231j**.

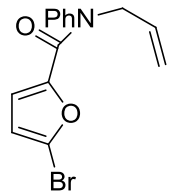
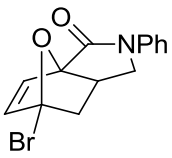
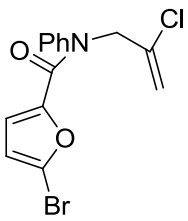
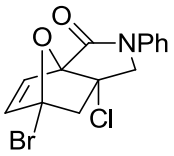
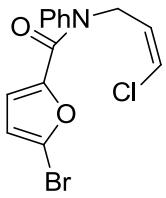
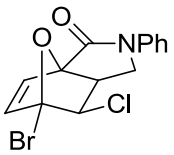
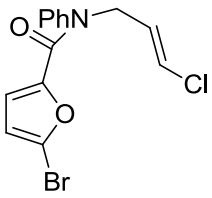
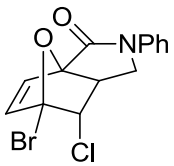
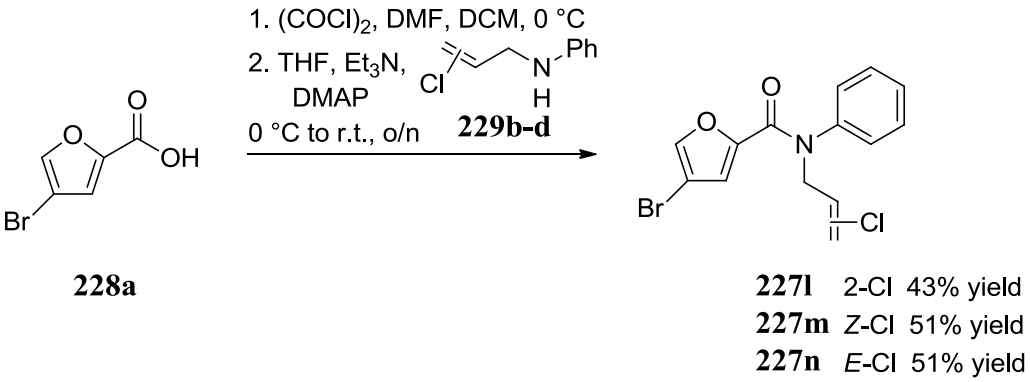
Precursor	Cycloadduct	Time/h	Ratio Adduct:S.M.	Yield %
 **227b**	 **231b**	24	100:0	100
 **227i**	 **231i**	24	85:15	61
 **227j**	 **231j**	24	14:86	12
 **227k**	 **231k**	8	83:17	60

Fig. 19: Summary of IMDAF results for substrates **227i-k**, *all reactions conducted in toluene at reflux.*

In order to establish whether or not the theory regarding steric hindrance preventing the cycloaddition substrate **227j** was true, it was necessary to analyse the analogous systems

to substrates **227i-k**, which were the 3- and 4-bromo analogues **227l-q** (*vide infra*). The 4-bromofuran analogues were synthesised in an identical manner to that of **227i-k**, except that 4-bromofuroic acid (**228a**) was employed instead of **214** in order to furnish substrates **227l-n** (*Scheme 118*). The isolated yields were not as impressive as for the analogous 5-bromofuran systems. However, appreciable quantities were still obtainable.



Scheme 118: Preparation of 4-bromofuran, N-chloroallyl IMDAF substrates **227l-n**.

Subjecting the above substrates to the IMDAF conditions appears to support our postulate as to why the conversion of **227j** into its adduct is more difficult (*Fig. 20*). Once again, conversions and yields were poorer than for the parent, mono-halogenated, 5-bromofuran substrate **227c**, but this time improvements were made in all cases in comparison to the conversions of substrates **227e-g** (where only the alkene functionality was halogenated). In the case of the formation of adduct **231m**, there is a marked improvement in comparison to both the conversions of **227f** and indeed **227j**, where we established previously that the *cis*- chlorine atom retards the IMDAF reaction despite the presence of a reaction-facilitating bromine on the furan moiety.

Thus, with the furan halogen further away from the dienophile halogen, the conversion of **227m** into **231m** proceeds with modest conversion and corresponding yield. Despite this, however, it is still clear that a conversion involving a substrate containing a *cis*- chlorine on the alkene moiety is still the least facile.

We observed that conversions of **227l** and **227n** into their corresponding adducts were improved in a similar fashion to that of their 5-bromofuran analogues **227i-k**.

Although this finding is not surprising with respect to Houk's calculations, it further highlights the mystery as to why 4-halogenation of the furan moiety still facilitates the IMDAF process at all - particularly in the absence of the charge stabilisation explanation resulting from a change in hybridisation, which is plausibly offered for the 5-halofuran systems.[112]

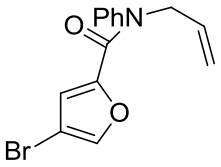
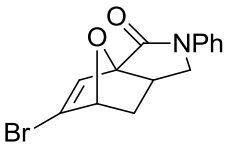
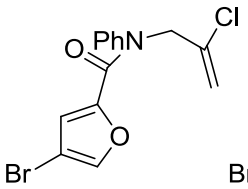
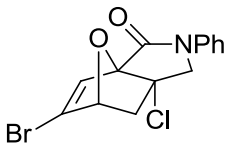
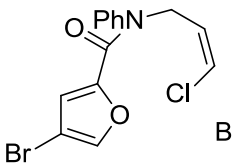
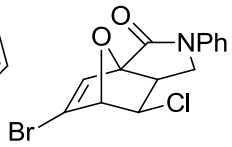
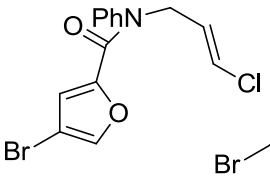
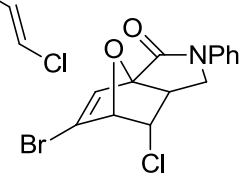
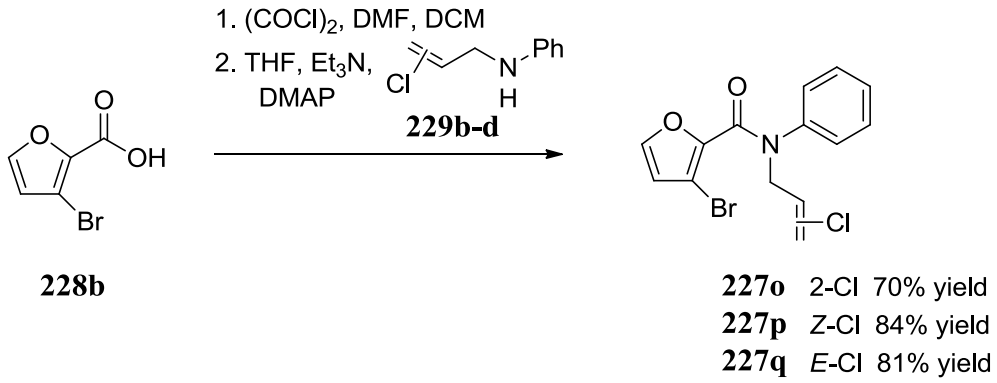
Precursor	Cycloadduct	Time/h	Ratio Adduct:S.M.	Yield %
		24	100:0	77
227c	**231c**			
		24	78:22	50
227l	**231l**			
		24	40:60	31
227m	**231m**			
		24	83:17	54
227n	**231n**			

Fig. 20: Summary of IMDAF results for substrates **227l-n**, *all reactions conducted in toluene at reflux.*

Syntheses of the remaining 3-bromofuran, dihalogenated substrates was then undertaken in order to complete the series of classes of IMDAF substrates. Once more, the previously established synthetic chemistry was employed, this time with 3-bromo-2-furoic acid (**228b**) to afford the desired products **227o-q** (*Scheme 119*). Yields for these compounds were better than those of the previously synthesised classes of IMDAF substrates.



Scheme 119: Preparation of 3-bromofuran, N-chloroallyl IMDAF substrates **227o-q**.

Our anticipation for these systems, given the conformational-based facilitation of such IMDAF processes detailed earlier, in addition to the evident electronic effects, was that furan halogenation in the 3-position would have the greatest promotion effect to counter the retardation properties of the halogen present on the alkene. Upon heating substrates **227o-q**, yet again under the same IMDAF conditions, we did indeed observe such an effect - but, somewhat peculiarly, not for all three cases as expected (*Fig. 21*).

These reactions proceeded more quickly than the 4- and 5-bromofuran analogues, as is evident from the timeframes listed below. Furthermore, these particular adducts were more sensitive to decomposition in a manner similar to that of adduct **231k** (*vide supra*), in addition to being more difficult to purify owing to similar retention factors of adducts and substrates. Nevertheless, isolated adducts were afforded in each case.

For of the formations of adducts **231p** and **231q**, impressive conversions (more than that of the analogous haloalkene species - *Fig. 16* - p.89) were observed along with corresponding good yields, which was in line with our expectations.

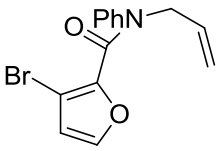
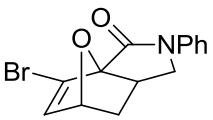
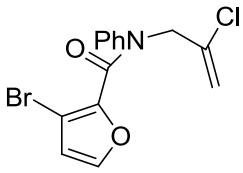
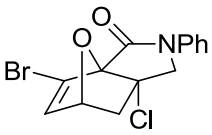
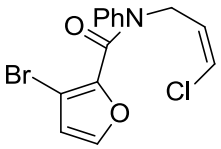
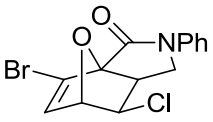
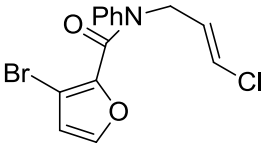
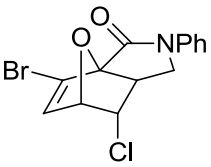
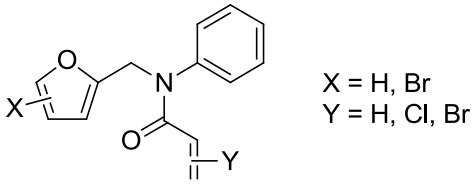
Precursor	Cycloadduct	Time/h	Ratio Adduct:S.M.	Yield %
		24	100:0	77
227d	**231d**			
		5	40:60	20
227o	**231o**			
		16	87:13	67
227p	**231p**			
		7	94:6	75
227q	**231q**			

Fig. 21: Summary of IMDAF results for substrates **227o-q**, *all reactions conducted in toluene at reflux.*

However, and somewhat anomalously, the conversion of substrate **227o** into corresponding adduct **231o** did not proceed with a likewise conversion. In fact, the majority of the product mixture after 5 hours was still starting material (heating for longer than this resulted in the beginnings of more serious decomposition, with no observed improvement on this ratio). This highlights the complex relationship between the steric and electronic effects presiding over these IMDAF reactions.

Finally, with respect to the different classes of IMDAF systems investigated and in contrast to the 'inverse demand' systems probed above, we also strived to elucidate the effects of halogen substitution on analogous 'normal demand' systems containing electron-poor alkenes. We envisaged that this could be easily investigated by simply reversing the orientation of the amide functionality within the substrates to give rise to substrates of structure **239**, i.e. the carbonyl moiety of the amide is now adjacent to the dienophile portion (as opposed to the diene) of the substrate (*Fig. 22*). As a reminder, the term 'normal demand' is purely a reflection of the orientation of the electron withdrawing amide oxygen within the substrate and *not* an indication of the HOMO-LUMO interaction taking place.



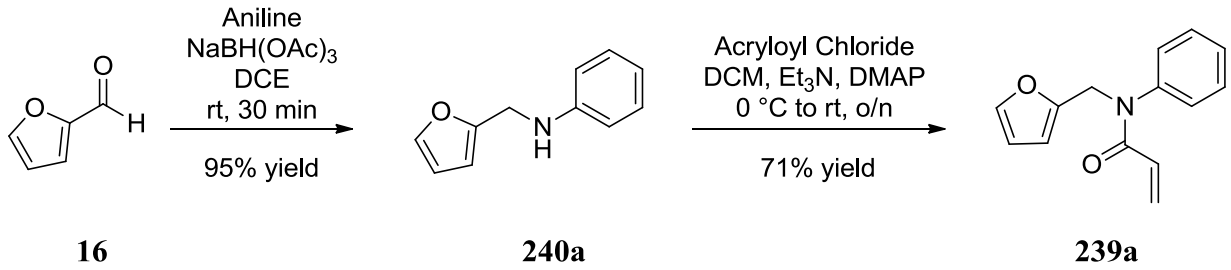
239

Fig. 22: Envisaged general structure of 'normal demand' IMDAF substrates.

In order to investigate IMDAF substrates of this class, we first synthesised the non-halogenated substrate **239a**. This demanded the synthesis of appropriate amines which we would then acylate with acryloyl chloride under standard conditions.

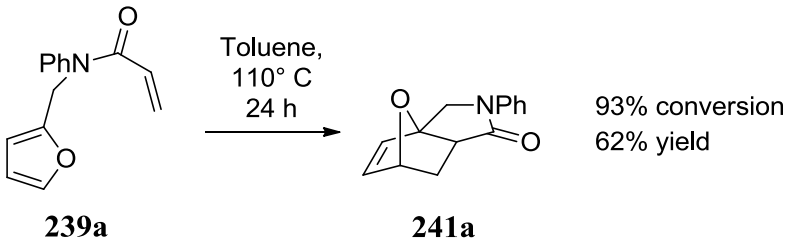
As such, amine **240a** was prepared *via* reductive amination between furfural (**16**) and aniline. However, due to the poor yield obtained by the previous methodology (*vide supra* - p.91), alternative conditions employing $NaBH(OAc)_3$ were used instead and were found to be superior (*Scheme 120*).[133] Furthermore, evidence of this procedure being used to synthesise one of our desired amines (**240c** - *vide infra*) was present in the literature already.[134]

After successfully isolating the desired amine **240a**, it was subsequently acylated with acryloyl chloride to afford the non-halogenated, 'normal demand' substrate **239a** in good yield (*Scheme 120*).



Scheme 120: Preparation of amine **240a** and subsequent formation of **239a**.

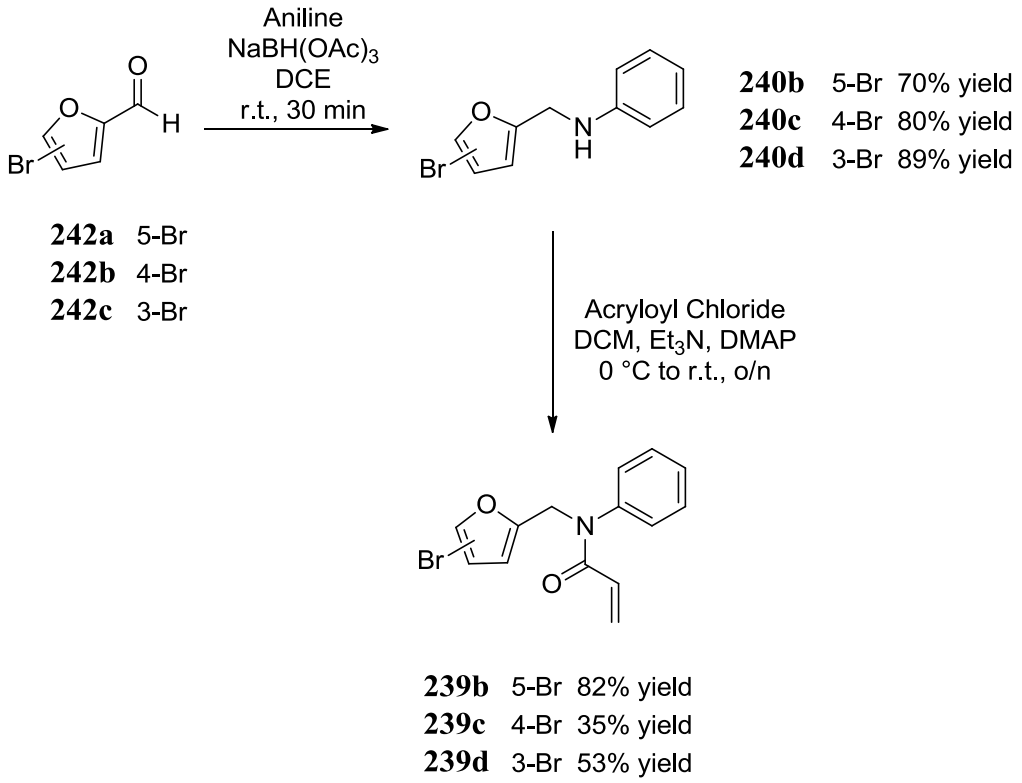
Upon subjecting **239a** to the IMDAF conditions (*Scheme 121*), we identified that the conversion to the corresponding adduct (**241a**) marginally exceeds that of the non-halogenated 'inverse demand' substrate **227a**. Incidentally, we recorded an identical isolated yield for **241a** as for adduct **231a**. A good conversion was not unexpected on a FMO basis, given that the electron-withdrawing functionality is now attached to the dienophile moiety as opposed to the diene.



Scheme 121: Formation of non-halogenated, 'normal demand' substrate **241a**.

Successful formation and isolation of this control substrate and adduct prompted us to then synthesise the three isomeric, brominated analogues of **239a** for IMDAF testing (**239b-d**). As such, the amines required for their syntheses (**240b-d**) were produced by combination of commercially available aldehydes **242a-c** and aniline *via* the same reductive amination methodology used for formation of **240a** (*Scheme 122*). The amines were then acylated to afford substrates **239b-d**.

Ultimately, the yields for these three substrates varied from modest to very good and enough isolated material was afforded in all cases to conduct the corresponding IMDAF reactions.



Scheme 122: Syntheses of bromofuran substrates **239b-d**.

Upon subjecting substrates **239b-d** to the IMDAF conditions, we established that all three bromofuran substrates were more reactive than their inverse demand counterparts and that longer reaction times resulted in some decomposition (*Fig. 23*). In fact, it was noted that simply leaving the substrates at room temperature over a prolonged time period (several weeks) would eventually result in transformation to the corresponding adduct (accompanied with decomposition) even in the absence of any solvent.

In addition, the differences in conversions between 5-bromofuran substrate **239b** and 4-bromofuran substrate **239c** to adducts **241b** and **241c**, respectively, were fairly marginal, further enshrouding the mystery as to why 4-halo substitution facilitates the process. Substrate **239d** also underwent cycloaddition rather well, displaying 100% conversion to **241d** after 6 hours (with minor signs of decomposition). The expected

additional conformational facilitation of the IMDAF process in this instance make this result unsurprising.

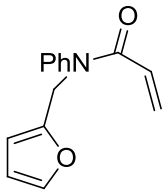
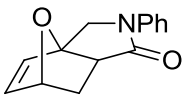
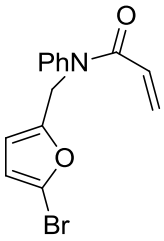
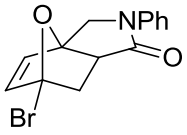
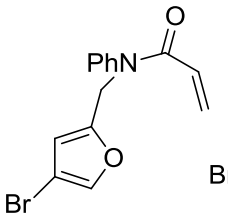
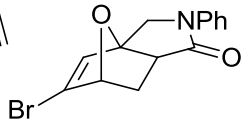
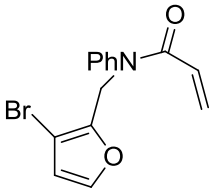
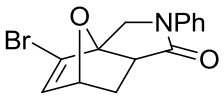
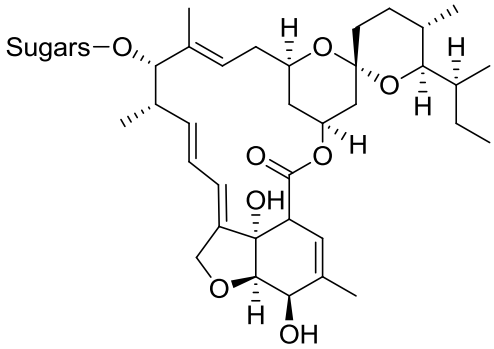
Precursor	Cycloadduct	Time/h	Ratio Adduct:S.M.	Yield %
 **239a**	 **241a**	24	93:7	62
 **239b**	 **241b**	2	90:10	70
 **239c**	 **241c**	12	>95:5	76
 **239d**	 **241d**	6	100:0	83

Fig. 23: Summary of IMDAF results for substrates **239a-d**, *all reactions conducted in toluene at reflux.*

Once we had demonstrated the transformations of substrates of type **239** into the adducts **241**, we then elected to try and synthesise the halo-alkene analogues in order to perform similar investigations to those that had been carried out on the 'inverse demand' substrates. However, upon trying to generate a suitable substrate, no evidence for product was seen on any occasion.

Several attempts were made to couple amine **240a** with either 2-chloroacrylic acid or *trans*-3-chloroacrylic acid but to no avail. Numerous acyl chloride formations were attempted on the acids, including variations on the methods we were familiar with, in addition to alternative methodologies[135] in order to react them with **240a** but to no avail. Attempts to directly couple the acids with amine **240a** with EDCI/HOBt also failed to yield any desired product.

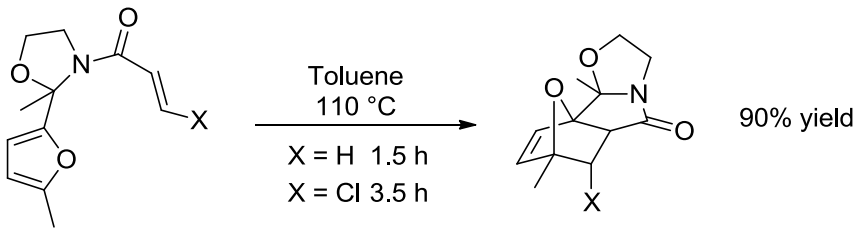
In any event, we surmise that a retardation effect would have once again been generally observed upon dienophile halogenation. This hypothesis is not only based on our observations on the 'inverse demand' systems, but also on literature precedence.[136] In their efforts to provide a synthetic strategy towards the bottom portion of avermectins (**243** - *Fig. 24*), Jung and Street observed some evidence for this retardation upon attempting relevant IMDAF chemistry of their own.



243

Fig. 24: General structure of avermectins.

As an example, they reported that transformation of substrate **244a** (which bears structural similarities with our 'normal demand' systems) into the corresponding adduct **245a** took less than half the time that haloalkene counterpart **244b** did in order to achieve the same yield (*Scheme 123*). Thus, we suspect that a similar effect would be observed on our own systems.



244a X = H
244b X = Cl

245a X = H
245b X = Cl

Scheme 123: Retardation of formation of **245** *when X = Cl.*

As a final piece of experimental work on our IMDAF systems, we decided to ascertain whether or not some of these reactions were reversible. Given that conversion of the chloroalkene substrates into their corresponding adducts was generally lower than other systems, we decided to subject a couple of these isolated adducts to the same conditions under which they were formed.

As such, we identified that chloroadducts **231e** and **238c** do indeed undergo the retro DA reaction upon heating, with substrates **227e** and **236c** beginning to form after 4 hours. Additionally, we also observed that isolated, non-halogenated *N*-Boc substrate **238a** also started to revert to substrate **236a**.

We also elected to heat dihalogenated adducts **231k, 231m** and **231q** to identify any reversibility in systems where both the furan and dienophile were halogenated. After 5 hours, adduct **231k** displayed no indication of reverting to substrate **227k**, perhaps indicating that reversibility is a feature more likely to be associated with adducts derived from non-halogenated and and haloalkene substrates. Adducts **231m** and **231q** began to decompose upon these reversal attempts. Thus, the nature of the reversibility of these reactions likely demands further exploration before any firm conclusions can be drawn.

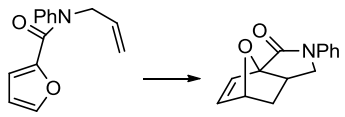
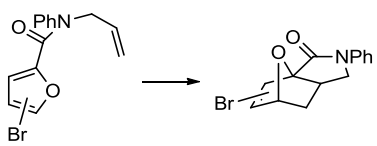
3.2.3 THEORETICAL CHEMISTRY

3.2.3.1 FMO Effects

In order to try and rationalise our experimental findings, we turned towards theoretical chemistry in order to calculate certain thermochemical data relating to our IMDAF

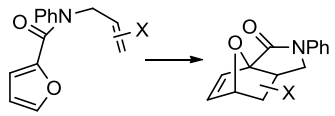
reactions. As such, we collaborated with Prof. Martin Paterson and Dr. Justyna MacKinlay who conducted the theoretical chemistry on our behalf (the results of which are shown and discussed below). Our initial thoughts were to attempt to explain our findings *via* examination of frontier orbital effects using DFT (B3LYP/6-31g(*d*)) calculations (*Fig. 25*). All calculations were performed in the gas phase with the Gaussian09 program (versions a and c).[137] The important frontier molecular orbital interaction in an IMDAF reacion is usually HOMO(furan)-LUMO(dienophile), due to furan normally being considered as an electron-rich diene in Diels-Alder processes.[72]

Many examples of IMDAF are consistent with this; however, in a number of cases the cycloaddition has been demonstrated still to occur readily when the furan bears an electron-withdrawing carbonyl group (as in our 'inverse demand' systems). As a result, there has been some debate regarding the true nature of frontier orbital effects in IMDAF. The effect of halogen substitution on frontier orbital energies is even less clear cut due to a mixture of electron-donating field/mesomeric and electron-withdrawing inductive effects that a halogen exhibits.[138]

Reaction	**$HOMO_{diene}$-$LUMO_{dienophile}$ gap (eV)**	**$LUMO_{diene}$-$HOMO_{dienophile}$ gap (eV)**
Furan/Ethylene	6.62	7.79
2-Chlorofuran/Ethylene	6.71	7.39
Non-halo 'Inverse Demand' Substrate		
		
227a → 231a	6.89	6.24
Bromofuran 'Inverse Demand' Substrates		
		
227b → 231b (5-Br)	6.80	6.10

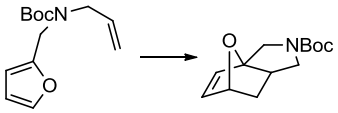
227c → 231c (4-Br)	6.92	6.12
227d → 231d (3-Br)	6.83	6.12

Haloalkene 'Inverse Demand' Substrates



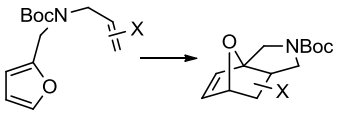
227e → 231e (2-Cl)	6.55	5.93
227f → 231f (*Z*-Cl)	6.42	5.98
227g → 231g (*E*-Cl)	6.22	5.92
227h → 231h (2-Br)	6.41	5.80

Non-halo *N*-Boc Substrate



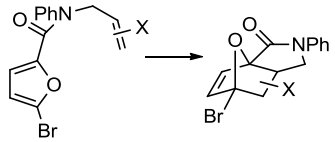
236a → 238a	6.61	7.26

Haloalkene *N*-Boc Substrates



236b → 238b (2-Cl)	6.22	7.05
236c → 238c (*Z*-Cl)	5.94	7.45
236d → 238d (*E*-Cl)	6.23	7.06
236e → 238e (2-Br)	6.25	7.10

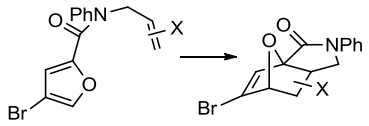
5-Bromofuran Dihalo 'Inverse Demand' Substrates



227i → 231i (2-Cl)	6.40	5.81

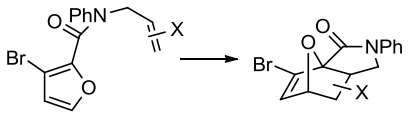
227j → 231j (*Z*-Cl)	6.41	5.86
227k → 231k (*E*-Cl)	6.42	5.68

4-Bromofuran Dihalo 'Inverse Demand' Substrates



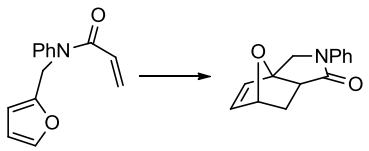
227l → 231l (2-Cl)	6.52	5.81
227m → 231m (*Z*-Cl)	6.50	5.87
227n → 231n (*E*-Cl)	6.54	5.68

3-Bromofuran Dihalo 'Inverse Demand' Substrates



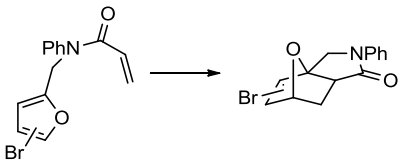
227o → 231o (2-Cl)	6.50	5.69
227p → 231p (*Z*-Cl)	6.37	5.85
227q → 231q (*E*-Cl)	6.49	5.60

Non-halo 'Normal Demand' Substrate



239a → 241a	5.38	7.76

Bromofuran 'Normal Demand' Substrates



239b → 241b (5-Br)	6.46	7.49
239c → 241c (4-Br)	6.58	7.60

239d → 241d (3-Br)	<u>6.68</u>	7.41

Fig. 25: Calculated HOMO-LUMO gaps (eV) for normal and inverse demand reactions (underlined value represents the smaller of the two calculated gaps).

According to our calculations, both furan and 2-chlorofuran are predicted to react with ethylene in a normal electron-demand sense. The presence of the chlorine atom results in only a very minor change (<0.1eV) in the HOMO-LUMO energy gap in these systems. Examination of the relevant orbitals in the more complex intramolecular reactions indicates that non-halogenated substrates **236a** and **239a** react with normal demand, whereas **227a**, with the electron-withdrawing functionality adjacent to the furan, reacts with inverse demand.

Halogenation does not appear to change the nature of the FMO interactions, and produces only minor changes in orbital energies (0.1-0.4 eV) across most of the substrates studied. The exceptions to this are substrates **239b-d**, where the FMO energy gap actually *increases* by 1.1-1.3 eV upon furan halogenation, despite the fact that the halogenated systems **239b-d** appear to react more rapidly than than non-halogenated analogue **239a**.

In addition, comparison of the HOMO-LUMO energy gap of non-halogenated substrate **227a** with haloalkene substrates **227e-h** suggests that halogenation *decreases* the energy gap by 0.3-0.4 eV, despite the fact that **227a** displays the greatest IMDAF reactivity out of the five. Likewise, the calculated HOMO-LUMO energy gaps would suggest that dienophile halogenation (substrates **227e-h**) actually facilitates the IMDAF reaction more than furan halogenation (although this also should mildly facilitate the process according to the calculations) of the same inverse demand system (substrates **227b-d**). However, experimentally we found that substrates **227b-d** were more reactive than haloalkene counterparts **227e-h**.

Furthermore, and to expand on the above, our calculations showed that dihalogenation gives rise to a slightly further decreased HOMO-LUMO energy gap within substrates **227i-q**, which demonstrates an additive effect of combining both halogenations. However, experimentally we determined that dihalogenation is still inferior to furan halogenation alone.

Indeed, very similar experimental and FMO trends are found in the normal demand, *N*-Boc substrates **236a-e**, where the FMO energy gap is predicted to decrease for halogenated systems **236b-d**, even though the cycloaddition appears marginally faster in the non-halogenated substrate **236a**.

The ultimate conclusion of these FMO calculations is that dienophile halogenation decreases the HOMO-LUMO energy gap for all normal and inverse demand systems. They also appear to indicate that diene halogenation *increases* the FMO energy gap for normal demand systems and *decreases* it slightly for inverse demand systems. Our experimental observations largely do not correlate with these calculations and consequently we hypothesise that FMO interactions are *not* the most important factor in controlling these reactions.

This is consistent with less exothermic Diels-Alder reactions giving rise to less reactant-like transition states in accordance with Hammond's postulate. As demonstrated by Houk,[112] non-aromatic dienes are expected to participate in Diels-Alder process more exergonically than furan. As such, Hammond's postulate would thus predict that the transition state of our IMDAF reactions are less reactant-like in nature - a consequence of which is that the FMO energies of the diene and dienophile of the starting materials would be less predictive of reactivity in these cases.

3.2.3.2 Dipolar Interactions

An additional contributing factor that goes towards rationalising our results lies in dipolar interactions between the C-X and furan C-O bonds in the transition states for all haloalkene substrates. This dipolar interaction raises the energies of substrates **227f** and **236c**, where the dipoles are not aligned. Thus, the dipolar interaction would have the opposite effect in the other substrates, where the dipoles would be more aligned. Indeed, such a possibility is supported by the calculations (*Fig. 26*).

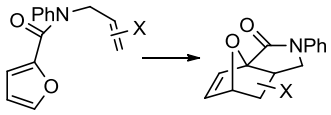
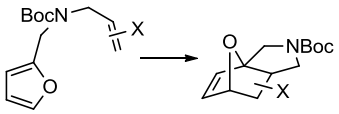
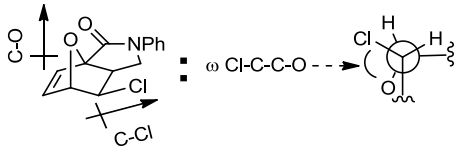
Reaction	ω Cl-C-C-O	Dipolar Orientational Term
Haloalkene 'Inverse Demand' Substrates		
		
227e → 231e (2-Cl)	160.14	-0.906
227f → 231f (*Z*-Cl)	86.95	0.068
227g → 231g (*E*-Cl)	160.8	-0.845
227h → 231h (2-Br)	-158.94	-0.902
Haloalkene *N*-Boc Substrates		
		
236c → 238c (*Z*-Cl)	85.08	0.084
236d → 238d (*E*-Cl)	-161.28	-0.894

Fig. 26: Cl-C-C-O Dihedral angles and corresponding orientational dipole terms for selected substrate transition state structures.

Using a simple approximation for the interaction of the two dipoles,[†] the orientational dependence of the dipolar interactions were calculated for the C-O and the dienophile C-X dipoles at the transition state structures.

[†]The dipolar orientational interaction term between the C-O and the dienophile C-X dipoles was calculated from the given formula (using the TS geometry): $f1(\theta A,\theta B,\omega) = \sin\theta A \sin\theta B \cos\omega - 2\cos\theta A \cos\theta B$, where: θA – angle between O-C-C, θB – angle between C-C-X, ω – dihedral angle X-C-C-O.



As can be seen, the calculated X-C-C-O dihedral angles in the transition states for reactions of **227f** and **236c** differ significantly from the other substrates, which leads to a notable difference in the dipolar interaction term. As a result, some repulsion is present in the structure of the transition states for the reactions of **227f** and **236c** which could potentially destabilise the transition state for both substrates. The transition states for transformations of **227e**, **227g**, **227h** and **236d** acquire a more attractive interaction which potentially stabilises the transition states, thus facilitating these IMDAF reactions.

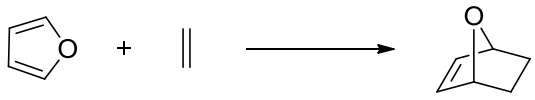
As detailed earlier in the experimental observations, both 2-bromoallyl substrates **227h** and **236e** undergo cycloaddition to a slightly greater extent than the corresponding 2-chloroallyl susbstrates **227a** and **236b** (and indeed any of the other chlorinated precursors) despite the fact that the bulky bromine atom is attached to a crowded tertiary centre. This demonstrates that steric influences alone do not account for these observations. Furthermore, however, neither does the above calculated dipolar interaction (in addition to positive charge stabilisation at the halogenated carbon in the transition state). All of these factors should be more significant for Cl-substituted systems and as such, it is yet to be elucidated as to why the brominated systems react marginally more rapidly than the chlorinated ones.

3.2.3.3 Thermochemical Data

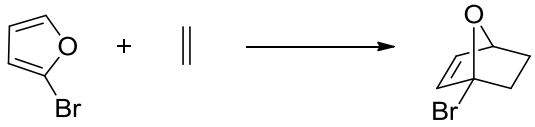
In addition to the HOMO-LUMO energy gap and transition state data, we also desired to calculate certain thermochemical data for our IMDAF reactions. The CBS set of methods of Petersson and co-workers was used to obtain the thermochemical data to a high degree of accuracy.[139] These methods are already known to be very accurate for thermochemical studies with the mean absolute deviation of around 1.1 kcal/mol for the CBS-QB3 model comparing to experimental data on G2/97 test set.[140] CBS methods are quantum chemistry composite methods that combine the results of several calculations in order to obtain high accuracies, which involves obtaining the desired energy values *via* extrapolation.

The specific extrapolation we used was the aforementioned CBS-QB3 model, which we identified as an excellent balance between computational cost and accuracy. This was ascertained by computational analyses of several benchmark systems involving intermolecular processes between furan/5-bromofuran and ethylene/chloroethylene (*vide infra*), where CBS-QB3 was compared against the CBS-

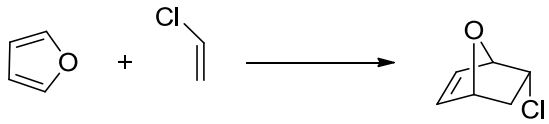
4M and B3LYP (6-31g(*d*)) models and was overall found to be the most accurate (*Fig. 27*). The energies were calculated for two temperatures: 298K and 383K (the temperature at which the experimental IMDAF reactions were conducted at).



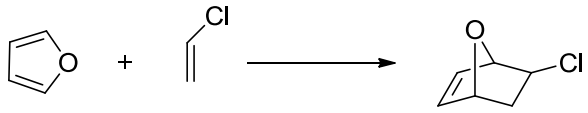
Thermochemical Data	Temperature (K)	DFT-B3LYP 6-31G(*d*)	CBS-4M	CBS-QB3
$\Delta_r H°$	298.15	-5.25	-13.9	-12.2
	383.00	-5.4	-14.0	-12.35
$\Delta_r G°$	298.15	8.6	-0.3	1.6
	383.00	12.5	3.65	5.5
$\Delta_{activ} H$	298.15	25.85	17.9	20.5
	383.00	25.85	15.5	20.5
$\Delta_{aciv} G$	298.15	38.8	30.85	33.35
	383.00	42.4	41.2	36.0



Thermochemical Data	Temperature (K)	DFT-B3LYP 6-31G(*d*)	CBS-4M	CBS-QB3
$\Delta_r H°$	298.15	-9.6	-20.4	-17.2
	383.00	-9.7	-20.5	-17.3
$\Delta_r G°$	298.15	4.4	-6.6	-3.3
	383.00	8.4	-2.7	0.7
$\Delta_{activ} H$	298.15	24.4	4.3	18.3
	383.00	23.6	4.3	18.4
$\Delta_{aciv} G$	298.15	37.3	17.3	31.3
	383.00	41.0	21.1	35.0



Thermochemical Data	Temperature (K)	DFT-B3LYP 6-31G	CBS-4M	CBS-QB3
$\Delta_r H°$	298.15	-4.1	-15.1	-13.3
	383.00	-4.2	-15.1	-13.4
$\Delta_r G°$	298.15	10.4	-0.7	1.1
	383.00	14.5	3.4	5.2
$\Delta_{activ} H$	298.15	27.2	17.4	19.8
	383.00	27.3	17.4	19.9
$\Delta_{aciv} G$	298.15	40.7	31.0	33.3
	383.00	44.6	34.9	37.1

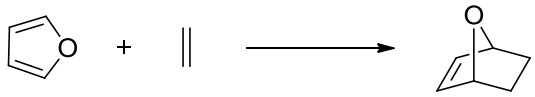


Thermochemical Data	Temperature (K)	DFT-B3LYP 6-31G(*d*)	CBS-4M	CBS-QB3
$\Delta_r H°$	298.15	-3.8	-14.6	-12.8
	383.00	-3.9	-14.6	-12.9
$\Delta_r G°$	298.15	10.7	-0.3	1.6
	383.00	14.8	3.8	5.7
$\Delta_{activ} H$	298.15	27.9	18.2	20.8
	383.00	28.0	18.3	20.8
$\Delta_{aciv} G$	298.15	41.5	31.9	34.2
	383.00	45.3	35.8	38.1

Fig. 27: Thermochemical data (kcal mol^{-1}) of benchmark Diels-Alder reactions comparing CBS-QB3, CBS-4M and DF-B3LYP (6-31g) methods.*

Additionally, the CBS-QB3 method was also compared with the extremely accurate W1BD model (which includes extended one-particle correlation extrapolation) in the simplest Diels-Alder reaction between furan and ethylene at room temperature (*Fig. 28*). The difference between free energies of the reaction obtained for W1BD and CBS-QB3 models is only 0.9 kcal/mol and around 3 kcal/mol for activation energies.

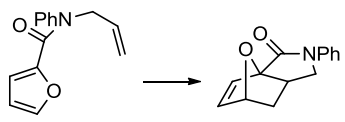
However, the computational time of the W1BD method for this reaction is approximately 3000 times greater than the CBS-QB3 model (which takes approximately 1000 CPU hours to calculate a thermochemical value for our IMDAF systems). Thus, it was concluded that the CBS-QB3 model provides an excellent balance between computational cost and accuracy for the IMDAF reactions.



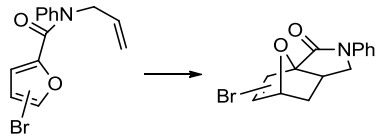
Thermochemical Data	CBS-QB3	W1BD
$\Delta_r H°$	-12.2	-11.3
$\Delta_r G°$	1.6	2.5
$\Delta_{activ} H$	20.5	24.1
$\Delta_{aciv} G$	33.35	36.9

Fig. 28: Thermochemical data (kcal mol^{-1}) of furan plus ethylene Diels-Alder reaction comparing the CBS-QB3 and W1BD models at room temperature.

With the computational method now selected, a series of calculations were conducted on each of our IMDAF reactions to afford the desired thermochemical data, which is compiled in *Fig. 29* (*vide infra*).

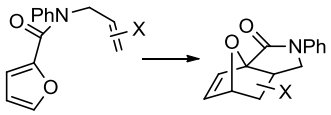
Reaction	**$\Delta_r H°$**	**$\Delta_r G°$**	**$\Delta_{activ} H$**	**$\Delta_{activ} G$**
		(kcal mol^{-1})		
Non-halo 'Inverse Demand' Substrate				
				
227a → 231a	-10.6	-5.2	19.4	23.8

Bromofuran 'Inverse Demand' Substrates



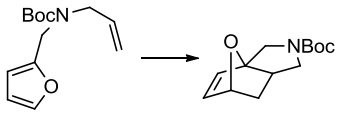
227b → 231b (5-Br)	-14.6	-9.1	17.9	22.4
227c → 231c (4-Br)	-14.0	-8.7	17.6	21.7
227d → 231d (3-Br)	-14.0	-8.1	16.4	21.3

Haloalkene 'Inverse Demand' Substrates



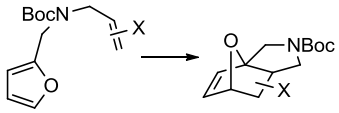
227e → 231e (2-Cl)	-9.6	-4.0	20.5	25.0
227f → 231f (*Z*-Cl)	-12.1	-5.3	18.1	23.9
227g → 231g (*E*-Cl)	-11.6	-5.9	19.4	23.9
227h → 231h (2-Br)	-9.9	-4.3	20.4	25.0

Non-halo *N*-Boc Substrate



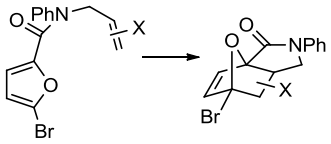
236a → 238a	-8.2	-2.7	19.9	24.5

Haloalkene *N*-Boc Substrates



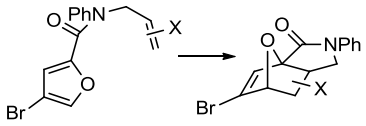
236b → 238b (2-Cl)	-8.2	-2.4	20.4	25.2
236c → 238c (*Z*-Cl)	-8.4	-2.7	20.0	24.7
236d → 238d (*E*-Cl)	-7.2	-0.1	21.5	27.6
236e → 238e (2-Br)	-8.6	-3.1	20.1	25.2

5-Bromofuran Dihalo 'Inverse Demand' Substrates



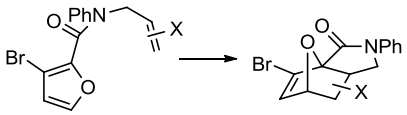
227i → 231i (2-Cl)	-13.5	-7.7	18.8	23.4
227j → 231j (*Z*-Cl)	-13.7	-8.0	18.4	22.9
227k → 231k (*E*-Cl)	-14.9	-9.2	20.6	21.6

4-Bromofuran Dihalo 'Inverse Demand' Substrates



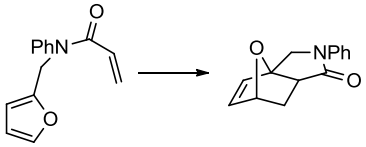
227l → 231l (2-Cl)	-13.0	-7.3	18.7	23.4
227m → 231m (*Z*-Cl)	-14.4	-8.6	17.7	22.4
227n → 231n (*E*-Cl)	-13.8	-7.9	17.6	22.6

3-Bromofuran Dihalo 'Inverse Demand' Substrates



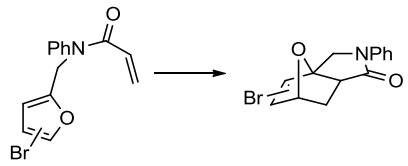
227o → 231o (2-Cl)	-12.6	-6.2	18.7	24.0
227p → 231p (*Z*-Cl)	-15.3	-10.1	15.6	19.7
227q → 231q (*E*-Cl)	-14.6	-8.5	16.2	21.4

Non-halo 'Normal Demand' Substrate



239a → 241a	-17.2	-9.9	15.6	21.8

Bromofuran 'Normal Demand' Substrates



239b → 241b (5-Br)	-20.7	-14.5	15.0	19.9
239c → 241c (4-Br)	-19.8	-13.7	14.5	19.1
239d → 241d (3-Br)	-18.8	-12.8	14.7	19.5

Fig. 29: Thermochemical data (kcal mol^{-1}) for IMDAF reactions.

Comparison between the calculated thermodynamic and experimental data is somewhat complicated by decomposition of several of the adducts at the extended reaction times (typically a number of days) sometimes needed for the reactions to go to completion. All of the IMDAF reactions studied are predicted to be exergonic in nature (even if only just, in the case of substrate **236d**). However, there are significant variations in both the activation and overall reaction free energies.

Generally, reactions which were calculated to have higher activation energies have been predominantly demonstrated to have lower conversions. However, a quantitative correlation between activation energy and yield was not identified.

Fig. 30 displays a scatter-plot graph of the Gibbs free energies of reactions for the different classes of substrate (*vide infra*). The various classes are colour coded; black representing non-halogenated systems, red for bromofuran systems, blue for haloalkene systems and yellow for dihalogenated systems. As is shown visually, the bromofuran substrates **227b-d** and **239b-d** all exhibit more exergonic reactions than their corresponding non-halogenated analogues, in addition to all haloalkene substrates **227e-h** and **236b-d**. Furthermore, the exergonicities of reactions involving the dihalo substrates **227i-q** are also greater than the haloalkene substrates, exhibiting a larger spread in comparison to the corresponding bromofuran substrates **227b-d**.

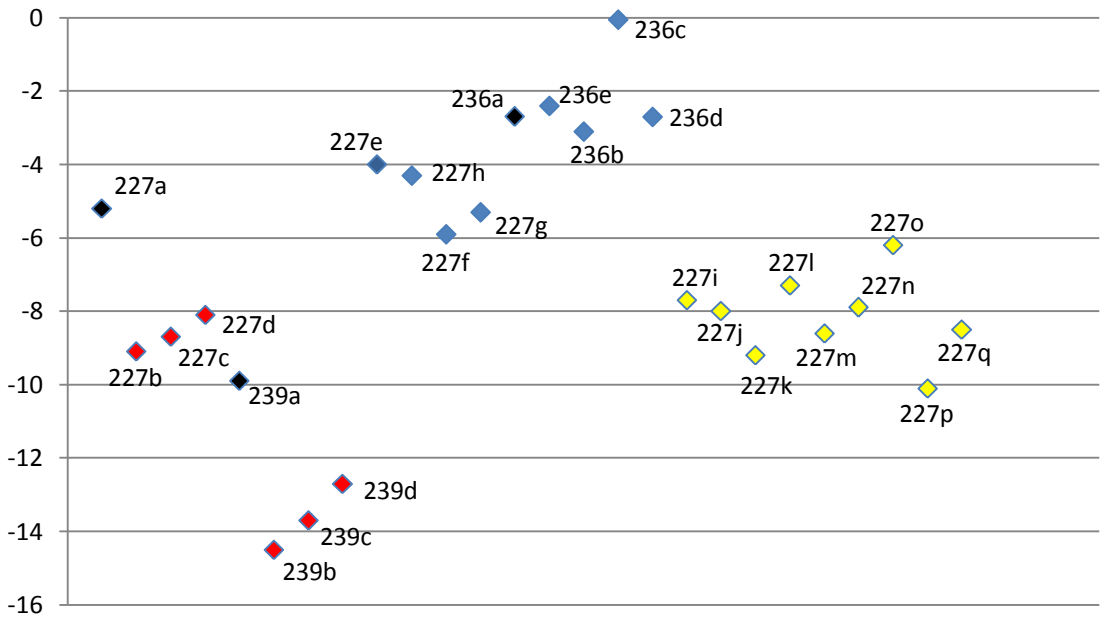


Fig. 30: Scatter plot of Gibbs free energies of reaction (kcal mol^{-1}) for all IMDAF reactions.

Additionally, the plot for activation barriers follows a similar trend (*Fig. 31*). Bromofuran substrates **227b-d** and **239b-d** possess lower activation barriers for cycloaddition than those with halogenated dienophiles (**227e-h** and **236b-e**) which lie between 23.9 and 27.5 kcal mol^{-1}. In turn, dihalogenated substrates **227i-q** have activation barriers that are more intermediate in value. Substrate **227p**, with a low calculated activation energy is rather anomalous, as it experimentally reacts similarly to other typical dihalogenated substrates.

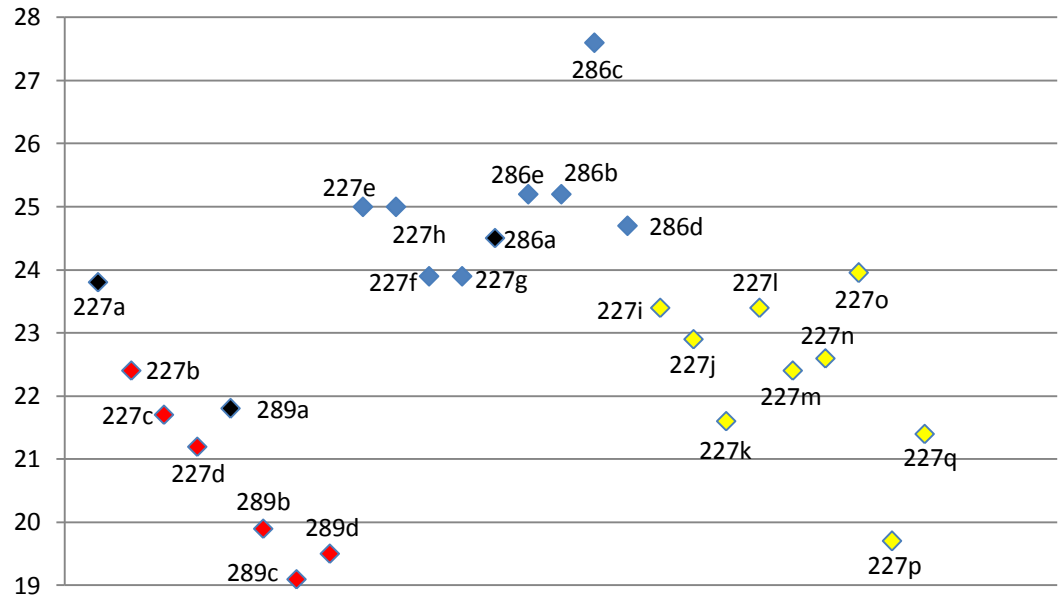


Fig. 31: Scatter plot of Gibbs free energies of activation (kcal mol^{-1}) for all IMDAF reactions.

3.2.3.4 Lateness of Transition States

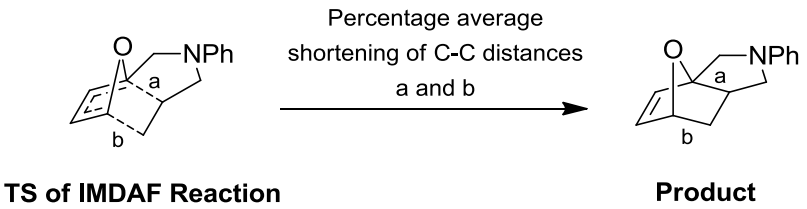
Finally, in order to further investigate the validity of our hypothesis from the previous studies on possible FMO effects, we embarked on quantifying the 'product-likeness' of the transition states in terms of the fractional shortening of the newly forming C-C σ-bonds in moving from transition state to product (*Fig. 32*).

Once again, a similar trend to that seen in both the activation and free energy plots is observed (*Fig. 33*). Thus, the more exothermic the reactions, the earlier their transition states, so that the percentage contraction of the C-C distance in going from transition state to product is greater. Conversely, those reactions that exhibit a lower percentage contraction are predicted to be less exergonic, consistent with later transition states. This data is thus supportive of our earlier conclusions on FMO energies (which do *not* correlate with the reactivities we observe).

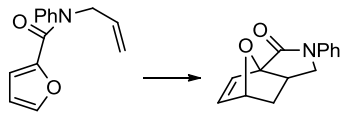
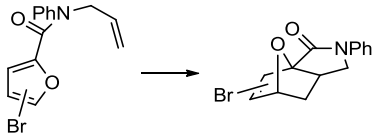
Additionally, a plot of $\Delta_{activ}G$ *vs* $\Delta_rG°$ was constructed for all substrates and is illustrated in *Fig. 34*. A line of best fit for the corresponding data points reveals a gradient of 0.55, which suggests that the transition state does not resemble the reactants, in accordance with the Leffler equation (*Fig. 35*).[141] The equation assumes that the

transition state is a linear, weighted sum of the starting material and product, with the Leffler paramater (α) determining how product-like or otherwise the transition state is. A gradient closer to 1 would represent a transition state more closely resembling the products. Thus, although we can deduce that the transition state is not early in nature, we can also conclude that is neither late.

Thus, FMO energies are likely to make less important contributions to the transition state energies for reactions with later transition states than is usual for Diels-Alder cycloadditions,[142] such as the IMDAF reactions we conducted.

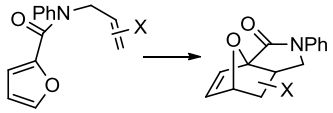


TS of IMDAF Reaction **Product**

	Transition State		Product		
Reaction	**C-C Distance a**	**C-C Distance b**	**C-C Bond Length a** (Å)	**C-C Bond Length b**	**Average %age change from TS**
Non-halo 'Inverse Demand' Substrate					
 **227a → 231a**	2.029	2.178	1.558	1.571	-25.55
Bromofuran 'Inverse Demand' Substrates					
 **227b → 231b** (5-Br)	2.044	2.199	1.558	1.565	-26.30

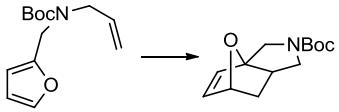
227c → 231c (4-Br)	2.053	2.179	1.556	1.568	-26.13
227d → 231d (3-Br)	2.004	2.227	1.555	1.570	-25.95

Haloalkene 'Inverse Demand' Substrates



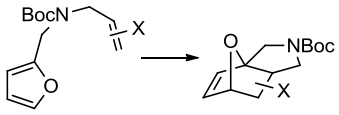
227e → 231e (2-Cl)	2.064	2.153	1.563	1.570	-25.67
227f → 231f (*Z*-Cl)	2.067	2.152	1.562	1.570	-25.74
227g → 231g (*E*-Cl)	1.995	2.225	1.557	1.569	-25.73
227h → 231h (2-Br)	1.987	2.231	1.555	1.570	-25.68

Non-halo *N*-Boc Substrate



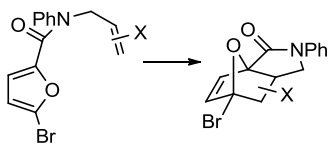
236a → 238a	2.095	2.111	1.576	1.572	-25.17

Haloalkene *N*-Boc Substrates



236b → 238b (2-Cl)	2.137	2.076	1.581	1.570	-25.19
236c → 238c (*Z*-Cl)	2.061	2.137	1.574	1.570	-25.08
236d → 238d (*E*-Cl)	2.067	2.146	1.574	1.570	-25.34
236e → 238e (2-Br)	2.139	2.077	1.579	1.571	-25.29

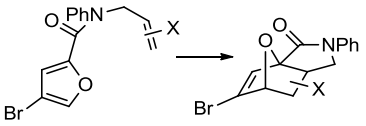
5-Bromofuran Dihalo 'Inverse Demand' Substrates



227i → 231i (2-Cl)	2.079	2.165	1.563	1.565	-26.26

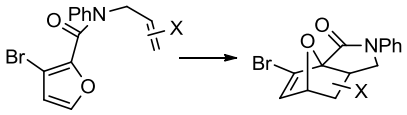
227j → 231j (*Z*-Cl)	1.950	2.332	1.553	1.583	-26.25
227k → 231k (*E*-Cl)	2.031	2.235	1.554	1.572	-26.56

4-Bromofuran Dihalo 'Inverse Demand' Substrates



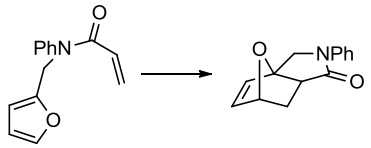
227l → 231l (2-Cl)	2.095	2.146	1.562	1.566	-26.23
227m → 231m (*Z*-Cl)	2.016	2.222	1.554	1.567	-26.17
227n → 231n (*E*-Cl)	1.986	2.253	1.552	1.570	-26.08

3-Bromofuran Dihalo 'Inverse Demand' Substrates



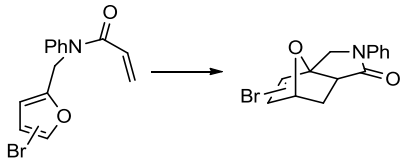
227o → 231o (2-Cl)	2.086	2.150	1.565	1.566	-26.08
227p → 231p (*Z*-Cl)	1.962	2.278	1.554	1.569	-25.97
227q → 231q (*E*-Cl)	1.968	2.275	1.553	1.570	-26.04

Non-halo 'Normal Demand' Substrates



239a → 241a	2.035	2.223	1.556	1.569	-26.50

Bromofuran 'Normal Demand' Substrate



239b → 241b (5-Br)	2.056	2.241	1.556	1.563	-27.30

239c → 241c (4-Br)	2.061	2.221	1.553	1.566	-27.06
239d → 241d (3-Br)	2.022	2.259	1.553	1.567	-26.91

Fig. 32: Calculated transition state and product C-C bond distances for all systems, including the % C-C bond contraction.

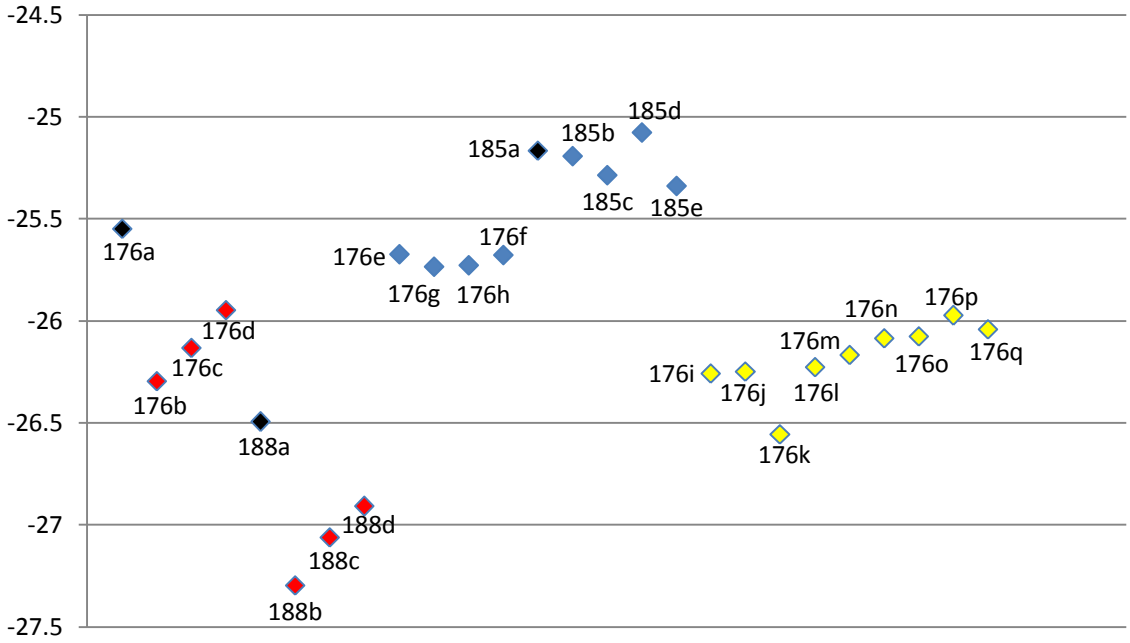


Fig. 33: Scatter plot of percentage change in C-C bond distances from transition state to product for all IMDAF reactions.

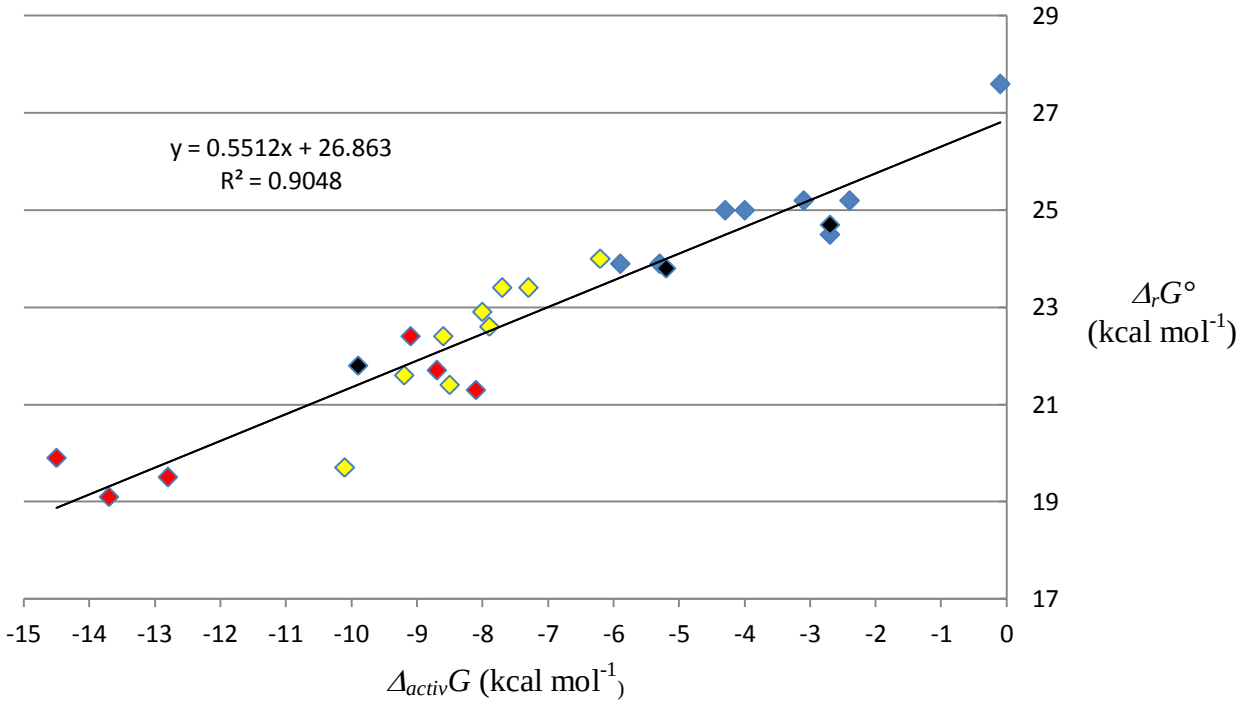


Fig. 34: A plot of $\Delta_{activ}G$ vs $\Delta_rG°$ for all reactions.

$$\partial G^{\ddagger} = \alpha \partial G°_{XP} + (1- \alpha)\partial G°_{XR} \qquad (1)$$

$$\partial G^{\ddagger} - \partial G°_{XR} = \alpha(\partial G°_{XP} - \partial G°_{XR}) \qquad (2)$$

Let $\Delta G^{\ddagger} = G^{\ddagger} - G°_{XR}$ and $\Delta G^{\circ}_{R} = G^{\circ}_{XP} - G°_{XR}$

Therefore $\partial\Delta G^{\ddagger} = \partial G^{\ddagger} - \partial G°_{XR}$ and $\partial\Delta G^{\circ}_{R} = \partial G^{\circ}_{XP} - \partial G°_{XR}$

Substituting for $\Delta G^{\ddagger}$ and ΔG°_{R} into Equation (2) gives:

$$\partial\Delta G^{\ddagger} = \alpha\, \partial\Delta G^{\circ}_{R} \qquad (3)$$

Fig. 35: The Leffler equation (3).

3.2.4 SUMMARY

The effect of both furan and dienophile halogenations in IMDAF reactions has been investigated and it appears both have profound but *opposing* effects. Specifically, it has been identified that (in agreement with the literature; both experimental and theoretical) halogenation of the furan is beneficial to the process, irrespective of the electronic effects of the other furan and dienophile substituents. Halogenation of the dienophile, on the other hand, was identified to hinder reactions in comparison to the corresponding non-halogenated dienophiles in all cases studied.

Additionally, FMO effects do not appear to have a huge influence on these reactions, and the observed experimental results have been attributed to a combination of positive charge stabilisation, simple steric effects and a contribution from a dipolar interaction between the furan C-O and the dienophile C-X dipoles, as supported by computational studies.

The detrimental effect of having a halogen present on the dienophile can be overcome in many cases by halogenating the diene. Thus, the use of dihalogenated substrates could provide a means of overcoming the effect of dienophile halogenations, leading to synthetically useful yields of highly functionalised cycloadducts with considerable potential for further transformation.

4. THE EFFECT OF NITRO AND ACYL GROUPS

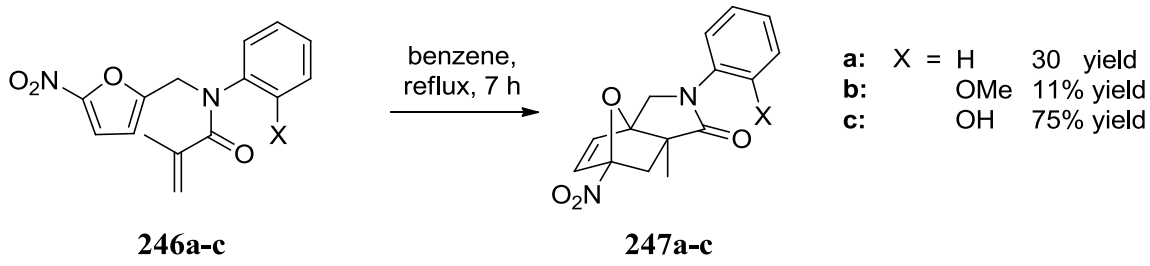
4. THE EFFECT OF NITRO AND ACYL GROUPS

In addition to investigating the effect that halogen substitution has on Diels-Alder reactions of furan, we also elected to study the effects that nitro and acyl groups (separately) have on the reaction when attached to the furan ring.

4.1 NITRO GROUPS

4.1.1 INTRODUCTION

The reactivity of nitrofuran substrates in IMDAF processes has previously been demonstrated in the literature by Mukaiyama and Takebayashi.[143] They recorded that upon heating substrates **246**, the phenol variant formed the corresponding adduct in the greatest yield by a considerable margin (*Scheme 124*).



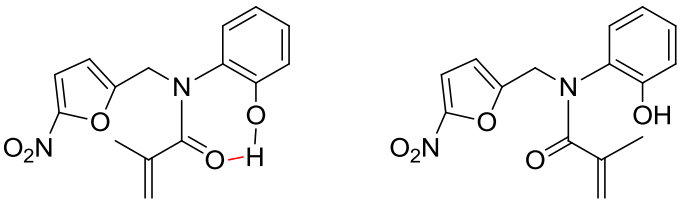
246a-c **247a-c**

Scheme 124: Findings of Mukaiyama and Takebayashi.

They attributed the increased reactivity of **246c** to an intramolecular H-bonding interaction between the phenolic proton and the oxygen of the amide moiety. This holds the molecule in a more reactive *s-cis* conformation as opposed to the alternative *s-trans* rotamer (*Fig. 36*). The methoxy and unsubstituted analogues **221a-b** cannot impart such an interaction and are thus less reactive.

Unfortunately, however, no comparison was made to systems where the nitro group was absent. As such, no conclusions can be made from this study on the effect the nitro group itself has on the IMDAF reaction. Nevertheless, the effect itself was a useful discovery and as such the authors went on to exploit this control by internal

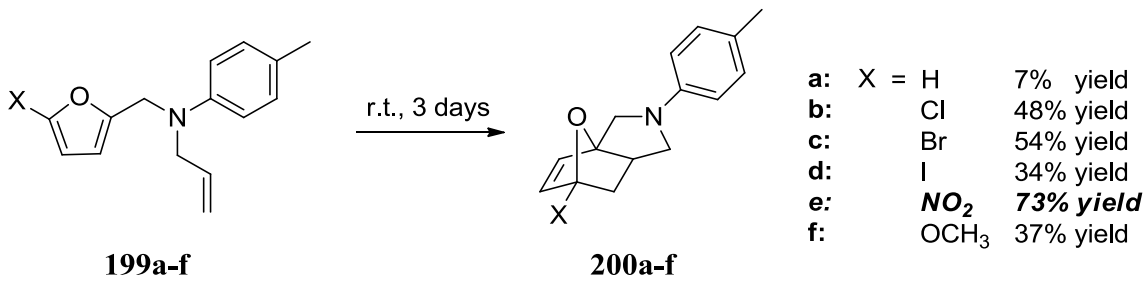
interaction in future endeavours through introducing Mg salts to similar systems.[144] In this work, the Mg 2+ cation from said salts chelates the two oxygen atoms (instead of H-bonding to one another) and thus facilitates the IMDA reaction to an even greater extent, resulting in an increase in efficiency compared to when the Mg is absent.



246c *s-cis* **246c** *s-trans*

Fig. 36: Different conformations of **221c**, *s-cis being preferred due to an intermolecular H-bond.*

Evidence for nitro substitutents themselves actually facilitating the Diels-Alder reaction also have literature precedence. In fact, Klepo and Jakopcic (*vide supra* - chapter three, p. 69) made such observations in the same set of work which identified halogens promoting the same process.[109] Furthermore, they noted that out of the intramolecular systems studied, 5-nitro substrate **199e** was actually the most reactive towards the IMDAF process. A recap of their findings (including that of 5-nitro substrate **199e**) is displayed below, detailing the adduct yield that greatly surpassed that of the halogen examples (*Scheme 125*).



199a-f **200a-f**

Scheme 125: Findings of Klepo and Jakopcic, including transformation of 5-nitro substrate **199e**.

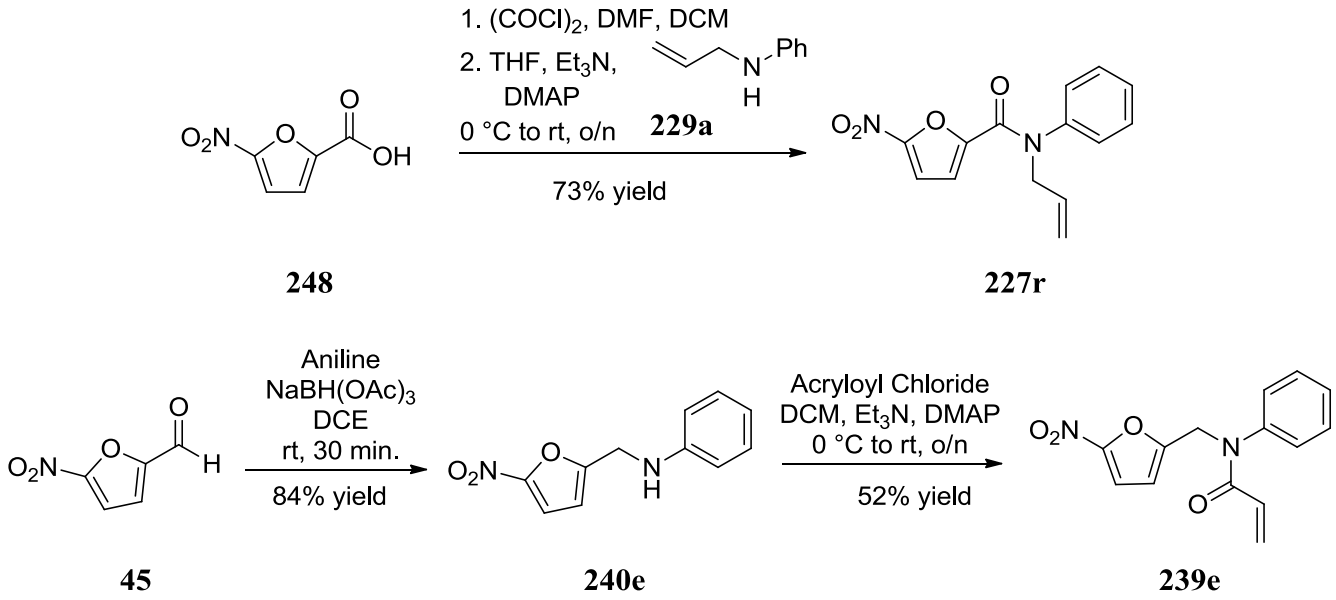
Additionally, the authors noted that 5-methoxy substrate **199f** also underwent the IMDAF reaction better than non-substituted analogue **199a**, which the authors reasonably attributed to the electron donating effect this group imparts on a seemingly 'normal' demand Diels-Alder system.

However, they also conceded that no firm conclusions could be made regarding the IMDAF facilitation imparted by the nitro group, which can only exhibit electron *withdrawing* properties on an otherwise identical system to that of methoxy substrate **199f**. One possible explanation is that the presence of nitro group has resulted in an inverse demand process.

4.1.2 RESULTS AND DISCUSSION

With these findings in mind, accompanied with the mystery regarding the true nature of the electron demand in the conversion of **199e**, we initially sought to highlight any differences in reactivity between two related, nominally 'normal' and 'inverse' demand systems.

As such, we turned towards synthesising systems analagous to those which we prepared to study the halogen effects, thus we elected to synthesise 'inverse' demand substrate **227r** and 'normal' demand substrate **239e** (*Scheme 126*). Both compounds were obtained *via* methods adopted previously in chapter three.[106,133]



Scheme 126: Syntheses of substrates **227r** *and* **239e**.

Note that as before, the terms 'inverse' and 'normal' demand are purely a reflection of the orientation of the amide carbonyl functionality within the molecule and not an indication of the HOMO-LUMO interaction involved in the reaction. With both substrates in our possession, we subjected each of them to the same IMDAF conditions to which we previously exposed their structural analogues (as in chapter 3). The findings are shown below, including a recap of the obtained results for substrates **227a** and **239a**, the non-substituted analogues of of the nitro substrates (*Fig. 37*).

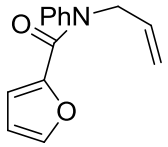
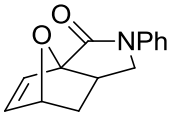
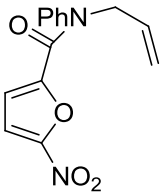
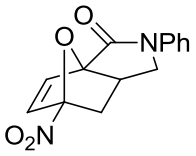
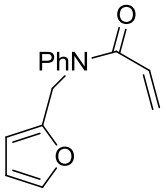
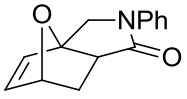
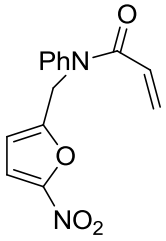
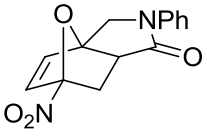
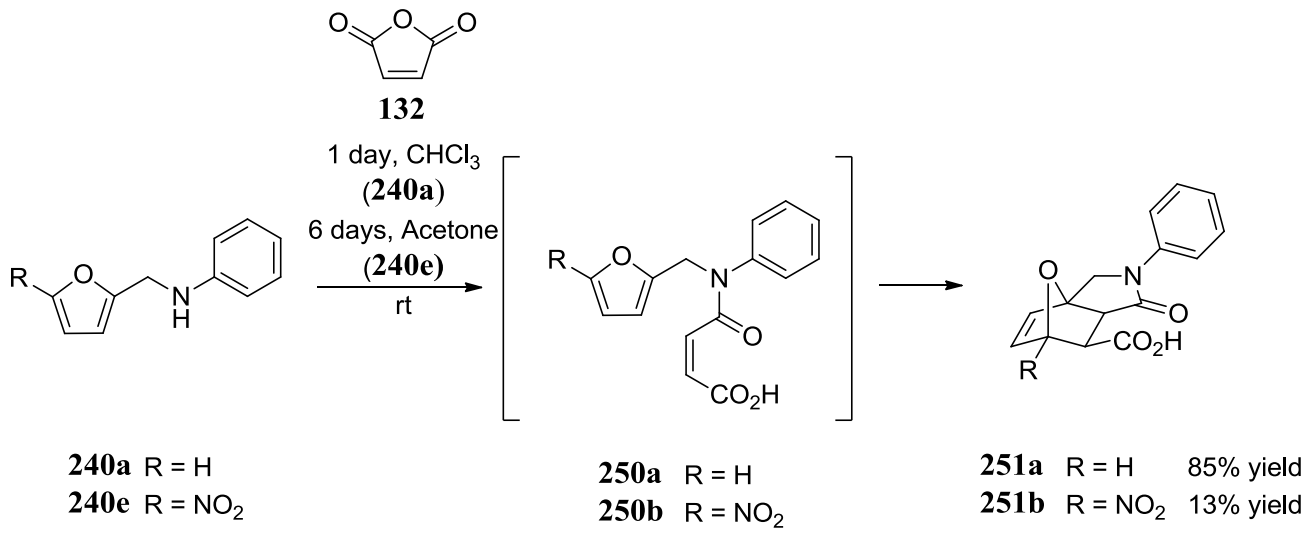
Precursor	Cycloadduct	Time/h	Ratio Adduct:S.M.	Yield %
		24	86:14	62
227a	**231a**			
		1.5	100:0	100
227r	**231r**			
		24	93:7	70
239a	**241a**			
		24	100:0	100
239e	**241e**			

Fig. 37: Summary of results for transformation of both 5-nitro substrates into their corresponding adducts.

Our findings indicate that in both the normal and inverse demand scenarios, 5-nitro substitution is beneficial to the reaction, with complete conversions and quantitative recoveries of adducts **231r** and **241e**. In addition, substrate **227r** appears to be more reactive than than **239e**, reaching complete conversion in just 1.5 hours. This may indicate that, in this case, the reaction is indeed inverse demand, as both electron withdrawing moieties are adjacent to the furan. Substrate **239e** has an electron withdrawing group on both the dienophile and diene components, which might suggest lower reactivity. However, a superior conversion and yield in comparison to the non-substituted analogue **239a** was observed.

To try and further investigate the effects of combining two electron deficient components, we elected to form substrates **250a** and **250b** by reacting amines **240a** and **240e** with maleic anhydride (**132**). An electron-deficient dienophile moiety would thus be present on both substrates after the addition of the corresponding amine to maleic anhydride. We envisaged that these substrates could potentially undergo IMDAF reactions *in situ* to afford adducts **251a** and **251b** (*Scheme 127*).



Scheme 127: Formation of **251a** *compared to that of* **251b**.

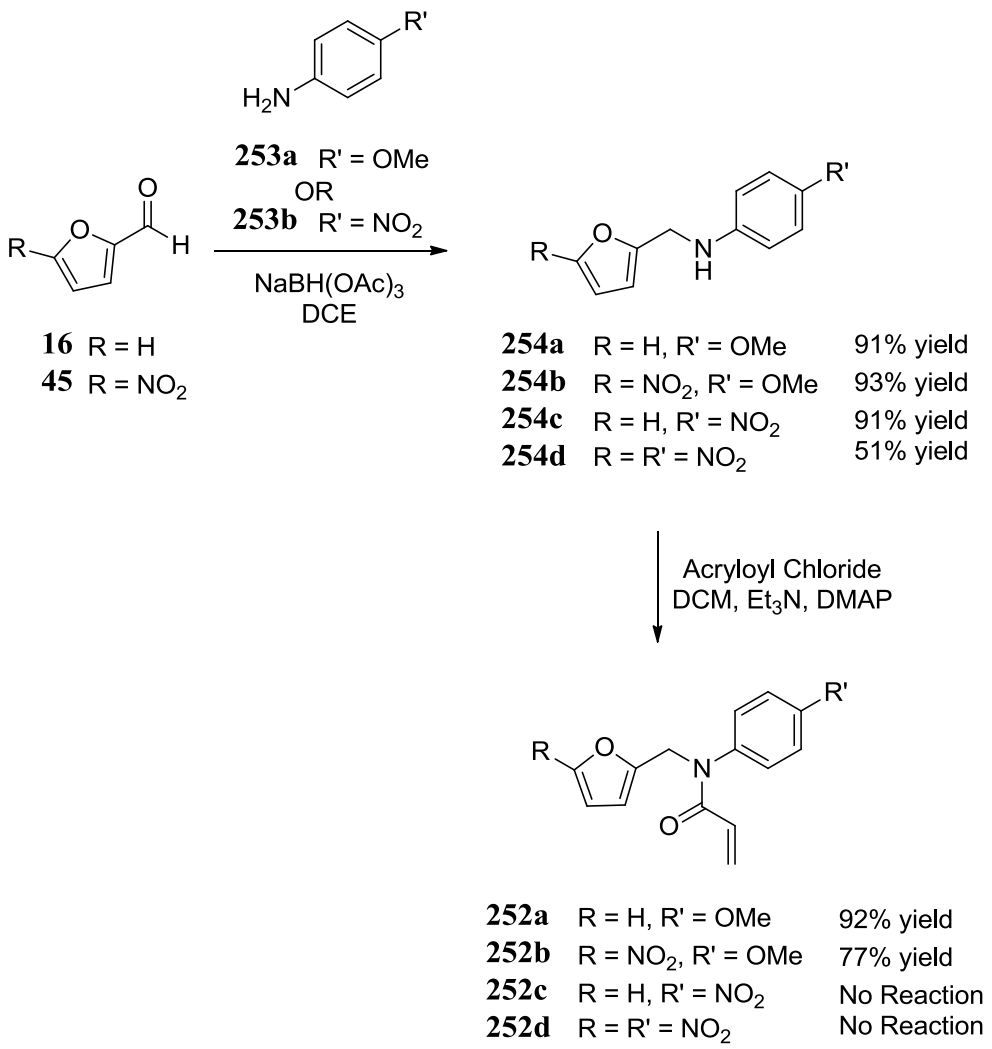
Although no detailed NMR study was conducted (as clearly the formation of **251b** was slower than that of **251a**), we observed that shortly after combination of the reactants, **240a** quickly formed the substrate **250a** and soon after adduct formation was visible.

Amine **240e**, however, was slow to initially react. This was not at all surprising given the diminished nucleophilicity one would expect compared to **240a**, caused by the presence of the highly electron-withdrawing nitro group. Furthermore, it could be seen that formation of adduct **251b** itself was progressing more slowly than that of the non-nitro analogue. Conducting the eventual conversion of **240e** into **251b** in acetone as opposed to chloroform resulted in a slightly better yield.

Again, this was not a surprise to us given that the reaction is taking place between two very electron deficient Diels-Alder components. On the contrary, we were actually impressed that the adduct even formed at all given such electronic circumstances.

In addition to altering components directly attached to the dienophile of these substrates, we elected to try and investigate any changes to the IMDAF reactions upon having either an electron donating or withdrawing moiety attached to the phenyl ring. As such, we attempted to synthesise compounds **252a-d** (*Scheme 128*).

Once again, the reductive amination procedures used previously were adopted (chapter 3), except that aniline was replaced by its *p*-methoxy (**253a**) and *p*-nitro (**253b**) analogues. All required amines were obtained in generally high yields, the exception being amine **254d**, where both electron deficient components were combined.



Scheme 128: Attempted formation of substrates **252a-d**.

The electron-withdrawing nature of the *p*-nitro aniline substituent also unfortunately prevented us synthesising desired substrates **252c** and **252d**. Presumably, the secondary amine has lost too much of its nucleophilicity to react with acryloyl chloride in both these cases. However, we did succesfully generate *p*-methoxy substrates **252a** and **252b**, as no such issue could arise here. As such, both substrates were subjected to the IMDAF conditions familiar to us (*vide supra*), the findings of which are visualised below in *Fig. 38*.

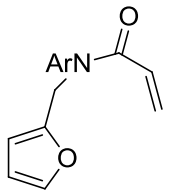
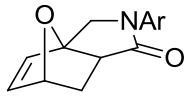
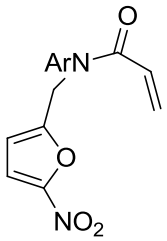
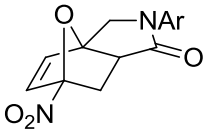
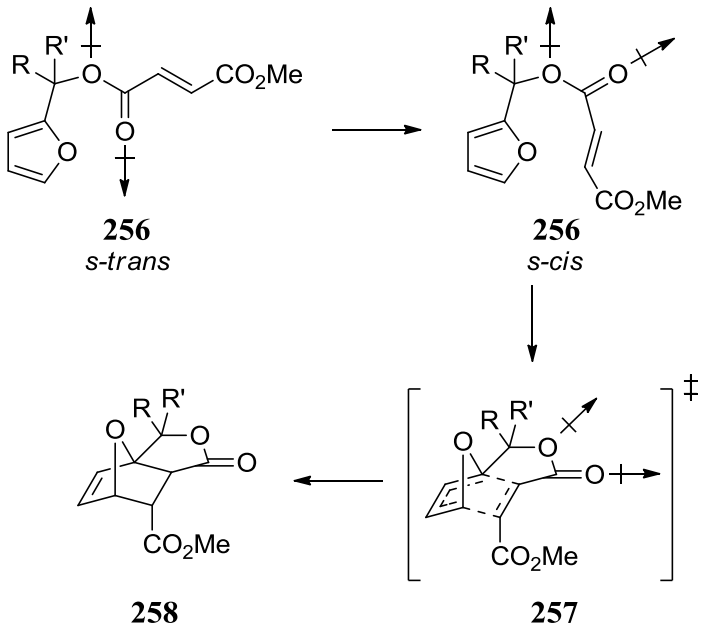
Precursor	Cycloadduct	Time/h	Ratio Adduct:S.M.	Yield %
 **252a**	 **255a**	18	66:34	53
 **252b**	 **255b**	18	89:11	86

Fig. 38: Findings of IMDAF reactions on substrates **252a** *and* **252b** *after 18h at reflux in toluene. N.B. Ar = 4-MeO-phenyl*

The nitro substrate appears to be more reactive than its non-substituted counterpart, having converted to its adduct much more in the same time frame. We also observed that after only one hour, **252a** had converted by 13% to **255a**, whereas **252b** had converted by 19% to **255b**. The electron-donating effect imparted onto the system by the methoxy moiety does not appear to have a profound effect on proceedings. It remains to be seen if the equivalent *p*-nitro aniline systems would likewise be largely unaffected by the *p*-phenyl substituent.

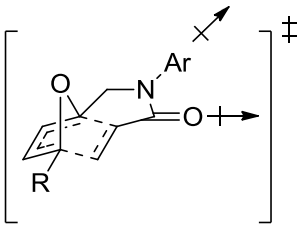
In addition to having mild electronic effects on the dienophile functionality, it was thought that the methoxy and nitro substituents present on the aryl moiety may also play a role in a dipolar transition state. On this note, Jung and Gervay demonstrated that polar solvents can affect the rates of IMDAF reactions should the transition state of such processes be sufficiently polar.[35] In the case of ester-tethered substrate **256**, the transition state (**257**) necessary in order to afford adduct **258** can only arise when an *s-cis* conformation exists around the amide functionality (*Scheme 129*). A result of this is an overlap of dipoles which causes the transition state to be more polar than the starting material. As such, more polar solvents should stabilise this transition state and thus facilitate the IMDAF reaction. Indeed, this is what the authors observed.



Scheme 129: Necessary s-cis conformation of **256** *to give rise to T.S.* **257**, *resulting in a more polar molecule than the starting material and preferred conformation.*

They noted that changing the solvent from toluene (ε_r = 2.38) to acetonitrile (ε_r = 37.5) in the above systems resulted in a significant increase in reaction rate, while a greater still increase was observed in the case of DMSO (ε_r = 46.7) acting as the reaction solvent. These observations are in agreement with the explanation involving dipolar transition-states provided by Jung and Gervay.

As such, we surmised that solvents of different polarity would perhaps have an effect on the reaction rates for the transformation of substrates **252a** and **252b** into their corresponding adducts due to a similar overlap of dipoles, arising from our substrates having to adapt a likewise confromation in order to form transition state **259** (*Fig. 39*).



259

Fig. 39: Dipole overlap in transition state **259**, *which could be stabilised by more polar solvents.*

In order to study this potential dipolar effect, we elected to conduct the IMDAF reactions on both substrates at 80 °C in both toluene and acetonitrile over a set time frame (*Fig. 40*). Conversions were still better overall in any given solvent for the conversion of **252b**, which is in accordance with the previous observations.

Increased conversions over the 16 hour period were observed in both substrates upon changing the solvent to acetonitrile. However, these changes were marginal, particularly given the drastic differences in relative permittivity between toluene and acteonitrile ($\varepsilon_r = 2.38$ *vs.* $\varepsilon_r = 37.5$). As such, we are unable to conclude from this data that there may be a dipolar transition state for these reactions.

4.1.3 SUMMARY

In summary, for systems where the dienophile is not extremely electron deficient, the presence of a nitro group on the furan appears to facilitate IMDAF reactivity. Indeed, nitrated furans still react with dienophiles that are very electron deficient (albeit not as well as non-nitrated analogues), which is most surprising given the electron deficient nature of both components. Furthermore, no conclusions about solvent effects can be made regarding these reactions at present.

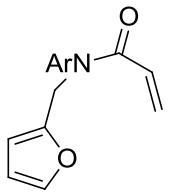
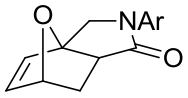
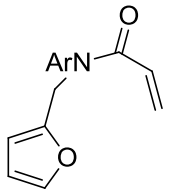
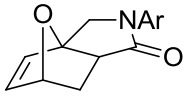
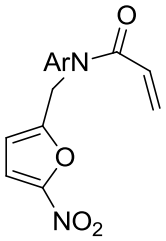
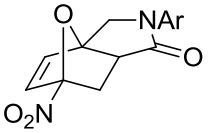
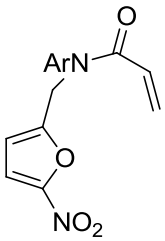
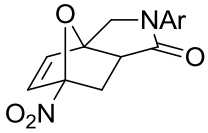
Precursor	Cycloadduct	Time/h	Ratio Adduct:S.M.	Solvent
 **252a**	 **255a**	16	11:89	Toluene
 **252a**	 **255a**	16	19:81	Acetonitrile
 **252b**	 **255b**	16	17:83	Toluene
 **252b**	 **255b**	16	22:78	Acetonitrile

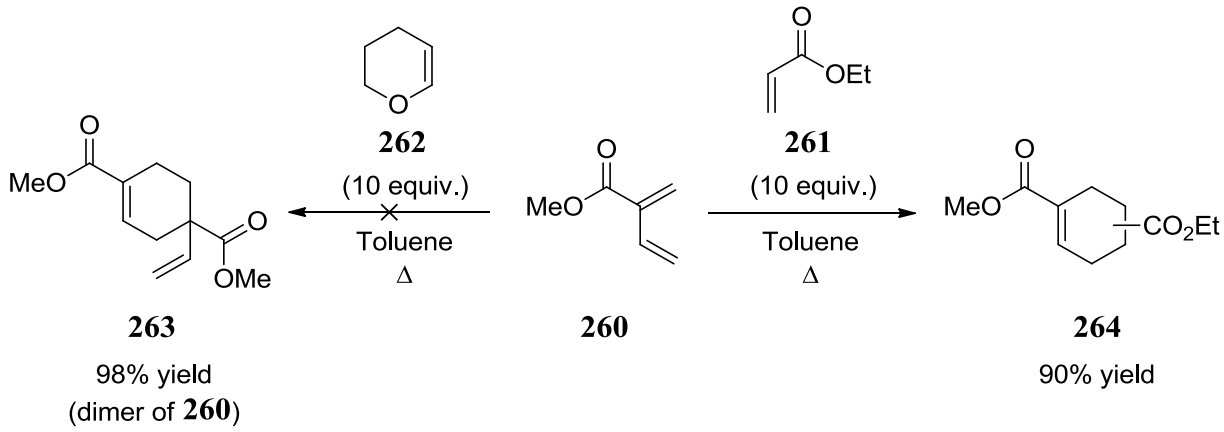
Fig. 40: Comparison of IMDAF reactions in toluene and acetonitrile. Reactions conducted at 80 °C in all cases.

4.2 ACYL GROUPS

4.2.1 INTRODUCTION

Literature precedence indicating the interesting reactivity of 2-carbomethoxy-1,3-butadiene (**260**) was one of the factors for prompting our investigations into acyl substitution (*Scheme 130*).[145] The authors identified that **260** reacts well with electron-

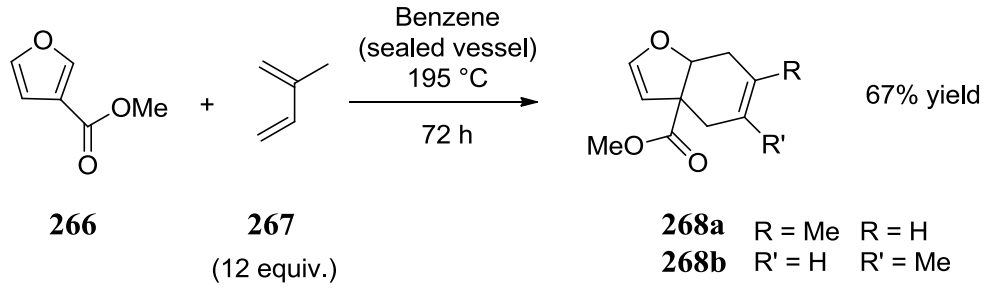
deficient dienophiles (such as **261**) and styrene but with simple alkenes and more electron-rich dienophiles (such as **262**) the desired cycloaddition could not compete with dimerisation of **260** (which affords adduct **263**).



Scheme 130: Highlighted reactivity of **260** *with electron deficient dienes* (**261**) *and inertness towards electron rich dienes* (**262**).

Notably, regioisomers of **264** were observed. In addition, evidence for two regioisomers of **263** were also identified in the NMR data, although definitive assignment of only one could be made. The salient point, however, is that the acyl functionality of **260** does not appear to be electron withdrawing enough to encourage an inverse demand process as demonstrated by the lack of reaction with electron rich dienes.

Additionally, evidence exists (in the literature) which details **265** (the furan analogue of **260**) behaving as a *dienophile* as opposed to a diene, as highlighted in the case of **266** reacting with isoprene (**267**) to afford regioisomers **268a** and **268b** in a 2:1 ratio (*Scheme 131*).[146] Although high temperatures were adopted in conjunction with a sealed reaction vessel, a decent yield was afforded of the corresponding adducts.

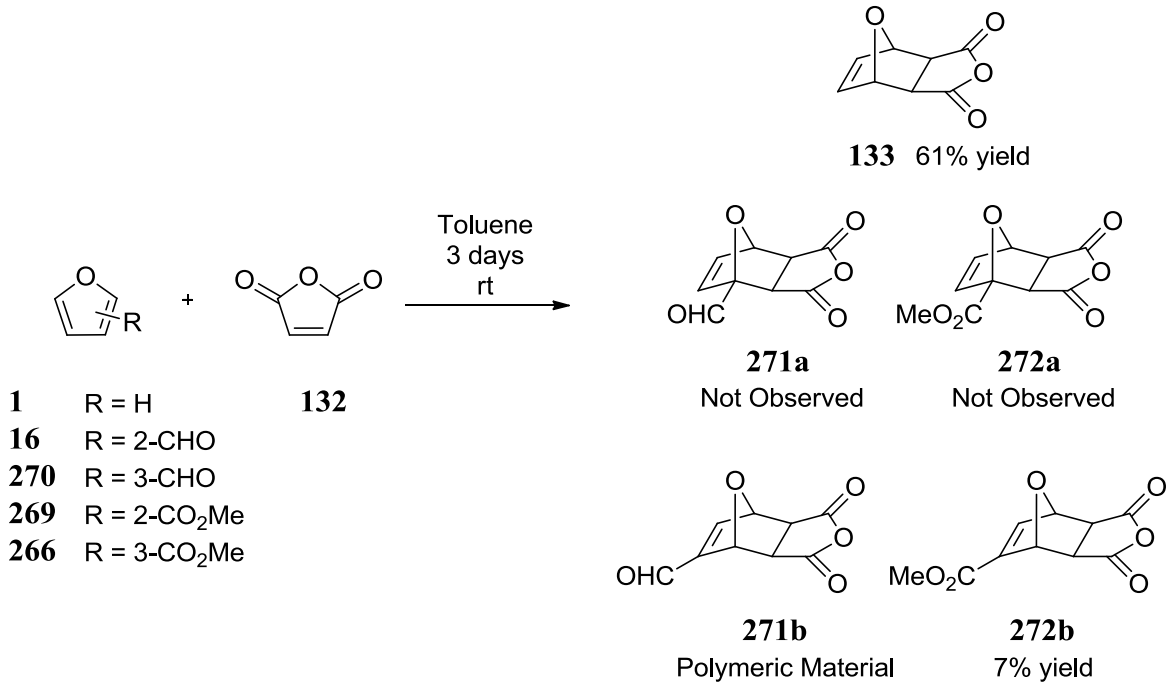


Scheme 131: Methyl-3-furoate (**266**) *behaving as a dienophile.*

4.2.2 RESULTS AND DISCUSSION

Due to intriguing reactivities such as the above, we decided to investigate the effects of furan acylation on Diels-Alder processes for ourselves. We initially focused on intermolecular processes, electing to investigate the reactivities of four different acyl furans in comparison to that of furan. Maleic anhydride (**132**) was chosen as our initial dienophile due to its well established reactivity with furan (*vide supra* - p.42)[66] in conjunction with the fact it cannot act as a diene, thus avoiding similar chemistry to that detailed in *Scheme 131*. As for the furan substrates, methyl-2- and 3-furoate (**269** and **266** respectively) were selected due to being simple acyl furans that were commercially available. Likewise, 2- and 3-furaldehyde (**16** and **270** respectively) were selected for similar reasons.

The reactivities of each of these substrates (compared to furan itself) were analysed by reacting each of them with **132** over a three day period at room temperature, following a simple procedure conducted by Tew *et al.* (*Scheme 132*).[147] The adducts formed precipitated out of solution, thus allowing facile filtration to collect products. Additionally, as detailed above when discussing the reactivity of furan with maleic anhydride, from the ^{1}H NMR data we concluded that the *exo*-adduct was the final product of any Diels-Alder process observed, in the form of analysing the coupling constant between the bridgehead proton and the adjacent proton on the sp^{3} carbon.



Scheme 132: Summary of results for formation of adducts.

Interestingly, we identified that in both variations of the reaction where the substrate contained a 2-acyl moiety, no reaction to afford adducts **271a** or **272a** were observed. No adduct precipitated out of solution in the attempted conversions of **16** and **199** into their corresponding adducts. Additionally, NMR analysis of the crude reaction mixture after solvent removal revealed only starting materials.

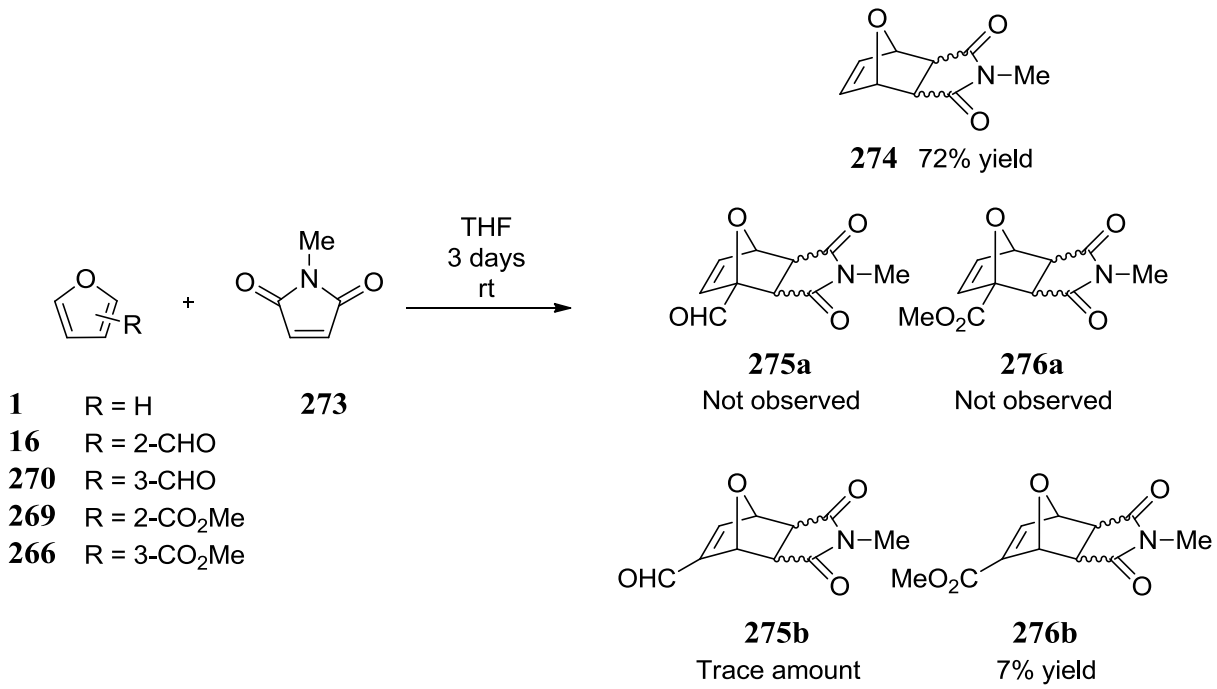
However, reactivity was observed in the cases of both 3-acyl furans. A small amount of solid did precipitate out of solution for the attempted conversion of **270** into adduct **271b** (8% mass recovery), but the material was identified to be potentially polymeric in nature *via* ^{1}H NMR analysis (which revealed a complex mixture). Repetition of this reaction afforded similar results, thus, we believe that this adduct is unstable and reacts on further/decomposes.

Unlike its aldehyde counterpart, however, reaction of **266** did indeed afford some adduct (**272b**) - a clean ^{1}H NMR spectrum of which was afforded and indicated the presence of only one isomer which we concluded to be the *exo*-adduct after analysis of the NMR data. Additionally, despite not undergoing conversion as readily as furan, it appears that **266** is still capable of somewhat competing with furan. Each furan (**1** and **266**) was reacted with one equivalent of maleic anhydride (**132**) under the same

reaction conditions used previously and it was identified that a 1:6 ratio (**272b**:**133**) of adducts was produced. The fact that **266** even competes at all is somewhat intriguing as well as surprising.

Thus, it would appear that **16** and **266** (the furan analogues of **260**) do not react very well with electron deficient dienes. Reactivity compared to furan (**1**) appears to be diminished. Additionally, 2-acyl furans were identified to be unreactive under the reaction conditions above.

In light of the result obtained when employing maleic anhydride (**132**) as the dienophile, we elected to investigate the reactivity of the same furans with *N*-methyl maleimide (**273**), which has also been demonstrated to react with furan (*Scheme 133*).[148]



Scheme 133: Summary of results for formation of adducts.

As is evident from *Scheme 133*, the results obtained were very similar to those for the reaction with maleic anhydride (**132**). Furans posessing 2-acyl substituents did not react with **273**, whereas those with 3-acyl substituents did. Furthermore, substrate **270** once again displayed evidence for reactivity (albeit a very small conversion), but efforts to

isolate these potential adducts were unsuccesful as it appeared that decomposition was occurring. Thus, it appears that instability is a more general feature for adducts of 3-formyl furans.

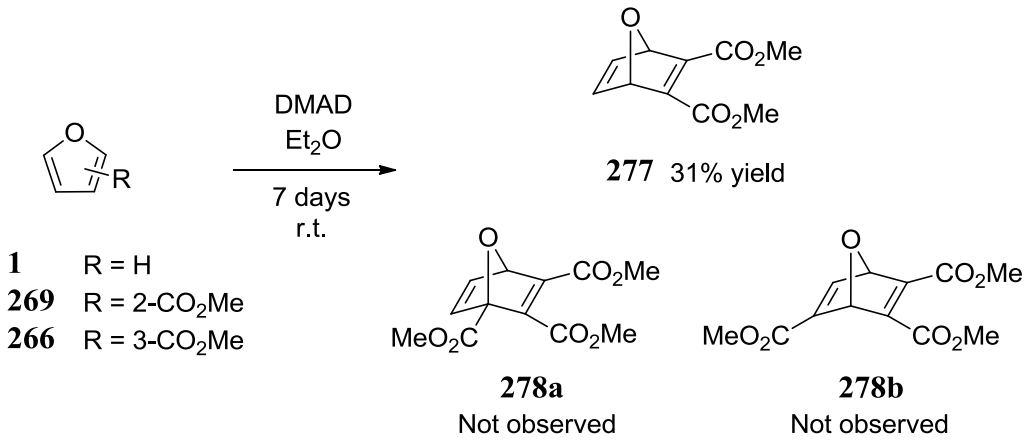
As a note, mixtures of *endo* and *exo* adducts were obtained for compounds **274** and **276b**, which is in contrast to the previous reactions with maleic anhydride (**132**), where only the *exo* isomer was observed.

Although no direct competition reaction was conducted on this occasion, we suspect that a similar result to that seen previously would be obtained given the overall similarity of results displayed when *N*-methyl maleimide (**273**) was used instead of maleic anhydride (**132**).

We decided to continue our investigation of intermolecular Diels-Alder processes by next employing DMAD as our dienophile. DMAD is an electron-deficient alkyne diester which is widely used as a dienophile in cycloaddition reactions.[149] It is widely available and known to be used as a standard in Diels-Alder reactions to check the efficiency of various dienes due to its reactive nature.

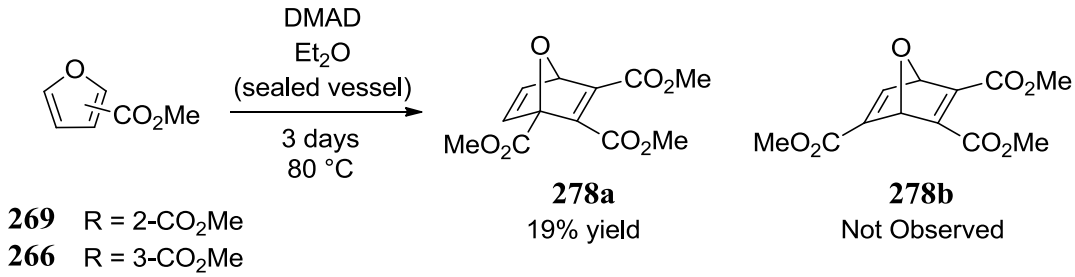
Given the issues identified previously upon reacting 3-furaldehyde (**270**), we decided to concentrate on investigating esters **269** and **266**, given that any reactions observed thus far were relatively clean in comparison to ones involving their aldehyde counterparts.

Upon subjecting our substrates to similar (but slightly modified) conditions to those used for the maleic anydride (**132**) and *N*-methyl maleimide reactions (**273**),[150] we observed once again that **269** (the 2-acyl furan) was reluctant to participate in any reaction (*Scheme 134*). However, we noted that in this instance, 3-acyl analogue **270** also reacted sluggishly - more so than previously demonstrated with alternative dienophiles.



Scheme 134: Results of attempted room temperature reaction of substrates with DMAD.

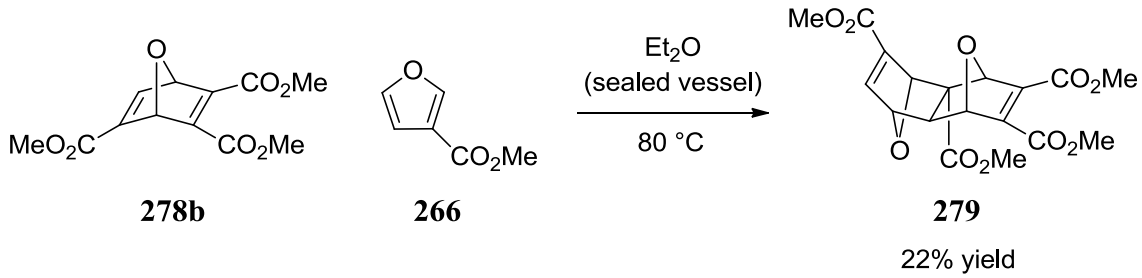
Although we cannot say with any certainty that adduct **278b** was present in the reaction mixture, small signals were seen in the crude ^{1}H NMR spectrum obtained from reacting **266** with DMAD, which we believed could be the adduct. However, we decided that repeating the reaction at elevated temperature in a sealed vessel was necessary to try and ascertain what reaction was actually occurring. Substrate **269** was subjected to the same, harsher conditions (*Scheme 135*).



Scheme 135: Exposure of **269** *and* **266** *to DMAD under harsher conditions.*

In both cases, precipitate was visible in the reaction vessels. Isolation of the precipitate from the attempted conversion of **269** afforded our first (clean) product containing a bridgehead acyl moiety. The low yield of **278a** was not a surprise given the consistent lack of reactivity exhibited by **269** up until this point.

Somewhat more intriguing, however, was the observed absence of adduct **278b**, despite the recovery of a precipitate from the reaction mixture, which we identified to be more complex in nature *via* ^{1}H NMR analysis. We suspected that **278b** was still a reactive dienophile under these reaction conditions and was likely to be reacting with more **266**. After some research, we uncovered evidence in the literature[151] to support the formation of polycyclic adduct **279** (*Scheme 136*). Barlow *et al.* had previously reacted the ethyl analogue of **266** with DMAD to afford the corresponding ethyl analogue of **279**, thus we ascertained the identity of our product by cross referencing our NMR data with theirs.



278b **266** **279**

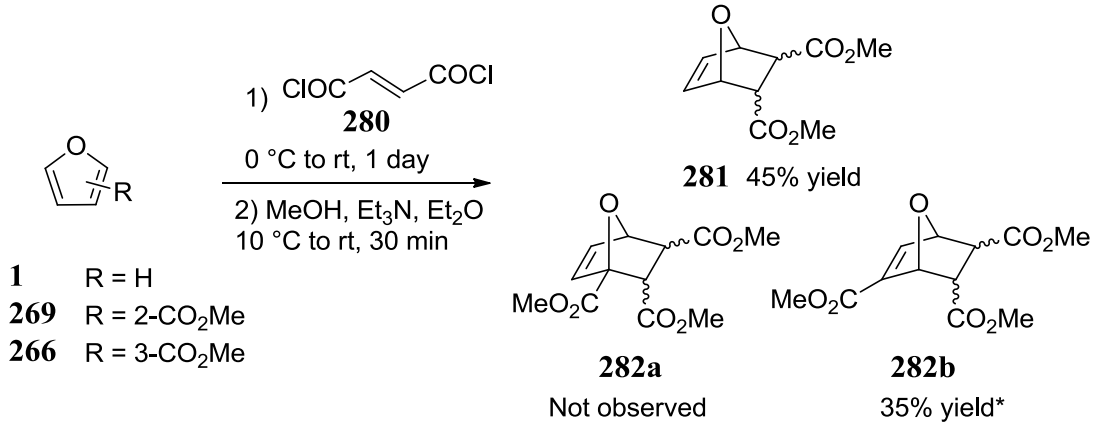
22% yield

Scheme 136: Additional reaction of adduct **278b** *with furan* **266**.

This peculiar discovery not only highlights the reactivity of **266**, but also of the initial adduct formed, **278b**. It is assumed that further Diels-Alder reactivity occurs at the tri-substituted alkene due to the additional steric strain that addition to the tetra-substituted moiety would incur. It would thus appear that although we observed reactivity of **269** under harsher conditions, **266** is still the more reactive of the two, while still being a poorer diene than furan.

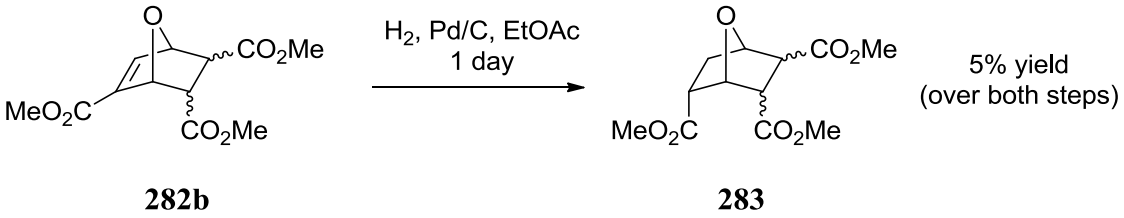
Having identified that elevated temperatures were required in order for **266** (and **269**) to react with DMAD, we turned our attention to fumaryl chloride (**280**) as a dienophile, which is more reactive than its ester analogues[152] and as such we hoped it would react at ambient temperature with **266**. Since generation of any adduct would retain the acyl chloride functionalities of fumaryl chloride, we elected to subsequently esterify these groups *via* reaction with methanol *in situ* in order to prevent any further side reactions occurring.

A two step procedure was thus conducted on our substrates to afford adducts from furan (**1**) and **266** (*Scheme 137*).[153,154] Acyl furan **269** yet again displayed no reactivity under such mild conditions (and as such no *in situ* esterification was even attempted), in keeping with the trend we observed thus far.



Scheme 137: Attempted reactions of substrates with fumaryl chloride. Asterix donates retro Diels-Alder reaction observed.

However, although reactivity was observed for substrate **266**, we also suspected that upon purification, the retro-cycloaddition was occurring on the adduct due to the presence of starting materials in the ^{1}H NMR spectrum. This was confirmed by leaving the sample overnight and recording another NMR spectrum. To combat this, we subjected the adduct to hydrogenation and isolated the reduced adduct **283** (*Scheme 138*).

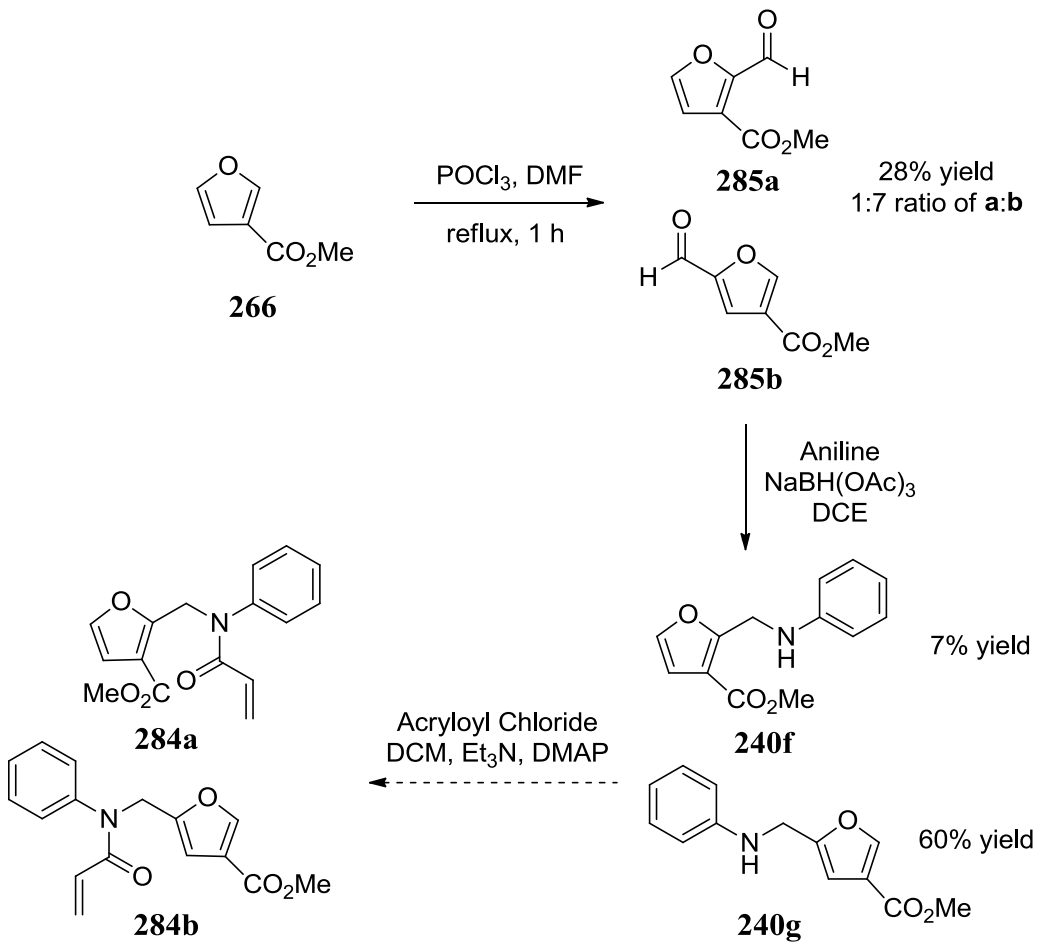


Scheme 138: Reduction of **282b** *to afford hydrogenated adduct* **283**.

The explanation for the consistently greater reactivity of **266** over **269** can potentially be explained by conjugative stabilisation of the newly forming π-bond in the transition states of these reactions.[155] Obviously, no such effect can be evoked by the acyl functionality on the π-bond when it is situated at the bridgehead of the newly forming adduct. Furthermore, it is possible that the different alterations to the HOMO energy (and the HOMO coefficients) that the ester group will have on furan in each case are responsible for the observed differences in reactivity. In such a scenario, the 3-acyl substituent is presumably not lowering the energy of the furan HOMO as much as the 2-acyl group. Additionally, the relative reluctance of 2-acyl furans to react may be a consequence of the steric strain induced around the quaternary, bridgehead carbon of the adduct.

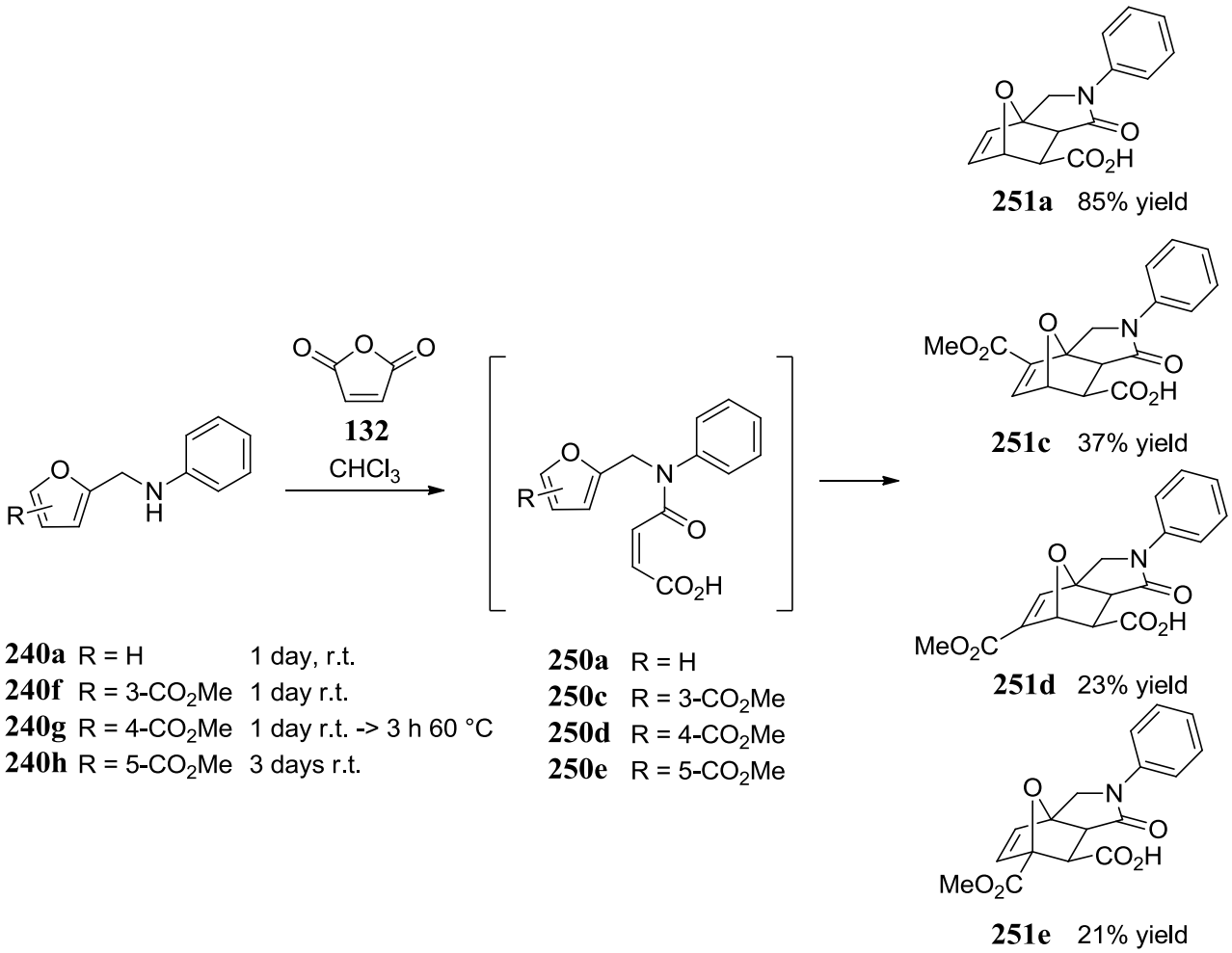
Having established the generality of reactivity differences between **266** and **269** *via* various *inter*molecular Diels-Alder processes, we elected to try and investigate *intra*molecular processes. Our initial thoughts were to prepare compounds **284a** and **284b**, which are analogous to those of the 'normal demand' substrates in our halogen series (*Scheme 139*). As such we firstly formylated **266** to afford an inseparable mixture of **285a** and **285b** in a 1:7 ratio respectively.[156] Subsequent reductive amination[133] with aniline then afforded the corresponding amines (**240f** and **240g**), which were separable by flash chromatography.

Transformation into the desired substrates was then attempted, again using the same methods as in chapter three, and evidence for adduct formation was visible in the NMR data. However, isolation of both substrates was not achieved after attempted purification *via* flash chromatography and the minor presence of unidentified impurities were observed.



Scheme 139: Synthetic route towards substrates **284a** and **284b**.

Fearing that decomposition may have been the source of such impurities, we decided to take a different approach in order to investigate intramolecular processes on acyl furan substrates. Our revised idea involved mirroring the *in situ* reactions studied on the analogous 5-nitro furan substrate (**250b** - *Scheme 127* - p. 132), *via* reacting amines **240f-h** with maleic anyhdride (**132**) as depicted in *Scheme 140*. The *in situ* transformations of corresponding substrates **250c-e** negated the need to isolate the substrate and as such avoided any potential decomposition issue that could occur during prolonged isolation.



Scheme 140: Production of adducts **251a-d** *via in situ transformation of substrates* **286a-d**.

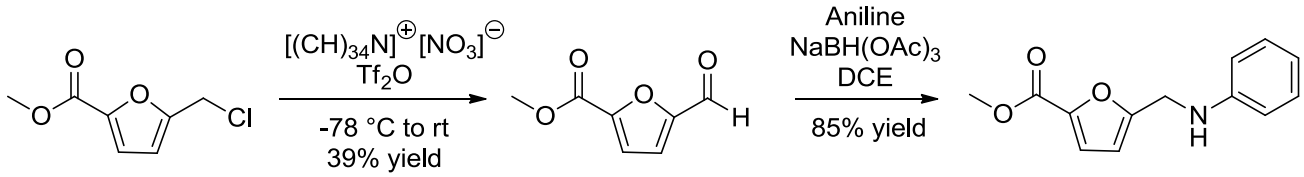
Unexpectedly, the adducts precipitated out of the chloroform solution, however this made isolation of the adducts *via* filtration a viable option. However, mechanical losses are believed to have occurred upon isolation attempts, owing to both the small reaction scales and the fact the adducts are not completely insoluble in chloroform. The non-halogenated substrate **250a** was unsurprisingly the most reactive of the series, as demonstrated previously with the intermolecular processes.

Rather unexpectedly, amine **240h** (synthesised from chloride **286** adopting procedures shown in *Scheme 141 - vide infra*)[133,157] produced a reactive substrate which went on to afford adduct **251e**, albeit after 3 days. Although not in such impressive a yield as **251a** (and obviously after a longer time frame), adduct **251e** was afforded in a yield very similar to that of its analogue **251d** which required heating to afford the

adduct (*vide infra*). These findings are in contrast to our previous intermolecular efforts, where substrates bearing an acyl substituent in the 3-position were *less* reactive than their 2-acyl counterparts.

As mentioned above, substrate **250d** was not as reactive as either **250c** or **250e** and required some additional heating in a sealed vessel in order to proceed. Precipitation did occur after heating which was indeed adduct **251d**, but this was most unexpected given the demonstrated reactivity of **250e** at ambient temperature.

Substrate **250c** appeared to be the most reactive of the three acyl substrates, with a 37% yield being recorded after 1 day without any heating required. We suspect that the relief of steric strain between the 2- and 3- substituents is likely to explain the differences in reactivity (see chapter 3), particularly between **250c** and **250d**.



286 **287** **240h**

Scheme 141: Synthesis of amine **240h**.

Given the insolubility of adducts **251a** and **251c-e** in chloroform, monitoring of the reaction progress by ^{1}H NMR was made difficult. Indeed, this was one of our initial intentions, so we switched the reaction solvent to deuterated acetone and scaled the experiments suitably for an NMR tube.

With the exception of adduct **251e**, the adducts remained fully in solution in acetone, thus the reactions could be monitored. As can be seen in the case of the non-acyl variant **240a**, the substrate is beginning to form minutes after combination of starting materials (*Fig. 41*). Starting amine **240a** had almost been completely consumed after 3 hours, with adduct formation clearly visible. After 1 day, the reaction mixture consisted nearly completely of adduct **251a** with some intermediate substrate **250a** remaining. After a 2 day period, only adduct was visible in the ^{1}H NMR spectrum.

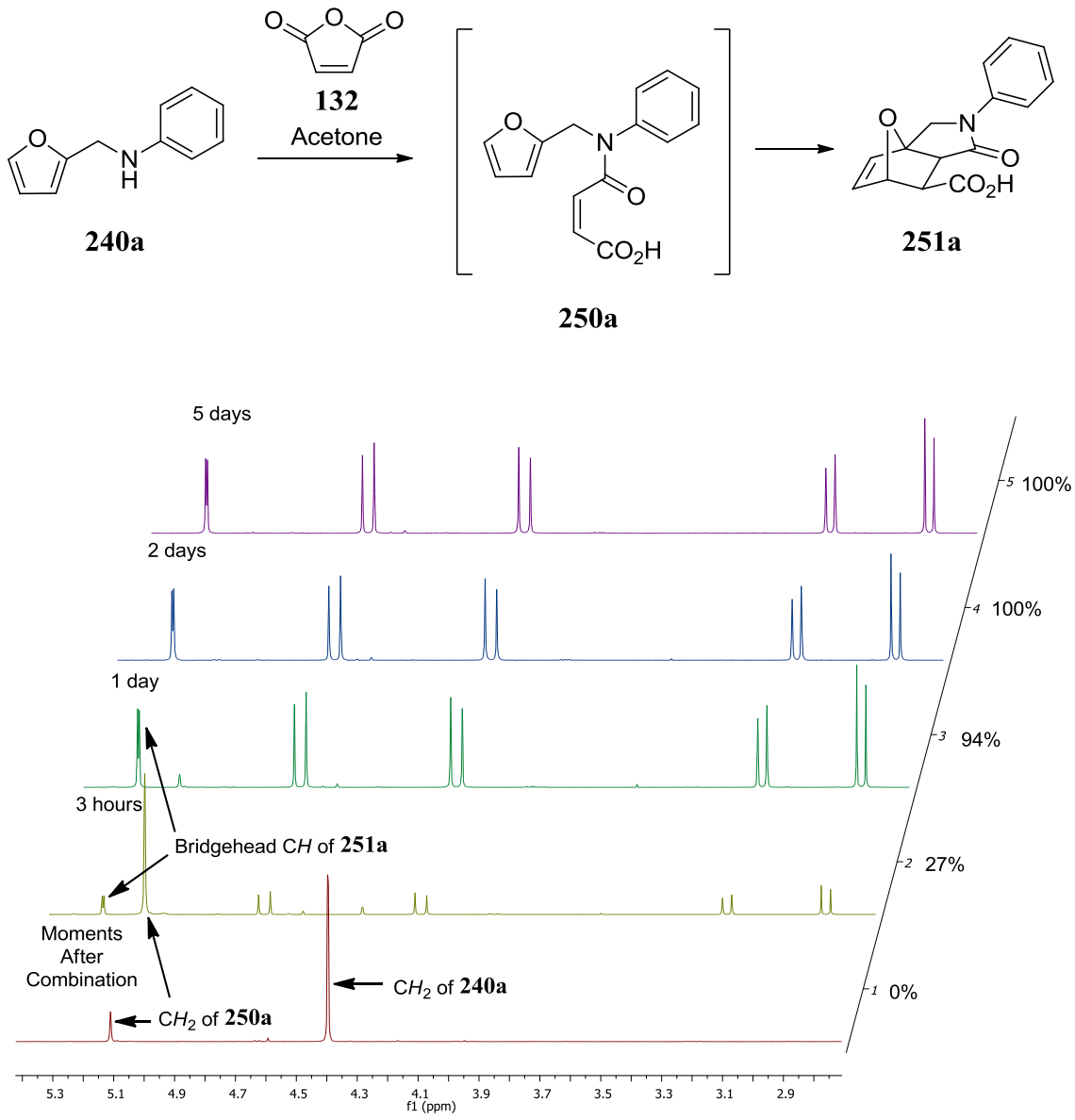
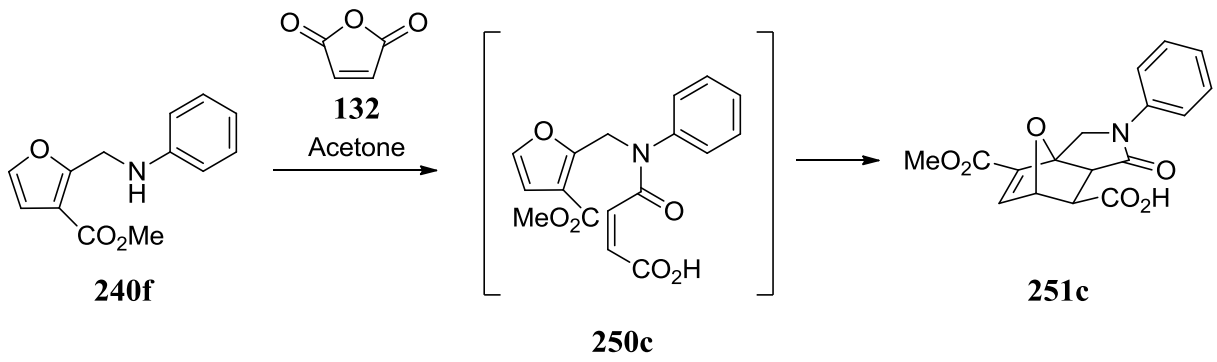


Fig. 41: Section of NMR following the conversion of **240a** *into* **251a** *(% conversion to adduct displayed on the right).*

The formation of the acyl adducts was shown to be slower than had been the case for **251a** after analysing the NMR data for each of them. In the case of adduct **251c**, after four days there was no sign of substrate **250c** (*Fig. 42*). However, as can be seen by comparing the conversion after 1 day with non-acylated adduct **251a**, the IMDAF reaction appears to be proceeding more slowly.

Formation of adduct **251d** appeared to be slower than that of **251c**, so much so that substrate **250d** was still present in the reaction mixture after a 5 day period (*Fig.*

43). Additionally, unlike in the cases of both **251a** and **251c**, barely any adduct was visible after 3 hours, despite confirmation of formation of substrate **250d** by this stage.



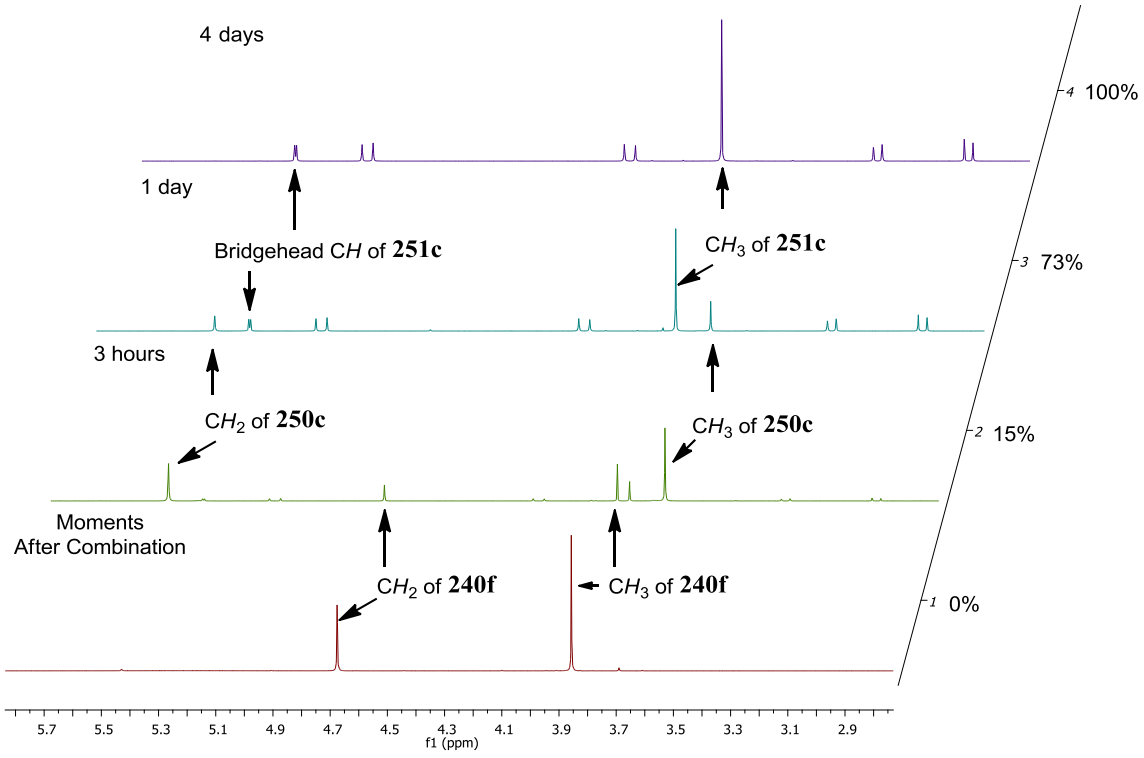


Fig. 42: Section of NMR following the conversion of **240f** *into* **251c** *(% conversion to adduct displayed on the right).*

As alluded to above, adduct **251h** once again precipitated out of the reaction mixture, making a direct NMR analysis as the reaction was running more difficult. However, after a 5 day period, the contents of the reaction mixture were successfully dissolved in

DMSO after removing acetone *in vacuo*. In a similar fashion to that of adduct **251d**, the majority of the content was the adduct (**251h**) with a small quantity of substrate **250h** remaining (*Fig. 44*).

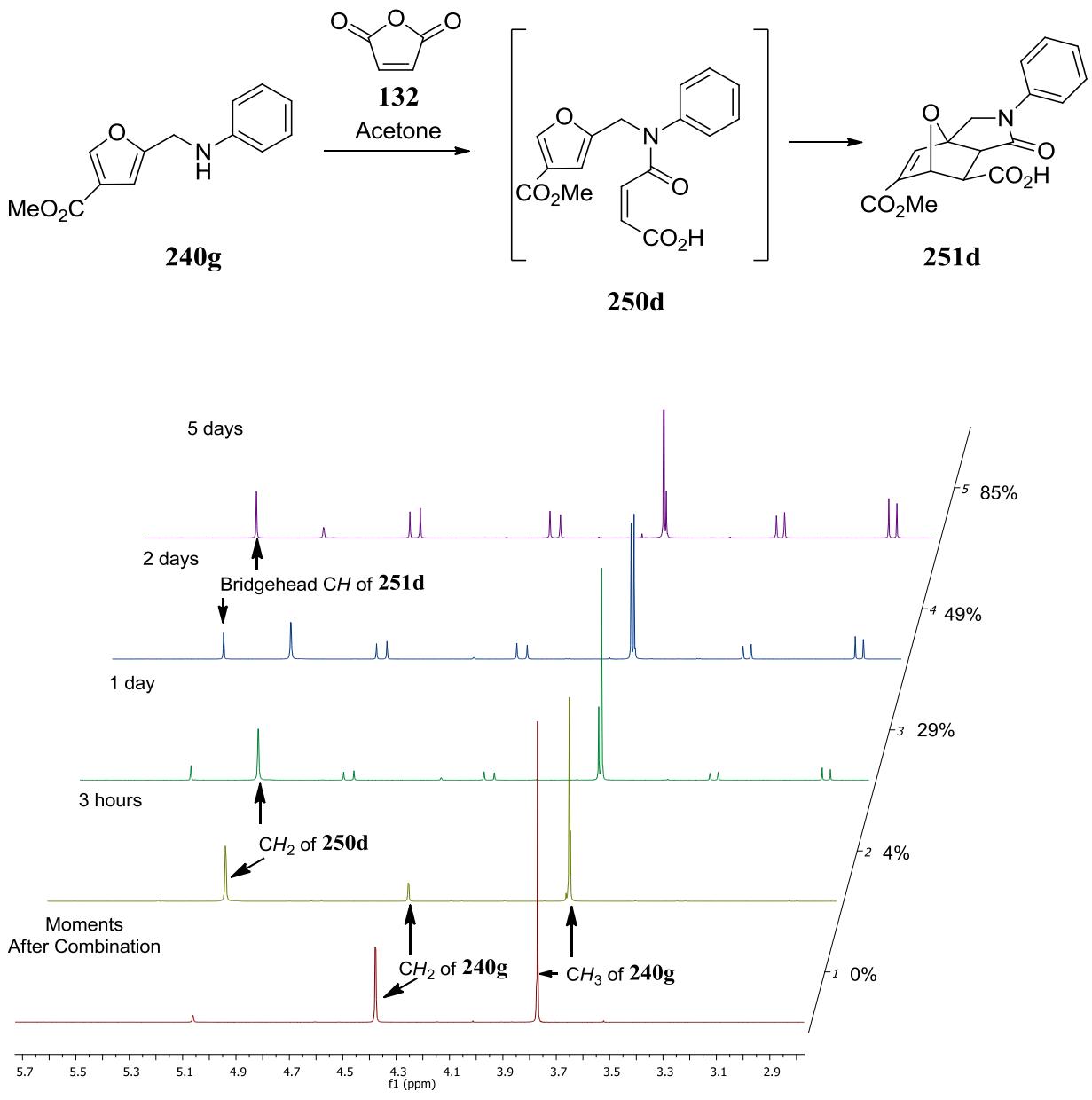


Fig.43: Section of NMR following the conversion of **240g** *into* **251d** *(% conversion to adduct displayed on the right).*

Overall these findings indicate that substrate **250c** was the most reactive of the three acyl substrates. This is not surprising to us given the observations made

previously regarding the differences in reactivity between 2- and 3- acyl furans towards Diels-Alder processes. Furthermore, the fact that this is an intramolecular process means there will be a steric relief between the 2- and 3-substituents as discussed earlier (*vide supra* - p.44) which will facilitate adduct formation in comparison to the case of formation of adduct **251d**, where such relief is less significant.

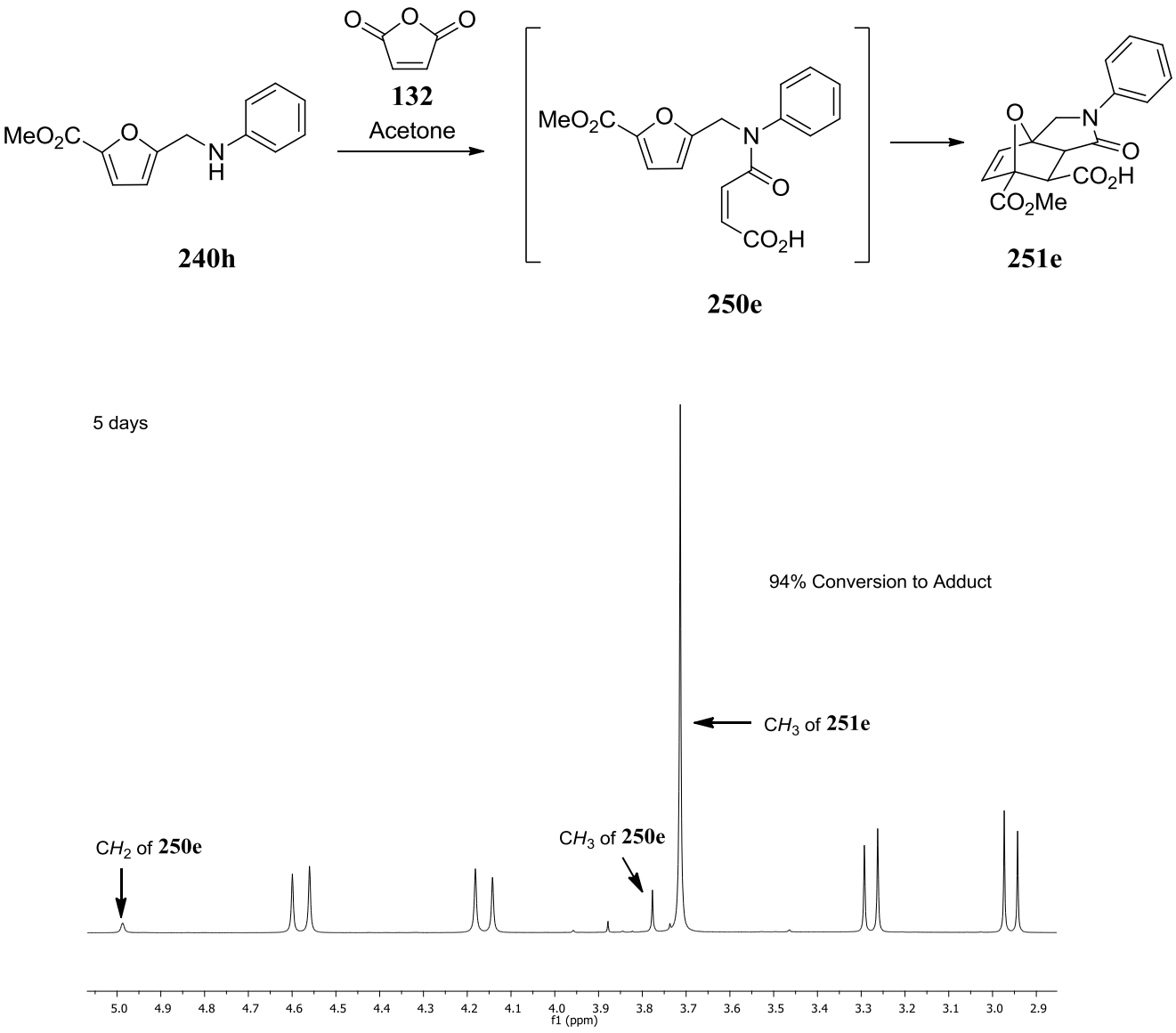
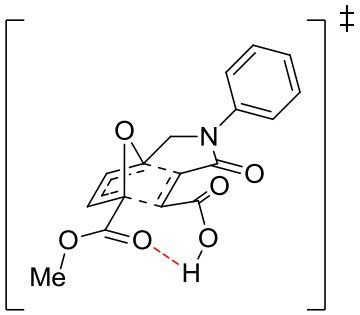


Fig. 44: Section of NMR displaying conversion of **240h** *into adduct* **251e** *on day 5 (NMR of final contents run in d_6-DMSO).*

Most surprising to us is that adduct **251e** is formed at all given we were expecting no reaction based on our intermolecular studies. Any argument based on charge stabilisation (chapter 3) of the bridgehead carbon does not suffice because the same argument should hold for intermolecular processes as well, yet we identified no reactivity of 2-acyl furans in most of our intermolecular studies. Furthermore, the conjugative stabilisation of the newly forming double bond in the reaction transition states discussed earlier cannot happen for the 5-acyl substituents. Thus, this result initially seems to be somewhat anomalous.

A possible explanation (which would be unique with respect to the acyl substrates we have studied) is the potential formation of an intramolecular H-bond within the transition state that exists between the carboxylic acid proton and the oxygen of the bridgehead acyl moiety which may facilitate formation of the adduct (*Fig. 45*).



251e

Fig. 45: Potential intramolecular H-bond that may facilitate the unexpected formation of adduct **251e**.

4.2.3 SUMMARY

The effect of having an acyl moiety present on the furan (regardless of position) appears to have a detrimental effect on Diels-Alder processes. Overall, the presence of an acyl group in the 2-position leads to poorer reactivity in comparison to 3-acylated analogues, that can still somewhat compete with non-acylated systems. Conjugative stabilization in the transition state offers an explanation for this observation.

5. CONCLUSIONS AND FUTURE WORK

5. CONCLUSIONS AND FUTURE WORK

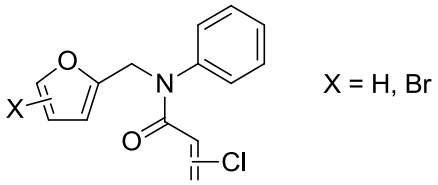
In conclusion, we have succesfully demonstrated two general effects regarding halogen substitutions in IMDAF reactions. Halogenation of the furan moiety (the diene component) appears to be beneficial for the cycloaddition, where we generally obtained superior yields and observed faster reaction rates in comparison to non-halogenated counterparts. These observations are in line with claims made previously from both synthetic and theoretical studies. Furthermore, we observed that this facilitation occurred irrespective of the position of the halogen atom on the furan as well as occurring in both 'normal' and 'inverse' demand systems. However, we did note that 3-halogenation generally appeared to aid the process slightly more than either 4- or 5-halogenation, likely due to an additional steric relief which accompanies adduct formation in these systems.

In addition, we have noted that halogenation of the dienophile component has the opposite effect on IMDAF reactions to diene halogenation. A retardation of the forward reaction was consistently observed, again irrespective of the halogens position on the alkene, although we did generally observe that conversions of substrates containing a *cis* chloro-alkene were the most arduous. This was a conclusion that added to studies previously conducted, where adducts from such species were identified but no comparison to the non-halogenated analogues were made. Indeed, some of our earlier studies were in contradiction to some of the claims made in these studies. Furthermore, we have demonstrated that the detrimental effect of having a halogen substiutent present in any given position on the dienophile moiety can be overcome by halogenating the furan component, although a dependence on the position of the furan halogen was noted in some cases (which we believe has a steric basis in most cases).

Thermochemical data on these systems, obtained from the theoretical studies conducted by Prof. Martin Paterson and Dr. Justyna MacKinlay, was generally in accordance with our observations. Additionally, HOMO-LUMO energy gap calculations afforded us with the conclusion that any FMO interactions are not the defining feature for these observed changes in reactivity upon halogen substitution. We identified only minor changes in $\Delta E_{HOMO\text{-}LUMO}$ in comparison to the parent, non-halogenated systems in each case.

A dipolar interaction between the C-O and C-X dipoles was also identified in the adducts, where more attractive interactions were observed for adducts derived from *E*-3 and 2-haloalkene substrates (thus, potentially stabilising the transition state) and conversely, repulsive interactions were identified for adducts derived from *Z*-3-haloalkene substrates (thus, potentially destabilising the transition state).

Future work to be conducted on halogen effects could include the formation of α- and β–chloroacrylamide substrates of structure **239**, which we failed to synthesise in our attempts, and thus investigate the effects on alkene halogenation on these 'normal' demand systems (*Fig. 45*). If successful, then investigation of the dihalogenated systems could be undertaken to ascertain which halogenation effect (if any) is dominant in IMDAF reactivity of these 'normal' demand substrates. Of course, further theoretical studies could then be employed to try and rationalise any observations for these systems, as was done so for the 'inverse' demand substrates above (chapter three).



239

Fig. 45: Desired α- and β–chloroacrylamide substrates.

Indeed, further functionilisation of substrates containing both the 'normal' and 'inverse' demand structures we studied is another possibility. Poly-halogenations may be of interest to try and identify any additive effects of such substitutions. Additionally, further functionalisation of any adducts formed (particularly exploiting the potentially reactive C-X bonds) could also be attempted, purely to demonstrate any potential synthetic utility of said adducts.

We have also demonstrated an effect on Diels-Alder reactivity of furans when an acyl substituent is introduced to the furan moiety. Overall, this effect appears to be detrimental in comparison to the parent, non-acylated systems, with 2-acylation appearing to be so detrimental in many cases that no reaction occurred whatsoever.

Intriguingly, we identified that a 3-acyl furan still competes with furan in Diels-Alder reactions, despite not being as reactive as furan.

Additionally, NMR studies verified that IMDAF reactions indeed occur slower for acyl-furan substrates, with differences in reactivity being observed between the 3-, 4- and 5-acyl furans themselves.

Future work regarding the acyl effect may include repeats of the chemistry discussed in chapter 4, in order to improve isolated yields. Another possibility is the poly-acylation of the furan moiety, which could perhaps demonstrate that the lack of reactivity that we observed for 2-acyl furans could be overcome by the presence of 3- (or 4-) acyl substituents. Similarly to adducts of our halogen substrates, further functionalisation of any adducts formed could also be attempted. Computational experiments could also be conducted to not only rationalise our current observations, but also any future ones made regarding this acyl effect.

Finally, our studies made on the effect of 5-nitro substitution on the furan moiety appear to indicate facilitation of IMDAF reactions on systems analogous to those explored in our halogen substitution studies. This facilitation occurred in both the 'normal' and 'inverse' demand systems.

Additionally, hard evidence for a dipolar effect in 5-nitro furan systems is yet to be observed and as such, no firm conclusions can be made regarding a solvent trend in these reactions.

Future work in this area includes the effects of 3- and 4-nitro substitution of the furan moiety. In these scenarios, any charge stabilisation (of the bridgehead carbon) argument invoked upon adduct formation in order to rationalise our observations does not hold, thus is an immediate point of interest. Furthermore, theoretical studies could once more be employed to rationalise any observations made, both past and future.

6. EXPERIMENTAL

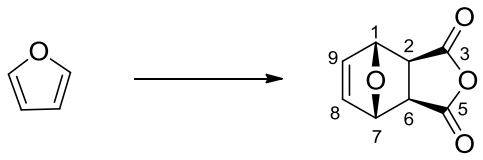
EXPERIMENTAL

General Information

Commercially available reagents from Aldrich, Acros Organics, TCI UK, Fluorochem, Apollo Scientific and Lancaster chemical companies were generally used without further purification. THF, Et_2O and toluene were distilled from sodium-benzophenone ketyl under nitrogen. DCM was distilled from CaH_2. Anhydrous DMF was purchased from Aldrich and used as supplied. Reactions were routinely carried out under an inert atmosphere of either argon or nitrogen unless otherwise specified.

^{1}H NMR spectra were recorded on Bruker AV 300 and AV 400 spectrometers at 300 and 400 MHz, respectively, and referenced to residual solvent. ^{13}C NMR spectrum were recorded using the same spectrometers at 75 and 100 MHz, respectively. Chemical shifts (δ in ppm) were referenced to tetramethylsilane (TMS at δ_H 0.00) or to residual solvent peaks ($CDCl_3$ at δ_H 7.26). *J* values are given in Hz and s, d, dd, ddd, t, dt, q, m, br and app. abbreviations correspond to singlet, doublet, doublet of doublet, doublet of doublet of doublet, triplet, triplet of doublet, quartet, multiplet, broad and apparent, respectively. Mass spectra were obtained at the EPSRC National Mass Spectrometry Service Centre in Swansea. Infrared spectra were obtained on Perkin-Elmer Spectrum 100 FT-IR Universal ATR Sampling Accessory, deposited neat to a diamond/ZnSe plate. Melting points were recorded on a Stuart SMP10 melting point apparatus. Flash column chromatography was carried out using Matrix silica gel 60 from Fisher Chemicals and TLC was performed using Merck silica gel 60 F254 precoated sheets and visualised by UV (254 nm) and stained by the use of aqueous acidic $KMnO_4$.

(1*S*,2*R*,6*S*,7*R*)-4.10-Dioxatricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione (133):[147]

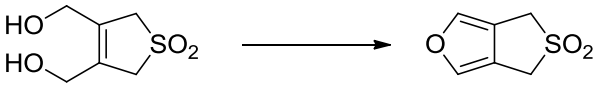


133

Furan (347 mg, 5.12 mmol) and maleic anhydride (250 mg, 2.56 mmol) were combined in toluene (2.50 ml) with stirring and left for 5 days. The precipitate that formed was

collected *via* filtration and rinsed with toluene. Remaining solvent was removed *in vacuo* to afford the title compound with no further purification required; Wt 261 mg; 61%; white solid; δ_H (300 MHz, $CDCl_3$) 6.61 (t, *J* = 1.0 Hz, 2H, *H*-8 and *H*-9), 5.49 (t, *J* = 1.0 Hz, 2H, *H*-1 and *H*-7), 3.20 (s, 2H, *H*-2 and *H*-6); δ_C (75 MHz, $CDCl_3$) 169.8 (2 × C=O), 137.0 (CH-8 and CH-9), 82.2 (CH-1 and CH-7), 48.7 (CH-2 and CH-6); ν_{max}/cm^{-1} 3004, 2922, 2607, 2579, 1702, 1638, 1588, 1425, 1310, 1255, 1212, 1020.

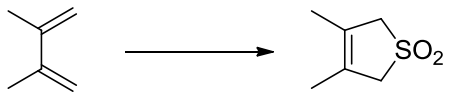
4,6-Dihydrothieno[3,4-c]furan 5,5-dioxide (178):[93]



178

A solution of PCC (1.96 g, 9.1 mmol) dissolved in DCM (50.0 ml) was added to a solution of **182** (1.00g, 5.6 mmol) in acetone (20.0 ml) with stirring. One minute later, TFA (2.25 ml) was added and the reaction mixture left to stir for 30 mins. Sat. $NaHCO_3$ solution (25 ml) was then added to the reaction mixture, followed by Et_2O (100 ml), EtOAc (100 ml) and water (100 ml) after effervescence had stopped. The resulting mixture was filtered through florisil (200 mesh) to remove Cr salts and the aqueous layer run off, and re-extracted with EtOAc (100 ml). The combined organic layers were then rinsed with brine (50 ml) before extraction and dried (Na_2SO_4). Concentration *in vacuo* afforded the crude product which was purified *via* column chromatography (40:60 ethyl acetate/petroleum ether) to afford the title compound: Wt 501 mg; 56%; green-tinted solid; m.p. 137-139 °C (lit. 139-140 °C); δ_H (200 MHz; $CDCl_3$) 7.43 (s, 2H, 2 × C*H*) 4.15 (s, 4H, 2 × CH_2); δ_C (75 MHz, $CDCl_3$) 137.5 (C_q), 116.6 (CH), 51.2 (CH_2).

3,4-Dimethyl-2,5-dihydrothiophene-1,1-dioxide (180):[93]

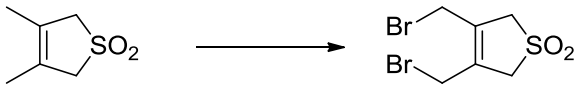


180

$SO_{2(g)}$ (~11 ml, ~250 mmol) was condensed at -78 °C into a solution of MeOH (6.10 ml) and 2,3-dimethylbuta-1,3-diene (10.2 g, 124 mmol) containing hydroquinone (0.12

g, 1.09 mmol). The resulting reaction mixture was then transferred to a pressure tube at reduced temperature which was then sealed and left to heat to room temperature over the course of 2 days. Re-cooling of the reaction vessel to -78 °C was followed by removal of the lid and excess $SO_{2(g)}$ was allowed to evaporate as the vessel returned to room temperature. Concentration of the reaction mixture *in vacuo* yielded the crude product that was purified *via* recrystallisation from MeOH to afford the title compound: Wt 19.4 g; 100%; white crystals; m.p. 136-137 °C (lit. 136-137 °C); δ_H (200 MHz, $CDCl_3$) 3.68 (s, 4H, 2 × C*H*$_2$), 1.73 (s, 6H, 2 × C*H*$_3$); δ_C (50 MHz, $CDCl_3$) 125.8 (C_q), 60.9 (CH_2), 14.8 (CH_3).

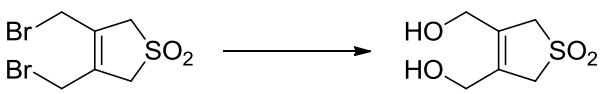
3,4-Bis(bromomethyl)-2,5-dihydrothiophene-1,1-dioxide (181):[93]



181

To a solution of **180** (31.2 g, 213 mmol) dissolved in dichloromethane (435 ml) was added *N*-bromosuccinimide (80.2 g, 451 mmol) with stirring, the solution was then heated to reflux and left overnight. Reaction mixture was then washed with water (2 × 200 ml) and brine (100 ml) before the organic layer was dried ($MgSO_4$). Concentration to dryness *in vacuo* yielded the crude product as a sticky off-white solid, which was recrystallised from dichloromethane and petroleum ether (40 – 60 °C) to afford the title compound: Wt 27.9 g; 43%; white crystalline solid; m.p. 121-123 °C (lit. 124-126 °C); δ_H (200 MHz, $CDCl_3$) 4.05 (s, 4H, Br-C*H*$_2$), 4.00 (4 H, s, S-C*H*$_2$); δ_C (50 MHz, $CDCl_3$) 131.4 (C_q), 58.6 (Br-CH_2), 24.2 (S-CH_2).

3,4-Bis(hydroxymethyl)-2,5-dihydrothiophene-1,1-dioxide (182):[93]

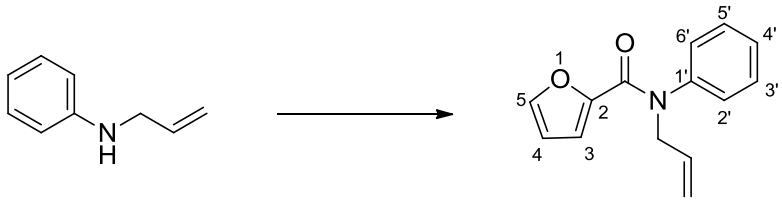


182

181 (500 mg, 1.65 mmol) was added to a solution of $AgCO_2CF_3$ (729 mg, 3.30 mmol) and water (6.00 ml) with stirring at ambient temperature for 3 days, ensuring that the

reaction mixture was concealed from light. Concentrating to dryness *in vacuo* afforded the crude product, which was purified by column chromatography (3% methanol in ethyl acetate) to afford the title compound: Wt 277 mg; 95%; white solid; m.p. 92-94 °C (lit. 92-94 °C); δ_H (200 MHz, $(CD_3)_2CO$) 4.15 (4 H, s, O-C*H*$_2$) 2.78 (2 H, br-s, O*H*), 3.77 (4 H, s, S-C*H*$_2$); δ_C (50 MHz, $(CD_3)_2CO$) 132 (C_q), 59 (O-CH_2), 58 (S-CH_2).

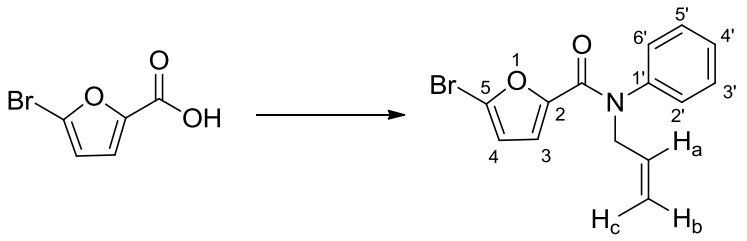
***N*-Allyl-*N*-phenylfuran-2-carboxamide (227a):**



227a

A solution of furoyl chloride (0.98 g, 7.50 mmol) in dry dichloromethane (2.60 ml) was added carefully to a stirring mixture of *N*-allyl aniline (1.00 g, 7.50 mmol), triethylamine (1.05 ml, 7.50 mmol) and DMAP (18 mg, 0.15 mmol) in dry dichloromethane (0.20 ml) at 0 °C. The reaction mixture was then allowed to rise to room temperature while stirring overnight. Water (10 ml) was then added to the reaction mixture and extracted with dichloromethane (3 × 25 ml). Combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (1:9 ethyl acetate/petroleum ether → 3:7 ethyl acetate/petroleum ether) afforded the title compound: Wt 1.34 g; 79%; golden brown solid; m.p. 62-65 °C; δ_H (300 MHz, $CDCl_3$) 7.43 – 7.34 (m, 3H, *H*-3', *H*-4' and *H*-5'), 7.32 (dd, *J* = 1.7, 0.8 Hz, 1H, *H*-5), 7.23 – 7.15 (m, 2H, *H*-2' and *H*-6'), 6.19 (dd, *J* = 3.5, 1.7 Hz, 1H, *H*-4), 5.96 (ddt, *J* = 16.7, 10.5, 6.2 Hz, 1H, *H*C=CH_2), 5.78 (app. d, *J* = 3.5 Hz, 1H, *H*-3), 5.16 (app. dq, *J* = 10.5, 1.3 Hz, 1H, HC=CHH_{cis}), 5.13 (app. dq, *J* = 16.8, 1.3 Hz, 1H, HC=CHH_{trans}), 4.45 (app. dt, *J* = 6.2, 1.3 Hz, 2H, C*H*$_2$).; δ_C (75 MHz, $CDCl_3$) 158.9 (C=O), 147.01 (C_q), 144.4 (CH), 142.6 (C_q), 132.8 (CH), 129.4 (CH), 128.3 (CH), 128.0 (CH), 118.2 (CH_2), 116.4 (CH), 110.9 (CH), 53.3 (CH_2); ν_{max}/cm^{-1} 3124, 3105, 3063, 1631, 1595, 1469, 1426, 1402, 1302, 1285, 1193, 1071; m/z HRMS (NSI+) found 228.1013, $C_{14}H_{14}NO_2$ $[M + H]^+$ requires 228.1019.

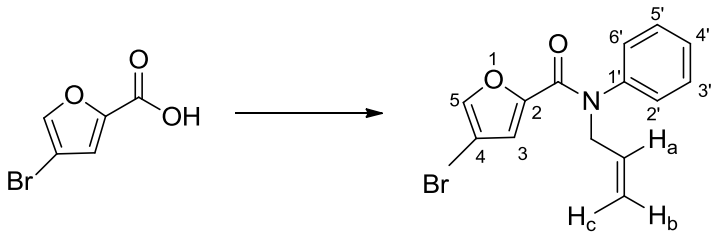
***N*-Allyl-5-bromo-*N*-phenylfuran-2-carboxamide (227b):**



227b

To a solution of 5-bromo-2-furoic acid (1.00 g, 5.24 mmol) in dry dichloromethane (6.50 ml) containing *N*,*N*-dimethylformamide (1 drop) was carefully added oxalyl chloride (1.00 g, 7.90 mmol) at 0 °C. The solution was allowed to rise to room temperature while stirring for 1.5 hours before the reaction mixture was concentrated *in vacuo*. Dry dichloromethane (2.00 ml) was introduced before a solution of *N*-allyl aniline (759 mg, 5.70 mmol) and triethylamine (1.50 ml, 10.0 mmol) in dry dichloromethane (2.00 ml) was then carefully added at 0 °C with stirring. The reaction mixture was then allowed to rise to room temperature while stirring overnight. Water (10 ml) was then added to the reaction mixture and extracted with dichloromethane (3 × 25 ml). Combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (3:7 ethyl acetate/ petroleum ether) afforded the title compound: Wt 1.29 g; 81%; white solid; m.p. 104-106 °C; δ_H (300 MHz, $CDCl_3$) 7.49 – 7.33 (m, 3H, *H*-2', *H*-4' and *H*-6'), 7.26 – 7.13 (m, 2H, *H*-3' and *H*-5'), 6.15 (d, *J* = 3.5 Hz, 1H, *H*-3), 5.96 (ddt, *J* = 16.9, 10.3, 6.3 Hz, 1H, $H_aC{=}CH_bH_c$), 5.81 (d, *J* = 3.5 Hz, 1H, *H*-4), 5.18 (ddt, *J* = 10.3, 1.4, 1.2 Hz, 1H, $H_aC{=}CH_bH_c$), 5.16 (app. dq, *J* = 16.9, 1.4 Hz, 1H, $H_aC{=}CH_bH_c$), 4.44 (app. dt, *J* = 6.3, 1.2 Hz, 2H, CH_2); δ_C (75 MHz, $CDCl_3$) 157.7 (C=O), 148.9 (C_q), 142.2 (C_q), 132.5 (CH), 129.5 (CH), 128.3 (CH), 128.2 (CH), 125.4 (C_q), 118.8 (CH), 118.5 ($C{=}CH_2$), 112.9 (CH_a), 53.4 (NCH_2); ν_{max}/cm^{-1} 3115, 3094, 3051, 1633, 1594, 1492, 1455, 1425, 1398, 1302, 1285, 1214, 1178, 1036; m/z HRMS (NSI+) found 306.0128, $C_{14}H_{13}BrNO_2$ $[M + H]^+$ requires 306.0124.

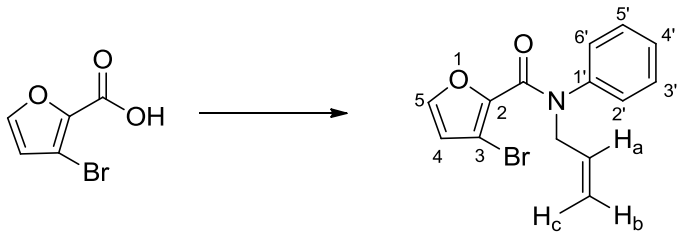
***N*-Allyl-4-bromo-*N*-phenylfuran-2-carboxamide (227c):**



227c

To a solution of 4-bromo-2-furoic acid (200 mg, 1.05 mmol) in dry dichloromethane (1.30 ml) containing *N,N*-dimethylformamide (1 drop) was carefully added oxalyl chloride (201 mg, 1.58 mmol) at 0 °C. The solution was allowed to rise to room temperature while stirring for 1.5 hours before the reaction mixture was concentrated *in vacuo*. Dry dichloromethane (0.80 ml) was introduced before a solution of *N*-allyl aniline (152 mg, 1.14 mmol) and triethylamine (0.28 ml, 2.00 mmol) in dry dichloromethane (0.80 ml) was then carefully added at 0 °C with stirring. The reaction mixture was then allowed to rise to room temperature while stirring overnight. Water (2 ml) was then added to the reaction mixture and extracted with dichloromethane (3 × 5ml). Combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (1:4 ethyl acetate/ petroleum ether) afforded the title compound: Wt 197 mg; 62%; white solid: m.p. 74-76 °C; δ_H (300 MHz, $CDCl_3$) 7.46 – 7.37 (m, 3H, *H*-2', *H*-4' and *H*-6'), 7.32 (d, *J* = 0.8 Hz, 1H, *H*-5), 7.22 – 7.10 (m, 2H, *H*-3' and *H*-5'), 5.93 (ddt, *J* = 17.0, 10.3, 6.3 Hz, 1H, $H_aC{=}CH_bH_c$), 5.73 (app. s, 1H, *H*-3), 5.16 (ddt, *J* = 10.3, 1.3, 1.1 Hz, 1H, $H_aC{=}CH_bH_c$), 5.14 (app. dq, *J* = 17.0, 1.4 Hz , 1H, $H_aC{=}CH_bH_c$), 4.43 (app. dt, *J* = 6.3, 1.2 Hz, 2H, CH_2); δ_C (75 MHz, $CDCl_3$) 157.8 (C=O), 147.4 (C_q), 142.6 (C_q), 141.9 (CH), 132.3 (CH), 129.6 (CH), 128.4 (CH), 128.2 (CH), 118.8 (CH), 118.6 ($C{=}CH_2$), 100.3 (C_q), 53.4 (NCH_2); ν_{max}/cm^{-1} 3121, 3058, 1636, 1594, 1479, 1399, 1294, 1283, 1196; m/z HRMS (NSI+) found 306.0131, $C_{14}H_{13}BrNO_2$ $[M + H]^+$ requires 306.0124.

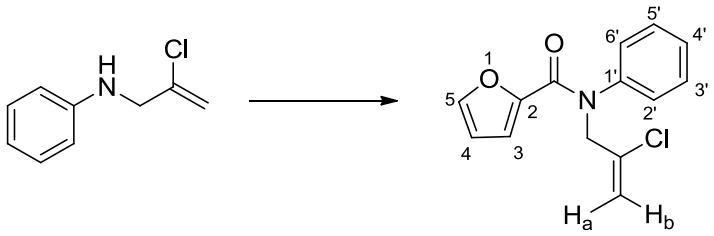
***N*-Allyl-3-bromo-*N*-phenylfuran-2-carboxamide (227d):**



227d

To a solution of **228b** (382 mg, 2.00 mmol) in dry dichloromethane (0.80 ml) containing *N*,*N*-dimethylformamide (1 drop) was carefully added oxalyl chloride (381 mg, 3.00 mmol) at 0 °C. The solution was allowed to rise to room temperature while stirring for 1.5 hours before the reaction mixture was concentrated *in vacuo*. Dry dichloromethane (0.80 ml) was introduced before a solution of *N*-allyl aniline (266 mg, 2.00 mmol) and triethylamine (0.28 ml, 2.00 mmol) in dry dichloromethane (0.80 ml) was then carefully added at 0 °C with stirring. The reaction mixture was then allowed to rise to room temperature while stirring overnight. Water (4 ml) was then added to the reaction mixture and extracted with dichloromethane (3 × 10 ml). Combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (1:4 diethyl ether/ petroleum ether) afforded the title compound: Wt 274 mg; 45%; white solid: m.p. 129-131 °C; δ_H (300 MHz, $CDCl_3$) 7.33 – 7.18 (m, 3H, *H*-2', *H*-4' and *H*-6'), 7.12 – 7.06 (m, 2H, *H*-3' and *H*-5'), 7.03 (d, *J* = 1.9 Hz, 1H, *H*-5), 6.35 (d, *J* = 1.9 Hz, 1H, *H*-4), 5.96 (ddt, *J* = 17.1, 10.2, 6.0 Hz, 1H, $H_aC{=}CH_bH_c$), 5.21 (ddt, *J* = 17.1, 1.3, 1.2 Hz, 1H, $H_aC{=}CH_bH_c$), 5.17 (ddt, 10.2, 1.4, 1.3 Hz, 1H, $H_aC{=}CH_bH_c$), 4.47 (app. dt, *J* = 6.0, 1.3 Hz, 2H, CH_2); δ_C (75 MHz, $CDCl_3$) 159.0 (C=O), 144.2 (C_q), 143.2 (C_q), 142.4 (CH), 132.6 (CH), 128.9 (CH), 126.9 (CH), 126.7 (CH), 118.1 ($C{=}CH_2$), 115.4 (CH), 104.5 (C_q), 53.0 (NCH_2); ν_{max}/cm^{-1} 3123, 1642, 1595, 1493, 1388, 1299, 1282, 1199 ; m/z HRMS (NSI+) found 306.0123, $C_{14}H_{13}BrNO_2$ $[M + H]^+$ requires 306.0124.

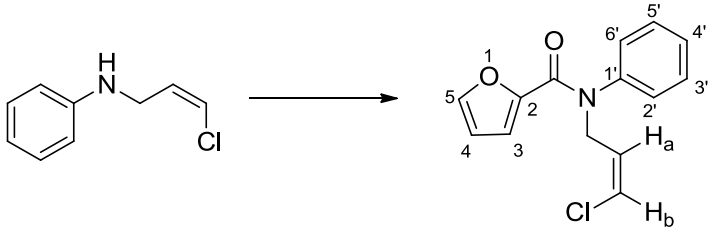
***N*-(2-Chloroallyl)-*N*-phenylfuran-2-carboxamide (227e):**



227e

2-Furoyl chloride (506 mg, 3.90 mmol) in dry dichloromethane (1.00 ml) was added carefully to a stirring solution of **229b** (650 mg, 3.90 mmol), triethylamine (0.54 ml, 3.90 mmol) and DMAP (13.0, 0.11 mmol mg) in dry dichloromethane (3.00 ml) at 0 °C. The solution was then allowed to rise to room temperature and stirred overnight. The solution was then diluted with dichloromethane (10 ml) and water (10 ml) was added. The mixture was extracted further with dichloromethane (2 × 10 ml) and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (1:19 ethyl acetate/ petroleum ether) afforded the title compound: Wt 770 mg; 76%; off-white solid: m.p. 100-102 °C δ_H (300 MHz, $CDCl_3$) 7.44 – 7.36 (m, 3H, *H*-2', *H*-4' and *H*-6'), 7.33 (dd, *J* = 1.7, 0.7 Hz, 1H, *H*-5), 7.30 – 7.23 (m, 2H, *H*-3' and *H*-5'), 6.21 (dd, *J* = 3.5, 1.7 Hz, 1H, *H*-4), 5.84 (app. d, *J* = 3.5 Hz, 1H, *H*-3), 5.33 (app. s, 2H, ClC=CH_2), 4.67 (s, 2H, NCH_2); δ_C (75 MHz, $CDCl_3$) 159.1 (C=O), 146.6 (C_q), 144.7 (CH-5), 142.0 (C_q), 137.1 (C_q), 129.5 (CH), 128.3 (CH), 128.1 (CH), 117.0 (CH), 115.4 (C=CH_2), 111.1 (CH), 55.7 (NCH_2); ν_{max}/cm^{-1} 3111, 1627, 1595, 1560, 1472, 1404, 1278, 1187, 1032; m/z HRMS (NSI+) found 262.0623, $C_{14}H_{13}ClNO_2$ $[M + H]^+$ requires 262.0629.

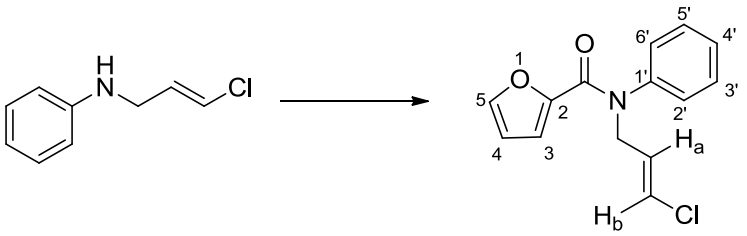
(*Z*)-*N*-(3-Chloroallyl)-*N*-phenylfuran-2-carboxamide (227f):



227f

2-Furoyl chloride (389 mg, 3.00 mmol) in dry dichloromethane (0.50 ml) was added carefully to a stirring solution of **229c** (500 mg, 3.00 mmol), triethylamine (0.40 ml, 3.00 mmol) and DMAP (7 mg, 0.06 mmol) in dry dichloromethane (2.00 ml) at 0 °C. The solution was then allowed to rise to room temperature and stirred overnight. The solution was then diluted with dichloromethane (10 ml) and water (10 ml) was added. The mixture was extracted further with dichloromethane (2 × 10 ml) and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (3:7 ethyl acetate/ petroleum ether) afforded the title compound: Wt 716 mg; 61%; white solid; m.p. 98-100 °C; δ_H (300 MHz, $CDCl_3$) 7.44 – 7.34 (m, 3H, *H*-2', *H*-4' and *H*-6'), 7.32 (dd, *J* = 1.7, 0.7 Hz, 1H, *H*-5), 7.23 – 7.15 (m, 2H, *H*-3' and *H*-5'), 6.19 (dd, *J* = 3.5, 1.7 Hz, 1H, *H*-4), 6.15 (dt, *J* = 7.2, 1.5 Hz, 1H, $H_aC{=}CH_bCl$), 6.02 (dt, *J* = 7.2, 6.5 Hz, 1H, $H_aC{=}CH_bCl$), 5.81 (app. d, *J* = 3.5 Hz, 1H, *H*-3), 4.66 (dd, *J* = 6.5, 1.5 Hz, 2H, CH_2); δ_C (75 MHz, $CDCl_3$) 159.2 (C=O), 146.8 (C_q), 144.5 (CH-5), 142.4 (C_q), 129.6 (CH), 128.2 (CH), 128.1 (CH), 126.7 (CH), 121.2 (CH), 116.7 (CH), 111.0 (CH), 47.3 (NCH_2); ν_{max}/cm^{-1} 3109, 3087, 1628, 1561, 1473, 1435, 1410, 1298, 1227, 1182, 1026; m/z HRMS (NSI+) found 262.0633, $C_{14}H_{13}ClNO_2$ $[M + H]^+$ requires 262.0629.

(*E*)-*N*-(3-Chloroallyl)-*N*-phenylfuran-2-carboxamide (227g):

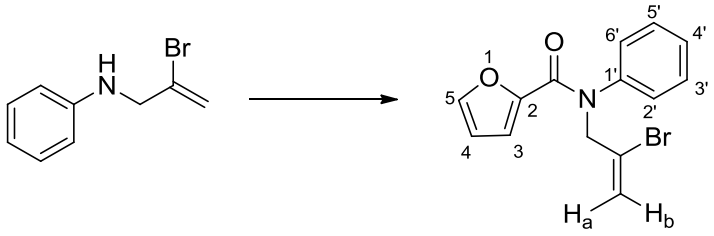


227g

2-Furoyl chloride (389 mg, 3.00 mmol) in dry dichloromethane (0.50 ml) was added carefully to a stirring solution of **229d** (500 mg, 3.00 mmol), triethylamine (0.40 ml, 3.00 mmol) and DMAP (7 mg, 0.06 mmol) in dry dichloromethane (2.00 ml) at 0 °C. The solution was then allowed to rise to room temperature and stirred overnight. The solution was then diluted with dichloromethane (10 ml) and water (10 ml) was added. The mixture was extracted further with dichloromethane (2 × 10 ml) and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (3:7 ethyl acetate/ petroleum ether) afforded the title compound: Wt

637 mg; 54%; off-white solid; m.p. 58-60 °C; δ_H (300 MHz, $CDCl_3$) 7.47 – 7.35 (m, 3H, *H*-2', *H*-4' and *H*-6'), 7.34 – 7.29 (m, 1H, *H*-5), 7.21 – 7.12 (m, 2H, *H*-3' and *H*-5'), 6.18 (dd, *J* = 3.5, 1.7 Hz, 1H, *H*-4), 6.13 (app. d, *J* = 13.3 Hz, 1H, $H_aC{=}CH_bCl$), 6.07 (dt, *J* = 13.3, 6.1 Hz, 1H, $H_aC{=}CH_bCl$), 5.77 (app. d, *J* = 3.5 Hz, 1H, *H*-3), 4.40 (app. dd, *J* = 6.1, 1.2 Hz, 2H, CH_2); δ_C (75 MHz, $CDCl_3$) 158.9 (C=O), 146.7 (C_q), 144.6 (CH-5), 142.1 (C_q), 129.7 (CH), 128.4 (CH), 128.4 (CH), 127.7 (CH), 122.5 (CH), 116.7 (CH), 111.0 (CH), 50.4 (NCH_2); ν_{max}/cm^{-1} 3111, 3067, 1631, 1561, 1473, 1408, 1302, 1283, 1227, 1183, 1026; m/z HRMS (NSI+) found 262.0633, $C_{14}H_{13}ClNO_2$ $[M + H]^+$ requires 262.0629.

***N*-(2-Bromoallyl)-*N*-phenylfuran-2-carboxamide (227h):**

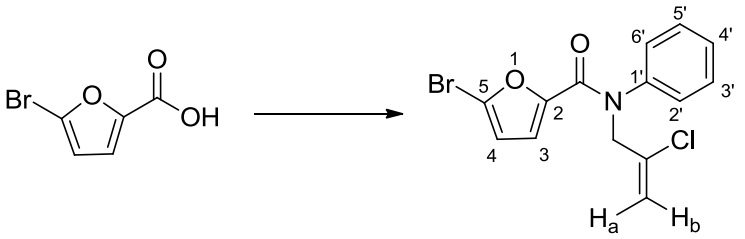


227h

2-Furoyl chloride (261 mg, 2.00 mmol) in dry dichloromethane (0.50 ml) was added carefully to a stirring solution of **229e** (424 mg, 2.00 mmol), triethylamine (0.27 ml, 2.00 mmol) and DMAP (5 mg, 0.04 mmol) in dry dichloromethane (1.50 ml) at 0 °C. The solution was then allowed to rise to room temperature and stirred overnight. The solution was then diluted with dichloromethane (10 ml) and water (10 ml) was added. The mixture was extracted further with dichloromethane (2 × 10 ml) and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (3:7 ethyl acetate/ petroleum ether) afforded the title compound: Wt 440 mg; 72%; white solid; m.p. 106-108 °C; δ_H (300 MHz, $CDCl_3$) 7.44 – 7.35 (m, 3H, *H*-2', *H*-4' and *H*-6'), 7.33 (dd, *J* = 1.7, 0.7 Hz, 1H, *H*-5), 7.31 – 7.24 (m, 2H, *H*-3' and *H*-5'), 6.21 (dd, *J* = 3.5, 1.7 Hz, 1H, *H*-4), 5.85 (app. d, *J* = 3.5 Hz, 1H, *H*-3), 5.77 (dt, *J* = 2.0, 1.3 Hz, 1H, $ClC{=}CH_bH_a$), 5.63 – 5.54 (m, 1H, $ClC{=}CH_bH_a$), 4.80 – 4.67 (m, 2H, NCH_2); δ_C (75 MHz, $CDCl_3$) 159.1 (C=O), 146.6 (C_q), 144.7 (CH-5), 142.0 (C_q), 129.5 (CH), 128.3 (CH), 128.1 (CH), 128.0 (C_q), 119.6 ($C{=}CH_2$), 117.1 (CH), 111.1 (CH), 57.4 (NCH_2); ν_{max}/cm^{-1} 3112, 3066, 3042, 2946, 1630, 1595, 1561, 1472, 1403, 1370,

1277, 1187, 1141, 1032; m/z HRMS (NSI+) found 306.0130, $C_{14}H_{13}BrNO_2$ $[M + H]^+$ requires 306.0124.

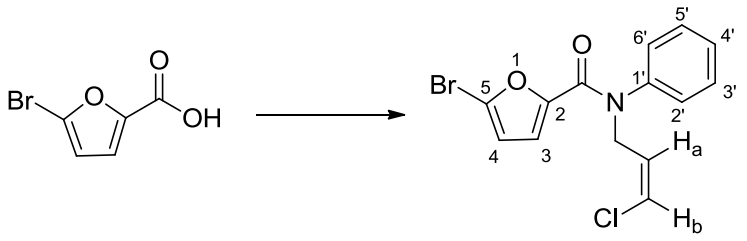
5-Bromo-*N*-(2-chloroallyl)-*N*-phenylfuran-2-carboxamide (227i):



227i

To a solution of 5-bromo-2-furoic acid (115 mg, 0.60 mmol) in dry dichloromethane (0.80 ml) containing *N*,*N*-dimethylformamide (1 drop) was carefully added oxalyl chloride (114 mg, 0.90 mmol) at 0 °C. The solution was allowed to rise to room temperature while stirring for 1 hour before the reaction mixture was concentrated *in vacuo*. A solution of (*E*)-*N*-(3-chloroallyl)aniline (100 mg, 0.60 mmol) and triethylamine (0.18 ml, 1.30 mmol) in dry dichloromethane (0.25 ml) was then carefully added at 0 °C and allowed to rise to room temperature while stirring overnight. If the solution became too viscous to stir efficiently, more dry dichloromethane was added until the reaction mixture dissolved. Water (10 ml) added to the reaction mixture and extracted with dichloromethane (3 × 10 ml). Combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (1:9 ethyl acetate/ petroleum ether) afforded the title compound: Wt 84 mg; 77%; clear golden oil: δ_H (300 MHz, $CDCl_3$) 7.47 – 7.33 (m, 3H, *H*-2', *H*-4' and *H*-6'), 7.32 – 7.20 (m, 2H, *H*-3' and *H*-5'), 6.14 (d, *J* = 3.6 Hz, 1H, C*H*$_{furan}$), 5.82 (d, *J* = 3.6 Hz, 1H, C*H*$_{furan}$), 5.32 (s, 1H, C*H*$_{alkene}$), 5.31 (s, 1H, C*H*$_{alkene}$), 4.64 (s, 2H, C*H*$_2$); δ_C (75 MHz, $CDCl_3$) 157.9 (C=O), 148.4 (C_q), 141.6 (C_q), 136.9 (C_q), 129.6 (CH), 128.6 (CH), 128.1 (CH), 125.9 (C_q), 119.4, 115.7 (C=*C*H_2), 113.1 (CH), 55.7 (NCH_2); ν_{max}/cm^{-1} 3063, 2926, 1644, 1595, 1494, 1462, 1382, 1281, 1210, 1154, 1125, 1008; m/z HRMS (NSI+) found 339.9736, $C_{14}H_{12}BrClNO_2$ $[M + H]^+$ requires 339.9734.

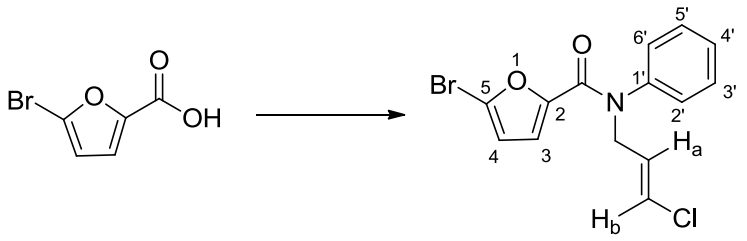
(*Z*)-5-Bromo-*N*-(3-chloroallyl)-*N*-phenylfuran-2-carboxamide (227j):



227j

To a solution of 5-bromo-2-furoic acid (191 mg, 1.00 mmol) in dry dichloromethane (2.60 ml) containing *N*,*N*-dimethylformamide (1 drop) was carefully added oxalyl chloride (191 mg, 1.50 mmol) at 0 °C. The solution was allowed to rise to room temperature while stirring for 1 hour before the reaction mixture was concentrated *in vacuo*. A solution of (*Z*)-*N*-(3-chloroallyl)aniline (168 mg, 1.00 mmol) and triethylamine (0.15 ml, 1.00 mmol) in dry dichloromethane (1.60 ml) was then carefully added at 0 °C and allowed to rise to room temperature while stirring overnight. If the solution became too viscous to stir efficiently, more dry dichloromethane was added until the reaction mixture dissolved. Water (10 ml) added to the reaction mixture and extracted with dichloromethane (3 × 10 ml). Combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (1:4 diethyl ether/ petroleum ether) afforded the title compound: Wt 282 mg; 83%; white solid; m.p. 80-82 °C; δ_H (300 MHz, $CDCl_3$) 7.48 – 7.35 (m, 3H, *H*-2', *H*-4' and *H*-6'), 7.21 – 7.11 (m, 2H, *H*-3' and *H*-5'), 6.14 (d, *J* = 13.3 Hz, 1H, $H_aC{=}CH_bCl$), 6.13 (d, *J* = 3.6 Hz, 1H, CH_{furan}), 6.07 (dt, *J* = 13.3, 6.1 Hz, 1H, $H_aC{=}CH_bCl$), 5.78 (d, *J* = 3.6 Hz, 1H, CH_{furan}), 4.38 (d, *J* = 6.1 Hz, 2H, NCH_2); δ_C (75 MHz, $CDCl_3$) 157.7 (C=O), 148.5 (C_q), 141.6 (C_q), 129.7 (CH), 128.6 (CH), 128.4 (CH), 127.5 (CH), 125.7 (C_q), 122.7 (CH), 119.0 (CH), 113.0 (CH), 50.4 (CH_2); ν_{max}/cm^{-1} 3064, 2931, 1640, 1594, 1494, 1462, 1391, 1295, 1209, 1168, 1013; m/z HRMS (NSI+) found 339.9741, $C_{14}H_{12}BrClNO_2$ $[M + H]^+$ requires 339.9734.

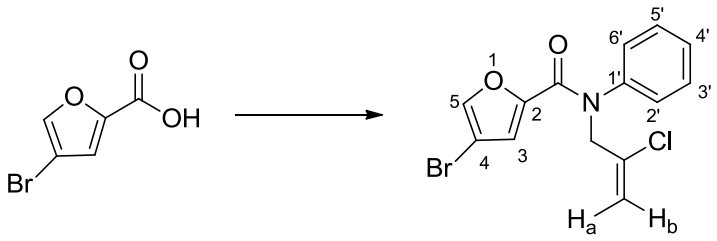
(*E*)-5-Bromo-*N*-(3-chloroallyl)-*N*-phenylfuran-2-carboxamide (227k):



227k

To a solution of 5-bromo-2-furoic acid (115 mg, 0.60 mmol) in dry dichloromethane (0.80 ml) containing *N*,*N*-dimethylformamide (1 drop) was carefully added oxalyl chloride (114 mg, 0.90 mmol) at 0 °C. The solution was allowed to rise to room temperature while stirring for 1 hour before the reaction mixture was concentrated *in vacuo*. A solution of (*E*)-*N*-(3-chloroallyl)aniline (100 mg, 0.60 mmol) and triethylamine (0.18 ml, 1.30 mmol) in dry dichloromethane (0.25 ml) was then carefully added at 0 °C and allowed to rise to room temperature while stirring overnight. If the solution became too viscous to stir efficiently, more dry dichloromethane was added until the reaction mixture dissolved. Water (10 ml) added to the reaction mixture and extracted with dichloromethane (3 × 10 ml). Combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (1:4 diethyl ether/ petroleum ether) afforded the title compound: Wt 263 mg; 77%; white solid: m.p. 54-56 °C; δ_H (300 MHz, $CDCl_3$) 7.45 – 7.35 (m, 3H, *H*-2', *H*-4' and *H*-6'), 7.22 – 7.14 (m, 2H, *H*-3' and *H*-5'), 6.16 (dt, *J* = 7.2, 1.5 Hz, 1H, $H_aC{=}CH_bCl$), 6.13 (d, *J* = 3.6 Hz, 1H, CH_{furan}), 6.01 (dt, *J* = 7.2, 6.6 Hz, 1H, $H_aC{=}CH_bCl$), 5.80 (d, *J* = 3.6 Hz, 1H, CH_{furan}), 4.64 (dd, *J* = 6.6, 1.5 Hz, 2H, NCH_2); δ_C (75 MHz, $CDCl_3$) 157.9 (C=O), 148.6 (C_q), 142.0 (C_q), 129.6 (CH), 128.4 (CH), 128.1 (CH), 126.5 (CH), 125.7 (C_q), 121.5 (CH), 119.0 (CH), 113.0 (CH), 47.3 (CH_2); ν_{max}/cm^{-1} 3118, 3070, 2926, 1632, 1460, 1430, 1404, 1317, 1294, 1215, 1170, 1028; m/z HRMS (NSI+) found 339.9740, $C_{14}H_{12}BrClNO_2$ $[M + H]^+$ requires 339.9734.

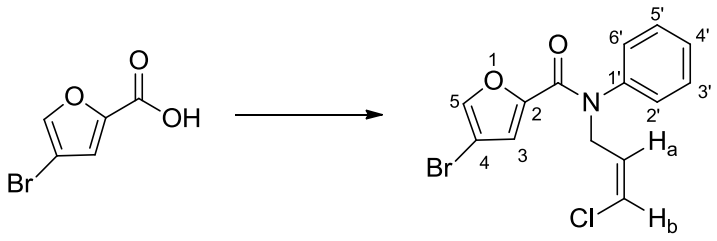
4-bromo-*N*-(2-chloroallyl)-*N*-phenylfuran-2-carboxamide (227l):



227l

To a solution of **228a** (115 mg, 0.60 mmol) in dry dichloromethane (0.80 ml) containing *N*,*N*-dimethylformamide (1 drop) was carefully added oxalyl chloride (114 mg, 0.90 mmol) at 0 °C. The solution was allowed to rise to room temperature while stirring for 1 hour before the reaction mixture was concentrated *in vacuo*. A solution of *N*-(2-chloroallyl)aniline (100 mg, 0.60 mmol) and triethylamine (0.18 ml, 1.30 mmol) in dry dichloromethane (0.25 ml) was then carefully added at 0 °C and allowed to rise to room temperature while stirring overnight. If the solution became too viscous to stir efficiently, more dry dichloromethane was added until the reaction mixture dissolved. Water (10 ml) added to the reaction mixture and extracted with dichloromethane (3 × 10 ml). Combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (1:4 diethyl ether/ petroleum ether) afforded the title compound: Wt 88 mg; 43%; white solid; m.p. 53-55 °C; δ_H (300 MHz, $CDCl_3$) 7.48 – 7.35 (m, 3H, *H*-2', *H*-4' and *H*-6'), 7.33 (d, *J* = 0.7 Hz, 1H, *H*-5), 7.31 – 7.18 (m, 2H, *H*-3' and *H*-5'), 5.78 (app. s, 1H, *H*-3), 5.34 (d, *J* = 1.5 Hz, 1H, CH_{alkene}), 5.31 (d, *J* = 1.5 Hz, 1H, CH_{alkene}), 4.65 (s, 2H, CH_2); δ_C (75 MHz, $CDCl_3$) 158.1 (C=O), 147.0 (C_q), 142.9 (CH-5), 141.3 (C_q), 136.8 (C_q), 129.7 (CH), 128.7 (CH), 128.1 (CH), 119.4 (CH), 115.8 ($C=CH_2$), 100.45 (C_q), 55.7 (NCH_2); ν_{max}/cm^{-1} 2967, 2938, 1639, 1594, 1494, 1476, 1392, 1302, 1279, 1196, 1142, 1017; m/z HRMS (NSI+) found 339.9727, $C_{14}H_{12}BrClNO_2$ $[M + H]^+$ requires 339.9734.

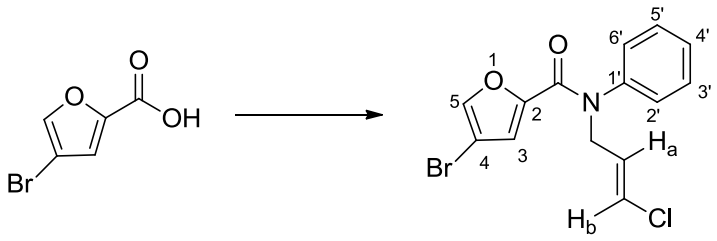
(*Z*)-4-Bromo-*N*-(3-chloroallyl)-*N*-phenylfuran-2-carboxamide (227m):



227m

To a solution of 4-bromo-2-furoic acid (115 mg, 0.60 mmol) in dry dichloromethane (0.80 ml) containing *N*,*N*-dimethylformamide (1 drop) was carefully added oxalyl chloride (114 mg, 0.90 mmol) at 0 °C. The solution was allowed to rise to room temperature while stirring for 1 hour before the reaction mixture was concentrated *in vacuo*. A solution of (*Z*)-*N*-(3-chloroallyl)aniline (100 mg, 0.60 mmol) and triethylamine (0.18 ml, 1.30 mmol) in dry dichloromethane (0.25 ml) was then carefully added at 0 °C and allowed to rise to room temperature while stirring overnight. If the solution became too viscous to stir efficiently, more dry dichloromethane was added until the reaction mixture dissolved. Water (10 ml) added to the reaction mixture and extracted with dichloromethane (3 × 10 ml). Combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (1:4 diethyl ether/ petroleum ether) afforded the title compound: Wt 103 mg; 51%; white solid; m.p. 69-71 °C; δ_H (300 MHz, $CDCl_3$) δ 7.47 – 7.36 (m, 3H, *H*-2', *H*-4' and *H*-6'), 7.32 (d, *J* = 0.8 Hz, 1H, *H*-5), 7.22 – 7.14 (m, 2H, *H*-3' and *H*-5'), 6.17 (dt, *J* = 7.2, 1.5 Hz, 1H, $H_aC{=}CH_bCl$), 6.00 (dt, *J* = 7.2, 6.6 Hz, 1H, $H_aC{=}CH_bCl$), 5.77 (app. s, 1H, *H*-3), 4.65 (dd, *J* = 6.6, 1.5 Hz, 2H, CH_2); δ_C (75 MHz, $CDCl_3$) 158.1 (C=O), 147.1 (C_q), 142.7 (CH-5), 141.7 (C_q), 129.8 (CH), 128.6 (CH), 128.1 (CH), 126.3 (CH), 121.61 (CH), 119.1 (CH), 100.4 (C_q), 47.3 (CH_2); ν_{max}/cm^{-1} 3146, 3128, 3052, 2923, 1640, 1595, 1556, 1494, 1476, 1424, 1400, 1287, 1200, 1186, 1139, 1027; m/z HRMS (NSI+) found 339.9737, $C_{14}H_{12}BrClNO_2$ $[M + H]^+$ requires 339.9734.

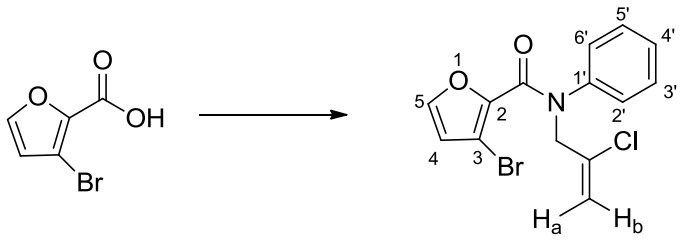
(*E*)-4-Bromo-*N*-(3-chloroallyl)-*N*-phenylfuran-2-carboxamide (227n):



227n

To a solution of 4-bromo-2-furoic acid (115 mg, 0.60 mmol) in dry dichloromethane (0.80 ml) containing *N*,*N*-dimethylformamide (1 drop) was carefully added oxalyl chloride (114 mg, 0.90 mmol) at 0 °C. The solution was allowed to rise to room temperature while stirring for 1 hour before the reaction mixture was concentrated *in vacuo*. A solution of (*E*)-*N*-(3-chloroallyl)aniline (100 mg, 0.60 mmol) and triethylamine (0.18 ml, 1.30 mmol) in dry dichloromethane (0.25 ml) was then carefully added at 0 °C and allowed to rise to room temperature while stirring overnight. If the solution became too viscous to stir efficiently, more dry dichloromethane was added until the reaction mixture dissolved. Water (10 ml) added to the reaction mixture and extracted with dichloromethane (3 × 10 ml). Combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (3:7 diethyl ether/ petroleum ether) afforded the title compound: Wt 104 mg; 51%; white solid; m.p. 60-62 °C; δ_H (300 MHz, $CDCl_3$) δ 7.49 – 7.37 (m, 3H, *H*-2', *H*-4' and *H*-6'), 7.32 (d, *J* = 0.8 Hz, 1H, *H*-5), 7.21 – 7.12 (m, 2H, *H*-3' and *H*-5'), 6.14 (d, *J* = 13.4 Hz, 1H, $H_aC{=}CH_bCl$), 6.11 – 6.01 (m, 1H, $H_aC{=}CH_bCl$), 5.73 (app. s, 1H, *H*-3), 4.39 (d, *J* = 6.2 Hz, 2H, CH_2); δ_C (75 MHz, $CDCl_3$) 157.8 (C=O), 147.0 (C_q), 142.8 (CH-5), 141.4 (C_q), 129.9 (CH), 128.8 (CH), 128.3 (CH), 127.4 (CH), 122.8 (CH), 119.09 (CH), 100.4 (C_q), 50.5 (CH_2); ν_{max}/cm^{-1} 3144, 3065, 2926, 2852, 1644, 1595, 1493, 1481, 1394, 1298, 1074; m/z HRMS (NSI+) found 339.9737, $C_{14}H_{12}BrClNO_2$ $[M + H]^+$ requires 339.9734.

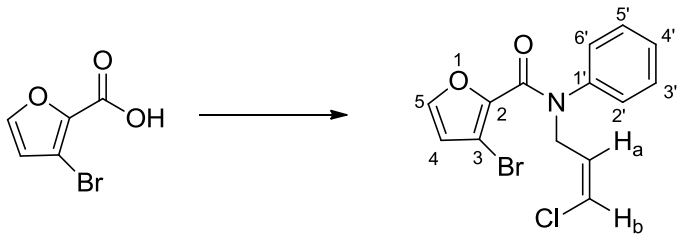
3-Bromo-*N*-(2-chloroallyl)-*N*-phenylfuran-2-carboxamide (227o):



227o

To a solution of 3-bromo-2-furoic acid (229 mg, 1.20 mmol) in dry dichloromethane (1.60 ml) containing *N*,*N*-dimethylformamide (1 drop) was carefully added oxalyl chloride (228 mg, 1.80 mmol) at 0 °C. The solution was allowed to rise to room temperature while stirring for 1 hour before the reaction mixture was concentrated *in vacuo*. A solution of *N*-(2-chloroallyl)aniline (200 mg, 1.20 mmol) and triethylamine (0.36 ml, 2.60 mmol) in dry dichloromethane (0.50 ml) was then carefully added at 0 °C and allowed to rise to room temperature while stirring overnight. If the solution became too viscous to stir efficiently, more dry dichloromethane was added until the reaction mixture dissolved. Water (15 ml) added to the reaction mixture and extracted with dichloromethane (3 × 15 ml). Combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (1:4 diethyl ether/ petroleum ether) afforded the title compound: Wt 286 mg; 70%; golden, viscous oil: δ_H (300 MHz, $CDCl_3$) δ 7.44 – 7.28 (m, 3H, *H*-2', *H*-4' and *H*-6'), 7.28 – 7.21 (m, 2H, *H*-3' and *H*-5'), 7.14 (d, *J* = 1.9 Hz, 1H, *H*-5), 6.46 (d, *J* = 1.9 Hz, 1H, *H*-4), 5.51 (dt, *J* = 2.9, 1.3 Hz, 1H, CH_{alkene}), 5.49 – 5.43 (m, 1H, CH_{alkene}), 4.75 (app. s, 2H, CH_2); δ_C (75 MHz, $CDCl_3$) 159.3 (C=O), 143.7 (C_q), 143.5 (CH-5), 142.1 (C_q), 136.7 (C_q), 129.0 (CH), 127.2 (CH), 126.5 (CH), 115.6 (CH), 115.0 (CH), 105.2 (C_q), 55.5 (CH_2); ν_{max}/cm^{-1} 3126, 3040, 1646, 1595, 1492, 1384, 1301, 1280, 1229, 1199, 1157, 1071, 1015; m/z HRMS (NSI+) found 339.9736, $C_{14}H_{12}BrClNO_2$ $[M + H]^+$ requires 339.9734.

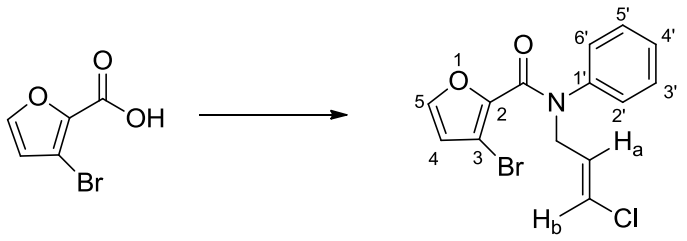
(*Z*)-3-Bromo-*N*-(3-chloroallyl)-*N*-phenylfuran-2-carboxamide (227p):



227p

To a solution of 3-bromo-2-furoic acid (229 mg, 1.20 mmol) in dry dichloromethane (1.60 ml) containing *N*,*N*-dimethylformamide (1 drop) was carefully added oxalyl chloride (228 mg, 1.80 mmol) at 0 °C. The solution was allowed to rise to room temperature while stirring for 1 hour before the reaction mixture was concentrated *in vacuo*. A solution of (*Z*)-*N*-(3-chloroallyl)aniline (200 mg, 1.2 mmol) and triethylamine (0.36 ml, 2.60 mmol) in dry dichloromethane (0.50 ml) was then carefully added at 0 °C and allowed to rise to room temperature while stirring overnight. If the solution became too viscous to stir efficiently, more dry dichloromethane was added until the reaction mixture dissolved. Water (15 ml) added to the reaction mixture and extracted with dichloromethane (3 × 15 ml). Combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (1:4 diethyl ether/ petroleum ether) afforded the title compound: Wt 343 mg; 84%; clear, yellow, viscous oil: δ_H (300 MHz, $CDCl_3$) 7.34 – 7.20 (m, 3H, *H*-2', *H*-4' and *H*-6'), 7.14 – 7.05 (m, 2H, *H*-3' and *H*-5'), 7.03 (d, *J* = 1.9 Hz, 1H, *H*-5), 6.36 (d, *J* = 1.9 Hz, 1H, *H*-4), 6.16 (dt, *J* = 7.2, 1.5 Hz, 1H, $H_aC{=}CH_bCl$), 6.02 (dt, *J* = 7.2, 6.4 Hz, 1H, $H_aC{=}CH_bCl$), 4.68 (dd, *J* = 6.4, 1.5 Hz, 2H, CH_2); δ_C (75 MHz, $CDCl_3$) 159.3 (C=O), 143.9 (C_q), 143.4 (CH-5), 142.1 (C_q), 129.0 (CH), 127.2 (CH), 126.74 (CH), 126.7 (CH), 121.2 (CH), 115.6 (CH), 105.0 (C_q), 47.2 (CH_2); ν_{max}/cm^{-1} 3124, 3039, 1643, 1595, 1563, 1492, 1387, 1367, 1293, 1180, 1075; m/z HRMS (NSI+) found 339.9732, $C_{14}H_{12}BrClNO_2$ $[M + H]^+$ requires 339.9734.

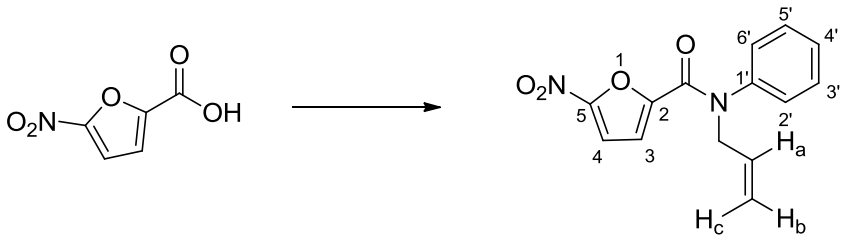
(*E*)-3-Bromo-*N*-(3-chloroallyl)-*N*-phenylfuran-2-carboxamide (227q):



227q

To a solution of 3-bromo-2-furoic acid (229 mg, 1.20 mmol) in dry dichloromethane (1.60 ml) containing *N*,*N*-dimethylformamide (1 drop) was carefully added oxalyl chloride (228 mg, 1.80 mmol) at 0 °C. The solution was allowed to rise to room temperature while stirring for 1 hour before the reaction mixture was concentrated *in vacuo*. A solution of (*E*)-*N*-(3-chloroallyl)aniline (200 mg, 1.20 mmol) and triethylamine (0.36 ml, 2.60 mmol) in dry dichloromethane (0.50 ml) was then carefully added at 0 °C and allowed to rise to room temperature while stirring overnight. If the solution became too viscous to stir efficiently, more dry dichloromethane was added until the reaction mixture dissolved. Water (15 ml) added to the reaction mixture and extracted with dichloromethane (3 × 15 ml). Combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (1:4 diethyl ether/ petroleum ether) afforded the title compound: Wt 331 mg; 81%; clear, yellow, viscous oil: δ_H ((300 MHz, $CDCl_3$) δ 7.30 – 7.13 (m, 3H, H-2', H-4' and H-6'), 7.06 – 6.97 (m, 2H, *H*-3' and *H*-5'), 6.94 (d, *J* = 1.9 Hz, 1H, *H*-5), 6.29 (d, *J* = 1.9 Hz, 1H, *H*-4), 6.10 (d, *J* = 13.4 Hz, 1H. $H_aC{=}CH_bCl$), 6.07 – 5.95 (m, 1H, $H_aC{=}CH_bCl$), 4.36 (d, *J* = 6.0 Hz, 2H, CH_2); δ_C (75 MHz, CDCl3) 156.0 (C=O), 143.8 (C_q), 143.4 (CH-5), 141.9 (C_q), 129.2 (CH), 127.6 (CH), 127.3 (CH), 127.0 (CH), 122.5 (CH), 115.6 (CH), 105.2 (C_q), 50.3 (CH_2); ν_{max}/cm^{-1} 3125, 3066, 1639, 1595, 1563, 1492, 1388, 1367, 1298, 1282, 1181, 1066; m/z HRMS (NSI+) found 339.9736, $C_{14}H_{12}BrClNO_2$ $[M + H]^+$ requires 339.9734.

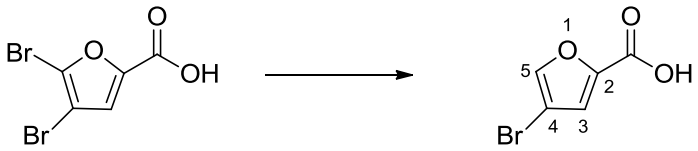
***N*-Allyl-5-nitro-*N*-phenylfuran-2-carboxamide (227r):**



227r

To a solution of 5-nitro-2-furoic acid (1.00 g, 6.40 mmol) in dry dichloromethane (8.00 ml) containing *N*,*N*-dimethylformamide (1 drop) was carefully added oxalyl chloride (1.23 g, 9.70 mmol) at 0 °C. The solution was allowed to rise to room temperature while stirring for 1.5 hours before the reaction mixture was concentrated *in vacuo*. Dry dichloromethane (2.50 ml) was introduced before a solution of *N*-allyl aniline (929 mg, 7.00 mmol) and triethylamine (1.80 ml, 12.0 mmol) in dry dichloromethane (2.50 ml) was then carefully added at 0 °C with stirring. The reaction mixture was then allowed to rise to room temperature while stirring overnight. Water (10 ml) was then added to the reaction mixture and extracted with dichloromethane (3 × 25 ml). Combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (3:7 diethyl ether/ petroleum ether) afforded the title compound: Wt 1.27 g; 73%; beige solid; m.p. 70-73 °C; δ_H (300 MHz, $CDCl_3$) 7.48 – 7.35 (m, 3H, *H*-2', *H*-4' and *H*-6'), 7.24 – 7.13 (m, 2H, *H*-3' and *H*-5'), 7.06 (d, *J* = 3.8 Hz, 1H, *H*-4), 6.29 (br s, 1H, *H*-3), 5.94 (ddt, *J* = 17.0, 10.2, 6.4 Hz, 1H, $H_aC{=}CH_bH_c$), 5.21 (app. dq, *J* = 10.2, 1.2 Hz, 1H, $H_aC{=}CH_bH_c$), 5.18 (app. dq, *J* = 17.0, 1.4 Hz, 1H, $H_aC{=}CH_bH_c$), 4.46 (d, *J* = 6.4 Hz, 2H, CH_2); δ_C (75 MHz, $CDCl_3$) 156.9 (C=O), 147.9 (C_q), 141.2 (C_q), 131.7 (CH), 129.7 (CH), 128.8 (CH), 128.0 (CH), 119.3 ($C{=}CH_2$), 117.6 (CH), 111.0 (CH), 53.7 (NCH_2); ν_{max}/cm^{-1} 3152, 3137, 3104, 2988, 2921, 1642, 1576, 1526, 1494, 1431, 1408, 1377, 1355, 1299, 1134, 1048, 1003; m/z HRMS (NSI+) found 295.0682, $C_{14}H_{12}N_2O_4Na$ $[M + Na]^+$ requires 295.0689.

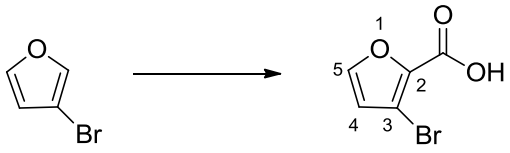
4-Bromo-2-furoic acid (228a):[129]



228a

Zn powder (242 mg, 3.70 mmol) was added to a vigorously stirring solution of 3,4-dibromo-2-furoic acid (1.00 g, 3.70 mmol) in water (11.5 ml) and NH_4OH (3.30 ml) and left stirring for 3 h. The reaction mixture was filtered through a pad of Celite and acidified to pH 2 with 2 M HCl. The filtrate was extracted with ethyl acetate (3 × 15 ml) and dried (Na_2SO_4) before being concentrated to dryness *in vacuo*. The crude product was recrystallised from toluene to afford the title compound in >96% purity: Wt 304 mg; 40%; white solid; δ_H (300 MHz, CDCl3) 11.09 (br s, 1H, CO_2H), 7.68 (d, J = 0.8 Hz, 1H. *H*-5), 7.37 (d, J = 0.8 Hz, 1H, *H*-3); δ_C (101 MHz, CDCl3) 161.1 (C=O), 145.0 (CH-5), 130.0 (C_q-2), 123.9 (CH-3), 104.3 (C_q-4); ν_{max}/cm^{-1} 3150, 3028, 2903, 2834, 1678, 1583, 1481, 1420, 1278, 1195, 1125, 1074.

3-Bromo-2-furoic acid (228b):[129]

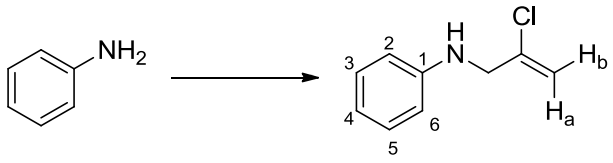


228b

3-Bromofuran (1.00 g, 6.80 mmol) was introduced slowly to a stirring solution of freshly prepared LDA (786 mg, 7.30 mmol) in anhydrous tetrahydrofuran at -78 °C and stirred for 30 mins at this temperature. The mixture was then carefully poured into a solution of anhydrous tetrahydrofuran saturated with CO_2 at -78 °C with stirring and left to stir for 10 mins at this temperature. The mixture was then allowed to rise to room temperature and the excess CO_2 allowed to sublime. The mixture was then carefully poured into water (50 ml) and acidified to pH 3 with 2 M HCl. This was then extracted with ethyl acetate (3 × 50 ml) and the combined extracts dried (Na_2SO_4) before being concentrated *in vacuo* to dryness to afford the title compound with no further purification required: Wt 1.02 g; 79%; brown/orange solid; δ_H (300 MHz, CDCl3)

10.94 (s, 1H, CO_2H), 7.58 (d, J = 1.9 Hz, 1H, *H*-5), 6.67 (d, J = 1.9 Hz, 1H, *H*-4); 162.3 (C=O), 146.9 (CH-5), 140.3 (C_q), 117.4 (CH-4), 111.1 (C_q); ν_{max}/cm^{-1} 3150, 2982, 2836, 2804, 2651, 1671, 1566, 1474, 1433, 1289, 1206, 1182, 1074.

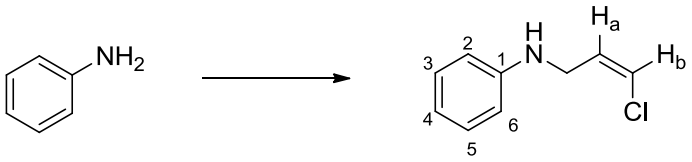
_N_-(2-Chloroallyl)aniline (229b):[130]



229b

2,3-dichloroprop-1-ene (1.11 g, 10.0 mmol) was added dropwise over 30 mins at 50 °C to a stirring mixture of aniline (0.93 g, 20.0 mmol) in water (4.00 ml) and left overnight at 50 °C. Reaction mixture then cooled to 10 °C and NaOH (1.00 g, 25.0 mmol) added and left for 1 hour with stirring. The mixture was then extracted with diethyl ether (3 × 10 ml) and the combined organic phases dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (5:95 ethyl acetate / petroleum ether) afforded the title compound: Wt 548 mg; 33%; yellow oil; δ_H (300 MHz, $CDCl_3$) 7.24 – 7.12 (m, 2H, *H*-3 and *H*-5), 6.84 – 6.70 (m, 1H, *H*-4), 6.70 – 6.55 (m, 2H, *H*-2 and *H*-6), 5.43 (dt, J = 2.9, 1.5 Hz, 1H, C=CH_aH_b), 5.33 (dt, J = 2.9, 1.3 Hz, 1H, C=CH_bH_a), 4.15 (br s, 1H, N*H*), 3.94 (app. t, J = 1.5, 1.3 Hz, 2H, CH_2); δ_C (75 MHz, $CDCl_3$) 146.8 (C_q-1), 139.3 (ClC_q), 129.3 (CH), 118.2 (CH), 113.0 (CH), 112.5 (C=CH_2), 50.2 (CH_2); ν_{max}/cm^{-1} 3417, 3087, 3054, 3023, 2920, 2843, 1644, 1603, 1507, 1322, 1266, 1154, 1093.

(*Z*)-*N*-(3-Chloroallyl)aniline (229c):

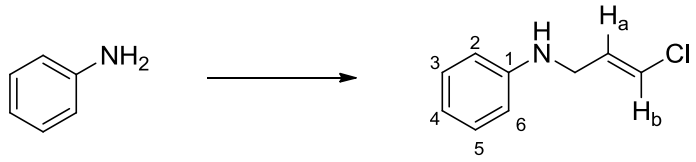


229c

(*Z*)-1,3-dichloroprop-1-ene (1.11 g, 10.0 mmol) was added dropwise over 30 mins at 50 °C to a stirring mixture of aniline (0.93 g, 20.0 mmol) in water (4.00 ml) and left overnight at 50 °C. Reaction mixture then cooled to 10 °C and NaOH (1.00 g, 25.0 mmol) added and left for 1 hour with stirring. The mixture was then extracted with

diethyl ether (3 × 10 ml) and the combined organic phases dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (5:95 ethyl acetate / petroleum ether) afforded the title compound: Wt 485 mg; 29%; yellow oil; δ_H (300 MHz, $CDCl_3$) 7.25 – 7.15 (m, 2H, *H*-3 and *H*-5), 6.75 (app. t, *J* = 7.3 Hz, 1H, *H*-4), 6.64 (dd, *J* = 8.5, 0.9 Hz, 2H, *H*-2 and *H*-6), 6.18 (dt, *J* = 7.1, 1.8 Hz, 1H, CH_a=C*H*$_b$Cl), 5.92 (dt, *J* = 7.1, 6.1 Hz, 1H, C*H*$_a$=CH_bCl), 3.99 (dd, *J* = 6.1, 1.8 Hz, 2H, C*H*$_2$), 3.86 (br s, 1H, N*H*); δ_C (75 MHz, $CDCl_3$) 147.6 (C_q), 129.8 (CH), 129.3 (CH), 120.1 (CH), 118.0 (CH), 113.1 (CH), 40.9 (CH_2); ν_{max}/cm^{-1} 3410, 3082, 3053, 3023, 2921, 1602, 1505, 1432, 1328, 1301, 1260, 1099; m/z HRMS (NSI+) found 168.0571, $C_9H_{11}ClN$ $[M + H]^+$ requires 168.0575.

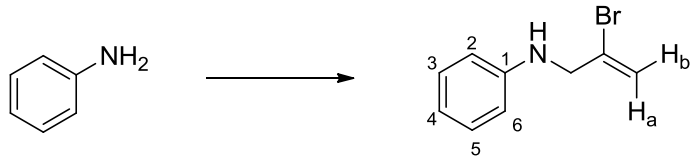
(*E*)-*N*-(3-Chloroallyl)aniline (229d):



229d

(*E*)-1,3-dichloroprop-1-ene (1.11 g, 10.0 mmol) was added dropwise over 30 mins at 50 °C to a stirring mixture of aniline (0.93 g, 20.0 mmol) in water (4.00 ml) and left overnight at 50 °C. Reaction mixture then cooled to 10 °C and NaOH (1.00 g, 25.0 mmol) added and left for 1 hour with stirring. The mixture was then extracted with diethyl ether (3 × 10 ml) and the combined organic phases dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (5:95 ethyl acetate / petroleum ether) afforded the title compound: Wt 624 mg; 37%; yellow oil; δ_H (300 MHz, $CDCl_3$) 7.20 (app. t, *J* = 7.4 Hz, 2H, *H*-3 and *H*-5), 6.76 (app. t, *J* = 7.3 Hz, 1H, *H*-4), 6.62 (app. d, *J* = 7.7 Hz, 2H, *H*-2 and *H*-6), 6.24 (dt, *J* = 13.3, 1.3 Hz, 1H, CH_a=C*H*$_b$Cl), 6.06 (dt, *J* = 13.3, 5.9 Hz, 1H, C*H*$_a$=CH_bCl), 3.80 (dd, *J* = 5.9, 1.3 Hz, 2H, C*H*$_2$), 3.76 (br s, 1H, N*H*); δ_C (75 MHz, $CDCl_3$) 147.3 (C_q), 130.6 (CH), 129.4 (CH), 120.3 (CH), 118.1 (CH), 113.1 (CH), 44.2 (CH_2); ν_{max}/cm^{-1} 3411, 3054, 3023, 2920, 2843, 1601, 1505, 1321, 1264, 1180, 1068; m/z HRMS (NSI+) found 168.0572, $C_9H_{11}ClN$ $[M + H]^+$ requires 168.0575.

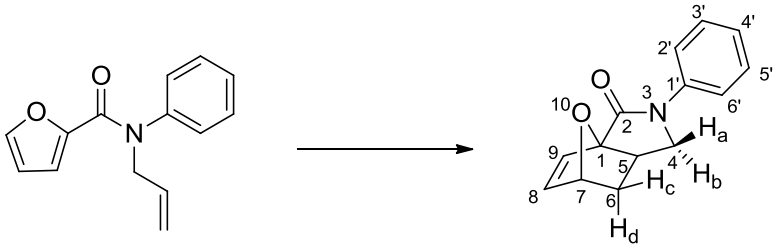
***N*-(2-Bromoallyl)aniline (229e):**



229e

2-bromo-3-chloroprop-1-ene (2.00 g, 10.0 mmol) was added dropwise over 30 mins at 50 °C to a stirring mixture of aniline (0.93 g, 20.0 mmol) in water (4.00 ml) and left overnight at 50 °C. Reaction mixture then cooled to 10 °C and NaOH (1.00 g, 25.0 mmol) added and left for 1 hour with stirring. The mixture was then extracted with diethyl ether (3 × 10 ml) and the combined organic phases dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (5:95 diethyl ether / petroleum ether) afforded the title compound: Wt 898 mg; 42%; yellow oil; δ_H (300 MHz, $CDCl_3$) 7.29 – 7.14 (m, 2H, *H*-3 and *H*-5), 6.79 (app. t, *J* = 7.3 Hz, 1H, *H*-4), 6.64 (dd, *J* = 8.5, 0.9 Hz, 2H, *H*-2 and *H*-6), 5.91 – 5.87 (m, 1H, C=C$H_b$$H_a$), 5.61 – 5.57 (m, 1H, C=C$H_b$$H_a$), 4.20 (br s, 1H, N*H*), 4.02 (app. s, 2H, CH_2); δ_C (75 MHz, $CDCl_3$) 146. 7 (C_q-1), 131.1 (BrC_q), 129.3 (CH), 118.2 (CH), 116.7 (C=*C*H_2), 113.0 (CH), 52.1 (CH_2); ν_{max}/cm^{-1} 3415, 3053, 3022, 2916, 2841, 1602, 1505, 1439, 1319, 1263, 1092, 1066; m/z HRMS (NSI+) found 212.0072, $C_9H_{11}BrN$ $[M + H]^+$ requires 212.0069.

(1*S*,5*R*,7*R*)-3-Phenyl-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-en-2-one (231a):[158]

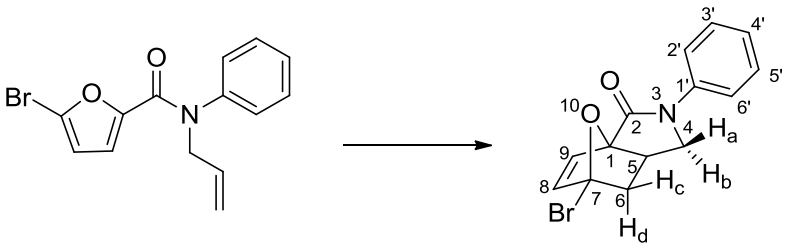


231a

A solution of **227a** (150.0 mg, 0.66 mmol) in toluene (7.00 ml) was heated to reflux with stirring for 24 hours. Toluene was then removed *in vacuo* and purification by column chromatography (3:7 ethyl acetate/petroleum ether) afforded the title compound: Wt 94 mg; 62%; golden brown solid; m.p. 118-120 °C; δ_H (300 MHz, $CDCl_3$) 7.70 – 7.59 (m, 2H, *H*-2' and *H*-6'), 7.46 – 7.32 (m, 2H, *H*-3' and *H*-5'), 7.23 – 7.11 (m, 1H, *H*-4'), 6.68 (d, *J* = 5.9 Hz, 1H, *H*-9), 6.51 (dd, *J* = 5.9, 1.7 Hz, 1H, *H*-8),

5.26 (dd, *J* = 4.4, 1.7 Hz, 1H, *H*-7), 4.02 (dd, *J* = 9.5, 8.4 Hz, 1H, H_a-4), 3.80 (dd, *J* = 9.5, 8.6 Hz, H_b-4), 2.42 (app. ddd, *J* = 8.4, 3.0 Hz, 1H, *H*-5), 2.04 (ddd, *J* = 11.7, 4.4, 3.0 Hz, 1H, H_c-6), 1.64 (dd, *J* = 11.7, 7.7 Hz, 1H, H_d-6); δ_C (75 MHz, $CDCl_3$) 167.2 (C=O), 139.2 (C_q-1'), 137.4 (CH), 133.4 (CH), 128.9 (CH), 125.1 (CH), 120.3 (CH), 92.7 (C_q-1), 81.9 (CH-7), 53.9 (CH_2-4), 38.4 (CH_2-6), 31.7 (CH-5); ν_{max}/cm^{-1} 3004, 2951, 2921, 2852, 1702, 1596, 1468, 1496, 1397, 1299, 1158, 1078, 1018.

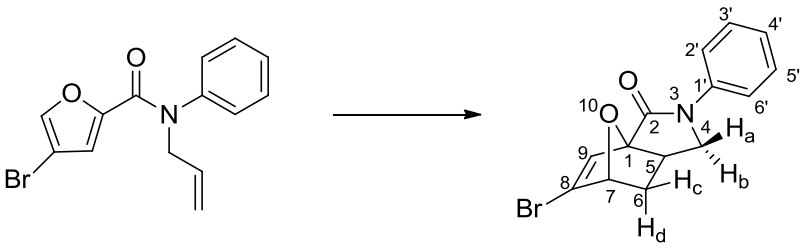
(1*S*,5*R*,7*S*)-7-Bromo-3-phenyl-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-en-2-one (231b):



231b

A solution of **227b** (202 mg, 0.66 mmol) in toluene (7.00 ml) was heated to reflux with stirring for 24 hours. Toluene was then removed *in vacuo* to afford the pure title compound: Wt 202 mg; 100%; white solid; m.p. 151-153 °C; δ_H (300 MHz, $CDCl_3$) 7.68 – 7.54 (m, 2H, *H*-2' and *H*-6'), 7.46 – 7.30 (m, 2H, *H*-3' and *H*-5'), 7.24 – 7.15 (m, 1H, *H*-4'), 6.71 (d, *J* = 5.7 Hz, 1H, CH_{alkene}), 6.55 (d, *J* = 5.7 Hz, 1H, CH_{alkene}), 4.05 (dd, *J* = 9.6, 8.4 Hz, 1H, H_b-4), 3.91 (dd, *J* = 9.6, 8.4 Hz, 1H, H_a-4), 2.62-2.48 (m, 1H, *H*-5), 2.39 (dd, *J* = 11.9, 3.1 Hz, 1H, H_c-6), 2.30 (dd, *J* = 11.9, 7.3 Hz, 1H, H_d-6); δ_C (75 MHz, $CDCl_3$) 164.9 (C=O), 141.4 (CH), 138.7 (C_q-1'), 134.3 (CH), 129.0 (CH), 125.5 (CH), 120.4 (CH), 91.4 ($C_{q\text{-bridgehead}}$), 90.8 ($C_{q\text{-bridgehead}}$), 53.6 (CH_2-4), 43.2 (CH_2-6), 41.3 (CH-5); ν_{max}/cm^{-1} 3070, 2957, 1695, 1594, 1492, 1473, 1403, 1299, 1255, 1164, 1073, 1018; m/z HRMS (NSI+) found 306.0128, $C_{14}H_{13}BrNO_2$ $[M + H]^+$ requires 306.0124.

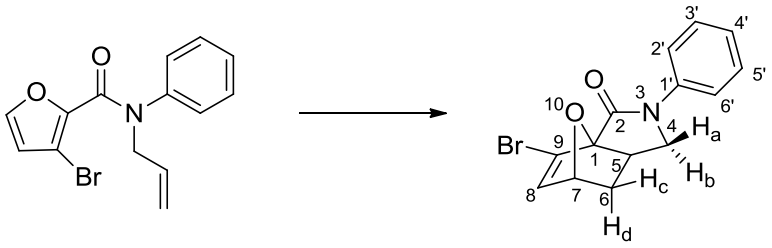
(1*S*,5*R*,7*R*)-8-Bromo-3-phenyl-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-en-2-one (231c):



231c

A solution of **227c** (173 mg, 0.57 mmol) in toluene (6.00 ml) was heated to reflux with stirring for 24 hours. Toluene was then removed *in vacuo* and purification by column chromatography (3:7 ethyl acetate/petroleum ether) afforded the title compound: Wt 133 mg; 77%; white solid; m.p. 207-209 °C; δ_H (300 MHz, $CDCl_3$) 7.70 – 7.61 (m, 2H, *H*-2' and *H*-6'), 7.46 – 7.38 (m, 2H, *H*-3' and *H*-5'), 7.26 – 7.19 (m, 1H, *H*-4'), 6.73 (s, 1H, *H*-9), 5.11 (d, *J* = 4.3 Hz, 1H, *H*-7), 4.06 (dd, *J* = 9.5, 8.4 Hz, 1H, H_a-4 or H_b-4), 3.82 (dd, *J* = 9.5, 8.4 Hz, 1H, H_a-4 or H_b-4), 2.64-2.51 (m, 1H, *H*-5), 2.08 (ddd, *J* = 12.0, 4.3, 2.9 Hz, 1H, H_c-6), 1.85 (dd, *J* = 12.0, 7.7 Hz, 1H, H_d-6); δ_C (75 MHz, $CDCl_3$) 165.8 (C=O), 138.9 (C_q-1'), 132.0 (CH), 129.0 (CH), 127.6 (C_q-8), 125.3 (CH), 120.3 (CH), 94.6 (C_q-1), 86.6 (CH-7), 53.4 (CH_2-4), 39.6 (CH-5), 31.1 (CH_2-6); ν_{max}/cm^{-1} 3088, 3001, 2975, 2948, 1686, 1597, 1567, 1494, 1407, 1390, 1301, 1200, 1152, 1043; m/z HRMS (NSI+) found 306.0132, $C_{14}H_{13}BrNO_2$ $[M + H]^+$ requires 306.0124.

(1*R*,5*R*,7*R*)-9-Bromo-3-phenyl-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-en-2-one (231d):

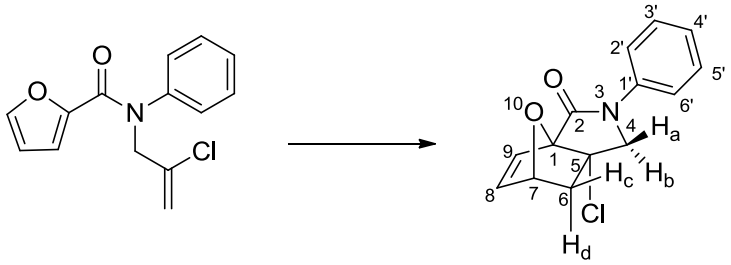


231d

A solution of **227d** (274 mg, 0.89 mmol) in toluene (18.3 ml) was heated to reflux with stirring for 24 hours. Toluene was then removed *in vacuo* and purification by column chromatography (3:7 ethyl acetate/petroleum ether) afforded the title compound: Wt

211 mg; 77%; white solid; m.p. 168-170 °C; δ_H (300 MHz, $CDCl_3$) δ 7.69 – 7.63 (m, 2H, *H*-2' and *H*-6'), 7.43 – 7.34 (m, 2H, *H*-3' and *H*-5'), 7.23 – 7.15 (m, 1H, *H*-4'), 6.51 (d, *J* = 1.8 Hz, 1H, *H*-8), 5.23 (dd, *J* = 4.2, 1.8 Hz, 1H, *H*-7), 4.05 (dd, *J* = 9.5, 8.5 Hz, 1H, H_a-4 or H_b-4), 3.77 (dd, *J* = 9.5, 8.5 Hz, 1H, H_a-4 or H_b-4), 2.63 – 2.50 (m, 1H, *H*-5), 2.10 (ddd, *J* = 11.8, 4.2, 3.3 Hz, 1H, H_c-6), 1.79 (dd, *J* = 11.8, 7.7 Hz, 1H, H_d-6); δ_C (75 MHz, $CDCl_3$) 164.5 (C=O), 138.9 (C_q-1'), 136.1 (CH), 128.91 (CH), 125.3 (CH), 123.4 (C_q-9), 120.2 (CH), 93.7 (CH-1), 83.4 (CH-7), 53.1 (CH_2-4), 37.8 (CH-5), 33.2 (CH_2-6); ν_{max}/cm^{-1} 3120, 2956, 1698, 1596, 1495, 1408, 1286, 1213, 1157, 1050, 1016; m/z HRMS (NSI+) found 306.0123, $C_{14}H_{13}BrNO_2$ $[M + H]^+$ requires 306.0124.

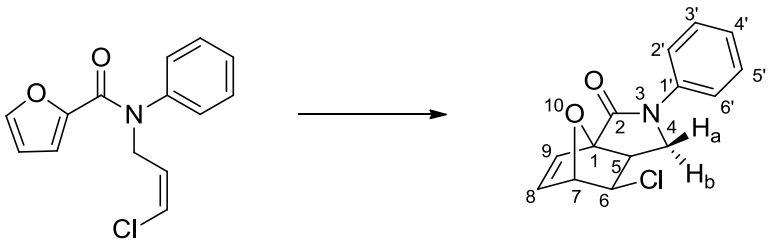
(1*S*,5*S*,7*R*)-5-Chloro-3-phenyl-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-en-2-one (231e):



231e

A solution of **227e** (173 mg, 0.66 mmol) in toluene (7.00 ml) was heated to reflux with stirring for 24 hours. Toluene was then removed *in vacuo* and purification by column chromatography (1:9 ethyl acetate/petroleum ether) afforded the title compound: Wt 47 mg; 27%; white solid; m.p. 126-128 °C; δ_H (300 MHz, $CDCl_3$) 7.64 – 7.56 (m, 2H, *H*-2' and *H*-6'), 7.46 – 7.36 (m, 2H, *H*-3' and *H*-5'), 7.25 – 7.18 (m, 1H, *H*-4'), 6.80 (d, *J* = 5.9 Hz, 1H, *H*-9), 6.68 (dd, *J* = 5.9, 1.8 Hz, 1H, *H*-8), 5.32 (dd, *J* = 4.5, 1.8 Hz, 1H, *H*-7), 4.36 (d, *J* = 11.0 Hz, 1H, H_a-4 or H_b-4), 4.24 (d, *J* = 11.0 Hz, 1H, H_a-4 or H_b-4), 2.81 (dd, *J* = 12.5, 4.5 Hz, 1H, H_c-6), 1.87 (d, *J* = 12.5 Hz, 1H, H_d-6); δ_C (75 MHz, $CDCl_3$) 164.8 (C=O), 138.6 (C_q-1'), 137.6 (CH), 132.5 (CH), 129.1 (CH), 125.6 (CH), 120.6 (CH), 94.2 (C_q-1), 83.1 (CH-7), 68.4 (C_q-5), 63.5 (CH_2-4), 42.5 (CH_2-6); ν_{max}/cm^{-1} 3042, 2957, 1709, 1594, 1494, 1465, 1400, 1303, 1212, 1162, 1092, 1048; m/z HRMS (NSI+) found 262.0635, $C_{14}H_{13}ClNO_2$ $[M + H]^+$ requires 262.0629.

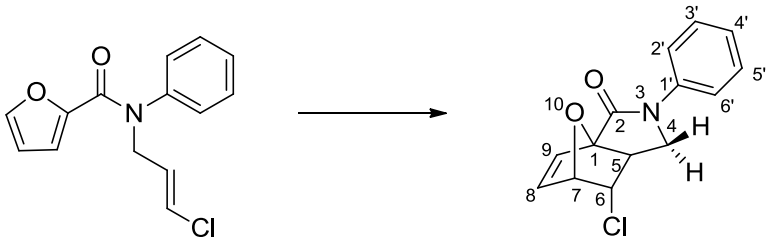
(1*S*,5*R*,6*R*,7*S*)-6-Chloro-3-phenyl-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-en-2-one (231f):



231f

A solution of **227f** (262 mg, 1.00 mmol) in toluene (20.4 ml) was heated to reflux with stirring for 24 hours. Toluene was then removed *in vacuo* and purification by column chromatography (3:7 ethyl acetate/petroleum ether) afforded the title compound: Wt 19 mg; 7%; white solid; m.p. 122-124 °C; δ_H (300 MHz, $CDCl_3$) 7.75 – 7.59 (m, 2H, *H*-2' and *H*-6'), 7.47 – 7.33 (m, 2H, *H*-3' and *H*-5'), 7.24-7.17 (m, 1H, *H*-4'), 6.81 (d, *J* = 5.9 Hz, 1H, *H*-9), 6.57 (dd, *J* = 5.9, 1.7 Hz, 1H, *H*-8), 5.13 (d, *J* = 1.7 Hz, 1H, *H*-7), 4.35 (dd, *J* = 10.0, 8.5 Hz, 1H, H_a-4 or H_b-4), 4.17 (d, *J* = 7.0 Hz, 1H, *H*-6), 3.85 (dd, *J* = 10.0, 8.8 Hz, 1H, H_a-4 or H_b-4), 2.78-2.68 (m, 1H, *H*-5); δ_C (75 MHz, $CDCl_3$) 165.3 (C=O), 138.8 (C_q-1'), 136.7 (CH), 136.1 (CH), 129.0 (CH), 125.4 (CH), 120.4 (CH), 93.3 (C_q-1), 89.3 (CH-7), 59.1 (CH-6), 49.52 (CH_2-4), 42.0 (CH-5); ν_{max}/cm^{-1} 3086, 3010, 2967, 1699, 1597, 1493, 1403, 1320, 1285, 1254, 1158, 1048; m/z HRMS (NSI+) found 262.0632, $C_{14}H_{13}ClNO_2$ $[M + H]^+$ requires 262.0629.

(1*S*,5*R*,6*S*,7*S*)-6-Chloro-3-phenyl-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-en-2-one (231g):

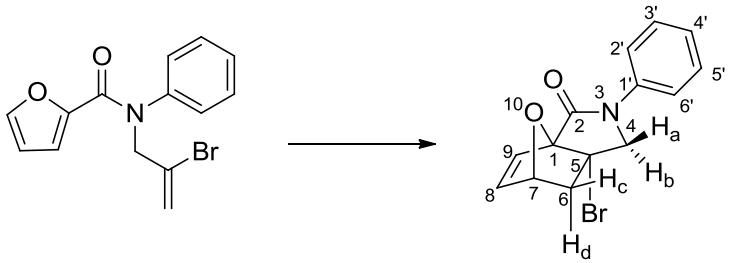


231g

A solution of **227g** (99 mg, 0.66 mmol) in toluene (4.00 ml) was heated to reflux with stirring for 24 hours. Toluene was then removed *in vacuo* and purification by column chromatography (1:4 ethyl acetate/petroleum ether) afforded the title compound: Wt 42

mg; 42%; white solid; m.p. 160-161 °C; δ_H (300 MHz, $CDCl_3$) 7.70 – 7.54 (m, 2H, *H*-2' and *H*-6'), 7.47 – 7.33 (m, 2H, *H*-3' and *H*-5'), 7.25 – 7.16 (m, 1H, *H*-4'), 6.88 (d, *J* = 5.9 Hz, 1H, *H*-9), 6.61 (dd, *J* = 5.9, 1.7 Hz, 1H, *H*-8), 5.32 (dd, *J* = 4.1, 1.7 Hz, 1H, *H*-7), 4.33 (dd, *J* = 4.1, 2.4 Hz, 1H, *H*-6), 4.21 (dd, *J* = 9.8, 8.8 Hz, 1H, H_a-4 or H_b-4), 3.87 (dd, *J* = 9.8, 8.5 Hz, 1H, H_a-4 or H_b-4), 2.51 (app. td, *J* = 8.5, 2.3 Hz, 1H, *H*-5); δ_C (75 MHz, $CDCl_3$) 165.6 (C=O), 138.7 (C_q-1'), 135.4 (CH), 135.0 (CH), 129.0 (CH), 125.5 (CH), 120.3 (CH), 93.8 (C_q-1), 84.3 (CH-7), 56.0 (CH-6), 51.51 (CH_2-4), 48.8 (CH-5); ν_{max}/cm^{-1} 3063, 2897, 1694, 1596, 1495, 1468, 1406, 1298, 1206, 1157, 1019; m/z HRMS (NSI+) found 262.0631, $C_{14}H_{13}ClNO_2$ $[M + H]^+$ requires 262.0629.

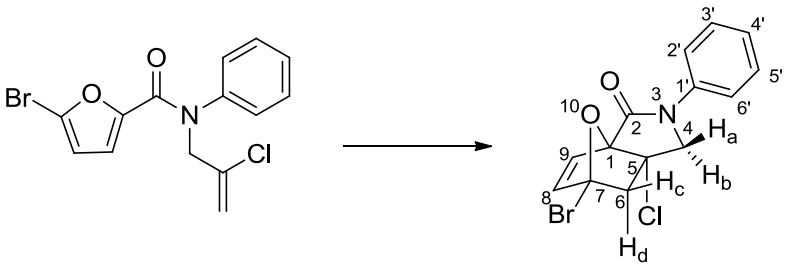
(1*S*,5*S*,7*R*)-5-Bromo-3-phenyl-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-en-2-one (231h):



231h

A solution of **227h** (153 mg, 0.50 mmol) in toluene (1.00 ml) was heated to reflux with stirring for 24 hours. Toluene was then removed *in vacuo* and purification by column chromatography (1:9 ethyl acetate/petroleum ether) afforded the title compound: Wt 68 mg; 44%; white solid; m.p. 137-139 °C; δ_H (300 MHz, $CDCl_3$) 7.63 – 7.55 (m, 2H, *H*-2' and *H*-6'), 7.45 – 7.36 (m, 2H, *H*-3' and *H*-5'), 7.25 – 7.18 (m, 1H, *H*-4'), 6.81 (d, *J* = 5.9 Hz, 1H, *H*-9), 6.62 (dd, *J* = 5.9, 1.8 Hz, 1H, *H*-8), 5.32 (dd, *J* = 4.5, 1.8 Hz, 1H, *H*-7), 4.41 (d, *J* = 11.3 Hz, 1H, H_a-4 or H_b-4), 4.31 (d, *J* = 11.3 Hz, 1H, H_a-4 or H_b-4), 2.78 (dd, *J* = 12.7, 4.5 Hz, 1H, H_c-6), 1.95 (d, *J* = 12.7 Hz, 1H, H_d-6); δ_C (75 MHz, $CDCl_3$) 164.7 (C=O), 138.6 (C_q-1'), 136.96 (CH), 133.70 (CH), 129.1 (CH), 125.6 (CH), 120.7 (CH), 94.5 (C_q-1), 83.1 (CH-7), 64.7 (CH_2-4), 59.7 (C_q-5), 42.2 (CH_2-6); ν_{max}/cm^{-1} 3036, 2954, 2925, 1708, 1494, 1464, 1400, 1302, 1210, 1160, 1092, 1046, ; m/z HRMS (APCI+) found 306.0128, $C_{14}H_{13}BrNO_2$ $[M + H]^+$ requires 306.0124.

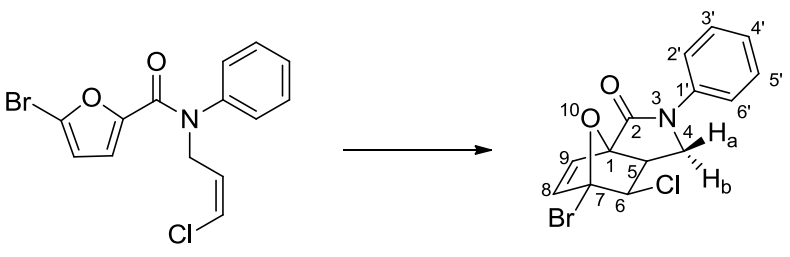
(1*S*,5*S*,7*S*)-7-Bromo-5-chloro-3-phenyl-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-en-2-one (231i):



231i

A solution of **227i** (49.0 mg, 0.14 mmol) in toluene (3.00 ml) was heated to reflux with stirring for 24 hours. Toluene was then removed *in vacuo* and purification by column chromatography (1:9 diethyl ether/petroleum ether) afforded the title compound: Wt 30 mg; 61%; white solid; m.p. 141-143 °C; δH (300 MHz, $CDCl_3$) δ 7.62 – 7.52 (m, 2H, *H*-2' and *H*-6'), 7.47 – 7.36 (m, 2H, *H*-3' and *H*-5'), 7.28 – 7.20 (m, 1H, *H*-4'), 6.81 (d, *J* = 5.7 Hz, 1H, CH_{alkene}), 6.70 (d, *J* = 5.7 Hz, 1H, CH_{alkene}), 4.47 (d, *J* = 11.1 Hz, 1H, H_a-4 or H_b-4), 4.26 (d, *J* = 11.1 Hz, 1H, H_a-4 or H_b-4), 3.07 (d, *J* = 12.7 Hz, 1H, H_c-4 or H_d-4), 2.51 (d, *J* = 12.7 Hz, 1H, H_c-4 or H_d-4); δ_C (75 MHz, $CDCl_3$) 162.6 (C=O), 141.4 (CH), 138.1 (C_q-1'), 133.6 (CH), 129.2 (CH), 126.0 (CH), 120.8 (CH), 92.8 ($C_{q\text{-bridgehead}}$), 90.8 ($C_{q\text{-bridgehead}}$), 69.3 (C_q-5), 63.2 (CH_2-4), 53.4 (CH_2-6); ν_{max}/cm^{-1} 3078, 2955, 1710, 1494, 1408, 1308, 1285, 1219, 1177, 1101, 1041; m/z HRMS (NSI+) found 339.9738, $C_{14}H_{12}BrClNO_2$ $[M + H]^+$ requires 339.9734.

(1*S*,5*R*,6*R*,7*R*)-7-Bromo-6-chloro-3-phenyl-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-en-2-one (231j):

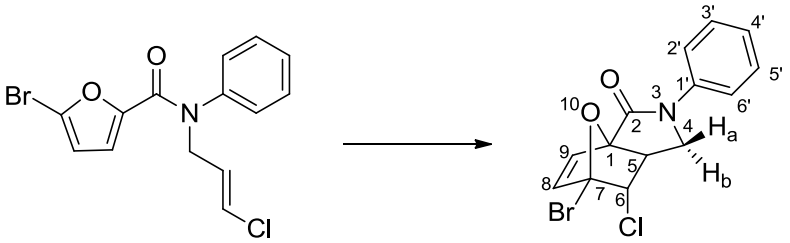


231j

A solution of **227j** (66.0 mg, 0.19 mmol) in toluene (4.00 ml) was heated to reflux with stirring for 24 hours. Toluene was then removed *in vacuo* and purification by column

chromatography (30:70 ethyl acetate/petroleum ether) afforded the title compound: Wt 8 mg; 12%; white solid; m.p. 179-181 °C; δ_H (300 MHz, CDCl3) 7.60 – 7.51 (m, 2H, *H*-2' and *H*-6'), 7.38 – 7.29 (m, 2H, *H*-3' and *H*-5'), 7.18 – 7.11 (m, 1H, *H*-4'), 6.77 (d, *J* = 5.6 Hz, 1H, CH_{alkene}), 6.56 (d, *J* = 5.6 Hz, 1H, CH_{alkene}), 4.22 (d, *J* = 7.0 Hz, 1H, *H*-6), 4.28 (dd, *J* = 10.1, 8.6 Hz, 1H, H_a-4 or H_b-4), 3.79 (dd, *J* = 10.1, 8.7 Hz, 1H, H_a-4 or H_b-4), 2.85 (app. t, *J* = 8.6, 7.0 Hz, 1H, *H*-5); δ_C (75 MHz, CDCl3) 163.4 (C=O), 140.9 (CH), 138.4 (C_q-1'), 137.1 (CH), 129.1 (CH), 125.8 (CH), 120.5 (CH), 96.3 ($C_{q\text{-bridgehead}}$), 91.4 ($C_{q\text{-bridgehead}}$), 63.9 (CH-6), 49.8 (CH_2-4), 43.6 (CH-5); ν_{max}/cm^{-1} 3136, 3094, 3076, 2915, 1690, 1595, 1491, 1477, 1405, 1294, 1275, 1259, 1172, 1061, 1033; m/z HRMS (NSI+) found 339.9729, $C_{14}H_{12}BrClNO_2$ $[M + H]^+$ requires 339.9734.

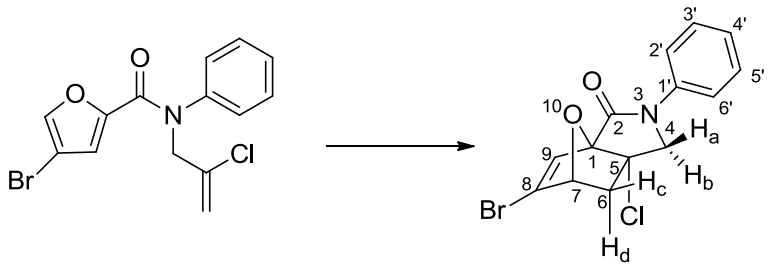
(1*S*,5*R*,6*S*,7*R*)-7-Bromo-6-chloro-3-phenyl-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-en-2-one (231k):



231k

A solution of **231k** (100 mg, 0.29 mmol) in toluene (5.90 ml) was heated to reflux with stirring for 8 hours. Toluene was then removed *in vacuo* and purification by column chromatography (1:4 diethyl ether/petroleum ether) afforded the title compound: Wt 60 mg; 60%; white solid; m.p. 196-198 °C; δ_H (300 MHz, CDCl3) 7.58 – 7.46 (m, 2H, *H*-2' and *H*-6'), 7.41 – 7.28 (m, 2H, *H*-3' and *H*-5'), 7.18 – 7.11 (m, 1H, *H*-4'), 6.79 (d, *J* = 5.7, 1H, CH_{alkene}), 6.56 (d, *J* = 5.7, 1H, CH_{alkene}), 4.31 (d, *J* = 2.4, 1H, *H*-6), 4.17 (dd, *J* = 9.9, 8.7, 1H, H_a-4 or H_b-4), 3.93 (dd, *J* = 9.9, 8.4, 1H, H_a-4 or H_b-4), 2.62 (app. td, *J* = 8.5, 2.4, 1H, *H*-5); δ_C (75 MHz, CDCl3) 163.7 (C=O), 139.6 (CH), 138.2 (C_q-1'), 135.3 (CH), 129.1 (CH), 125.9 (CH), 120.5 (CH), 93.8 ($C_{q\text{-bridgehead}}$), 91.9 ($C_{q\text{-bridgehead}}$), 65.1 (CH-6), 52.0 (CH_2-4), 51.0 (CH-5); ν_{max}/cm^{-1} 3098, 3075, 2997, 2897, 1707, 1497, 1472, 1402, 1301, 1284, 1240, 1161, 1091, 1050, 1008; m/z HRMS (APCI+) found 339.9739, $C_{14}H_{12}BrClNO_2$ $[M + H]^+$ requires 339.9734.

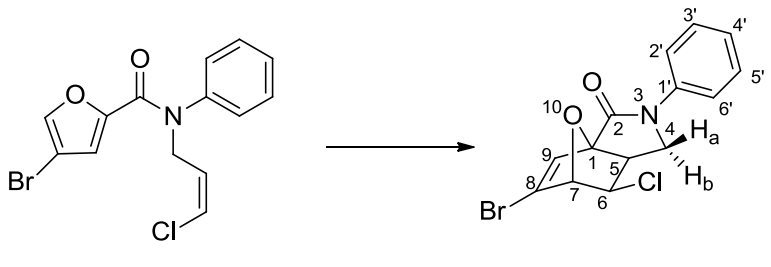
(1*S*,5*S*,7*R*)-8-Bromo-5-chloro-3-phenyl-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-en-2-one (231l):



231l

A solution of **227l** (68.0 mg, 0.20 mmol) in toluene (4.10 ml) was heated to reflux with stirring for 24 hours. Toluene was then removed *in vacuo* and purification by column chromatography (1:5 diethyl ether/petroleum ether) afforded the title compound: Wt 34 mg; 50%; white solid; m.p. 162-164 °C; δ_H (300 MHz, CDCl3) 7.56 – 7.45 (m, 2H, *H*-2' and *H*-6'), 7.40 – 7.28 (m, 2H, *H*-3' and *H*-5'), 7.19 – 7.12 (m, 1H, *H*-4'), 6.77 (s, 1H, *H*-9), 5.06 (d, *J* = 4.5 Hz, 1H, *H*-7), 4.29 (d, *J* = 11.0 Hz, 1H, H_a-4 or H_b-4), 4.16 (d, *J* = 11.0 Hz, 1H, H_a-4 or H_b-4), 2.73 (dd, *J* = 12.8, 4.5 Hz, 1H, H_c-6), 1.96 (d, *J* = 12.8 Hz, 1H, H_d-6); δ_C (75 MHz, CDCl3) 163.5 (C=O), 138.3 (C_q-1'), 131.3 (CH), 129.1 (C_q-8), 127.9 (CH), 125.9 (CH), 120.7 (CH), 95.9 (C_q-1), 87.6 (CH-7), 69.3 (C_q-5), 63.1 (CH_2-4), 42.0 (CH_2-6); ν_{max}/cm^{-1} 3093, 3068, 3046, 2958, 1708, 1596, 1567, 1493, 1465, 1408, 1302, 1199, 1157, 1045; m/z HRMS (NSI+) found 339.9729, $C_{14}H_{12}BrClNO_2$ [M + H]$^+$ requires 339.9734.

(1*R*,5*R*,6*R*,7*R*)-8-Bromo-6-chloro-3-phenyl-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-en-2-one (231m):

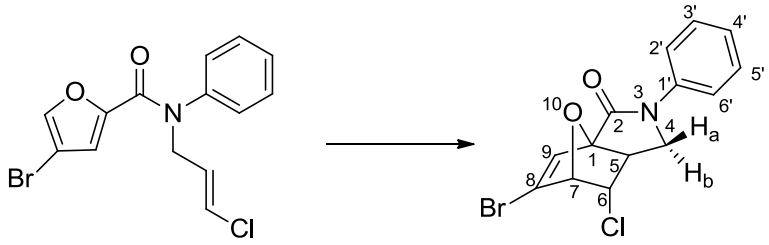


231m

A solution of **227m** (29.0 mg, 0.09 mmol) in toluene (1.70 ml) was heated to reflux with for 24 hours. Toluene was then removed *in vacuo* and purification by column

chromatography (30:70 diethyl ether/petroleum ether) afforded the title compound: Wt 9 mg; 31%; off-white solid; m.p. 188-190 °C; δ_H (300 MHz, $CDCl_3$) 7.65 – 7.53 (m, 2H, *H*-2' and *H*-6'), 7.41 – 7.26 (m, 2H, *H*-3' and *H*-5'), 7.18 – 7.10 (m, 1H, *H*-4'), 6.75 (s, 1H, *H*-9), 4.90 (s, 1H, *H*-7), 4.27 (dd, *J* = 10.1, 8.5, 1H, H_a-4 or H_b-4), 4.22 (d, *J* = 7.0, 1H, *H*-6), 3.79 (dd, *J* = 10.1, 8.8, 1H, H_a-4 or H_b-4), 2.82 (app. td, *J* = 8.6, 7.0, 1H, *H*-5); δ_C (75 MHz, CDCl3) 164.0 (C=O), 138.6 (C_q-1'), 134.7 (CH), 129.1 (CH), 126.5 (C_q-8), 125.7 (CH), 120.4 (CH), 95.2 (C_q-1), 93.3 (CH-7), 58.0 (CH-6), 49.1 (CH_2-4), 43.5 (CH-5); ν_{max}/cm^{-1} 3103, 3027, 2964, 2920, 1696, 1597, 1490, 1406, 1296, 1251, 1193, 1010; m/z HRMS (NSI+) found 339.9738, $C_{14}H_{12}BrClNO_2$ $[M + H]^+$ requires 339.9734.

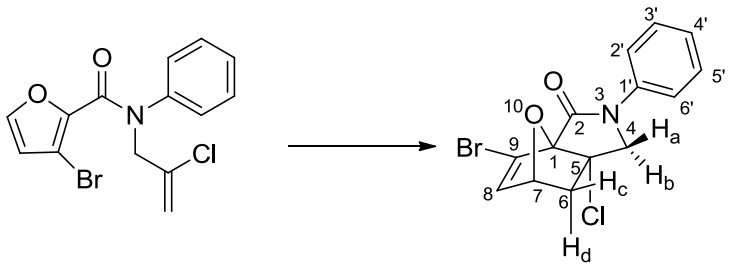
(1*R*,5*R*,6*S*,7*R*)-8-Bromo-6-chloro-3-phenyl-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-en-2-one (231n):



231n

A solution of **227n** (68.0 mg, 0.20 mmol) in toluene (4.00 ml) was heated to reflux with stirring for 24 hours. Toluene was then removed *in vacuo* and purification by column chromatography (1:4 diethyl ether/petroleum ether) afforded the title compound: Wt 37 mg; 54%; white solid; m.p. 167-169 °C; δ_H (300 MHz, $CDCl_3$) 7.56 – 7.48 (m, 2H, *H*-2' and *H*-6'), 7.37 – 7.27 (m, 2H, *H*-3' and *H*-5'), 7.17 – 7.11 (m, 1H, *H*-4'), 6.89 (s, 1H, *H*-9), 5.10 (d, *J* = 4.0, 1H, *H*-7), 4.39 (dd, *J* = 4.0, 2.3, 1H, *H*-6), 4.15 (dd, *J* = 9.9, 8.7, 1H, H_a-4 or H_b-4), 3.80 (dd, *J*=9.9, 8.4, 1H, H_a-4 or H_b-4), 2.63 (app. td, *J*=8.5, 2.3, 1H, *H*-5); δ_C (75 MHz, CDCl3) 164.4 (C=O), 138.4 (C_q-1'), 133.6 (CH), 129.1 (CH), 126.0 (C_q-8), 125.8 (CH), 120.4 (CH), 95.2 (C_q-1), 88.0 (CH-7), 55.4 (CH-6), 52.0 (CH_2-4), 48.6 (CH-5); ν_{max}/cm^{-1} 3063, 2896, 1692, 1597, 1572, 1494, 1469, 1407, 1299, 1287, 1198, 1150, 1078, 1022, 1002; m/z HRMS (NSI+) found 339.9735, $C_{14}H_{12}BrClNO_2$ $[M + H]^+$ requires 339.9734.

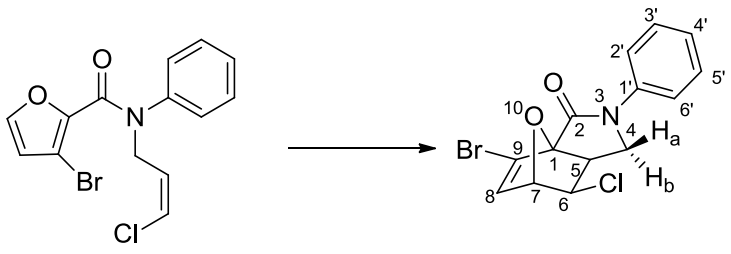
(1*S*,5*S*,7*R*)-9-Bromo-5-chloro-3-phenyl-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-en-2-one (231o):



231o

A solution of **227o** (100 mg, 0.30 mmol) in toluene (6.00 ml) was heated to reflux with stirring for 5 hours. Toluene was then removed *in vacuo* and purification by column chromatography (30:70 diethyl ether/petroleum ether) afforded the title compound: Wt 20 mg; 20%; yellow solid; m.p. 172-174 °C; δ_H (300 MHz, CDCl3) 7.70 – 7.43 (m, 2H, *H*-2' and *H*-6'), 7.45 – 7.24 (m, 2H, *H*-3' and *H*-5'), 7.19 – 7.12 (m, 1H, *H*-4'), 6.70 (d, *J* = 2.1 Hz, 1H, *H*-8), 5.19 (dd, *J* = 4.5, 2.1 Hz, 1H, *H*-7), 4.26 (d, *J* = 11.0 Hz, 1H, H_a-4 or H_b-4), 4.18 (d, *J* = 11.0 Hz, 1H, H_a-4 or H_b-4), 2.74 (dd, *J* = 12.6, 4.5 Hz, 1H, H_c-6), 1.99 (d, *J* = 12.6 Hz, 1H, H_d-6); δ_C (75 MHz, CDCl3) 162.3 (C=O), 138.3 (C_q-1'), 136.5 (CH), 129.1 (CH), 125.8 (CH), 122.8 (C_q-9), 120.6 (CH), 93.7 (C_q-1), 83.9 (CH-7), 68.1 (C_q-5), 63.1 (CH_2-4), 42.2 (CH_2-6); ν_{max}/cm^{-1} 3035, 2924, 1709, 1492, 1396, 1300, 1284, 1166, 1066; m/z HRMS (NSI+) found 339.9736, $C_{14}H_{12}BrClNO_2$ $[M + H]^+$ requires 339.9734.

(1*R*,5*R*,6*R*,7*S*)-9-Bromo-6-chloro-3-phenyl-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-en-2-one (231p):

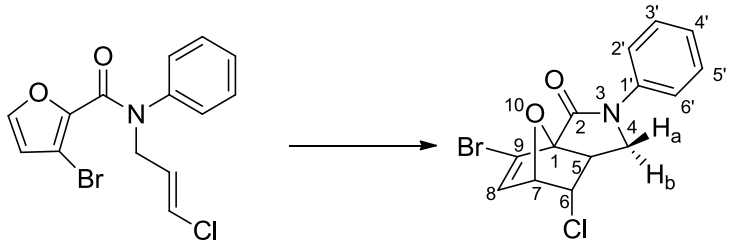


231p

A solution of **227p** (100 mg, 0.30 mmol) in toluene (6.00 ml) was heated to reflux with stirring for 16 hours. Toluene was then removed *in vacuo* and purification by column

chromatography (30:70 diethyl ether/petroleum ether) afforded the title compound: Wt 67 mg; 67%; white solid; m.p. 195-197 °C; δ_H (300 MHz, CDCl3) 7.67 – 7.57 (m, 2H, *H*-2' and *H*-6'), 7.41 – 7.27 (m, 2H, *H*-3' and *H*-5'), 7.18 – 7.08 (m, 1H, *H*-4'), 6.50 (d, *J* = 1.9, 1H, *H*-8), 5.03 (d, *J* = 1.9, 1H, *H*-7), 4.25 (dd, *J* = 10.0, 8.4, 1H, H_a-4 or H_b-4), 4.17 (d, *J* = 7.0, 1H, *H*-6), 3.81 (dd, *J* = 10.0, 8.9, 1H, H_a-4 or H_b-4), 2.78 (app. td, *J* = 8.6, 7.0, 1H, *H*-5); δ_C (75 MHz, CDCl3) 162.6 (C=O), 138.6 (C_q-1'), 134.1 (CH), 129.0 (CH), 127.6 (C_q-9), 125.6 (CH), 120.3 (CH), 94.1 (C_q-1), 90.3 (CH-7), 58.9 (CH-7), 48.8 (CH_2-4), 41.2 (CH-5); ν_{max}/cm^{-1} 3001, 2980, 2924, 1702, 1597, 1575, 1493, 1403, 1284, 1238, 1164, 1056, 1016; m/z HRMS (NSI+) found 339.9734, $C_{14}H_{12}BrClNO_2$ [M + H]$^+$ requires 339.9734.

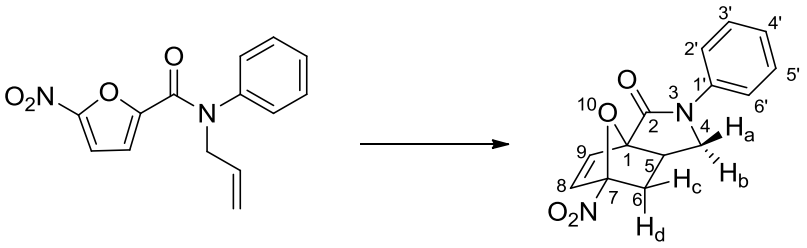
(1*R*,5*R*,6*S*,7*S*)-9-Bromo-6-chloro-3-phenyl-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-en-2-one (231q):



231q

A solution of **227q** (100 mg, 0.30 mmol) in toluene (6.00 ml) was heated to reflux with stirring for 7 hours. Toluene was then removed *in vacuo* and purification by column chromatography (30:70 diethyl ether/petroleum ether) afforded the title compound: Wt 75 mg; 75%; white solid; m.p. 208-210 °C: δ_H (300 MHz, $CDCl_3$) 7.72 – 7.60 (m, 2H, *H*-2' and *H*-6'), 7.47 – 7.31 (m, 2H, *H*-3' and *H*-5'), 7.22 (tt, *J* = 7.4, 1.1 Hz, 1H, *H*-4'), 6.65 (d, *J* = 1.9 Hz, 1H, *H*-8), 5.28 (dd, *J* = 4.0, 1.9 Hz, 1H, *H*-7), 4.36 (dd, *J* = 4.0, 2.6 Hz, 1H, *H*-6), 4.24 (dd, *J* = 9.8, 8.8 Hz, 1H, H_a-4 or H_b-4), 3.87 (dd, *J* = 9.8, 8.4 Hz, 1H, H_a-4 or H_b-4), 2.65 (app. td, *J* = 8.5, 2.6 Hz, 1H, *H*-5).; δ_C (75 MHz, CDCl3) 163.0 (C=O), 138.4 (C_q-1'), 133.9 (CH), 129.0 (CH), 125.7 (CH), 125.0 (C_q-9), 120.3 (CH), 94.5 (C_q-1), 85.4 (CH-7), 57.1 (CH-6), 51.5 (CH_2-4), 48.3 (CH-5); ν_{max}/cm^{-1} 2973, 2896, 1697, 1597, 1497, 1473, 1410, 1300, 1242, 1204, 1160, 1049, 1019; m/z HRMS (NSI+) found 339.9735, $C_{14}H_{12}BrClNO_2$ [M + H]$^+$ requires 339.9734.

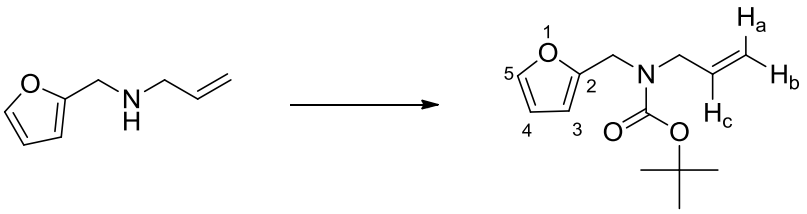
(1*S*,5*R*,7*R*)-7-Nitro-3-phenyl-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-en-2-one (231r):



231r

A solution of **227r** (502 mg, 1.84 mmol) in toluene (19.5 ml) was heated to reflux with stirring for 1.5 hours. Toluene was then removed *in vacuo* to afford the pure title compound: Wt 502 mg; 100%; beige solid; m.p. 170-171 °C; δ_H (300 MHz, $CDCl_3$) 7.67 – 7.55 (m, 2H, *H*-2' and *H*-6'), 7.48 – 7.35 (m, 2H, *H*-3' and *H*-5'), 7.26 – 7.19 (m, 1H, *H*-4'), 6.96 (d, *J* = 5.8 Hz, 1H, CH_{alkene}), 6.84 (d, *J* = 5.8 Hz, 1H, CH_{alkene}), 4.13 (dd, *J* = 9.8, 8.4 Hz, 1H, H_a-4 or H_b-4), 3.99 (dd, *J* = 9.8, 8.4 Hz, 1H, H_a-4 or H_b-4), 2.77 – 2.60 (m, 1H, *H*-5), 2.49 – 2.39 (m, 2H, H_c-6 and H_d-6); δ_C (75 MHz, $CDCl_3$) 172.8 (C=O), 138.4 (C_q-1'), 136.3 (CH), 134.8 (CH), 129.1 (CH), 125.9 (CH), 120.5 (CH), 109.3 (C_q-7), 91.0 (C_q-1), 53.4 (CH_2-4), 40.4 (CH-6), 37.1 (CH_2-6); ν_{max}/cm^{-1} 3101, 3078, 3048, 3004, 2977, 2936, 1699, 1672, 1595, 1557, 1509, 1492, 1473, 1405, 1382, 1298, 1256, 1167, 1117, 1059, 1003; m/z HRMS (NSI+) found 273.0873, $C_{14}H_{13}N_2O_4$ $[M + H]^+$ requires 273.0870.

***tert*-Butyl allyl(furan-2-ylmethyl)carbamate (236a):**

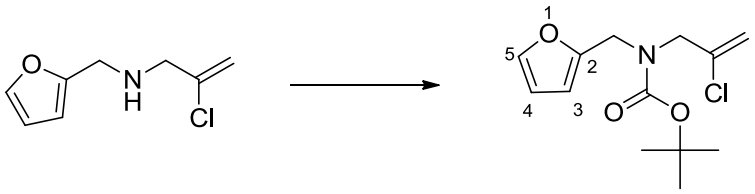


236a

To a solution of **237a** (823 mg, 6.00 mmol) and $(Boc)_2O$ (1.31 g, 6.00 mmol) in dry dichloromethane (11.2 ml) was added DMAP (7.30 mg, 1 mol %) at 0 °C with stirring. The solution was allowed to rise to room temperature and left stirring for 24 hours. The solvent was then removed *in vacuo* to afford the title compound with no further purification necessary: Wt 907 mg; 64%; colourless oil: δ_H (300 MHz, $CDCl_3$) 7.34 (br

app. d, J = 1.0 Hz, 1H, *H*-5), 6.30 (dd, J = 3.2, 1.8 Hz, 1H, *H*-4), 6.18 (br s, 1H, *H*-3), 5.72 (br s, 1H, CH_{alkene}), 5.14 (br s, 1H, CH_{alkene}), 5.11 (br s, 1H, CH_{alkene}), 4.36 (br s, 2H, OC-CH_2N), 3.84 (br s, 2H, NCH_2-CH), 1.46 (s, 9H, 3 × CH_3); δ_C (75 MHz, $CDCl_3$) 155.3 (C=O), 151.9 (C_q), 141.9 (CH), 133.6 (CH), 116.7 (br - C=*C*H_2), 110.2 (CH), 107.7 (br - CH_{alkene}), 79.9 ($C_{q\text{-}Boc}$), 48.8 (OC-CH_2N), 42.5 (N*C*H_2-CH), 28.4 (3 × CH_3); ν_{max}/cm^{-1} 2977, 2931, 1693, 1454, 1406, 1366, 1249, 1161, 1011; m/z HRMS (NSI+) found 238.1437, $C_{13}H_{20}NO_3$ $[M + H]^+$ requires 238.1438.

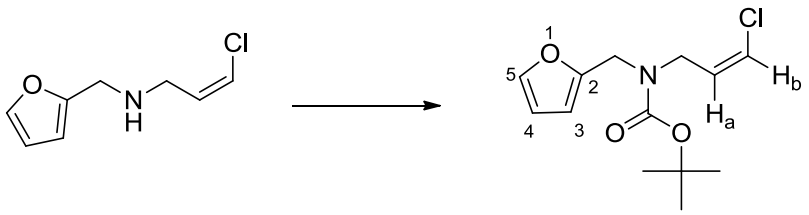
***tert*-Butyl (2-chloroallyl)(furan-2-ylmethyl)carbamate (236b):**[113]



236b

To a solution of **237b** (850 mg, 4.95 mmol) and $(Boc)_2O$ (1.31 g, 6.00 mmol) in dry dichloromethane (11.2 ml) was added DMAP (7.30 mg, 1 mol %) at 0 °C with stirring. The solution was allowed to rise to room temperature and left stirring for 3 hours. The reaction mixture was then concentrated *in vacuo*. Purification by column chromatography (1:9 ethyl acetate/ petroleum ether) afforded the title compound: Wt 1.13 g; 84%; colourless oil: δ_H (300 MHz, $CDCl_3$, pairs of 1:1 rotameric signals observed for certain H atoms) 7.35 (s, 1H, *H*-5), 6.31 (dd, J = 3.1, 1.9 Hz, 1H, *H*-4), 6.23 and 6.17 (2 × br s, 1H, *H*-3), 5.31 and 5.21 (2 × br s, 2H, 2 × CH_{alkene}), 4.46 and 4.38 (2 × br s, 2H, OC-CH_2N), 4.06 and 3.97 (2 × br s, 2H, NCH_2-CCl), 1.47 (s, 9H, 3 × CH_3); δ_C (75 MHz, $CDCl_3$, pairs of rotameric signals observed for certain C atoms) 150.2 (C=O), 146.3 (br, C_q), 137.5 (CH-5), 133.2 (C_q), 108.6 and 107.9 (C=*C*H_2), 105.5 (CH), 103.7 and 103.1 (CH), 75.9 ($C_{q\text{-}Boc}$), 47.1 and 47.0 (NCH_2), 38.2 and 37.5 (NCH_2), 23.5 (3 × CH_3); ν_{max}/cm^{-1} 2979, 2935, 1696, 1636, 1477, 1455, 1407, 1394, 1367, 1249, 1212, 1155, 1118, 1072; m/z HRMS (NSI+) found 294.0868, $C_{13}H_{18}ClNO_3Na$ $[M + Na]^+$ requires 294.0867.

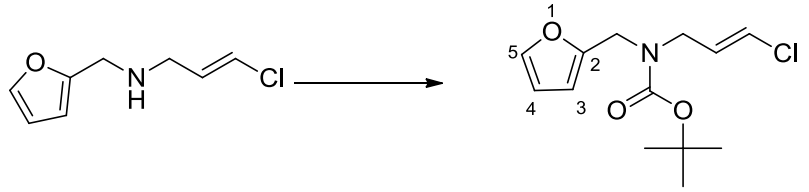
(*Z*)-*tert*-Butyl (3-chloroallyl)(furan-2-ylmethyl)carbamate (236c):



236c

To a solution of **237c** (172 mg, 1.00 mmol) and $(Boc)_2O$ (219 mg, 1.00 mmol) in dry dichloromethane (1.90 ml) was added DMAP (0.60 mg, 1 mol %) at 0 °C with stirring. The solution was allowed to rise to room temperature and left stirring for 72 hours. More $(Boc)_2O$ (219 mg, 1.00 mmol) was then added and the solution left to stir for 30 mins. Solvent was then removed *in vacuo* and ethanol (5.00 ml) was then added to the crude reaction mixture. Imidazole (204 mg, 3.00 mmol) was then added and the reaction allowed to stir for 20 mins. Solvent was then removed *in vacuo* and dichloromethane (20 ml) added. The solution was then rinsed with 1% HCl solution (2 × 30 ml), the organic phase was then dried (Na_2SO_4) and the solvent removed *in vacuo* to afford the pure title compound: Wt 238 mg; 88%; colourless oil: δ_H (300 MHz, $CDCl_3$) 7.38 (dd, *J* = 1.8, 0.8 Hz, 1H, *H*-5), 6.34 (dd, *J* = 3.2, 1.8 Hz, 1H, *H*-4), 6.25 (br s, 1H, *H*-3), 6.14 (br app. d, *J* = 6.4 Hz, 1H, CH_{alkene}), 5.75 (br s, 1H, CH_{alkene}), 4.40 (br s, 2H, OC-CH_2N), 4.08 (br s, 2H, NCH_2-CH), 1.50 (s, 9H, 3 × CH_3); δ_C (75 MHz, $CDCl_3$) 155.2 (C=O), 151.5 (C_q), 142.1 (CH-5), 128.2 (CH), 119.9 (br), 110.3 (CH), 108.0 (br), 80.3 ($C_{q\text{-}Boc}$), 43.5 (NCH_2), 43.3 (NCH_2), 28.4 (3 × CH_3); ν_{max}/cm^{-1} 2978, 2934, 1690, 1456, 1410, 1394, 1367, 1250, 1155, 1029; m/z HRMS (NSI+) found 294.0870, $C_{13}H_{18}ClNO_3Na$ $[M + Na]^+$ requires 294.0867.

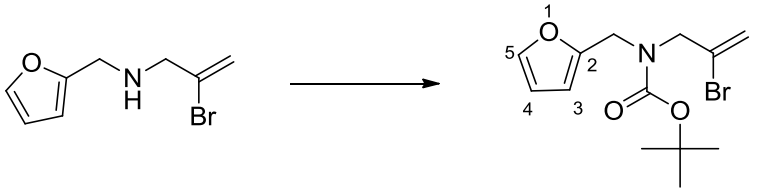
(*E*)-*tert*-Butyl (3-chloroallyl)(furan-2-ylmethyl)carbamate (236d):



236d

To a solution of **237d** (514mg, 3.00 mmol) and $(Boc)_2O$ (953 mg, 4.50 mmol) in dichloromethane (4.90 ml) was added DMAP (1.90 mg, 1 mol %) at 0 °C with stirring. The solution was allowed to rise to room temperature and left stirring overnight. Solvent was then removed *in vacuo* and ethanol (5.00 ml) was then added to the crude reaction mixture. Imidazole (204 mg, 3.00 mmol) was then added and the reaction allowed to stir for 30 mins. Solvent was then removed *in vacuo* and chloroform (20 ml) added. The solution was then rinsed with 1% HCl solution (2 × 30 ml), the organic phase was then dried (Na_2SO_4) and the solvent removed *in vacuo* to afford the pure title compound: Wt 500 mg; 61%; colourless oil: δ_H (300 MHz, $CDCl_3$) 7.43 – 7.32 (m, 1H, *H*-5), 6.33 (dd, *J* = 3.1, 1.9 Hz, 1H, *H*-4), 6.21 (br s, 1H, *H*-3), 6.10 (br app. d, *J* = 12.4 Hz, 1H, CH_{alkene}), 5.87 (br s, 1H, CH_{alkene}), 4.38 (br s, 2H, OC-CH_2N), 3.84 (br s, 2H, NCH_2-CH), 1.49 (s, 9H, 3 × CH_3); δ_C (75 MHz, $CDCl_3$) 155.0 (C=O), 151.4 (C_q), 142.1 (CH), 128.9 (CH), 120.8 (br - CH), 110.3 (CH), 108.1 (br - CH), 80.4 ($C_{q\text{-}Boc}$), 46.2 (br - NCH_2), 42.7 (br - NCH_2), 28.4 (3 × CH_3); ν_{max}/cm^{-1} 2978, 2932, 1692, 1454, 1408, 1366, 1269, 1253, 1223, 1159, 1115, 1011; m/z HRMS (NSI+) found 272.1049, $C_{13}H_{19}ClNO_3$ $[M + H]^+$ requires 272.1048.

***tert*-Butyl (2-bromoallyl)(furan-2-ylmethyl)carbamate (236e):**[113]

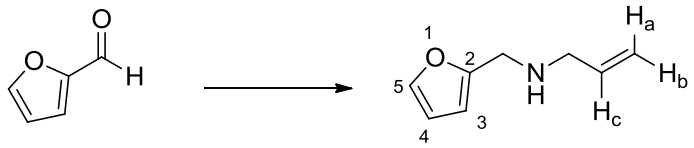


236e

To a solution of **237e** (216 mg, 1.00 mmol) and $(Boc)_2O$ (219 mg, 1.00 mmol) in dry dichloromethane (1.90 ml) was added DMAP (1.20 mg, 1 mol %) at 0 °C with stirring. The solution was allowed to rise to room temperature and left stirring for 24 hours. Solvent was then removed *in vacuo* and ethanol (5.00 ml) was then added to the crude reaction mixture. Imidazole (204 mg, 3.00 mmol) was then added and the reaction allowed to stir for 30 mins. Solvent was then removed *in vacuo* and chloroform (20 ml) added. The solution was then rinsed with 1% HCl solution (2 × 30 ml), the organic phase was then dried (Na_2SO_4) and the solvent removed *in vacuo* to afford the pure title compound: Wt 257 mg; 81%; colourless oil: δ_H (300 MHz, $CDCl_3$, pairs of 1:1 rotameric signals observed for certain H atoms) 7.35 and 7.34 (2 × br s, 1H, *H*-5), 6.31

(dd, *J* = 3.2, 1.9 Hz, 1H, *H*-4), 6.23 and 6.17 2 × br s, 1H, *H*-3), 5.72 and 5.65 (2 × br s, 1H, CH_{alkene}), 5.56 and 5.55 (2 × br s, 1H, CH_{alkene}), 4.46 and 4.37 (2 × br s, 2H, 2 × OC-CH_2N), 4.12 and 4.04 (2 × br s, 2H, 2 × NCH_2-CBr), 1.49 (s, 9H, 3 × CH_3); δ_C (75 MHz, $CDCl_3$, pairs of rotameric signals observed for certain C atoms) 154.9 (C=O), 151.3 and 151.0 (C_q), 142.2 and 142.1 (CH-5), 129.3 (C_q), 117.6 and 116.9 (C=CH_2), 110.2 (CH), 108.5 and 107.8 (CH), 80.6 ($C_{q\text{-}Boc}$), 53.8 and 53.5 (NCH_2), 42.9 and 42.1 (NCH_2), 28.2 (3 × CH_3); ν_{max}/cm^{-1} 2978, 2932, 1696, 1630, 1453, 1405, 1366, 1249, 1149, 1074, 1011.

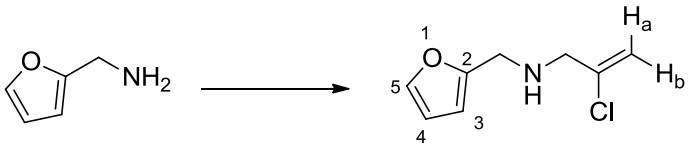
_N_-(Furan-2-ylmethyl)prop-2-en-1-amine (237a):[131]



237a

A suspension of allyl amine (2.85 g, 50.0 mmol) and $MgSO_4$ (7.50 g, 62.3 mmol) in dichloromethane was stirred for 1 hour. The mixture was then cooled in an ice bath before furfural (4.80 g, 50.0 mmol) was added dropwise, the mixture was stirred for 3 hours. The reaction mixture was then filtered and the filtrate concentrated *in vacuo* to afford the crude imine. This was then dissolved in methanol (150 ml) and with vigorous stirring $NaBH_4$ (946 mg, 25.0 mmol) was gradually added while controlling reaction mixture temperature with a water bath, then allowed to stir for 4.5 hours. The mixture was then diluted with water (300 ml) and extracted with diethyl ether (3 × 200 ml). The combined organic phase was rinsed with more water (2 × 200 ml) before being dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound without further purification required: Wt 1.00g; 15%; brown oil; δ_H (300 MHz, $CDCl_3$) 7.35 (dd, *J* = 1.9, 1.1 Hz, 1H, *H*-5), 6.30 (dd, *J* = 3.1, 1.9 Hz, 1H, *H*-4), 6.16 (app. d, *J* = 3.1 Hz, 1H, *H*-3), 5.89 (ddt, *J* = 17.2, 10.2, 6.0 Hz, 1H, CH_c=C$H_b$$H_a$), 5.18 (ddd, *J* = 17.2, 3.2, 1.6 Hz, 1H, CH_c=C$H_b$$H_a$), 5.15 – 5.10 (m, 1H, C$H_c$=C$H_b$$H_a$), 3.77 (s, 2H, OC-C$H_2$N), 3.25 (app. dt, *J* = 6.0, 1.3 Hz, 2H, CH_2CH_c), 1.48 (br s, 1H, N*H*); δ_C (75 MHz, CDCl3) 153.8 (C_q), 141.8 (CH-5), 136.5 (CH-4), 116.3 (H_cC=CH_2), 110.1 (CH-3), 106.9 (H_cC=CH_2), 51.4 (OC-CH_2N), 45.4 (CH_2CH_c); ν_{max}/cm^{-1} 3325, 3080, 2917, 2819, 1507, 1458, 1332, 1148, 1104, 1017.

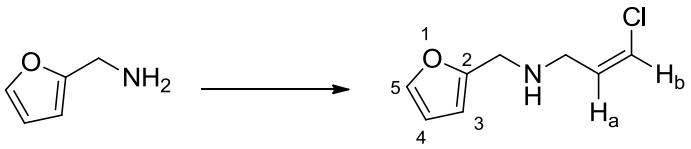
2-Chloro-*N*-(furan-2-ylmethyl)prop-2-en-1-amine (237b):[130]



237b

2,3-Dichloroprop-1-ene (4.44 g, 40.0 mmol) was added dropwise over 30 mins at 50 °C to a stirring mixture of furfurylamine (1.94 g, 20.0 mmol) in water (8 ml) and left overnight at 50 °C. Reaction mixture then cooled to 10 °C and NaOH (1.00 g, 25.0 mmol) added and left for 1 hour with stirring. The mixture was then extracted with diethyl ether (3 × 10 ml) and the combined organic phases dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (1:4 ethyl acetate / petroleum ether) afforded the title compound: Wt 958 mg; 28%; yellow oil; δ_H (300 MHz, $CDCl_3$) 7.36 (dd, *J* = 1.8, 0.7 Hz, 1H, *H*-5), 6.30 (dd, *J* = 3.1, 1.8 Hz, 1H, *H*-4), 6.17 (dd, *J* = 3.1, 0.7 Hz, 1H, *H*-3), 5.38 – 5.34 (m, 1H, ClC=CH_bH$_a$), 5.33 (app. s, 1H, ClC=CH$_b$$H_a$), 3.75 (s, 2H, OC-C$H_2$N), 3.40 (app. s, 2H, NC$H_2$CCl), 1.81 (br s, 1H, N*H*); δ_C (75 MHz, $CDCl_3$) 153.2 (C_q-2), 142.0 (CH-5), 140.4 (C_q-Cl), 113.7 (C=*C*H$_2$), 110.1 (CH-4), 107.3 (CH-3), 54.5 (OC-*C*H$_2$), 44.2 (*C*H$_2$CCl); ν_{max}/cm^{-1} 3339, 3116, 2922, 2834, 1634, 1604, 1430, 1356, 1221, 1186, 1147, 1074.

(*Z*)-3-Chloro-*N*-(furan-2-ylmethyl)prop-2-en-1-amine (237c):

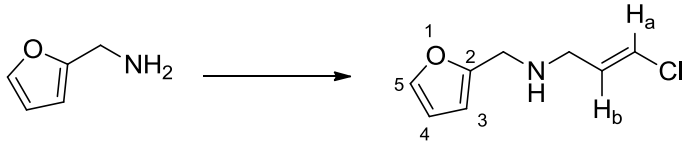


237c

(*Z*)-1,3-Dichloroprop-1-ene (1.11 g, 10.0 mmol) was added dropwise over 30 mins at 50 °C to a stirring mixture of furfurylamine (1.94 g, 20.0 mmol) in water (8.00 ml) and left overnight at 50 °C. Reaction mixture then cooled to 10 °C and NaOH (1.00 g, 25 mmol) added and left for 1 hour with stirring. The mixture was then extracted with diethyl ether (3 × 10 ml) and the combined organic phases dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (1:4 ethyl acetate / petroleum ether → 1:1 ethyl acetate/petroleum ether) afforded the title compound: Wt 549 mg; 32%; yellow oil; δ_H (300 MHz, $CDCl_3$) 7.39 (dd, *J* = 1.8, 0.8 Hz, 1H, *H*-5),

6.34 (dd, *J* = 3.2, 1.8 Hz, 1H, *H*-4), 6.22 (dd, *J* = 3.2, 0.8 Hz, 1H, *H*-3), 6.15 (dt, *J* = 7.2, 1.6 Hz, 1H, CH_a=C*H*$_b$Cl), 5.90 (dt, *J* = 7.2, 6.5 Hz, 1H, C*H*$_a$=CH_bCl), 3.81 (s, 2H, OC-C*H*$_2$N), 3.48 (dd, *J* = 6.5, 1.6 Hz, 2H, NC*H*$_2$-CH_a), 1.52 (br s, 1H, N*H*); δ_C (101 MHz, $CDCl_3$) 153.5 (C_q), 141.9 (CH-5), 130.0 (CH-4), 119.8 (CH), 110.1 (CH), 107.1 (CH), 45.6 (CH_2), 45.1 (CH_2); ν_{max}/cm^{-1} 3394, 3116, 3082, 2928, 2834, 1602, 1504, 1437, 1359, 1243, 1189, 1147, 1074; m/z HRMS (NSI+) found 172.0519, C_8H_9ClNO [M + H]$^+$ requires 172.0524.

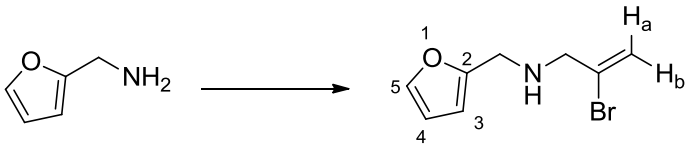
(*E*)-3-Chloro-*N*-(furan-2-ylmethyl)prop-2-en-1-amine (237d):



237d

(*E*)-1,3-Dichloroprop-1-ene (1.11 g, 10.0 mmol) was added dropwise over 30 mins at 50 °C to a stirring mixture of furfuryl amine (1.94 g, 20.0 mmol) in water (4.00 ml) and left overnight at 50 °C. Reaction mixture then cooled to 10 °C and NaOH (1.00 g, 25.0 mmol) added and left for 1 hour with stirring. The mixture was then extracted with diethyl ether (3 × 10 ml) and the combined organic phases dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (3:7 ethyl acetate / petroleum ether) afforded the title compound: Wt 697 mg; 41%; yellow oil; δ_H (300 MHz, $CDCl_3$) 7.36 (dd, *J* = 1.8, 0.6 Hz, 1H, *H*-5), 6.31 (dd, *J* = 3.1, 1.8 Hz, 1H, *H*-4), 6.19 – 6.16 (m, 1H, *H*-3), 6.15 (dt, *J* = 13.3, 1.3 Hz, 1H, H_bC=C*H*$_a$Cl), 5.98 (dt, *J* = 13.3, 6.6 Hz, 1H, *H*$_b$C=CH_aCl), 3.77 (s, 2H, OC-C*H*$_2$N), 3.23 (dt, *J* = 6.6, 1.3 Hz, 2H, NC*H*$_2$-CH_b), 1.50 (br s, 1H, N*H*); δ_C (75 MHz, $CDCl_3$) 153.4 (C_q), 142.0 (CH-5), 131.7 (CH-4), 119.8 (CH), 110.1 (CH), 107.2 (CH), 48.5 (CH_2), 45.2 (CH_2); ν_{max}/cm^{-1} 3325, 3064, 2928, 2830, 1605, 1453, 1360, 1219, 1148, 1012; m/z HRMS (NSI+) found 172.0523, $C_8H_{11}ClNO$ [M + H]$^+$ requires 172.0524.

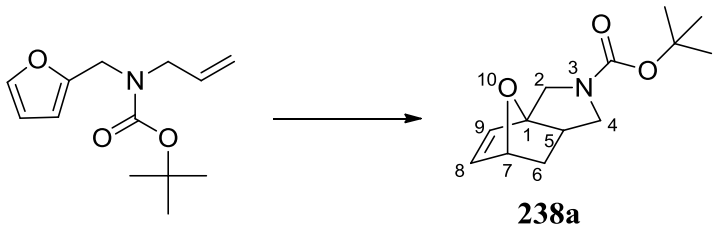
2-Bromo-*N*-(furan-2-ylmethyl)prop-2-en-1-amine (237e):



237e

2-Bromo-3-chloroprop-1-ene (2.00 g, 10.0 mmol) was added dropwise over 30 mins at 50 °C to a stirring mixture of furfuryl amine (1.94 g, 20.0 mmol) in water (4 ml) and left overnight at 50 °C. Reaction mixture then cooled to 10 °C and NaOH (1.00 g, 25.0 mmol) added and left for 1 hour with stirring. The mixture was then extracted with diethyl ether (3 × 10 ml) and the combined organic phases dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (1:4 diethyl ether / petroleum ether) afforded the title compound: Wt 1.09 g; 50%; yellow oil; δ_H (300 MHz, $CDCl_3$) 7.35 (dd, *J* = 1.8, 0.8 Hz, 1H, *H*-5), 6.30 (dd, *J* = 3.2, 1.8 Hz, 1H, *H*-4), 6.17 (dd, *J* = 3.2, 0.8 Hz, 1H, *H*-3), 5.84 – 5.73 (m, 1H, C=C*H*$_a$H$_b$), 5.58 (d, *J* = 1.7 Hz, 1H, C=CH$_a$*H*$_b$), 3.74 (s, 2H, OC-C*H*$_2$N), 3.44 (app. s, 2H, NC*H*$_2$CBr), 1.81 (br s, 1H, N*H*); δ_C (101 MHz, $CDCl_3$) 153.3 (C_q-2), 142.0 (CH-4), 132.8 (C_qBr), 117.9 (BrC=*C*H$_2$), 110.1 (CH), 107.2 (CH), 56.4 (OC-*C*H$_2$N), 44.1 (N*C*H$_2$CBr); ν_{max}/cm^{-1} 3243, 3118, 2928, 1681, 1632, 1610, 1436, 1404, 1153, 1072, 1017.

***tert*-Butyl (1*S*,5*R*,7*R*)-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-ene-3-carboxylate (238a):**

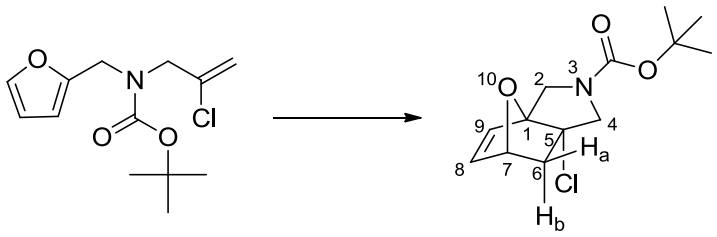


238a

A solution of **236a** (593 mg, 2.50 mmol) in toluene (5.00 ml) was heated to reflux with stirring for 24 hours. Toluene was then removed *in vacuo* and purification by column chromatography (1:4 ethyl acetate/petroleum ether) afforded the title compound: Wt 272 mg; 7%; white solid; m.p. 63-65 °C; δ_H (300 MHz, $CDCl_3$) 6.40 (dd, *J* = 5.8, 1.5 Hz, 1H, *H*-8), 6.36 (d, *J* = 5.8 Hz, 1H, *H*-9), 5.08 (dd, *J* = 4.5, 1.5 Hz, 1H, *H*-7), 3.98 – 3.86 (m, 1H, *H* of CH_2), 3.86 – 3.81 (m, 1H, *H* of CH_2), 3.81 – 3.72 (m, 1H, *H* of CH_2),

3.06 – 2.89 (m, 1H, *H* of CH_2), 2.18 – 2.00 (m, 1H, *H* of CH_2), 1.87 – 1.70 (m, 1H, *H* of CH_2), 1.48 (s, 9H, 3 × C*H*$_3$), 1.47 – 1.40 (m, 1H, *H*-5); δ_C (75 MHz, $CDCl_3$, pairs of rotameric signals observed for certain C atoms) 154.3 and 154.1 (C=O), 137.2 and 137.1 (CH_{alkene}), 134.4 and 134.2 (CH_{alkene}), 95.4 and 94.6 (C_q-1), 80.3 (CH-7), 79.4 (O-C_q), 51.6 and 51.1 (NCH_2), 47.9 and 47.5 (NCH_2), 42.2 and 41.3 (CH-5), 31.3 and 31.2 (CH_2-6), 28.5 (CH_3); ν_{max}/cm^{-1} 2973, 2873, 1687, 1400, 1364, 1262, 1221, 1177, 1155, 1109, 1084, 1062, 1009; m/z HRMS (NSI+) found 238.1438, $C_{13}H_{20}NO_3$ $[M + H]^+$ requires 238.1438.

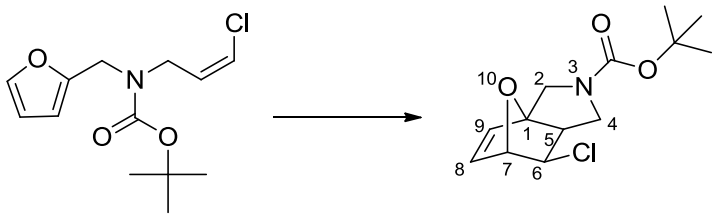
***tert*-Butyl (1*R*,5*S*,7*R*)-5-chloro-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-ene-3-carboxylate (238b):**



238b

A solution of **236b** (679 mg, 2.50 mmol) in toluene (5.00 ml) was heated to reflux with stirring for 96 hours. Toluene was then removed *in vacuo* and purification by column chromatography (1:9 ethyl acetate/petroleum ether) afforded the title compound: Wt 105 mg; 15%; off-white solid; 117-120 °C; δ_H (300 MHz, $CDCl_3$, pairs of 1:1 rotameric signals observed for certain H atoms) 6.55 (dd, *J* = 5.9, 1.7 Hz, 1H, *H*-8), 6.47 and 6.44 (2 × br d, *J* = 5.9 Hz, 1H, *H*-9), 5.09 (dd, *J* = 4.6, 1.7 Hz, 1H, *H*-7), 4.16 – 3.96 (m, 2H, 2 × *H* of CH_2), 3.80 and 3.75 (2 × d, *J* = 12.2 Hz, 1H, *H* of CH_2), 3.53 (d, *J* = 12.2 Hz, 1H, *H* of CH_2), 2.57 and 2.53 (2 × dd, *J* = 12.5, 4.6 Hz, 1H, H_a-6), 1.66 and 1.65 (2 × d, *J* = 12.5 Hz, 1H, H_b-6), 1.47 and 1.45 (2 × s, 9H, 3 × C*H*$_3$); δ_C (75 MHz, $CDCl_3$, pairs of rotameric signals observed for certain C atoms) 154.1 and 154.0 (C=O), 137.5 and 137.4 (CH_{alkene}), 133.5 and 133.3 (CH_{alkene}), 96.7 and 96.0 (C_q-1), 80.8 and 80.8 (CH-7), 79.8 (O-C_q), 72.5 and 71.5 (C_q-6), 61.0 and 60.4 (NCH_2), 46.0 and 45.6 (NCH_2), 41.4 and 41.3 (CH_2), 28.4 (CH_3); ν_{max}/cm^{-1} 2988, 2974, 2933, 2873, 1687, 1458, 1400, 1364, 1341, 1328, 1244, 1245, 1164, 1127, 1079, 1036; m/z HRMS (NSI+) found 294.0869, $C_{13}H_{18}ClNO_3Na$ $[M + Na]^+$ requires 294.0867.

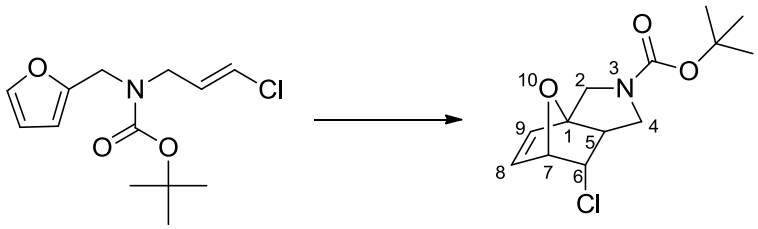
***tert*-Butyl (1*R*,5*R*,6*R*,7*S*)-6-chloro-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-ene-3-carboxylate (238c):**



238c

A solution of **236c** (272 mg, 1.00 mmol) in toluene (2.00 ml) was heated to reflux with stirring for 48 hours. Toluene was then removed *in vacuo* and purification by column chromatography (1:9 ethyl acetate/petroleum ether) afforded the title compound: Wt 20 mg; 7%; off-white solid; m.p. 106-108 °C; δ_H (300 MHz, $CDCl_3$) 6.46 – 6.40 (m, 1H, *H*-9), 6.39 (dd, *J* = 5.8, 1.7 Hz, 1H, *H*-8), 4.90 (d, *J* = 1.7 Hz, 1H, *H*-7), 4.03 (d, *J* = 7.0 Hz, 1H, *H*-6), 3.87 – 3.78 (m, 1H, *H* of CH_2), 3.77 – 3.68 (m, 1H, *H* of CH_2), 3.68 – 3.55 (m, 1H, *H* of CH_2), 3.54 – 3.43 (m, 1H, *H* of CH_2), 2.43 – 2.28 (m, 1H, *H*-5), 1.41 (s, 9H, 3 × C*H*$_3$); δ_C (100 MHz, $CDCl_3$, pairs of rotameric signals observed for certain C atoms) 153.4 (C=O), 134.0 and 136.8 (CH_{alkene}), 134.8 and 134.7 (CH_{alkene}), 95.4 and 94.6 (C_q-1), 86.9 (CH-7), 78.8 (O-C_q), 58.1 and 58.3 (CH-6), 47.2 and 46.8 (NCH_2), 46.5 and 46.1 (NCH_2), 44.5 and 43.8 (CH-5), 27.5 (CH_3); ν_{max}/cm^{-1} 3006, 2973, 2920, 2850, 1678, 1405, 1380, 1363, 1258, 1243, 1167, 1118, 1086, 1065, 1025; m/z HRMS (NSI+) found 294.0869, $C_{13}H_{18}ClNO_3Na$ $[M + Na]^+$ requires 294.0867.

***tert*-Butyl (1*R*,5*R*,6*S*,7*S*)-6-chloro-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-ene-3-carboxylate (238d):**

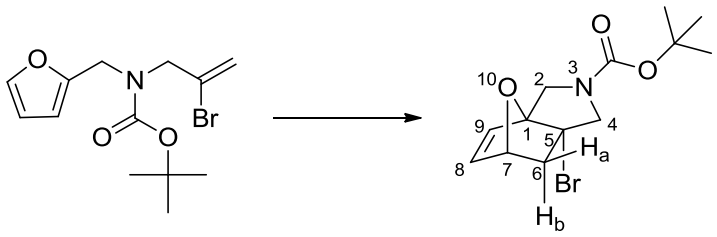


238d

A solution of **236d** (272 mg, 1.00 mmol) in toluene (2.00 ml) was heated to reflux with stirring for 24 hours. Toluene was then removed *in vacuo* and purification by column chromatography (1:4 ethyl acetate/petroleum ether) afforded the title compound: Wt 83

mg; 31%; white solid; m.p. 138-140 °C; δH (300 MHz, $CDCl_3$) 6.51 (app. t, *J* = 6.2, 1H, *H*-9), 6.42 (dd, *J* = 5.8, 1.7, 1H, *H*-8), 5.08 (dd, *J* = 4.3, 1.7, 1H, *H*-7), 4.08 – 4.01 (m, 1H, *H*-6), 4.01 – 3.90 (m, 1H, *H* of CH_2), 3.76 (app. t, *J* = 12.9, 1H, *H* of CH_2), 3.66 (app. t, *J* = 13.2, 1H, *H* of CH_2), 3.02 (app. t, *J* = 9.6, 1H, *H* of CH_2), 2.16 (app. qd, *J* = 9.2, 1.8, 1H, *H*-5), 1.40 (s, 9H, 3 × C*H*$_3$); δ_C (75 MHz, $CDCl_3$, pairs of rotameric signals observed for certain C atoms) 154.0 (C=O), 136.0 and 135.7 (CH_{alkene}), 135.2 and 135.0 (CH_{alkene}), 97.0 and 96.2 (C_q-1), 82.7 (CH-7), 79.8 (O-C_q), 56.4 and 56.3 (CH-6), 53.3 and 52.4 (CH-5), 49.8 and 49.3 (NCH_2), 48.0 and 47.6 (NCH_2), 28.5 (CH_3); ν_{max}/cm^{-1} 2978, 2934, 2901, 1683, 1477, 1402, 1364, 1317, 1248, 1168, 1112, 1077, 1057, 1021; m/z HRMS (NSI+) found 294.0869, $C_{13}H_{18}ClNO_3Na$ $[M + Na]^+$ requires 294.0867.

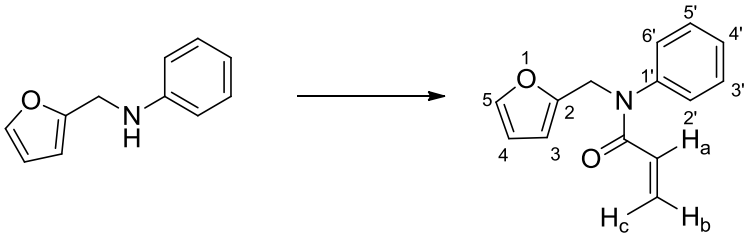
***tert*-Butyl (1*R*,5*S*,7*R*)-5-bromo-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-ene-3-carboxylate (238e):**



238e

A solution of **236e** (221 mg, 0.70 mmol) in toluene (1.40 ml) was heated to reflux with stirring for 24 hours. Toluene was then removed *in vacuo* and purification by column chromatography (1:9 ethyl acetate/petroleum ether) afforded the title compound: Wt 61 mg; 28%; white solid; 117-120 °C; δ_H (300 MHz, $CDCl_3$, pairs of 1:1 rotameric signals observed for certain H atoms) 6.56 – 6.41 (m, 2H, 2 × C*H*$_{alkene}$), 5.11 (dd, *J* = 4.6, 1.4 Hz, 1H, *H*-7), 4.29 – 4.00 (m, 2H, 2 × *H* of CH_2), 3.86 – 3.71 (m, 1H, *H* of CH_2), 3.59 (d, *J* = 12.6 Hz, 1H, *H* of CH_2), 2.55 and 2.51 (2 × dd, *J* = 12.7, 4.6 Hz, 1H, H_a-6), 1.74 (2 × d, *J* = 12.7 Hz, 1H. H_b-6), 1.47 (2 × s, 9H, 2 × C*H*$_3$); δ_C (75 MHz, $CDCl_3$, pairs of rotameric signals observed for certain C atoms) 154.2 and 154.0 (C=O), 136.9 and 136.9 (CH_{alkene}), 134.6 and 134.5 (CH_{alkene}), 97.1 and 96.4 (C_q-1), 80.9 and 80.8 (CH-7), 79.8 (O-C_q), 64.3 and 63.3 (C_q-5), 62.4 and 61.8 (NCH_2), 46.0 and 45.6 (NCH_2), 41.3 and 41.2 (CH_2), 28.5 (CH_3); ν_{max}/cm^{-1} 2984, 2966, 2932, 2881, 1683, 1475, 1392, 1371, 1326, 1256, 1220, 1170, 1132, 1069, 1043; m/z HRMS (NSI+) found 338.0366, $C_{13}H_{18}BrNO_3Na$ $[M + Na]^+$ requires 338.0362.

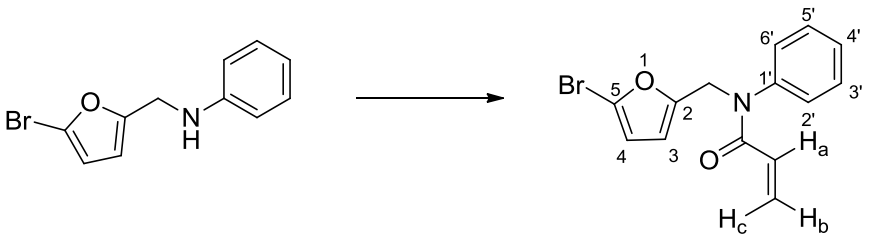
***N*-(Furan-2-ylmethyl)-*N*-phenylacrylamide (239a):**



239a

Acryloyl chloride (157 mg, 1.73 mmol) was added carefully to a solution of **240a** (300 mg, 1.73 mmol), triethylamine (0.23 ml. 3.20 mmol) and DMAP (5 mg, 0.04 mmol) in dry dichloromethane (1.30 ml) at 0 °C with stirring. The reaction mixture was allowed to rise to room temperature and stirred overnight. The reaction mixture was then diluted with dichloromethane (5 ml) and water (5 ml) was added. The mixture was further extracted with dichloromethane (2 × 5 ml) and the combined organic phase dried (Na_2SO_4). Purification by column chromatography (3:7 ethyl acetate/ petroleum ether) afforded the title compound: Wt 278 mg; 71%; golden viscous oil: δ_H (300 MHz, $CDCl_3$) 7.43 – 7.27 (m, 3H, *H*-2', *H*-4' and *H*-6'), 7.32 (dd, *J* = 1.8, 0.8 Hz, 1H, *H*-5), 7.10 – 7.00 (m, 2H, *H*-3' and *H*-5'), 6.41 (dd, *J* = 16.8, 2.0 Hz, 1H, $H_aC{=}CH_bH_c$), 6.26 (dd, *J* = 3.2, 1.8 Hz, 1H, *H*-4), 6.17 (dd, *J* = 3.2, 0.8 Hz, 1H, *H*-3), 5.99 (dd, *J* = 16.8, 10.3 Hz, 1H, $H_aC{=}CH_bH_c$), 5.52 (dd, *J* = 10.3, 2.0 Hz, 1H, $H_aC{=}CH_bH_c$), 4.94 (s, 2H, CH_2); δ_C (75 MHz, $CDCl_3$) 165.4 (C=O), 150.6 (C_q), 142.1 (CH-5), 141.6 (C_q), 129.5 (CH), 128.5 (CH), 128.3 (CH), 128.1 ($C{=}CH_2$), 128.0 (CH), 110.3 (CH), 109.0 (CH), 45.8 (NCH_2); ν_{max}/cm^{-1} 3118, 3062, 1655, 1594, 1494, 1407, 1364, 1253, 1181, 1147, 1014; m/z HRMS (NSI+) found 228.1018, $C_{14}H_{14}NO_2$ $[M + H]^+$ requires 228.1019.

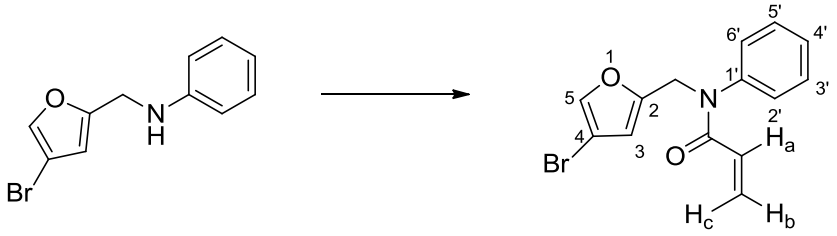
***N*-((5-Bromofuran-2-yl)methyl)-*N*-phenylacrylamide (239b):**



239b

Acryloyl chloride (462 mg, 5.10 mmol) was added carefully to a solution of **240b** (1.29 g, 5.10 mmol), triethylamine (0.72 ml. 5.10 mmol) and DMAP (14 mg, 0.11 mmol) in dry dichloromethane (5.00 ml) at 0 °C with stirring. The reaction mixture was allowed to rise to room temperature and stirred overnight. The reaction mixture was then diluted with dichloromethane (20 ml) and water (20 ml) was added. The mixture was further extracted with dichloromethane (2 × 20 ml) and the combined organic phase dried (Na_2SO_4). Purification by column chromatography (1:4 ethyl acetate/ petroleum ether) afforded the title compound: Wt 1.29 g; 82%; colourless oil: δ_H (300 MHz, $CDCl_3$) 7.44 – 7.27 (m, 3H, *H*-2', *H*-4' and *H*-6'), 7.14 – 7.04 (m, 2H, *H*-3' and *H*-5'), 6.39 (dd, *J* = 16.8, 2.0 Hz, 1H, $H_aC{=}CH_bH_c$), 6.18 (d, *J* = 3.5 Hz, 1H, CH_{furan}), 6.17 (d, *J* = 3.5 Hz, 1H, CH_{furan}), 5.99 (dd, *J* = 16.8, 10.3 Hz, 1H, $H_aC{=}CH_bH_c$), 5.52 (dd, *J* = 10.3, 2.0 Hz, 1H, $H_aC{=}CH_bH_c$), 4.88 (s, 2H, CH_2); δ_C (75 MHz, $CDCl_3$) 165.4 (C=O), 152.7 (C_q), 141.5 (C_q), 129.6 (CH), 128.3 (CH), 128.2 (CH), 128.2 ($C{=}CH_2$), 128.1 (CH), 121.0 (C_q), 112.1 (CH), 111.8 (CH), 45.8 (NCH_2); ν_{max}/cm^{-1} 3063, 3039, 2984, 2933, 1656, 1594, 1494, 1407, 1253, 1172, 1123, 1016; m/z HRMS (NSI+) found 306.0132, $C_{14}H_{13}BrNO_2$ $[M + H]^+$ requires 306.0124.

***N*-((4-Bromofuran-2-yl)methyl)-*N*-phenylacrylamide (239c):**

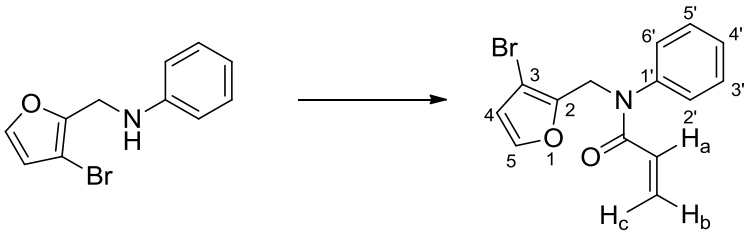


239c

Acryloyl chloride (41.0 mg, 1.00 mmol) was added carefully to a solution of **240g** (115 mg, 0.46 mmol), triethylamine (0.07 ml. 0.50 mmol) and DMAP (2 mg, 0.02 mmol) in dry dichloromethane (2.00 ml) at 0 °C with stirring. The reaction mixture was allowed to rise to room temperature and stirred overnight. The reaction mixture was then diluted with dichloromethane (5 ml) and water (5 ml) was added. The mixture was further extracted with dichloromethane (2 × 5 ml) and the combined organic phase dried (Na_2SO_4). Purification by column chromatography (15:85 ethyl acetate/ petroleum ether) afforded the title compound: Wt 49 mg; 35%; colourless oil: δ_H (300 MHz, $CDCl_3$) 7.43 – 7.33 (m, 3H, *H*-2', *H*-4' and *H*-6'), 7.31 (d, *J* = 0.8 Hz, 1H, *H*-5), 7.13 –

7.02 (m, 2H, *H*-3' and *H*-5'), 6.41 (dd, *J* = 16.8, 2.0 Hz, 1H, $H_aC=CH_bH_c$), 6.27 (d, *J* = 0.8 Hz, 1H, *H*-3), 5.99 (dd, *J* = 16.8, 10.3 Hz, 1H, $H_aC=CH_bH_c$), 5.54 (dd, *J* = 10.3, 2.0 Hz, 1H, $H_aC=CH_bH_c$), 4.89 (s, 2H, CH_2); δ_C (75 MHz, $CDCl_3$) 165.5 (C=O), 151.8 (C_q), 141.5 (C_q) , 140.3 (CH), 129.6 (CH), 128.4 (CH), 128.2 (CH), 128.2 ($C=CH_2$), 128.1 (CH), 112.3 (CH), 100.1 (C_q), 45.8 (NCH_2); ν_{max}/cm^{-1} 3147, 1656, 1593, 1493, 1406, 1256, 1218, 1172, 1122; m/z HRMS (NSI+) found 306.0131, $C_{14}H_{13}BrNO_2$ $[M + H]^+$ requires 306.0124.

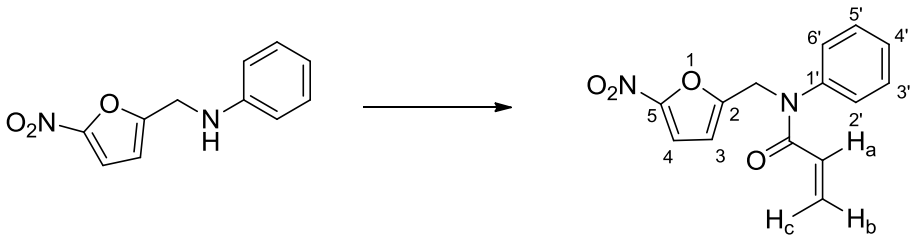
***N*-((3-Bromofuran-2-yl)methyl)-*N*-phenylacrylamide (239d):**



239d

Acryloyl chloride (91.0 mg, 1.00 mmol) was added carefully to a solution of *N*-((3-bromofuran-2-yl)methyl)aniline (252 mg, 1.00 mmol), triethylamine (0.15 ml. 1.00 mmol) and DMAP (4 mg, 0.03 mmol) in dry dichloromethane (5.00 ml) at 0 °C with stirring. The reaction mixture was allowed to rise to room temperature and stirred overnight. The reaction mixture was then diluted with dichloromethane (10 ml) and water (10 ml) was added. The mixture was further extracted with dichloromethane (2 × 10 ml) and the combined organic phase dried (Na_2SO_4). Purification by column chromatography (1:4 diethyl ether/ petroleum ether) afforded the title compound: Wt 162 mg; 53%; colourless oil: δ_H (300 MHz, $CDCl_3$) 7.39 – 7.31 (m, 3H, *H*-2', *H*-4' and *H*-6'), 7.30 (d, *J* = 2.0 Hz, 1H, *H*-5), 7.10 – 6.98 (m, 2H, *H*-3' and *H*-5'), 6.43 (dd, *J* = 16.8, 2.0 Hz, 1H, $H_aC=CH_bH_c$), 6.29 (d, *J* = 2.0 Hz, 1H, *H*-4), 5.99 (dd, *J* = 16.8, 10.3 Hz, 1H, $H_aC=CH_bH_c$), 5.53 (dd, *J* = 10.3, 2.0 Hz, 1H, $H_aC=CH_bH_c$), 5.01 (s, 2H, CH_2); δ_C (75 MHz, $CDCl_3$) 165.5 (C=O), 147.5 (C_q), 142.7 (CH-5), 140.9 (C_q), 129.5 (CH), 128.4 (CH), 128.3 ($C=CH_2$), 128.2 (CH), 128.1 (CH), 113.7 (CH), 100.0 (C_q), 43.4 (NCH_2); ν_{max}/cm^{-1} 3121, 1657, 1594, 1494, 1407, 1253, 1075; m/z HRMS (NSI+) found 306.0133, $C_{14}H_{13}BrNO_2$ $[M + H]^+$ requires 306.0124.

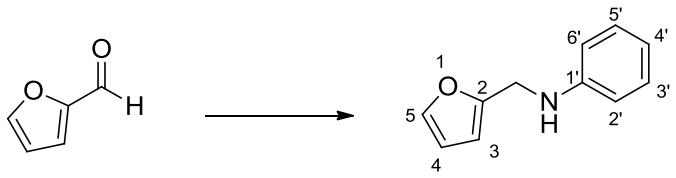
***N*-Allyl-5-nitro-*N*-phenylfuran-2-carboxamide (239e):**



239e

Acryloyl chloride (415 mg, 4.60 mmol) was added carefully to a solution of *N*-(furan-2-ylmethyl)aniline (1.00 g, 4.60 mmol), triethylamine (0.23 ml. 9.60 mmol) and DMAP (13 mg, 0.11 mmol) in dry dichloromethane (5.00 ml) at 0 °C with stirring. The reaction mixture was allowed to rise to room temperature and stirred overnight. The reaction mixture was then diluted with dichloromethane (10 ml) and water (10 ml) was added. The mixture was further extracted with dichloromethane (2 × 10 ml) and the combined organic phase dried (Na_2SO_4). Purification by column chromatography (1:4 ethyl acetate/ petroleum ether) afforded the title compound: Wt 647 mg; 52%; brown/orange oil: δ_H (300 MHz, $CDCl_3$) 7.47 – 7.34 (m, 3H, C*H*$_{aromatic}$), 7.24 (d, *J* = 3.6 Hz, 1H, *H*-4), 7.21 – 7.16 (m, 2H, C*H*$_{aromatic}$), 6.55 (d, *J* = 3.6 Hz, 1H, *H*-3), 6.42 (dd, *J* = 16.8, 1.9 Hz, 1H, $H_aC{=}CH_bH_c$), 6.04 (dd, *J* = 16.8, 10.3 Hz, 1H, $H_aC{=}CH_bH_c$), 5.59 (dd, *J* = 10.3, 1.9 Hz, 1H, $H_aC{=}CH_bH_c$), 4.98 (s, 2H, C*H*$_2$); δ_C (75 MHz, $CDCl_3$) 165.7 (C=O), 154.6 (C_q-2), 151.5 (br - C_q-5), 141.3 (C_q-1'), 123.0 (CH), 129.0 ($CH_{2\text{-alkene}}$), 128.6 (CH), 127.9 (CH), 127.7 (CH), 112.6 (CH_{alkene}), 112.1 (CH_{alkene}), 46.5 (NCH_2); ν_{max}/cm^{-1} 3134, 3064, 3040, 2928, 1656, 1593, 1528, 1489, 1408, 1352, 1255, 1230, 1170, 1018; m/z HRMS (NSI+) found 295.0681, $C_{14}H_{12}N_2O_4Na$ $[M + Na]^+$ requires 295.0689.

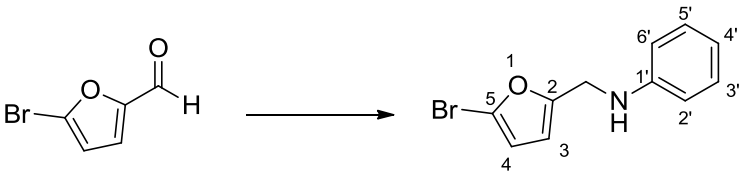
***N*-(Furan-2-ylmethyl)aniline (240a):**[131]



240a

Aniline (2.05 g, 22.0 mmol) was introduced to a stirring solution of furfural (1.92 g, 20.0 mmol) in dichloroethane (73.5 ml) and left stirring for several minutes, the colour of the solution went deep red. $NaBH(OAc)_3$ (6.78 g, 32.0 mmol) was then added and the reaction mixture stirred overnight. The reaction mixture was quenched using saturated $NaHCO_3$ solution (50 ml) and extracted with dichloromethane (3 × 50 ml). The combined organic phase was dried (Na_2SO_4) before being concentrated *in vacuo* to afford the title compound without further purification necessary: Wt 3.30 g; 95%; brown oil; δ_H (300 MHz, $CDCl_3$) 7.39 (dd, *J* = 1.8, 0.8 Hz, 1H, *H*-5), 7.25 – 7.17 (m, 2H, *H*-3' and *H*-5'), 6.81 – 6.73 (m, 1H, *H*-4'), 6.73 – 6.66 (m, 2H, *H*-2' and *H*-6'), 6.34 (dd, *J* = 3.2, 1.8 Hz, 1H, *H*-4), 6.26 (dd, *J* = 3.2, 0.8 Hz, 1H, *H*-3), 4.34 (s, 2H, C*H*$_2$), 4.24 (s, 1H, N*H*); δ_C (75 MHz, $CDCl_3$) 152.7 (C_q), 147.6 (C_q), 142.0 (CH-5), 129.2 (CH), 118.0 (CH), 113.2 (CH), 110.4 (CH), 107.0 (CH), 41.5 (CH_2); ν_{max}/cm^{-1} 3409, 3053, 3024, 2924, 2845, 1602, 1503, 1432, 1316, 1253, 1180, 1145, 1073, 1011.

_N_-((5-Bromofuran-2-yl)methyl)aniline (240b):[159]

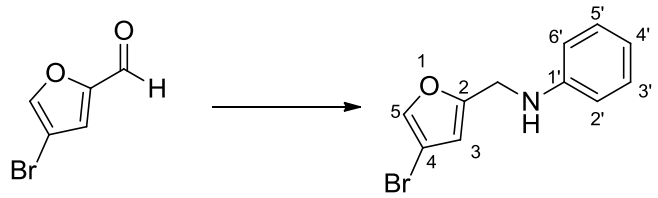


240b

To a stirring solution of aniline (106.0 mg, 1.14 mmol) in diethyl ether (2.00 ml) was added 5-bromo-2-furaldehyde (200 mg, 1.14 mmol) and the mixture left to stir for 3 hours. Removal of the solvent *in vacuo* afforded the imine as a bright yellow precipitate, which was dissolved in methanol (5.70 ml) and treated with $NaBH_4$ (56.0 mg, 1.48 mmol) with stirring for 2 hours. Water (10 ml) was then added to the reaction mixture followed by extraction with dichloromethane (3 x 10) ml. The combined organic phase was dried (Na_2SO_4) before being concentrated *in vacuo* to afford the title compound with no further purification required; Wt 202 mg; 70%; yellow oil; δ_H (300 MHz, $CDCl_3$) 7.24 – 7.15 (m, 2H, *H*-3' and *H*-5'), 6.76 (tt, *J* = 7.5, 1.0 Hz, 1H, *H*-4'), 6.70 – 6.63 (m, 2H, *H*-2' and *H*-6'), 6.23 (d, *J* = 3.3 Hz, 1H, *H*-4), 6.21 (d, *J* = 3.3 Hz, 1H, *H*-3), 4.30 (s, 2H, C*H*$_2$), 4.03 (br s, 1H, N*H*); δ_C (75 MHz, $CDCl_3$) 154.8 (C_q), 147.3 (C_q), 129.3 (CH), 120.8 (C_q), 118.3 (CH), 113.2 (CH), 112.1 (CH), 109.9 (CH), 41.4

(CH_2); ν_{max}/cm^{-1} 3414, 3055, 3022, 2919, 2842, 1603, 1505, 1432, 1312, 1253, 1181, 1123, 1013.

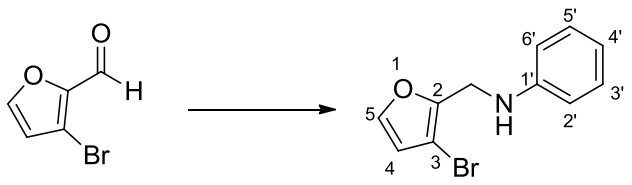
***N*-((4-Bromofuran-2-yl)methyl)aniline (240c):**[134]



240c

Aniline (56 mg, 0.60 mmol) was introduced to a stirring solution of 4-bromo-2-furaldehyde (100 mg, 0.57 mmol) in dichloroethane (2.1 ml) and left stirring for several minutes, the colour of the solution went deep red. $NaBH(OAc)_3$ (194 mg, 0.91 mmol) was then added and the reaction mixture stirred overnight. The reaction mixture was quenched using saturated $NaHCO_3$ solution (2 ml) and extracted with dichloromethane (3 × 5 ml). The combined organic phase was dried (Na_2SO_4) before being concentrated *in vacuo*. Purification by column chromatography (1:9 ethyl acetate / petroleum ether) afforded the title compound: Wt 115 mg; 80%; yellow oil; δ_H (300 MHz, $CDCl_3$) 7.36 (d, *J* = 0.8 Hz, 1H, *H*-5), 7.24 – 7.14 (m, 2H, *H*-3' and *H*-5'), 6.76 (tt, *J* = 7.5, 1.1 Hz, 1H, *H*-4'), 6.70 – 6.62 (m, 2H, *H*-2' and *H*-6'), 6.29 (d, *J* = 0.8 Hz, 1H, *H*-3), 4.31 (s, 2H, C*H*$_2$), 4.05 (s, 1H, N*H*); δ_C (75 MHz, $CDCl_3$) 154.0 (C_q), 147.2 (C_q), 140.1 (CH-5), 129.3 (CH), 118.3 (CH), 113.1 (CH), 110.5 (CH), 100.1 (C_q), 41.3 (CH_2); ν_{max}/cm^{-1} 3415, 3053, 3022, 2921, 2846, 1602, 1504, 1432, 1313, 1254, 1218, 1180, 1122, 1067.

***N*-((3-Bromofuran-2-yl)methyl)aniline (240d):**

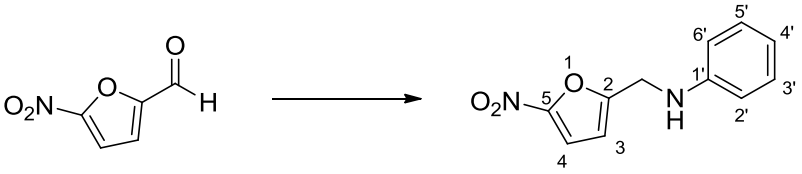


240d

Aniline (140 mg, 1.50 mmol) was introduced to a stirring solution of 3-bromo-2-furaldehyde (250 mg, 1.93 mmol) in dichloroethane (5.00 ml) and left stirring for

several minutes, the colour of the solution went deep red. $NaBH(OAc)_3$ (194 mg, 0.91 mmol) was then added and the reaction mixture stirred overnight. The reaction mixture was quenched using saturated $NaHCO_3$ solution (5 ml) and extracted with dichloromethane (3 × 10 ml). The combined organic phase was dried (Na_2SO_4) before being concentrated *in vacuo*. Purification by column chromatography (1:4 diethyl ether / petroleum ether) afforded the title compound: Wt 338 mg; 89%; yellow oil; δ_H (300 MHz, $CDCl_3$) 7.33 (d, *J* = 2.0 Hz, 1H, *H*-5), 7.25 – 7.15 (m, 2H, *H*-3' and *H*-5'), 6.81 – 6.68 (m, 3H, *H*-2', *H*-4' and *H*-6'), 6.39 (d, *J* = 2.0 Hz, 1H, *H*-4), 4.34 (s, 2H, C*H*$_2$), 4.05 (s, 1H, N*H*); δ_C (75 MHz, $CDCl_3$) 149.6 (C_q), 147.3 (C_q), 142.3 (CH-5), 129.2 (CH), 118.3 (CH), 113.8 (CH), 113.3 (CH), 98.0 (C_q), 39.4 (CH_2); ν_{max}/cm^{-1} 3404, 3147, 3052, 3023, 2923, 2850, 1601, 1501, 1442, 1316, 1251, 1181, 1136, 1052; m/z HRMS (NSI+) found 252.0013, $C_{11}H_{11}BrNO$ $[M + H]^+$ requires 252.0019.

***N*-((5-Nitrofuran-2-yl)methyl)aniline (240e):**

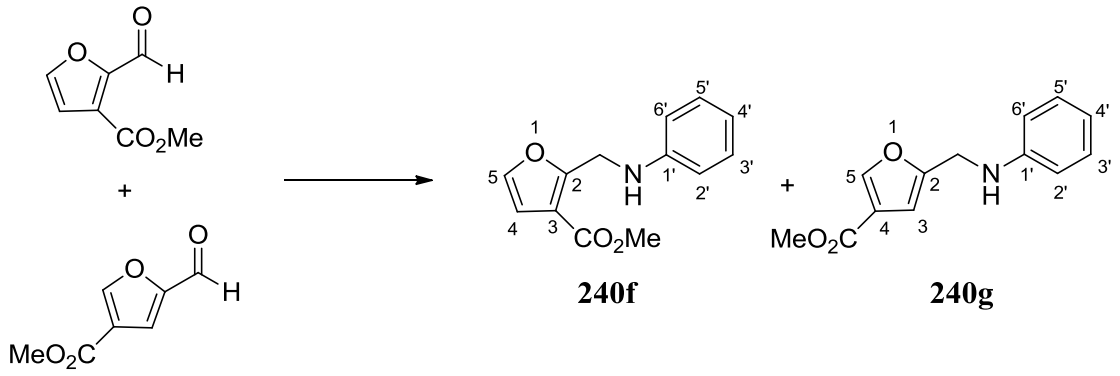


240e

Aniline (1.39 g, 14.9 mmol) was introduced to a stirring solution of 5-nitro-2-furaldehyde (2.00 g, 14.2 mmol) in dichloroethane (54.0 ml) and left stirring for several minutes, the colour of the solution went deep red. $NaBH(OAc)_3$ (4.82 g, 22.7 mmol) was then added and the reaction mixture stirred overnight. The reaction mixture was quenched using saturated $NaHCO_3$ solution (50 ml) and extracted with dichloromethane (3 × 50 ml). The combined organic phase was dried (Na_2SO_4) before being concentrated *in vacuo*. Purification by column chromatography (1:4 ethyl acetate / petroleum ether) afforded the title compound: Wt 2.61 g; 84%; red solid; δ_H (300 MHz, $CDCl_3$) 7.25 (d, *J* = 3.7 Hz, 1H, *H*-4), 7.23 – 7.17 (m, 2H, *H*-3' and *H*-5'), 6.83 – 6.75 (m, 1H, *H*-4'), 6.69 – 6.60 (m, 2H, *H*-2' and *H*-6'), 6.46 (dt, *J* = 3.7, 0.8 Hz, 1H, *H*-3), 4.45 (app. d, *J* = 4.0 Hz, 2H, C*H*$_2$), 4.13 (br s, 1H, N*H*); δ_C (75 MHz, $CDCl_3$) 157.2 (C_q-2), 151.7 (br - C_q-5), 146.5 (C_q-1'), 129.4 (CH), 118.9 (CH), 113.2 (CH), 112.5 (CH), 110.3 (CH), 41.6 (NCH_2); ν_{max}/cm^{-1} 3412, 3132, 3053, 3025, 2846, 1602, 1484,

1351, 1254, 1234, 1182, 1168, 1098, 1016; m/z HRMS (NSI+) found 219.0763, $C_{11}H_{11}N_2O_3$ $[M + H]^+$ requires 219.0764.

Methyl 2-((phenylamino)methyl)furan-3-carboxylate (240f) & methyl 2-((phenylamino)methyl)furan-4-carboxylate (240g):

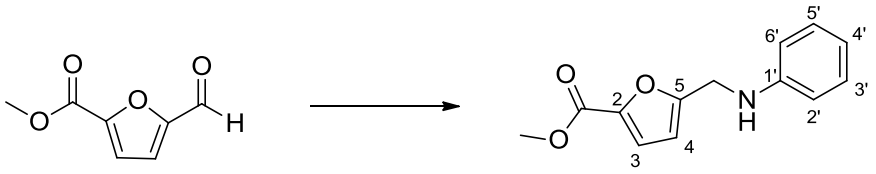


Aniline (272 mg, 2.9 mmol) was introduced to a stirring solution of **285** (429 mg, 2.80 mmol) in dichloroethane (10.0 ml) and left stirring for several minutes. $NaBH(OAc)_3$ (943 mg, 4.50 mmol) was then added and the reaction mixture stirred overnight. The reaction mixture was quenched using saturated $NaHCO_3$ solution (10 ml) and extracted with dichloromethane (3 × 10 ml). The combined organic phase was dried (Na_2SO_4) before being concentrated *in vacuo*. Purification by column chromatography (1:4 ethyl acetate / petroleum ether) afforded the isolated title compounds: **240f**: Wt 46 mg; 7%; brown oil; δ_H (300 MHz, $CDCl_3$) 7.29 (d, *J* = 1.9 Hz, 1H, *H*-5), 7.21 – 7.13 (m, 2H, 2 × C*H*$_{phenyl}$), 6.77 – 6.69 (m, 3H, 3 × C*H*$_{phenyl}$), 6.65 (d, *J* = 1.9 Hz, 1H, *H*-4), 4.64 (s, 2H, NCH_2), 4.50 (br s, 1H, N*H*), 3.87 (s, 3H, OCH_3); δ_C (101 MHz, $CDCl_3$) 164.1 (C=O), 159.6 (C_q), 143.9 (C_q), 141.4 (CH), 129.6 (C_q), 129.2 (CH), 118.2 (CH), 113.4 (CH), 110.8 (CH), 51.6 (CH_3), 40.4 (CH_2); ν_{max}/cm^{-1} 3405, 3053, 3023, 2952, 1709, 1601, 1505, 1438, 1302, 1252, 1197, 1168, 1132, 1056, 1031; m/z HRMS (NSI+) found 232.0969, $C_{13}H_{14}NO_3$ $[M + H]^+$ requires 232.0968.

240g: Wt 389g; 60%; brown oil; δ_H (300 MHz, $CDCl_3$) 7.94 (d, *J* = 0.8 Hz, 1H, *H*-5), 7.24 – 7.15 (m, 2H, *H*-3' and *H*-5'), 6.82 – 6.72 (m, 1H, *H*-4'), 6.71 – 6.63 (m, 2H, *H*-2' and *H*-6'), 6.59 (d, *J* = 0.8 Hz, 1H, *H*-3), 4.32 (s, 2H, NCH_2), 4.08 (br s, 1H, N*H*), 3.82 (s, 3H, OCH_3); δ_C (75 MHz, $CDCl_3$) 163.4 (C=O), 154.3 (C_q), 147.1 (C_q), 146.9 (CH), 129.2 (CH), 119.74 (C_q), 118.2 (CH), 113.1 (CH), 106.9 (CH), 51.5 (CH_3), 41.1 (CH_2); ν_{max}/cm^{-1} 3405, 3054, 3024, 2952, 1714, 1602, 1547, 1505, 1437, 1303, 1255, 1203,

1137, 1104, 1067; m/z HRMS (NSI+) found 232.0969, $C_{13}H_{14}NO_3$ $[M + H]^+$ requires 232.0968.

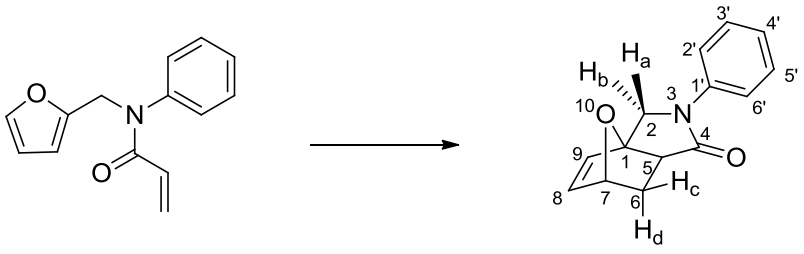
Methyl 5-((phenylamino)methyl)furan-2-carboxylate (240h):



240h

Aniline (98.0 mg, 1.05 mmol) was introduced to a stirring solution of **287** (154 mg, 1.00 mmol) in dichloroethane (4.10 ml) and left stirring for several minutes, the colour of the solution went deep red. $NaBH(OAc)_3$ (339 mg, 1.60 mmol) was then added and the reaction mixture stirred overnight. The reaction mixture was quenched using saturated $NaHCO_3$ solution (10 ml) and extracted with dichloromethane (3 × 15 ml). The combined organic phase was dried (Na_2SO_4) before being concentrated *in vacuo* to afford the title compound without any further purification necessary: Wt 196 mg; 85%; brown oil; δ_H (300 MHz, $CDCl_3$) 7.23 – 7.13 (m, 2H, *H*-3' and *H*-5'), 7.11 (d, *J* = 3.5 Hz, 1H, *H*-3), 6.80 – 6.72 (m, 1H, *H*-4'), 6.67 – 6.60 (m, 2H, *H*-2' and *H*-6'), 6.34 (d, *J* = 3.5 Hz, 1H, *H*-4), 4.41 (s, 2H, C*H*$_2$), 3.89 (s, 3H, OC*H*$_3$); δ_C (101 MHz, $CDCl_3$) 159.1 (C=O), 157.6 (C_q), 147.0 (C_q), 143.8 (C_q), 129.3 (CH), 119.0 (CH), 118.4 (CH), 113.2 (CH), 109.2 (CH), 51.9 (CH_3), 41.6 (CH_2); ν_{max}/cm^{-1} 3390, 3053, 3025, 2951, 2846, 1716, 1602, 1505, 1435, 1302, 1263, 1206, 1135, 1018; m/z HRMS (NSI+) found 232.0967, $C_{13}H_{14}NO_3$ $[M + H]^+$ requires 232.0968.

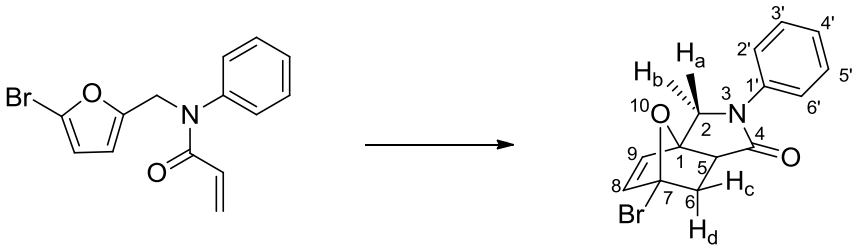
(1*S*,5*S*,7*R*)-3-Phenyl-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-en-4-one (241a):



241a

A solution of **239a** (150 mg, 0.66 mmol) in toluene (7.00 ml) was heated to reflux with stirring for 24 hours. Toluene was then removed *in vacuo* and purification by column chromatography (3:7 ethyl acetate/petroleum ether) afforded the title compound: Wt 93 mg; 62%; white solid; m.p. 133-135 °C; δ_H (300 MHz, $CDCl_3$) δ 7.62 – 7.49 (m, 2H, *H*-2' and *H*-6'), 7.37 – 7.24 (m, 2H, *H*-3' and *H*-5'), 7.14 – 7.02 (m, 1H, *H*-4'), 6.41 (d, *J* = 5.8 Hz, 1H, *H*-9), 6.38 (dd, *J* = 5.8, 1.5 Hz, 1H, *H*-8), 5.05 (dd, *J* = 4.5, 1.5 Hz, 1H, *H*-7), 4.40 (d, *J* = 11.5 Hz, 1H, H_a-2 or H_b-2), 4.08 (d, *J* = 11.5 Hz, 1H, H_a-2 or H_b-2), 2.58 (dd, *J* = 8.8, 3.5 Hz, 1H, *H*-5), 2.26 (ddd, *J* = 11.9, 4.5, 3.5 Hz, 1H, H_c-6), 1.62 (dd, *J* = 11.9, 8.8 Hz, 1H, H_d-6); δ_C (75 MHz, $CDCl_3$) 173.4 (C=O), 139.4 (C_q-1'), 137.5 (CH), 133.0 (CH), 128.9 (CH), 124.7 (CH), 120.3 (CH), 88.1 (C_q-1), 79.3 (CH-7), 50.9 (CH_2-2), 48.8 (CH-5), 28.9 (CH_2-6); ν_{max}/cm^{-1} 3135, 3010, 2982, 2953, 1686, 1600, 1495, 1396, 1358, 1196, 1125, 1047; m/z HRMS (NSI+) found 228.1022, $C_{14}H_{14}NO_2$ $[M + H]^+$ requires 228.1019.

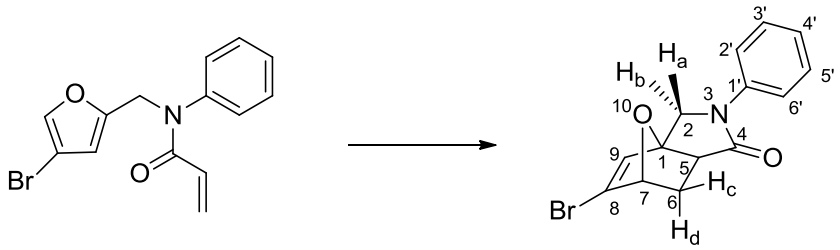
(1*S*,5*S*,7*S*)-7-Bromo-3-phenyl-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-en-4-one (241b):



241b

A solution of **239b** (100 mg, 0.33 mmol) in toluene (6.50 ml) was heated to reflux with stirring for 2 hours. Toluene was then removed *in vacuo* and purification by column chromatography (7:3 diethyl ether/petroleum ether) afforded the title compound: Wt 70 mg; 70%; white solid; m.p. 138-140 °C; δ_H (300 MHz, $CDCl_3$) δ 7.63 – 7.55 (m, 2H, *H*-2' and *H*-6'), 7.44 – 7.32 (m, 2H, *H*-3' and *H*-5'), 7.18 (tt, *J* = 7.4, 1.1 Hz, 1H, *H*-4'), 6.52 (d, *J* = 5.7 Hz, 1H, CH_{alkene}), 6.49 (d, *J* = 5.7 Hz, 1H, CH_{alkene}), 4.43 (d, *J* = 11.8 Hz, 1H, H_a-2 or H_b-2), 4.17 (d, *J* = 11.8 Hz, 1H, H_a-2 or H_b-2), 2.82 (dd, *J* = 8.6, 3.5 Hz, 1H, *H*-5), 2.66 (dd, *J* = 12.0, 3.5 Hz, 1H, H_c-6), 2.30 (dd, *J* = 12.0, 8.6 Hz, 1H, H_d-6); δ_C (75 MHz, $CDCl_3$) 171.6 (C=O), 141.4 (CH), 138.9 (C_q-1'), 133.9 (CH), 129.0 (CH), 125.2 (CH), 120.4 (CH), 88.8 ($C_{q\text{-bridgehead}}$), 87.6 ($C_{q\text{-bridgehead}}$), 51.7 (CH-5), 50.7 (CH_2-2), 39.8 (CH_2-6); ν_{max}/cm^{-1} 3064, 2954, 1687, 1499, 1400, 1355, 1243, 1200, 1186, 1064; m/z HRMS (NSI+) found 306.0129, $C_{14}H_{13}BrNO_2$ $[M + H]^+$ requires 306.0124.

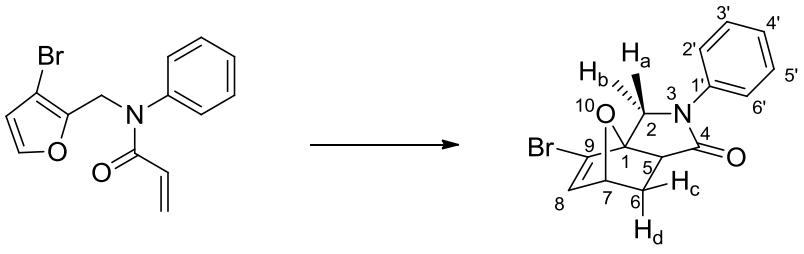
(1*S*,5*S*,7*R*)-8-Bromo-3-phenyl-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-en-4-one (241c):



241c

A solution of **239c** (100 mg, 0.33 mmol) in toluene (6.50 ml) was heated to reflux with stirring for 12 hours. Toluene was then removed *in vacuo* and purification by column chromatography (2:3 diethyl ether/petroleum ether) afforded the title compound: Wt 76 mg; 76%; white solid; m.p. 145-147 °C; δ_H (300 MHz, $CDCl_3$) 7.67 – 7.54 (m, 2H, *H*-2' and *H*-6'), 7.47 – 7.29 (m, 2H, *H*-3' and *H*-5'), 7.23 – 7.11 (m, 1H, *H*-4'), 6.52 (s, 1H, *H*-9), 4.95 (d, *J* = 4.5 Hz, 1H, *H*-7), 4.43 (d, *J* = 11.6 Hz, 1H, H_a-2 or H_b-2), 4.14 (d, *J* = 11.6 Hz, 1H, H_a-2 or H_b-2), 2.81 (dd, *J* = 8.8, 3.4 Hz, 1H, *H*-5), 2.34 (ddd, *J* = 12.2, 4.5, 3.4 Hz, 1H, H_c-6), 1.85 (dd, *J* = 12.2, 8.8 Hz, 1H, H_d-6); δ_C (75 MHz, $CDCl_3$) 172.4 (C=O), 139.1 (C_q-1'), 131.7 (CH), 129.0 (CH), 127.7 (C_q-8), 125.0 (CH), 120.3 (CH), 90.1 (C_q-1), 84.3 (CH-7), 50.6 (CH_2-2), 49.9 (CH-5), 28.4 (CH_2-6); ν_{max}/cm^{-1} 3064, 2952, 1695, 1597, 1499, 1397, 1353, 1297, 1203, 1124, 1034; m/z HRMS (NSI+) found 306.0132, $C_{14}H_{13}BrNO_2$ $[M + H]^+$ requires 306.0124.

(1*R*,5*S*,7*R*)-9-Bromo-3-phenyl-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-en-4-one (241d):

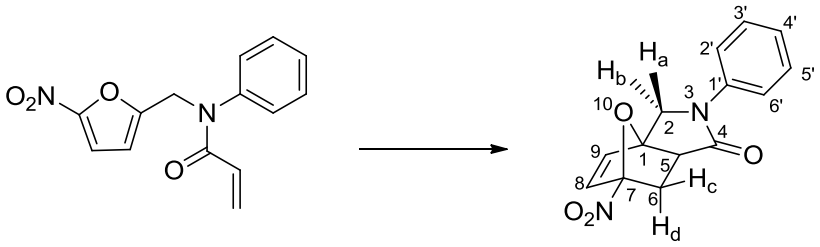


241d

A solution of **239d** (100 mg, 0.33 mmol) in toluene (6.50 ml) was heated to reflux with stirring for 6 hours. Toluene was then removed *in vacuo* and purification by column chromatography (1:1 diethyl ether/petroleum ether) afforded the title compound: Wt 83 mg; 83%; white solid; m.p. 144-146 °C; δ_H (300 MHz, $CDCl_3$)7.73 – 7.60 (m, 2H, H-2'

and H-6'), 7.49 – 7.33 (m, 2H, *H*-3' and *H*-5'), 7.27 – 7.13 (m, 1H, *H*-4'), 6.52 (d, *J* = 1.9 Hz, 1H, *H*-8), 5.14 (dd, *J* = 4.4, 1.9 Hz, 1H, *H*-7), 4.56 (d, *J* = 11.6 Hz, 1H, H_a-2 or H_b-2), 4.10 (d, *J* = 11.6 Hz, 1H, H_a-2 or H_b-2), 2.82 (dd, *J* = 8.8, 3.7 Hz, 1H, *H*-5), 2.41 (ddd, *J* = 12.0, 4.4, 3.7 Hz, 1H, H_c-6), 1.86 (dd, *J* = 12.0, 8.8 Hz, 1H, H_d-6); δ_C (75 MHz, $CDCl_3$) 172.1 (C=O), 139.1 (C_q-1'), 135.9 (CH), 129.0 (CH), 125.0 (CH), 123.7 (C_q-9), 120.3 (CH), 90.3 (C_q-1), 80.7 (CH-7), 49.4 (CH_2-2), 48.1 (CH-5), 30.3 (CH_2-6); ν_{max}/cm^{-1} 3035, 2960, 2930, 1700, 1593, 1571, 1493, 1392, 1346, 1274, 1189, 1124, 1066; m/z HRMS (NSI+) found 306.0123, $C_{14}H_{13}BrNO_2$ $[M + H]^+$ requires 306.0124

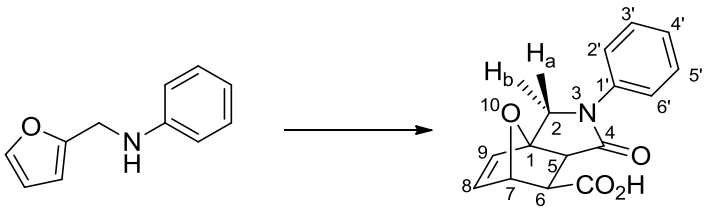
(1*S*,5*S*,7*R*)-7-Nitro-3-phenyl-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-en-4-one (241e):



241e

A solution of **239e** (64.0 mg, 23.5 mmol) in toluene (2.50 ml) was heated to reflux with stirring for 24 hours. Toluene was then removed *in vacuo* to afford the pure title compound: Wt 64 mg; 100%; beige solid; m.p. 165-166 °C; δ_H (300 MHz, $CDCl_3$) 7.66 – 7.54 (m, 2H, *H*-2' and *H*-6'), 7.46 – 7.33 (m, 2H, *H*-3' and *H*-5'), 7.24 – 7.16 (m, 1H, *H*-4'), 6.79 (s, 2H, 2 × CH_{alkene}), 4.50 (d, *J* = 12.0 Hz, 1H, H_a-2 or H_b-2), 4.30 (d, *J* = 12.0 Hz, 1H, H_a-2 or H_b-2), 2.95 (dd, *J* = 8.7, 3.6 Hz, 1H, *H*-5), 2.71 (dd, *J* = 11.7, 3.6 Hz, 1H, H_c-6), 2.44 (dd, *J* = 11.7, 8.7 Hz, 1H, H_d-6); δ_C (75 MHz, $CDCl_3$) 170.5 (C=O), 138.6 (C_q-1'), 135.9 (CH), 135.0 (CH), 129.1 (CH), 125.5 (CH), 120.4 (CH), 111.7 (C_q-7), 87.8 (C_q-1), 50.8 (CH-5), 50.4 (CH_2-2), 34.0 (CH_2-6); ν_{max}/cm^{-1} 3117, 3098, 3067, 2992, 1688, 1552, 1500, 1489, 1472, 1358, 1292, 1156, 1116, 1055; m/z HRMS (APCI+) found 273.0869, $C_{14}H_{13}N_2O_4$ $[M + H]^+$ requires 273.0870.

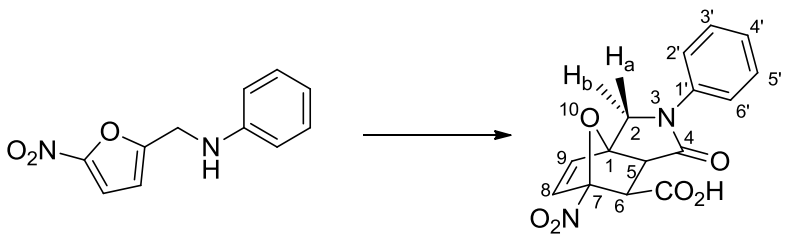
(1*S*,5*S*,6*R*,7*S*)-4-Oxo-3-phenyl-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (251a):



251a

A solution of **240a** (17.3 mg, 0.10 mmol) dissolved in deuterated chloroform (0.25 ml) was introduced to a solution of maleic anhydride (9.80 mg, 0.10 mmol) dissolved in deuterated chloroform (0.25 ml) in an NMR tube and left overnight . The solution was then filtered to collect the precipitate, which was the title compound without any further purification necessary: Wt 23 mg; 85%; white solid; m.p. 189-191 °C; δ_H (300 MHz, $CDCl_3$) 7.55 – 7.47 (m, 2H, *H*-2' and *H*-6'), 7.39 – 7.28 (m, 2H, *H*-3' and *H*-5'), 7.15 (t, *J* = 7.4 Hz, 1H, *H*-4'), 6.56 (d, *J* = 5.8 Hz, 1H, *H*-9), 6.48 (dd, *J* = 5.8, 1.4 Hz, 1H, *H*-8), 5.20 (d, *J* = 1.4 Hz, 1H, *H*-7), 4.44 (d, *J* = 11.6 Hz, 1H, H_a-2 or H_b-2), 4.20 (d, *J* = 11.6 Hz, 1H, H_a-2 or H_b-2), 2.99 (d, *J* = 9.0 Hz, 2H, *H*-5 or *H*-6), 2.79 (d, *J* = 9.0 Hz, 1H, *H*-5 or *H*-6); δ_C (101 MHz, $CDCl_3$) 172.0 (C=O), 170.3 (C=O), 140.1 (C_q-1'), 137.1 (CH), 135.3 (CH), 128.5 (CH), 123.8 (CH), 119.4 (CH), 87.7 (C_q-1), 81.9 (CH-7), 51.6 (CH-5 or CH-6), 49.4 (CH_2), 45.7 (CH-5 or CH-6); ν_{max}/cm^{-1} 3103, 3085, 3063, 3012, 2946, 2903, 1698, 1598, 1495, 1470, 1399, 1355, 1284, 1237, 1190, 1124, 1076; m/z HRMS (NSI+) found 272.0915, $C_{15}H_{14}NO_4$ $[M + H]^+$ requires 272.0917.

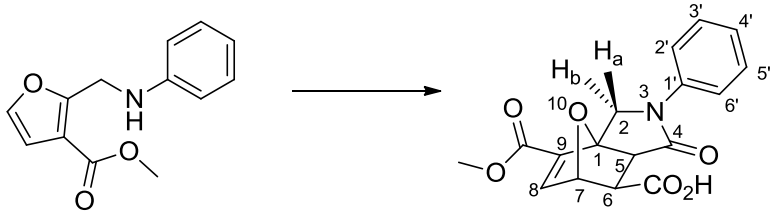
(1*S*,5*S*,6*R*,7*S*)-7-Nitro-4-oxo-3-phenyl-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (251b):



251b

A solution of **240e** (218 mg, 1.00 mmol) dissolved in acetone (2.50 ml) was introduced to a solution of maleic anhydride (98.0 mg, 1.00 mmol) dissolved in chloroform (2.50 ml) with stirring and left for 6 days. The solution was then filtered to collect the precipitate, which was the title compound without any further purification necessary: Wt 41 mg; 13%; white solid; m.p. 220-222 °C; δ_H (300 MHz, $(CD_3)_2CO$) 7.74 – 7.65 (m, 2H, *H*-2' and *H*-6'), 7.43 – 7.33 (m, 2H, *H*-3' and *H*-5'), 7.20 – 7.12 (m, 1H, *H*-4'), 7.15 (d, *J* = 5.5 Hz, 1H, *H*-8), 6.86 (d, *J* = 5.5 Hz, 1H, *H*-9), 4.75 (d, *J* = 12.0 Hz, 1H, H_a-2 or H_b-2), 4.31 (d, *J* = 12.0 Hz, 1H, H_a-2 or H_b-2), 3.61 (d, *J* = 9.1 Hz, 1H, *H*-5 or *H*-6), 3.55 (d, *J* = 9.1 Hz, 1H, *H*-5 or *H*-6); δ_C (101 MHz, $(CD_3)_2CO$) 168.6 (C=O), 168.3 (C=O), 139.52 (C_q-1'), 138.52 (CH), 135.72 (CH), 128.65 (CH), 124.41 (CH), 119.71 (CH), 112.73 (C_q-7), 86.82 (C_q-1), 53.30 (CH-6), 49.16 (CH_2), 48.5 (CH-5); ν_{max}/cm^{-1} 3091, 3072, 3026, 1743, 1669, 1597, 1553, 1492, 1471, 1450, 1429, 1409, 1368, 1237, 1194, 1139, 1072; m/z HRMS (APCI+) found 317.0765, $C_{15}H_{13}N_2O_6$ $[M + H]^+$ requires 317.0768.

(1*R*,5*S*,6*R*,7*S*)-9-Methoxycarbonyl-4-oxo-3-phenyl-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (251c):

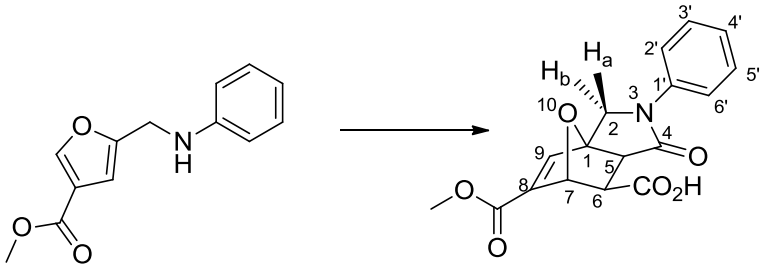


251c

A solution of **240f** (23.1 mg, 0.10 mmol) dissolved in deuterated chloroform (0.30 ml) was introduced to a solution of maleic anhydride (9.80 mg, 0.10 mmol) dissolved in deuterated chloroform (0.30 ml) in an NMR tube and left for 3 days. The solution was then filtered to collect the precipitate. This was washed with chloroform to afford the title compound without any further purification necessary: Wt 11.7 mg; 37%; white solid; m.p. 177-179 °C; δ_H (300 MHz, $(CD_3)_2CO$) 7.81 – 7.64 (m, 2H, *H*-2' and *H*-6'), 7.42 – 7.34 (m, 2H, *H*-3' and *H*-5'), 7.34 (d, 1H, *J* = 1.8 Hz, *H*-8), 7.14 (t, *J* = 7.4 Hz, 1H, *H*-4'), 5.28 (d, *J* = 1.8 Hz, 1H, *H*-7), 5.04 (d, *J* = 11.6 Hz, 1H, H_a-2 or H_b-2), 4.11 (d, *J* = 11.6 Hz, 1H, H_a-2 or H_b-2), 3.80 (s, 3H, OCH_3), 3.24 (d, *J* = 9.2 Hz, 1H, *H*-5 or *H*-6), 2.93 (d, *J* = 9.2 Hz, 1H, *H*-5 or *H*-6); δ_C (101 MHz, $(CD_3)_2CO$)) 169.4 (C=O),

162.5 (C=O), 146.7 (CH), 139.9 (C_q), 139.6 (C_q), 128.6 (CH), 124.1 (CH), 119.6 (CH), 87.6 (C_q-1), 81.7 (CH-7), 51.3 (CH), 48.3 (CH_2), 45.5 (CH_3); ν_{max}/cm^{-1} 3170, 3076, 3048, 2980, 1721, 1682, 1595, 1494, 1438, 1413, 1367, 1328, 1298, 1238, 1207, 1176, 1129, 1116, 1080; m/z HRMS (NSI+) found 330.0975, $C_{17}H_{16}NO_6$ $[M + H]^+$ requires 330.0972.

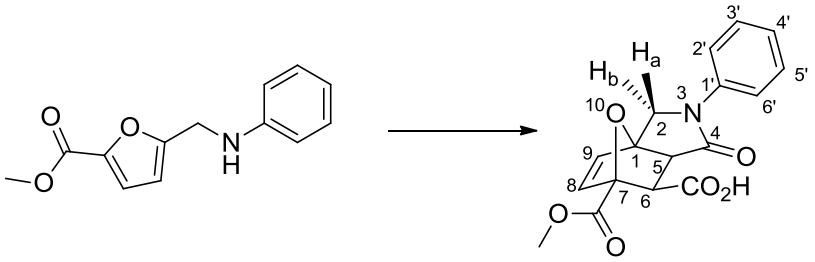
(1*S*,5*S*,6*R*,7*R*)-8-Methoxycarbonyl-4-oxo-3-phenyl-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (251d):



251d

A solution of **240g** (23.1 mg, 0.10 mmol) dissolved in deuterated chloroform (0.30 ml) was introduced to a solution of maleic anhydride (9.80 mg, 0.10 mmol) dissolved in deuterated chloroform (0.30 ml) in an NMR tube and left for 3 days. The solution was then filtered to collect the precipitate. This was washed with chloroform to afford the title compound without any further purification necessary: Wt 7.3 mg; 23%; white solid; m.p. 191-193 °C; δ_H (300 MHz, $(CD_3)_2CO$) 7.80 – 7.64 (m, 2H, *H*-2' and *H*-6'), 7.46 (s, 1H, *H*-9), 7.42 – 7.29 (m, 2H, *H*-3' and *H*-5'), 7.22 – 7.07 (m, 1H, *H*-4'), 5.29 (s, 1H, *H*-7), 4.71 (d, *J* = 11.6 Hz, 1H, H_a-2 or H_b-2), 4.18 (d, *J* = 11.6 Hz, 1H, H_a-2 or H_b-2), 3.77 (s, 3H, OCH_3), 3.33 (d, *J* = 9.2 Hz, 1H, *H*-5 or *H*-6), 2.91 (d, *J* = 9.2 Hz, 1H, *H*-5 or *H*-6); δ_C (101 MHz, $(CD_3)_2CO$)) 169.4 (C=O), 162.4 (C=O), 144.3 (CH), 142.4 (C_q), 139.8 (C_q), 128.6 (CH), 124.1 (CH), 119.6 (CH), 89.3 (C_q-1), 81.5 (CH-7), 51.9 (CH), 51.2 (CH_3), 49.2 (CH_2), 45.4 (CH); ν_{max}/cm^{-1} 3171, 3051, 2957, 1743, 1717, 1685, 1666, 1596, 1494, 1439, 1407, 1362, 1242, 1207, 1176, 1067; m/z HRMS (NSI+) found 330.0973, $C_{17}H_{16}NO_6$ $[M + H]^+$ requires 330.0972.

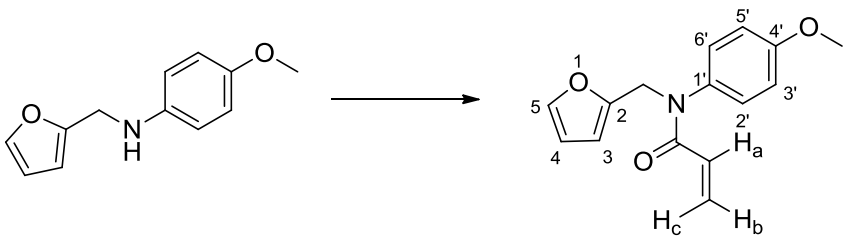
(1*S*,5*S*,6*R*,7*S*)-7-Methoxycarbonyl-4-oxo-3-phenyl-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (251e):



251e

A solution of **240h** (23.1 mg, 0.10 mmol) dissolved in deuterated chloroform (0.30 ml) was introduced to a solution of maleic anhydride (9.80 mg, 0.10 mmol) dissolved in deuterated chloroform (0.30 ml) in an NMR tube and left for 3 days. The solution was then filtered to collect the precipitate. This was washed with chloroform to afford the title compound without any further purification necessary: Wt 6.8 mg; 21%; white solid; m.p. 159-162 °C; δ_H (300 MHz, $(CD_3)_2CO$)) 7.72 (app. d, *J* = 7.8 Hz, 2H), 7.37 (app. t, *J* = 8.0 Hz, 2H), 7.14 (app. t, *J* = 7.4 Hz, 1H), 6.88 (d, *J* = 5.5 Hz, 1H, C*H*$_{alkene}$), 6.59 (d, *J* = 5.5 Hz, 1H, C*H*$_{alkene}$), 4.67 (d, *J* = 11.6 Hz, 1H, *H*$_a$-2 or *H*$_b$-2), 4.20 (d, *J* = 11.6 Hz, 1H, *H*$_a$-2 or *H*$_b$-2), 3.77 (s, 3H, OC*H*$_3$), 3.29 (d, *J* = 9.0 Hz, 1H, *H*-5 or *H*-6), 3.17 (br s, 1H, *H*-5 or *H*-6); δ_C (101 MHz, $(CD_3)_2CO$)) 169.4 (C=O), 168.2 (C=O), 139.9 (C$_q$-1'), 137.3 (CH), 136.1 (CH), 128.0 (CH), 124.0 (CH), 119.6 (CH), 80.7 (C$_{q\text{-bridgehead}}$), 79.0 (C$_{q\text{-bridgehead}}$), 52.4 (CH-5 or CH-6), 51.5 (CH$_3$), 51.0 (CH-5 or CH-6), 49.3 (CH$_2$); ν_{max}/cm^{-1} 3041, 3018, 2975, 2956, 2923, 1728, 1661, 1598, 1500, 1478, 1449, 1432, 1372, 1346, 1300, 1285, 1221, 1192, 1122, 1060; m/z HRMS (NSI+) found 330.0973, $C_{17}H_{16}NO_6$ $[M + H]^+$ requires 330.0972.

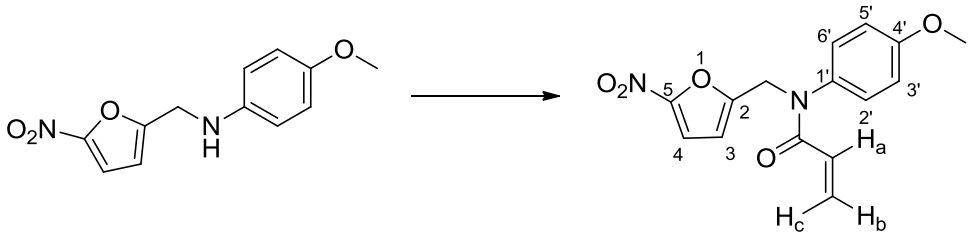
***N*-(Furan-2-ylmethyl)-*N*-(4-methoxyphenyl)acrylamide (252a):**



252a

Acryloyl chloride (95.0 mg, 1.05 mmol) was added carefully to a solution of **254a** (203 mg, 1.00 mmol), triethylamine (0.15 ml. 1.00 mmol) and DMAP (5.00 mg, 0.11 mmol) in dry dichloromethane (5.00 ml) at 0 °C with stirring. The reaction mixture was allowed to rise to room temperature and stirred overnight. The reaction mixture was then diluted with dichloromethane (10 ml) and water (10 ml) was added. The mixture was further extracted with dichloromethane (2 × 10 ml) and the combined organic phase dried (Na_2SO_4). Purification by column chromatography (1:1 diethyl ether/ petroleum ether) afforded the title compound: Wt 236 mg; 92%; brown oil: δ_H (300 MHz, $CDCl_3$) 7.32 (dd, *J* = 1.8, 0.8 Hz, 1H, *H*-5), 7.00 – 6.92 (m, 2H, *H*-2' and *H*-6' or *H*-3' and *H*-5'), 6.90 – 6.82 (m, 2H, *H*-2' and *H*-6' or *H*-3' and *H*-5'), 6.39 (dd, *J* = 16.8, 2.1 Hz, 1H, $H_aC{=}CH_bH_c$), 6.27 (dd, *J* = 3.2, 1.8 Hz, 1H, *H*-4), 6.17 (dd, *J* = 3.2, 0.8 Hz, 1H, *H*-3), 6.01 (dd, *J* = 16.8, 10.3 Hz, 1H, $H_aC{=}CH_bH_c$), 5.51 (dd, *J* = 10.3, 2.0 Hz, 1H, $H_aC{=}CH_bH_c$), 4.90 (s, 2H, CH_2), 3.81 (s, 3H, OCH_3); δ_C (101 MHz, $CDCl_3$) 165.7 (C=O), 159.1(C_q), 150.7 (C_q), 142.9 (CH), 139.2 (C_q), 129.4 (CH), 128.5 (CH), 127.9 ($C{=}CH_2$), 114.6 (CH), 110.3 (CH), 109.0 (CH), 55.4 (OCH_3), 45.8 (NCH_2); ν_{max}/cm^{-1} 2960, 2935, 2874, 2839, 1655, 1617, 1508, 1408, 1295, 1245, 1180, 1147, 1037, 1017; m/z HRMS (NSI+) found 258.1126, $C_{15}H_{16}NO_3$ $[M + H]^+$ requires 258.1126.

***N*-(4-Methoxyphenyl)-*N*-((5-nitrofuran-2-yl)methyl)acrylamide (252b):**

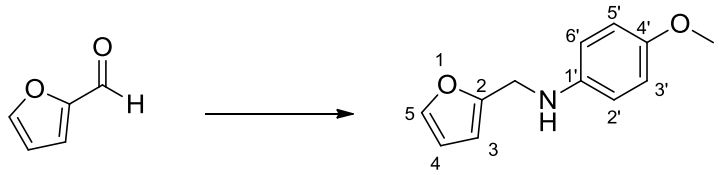


252b

Acryloyl chloride (95.0 mg, 1.05 mmol) was added carefully to a solution of **254b** (248 mg, 1.00 mmol), triethylamine (0.15 ml. 1.00 mmol) and DMAP (5.00 mg, 0.11 mmol) in dry dichloromethane (5.00 ml) at 0 °C with stirring. The reaction mixture was allowed to rise to room temperature and stirred overnight. The reaction mixture was then diluted with dichloromethane (10 ml) and water (10 ml) was added. The mixture was further extracted with dichloromethane (2 × 10 ml) and the combined organic phase dried (Na_2SO_4). Purification by column chromatography (7:3 diethyl ether/ petroleum ether) afforded the title compound: Wt 233 mg; 77%; brown/red solid; m.p. 95-98 °C;

δ_H (300 MHz, $CDCl_3$) 7.27 (d, *J* = 3.7 Hz, 1H, *H*-4), 7.16 – 7.08 (m, 2H, *H*-2' and *H*-6' or *H*-3' and *H*-5'), 6.99 – 6.90 (m, 2H, *H*-2' and *H*-6' or *H*-3' and *H*-5'), 6.57 (d, *J* = 3.7 Hz, 1H, *H*-3), 6.43 (dd, *J* = 16.8, 1.9 Hz, 1H, $H_aC{=}CH_bH_c$), 6.08 (dd, *J* = 16.8, 10.3 Hz, 1H, $H_aC{=}CH_bH_c$), 5.61 (dd, *J* = 10.3, 1.9 Hz, 1H, $H_aC{=}CH_bH_c$), 4.98 (s, 2H, CH_2), 3.86 (s, 3H, OCH_3); δ_C (75 MHz, $CDCl_3$) 166.0 (C=O), 159.4 (C_q), 154.7 (C_q), 133.9 (C_q), 129.2 (CH), 128.8 ($C{=}CH_2$), 127.8 (CH), 115.0 (CH), 112.6 (CH), 112.1 (CH), 55.5 (OCH_3), 46.6 (NCH_2); ν_{max}/cm^{-1} 3125, 3029, 2962, 2932, 2836, 1657, 1621, 1508, 1488, 1417, 1405, 1353, 1332, 1247, 1169, 1109, 1024, 1003; m/z HRMS (NSI+) found 303.0978, $C_{15}H_{15}NO_2$ $[M + H]^+$ requires 303.0975.

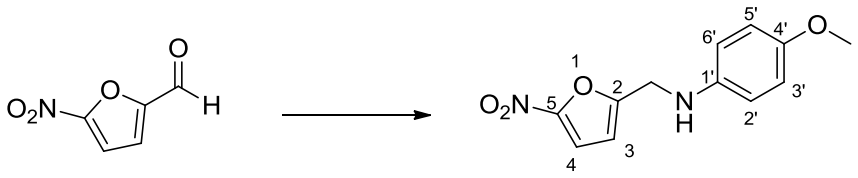
_N_-(Furan-2-ylmethyl)-4-methoxyaniline (254a):



254a

Para-anisidine (336 mg, 2.70 mmol) was introduced to a stirring solution of furfural (250 mg, 2.60 mmol) in dichloroethane (9.50 ml) and left stirring for several minutes. $NaBH(OAc)_3$ (882 mg, 4.20 mmol) was then added and the reaction mixture stirred overnight. The reaction mixture was quenched using saturated $NaHCO_3$ solution (10 ml) and extracted with dichloromethane (3 × 15 ml). The combined organic phase was dried (Na_2SO_4) before being concentrated *in vacuo*. Purification by column chromatography (1:4 diethyl ether / petroleum ether) afforded the title compound: Wt 480 mg; 91%; off-white solid; m.p. 49-51 °C; δ_H (300 MHz, $CDCl_3$) 7.37 (dd, *J* = 1.8, 0.8 Hz, 1H, *H*-5), 6.85 – 6.74 (m, 2H, *H*-2' and *H*-6' or *H*-3' and *H*-5'), 6.71 – 6.60 (m, 2H, *H*-2' and *H*-6' or *H*-3' and *H*-5'), 6.33 (dd, *J* = 3.2, 1.8 Hz, 1H, *H*-4), 6.23 (dd, *J* = 3.2, 0.8 Hz, 1H, *H*-3), 4.28 (s, 2H, CH_2), 3.75 (s, 3H, OCH_3); δ_C (75 MHz, $CDCl_3$) 153.0 (C_q), 152.6 (C_q), 141.8 (CH), 141.7 (C_q), 114.8 (CH), 114.7 (CH), 110.3 (CH), 106.95 (CH), 55.8 (CH_3), 42.5 (CH_2); ν_{max}/cm^{-1} 3397, 3143, 3120, 3036, 2995, 2953, 2834, 1511, 1461, 1407, 1295, 1267, 1235, 1195, 1180, 1146, 1069, 1035; m/z HRMS (NSI+) found 204.1016, $C_{12}H_{14}NO_2$ $[M + H]^+$ requires 204.1019.

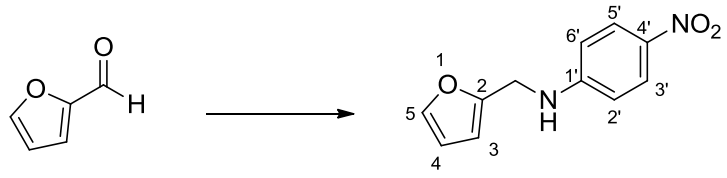
4-Methoxy-*N*-((5-nitrofuran-2-yl)methyl)aniline (254b):



254b

Para-anisidine (336 mg, 2.70 mmol) was introduced to a stirring solution of 5-nitro furfural (367 mg, 2.60 mmol) in dichloroethane (9.50 ml) and left stirring for several minutes. $NaBH(OAc)_3$ (882 mg, 4.20 mmol) was then added and the reaction mixture stirred overnight. The reaction mixture was quenched using saturated $NaHCO_3$ solution (10 ml) and extracted with dichloromethane (3 × 15 ml). The combined organic phase was dried (Na_2SO_4) before being concentrated *in vacuo*. Purification by column chromatography (1:4 diethyl ether / petroleum ether) afforded the title compound: Wt 599 mg; 93%; red solid; m.p. 85-88 °C; δ_H (300 MHz, $CDCl_3$) 7.24 (d, *J* = 3.7 Hz, 1H, *H*-4), 6.83 – 6.75 (m, 2H, *H*-2' and *H*-6' or *H*-3' and *H*-5'), 6.65 – 6.57 (m, 2H, *H*-2' and *H*-6' or *H*-3' and *H*-5'), 6.44 (dt, *J* = 3.7, 0.9 Hz, 1H, *H*-3), 4.40 (app. s, 2H, C*H*$_2$), 3.92 (br s, 1H, N*H*), 3.74 (s, 3H, OC*H*$_3$); δ_C (75 MHz, $CDCl_3$) 157.6 (C_q), 153.1 (C_q), 140.5 (C_q), 115.0 (CH), 114.7 (CH), 112.7 (CH), 110.4 (CH), 55.7 (CH_3), 42.5 (CH_2); ν_{max}/cm^{-1} 3492, 3408, 3174, 3126, 3043, 2951, 2832, 1588, 1512, 1478, 1462, 1397, 1356, 1333, 1251, 1232, 1177, 1129, 1036; m/z HRMS (APCI+) found 249.0870, $C_{12}H_{13}N_2O_4$ $[M + H]^+$ requires 249.0865.

***N*-(Furan-2-ylmethyl)-4-nitroaniline (254c):**

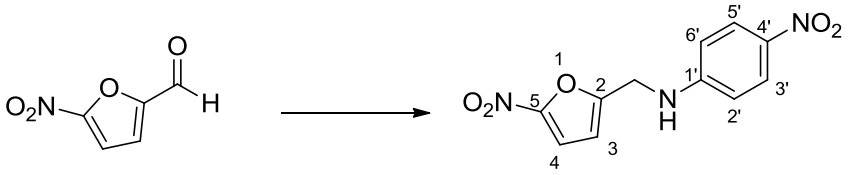


254c

Para-nitroaniline (377 mg, 2.70 mmol) was introduced to a stirring solution of furfural (250 mg, 2.60 mmol) in dichloroethane (9.50 ml) and left stirring for several minutes. $NaBH(OAc)_3$ (882 mg, 4.2 mmol) was then added and the reaction mixture stirred overnight. The reaction mixture was quenched using saturated $NaHCO_3$ solution (10 ml) and extracted with dichloromethane (3 × 15 ml). The combined organic phase was

dried (Na_2SO_4) before being concentrated *in vacuo*. Purification by column chromatography (2:3 diethyl ether / petroleum ether) afforded the title compound: Wt 436 mg; 91%; yellow solid; m.p. 108-111 °C; δ_H (300 MHz, $CDCl_3$) 8.16 – 8.03 (m, 2H, *H*-3' and *H*-5'), 7.39 (dd, *J* = 1.8, 0.8 Hz, 1H, *H*-5), 6.67 – 6.57 (m, 2H, *H*-2' and *H*-6'), 6.35 (dd, *J* = 3.2, 1.8 Hz, 1H, *H*-4), 6.28 (dd, *J* = 3.2, 0.8 Hz, 1H, *H*-3), 4.81 (br app. s, 1H, N*H*), 4.42 (d, *J* = 5.7 Hz, 2H, C*H*$_2$); δ_C (75 MHz, $CDCl_3$) 152.3 (C_q), 150.7 (C_q), 142.5 (CH), 138.7 (C_q), 126.3 (CH), 111.5 (CH), 110.5 (CH), 107.8 (CH), 40.7 (CH_2); ν_{max}/cm^{-1} 3355, 3177, 3117, 3073, 2959, 2923, 1597, 1536, 1474, 1271, 1184, 1143, 1099, 1065; m/z HRMS (APCI+) found 219.0764, $C_{11}H_{11}N_2O_3$ $[M + H]^+$ requires 219.0764.

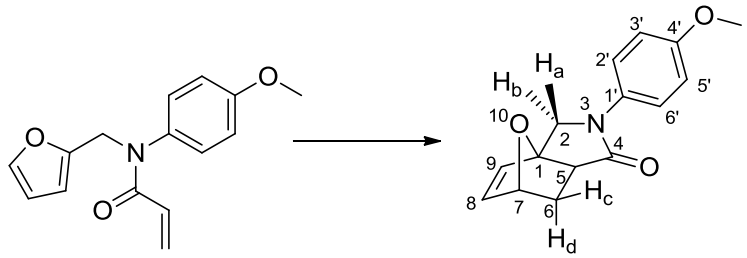
4-Nitro-*N*-((5-nitrofuran-2-yl)methyl)aniline (254d):



254d

Para-nitroaniline (377 mg, 2.70 mmol) was introduced to a stirring solution of 5-nitro furfural (367 mg, 2.60 mmol) in dichloroethane (9.50 ml) and left stirring for several minutes. $NaBH(OAc)_3$ (882 mg, 4.20 mmol) was then added and the reaction mixture stirred overnight. The reaction mixture was quenched using saturated $NaHCO_3$ solution (10 ml) and extracted with dichloromethane (3 × 15 ml). The combined organic phase was dried (Na_2SO_4) before being concentrated *in vacuo*. Purification by column chromatography (2:3 diethyl ether / petroleum ether) afforded the title compound: Wt 347 mg; 51%; yellow solid; m.p. 137-139 °C; δ_H (300 MHz, $CDCl_3$) 8.20 – 8.02 (m, 2H, *H*-3' and *H*-5'), 7.27 (d, *J* = 3.7 Hz, 1H, *H*-4), 6.71 – 6.56 (m, 2H, *H*-2' and *H*-6'), 6.51 (d, *J* = 3.7 Hz, 1H, *H*-3), 4.96 (br app. s, 1H, N*H*), 4.55 (d, *J* = 6.1 Hz, 2H, C*H*$_2$); δ_C (75 MHz, $CDCl_3$) 154.6 (C_q), 151.6 (C_q), 139.6 (C_q), 126.3 (CH), 112.3 (CH), 111.7 (CH), 110.9 (CH), 40.8 (CH_2); ν_{max}/cm^{-1} 3358, 3163, 3143, 3120, 3089, 2959, 2853, 1599, 1523, 1498, 1476, 1358, 1336, 1320, 1278, 1234, 1207, 1180, 1108, 1022; m/z HRMS (APCI+) found 264.0616, $C_{11}H_{10}N_3O_5$ $[M + H]^+$ requires 264.0615.

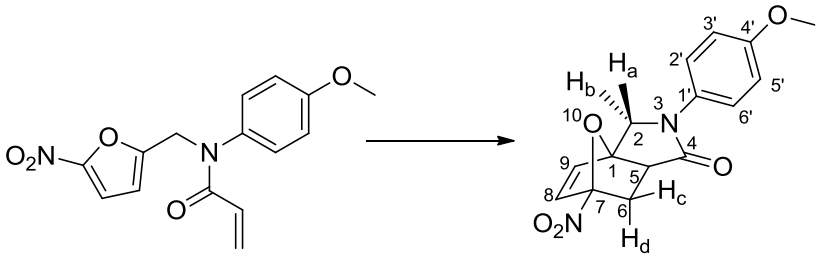
(1*S*,5*S*,7*R*)-3-(*p*-Methoxyphenyl)-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-en-4-one (255a):



255a

A solution of **252a** (52.0 mg, 0.20 mmol) in toluene (4.00 ml) was heated to reflux with stirring for 18 hours. Toluene was then removed *in vacuo* and purification by column chromatography (1:1 diethyl ether/petroleum ether) afforded the title compound: Wt 27 mg; 53%; white solid; m.p. 125-127 °C; δ_H (300 MHz, $CDCl_3$) 7.55 – 7.44 (m, 2H, *H*-2' and *H*-6' or *H*-3' and *H*-5'), 6.97 – 6.85 (m, 2H, *H*-2' and *H*-6' or *H*-3' and *H*-5'), 6.48 (d, *J* = 5.8 Hz, 1H, *H*-9), 6.44 (dd, *J* = 5.8, 1.6 Hz, 1H, *H*-8), 5.12 (dd, *J* = 4.5, 1.6 Hz, 1H, *H*-7), 4.44 (d, *J* = 11.5 Hz, 2H, H_a-2 or H_b-2), 4.09 (d, *J* = 11.5 Hz, 2H, H_a-2 or H_b-2), 3.80 (s, 3H, OCH_3), 2.63 (dd, *J* = 8.8, 3.5 Hz, 1H, *H*-5), 2.32 (ddd, *J* = 11.8, 4.5, 3.6 Hz, 1H, H_c-6), 1.67 (dd, *J* = 11.8, 8.8 Hz, 1H, H_d-6); δ_C (101 MHz, CDCl3) 173.1 (C=O), 156.8 (C_q), 137.4 (CH), 133.1 (CH), 132.5 (C_q), 122.4 (CH), 114.2 (CH), 88.3 (C_q-1), 79.3 (CH-7), 55.5 (OCH_2), 51.4 (NCH_3), 48.5 (CH-5), 28.8 (CH_2-6); ν_{max}/cm^{-1} 3080, 3057, 2997, 2952, 2836, 1689, 1612, 1585, 1512, 1463, 1400, 1357, 1299, 1246, 1197, 1183, 1089 1037; m/z HRMS (NSI+) found 258.1127, $C_{15}H_{16}NO_3$ $[M + H]^+$ requires 258.1125.

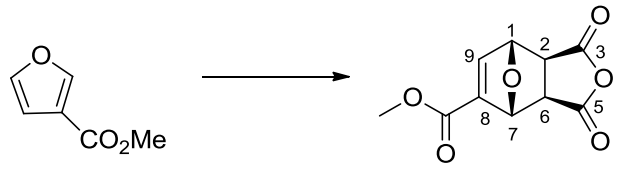
(1*S*,5*S*,7*R*)-3-(*p*-Methoxyphenyl)-7-nitro-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-en-4-one (255b):



255b

A solution of **252b** (61.0 mg, 0.20 mmol) in toluene (4.00 ml) was heated to reflux with stirring for 18 hours. Toluene was then removed *in vacuo* and purification by column chromatography (diethyl ether) afforded the title compound: Wt 52 mg; 86%; white solid; m.p. 173-175 °C; δ_H (300 MHz, $CDCl_3$) 7.56 – 7.47 (m, 2H, *H*-2' and *H*-6' or *H*-3' and *H*-5'), 7.01 – 6.90 (m, 2H, *H*-2' and *H*-6' or *H*-3' and *H*-5'), 6.81 (s, 2H, 2 × CH_{alkene}), 4.49 (d, *J* = 12.1 Hz, 1H, H_a-2 or H_b-2), 4.27 (d, *J* = 12.1 Hz, 1H, H_a-2 or H_b-2), 2.96 (dd, *J* = 8.7, 3.6 Hz, 1H, *H*-5), 2.73 (dd, *J* = 11.7, 3.6 Hz, 1H, H_c-6), 2.46 (dd, *J* = 11.7, 8.7 Hz, 1H, H_d-6); δ_C (101 MHz, CDCl3) 170.3 (C=O), 157.3 (C_q), 136.0 (CH), 134.9 (CH), 131.6 (C_q), 122.6 (CH), 114.3 (CH), 111.7 (C_q-7), 87.9 (C_q-1), 55.5 (OCH_3), 50.94 (NCH_2), 50.5 (CH-5), 33.9 (CH_2-6); ν_{max}/cm^{-1} 3150, 3112, 3007, 2956, 2931, 2835, 1680, 1554, 1508, 1476, 1355, 1298, 1239, 1206, 1182, 1092, 1059; m/z HRMS (NSI+) found 303.0978, $C_{15}H_{15}N_2O_5$ $[M + H]^+$ requires 303.0978.

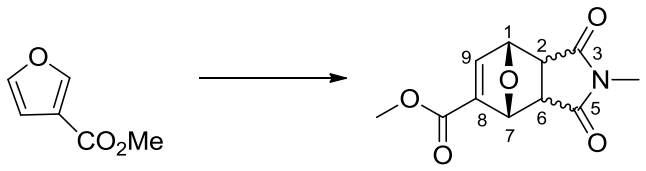
Methyl (1*S*,2*R*,6*S*,7*S*)-3,5-dioxo-4.10-dioxatricyclo[5.2.1.0^{2,6}]dec-8-ene-8-carboxylate (272b):



272b

Methyl 3-furoate (646 mg, 5.12 mmol) and maleic anhydride (250 mg, 2.56 mmol) were combined in toluene (2.50 ml) with stirring and left for 5 days. The precipitate that formed was collected *via* filtration and rinsed with toluene. Remaining solvent was removed *in vacuo* to afford the title compound with no further purification required; Wt 42 mg; 7%; white solid; δ_H (300 MHz, $CDCl_3$) 7.24 (d, *J* = 1.8 Hz, 1H, *H*-9), 5.66 (s, 1H, *H*-7), 5.57 (d, *J* = 1.8 Hz, 1H, *H*-1), 3.83 (s, 3H, OCH_3), 3.31 (d, *J* = 6.9 Hz, 1H, *H*-2 or *H*-6), 3.26 (d, *J* = 6.9 Hz, 1H, *H*-2 or *H*-6); δ_C (75 MHz, $CDCl_3$); ν_{max}/cm^{-1} 3022, 3004, 2958, 2845, 1735, 1714, 1637, 1612, 1432, 1309, 1240, 1191, 1110, 1091.

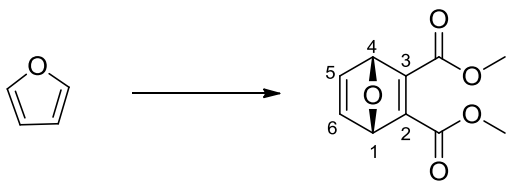
Methyl (1*S*,2*R/S*,6*S/R*,7*S*)-4-methyl-3,5-dioxo-10-oxa-4-azatricyclo[5.2.1.0^{2,6}] decane-8-carboxylate (276b):



276b

Methyl 3-furoate (370 mg, 2.93 mmol) and *N*-methyl maleimide (163 mg, 2.56 mmol) were combined in tetrahydrofuran (2.00 ml) with stirring and left for 5 days. The solvent was then removed *in vacuo*. Purification *via* column chromatography (2:3 diethyl ether/petroleum ether) afforded the title compound as a mixture of diastereoisomers; Wt 188 mg; 7%; white solid; δ_H (300 MHz, $CDCl_3$) *Exo* adduct; 7.16 (d, *J* = 1.9 Hz, 1H, *H*-9), 5.36 – 5.34 (m, 1H, C*H*$_{bridgehead}$), 5.30 – 5.28 (m, 1H, C*H*$_{bridgehead}$), 3.73 (s, 3H, OC*H*$_3$), 2.95 – 2.86 (m, 2H, *H*-2 and *H*-6), 2.90 (s, 3H, NC*H*$_3$) *Endo* adduct; 7.04 (d, *J* = 1.7 Hz, 1H, *H*-9), 5.48 (d, *J* = 5.1 Hz, 1H, *H*-7), 5.40 – 5.36 (m, 1H, *H*-1), 3.69 (s, 3H, OC*H*$_3$), 3.64 – 3.53 (m, 2H, *H*-2 and *H*-6), 2.70 (s, 3H, NC*H*$_3$) ; δ_C (75 MHz, $CDCl_3$) 175.2 (C=O), 174.0 (C=O), 173.3 (C=O), 162.1 (C_q), 161.4 (C_q), 144.8 (CH), 142.8 (CH), 140.9 (C_q), 82.1 (CH), 80.5 (CH), 80.4 (CH), 79.2 (CH), 52.1 (OCH_3), 52.0 (OCH_3), 47.4 (CH), 47.1 (CH), 46.5 (CH), 46.0 (CH), 25.0 (CH_3), 24.5 (CH_3); ν_{max}/cm^{-1} 3001, 2955, 1693, 1616, 1435, 1383, 1284, 1247, 1217, 1134, 1106, 1078, 1023; m/z HRMS (NSI+) found 238.0713, $C_{11}H_{12}NO_5$ $[M + H]^+$ requires 238.0710.

Dimethyl (1*S*,4*R*)--7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate (277):[160]

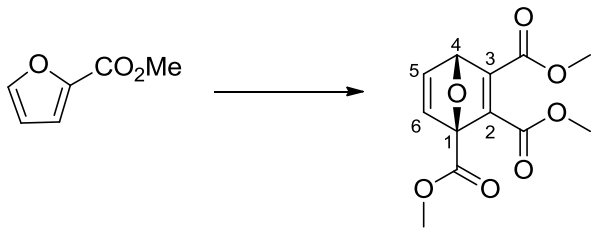


277

Furan (340 mg, 5.00 mmol) and DMAD (711 mg, 5.00 mmol) were combined in diethyl ether (2.00 ml) with stirring and left for 7 days. Water (5 ml) was then added followed by extraction with diethyl ether (3 × 5 ml). Combined organic phase was dried (Na_2SO_4) before being concentrated to dryness *in vacuo*. Purification *via* column

chromatography (1:4 ethyl acetate / petroleum ether) afforded the title compound: Wt 326 mg; 31%; pale yellow oil; δ_H (300 MHz, $CDCl_3$) 7.22 (t, *J* = 1.0 Hz, 2H, *H*-5 and *H*-6), 5.71 – 5.64 (t, *J* = 1.0 Hz, 1H, *H*-1and *H*-4), 3.82 (s, 3H, 2 × OC*H*$_3$); δ_C (75 MHz, $CDCl_3$) 163.2 (2 × C=O), 153.0 (C_q-2 and C_q-3), 143.3, (C_q-5 and C_q-6), 85.1 (CH-1 and CH-4), 48.7 (2 × CH_3); ν_{max}/cm^{-1} 3010, 2958, 1717, 1436, 1251, 1107, 1078, 1039.

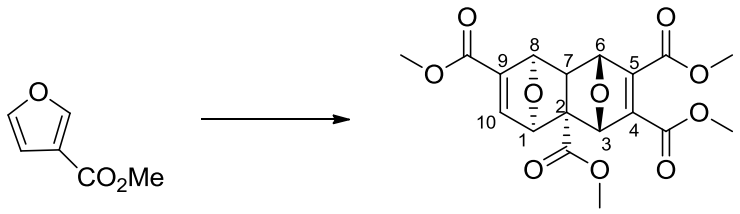
Trimethyl (1*S*,4*R*)--7-oxabicyclo[2.2.1]hepta-2,5-diene-1,2,3-tricarboxylate (278a):



278a

Methyl 3-furoate (315 mg, 2.50 mmol) and DMAD (356 mg, 2.50 mmol) were combined in diethyl ether (1.00 ml) within a sealed pressure tube with stirring. The reaction mixture was heated within the pressure tube to 80 °C for 3 days. The solvent was removed *in vacuo* and the crude material was subjected to column chromatography (2:3 ethyl acetate / petroleum ether) to afford the title compound: Wt 125 mg; 19%; colourless oil; δ_H (300 MHz, $CDCl_3$) 7.25 – 7.24 (m, 2H, *H*-5 and *H*-6), 5.70 (dd, *J* = 1.5, 0.8 Hz, 1H, *H*-4), 3.85 (s, 3H, OC*H*$_3$), 3.77 (s, 3H, OC*H*$_3$), 3.75 (s, 3H, OC*H*$_3$); δ_C (75 MHz, $CDCl_3$) 165.9 (C=O), 162.7 (C=O), 162.1 (C_q), 153.4 (C_q), 150.7 (C_q), 144.1 (CH_{alkene}), 142.0 (CH_{alkene}), 93.9 (C_q-1), 84.5 (CH-4), 52.9 (CH_3), 52.4 (CH_3), 52.3 (CH_3); ν_{max}/cm^{-1} 3008, 2957, 1718, 1643, 1437, 1266, 1246, 1201, 1147, 1118, 1072; m/z HRMS (NSI+) found 269.0656, $C_{12}H_{13}O_7$ $[M + H]^+$ requires 269.0656.

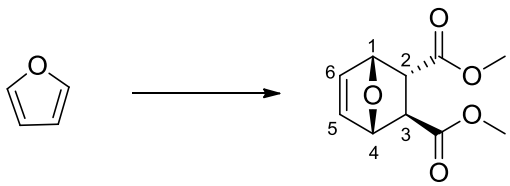
Tetramethyl (1*R*,2*S*,3*S*,6*S*,8*R*)-11.12-dioxatetracyclo[6.2.1.1^{3,6}.0^{2,7}]dodeca-4,9-diene-2,4,5,9-tetracarboxylate (279):



279

Methyl 3-furoate (315 mg, 2.50 mmol) and DMAD (356 mg, 2.50 mmol) were combined in diethyl ether (1.00 ml) within a sealed pressure tube with stirring. The reaction mixture was heated within the pressure tube to 80 °C for 3 days. The precipitate was collected *via* filtration and rinsed with diethyl ether, which after allowing to dry afforded the product without any further purification necessary: Wt 107 mg; 11%; white solid; 160-164 °C; δ_H (300 MHz, $CDCl_3$) 7.05 (d, *J* = 1.9 Hz, 1H, *H*-10), 5.32 (dd, *J* = 1.9, 1.1 Hz, 1H, *H*-1), 5.22 (dd, *J* = 4.9, 1.1 Hz, 1H, *H*-3), 4.93 (d, *J* = 1.0 Hz, 1H, *H*-6 or *H*-8), 4.87 (d, *J* =, 1.0 Hz, 1H, *H*-6 or *H*-8), 3.83 (s, 3H), 3.79 (s, 3H), 3.77 (s, 3H), 3.69 (s, 3H), 3.43 (d, *J* = 4.9 Hz, 1H, *H*-2); δ_C (75 MHz, $CDCl_3$) 171.1(C=O), 163.6(C=O), 162.3 (C=O), 161.8 (C=O), 148.0 (C_q), 145.1 (C_q), 142.6 (CH-10), 141.5 (C_q), 84.0 (CH), 80.7 (CH), 80.1 (CH), 79.4 (CH), 66.2 (C_q-2), 52.7 (CH_3), 52.4 (CH_3), 52.3 (CH_3), 51.9 (CH_3), 51.5 (CH-7); ν_{max}/cm^{-1} 3011, 2957, 1739, 1712, 1647, 1434, 1317, 1286, 1250, 1209, 1150, 1121, 1039.

Dimethyl (1*S*,2*R*,3*R*,4*R*)--7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (281):[161]

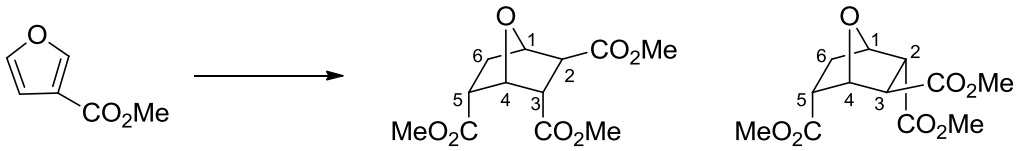


281

Furan (340 mg, 5.00 mmol) and fumaryl chloride (765 mg, 5.00 mmol) were combined in diethyl ether (5.00 ml) at 0 °C and stirred at this temperature for 30 mins. The reaction mixture was then allowed to rise to room temperature and stirred overnight. Methanol (0.5 ml) and triethylamine (1.75 ml) were then added at 10 °C and stirred at this temperature for 30 mins. The reaction mixture was then extracted with diethyl

ether (3 × 5 ml). Combined organic phase was dried (Na_2SO_4) before being concentrated to dryness *in vacuo*. Purification *via* column chromatography (1:9 ethyl acetate / petroleum ether) afforded the title compound: Wt 527 mg; 45%; white solid; δ_H (300 MHz, $CDCl_3$) 6.52 (dd, *J* = 5.8, 1.7 Hz, 1H, C*H*$_{alkene}$), 6.36 (dd, *J* = 5.8, 1.5 Hz, 1H, C*H*$_{alkene}$), 5.26 – 5,23 (m, 2H, *H*-1 and *H*-4), 3.76 (s, 3H, OC*H*$_3$), 3.67 (s, 3H, OC*H*$_3$), 3.65 – 3.59 (m, 1H, *H*-2), 2.86 (d, *J* = 4.0 Hz, 1H, *H*-3); δ_C (75 MHz, $CDCl_3$) 172.5 (C=O), 171.3 (C=O), 136.8 (CH$_{alkene}$), 135.0 (CH$_{alkene}$), 82.5 (CH$_{bridgehead}$), 82.4 (CH$_{bridgehead}$), 79.3 (CH), 79.2 (CH), 52.1 (CH_3), 47.4 (CH_3); ν_{max}/cm^{-1} 3077, 2964, 2922, 2853, 1713, 1673, 1438, 1303, 1198, 1155.

Trimethyl (1*S*,2*S*,3*S*,4*S*,5*S*)--7-oxabicyclo[2.2.1]heptane-2,3,5-tricarboxylate & Trimethyl (1*S*,2*R*,3*R*,4*S*,5*S*)--7-oxabicyclo[2.2.1]heptane-2,3,5-tricarboxylate (283)

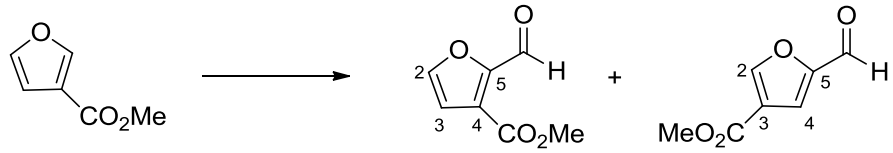


1 : 283 **2**

Methyl 3-furoate (631 mg, 5.00 mmol) and fumaryl chloride (765 mg, 5.00 mmol) were combined in diethyl ether (5.00 ml) at 0 °C and stirred at this temperature for 30 mins. The reaction mixture was then allowed to rise to room temperature and stirred overnight. More diethyl ether (10 ml) was added before methanol (0.5 ml) and triethylamine (1.75 ml) were then added at 10 °C and stirred at this temperature for 30 mins. The reaction mixture was allowed to rise to room temperaturethen left stirring overnight before extraction with dichloromethane (3 × 15 ml). Combined organic phase was dried (Na_2SO_4) before being concentrated to dryness *in vacuo*. Purification *via* column chromatography (2:3 ethyl acetate / petroleum ether) afforded the reaction intermediate (460 mg, 34%), which was taken on quickly for hydrogenation due to undergoing the retro reaction. The intermediate (359 mg, 1.3 mmol) was dissolved in ethyl acetate (53 ml), to which 10% Pd/C (71 mg, 5 mol %) was carefully added. The reaction vessel was then placed under an atmosphere of $H_{2(g)}$ and left stirring at ambient temperature and pressure overnight. The reaction mixture was filtered through a pad of Celite, and the filtrate concentrated to dryness *in vacuo*. Purification *via* column chromatography (3:7 ethyl acetate / petroleum ether) afforded the title compound in a

2:1 mixture of diastereoisomers: Wt 70 mg; 5% (over both steps); white solid; δ_H (300 MHz, $CDCl_3$) 5.03 – 4.95 (m, 1H + 1H, *H*-4_{minor} and *H*-4_{major}), 4.88 (d, *J* = 5.4 Hz, 1H, *H*-1_{minor}), 4.83 (t, *J* = 5.2 Hz, 1H, *H*-1_{major}), 3.76 – 3.68 (m, 9H + 3H, 3 × OC*H*$_{3major}$ and 1 × OC*H*$_{3minor}$), 3.64 (s, 3H, OC*H*$_{3minor}$), 3.63 (s, 3H, OC*H*$_{3minor}$), 3.61 – 3.56 (m, 1H, C*H*$_{minor}$), 3.54 (td, *J* = 5.5, 1.7 Hz, 1H, C*H*$_{major}$), 3.26 (d, *J* = 5.5 Hz, 1H, C*H*$_{major}$), 3.18 – 3.05 (m, 1H + 2H, C*H*$_{major}$ and 2 × C*H*$_{minor}$), 2.21 – 1.87 (m, 2H + 2H, C*H*$_{2major}$ + C*H*$_{2minor}$); ν_{max}/cm^{-1} 3077, 2964, 2922, 2853, 1713, 1673, 1438, 1303, 1198, 1155; m/z HRMS (NSI+) found 290.1238, $C_{12}H_{20}NO_7$ $[M + NH_4]^+$ requires 290.1234.

Methyl 5-formylfuran-4-carboxylate (285a) & methyl 5-formylfuran-3-carboxylate (285b):[156]

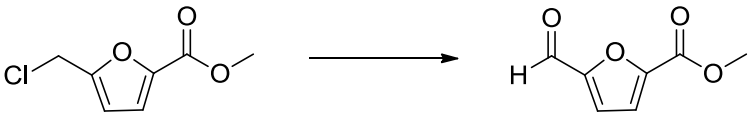


1 : **7**

285a **285b**

$POCl_3$ (7.87 g, 52.0 mmol) was added carefully to DMF (4.95 g, 68.0 mmol) at 0 °C with stirring. The mixture was allowed to rise to room temperaturebefore methyl 3-furoate (5.00 g, 40.0 mmol) was introduced and the reaction mixture heated to reflux with stirring for 1 hour. The mixture was allowed to cool to room temperaturebefore being poured into cold water (100 ml), followed by extraction with diethyl ether (3 x 100 ml). The combined organic extracts were then rinsed several times with water, before being concentrated to dryness *in vacuo*. Purification by column chromatography (1:4 ethyl acetate / petroleum ether) afforded the title compounds as an inseparable mixture in the ratio shown above: Wt 1.70 g; 28%; beige/yellow solid; m.p. 93-95 °C; δ_H (300 MHz, $CDCl_3$) **285b**; 9.69 (s, 1H, O=C-*H*), 8.20 (s, 1H, *H*-2), 7.53 (s, 1H, *H*-4), 3.88 (s, 3H, OC*H*$_3$); δ_H (300 MHz, $CDCl_3$) **285a**; 10.23 (app. s, 1H, O=C-*H*), 7.64 (dd, *J* = 1.8, 0.8 Hz, 1H, *H*-2), 6.89 (d, *J* = 1.8 Hz, 1H, *H*-3), 3.95 (s, 3H, OC*H*$_3$); δ_C (101 MHz, $CDCl_3$); δ_C (101 MHz, $CDCl_3$) MIXTURE; 178.8 (HC=O), 177.7 (HC=O), 162.0 (C=O), 161.9 (C=O), 153.2 (Cq), 152.3 (Cq), 151.4 (CH), 146.6 (CH), 126.1 (Cq), 121.5 (Cq), 119.5 (CH), 112.82 (CH), 52.50 (CH_3), 52.07 (CH_3); ν_{max}/cm^{-1} 3140, 3112, 2963, 2849, 1719, 1677, 1580, 1432, 1388, 1245, 1212, 1155, 1097.

Methyl 5-formylfuran-2-carboxylate (287):



287

Triflic anhydride (2.45 g, 8.50 mmol) was added dropwise to a stirring suspension of tetramethylammonium nitrate (1.14 g, 8.20 mmol) in dry dichloromethane (28.0 ml) and left for 1.5 h. The reaction mixture was then cooled to - 78 °C before methyl 5-(chloromethyl)furan-2-carboxylate (1.31 g, 7.50 mmol) was carefully added. The reaction mixture was then allowed to rise to room temperature and stirred for 76 h. The reaction was then quenched with 5% $NaHCO_3$ solution (20 ml) and the organic phase separated. This was then rinsed with water (2 × 15 ml) and the combined aqueous layers back-extracted with dichloromethane (2 × 20 ml). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (1:4 diethyl ether / petroleum ether) afforded the title compound: Wt 447 mg; 39%; white solid; m.p. 93-95 °C; δ_H (300 MHz, $CDCl_3$) 9.81 (s, 1H, OC*H*), 7.27 (s, 2H, 2 × C$H_{aromatic}$), 3.95 (s, Hz, 3H, OCH_3); δ_C (101 MHz, $CDCl_3$) 179.0 (HC=O), 158.4 (C=O), 153.9 (C_q), 147.6 (C_q), 118.8 (CH), 118.7 (CH), 52.6 (CH_3); ν_{max}/cm^{-1} 3157, 3139, 3122, 2959, 2883, 1725, 1680, 1569, 1508, 1438, 1296, 1255, 1211, 1142, 1019; m/z HRMS (APCI+) found 155.0336, $C_7H_7O_4$ $[M + H]^+$ requires 155.0339.

(i) CBS Calculations

Two complete basis set (CBS) models, CBS-QB3 and CBS-4M, have been used to obtain the thermochemical data of studied Diels-Alder reactions. These results, were compared also against the DFT-B3LYP/6-31G(d) basis for four of the simplest DA reactions. Free energies for both CBS models were calculated for two temperatures: 298K and 383K (temperature of experimental studies) and 298 K for B3LYP. It should be noted that 6-31G(d) basis set used for DFT-B3LYP studies can be poorer for elements such as halogens, thus the thermochemical values obtained here may not be of great accuracy and they are presented only for a qualitative comparison of a relatively cheap quantum chemical model with more expensive high accuracy ones.

The CBS models employed use N^{-1}asymptotic convergence of second-order Moller-Plesst pair energies calculated from pair natural orbital expansions to extrapolate to the CBS limit. Application of CBS extrapolations enables the use of smaller basis sets at second-order, which reduces the calculation time and allows such methods to be used on wider range of systems. Low levels of theory are used for geometries and vibrational zero-point energies. To obtain a total molecular energy they are combined with higher-level calculalations of the total electronic energy. The CBS-QB3 model consists of following calculations:

a) B3LYP/6-311G(2d,d,p) - geometry optimisation and frequencies

b) CCSD(T)/6-31+G(d') - energy

c) MP4(SDQ)/CBSB4 - energy

d) MP2/CBSB3 - energy and CBS extrapolation (with the G09c, default number of minimum 10 pair natural orbitals for this specific basis set used)

Geometries and frequencies in CBS-QB3 model are obtained with DFT-B3LYP calculations, unlike the original CBS-Q method. The CBS-Q model uses UHF with the 6-31G basis set for initial geometry and frequency calculations and then MP2(FC) with the same basis set for the final geometry optimisation. Changing to DFT-B3LYP with a larger basis set in CSB-QB3 method gives more reliable geometries and zero-point energies of stable molecules included in G2 test set relative to MP2, and gives more consistent structures for transition states.

Early work showed that such CBS models would fail in some cases (e.g., some polycyclic systems, perchlorates etc.). As it was found later the reason for it was the use of Mulliken analysis in Pipek and Mezey occupied orbital localisation methods, which due to its unphysical behaviour in some cases, obtained from the extended basis sets, results in unphysical energy contributions. A new algorithm for localisation was since then employed in which the populations are measured in a minimal basis (minimum population localisation) and not extended ones. This population method is now implemented in both CBS-QB3 and CBS-4M methods. It improves their reliability and sorts the previous anomalies caused by the abnormal behaviour of the older population method. The CBS-4M model is composed of following calculations:

a) HF/3-21G(d) - geometry optimisation and frequencies

b) MP4SDQ/6-31G - energy

c) MP2/(6-31+G(d',p')) - energy and CBS extrapolation (with the G09c, default number of minimum 5 pair natural orbitals for this specific basis set used)

d) HF/CBSB1 with tight convergence of SCF energy

CBS methods are found to be very accurate for thermochemical studies with the mean absolute deviation of around 1.1 kcal/mol for the CBS-QB3 model and around 3.26 kcal/mol for CBS-4M method comparing to experimental data on G2/97 test set. The accuracy of CBS-4M model is compromised here due to the use of HF with very small basis set 3-21G(d) for geometries. The CBS-QB3 model when used on larger systems can be computationally very expensive and unpractical. If this is the case CBS-4M model can be used as an alternative, which is much less expensive, thus can be used on larger systems with reasonable accuracy.

There have been other so-called “black box” methods, which offer very accurate results for thermochemical data. One popular and often used for benchmark data of small and medium sized molecules is W1 theory. It belongs to the hierarchy of Wn computational protocols of Martin and co-workers in which cost and accuracy increases in a sequence (n={1-4.4}).16-19 W1 theory returns a 0.44 kcal/mol mean absolute deviation for 220 total atomisation energies, electron affinities, ionisation potentials and proton affinities of the G2/97 test set. Due to the high cost of these methods such studies on all the reactions presented here could not be performed. The W1 model with unrestricted Brueckner doubles (W1BD) was chosen to obtain thermochemical data of

the simplest Diels-Alder reaction between furan and ethylene as a benchmark for the other CBS models used. These results together with data obtained from CBS models discussed before, and DFT-B3LYP, have been compared.

The difference between free energies of the reaction obtained for W1BD and CBS-QB3 models is only 0.9 kcal/mol and around 3 kcal/mol for activation energies. The computational time of W1BD method for this reaction is around 3000 times higher than CBS-QB3 model, around 6000 times higher than CBS-4M model and around 8000 higher than DFT-B3LYP method. Thus the CBS-QB3 model provides an excellent balance between computational cost and accuracy for the series of reactions studied.

REFERENCES

REFERENCES

1. J. A. Joule and K. Mills, *Heterocyclic Chemistry*, 5th Edition, **2010**.
2. T. L. Gilchrist, *Heterocyclic Chemistry*, 2nd Edition, **1992**.
3. W. Brown, C. Foote, B. Iverson and E. Anslyn, *Organic Chemistry*, 6th Edition, **2011**.
4. N. D. Epiotis , W. R. Cherry , F. Bernardi and W. J. Hehre, *J. Am. Chem. Soc.*, **1976**, *98*, 4361.
5. A. Ghomri and S. M. Mekelleche, *J. Mol. Struct.: THEOCHEM*, **2010**, *941*, 36.
6. C. Friedel and J.-M. Crafts, *Compt. Rend.*, **1877**, *84*, 1392 & 1450.
4. C. C. Price, *Org. React.*, **1946**, *3*, 1.
8. J. K. Groves, *Chem. Soc. Rev.*, **1972**, *1*, 73.
9. P. A. Finan and G. A. Fothergill, *J. Chem. Soc.*, **1963**, 2723.
10. H. Liu, J. Xu and D.-M. Du, *Org. Lett.*, **2007**, *9*, 4725.
11. (a) A. Vilsmeier and A. Haack, *Chem. Ber.*, **1927**, *60*, 121. (b) A. Vilsmeier, *Chem. Ztg.*, **75,** 133 (1951).
12. W. G. Shan, X. J. Shi and W. K. Su, *Org. Prep. Proc. Int.*, **2004**, *36*, 337.
13. H. Gilman and R. V. Young, *J. Am. Chem. Soc.*, **1934**, *56*, 464.
14. A. R. Katritzky, E. F. V. Scriven, S. Majumder, R. G. Akhmedova, N. G. Akhmedov and A. V. Vakulenko, *ARKIVOC*, **2005**, *3*, 179.
15. (a) H. Gilman, and G. F. Wright, *J. Am. Chem. Soc.*, **1930**, *52*, 2550. (b) D. Vlaovic, B. L. Milic and K. Mackenzie, *J. Chem. Res.*, **1989**, 156. (c) K. K. Venters, M. A. Trushule, G. F. Kumerov, *Khim.-Farm. Zh.* **1989**, *23*, 1506. (d) D. O. Lolya, K. K. Venter, E. E. Liepin'sh, A. M. Trushule ans S. A. Giller, *Chem. Heterocycl. Compd. (Engl. Transl.)*, **1976**, 502. (e) M. Witte and C. J. Lind, *Chem. Abstr.* **1950**, *44*, 27525.
16. J. F. Scully and E. V. Brown, *J. Org. Chem.*, **1978**, *43*, 4303.
17. A. P. Terent'ev, L. I. Belen'kii and L. A. Yanovskaya, *Chem. Abstr.*, **1955**, *49*, 12327.
18. M. A. Keegstra, A. J. A. Klomp and L. Brandsma, *Synth. Commun.*,**1990**, *20*, 3371.
19. E. Baciocchi, S. Clementi, G. V. Sebastiani, *J. Chem. Soc.*, **1975**, 875.
20. V. M. Kolb, S. D. Darling, D. F. Koster, and C. Y. Meyers, *J. Org. Chem.*, **1984**, *49*, 1636.
21. E. Nieto-Mendoza, J. A. Guevara-Salazar, M. T. Ramirez-Apan, B. A. Frontana-Uribe, J. A. Cogordan and J. Cardenas, *J. Org. Chem.* **2005**, *70*, 4538.
22. S. Srivastava, J. Minore, C. K. Cheung and W. J. Le Noble, *J. Org. Chem.*, **1985**, *50*, 394.
23. T. J. Donohoe, J.-B. Guillermin, A. A. Calabresea and D. S. Walter, *Tetrahedron Lett.*, **2001**, *42*, 5841.
24. T. J. Donohoe, M. Helliwell, C. A. Stevenson, T. Ladduwahetty, *Tetrahedron Lett.*, **1998**, 39, 3071.
25. O. Achmatowicz Jr., P. Bukowski, B. Szechner, Z. Zwierzchowska and A. Zamojski, *Tetrahedron*, **1971**, *27*, 1973.
26. J. W. Döbereiner, *Liebigs Ann.*, **1832**, *3*, 141.
27. C.-F. Yang, Y.-M. Xu, Li-X. Liao, W.-S. Zhou, *Tetrahedron Lett.*, **1998**, *39*, 9227.
28. F. Lieb and K. Eiter, *Liebigs Ann.*, **1972**, *761*, 130.
29. F. Terrier, *Chem. Rev.* **1982**, *82*, 78.
30. A. Padwa and A. G. Waterson, *ARKIVOC*, **2001**, *4*, 29.

31. M. R. Iesce, M. L. Graziano, F. Cermola, S. Montella and L. Di Gioia, *Tetrahedron Lett.*, **2003**, *44*, 5781.
32. A. I. Meyers, R. Gabel and E. D. Mihelich, *J. Org. Chem.*, **1978**, *43*, 1372.
33. K.-S. Yeung, *Top. Heterocycl. Chem.*, **2012**, *29*, 47.
34. M. Schlosser, *Organometallics in Synthesis*, 2nd Ed, **2002**, Chapter I.
35. M. E. Jung and J. Gervay, *J. Am. Chem. Soc.*, **1991**, *113*, 224.
36. J. Clayden and S. A. Yasin, *New J. Chem.*, **2002**, *26*, 191.
37. H. K. Lee and H. N. C. Wong, *Chem. Commun.*, **2002**, 2114.
38. H. Gilman, R. G. Jones, *Org. React.*, **1951**, *6*, 339.
39. J. Boukouvalas and R. P. Loach, *J. Org. Chem.*, **2008**, *73*, 8109.
40. F. Mongin, A. Bucher, J. P. Bazureau, O. Bayh, H. Awad and F. Trécourt, *Tetrahedron Lett.*, **2005**, *46*, 7989.
41. X.-J. Wang, X. Sun, L. Zhang, Y. Xu, D. Krishnamurthy, and C. H. Senanayake, *Org. Lett.*, **2006**, *8*, 305.
42. T. Kinzel, Y. Zhong and S. L. Buchwald, *J. Am. Chem. Soc.*, **2010**, *132*, 14073.
43. B. P. Bandgar, S. V. Bettigeri and J. Phopase, *Org. Lett.*, **2004**, *6*, 2105.
44. S. R. Dabbaka, P. Vogel, *J. Am. Chem. Soc.*, **2003**, *125*, 15292.
45. G. A. Molander and F. Beaumard, *Org. Lett.*, **2010**, *12*, 4022.
46. D. M. Knapp, E. P. Gillis and M. D. Burke, *J. Am. Chem. Soc.*, **2009**, *131*, 6961.
47. A. Boudier, L. O. Bromm, M. Lotz and P. Knochel, *Angew. Chem., Int. Ed.*, **2000**, *39*, 4414.
48. R. D. Rieke, S.-H. Kim, *Tetrahedron Lett.*, **2011**, *52*, 1128.
49. R. D. Rieke, *Science*, **1989**, *246*, 1260.
50. Q. Huang and V. H. Rawal, *Org. Lett.*, **2006**, *8*, 543.
51. A. E. Shilov and G. B. Shul'pin, *Chem. Rev.*, **1997**, *97*, 2879.
52. K. A. Pittard, J. P. Lee, T. R. Cundari, T. B. Gunnoe and J. L. Petersen, *Organometallics*, **2004**, *23*, 5514.
53. E. Thiery, D. Harakat, J. Le Bras and J. Muzart, *Organometallics*, **2008**, *27*, 3996.
54. R. Adams and V. Voorhees, *Org. Synth., Coll. Vol. I*, **1932**, 280.
55. C. Paal, *Chem. Ber.*, **1884**, *17*, 2756.
56. L. Knorr, *Chem. Ber.*, **1884**, *17*, 2863.
57. (a) D. W. Custar, H. Le, J. P. Morken, *Org. Lett.*, **2010**, *12*, 3760. (b) R. Ballini, L. Barboni, G. Bosica, D. Fiorini, *Synthesis*, **2002**, 2725. (c) Z.-L. Shen, K. K. K. Goh, H.-L. Cheong, C. H. A. Wong, Y.-C. Lai, Y.-S. Yang, T.-P. Loh, *J. Am. Chem. Soc.*, **2010**, *132*, 15852. (d) Y. Liu, Y. Li, Y. Qi, J. Wan, *Synthesis*, **2010**, 4188.
58. F. Feist, *Chem. Ber.*, **1902**, *35*, 1537.
59. E. Benary, *Chem. Ber.*, **1911**, *44*, 489.
60. R. A. Cormier, C. A. Grosshans and S. L. Skibbe, *Synth. Comm.*, **1988**, *18*, 677.
61. R. A. Cormier and M. D. Francis, *Synth. Comm.*, **1981**, *11*, 365.
62. H. E. Seyferth, *Chem. Ber.*, **1968**, *101*, 619.
63. R. Diaz-Cortes, A. L. Silva and L. A. Maldonado, *Tetrahedron Lett.*, **1997**, *38*, 2207.
64. T. J. Donohoe, J. F. Bower and L. K. M. Chan, *Org. Biomol. Chem.*, **2012**, *10*, 1322.
65. L. Mavoungou-Gomès, J. Bruneton and M. Aicart, *J. Heterocycl. Chem.*, **1985**, *22*, 1233.
66. O. Diels and K. Alder, *Chem. Ber.*, **1929**, *62*, 554.
67. A. Zamojski and T. Kozluk, *J. Org. Chem.*, **1977**, *42*, 1089.
68. I. Muller and V. Jager, *Tetrahedron Lett.*, **1982**, *23*, 4777.

69. G. O. Schenck and R. Steinmetz, *Liebigs Ann. Chem.*, **1963**, *668*, 19.
70. R. Faragher and T. L. Gilchrist, *J. Chem. Soc., Perkin Trans. I*, **1979**, 249.
71. D. I. Rawson, B. K. Carpenter and H. M. R. Hoffmann, *J. Am. Chem. Soc.*, **1979**, *101*, 1786.
72. C. O. Kappe, S. S. Murphree and A. Padwa, *Tetrahedron*, **1997**, *53*, 14179.
73. B. H. Lipshutz, *Chem. Rev.*, **1986**, *86*, 795.
74. P. Lazlo and J. Luchetti, *Tetrahedron Lett.*, **1984**, *25*, 4387.
75. M. W. Lee and W. C. Herndon, *J. Org.Chem.*, **1978**, *43*, 518.
76. D. D. Sternbach, D. M. Rossana and K. D. J. Onan, *J. Org. Chem.*, **1984**, *49*, 3427.
77. M. Lautens and E. Fillions, *J. Org. Chem.*, **1997**, *62*, 4418.
78. L. L. Klein, *J. Org. Chem.*, **1985**, *50*, 1770.
79. F. De Corte, F. Nuyttens, S. Cauwberghs and P. De Clercq, *Tetrahedron Lett.*, **1993**, *34*, 1831.
80. M. E. Jung and J. Gervay, *J. Am. Chem. Soc.*, **1991**, *113*, 224.
81. R. M. Beesley, C. K. Ingold, C. Kelk and J. F. Thorpe, *J. Chem. Soc. Trans.*, **1915**, *107*, 1080.
82. A. L. Parrill and D. P. Dolata, *Tetrahedron Lett.*, **1994**, *35*, 7319.
83. J. E. Hernandez, S. Fernandez and G. Arias, *Synth. Commun.*, **1988**, *18*, 2055.
84. Y. Wang, S.-Y. Mo, S.-J. Wang, S. Li, Y.-C. Yang and J.-G. Shi, *Org. Lett*., **2005**, *7*, 1675.
85. H. D. Cooper and D. L. Wright, *Molecules*, **2013**, *18*, 2438.
86. R. Bennes, D. Philp, N. Spencer, B. M. Kariuki and K. D. Harris, *Org. Lett*., **1999**, *1*, 1087.
87. B. M. O'Keefe, D. M. Mans, D. E. Kaelin Jr. and S. F. Martin, *J. Am. Chem. Soc.*, **2010**, *132*, 15528.
88. (a) D. E. Kaelin Jr., O. D. Lopez and S. F. Martin, *J. Am. Chem. Soc.*, **2001**, *123*, 6937. (b) S. F. Martin, *Pure Appl. Chem.*, **2003**, *75*, 63. (c) D. E. Kaelin, Jr., S. M. Sparks, H. R. Plake and S. F. Martin, *J. Am. Chem. Soc.*, **2003**, *125*, 12994.
89. Y.-P. Xue and W.-D. Z. Lei, *J. Org. Chem.*, **2011**, *76*, 57.
90. H. Zheng and D. G. Hall, *Tetrahedron Lett.*, **2010**, *51*, 3561.
91. S. J. Martinez and J. A. Joule, *J. Chem. Soc. Perkin Trans. 1*, **1979**, 3155.
92. T. Hayashi, Y. Kawakami, K. Konno and H. Takayama, *J. Chem. Soc. Perkin Trans. 1*, **1993**, 2387.
93. K. Ando, N. Akadegawa and H. Takayama, *J. Chem. Soc. Perkin Trans. 1*, **1993**, 2263.
94. T. Arenz, M. Vostell and H. Fraunrath, *Synlett*, **1991**, *1*, 23.
95. Y. Nishii, T. Yoshida, H. Asano, K. Wakasugi, J. Morita, Y. Aso, E. Yoshida, J. Motoyoshiya, H. Aoyama and Y. Tanabe, *J. Org. Chem.*, **2005**, *70*, 2667.
96. A. Nudelman, H. E. Gottlieb, B. Fischer and J. Herzig, *J. Org. Chem.*, **1986**, *51*, 727.
97. T. Neilson and E. S. Werstiuk, *Can. J. Chem.*, **1971**, *49*, 493.
98. X.-F. Lin and W. R. Roush, *J. Am. Chem. Soc.*, **1995**, *117*, 2236.
99. D. Alivertis, V. Theodorou, G. Paraskevopoulos, K. Skobridis, *Tetrahedron Lett.*, **2007**, *48*, 4091.
100. N. A. Reynolds, P. W. Le Quesre and S. E. Beder, *J. Org. Chem.*, **1975**, *40*, 1, 142.
101. Y. Gaoni and S. Sadeh, *J. Org. Chem.*, **1980**, *45*, 870.
102. J. Lambert, F. Koenig and J. Hamersma, *J. Org. Chem.*, **1971**, *36*, 2941.
103. K. Ando, M. Kankake, T. Suzuki and H. Takayama, *Tetrahedron*, **1995**, *51*, 129.
104. M. Mihara, Y. Ishino, S. Minakata and M. Komatsu, *Synlett*, **2002**, *9*, 1526.

105. A. M. Deshpande, A. A. Natu, N. P. Argade, *Synthesis*, **2002**, *8*, 1010.
106. R. Balamurugan, N. Ramesh and A. K. Mohanakrishnan, *Tetrahedron Lett.*, **2005**, *46*, 8189.
107. Y. N. Ogibin, E. K. Starostin, A. V. Aleksandrov, K. K. Pivnitsky and G. I. Nikishin, *Synthesis*, **1994**, *9*, 901.
108. E. K. Starostin, A. V. Ignatenko, M. A. Lapitskaya, K. Pivnitsky and G. I. Nikishin, *Russ. Chem. Bull. Int. Ed.*, **2001**, *50*, 833.
109. Z. Klepo and K. Jakopcic, *J. Heterocyclic Chem.*, **1987**, *24*, 1787.
110. (a) S. Woo and B. A. Keay, *Tetrahedron: Asymmetry*, **1994**, *5*, 1411. (b) C. Rogers and B. A. Keay, *Tetrahedron Lett.*, **1991**, *32*, 6477. (c) C. Rogers and B. A. Keay, *Synlett*, **1991**, 353. (d) C. Rogers and B. A. Keay, *Can. J. Chem.* **1992**, *70*, 2929. (e) P. J. DeClercq and L. A. Van Royen, *Synth. Commun.*, **1979**, *9*, 771. (f) L. A. Van Royen, R. Mijngher and P. J. DeClercq, *Bull. Soc. Chim. Belg.*, **1984**, *93*, 1019. (g) K. Fischer and S. J. Hunig, *Org. Chem.*, **1987**, *52*, 564. (h) A. Padwa, M. A. Brodney, K. Satake and C. S. Straub, *J. Org. Chem.* **1999**, *64*, 4617.
111. A. Padwa, K. R. Crawford, C. S. Straub, S. N. Pieniazek and K. N. Houk, *J. Org. Chem*., **2006**, *71*, 5432.
112. S. N. Pienazek and K. N. Houk, *Angew. Chem. Int. Ed.*, **2006**, *45*, 1442.
113. (a) M. Karaarslan and A. Demircan, *Asian. J. Chem.*, **2007**, *19*, 2999. (b) A. Demircan, M. Karaarslan and E. Turac, *Het. Commun.*, **2006**, *12*, 233.
114. O. Serdyuk, A. Butin and V. Abaev, *J. Fluorine Chem.*, **2010**, *131*, 296.
115. P. LaBeaume, M. Placzek, M. Daniels, I. Kendrick, P. Ng, M. McNeel, R. Afroze, A. Alexander, R. Thomas, A. E. Kallmerten and G. B. Jones, *Tetrahedron Lett.*, **2010**, *51*, 1906.
116. G. S. Lal, *J. Org. Chem.*, **1993**, *58*, 2791.
117. S. Yamada, A. Gavryushin and P. Knochel, *Angew. Chem., Int. Ed.*, **2010**, *49*, 2215.
118. E. J. Corey and M. C. Noe, *J. Am. Chem. Soc.*, **1996**, *118*, 319.
119. D. W. Knight and A. P. Nott, *J. Chem. Soc. Perkin Trans. I*, **1981**, 1125.
120. F. Kopp, S. Wunderlich and P. Knochel, *Chem. Commun.*, **2007**, 2075.
121. S. K. Hashmi, J. P. Weyrauch, E. Kurpejović, T. M. Frost, B. Miehlich, W. Frey and J. W. Bats, *Chem.-Eur. J.*, **2006**, *12*, 5806.
122. M. L. R. Heffernan, J. M. Dorsey, Q. K. Fang, R. J. Foglesong, S. C. Hopkins, M. L. Jones, S. W. Jones, C. O. Ogbu, J. B. Perales Jr., M. Soukri, K. L. Spear and M. A. Varney, *U.S. Pat. Appl. Publ.*, **2008**, Pat. No. 20080058395.
123. I. Heinze, *Chem. Ber.*, **1989**, *122*, 2147.
124. A. G. Taveras, J. Zheng, P. J. Biju, Y. Yu, J. Chao, J. Fine, D. Lundell, T. Priestley, A. Regianni, J. R. Merritt, J. J. Baldwin, G. Lai and M. Wu, *PCT Int. Appl.*, **2005**, *WO/2005/068460*.
125. M. D'auria, G. Piancatelli and A. Scettri, *Tetrahedron*, **1980**, *36*, 3071.
126. E. L. Pearson, L. C. H. Kwan, C. I. Turner, G. A. Jones, A. C. Willis, M. N. Paddon-Row and M. S. Sherburn, *J. Org. Chem.*, **2006**, *71*, 6099.
127. Y. A. Lin, J. M. Chalker, N. Floyd, G. J. L. Bernardes and B. G. Davis, *J. Am. Chem. Soc.*, **2008**, *130*, 9642.
128. M. E. Kort, I. Drisin, R. J. Gregg, M. J. C. Scanio, L. Shi, M. F. Gross, R. N. Atkinson, M. S. Johnson, G. J. Pacofsky, J. B. Thomas, W. A. Carroll, M. J. Krambis, D. Liu, C.-C.Shieh, X. Zhang, G. Hernandez, J. P. Mikusa, C. Zhong, S. Joshi, P. Honore, R. Roeloffs, K. C. Marsh, B. P. Murray, J. Liu, S. Werness, C. R. Faltynek, D. S. Krafte, M. F. Jarvis, M. L. Chapman and B. E. Marron, *J. Med. Chem.*, **2008**, *51*, 407.

129. H.-Z. Zhang, S. Kasibhatla, J. Kuemmerle, W. Kemnitzer, K. Ollis-Mason, L. Qiu, C. Crogan-Grundy, B. Tseng, J. Drewe and S. X. Cai, *J. Med. Chem.*, **2001**, *48*, 5215.
130. J. Barluenga, F. Foubelo, F. J. Fañanás and M. Yus, *J. Chem. Soc. Perkin. Trans. 1*, **1989**, 553.
131. F. Ghelfi, A. F. Parsons, D. Tommasini and A. Mucci, *Eur. J. Org. Chem.*, **2001**, *10*, 1845.
132. Y. Basel and A. Hassner, *Synthesis*, **2001**, *4*, 550.
133. A. F. Abdel-Magid, K. G. Carson, B. D. Harris, C. A. Maryanoff and R. D. Shah, *J. Org. Chem.*, **1996**, *61*, 3849.
134. K. L. Milkiewicz, I. B. Neagu, D. J. Parks, T. Lu, *Tetrahedron Lett.*, **2003**, *44*, 7341.
135. D. P. Stack and R. M. Coates, *Synthesis*, **1984**, *5*, 434.
136. M. E. Jung and L. J. Street, *J. Am. Chem. Soc.*, **1984**, *106*, 8327.
137. M. J. T. Frisch, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Ismaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, N.J. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, ö. Farkas, J. B. Foresman, J. V. Ortis, J. Cioslowski, D. J. Fox, *Gaussian 09, Revision A.02*., **2009**.
138. R. Robiette, J. Marchand-Brynaert and D. Peeters, *J. Org. Chem*., **2002**, *67*, 6823.
139. (a) M. R. Nyden, G. A. Petersson, *J. Chem. Phys.*, **1981**, *75*, 1843. (b) J. W. Ochterski, G. A. Petersson, J. A. Montgomery, *J. Chem. Phys.*, **1996**, *104*, 2598. (c) J. A. Montgomery, M. J. Frisch, J. W. Ochterski, G. A. Petersson, *J. Chem. Phys.*, **1999**, *110*, 2822. (c) J. A. Montgomery, M. J. Frisch, J. W. Ochterski, G. A.Petersson, *J. Chem. Phys.*, **2000**, *112*, 6532.
140. (a) J. A. Montgomery, M. J. Frisch, J. W. Ochterski, G. A. Petersson, *J. Chem. Phys.*, **2000**, *112*, 6532. (b) L. A. Curtiss, K. Raghavachari, P. C. Redfern, J. A. Pople, *J. Chem. Phys.*, **1997**, *106*, 1063. (c) L. A. Curtiss, P. C. Redfern, K. Raghavachari, J. A. Pople, *J. Chem. Phys.*, **1998**, *109*, 42.
141. A. Williams, *Free Energy Relationships in Organic and Bio-Organic Chemistry*, 1st Edition, **2003**.
142. J. J. Gajewski, K. B. Peterson and J. R. Kagel, *J. Am. Chem. Soc.*, **1987**, *109*, 5546.
143. T. Mukaiyama and T. Takebayashi, *Chem. Lett.*, **1980**, 1013.
144. T. Takebayashi, N. Iwasawa and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, **1983**, *56*, 1107.
145. J. M. McIntosh and R. A. Sieler, *J. Org. Chem.*, **1978**, *43*, 4431.
146. E. Wenkert, P. D. R. Moeller and S. R. Piettre, *J. Am. Chem. Soc.*, **1988**, *11*, 1188.
147. G. N. Tew, A. E. Madkour, K. Lienkamp and A. M. Musante, *PCT Int. Appl.*, 2010144386, **2010**, *WO/2010/144386.*
148. Y. W. Goh, B. R. Pool and J. M. White, *J. Org. Chem.*, **2008**, *73*, 151.

149. M. K. Sahoo, *Synlett*, **2007**, *13*, 2142.
150. F. P. J. Rutjes, J. J. L. Cornellisen, S. S. Van Berkel and A. J. Dirks, *PCT Int. Appl.*, 2008075955, **2008**, *WO/2010/075955*.
151. M. G. Barlow, N. N. E. Suliman, A. E. Tipping, *J. Fluorine Chem.*, **1995**, *70*, 95.
152. C. L. D. Jennings-White, A. B. Holmes and P. R. Raithby, *J. Chem. Soc., Chem. Commun.*, **1979**, *12*, 542.
153. L. A. Paquette, T. M. Kravetz, P. Charumilind, *Tetrahedron*, **1986**, *42*, 1789.
154. S. Inokuma, A. Sugie, K. Moriguchi and J. Katsube, *Heterocycles*, **1983**, *20*, 1109.
155. C. Spino, M. Pesant and Y. Dory, *Angew. Chem. Int. Ed.*, **1998**, *37*, 3262.
156. D. H. Williams and D. J. Faulkner, *Tetrahedron*, **1996**, *52*, 4245.
157. S. A. Shackelford, M. B. Anderson, L. C. Christie, T. Goetzen, M. C. Guzman, M. A. Hananel, W. D. Kornreich, H. Li, V. P. Pathak, A. K. Rabinovich, R. J. Rajapakse, L. K. Truesdale, S. M. Tsank, and H. N. Vazir, *J. Org. Chem.*, **2003**, *68*, 267.
158. M. Nakamura, I. Takahashi, S. Yamada, Y. Dobashi and O. Kitagawa, *Tetrahedron Lett.*, **2011**, *52*, 53.
159. F. I. Zubkov, V. P. Zaytsev, E. V. Nikitina, V. N. Khrustalev, S. V. Gozun, E. V. Boltukhina and A. V. Varlamov, *Tetrahedron*, **2011**, *67*, 9148.
160. M. Avalos, R. Babiano, J. L. Bravo, P. Cintas, J. L. Jiminez and J. C. Palacios, *Tetrahedron Lett.*, *39*, 9301.
161. S. Inokuma, A. Sugie, K. Moriguchi and J. Katsube, *Heterocycles*, **1983**, *20*, 1109.