THE UNIVERSITY OF
SYDNEY

Studies Toward the Total Synthesis of Hinckdentine A using Under-Utilised Reactions and Functional Groups

A thesis submitted in fulfilment of the

requirements for the degree of

Doctor of Philosophy

By

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Declaration

This thesis is a summary of work carried out in the School of Chemistry, the University of Sydney, under the supervision of Dr. Christopher S. P. McErlean between March 2010 and February 2014.

This thesis contains no material published or extracted in whole or in part from a thesis presented by me for any other degree or diploma. No other person's work has been used without due acknowledgment and every effort has been made to acknowledge previously published material. Quantum mechanical modelling shown in Chapter 2, *Section 2.12*, was performed by Dr. Bun Chan. The X-Ray Crystal structure of compound **219** (Chapter 3, *Section 3.14*) was obtained by Dr. Peter Turner. High-Resolution mass spectrometry was performed by Dr. Keith Fisher, Dr. Nicholas Proschogo and myself. All NMR spectra were obtained and analysed by myself. Any time the words "we" or "our" appear herein I am referring to myself. This thesis contains fewer than 80,000 words.

Sections of this work have been published in peer reviewed journals and presented at scientific conferences.

Christopher B. W. Phippen

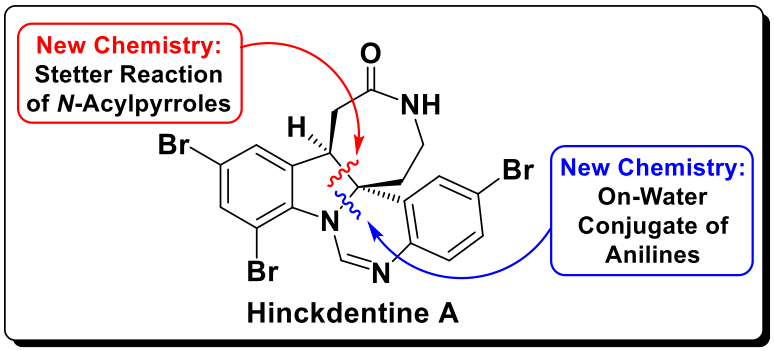
March 2014

Abstract

On the instigation of Dr C. S. P. McErlean I investigated a variety of chemical transformations which have been underutilised in the literature.

Many useful organic transformations remain underutilised because they have not been thoroughly investigated and understood. We have sought to expand the utility of neglected reactions and functional groups by investigating their mechanism and examining their scope.

We planned to demonstrate utility of these transformations by incorporating them as key steps in the total synthesis of the natural product hinckdentine A.



We developed a rational and consistent theory for mechanism of on-water catalysis.[1] This new theory has allowed us to identify previously unrecognised examples of this phenomenon. The traditionally difficult conjugate addition of anilines was found to be facile under on-water conditions and this reaction was further improved through the incorporation of *N*-acylpyrroles.[2] *N*-Acylpyrroles were also found to facilitate the Stetter reaction and expand the scope of subsequent transformations.[3]

The understanding gained from these studies allowed us to undertake studies toward the total synthesis of hinckdentine A, by an innovative route which included the aforementioned reactions as integral transformations.

Acknowledgements

I would like to thank Dr. C. S. P. McErlean for his supervision and support as well as Dr. Peter Rutledge for his reassuring associate supervision. I would also likely to thank the friends with whom I have shared the laboratory, especially Carl Recsei, Dr. Kaitlin Beare, Dr. Caroline Nesbitt and Anna Goldys. Thanks must also go to Dr. Keith Fisher and Dr. Nick Proschogo for my employment in the mass spectrometry facility and all they have taught me.

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Contents

Chapter 3

Chapter 4

Chapter 5

Abbreviations

Ac	acetyl
Å	Angstrom (1×10^{-10} m)
aq	aqueous
APCI	atmospheric pressure chemical ionisation
Ar	aromatic
Bn	benzyl
br	broad
Bu, n-Bu	primary butyl
t-Bu	tertiary butyl
Boc	di-*tert*-butyloxy
˚C	degrees Celsius
CBS	Corey-Bakshi-Shibata
calcd	calculated
c.e.d.	cohesive energy density
cm^{-1}	wavenumber(s)
m-CPBA	meta-chloroperoxybenzoic acid
CSA	camphorsulfonic acid
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
decomp.	Decomposed
δ	chemical shift in parts per million downfield from trimethylsilane
DEPT	distortionless enhancement by polarisation transfer
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DIE	deuterium isotope effect
DMAD	dimethyl azodicarboxylate
DMAP	4-(*N,N*-dimethylamino)pyridine
DMBn	2,4-dimethoxybenzyl
DMF	*N,N*-dimethylformamide
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
DPPP	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio

ee	enantiomeric excess
EI	electron impact
equiv.	equivalent/s
ESI	electrospray ionisation
Et	ethyl
EWG	electron withdrawing group
FMO	frontier molecular orbital theory
g	gram(s)
h	hour(s)
HFIP	1,1,1,3,3,3-hexafluropropan-2-ol
HOMO	highest occupied molecular orbital
HMDS	hexamethyldisilazane , hexamethyldisilazide
HMPA	hexamethylphosphoramide
HRMS	high-resolution mass spectrometry
HWE	Horner-Wadsworth-Emmons olefination
Hz	hertz
IR	infrared
J	coupling constant
KIE	kinetic isotope effect
L	litre(s)
LG	leaving group
lit.	literature value
LUMO	lowest unoccupied molecular orbital
μ	micro
m	multiplet; meter(s); milli
M	molar (moles per litre), Metal
M^+	parent molecular ion
Me	methyl
MHz	megahertz
min.	minute(s)
mol	mole(s)
mol. sieve	molecular sieve
mp	melting point
Ms	methanesulfonyl (mesyl)
MS	mass spectrometry

m/z	mass-to-charge ratio
NBS	*N*-bromosuccinimide
NHC	N-heterocyclic carbene
NMM	*N*-methylmorpholine
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NR	no reaction
Ns	4-nitrobenzenesulfonyl (nosyl)
Nu	nucleophile
PG	protecting group
Ph	phenyl
PMB	*para*-methoxybenzyl
PMP	*para*-methoxylphenyl
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
i-Pr	isopropyl
py	pyridine
q	quartet
quant.	quantitative yield
quin.	quintet
RDS	rate determining step
R_f	retention factor
RT	room temperature
SEM	2-(trimethylsilyl)ethoxymethyl
t	triplet
TBAF	tetra(n-butyl)ammonium fluoride
TBAI	tetra(n-butyl)ammonium iodide
TBS	tertiary-butyldimethylsilyl
TBDPS	tertiary-butyldiphenylsilyl
temp.	temperature
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxy
tert	tertiary
Tf	trifluoromethylsulfonyl
TFA	trifluoroacetic acid

TFAA	trifluoroacetic anhydride
TFE	1,1,1-trifluroethanol
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TPAP	tetra-(n-propyl)ammonium perruthenate
Ts	*para*-toluenesulfonyl (tosyl)
UV	ultraviolet light
v/v	volume per volume
W	Watt/s
w/v	weight per volume
w/w	weight per weight

Chapter 1

Introduction

1.1 Introduction to hinckdentine A

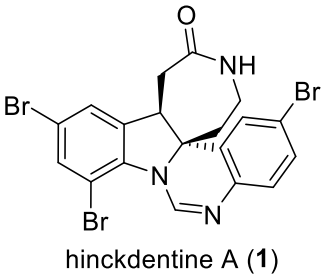


Figure 1.1: *Structure of hinckdentine A*

Hinckdentine A (**1**) is a brominated alkaloid that was isolated from the marine bryozoan *Hincksinoflustra denticulata* (*Figure 1.2*).[4] Bryozoans, also known as sea mosses or moss animals, are a phylum of aquatic fauna measuring approximately 500 μm in length but growing in large colonies up to 50 cm long. As their name suggests these colonies often resemble moss, but colonies of bryozoans can also be mistaken for soft corals, seaweeds and sponges.

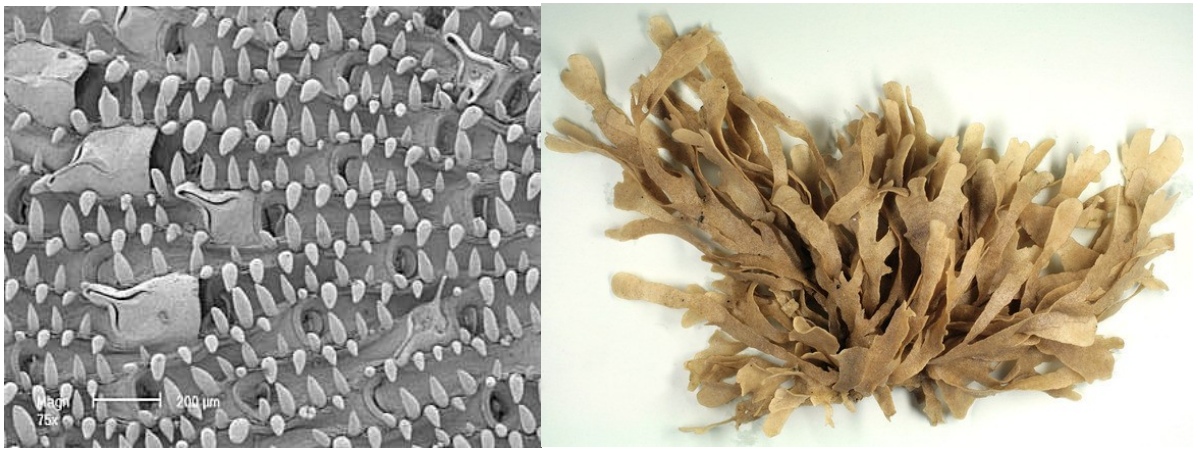


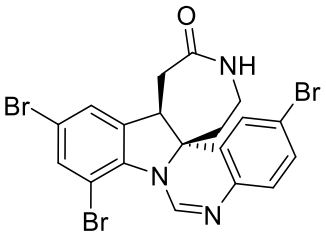
Figure 1.2: *Detail of Hincksinoflustra denticulata*[5] *(left) and a bryozoan of the same family Flustra foliacea*[6] *(right)*

H. denticulata occurs in the temperate coastal waters off southern Australian, New Zealand and southern Africa.[7] As with many marine natural products, it is not clear whether hinckdentine A is produced by the bryozoan or by microorganisms associated with it.[8] The structure and absolute stereochemistry of this natural product were unambiguously established at the University of Sydney in 1987 by single crystal X-ray diffraction.[4]

The focus of natural product isolation has recently shifted from terrestrial to marine sources

due to the hitherto unexplored diversity available in aquatic environments and the potential these compounds offer to chemistry and medicine. Despite this interest, bryozoans represent a largely unexplored source of natural products; of the 8000 species known only 32 have been examined for interesting natural products. Even this relatively small number of species has yielded 200 previously unknown natural products[9] and one, bryostatin,[10] has shown promising results in trials for the treatment of a range of diseases, including Alzheimer's disease and cancer.[11] Synthesis is the only reliable way to ascertain whether other compounds found in bryozoans possess biological potential as even the largest colonies of bryozoans yield minute quantities of these compounds. Isolation is often non-trivial and is necessarily destructive to the environment.

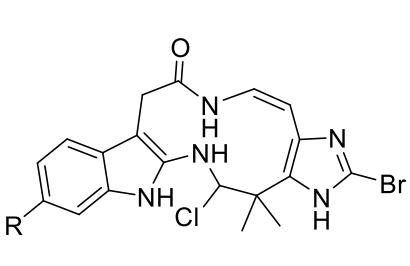
1.1.2 Structure of hinckdentine A



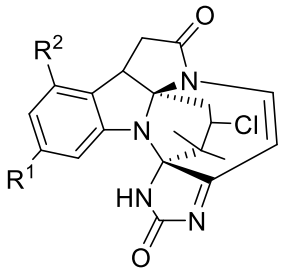
hinckdentine A (**1**)

Figure 1.3: *Structure of hinckdentine A*

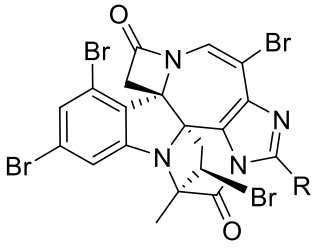
Hinckdentine A (**1**) possesses a unique fused pentacyclic ring system featuring a seven-membered lactam, a tribromoindolo[1,2-*c*]quinazoline and an amine bearing quaternary stereocentre (*Figure 1.3*). Although the structure of hinckdentine A is unique, many bryozoans are known to produce halogenated indole alkaloids.[9] The flustridae family, to which *H. denticulata* belongs, produces the most closely related alkaloids. These include the securines (**2-3**) and securamines (**4-6**) from *Securiflustra securifrons*[12] and the chartellamides (**7–8**) from *Chartella papyracea*[13] *(Figure 1.4).*



R = H: securine A (**2**)
R = Br: securine B (**3**)



R^1 = Br, R^2 = H: securamine C (**4**)
R^1 = H, R^2 = Br: securamine D (**5**)
R^1 = Br, R^2 = Br: securamine E (**6**)



R = H: chartellamide A (**7**)
R = Br: chartellamide B (**8**)

Figure 1.4*: Related natural products*

No biological testing of hinckdentine A has been reported, although alkaloids in general are widely used for their medicinal properties. Hinckdentine A possesses many structural features that are known to have biological functions (*Figure 1.5*). The specific biologically active substructures include dihydrotryptamine which is an important medicinal substructure.[14] Hinckdentine A also contains a dihydropyrimidine moiety, which is the substrate for the dihydropyrimidine dehydrogenase enzyme responsible for the metabolism of the nucleobases uracil and thymine.[15] Simplified structures of hinckdentine A which have been tested for biological activity include the indolo[1,2-*c*]quinazoline unit which has been shown to be antimicrobial[16] and cataleptogenic.[17] Consequently it is anticipated that hinckdentine A (**1**) will also display useful pharmacological properties in future assays, but the current lack of material has prevented testing of this optically active natural product.

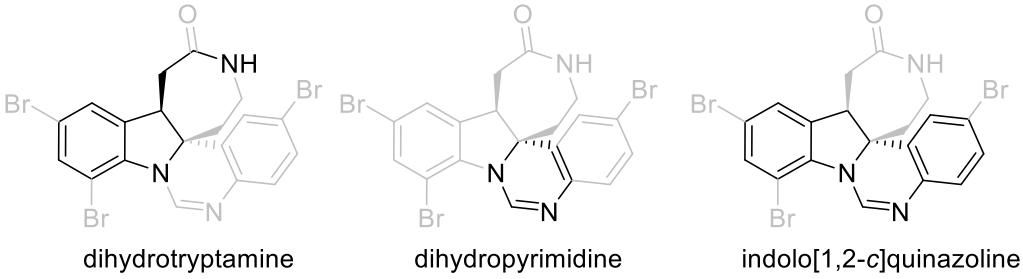
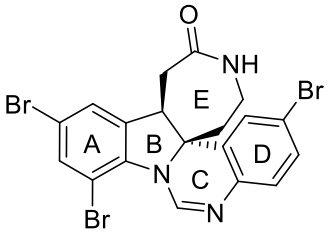


Figure 1.5: *Known biologically active substructures of hinckdentine A*

Despite being described more than 25 years ago and possessing several features which are attractive to synthetic chemists (alkaloid, a unique heterocyclic ring system, quaternary stereocentre, unusual bromination) there has only been a single successful total synthesis of racemic hinckdentine A (**1**),[18] and one synthesis of the 8-desbromo analogue.[19] There have been no reports of an asymmetric synthesis. The dearth of synthetic approaches and the lack of an asymmetric synthesis demonstrate how challenging the unique architecture of hinckdentine A is.

1.2 Previous synthetic approaches

There is no established ring lettering system for hinckdentine A. In this thesis the rings will be as designated A – E in the order depicted in *Figure 1.6*.



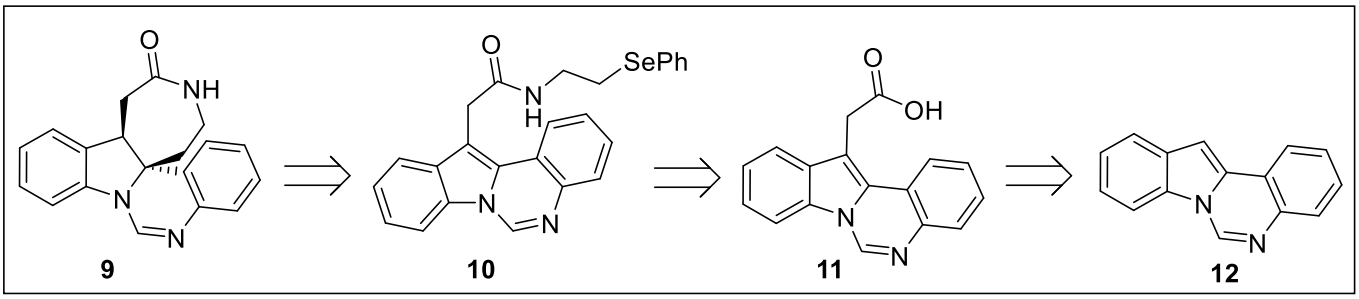
hinckdentine A (**1**)

Figure 1.6: *Ring letting system of hinckdentine A*

In total there have been three published attempts at the total synthesis of hinckdentine A, all of which possess strong similarities.

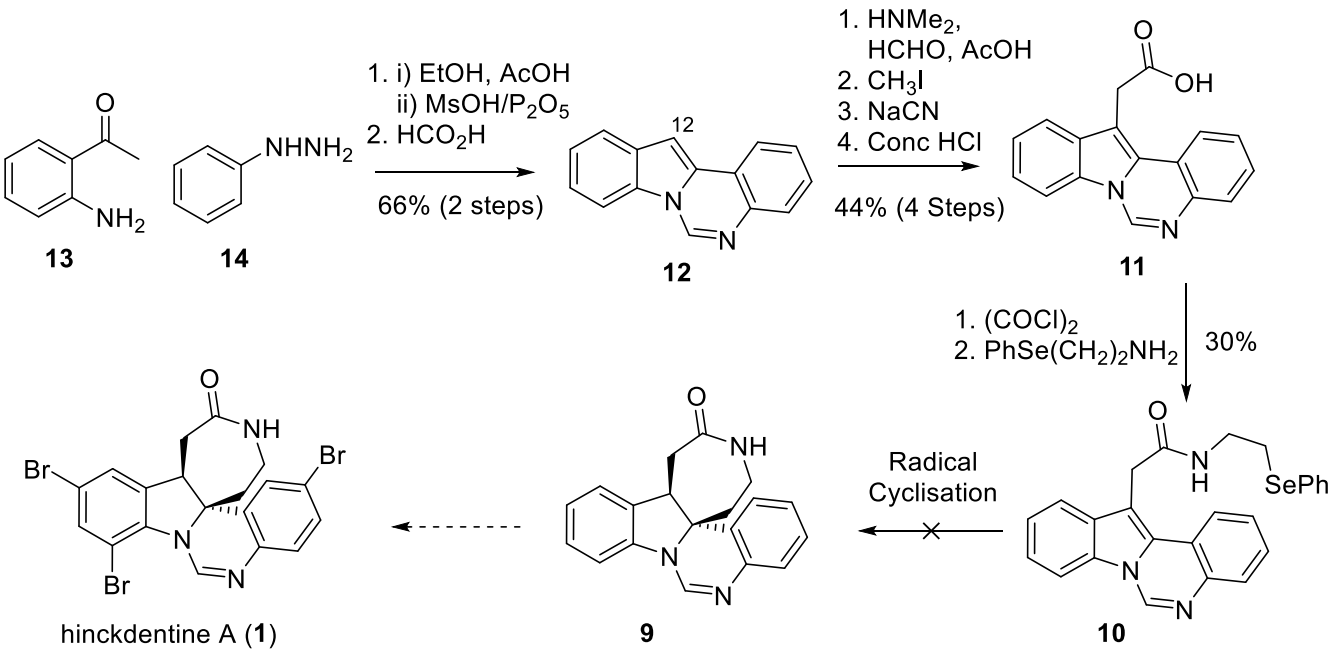
1.2.1 Cava – Synthesis of the tetracyclic core (1994)

The first reported approach to the synthesis of hinckdentine A was disclosed in 1994 by Cava and Billimoria.[20] Their strategy was to construct the fully aromatic equivalent of the indolo[1,2-*c*]quinazoline core, **10**, followed by a radical alkylation to complete to ε-lactam, **9** (*Scheme 1.1*).



Scheme 1.1: *Retrosynthesis of Cava's strategy*

Cava's synthesis began with the rapid construction of the aromatic core (**12**) using a Fischer indole synthesis between 2-aminoacetophenone (**13**) and phenylhydrazine (**14**), followed by a condensation with formic acid to give four of the five rings in hinckdentine A, **12**, in two steps and in high yield (*Scheme 1.2*).



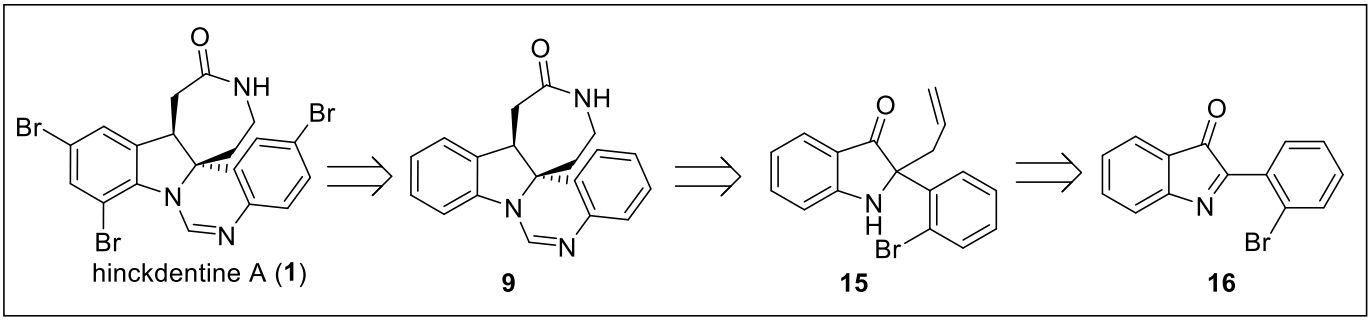
Scheme 1.2: *First attempted total synthesis of hinckdentine A*

After some experimentation, it was found that the best way to alkylate the 12 position of the indoloquinazoline system, **12**, was to utilise the innate reactivity of this position and perform a Mannich reaction to give a dimethyl amine. This was followed by conversion into the nitrile and hydrolysis of the nitrile to the acid, **11**. Formation of the acid chloride and addition of 2-(phenylselanyl)-ethanamine formed the required amide (**10**) as well as introducing the selenium which would allow for radical mediated bond formation. All attempts at the radical cyclisation failed to give the desired pentacyclic product, **9**. This was despite deselenation occurring in good yields with a range of initiators (e.g. tributyltin hydride, azobisisobutyronitrile and tris-(trimethylsilyl)silane). Further work on the radical cyclisation found that neither reduction of the pyrimidine ring nor modification of the carbonyl unit allowed the reaction to occur. Some investigations into the tri-bromination were performed which suggested that bromination of the indolo[1,2-*c*]quinazoline unit (such as in **10** or **11**) was not feasible.

This approach to hinckdentine A rapidly obtained the ABCD ring system and in only 7 steps (9% yield) Cava's synthesis also installed all the necessary carbon atoms, and did not employ any protecting groups. Completion of the total synthesis would have required only two further steps (formation of a carbon-carbon bond and selective bromination). Cava's inability to generate the final carbon-carbon bond by radical cyclisation exemplifies the challenges that arise when creating quaternary stereocentres.

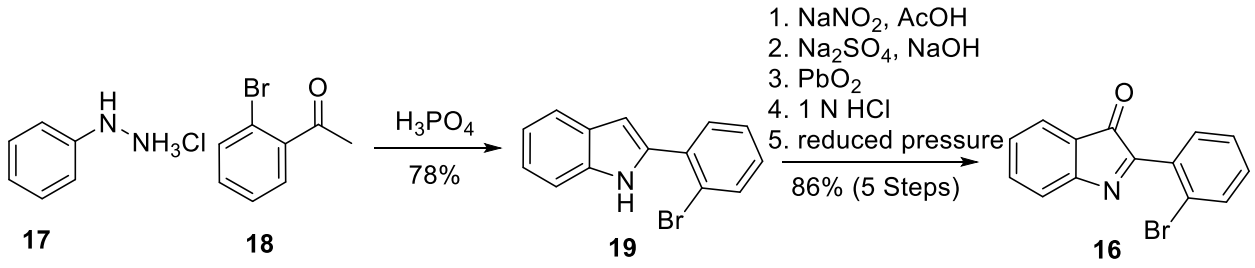
1.2.2 McWhorter – Synthesis of 8-desbromo hinckdentine A (2003)

The next approach towards hinckdentine A was published nine years later by McWhorter and Liu. Citing the difficulty that Cava had experienced when attempting to install the quaternary centre late in the synthesis, McWhorter and Liu planned to generate this position as early as possible in their synthesis. The key step in their approach was an organometallic addition onto a 3*H*-indol-3-one, such as **16** to create the quaternary stereocentre present in **15**. From a suitable functionalised compound such as **15** (*Scheme 1.3*) it was anticipated that there would be many avenues available to complete the total synthesis.



Scheme 1.3: *Retrosynthesis of McWhorter's synthesis*

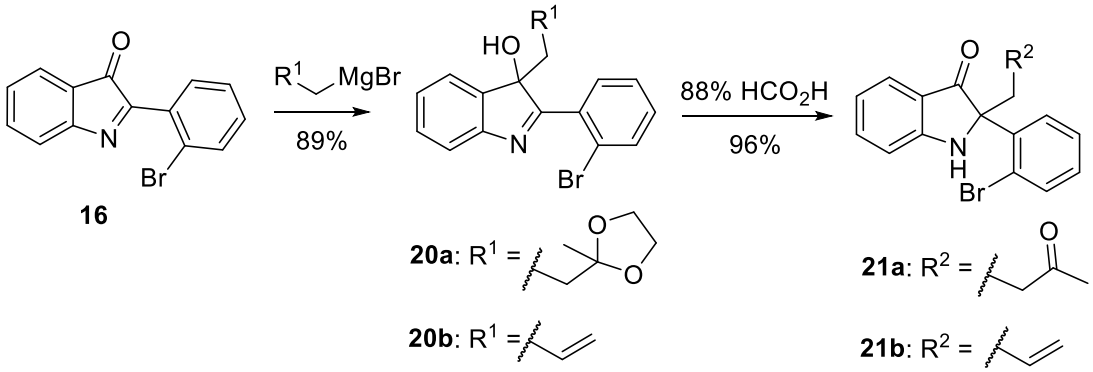
Again, this approach began with a Fischer indole synthesis, this time between phenylhydrazine (**17**) and bromoacetophenone (**18**) to give 2-(2-bromophenyl)indole (**19**). The indole was converted into the required 3*H*-indol-3-one, **16**, by a five step sequence of nitrosylation, reduction of the nitroso group to an amine, dehydrogenative reduction, hydration and hydrolysis, and finally, dehydration. Although this was a long series of reactions, the yield from compounds **17** and **18** was 68% and could be performed on a greater than 20 gram scale.



Scheme 1.4: *Synthesis of key intermediate*

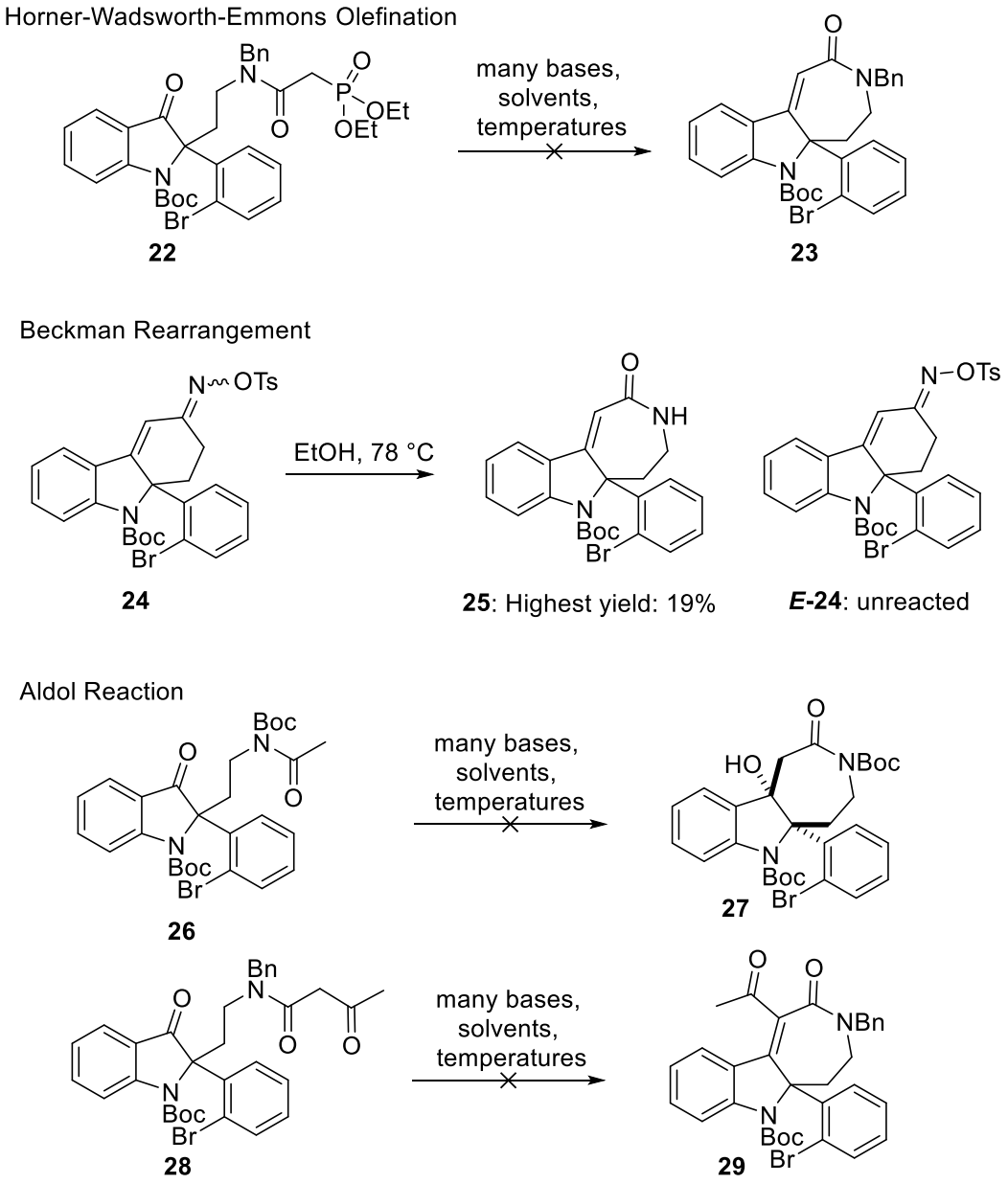
Two different Grignard reagents were added to this key intermediate. McWhorter was surprised to find both the organometallic reagents added predominantly to the carbonyl of the indolone (**20a** and **20b**) rather than the imine and the compound with the required quaternary stereocentre was produced in only trace amounts (*Scheme 1.5*). Although McWhorter did not offer an

explanation for this outcome, the observed chemoselectivity indicates the reaction is likely to be occurring by a single electron transfer mechanism. The addition of Grignard reagents to aromatic ketones is known to proceed by a radical mechanism and the carbonyl will offer a greater stabilisation to the radical intermediate than the imine.[21] To achieve the necessary aza-quaternary stereocentre a pinacol-type rearrangement was performed under acidic conditions, giving the key compounds **21a** and **21b**, in good yield (*Scheme 1.5*).



Scheme 1.5: *Synthesis of quaternary stereocentre*

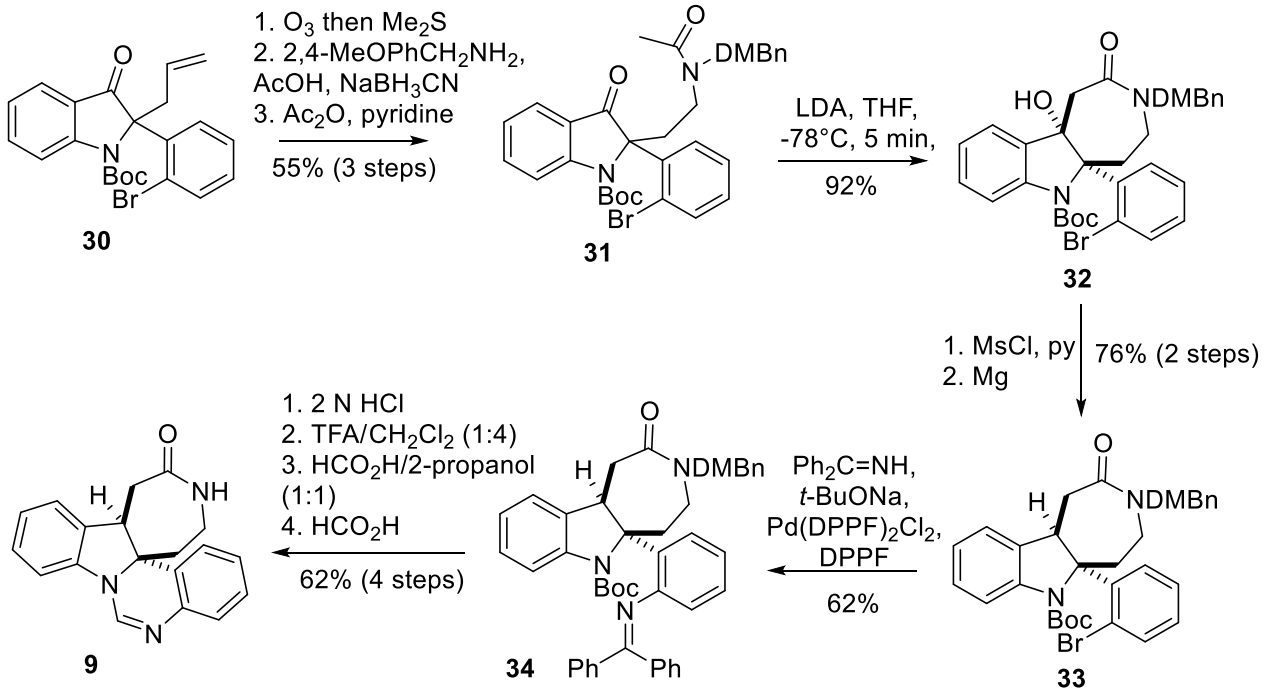
From intermediates **21a** and **21b**, a multitude of approaches to generate the ε-lactam were attempted. Some instructive outcomes are detailed in *Scheme 1.6*. The Horner-Wadsworth-Emmons olefination of phosphonate **22** did not give the desired product, **23**, under any circumstances. The Beckman rearrangement of oxime **24** gave a low yield of the desired lactam **25** which proved inseparable from the unreactive isomer of the intermediate *O*-tosyloxime, ***E*-24**. The Aldol reaction of compounds **26** and **28** to give lactams **27** and **29** was also fruitless under all conditions attempted.



Scheme 1.6: *McWhorter's attempts to perform cyclisation*

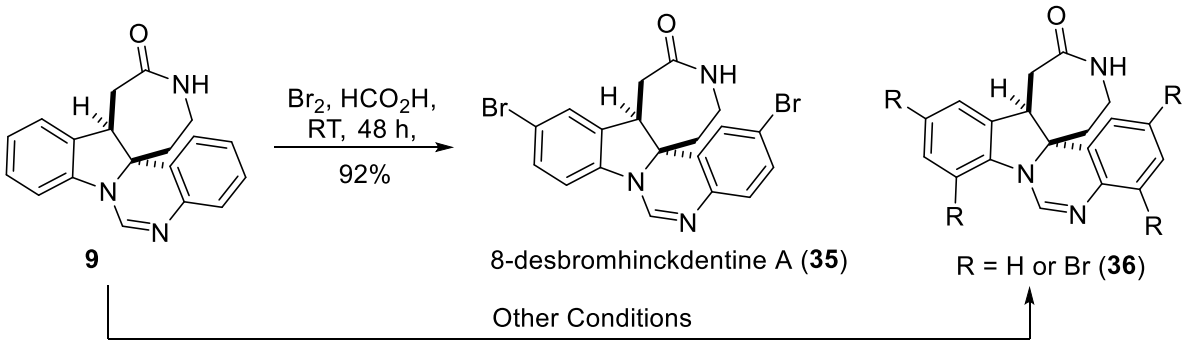
Eventually, a successful strategy to the hinckdentine A architecture was found based on a change in protecting groups. As shown in *Scheme 1.7*, ozonolysis of indolone **30** was performed and the resulting aldehyde was reductively aminated with 2,4-dimethoxybenzylamine and acylated to give amide **31**. With the dimethoxybenzyl group present the aldol reaction, which formerly would not occur under any circumstances, now occurred after only five minutes to give lactam **32**. This highlights the critical nature of protecting group choice and the value of experimentation, as it could not be predicted that this reaction would give such different results with seemingly similar substrates. The aldol reaction was followed by a dehydration and reduction of the resulting alkene to give the cis-fused tetracyclic compound **33** as a single diastereomer (*Scheme 1.7*). The palladium-catalysed

amination was optimised and ultimately gave compound **34** in moderate yield. From this point the three orthogonal *N*-protecting groups were sequentially removed using three different acids. First the diphenylmethylidene protecting the primary amine was hydrolysed, and then the indoline nitrogen was freed by removal of the carbamate group with trifluoroacetic acid. Condensation with formic acid generated the dihydropyrimidine ring, and finally the dimethoxybenzyl group was removed, also with formic acid, resulting in compound **9**.



Scheme 1.7: *Synthesis of hinckdentine A skeleton*

This constituted the first synthesis of the core of hinckdentine A and only the installation of the three bromine atoms was required to complete the total synthesis. This was expected to be achieved by electrophilic bromination of the electron-rich aromatic rings. The enzyme responsible for bromination in natural products is known to be largely non-selective,[22] as such it is probable the bromination occurs late in the biosynthesis of hinckdentine A and the sites of bromination are likely to be the most inherently reactive positions.



Scheme 1.8: *Attempts to tri-brominate the hinckdentine A core*

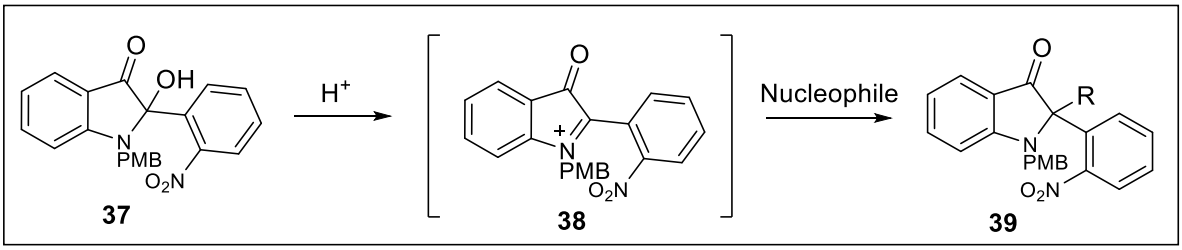
When the bromination was performed with bromine in formic acid the di-brominated product **35** was formed. Attempts to generate the tri-brominated natural product gave only inseparable regioisomeric mixtures of tri- and tetra- brominated compounds (**36**).

McWhorter and Liu were unable to selectively install the three bromine atoms as found in the natural product but did synthesise 8-desbromohinckdentine A (**35**) in 19 steps and 9% overall yield. In accordance with Cava's experience they had found the formation of the ε-lactam to be very challenging. The strength of this synthesis was that it was performed on a gram scale up until the penultimate step.

1.2.3 Kawasaki - First total synthesis of hinckdentine A (2008)

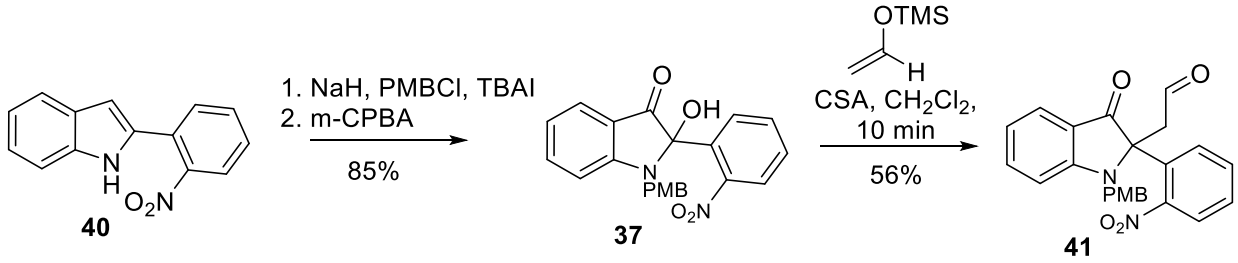
The third approach toward hinckdentine A was published in 2008 by the group headed by Kawasaki, and constitutes the only total synthesis of hinckdentine A to date.[18] The strategy employed by Kawasaki closely parallels the strategy used by McWhorter.

To circumvent the regioselectivity problems that McWhorter had experienced when adding Grignard reagents into 3*H*-indol-3-one **16** (see *Scheme 1.5*), Kawasaki and co-workers planned to increase the electrophilicity of the imine by performing nucleophilic attack onto an iminium ion (**38**, *Scheme 1.9*) to give the quaternary centre of indolone **39**. The iminium species was to be obtained by dehydration of an *N*-protected 2-hydroxyindolin-3-one (**37**). It was anticipated that the greater electrophilicity of the iminium would have two benefits; it would circumvent the regioselectivity problems, and it would allow for the use of a larger range of nucleophiles thereby broadening the range of synthetic options available.



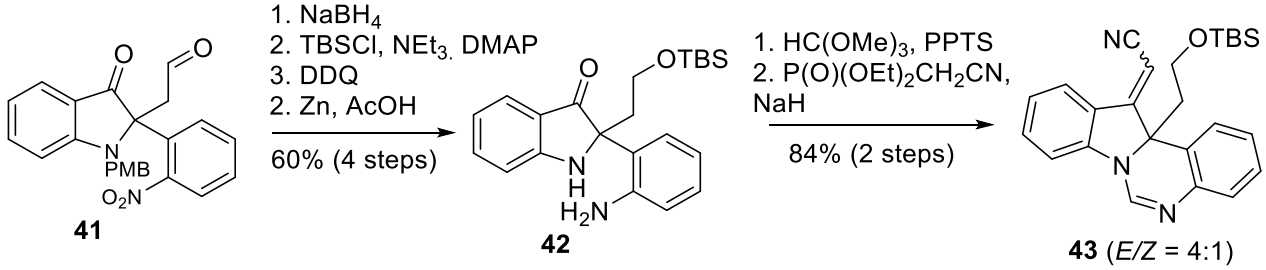
Scheme 1.9: *Kawasaki's Synthetic strategy*

Kawasaki's synthesis of hinckdentine A began at a similar point to the previous two; a 2-arylindole (**40**, *Scheme 1.10*).



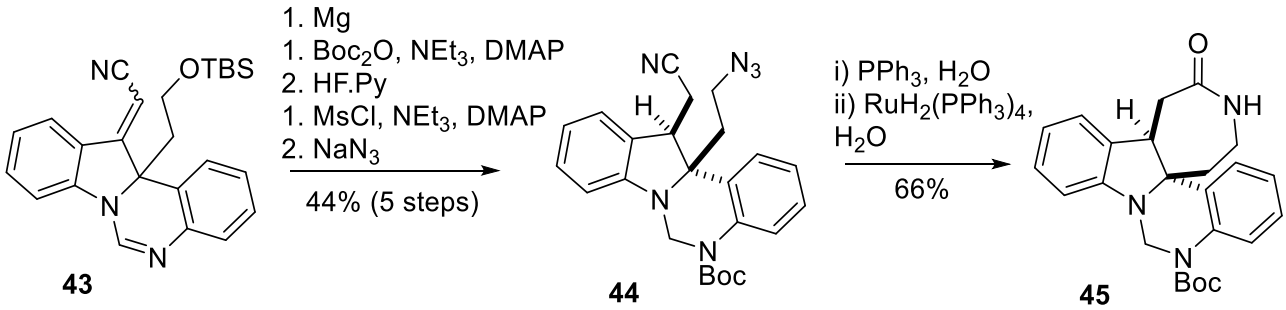
Scheme 1.10: *Synthesis of quaternary stereocentre*

The indole nitrogen was protected with a *p*-methoxybenzyl group then the 3-position was oxidised with *m*-chloroperbenzoic acid to the 2-hydroxyindol-3-one **37**. At this point the key dehydration/nucleophilic addition sequence was performed using the silyl enol ether derived from acetaldehyde as the nucleophile. Upon aqueous work up this gave aldehyde **41** in moderate yield. The selectivity for the imine functionality further suggests the Grignard reagent used by McWhorter reacted by a single electron transfer mechanism as the enolates react through the attack of paired electrons and will react with the most electrophilic portion of the molecule. Compound **41** contains the same functionality as compound **30** from the McWhorter's 2003 synthesis (after ozonolysis, see *Scheme 1.7*) highlighting the similarities between these syntheses, however, compound **41** was synthesised in just four steps from commercially available materials compared to ten steps in McWhorter's synthesis.



Scheme 1.11: *Preparation for lactamisation*

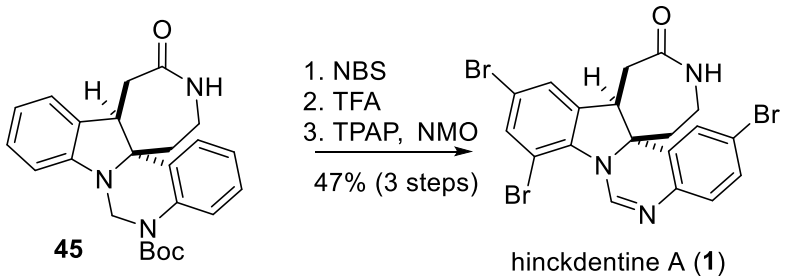
Having prepared **41**, the aldehyde was reduced and protected as a silyl ether, then the *N*-protecting group was removed and the nitro group was reduced to give the aniline **42** (*Scheme 1.11*). Condensation of trimethylorthoformate between the newly exposed amines gave the requisite dihydropyrimidine. Horner-Wadsworth-Emmons olefination gave the tetracyclic intermediate **43** as a four to one mixture of *E* and *Z* isomers (*Scheme 1.11*).



Scheme 1.12: *Synthesis of hinckdentine A skeleton*

Reduction of the olefin gave a separable mixture of *syn*- and *anti*- compounds in a five to one ratio. This reaction also reduced the dihydropyrimidine to a tetrahydropyrimidine and whether by design or fortune, this proved to be vital later in the synthesis. Proceeding with only the major *anti*-isomer (*Scheme 1.12*), the secondary amine was protected as a *tert*-butyl carbamate. The silyl ether was hydrolysed and the resulting alcohol was activated as a mesylate and then substituted with azide (**44**). A one pot Staudinger reduction and ruthenium catalysed lactamisation afforded the ε-lactam (**45**).

At this point in Kawasaki's synthesis, compound **45** closely resembled the intermediate **9** (see *Scheme 1.7*) from McWhorter's synthesis with the only difference being the oxidation state of the pyrimidine and the consequent presence of the *tert*-butylcarbamate protecting group.



Scheme 1.13: *Completion of hinckdentine A*

When Kawasaki attempted bromination with nothing more than *N*-bromosuccinimide in tetrahydrofuran at room temperature, the desired tribrominated compound (**1**) was the exclusive product (*Scheme 1.13*). This success was attributed ostensibly to the presence of the large *tert*-butylcarbamate blocking access to the potential fourth bromination site *ortho* to the carbamate. While this explanation is plausible, the results obtained by Cava[20] and McWhorter[23] suggest that the oxidation state of the pyrimidine ring might also be an contributing factor.

Having successfully brominated compound **45** at the correct positions the *tert*-butylcarbamate was removed with trifluoroacetic acid and the tetrahydropyrimidine was oxidised with TPAP to complete the first total synthesis of hinckdentine A (*Scheme 1.13*).

Kawasaki's work is highly significant in that it is still the only completed total synthesis of hinckdentine A, albeit using a strategy which relies heavily to the previous work of McWhorter. The major achievements were the rapid formation of the 2-hydroxyindolin-3-one intermediate **37** and their method for obtaining the correct bromination pattern of hinckdentine A. The drawbacks of this approach are the long synthetic sequence and the poor selectivity observed for the lactam formation. This synthesis gave hinckdentine A in 19 steps from commercially available materials in 3% overall yield.

1.2.4 Other approaches to hinckdentine A

The synthesis of polycyclic aromatic heterocycles can be achieved via a multitude of methodologies and as such there have been many incidental and apparently unintentional syntheses of large fragments of hinckdentine. These include at least five methods to synthesise the ABCD indolo[1,2-*c*]quinazoline ring system. This ring system has been constructed by acid catalysed condensation,[24] palladium-catalyzed cyclocarbonylation[25] condensation of 2-(2-aminophenyl)indoles with 2-cyanobenzothiazoles[26] Ullmann reactions[27] and zinc bromide catalysed domino hydroamination-cyclization.[28] Most of these methods require many steps to prepare unusual, pre-organised starting materials and use expensive transition metal catalysts. Therefore they confer no particular advantage over the two robust steps reported by Cava.

There are methods available to synthesise 2-(2-aminophenyl)indoles with the bromine atoms in the correct positions for hinckdentine A via alkaline metal base catalysed alkyne cyclisations.[29] However, with the ubiquity of palladium catalysed cross coupling it would seem unwise to install so many aryl-bromides so early in a synthesis.

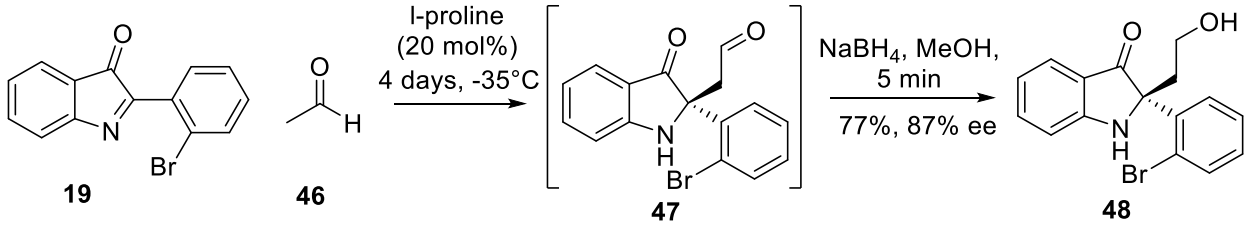
The only other published synthesis which constructs a system resembling hinckdentine A is the synthesis of 8,9-didehydroazepino[4,5-*b*]indolines by copper-catalysed ring expansion. However,

this is incidental, poor yielding and specific to substrates which could not be efficiently elaborated to hinckdentine A.[30]

1.2.5 Asymmetric approaches to hinckdentine A

There are several ways to create stereogenic centres at the 2-position of indoles. A popular example is the aza-Henry reaction.[31] Most of these are not designed with the synthesis of hinckdentine A in mind and consequently it is difficult to see how applicable they would be to a synthesis of this natural product.

At the commencement of this project there were no asymmetric strategies disclosed with hinckdentine A specifically in mind. Recently, an asymmetric addition into 3*H*-indol-3-ones has been published by Rueping and co-workers (*Scheme 1.14*).[32] The proline catalysed Mannich reaction between 2-(2-bromophenyl)-3*H*-indol-3-one (**19**) and acetaldehyde (**46**) gave compound **48** in good yield and enantiomeric excess after a long reaction time at low temperature.



Scheme 1.14: *Possible asymmetric route to hinckdentine A*

This asymmetric reaction is an amalgamation of the strategies used previously. Rueping utilised the electrophile from McWhorter's synthesis (**19**, see *Scheme 1.5*) and a similar nucleophile to Kawasaki's synthesis (see *Scheme 1.10*). Although no further studies toward the synthesis of hinckdentine A have yet been disclosed by Rueping, the authors have stated that this is their purpose. The highly specific reaction conditions required to find an acceptable balance between enantiomeric excess and yield suggest this reaction will be difficult to perform on a scale appropriate for a multi-step synthesis and the asymmetric synthesis of hinckdentine A remains a challenge.

1.2.6 Summary of previous approaches

Three serious attempts at the synthesis of hinckdentine A have been published along with one asymmetric approach to a key intermediate. The first attempt, that of Cava in 1994, appears to face insurmountable reactivity problems and subsequent syntheses have adopted alternate reactions. The

three ensuing reports all utilise an almost identical strategy; the addition of a two or three carbon nucleophile into a 3*H*-indol-3-one (*Figure 1.7*).

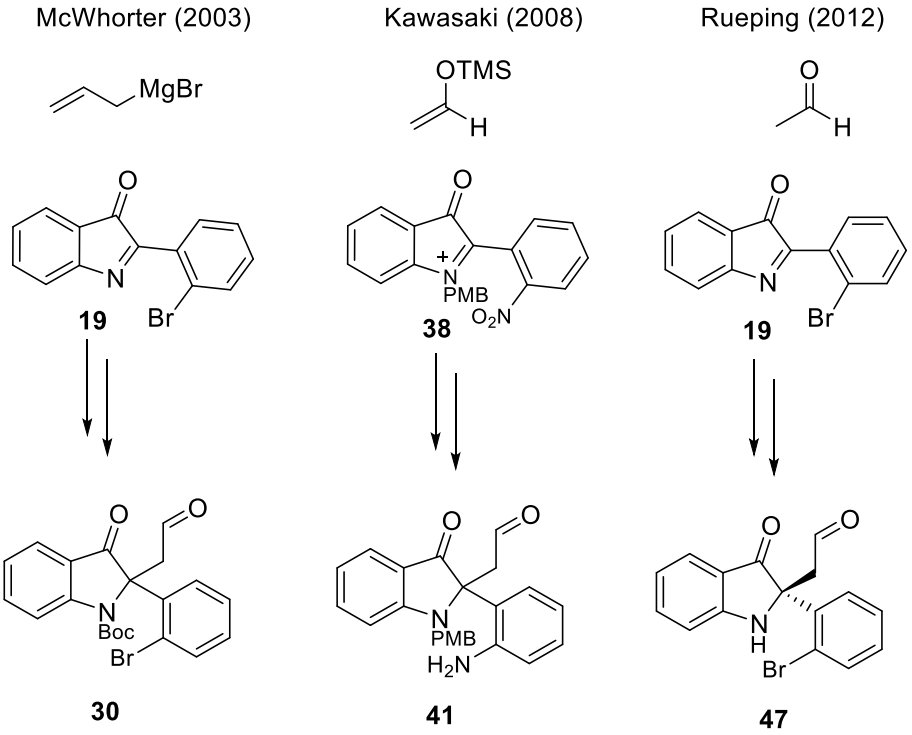


Figure 1.7: *Comparison of published approaches*

These three approaches begin with the synthesis of a 2-arylindole as the first step, as such three out of the five rings of the hinckdentine A architecture are present from the outset, and all the subsequent reactions are employed to construct two heterocycles. Given the ease with which the dihydropyrimidine is formed through condensation, it is reasonable to say that most of the steps are focused on making the 7-membered lactam.

Efforts towards the total synthesis of hinckdentine A have been suffering from a lack of original chemistry. We felt that the prospects of an efficient synthesis being performed could be improved by using neglected reactions and functional groups.

By using underutilised chemistry we can not only uncover novel and efficient route to an interesting molecular architecture, we can also gain a deeper understanding of potentially advantageous transformations.

1.3 Retrosynthesis of hinckdentine A

Although hinckdentine A is likely to be a medicinally interesting compound, obtaining the final compound is not the only value to be derived from its synthesis. If we simply wished to construct this compound in its optically active form, we could modify the existing approaches of Kawasaki and Rueping.

The real value of performing a total synthesis is to be found in understanding new chemistry and developing new reactions. As such, we intend to construct hinckdentine A using an entirely new synthetic route.

When designing a chemical synthesis there are an almost infinite number of synthetic pathways available and a near equal number of individual reactions to choose from. Illustrating this wealth of choices are textbooks wholly devoted to named reactions.[33] Despite the great diversity of synthetic sequences available, most syntheses exploit the same subset of reactions and functional groups; for example the Swern oxidation, silyl ether protecting groups and the Wittig reaction are ubiquitous. The ubiquity of a small number of chemical transformations is particularly the case for syntheses by chemists not specialising in synthesis. By mechanically choosing the same disconnections and transformations chemists are missing the opportunity to perform more efficient, stimulating and innovative syntheses.

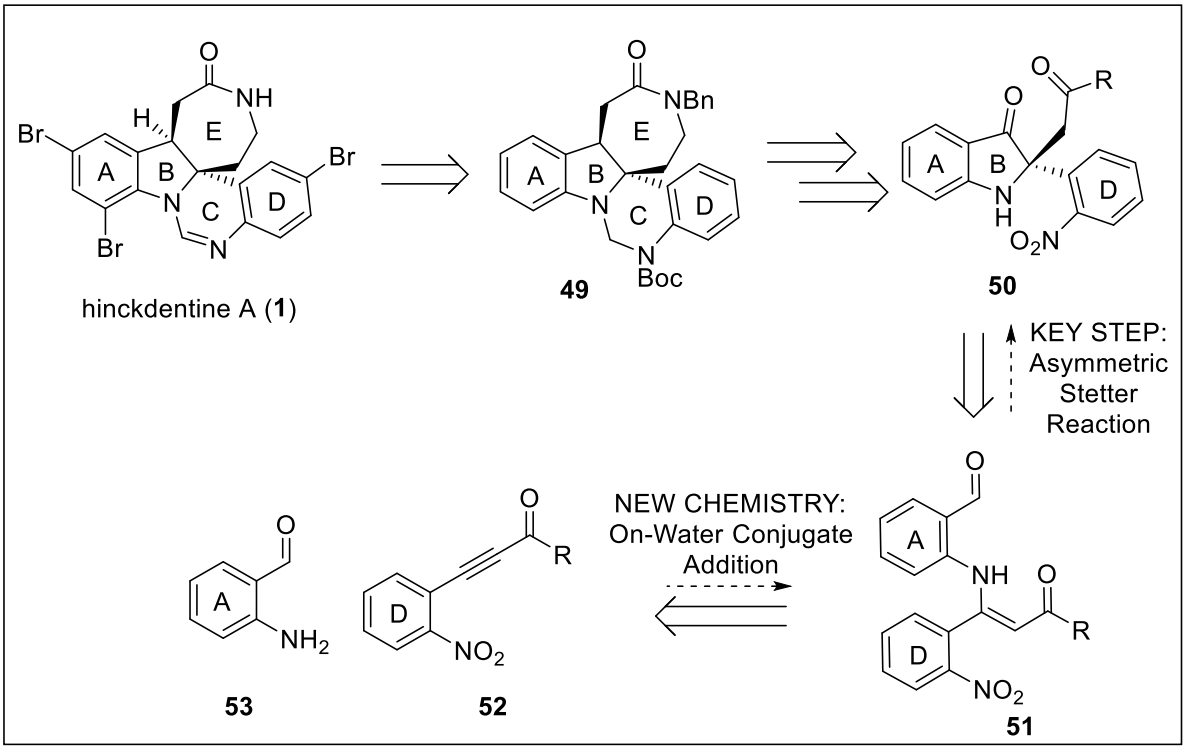
The majority of the reactions which are pervasive in synthesis have become so not because they are necessarily the optimal reactions but because of their perceived generality and reproducibility - a reputation reinforced by their continual use. The prevalence of certain reactions leaves other, possibly equally advantageous reactions, neglected, poorly understood and generally underutilised.

There are many reactions and functional groups which are overlooked as they have yet to be be thoroughly studied. Consequently chemists are unaware of their benefits, are unsure when they are applicable, and are uncertain of their limitations. Chemists are therefore justifiably hesitant in their use. Ideally these under-utilised reactions would be developed to a point where they can be widely applied by novice organic chemists.

This thesis will focus on furthering the understanding, scope and application of some under-utilised reactions and functional groups. We will concentrate on three under-utilised areas of chemistry; on-water catalysis, *N*-acylpyrroles and the Stetter reaction. We will do this by performing individual studies then applying the aforementioned reactions to the total synthesis of hinckdentine A. Total synthesis is an ideal trial for the scope and limitations of a reaction or functional group due to the stringencies of molecular design and measurable markers of success.

A retrosynthetic analysis of hinckdentine A is shown in *scheme 1.15*. A more detailed synthetic plan will be described in chapter 6. The synthetic strategy we have chosen involved a reaction which was unknown at the outset and another which was severely limited.

The synthesis will begin with an "on water" conjugate addition of an aniline (**53**) to a propiolate Michael acceptor (**52**). The product of the conjugate addition (**51**) will be suitably functionalised to undergo an asymmetric Stetter reaction to give compound **50**. Installation of a 2-carbon unit and condensation of the pyrimidine will be possible by a number of routes and lead to compound **49** which will be selectively brominated to give hinckdentine A (**1**). This route will enable efficient entry to the hinckdentine A scaffold as a single enantiomer.



***Scheme 1.15**: Retrosynthesis of hinckdentine A*

At the outset of this project the key transformations proposed in *Scheme 1.15* were unknown in the literature. To complete our innovative synthesis of hinckdentine A these reactions will have to be developed.

We will begin our exploration of underutilised reactions with the field of on-water catalysis, which is a relatively new, unexplored and poorly understood mode of catalysis. By determining the mechanism by which this mode of catalysis operates we hope to develop it into a worthwhile synthetic technique.

We will then move on to a study of *N*-acylpyrroles, which are a functional group possessing great potential but that have been neglected due to uncertainty about their use. The study of *N*-acylpyrroles will be combined with our research into on-water catalysis through the investigation of on-water catalysed conjugate additions of anilines onto α,β-unsaturated ketones, esters and *N*-acylpyrroles.

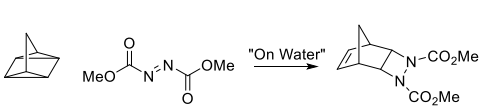
The use of *N*-acylpyrroles will then facilitate the Stetter reaction and will help overcome several of the deficiencies associated with this reaction.

Finally, exemplifying the utility of these reactions, this thesis will culminate with the use of these transformations as key steps toward the total synthesis of the natural product hinckdentine A (*Scheme 1.15*). By performing these studies we aim to assist chemists in making better use of the chemical tools which are already available.

The first challenge associated with this work was that on-water catalysis was a poorly understood phenomenon with no consistent theory to describe the mechanism of action. As such, before we could begin the total synthesis we needed to develop a predictive model for this mode of catalysis.

Chapter 2

Introduction to On-Water Catalysis



2.1 Organic synthesis in water

Water is often considered to be an ideal solvent for pragmatic reasons but also because of its unique physical properties. The notable properties of water include natural abundance, low cost, non-toxicity, non-flammability, wide liquid range, low vapour pressure, high heat capacity, high dielectric constant and an extensive hydrogen bonding network.

Water is often overlooked as a viable solvent for organic transformations because it does not substantially dissolve non-polar organic molecules and dissolution is generally considered a prerequisite for controlled reactivity. Furthermore, most organic reactions are habitually performed under anhydrous conditions as water is assumed to be universally detrimental to organic transformations. Surprise is often noted when water is found to be beneficial for a given reaction. Nonetheless, the field of aqueous organic chemistry is flourishing. The lack of dissolution of organic molecules in water has been circumvented by performing reactions at high dilution or through the addition of co-solvents, solubilising groups and surfactants,[34] even though these additives diminish many of the advantages originally associated with water. As such there is great interest in the exclusive use of water in organic chemistry.

Despite this recent interest, water remains an underutilised and under-appreciated solvent among synthetic organic chemists.

2.2 On-water catalysis

"On water" catalysis is the term used to describe the rate enhancement observed in reactions between hydrophobic organic molecules when they are reacted as a suspension in water, without any other catalyst.[35] The suspension is usually obtained with vigorous stirring. This phenomenon is termed "*on* water" catalysis to recognise that the rate enhancement is occurring *on* the surface of the water; not *in* dilute aqueous solution or because of water dissolved *in* the organic phase.

Sharpless and co-workers first introduced the term "on water" catalysis in 2005 to describe a range of reactions which were accelerated by vigorous stirring with water.[35b] This unexpected and counter-intuitive result is not only of scientific interest but could reduce the use of heavy metal catalysts and toxic and flammable organic solvents. It is also operationally simple, can help dissipate heat generated in exothermic reactions, and finally, the products can often easily be removed by separation.

2.2.1 History of on-water catalysis

Although Sharpless coined the term "on-water catalysis" within the last decade, reactions in this class have been known for at least 70 years and many of the examples in Sharpless' report were foreshadowed by Engberts in 2003.[36] The first reports of reactions which were accelerated when performed as oil-in-water emulsions were a series of Diels-Alder reactions which were disclosed in patents in the 1940's.[37] Aqueous acceleration of Diels-Alder reactions became a subject of intense interest in the scientific community in 1980 when Breslow published a report of "hydrophobic acceleration".[38] Grieco later also noted "micellar catalysis" which enhanced the rate of Diels-Alder reactions and even noted "vigorous stirring" was necessary for certain examples.[39]

Reports of other reactions such as 1,3-dipolar cycloadditions[40] and the Claisen rearrangement[41] which were accelerated by stirring with water occurred sporadically throughout the twentieth century. It was not until Sharpless unified these seemingly disparate reactions (and other examples) under the banner "on-water catalysis", that their similarities were recognised. This seminal report has precipitated the establishment of a burgeoning field of chemistry[42] and has become the focus of many researchers around the world. In recognition of the importance of this work, Sharpless' original report has attracted more than 600 citations, at an increasing rate, in the nine years since it was first published (*Figure 2.1*).

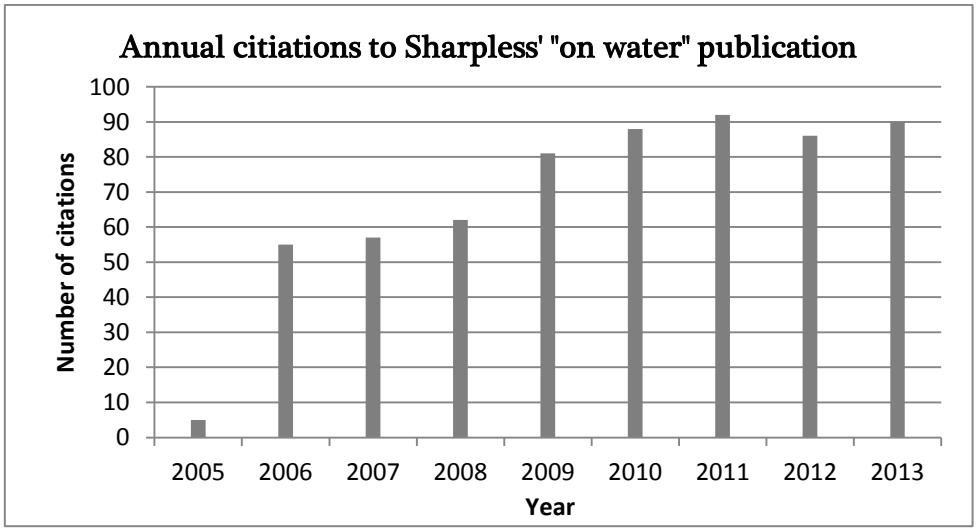


Figure 2.1: *Number of citations per year*

The acceleration of organic reactions by water was first studied in depth by Breslow in the early 1980's. The studies of Breslow and others into aqueous rate acceleration are important to the field of on-water catalysis as these explanations have been invoked to explain some of the features of on-water catalysis.

2.2.2 The hydrophobic effect

Breslow studied the acceleration of some Diels-Alder reactions in dilute aqueous solution[38, 43] and attributed the acceleration shown to the hydrophobic effect (*Figure 2.2*).[44] Breslow suggested the insoluble reactants aggregated to reduce the area of hydrocarbon-water interface thus bringing the reactants into closer proximity. The aggregation also reduces the number of water molecules which must be ordered around the non-polar molecules resulting in an entropic gain.

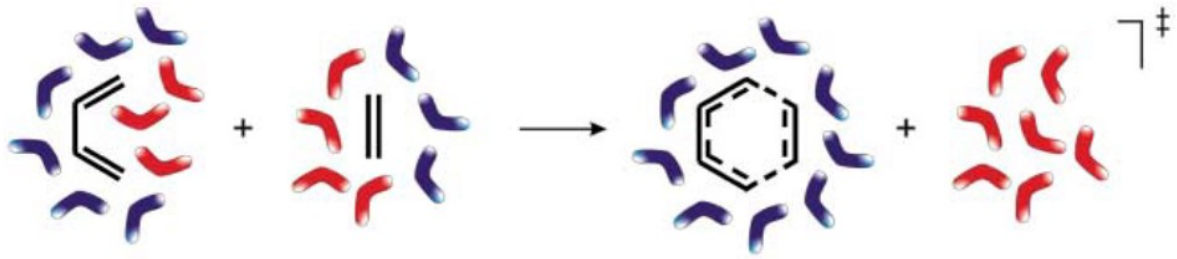
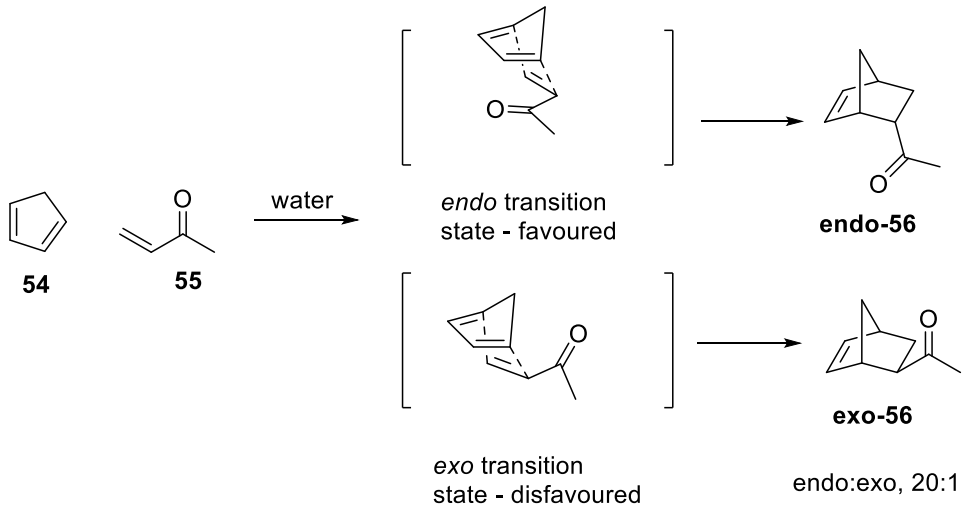


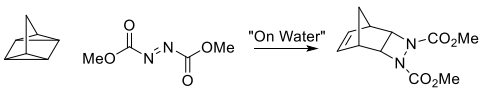
Figure 2.2: *Hydrophobic effect in the Diels-Alder reaction (the red water molecules are not ordered after the reaction)* [36]

It is well known Diels-Alder reactions are most often *endo* selective due to secondary orbital interactions. The high *endo* selectivity is observed despite the *endo* transition state being more sterically hindered (*Scheme 2.1*).



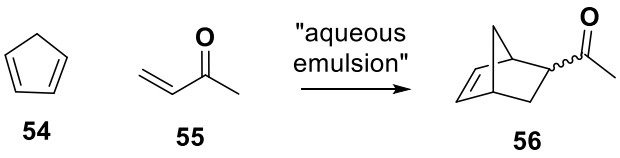
Scheme 2.1: *Proposed hydrophobic effect to accelerate Diels-Alder reactions*

Breslow found the Diels-Alder reactions between cyclopentadiene (**54**) and methyl vinyl ketone (**55**) displayed exceptionally high *endo* selectivity (>20:1) when performed in water.[43] This observation was justified with the suggestion that hydrophobic packing reduces the energy of the *endo* transition state which exposes less hydrophobic surface to the water (*Scheme 2.1*). Breslow



hypothesised the efficient packing driven by the hydrophobic effect, in conjunction with stabilising interactions with water to polar groups were responsible for the observed acceleration of Diels-Alder reactions in aqueous solution. It is important to note that these reactions occurred *in* dilute aqueous solution rather than on-water.

Amongst these accounts of reactions performed in water were isolated examples of Diels-Alder reactions which Breslow noted were also accelerated when performed at concentrations high enough to form two phases (*Scheme 2.2*). Describing the reaction depicted in *Scheme 2.2* Breslow states: *"An undiluted equimolar mixture of cyclopentadiene and butenone at 20°C is 50% reacted in ca. 35-40 minutes, while in a well stirred aqueous emulsion […] the 50% point is reached in 10-15 minutes."*, that is, the reaction was faster "on water" than neat.

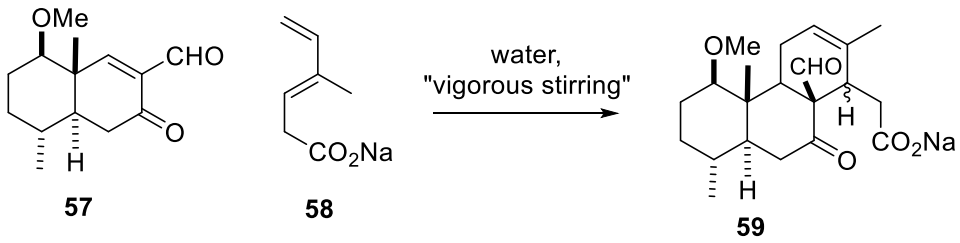


Neat: 35 minutes (50% conversion)
Aqueous emulsion: 10 minutes (50% conversion)

Scheme 2.2: *Possible on-water reaction reported by Breslow*

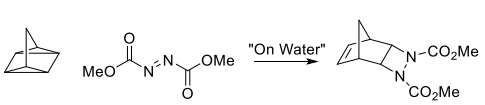
Breslow even anticipated the rate acceleration may not be entirely due to the reaction occurring in solution by stating: *"Even with a considerable layer of "neat" diene-dienophile solution the selectivities suggest that much of the reaction occurs […] at the water phase".*

These isolated results of Breslow were paralleled by the findings of Grieco who was also studying Diels-Alder reactions in solution and noted some reactions were also accelerated with water insoluble reagents (*Scheme 2.3*) and went so far to suggest: *"Due to the heterogeneous nature of this system in water, vigorous stirring is essential".* [39]



Scheme 2.3: *Possible on-water reaction reported by Grieco*[39]

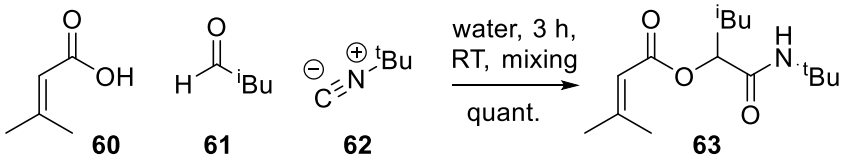
At this time the field on-water catalysis was still 25 years into the future, nonetheless, the hydrophobic effect remains an important consideration and the anomalous reactions found during the course of these investigations are the progenitors of the on-water catalysis noted by Sharpless.



Aside from the hydrophobic effect, other properties of water have been invoked to explain the acceleration of organic reactions in water.

2.2.3 Compression of transition state

Pirrung and Sarma have proposed a theory for the acceleration observed in the multi-component Ugi and Passerini reactions when they are performed as heterogeneous organic/water mixtures (*Scheme 2.4*).[45] The Passerini reaction depicted in *Scheme 2.4* was found to be accelerated when performed using water as the solvent, ostensibly by compression of the transition state of the reaction occurring in dilute solution.



Scheme 2.4: *An example of a Passerini reaction accelerated by water*

Pirrung and Sarma sought to exploit the high cohesive energy density of water to cause acceleration in reactions possessing a negative volume of activation. The specific reactions they identified were the Ugi and Passerini reactions (*Scheme 2.4*).

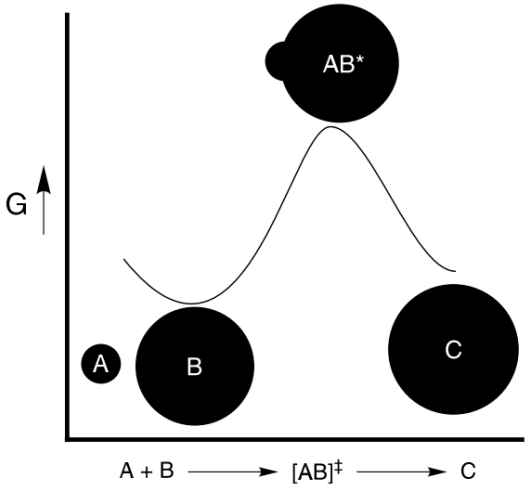
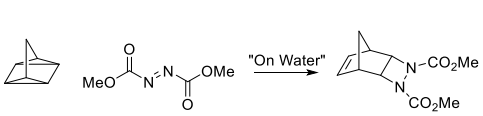


Figure 2.3: *Negative volume of activation: the volume of the transition state AB* is less than the sum of the volumes of starting materials A and B.*[45]

Reactions with a negative volume of activation are smaller in the transition state than in the starting materials, thus a significant part of the activation energy is the entropic cost of associating



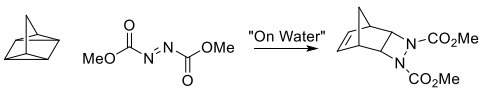
both reactants in a small space (*Figure 2.3*). Reactions with a negative volume of activation are frequently accelerated through exposure to high pressures. Pirrung and Sarma hypothesised the same result could be achieved by taking advantage of the physical properties of water rather than utilising a pressure vessel. Pirrung and Sarma propose the high pressure from the cohesion of water can provide the energy associated with the volume of activation.

Cohesive energy density (c.e.d.) is the energy required to remove a molecule from the bulk and replace it with a void. In the case of an aqueous emulsion, this means the water surface around droplets of the insoluble oil is applying pressure to balance the energy lost by creating the "hole" filled by the oil droplet. As such, the oil droplets are at a higher pressure than the surrounding medium. Pirrung and Sarma note that the cohesive energy density of water corresponds to a pressure of approximately 20 kbar on dissolved non-polar reactants. Cohesive energy density is usually expressed using the non-standard unit of calories per cubic centimetre (cal/cm^3). The cohesive energy density of water (550 cal/cm^3) is much higher than other solvents (for example acetone; 93 cal/cm^3, n-hexane; 53 cal/cm^3) due to the extensive hydrogen bond network.

The explanation for acceleration provided by Pirrung and Sarma is complicated in that both the Ugi and Passerini reactions are multi-component reactions for which we possess an incomplete understanding of the mechanism and no knowledge of the rate determining step. This theory does not explain why this phenomenon is specific to water and there is not a continuum of rate enhancement across all solvents, especially those with cohesive energy density closer to water, such as glycerol (c.e.d. = 313 cal/cm^3).

Pirrung and Sarma indeed found an acceleration of the Ugi and Passerini reactions when they were performed using water as a solvent but several factors suggest the acceleration was occurring in the organic phase rather than in dilute solution. Firstly, the authors note all of the reactions were all heterogeneous (*"The reactants […] are only marginally soluble in water, and the products are widely insoluble")* and the results were dependant on the degree of mixing obtained (*"The influence of mixing ferocity and method on reactions of organic compounds in water are subjects of our ongoing investigations")*. This strongly indicates these reactions are occurring at the interface or by a phase transfer mechanism. Pirrung and Sarma also noted adding a small amount of organic solvent (chloroform or toluene) assisted the reaction in the cases where one reactant was a solid. If the reaction were occurring in water as the authors suggest the identity of the components of the organic phase should be irrelevant. These results suggest the reaction was in fact occurring in the organic droplets and that it may be another forerunner to on-water catalysis.

This study of the Ugi and Passerini reactions was published just months after Sharpless' 2005 report so the c.e.d. theory was not intended to be a complete explanation for on-water catalysis.

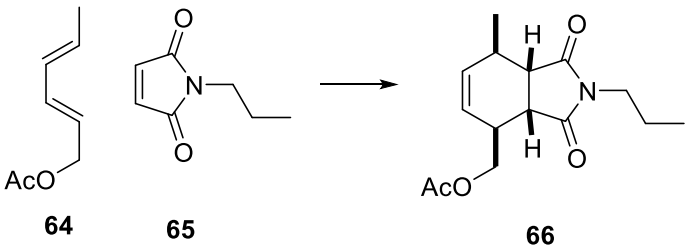


The investigations of Breslow, Grieco, Pirrung and Sarma were not studies into on-water catalysis but were studies into related fields; these studies do however contain examples of reactions which appear to be catalysed on-water. To develop a more complete understanding of on-water catalysis one must examine the reactions which are known to be catalysed on-water.

2.3 On-water catalysed reactions

A wide range of seemingly dissimilar reactions have been found to be subject to on-water catalysis. There are examples of unimolecular and bimolecular reactions catalysed on-water as well as rearrangements, cycloadditions and displacements. Some representative reactions are discussed below (For a comprehensive account of all the known on-water reactions see the review by Fokin[42]).

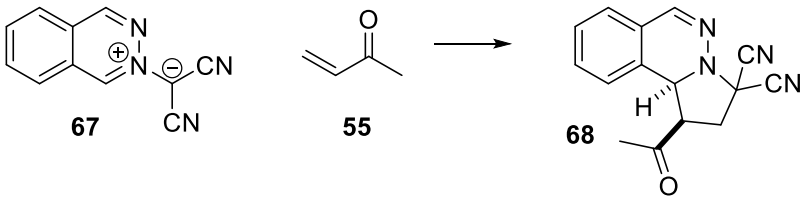
[4 + 2] Cycloadditions – The Diels-Alder reaction



Scheme 2.5: *An on-water Diels-Alder reaction reported by Sharpless*[35b]

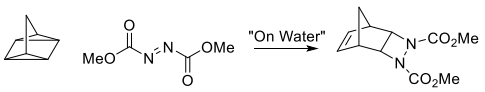
The Diels-Alder reaction was the first reaction known to be substantially accelerated as an aqueous emulsion. Consequently there are numerous studies examining the role of water in the acceleration.[36, 46] Performing the Diels-Alder reaction "on-water" produces substantially increased *endo/exo* ratios. As mentioned previously, Breslow also noted the Diels-Alder reaction is accelerated in dilute aqueous solution.[44]

Dipolar cycloadditions[40, 47]



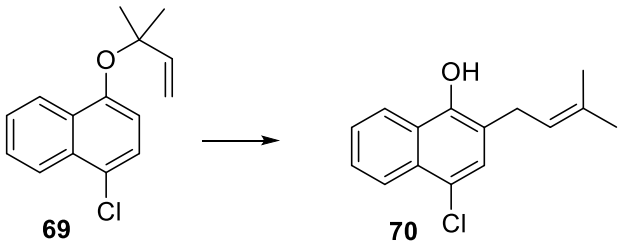
Scheme 2.6: *An aqueous dipolar cycloaddition performed by Butler*[47]

Dipolar cycloadditions which do not occur in organic solvents have been found to proceed quickly in the presence of water.[47] This has been found to be true for a large range of dipoles and



dipolarophiles.[42] It is also known that water facilitates some Huisgen azide/alkyne 1,3-dipolar cycloadditions.[48]

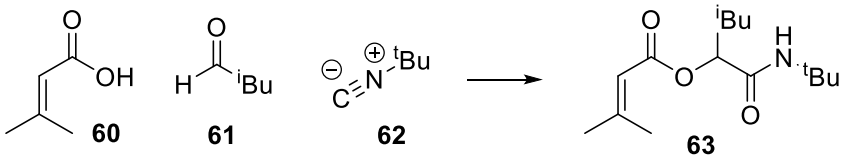
Claisen rearrangement[35b, 41, 49]



Scheme 2.7: *An on-water Claisen rearrangement reported by Sharpless*[35b]

The acceleration of Claisen reaction with water was first noted by Grieco[41] but several further examples from this class were identified by Sharpless, and the catalysis has since been found to be general.[50] Nicolaou has used an aqueous Claisen rearrangement as a key step in his biomimetic synthesis of the natural product gambogin.[49]

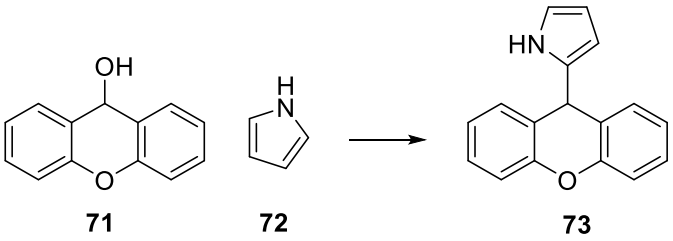
Passerini and Ugi reactions[45]



Scheme 2.8: *Passerini reaction by Pirrung and Sarma*[45]

As discussed above (see *Section 2.2.3*) Pirrung and Sarma have proposed a theory to explain the mechanism of aqueous acceleration of organic reactions. They used their theory to predict that Passerini and Ugi reactions would be subject to catalysis by water.

Nucleophilic substitution[51]



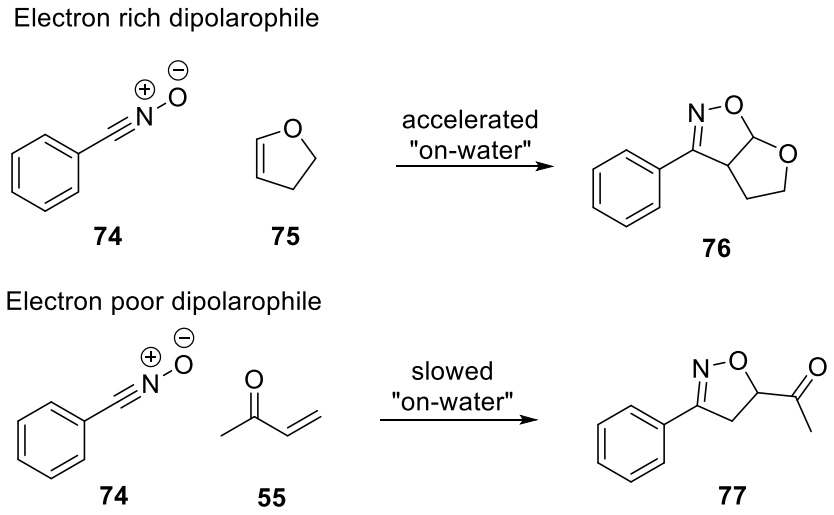
Scheme 2.9: *A nucleophilic substitution reaction reported by Cozzi*[51]

The nucleophilic substitution reactions between pyrroles and 9*H*-xanthen-9-ols reported by Cozzi are interesting in that they are a dehydration reaction, which would generally be performed under anhydrous conditions. This example highlights the counterintuitive reactions which water can facilitate.

Among the other reactions which are reported to be catalysed on-water are epoxide opening,[35b] the ene reaction,[35b] activated ester hydrolysis[36] and many transition metal catalysed reactions.[42]

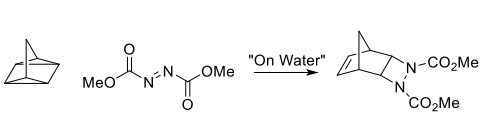
2.4 Reaction slowed on-water

As already stated, many dipolar cycloadditions are amenable to on-water catalysis. An interesting case involving 1,3-dipolar cycloaddition reactions has been noted by Engberts (*Scheme 2.10*).[40]



Scheme 2.10: *An example of a cycloaddition slowed on-water*

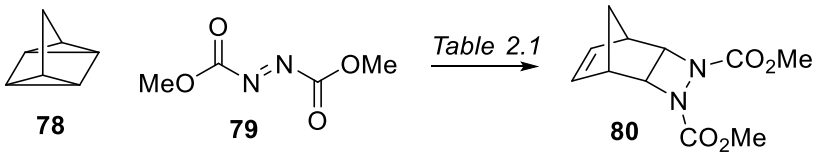
Engberts observed the 1,3-dipolar cycloaddition between benzonitrile oxide (**74**) and electron-rich dipolarophiles (**75**) was accelerated on-water, whereas the rate of the reaction between the same



dipole and electron-poor dipolarophiles (**55**) was retarded (*Scheme 2.10*). We can be certain this is not an esoteric feature of methyl vinyl ketone, as the use of a different dipole in combination with methyl vinyl ketone results in rate acceleration (see *Scheme 2.6*).

2.5 Features of on-water catalysis

The salient features of on-water catalysis are exemplified the [2σ+2σ+2π] cycloaddition between quadricyclane (**78**) and dimethyl azodicarboxylate (**79**) which Sharpless has examined in detail (*Scheme 2.11, Table 2.1*).[35b]

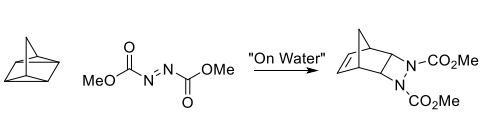


Scheme 2.11: *Cycloaddition between quadricyclane and dimethyl azodicarboxylate*

	Solvent	Concentration (M)	Time to completion
1	Neat	4.53	48 h
2	Toluene	2	>120 h
3	EtOAc	2	>120 h
4	CH_3CN	2	82 h
5	CH_2Cl_2	2	72 h
6	DMSO	2	36 h
7	Methanol	2	18 h
8	**On Water**	**4.53**	**10 min**
9	MeOH/H_2O (1:3, Heterogeneous)	4.53	10 min
10	MeOH/H_2O (1:1, Heterogeneous)	4.53	10 min
11	MeOH/H_2O (3:1, Homogeneous)	2	4 h
12	On C_6F_{14}	4.53	36 h
13	On D_2O	4.53	45 min

Table 2.1: *Feature of on-water catalysis*

It can be observed from *Table 2.1* that the cycloaddition between quadricyclane (**78**) and dimethyl azodicarboxylate (**79**) was slow in non-polar organic solvents and was also slow in the absence



of solvent but displayed a gradual increase in rate in line with the increase in polarity of the solvent in which it was performed (*Table 2.1*, entries 1 – 7). This demonstrates that the reaction proceeds via a polar transition state which can be better stabilised by a polar solvent. A remarkable acceleration was observed when the reactants were stirred as an aqueous emulsion (*Table 2.1*, entry 8), that is, using on-water catalysis. Under the on-water conditions the time to completion dropped dramatically, from 48 hours to ten minutes. As the on-water reaction was much faster than the neat reaction, the acceleration observed was not a result of increased concentration but was due to the presence of the emulsion.

Performing the cycloaddition on-perfluorohexane (both reactants are insoluble in perfluorohexane) did not result in a significant rate enhancement over the neat reaction (*Table 2.1,* entry 12). From this experiment we can see that heterogeneity alone was not the cause of the catalytic activity.

The addition of methanol did not affect the rate enhancement (*Table 2.1*, entries 9 and 10) until enough methanol was added to dissolve the reagents at which point the mixture became homogeneous (*Table 2.1*, entry 11). In the homogenous methanol/water reaction (*Table 2.1,* entry 11) the rate of reaction was consistent with the polarity trend observed for the other solvents.

The final notable result was the deuterium isotope effect; the reaction was significantly slower on-D_2O (*Table 2.1*, entry 13) than on-water. The reduced rate with deuterium oxide suggests an O-H (or O-D) bond is broken during the rate determining step, although it is also possible this kinetic isotope effect is the result of a tunnelling mechanism.

2.6 Mechanism of on-water catalysis

Although on-water catalysis has become a field of intense research, the progression of the field has been hampered by the lack of a definitive theory to describe the mechanism of action. Without a plausible mechanism it is impossible to predict which reactions will be catalysed on-water and the full utility of on-water catalysis cannot be realised. To be a comprehensive theory for on-water catalysis the following four salient features noted by Sharpless need to be accounted for:

1. The need for an interface. On-water reactions are faster than the neat reaction.

2. The need for the interface to be between an organic phase and water. Sharpless showed emulsifying on-perfluorohexane did not significantly affect the rate.

3. The aqueous phase does not have to be pure water. Methanol could be added to the water without affecting the rate until the reaction became homogeneous.

4. The significant kinetic isotope effect. The on-D_2O reaction was slower than the on-water reaction.

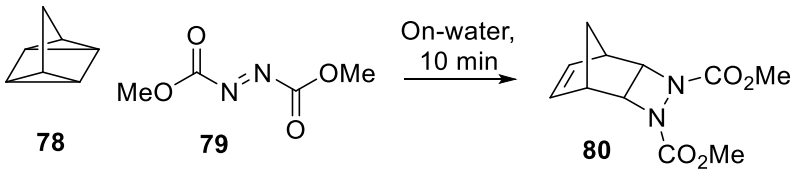
2.6.1 Theories to describe the mechanism of on-water catalysis

At the outset of this project no comprehensive and consistent theory to describe the mechanism of action of this phenomenon had been put forward.

Emulsions of hydrophobic organic molecules in water have been long been studied for their own sake and have high impact journals dedicated to them (e.g. *Langmuir*). As such, there is a wealth of science available to help provide an explanation for on-water catalysis.

At the time we began our work, on-water catalysis was an emerging field and the only theory which was explicitly intended to provide mechanism for on-water was that proposed by Marcus and Jung.

Marcus and Jung,[52] and Domingo[53] have reported computer simulations of the [2σ+2σ+2π] cycloaddition between quadricyclane (**78**) and dimethyl azodicarboxylate (**79**, *Scheme 2.12*). Focus has been on this cycloaddition reaction as it shows the greatest rate enhancement of any known on-water reaction, so the mode of catalysis should be most pronounced for this reaction.



Scheme 2.12: *The [2σ+2σ+2π] cycloaddition modelled by Marcus, Jung and Domingo*

It is generally acknowledged that effects of solvents on reactions are challenging to model with computational methods. By definition, solvents occur in large numbers and the inclusion of large numbers of molecules in a calculation exponentially increases the complexity. Consequently modelling of solvents effects tend to only include a handful of discrete molecules or alternately apply a continuum model, focusing on the specific property of interest. As a result of the unique properties of water it is of particular difficulty to successfully model.

2.6.2 Dangling hydrogen bonds

Marcus and Jung have proposed that the acceleration observed in on-water catalytic reactions is due to a network of "dangling" hydroxyl groups at the oil-water interface which are able to provide hydrogen bonds to components of the non-polar phase (*Figure 2.4*).[52]

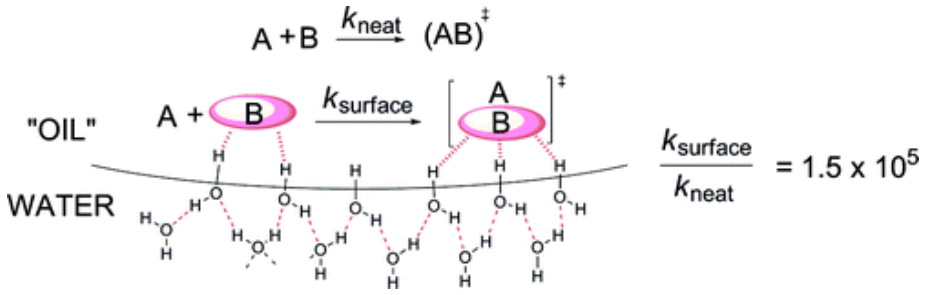


Figure 2.4: *Marcus and Jung's theory of on-water catalysis*

Marcus and Jung performed DFT modelling of the [2σ+2σ+2π] cycloaddition between quadricyclane (**78**) and dimethyl azodicarboxylate (**79**, *Scheme 2.12*) with the UB3LYP/6-31G* level of theory. The modelling used just 3 explicit water molecules to represent the entirety of the aqueous phase.

It is known from multiple experimental measurements that at the interface between pure water and a non-polar material approximately 25% of the water molecules possess "dangling" or "free" OH groups due to the disruption to the normal hydrogen bond network of water.[54] After analysing the results of the DFT modelling, Marcus and Jung determined these "dangling" OH groups from "interfacial water" would hydrogen bond specifically to the nitrogen in the dimethyl azodicarboxylate (**79**) making it resemble the transition state and thereby lowering the activation energy. The magnitude of the acceleration predicted by this model was found to be consistent with that observed by Sharpless.

The theory for the mechanism of on-water catalysis proposed by Marcus and Jung is becoming popular but before it can become accepted the theory must be tested against the features of the cycloaddition which were observed by Sharpless.

1. The need for an interface: The hydrogen bond theory is consistent with this observation. Without the disruption to the hydrogen bond network of water caused by an interface there can be no "dangling" hydrogen bonds.

2. The need for the interface to be with water: The hydrogen bond theory is also consistent with this observation. The existence of "dangling" hydrogen bonds at an interface is a feature specific to water. It has been observed experimentally with vibrational sum frequency spectroscopy that other solvents do not possess free OH groups at the interface with a non-polar material, even those most similar to water such as ethylene glycol[55] and glycerol.[56]

3. Methanol does not affect the rate "until dissolution occurs": The hydrogen bond theory is *not* consistent with this observation. In pure water approximately 25% of interfacial water molecules possess "dangling" or "free" OH groups,[54] however the addition of alcoholic cosolvents suppresses the

free OH groups at the interface. Solvents such as methanol are preferentially adsorbed at water/non-polar interfaces as they are able to act akin to surfactants by aligning perpendicular to the surface with the non-polar alkyl group pointing into the non-polar phase and the polar alcohol projecting into the water (*Figure 2.5*).

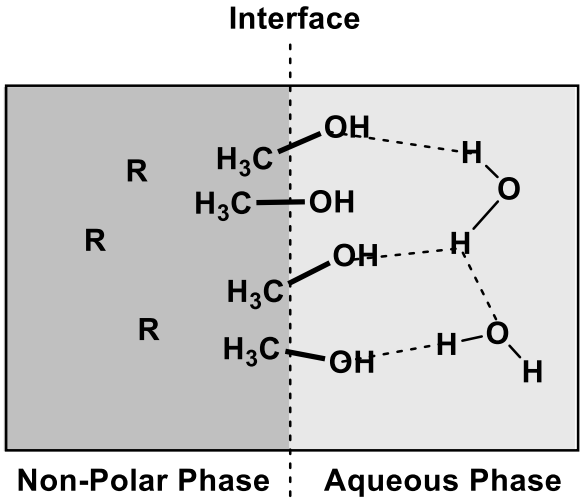


Figure 2.5: *Arrangement of methanol at an interface*

This preferential concentration at the surface minimises the disruption to the hydrogen bond network of water and avoids the energetic cost of having polar groups in contact with the non-polar phase. Long before Marcus and Jung proposed this theory a plethora experimental studies[57] as well as computer studies[57b, 58] determined that the "dangling" OH groups are completely quenched upon the addition of between 11% and 20% methanol in water. The consistency of the results across a range of different measurement techniques (sum-frequency vibrational spectroscopy,[57a-c] infrared spectroscopy,[57d] surface tension measurement, computer simulation[58]) suggests these results are reliable. Sharpless observed no reduction in acceleration when using a 1 : 1 mixture of water and methanol (see *Table 2.1*) which is more than enough methanol to completely rule out the presence of any "dangling" OH groups to perform catalysis.

4. Kinetic isotope effect (KIE): The hydrogen bond theory is *not* consistent with this observation. This theory is unable to account for the comparatively reduced acceleration when reactions are performed "on-deuterium oxide" compared with water. It was acknowledged by Marcus and Jung that their proposal is inconsistent with the observed kinetic isotope effect. They state:

> *"Since the rate acceleration mechanism suggested here does not involve the breaking of any chemical bond of water, explaining such a large deuterium isotope effect remains a challenge"* [52]

In fact, the hydrogen bonding model predicts the inverse kinetic isotope effect to that observed. That is, a faster rate on-D_2O would be expected because deuterium oxide forms stronger

hydrogen bonds than normal water. The stronger deuterium bonds should give the dimethyl azodicarboxylate an even more product-like character, thereby lowering the activation energy even further.

2.6.3 Other problems with the hydrogen bond theory

Marcus and Jung's theory for the mechanism for on-water catalysis is inconsistent with two of the four conditions for on-water catalysis spelled out by Sharpless. This theory also presents several further deficiencies.

Marcus and Jung assert hydrogen bonding from water to the nitrogen of the azodicarboxylate is responsible for the acceleration of the on-water cycloaddition documented by Sharpless (see *Figure 2.4*). Despite this assertion the pictorial representations of the transitions states shown by Marcus does not contain a hydrogen bond between water and nitrogen (*Figure 2.6*).[52]

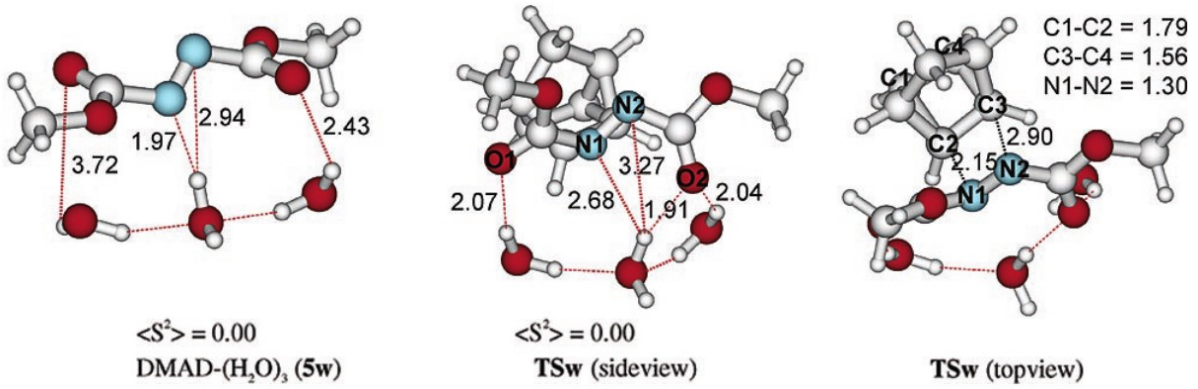
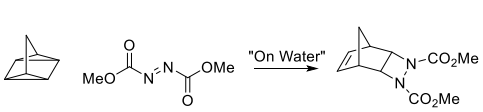


Figure 2.6: *Transition states calculated by Marcus and Jung with 3 explicit water molecules*[52]

From *Figure 2.6* it can be seen in the transition state only one of the three water molecules included in the calculation is close to the nitrogen atoms. *The other two water molecules are hydrogen bonded to the carbonyl units.* The side view of the transition state shows the shortest distance from the hydrogen of the water molecules to the azo-group is 2.68 Å. For a normal hydrogen bond the distance between the hydrogen and heteroatom is usually 1.5 to 2 Å but can be up to 2.2 Å long in weak interactions.[59] Separations greater than this represent purely electrostatic interactions. As such there is at best an extremely weak interaction between the water molecules and the azo-group in the transition state depicted and the only strong interactions are with the carbonyl units. From the transition states published by Marcus there is little evidence of hydrogen bonding to the nitrogen occurring, let alone resulting in catalysis.

Marcus and Jung have also based their entire theory for on-water catalysis on calculations based on qualitative rate data derived from a reaction which is an outlier in the field. They state:



> *"The reduction in reaction time for a case of the most accelerated on-water reaction, the cycloaddition reaction* [between quadricyclane and dimethyl azodicarboxylate]*, by Sharpless and co-workers was 300-fold relative to that of the neat reaction. All other on-water reactions studied by Breslow et al. and Narayan et al. typically showed a 1- to 5-fold decrease in reaction time relative to that of the neat reaction."*[52]

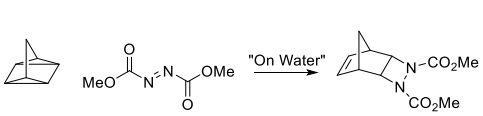
This extraordinary acceleration is specific to dimethyl azodicarboxylate. Sharpless reported that for the same reaction, but with di*ethyl* azodicarboxylate, 69% conversion was reached after 17 hours for the on-water reaction compared to 18% conversion in toluene. The more characteristic 4 fold increase with di*ethyl* azodicarboxylate suggests there are other factors significantly influencing the reaction between quadricyclane and dimethyl azodicarboxylate and that the results may not be generalisable to other, less accelerated reactions. Sharpless also noted the stability of dimethyl azodicarboxylate to water varies greatly between batches, further suggesting other factors may be at play.

Computational studies by Domingo on the same reaction obtained different results to Marcus and Jung and found the quadricyclane nucleophile to be equally important to the acceleration.[53] Logically, this outcome is reasonable. If only the azodicarboxylate was subject to activation the reaction would be insensitive to the nucleophile whereas the extraordinary acceleration is, in fact, specific to quadricyclane. Domingo also found that in the presence of water the reaction occurred through a two-step process which is contrary to Marcus who found it occurred as a single step. These differing results highlight the fact that although this cycloaddition is formally allowed by the Woodward-Hoffman symmetry rules the actual mechanism is not well understood.

Another discrepancy in Marcus' explanation for on-water catalysis was found by Jorgensen when performing Monte Carlo simulations of aqueous Diels-Alder reactions to determine the role of water in these reactions.[60] Jorgensen's findings were directly contrary to those of Marcus. Jorgensen found hydrogen bonding could not be the cause of the on-water effect as the acceleration would be greatest "in water", where even more hydrogen bonds are available. Jorgensen states:

> *"the present results do not support the notion that dangling OH bonds at the water surface lead to enhanced catalysis"*[60]

Marcus' results did not show a difference between the rate of reaction in-water and on-water as he only simulated three explicit water molecules in his modelling and condensed-phase simulations were not reported. That is, Marcus did not perform modelling of the interface of water, he only



modelled generic water, which he asserted was analogous to the interface. Consequently, from Marcus' results it is impossible to determine where the reported effect is occurring.

Breslow and Pirrung also explicitly ruled out hydrogen bonding as the cause of the rate acceleration for "in water" reactions. Breslow states the acceleration of Diels-Alder reactions in water is "*not [...] a simple polarity or hydrogen-bonding effect*"[46c] and Pirrung and Sarma ruled out hydrogen bonding as the cause of acceleration for the Passerini reaction because *"the Passerini reaction… does not proceed at all in methanol".*[45]

A final flaw in the theory proposed by Marcus and Jung is that the hydrogen bonding model offers no explanation as to why some reactions are slowed on-water.[40]

2.6.4 Summary of existing theories

Breslow, as well as Pirrung and Sarma, have proposed theories for reactions which occur in water. These theories are highly specific and cannot be expected to anticipate or explain this new field of on-water catalysis. Regardless of this, these theories have occasionally been invoked as such.

The only theory which is explicitly intended to explain on-water catalysis is that proposed by Marcus and Jung. This theory is clearly deficient.

Until there is a consistent explanation for the mechanism of on-water catalysis it will remain a curiosity and it is impossible to envisage on-water catalysis being used to its full potential without a complete understanding of how it occurs. The potential of on-water catalysis has already been highlighted by the fact that despite not being well understood it has been used in multiple syntheses.[42, 61] If the mechanism of on-water catalysis were understood it could only assist in the widespread adoption of this mode of catalysis.

2.6.5 Requirements for a new theory

It is an obvious prerequisite for any theory for the mechanism of on-water catalysis to explain the four observations made by Sharpless. These are:

1. Need for an interface.
2. Need for the interface to be with water.
3. Observation that the water need not be pure.
4. Kinetic isotope effect.

The need to explain the kinetic isotope effect is the most pressing. None of the current theories have made any attempt to satisfactorily explain this observation. To justify the slower rate on-deuterium oxide the mechanism for on-water catalysis needs to involve breaking a chemical bond.

Further to the observations made by Sharpless two additional features of on-water catalysis need to explained:

5. Reactions slowed on water (see *Section 2.4*).

   The observations by Engberts that some dipolar cycloadditions are slowed under on-water conditions (see *Scheme 2.10*) gives insight into the mechanism of on-water catalysis. Justification of these results will clearly be of critical importance to any proposed theory for on-water catalysis.

6. All on-water reactions are also known to be acid catalysed.

   This last feature of on-water catalysed reactions was unnoticed prior to beginning this work. However, we believed that this observation could be used as a guiding principle to develop a mechanism for on-water catalysis.

With these six points in mind Beattie and McErlean proposed a new mechanism for the action of on-water catalysis.

2.7 On-water catalysis by adsorption of hydroxide at the interface

2.7.1 Introduction

The new theory we proposed for on-water catalysis is that the strong propensity of hydroxide ions to adsorb at oil/water interfaces facilitates the transfer of protons into the organic phase thus resulting in simple Brønsted acid catalysis (*Figure 2.7*).

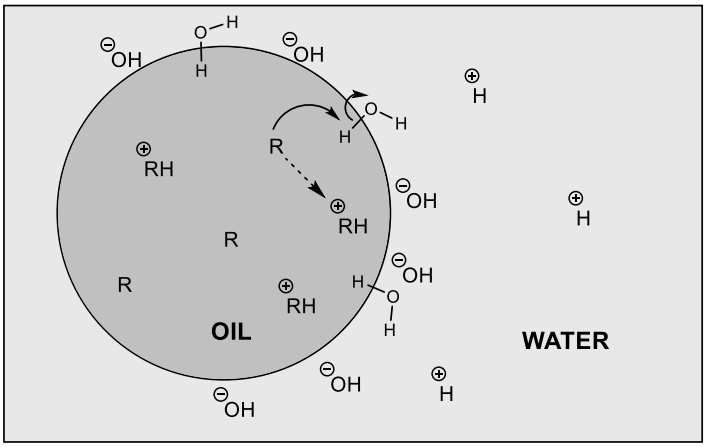


Figure 2.7: *The Beattie and McErlean model for on-water catalysis*

2.7.2 The mechanism of on-water catalysis

Experimental evidence to demonstrate that the non-polar/water interface is negatively charged in neutral water has been available for decades.[62] This is because hydroxide ions resulting from the autolysis of water are preferentially and strongly adsorbed at the interface. Measurements of the ζ potential of a hexadecane emulsion in water have found a surface charge density of -5 to -7 μC cm^{-2} which corresponds to one hydroxide ion for every 3 nm^2 of the interface.[62] Beattie was able to determine this surface charge corresponds to an isoelectric point of pH 3 to 4.[63]

The cause of this charge accumulation has been contentious but the most accepted explanation invokes the high entropic cost of solvating a hydroxide ion. The dipoles around hydroxide ion are highly ordered, (*Figure 2.8*) so there is a significant entropic cost to solvating it.[64] By placing the hydroxide near the interface, some of the region which would ordinarily be ordered is pushed into the non-polar phase. The non-polar material will by definition have a low dielectric constant, so will not become organised in response to the proximity of the anion. This reduces the number of dipoles which are ordered around the hydroxide, so there is a significant energetic driving force for placing hydroxide ions at the interface.

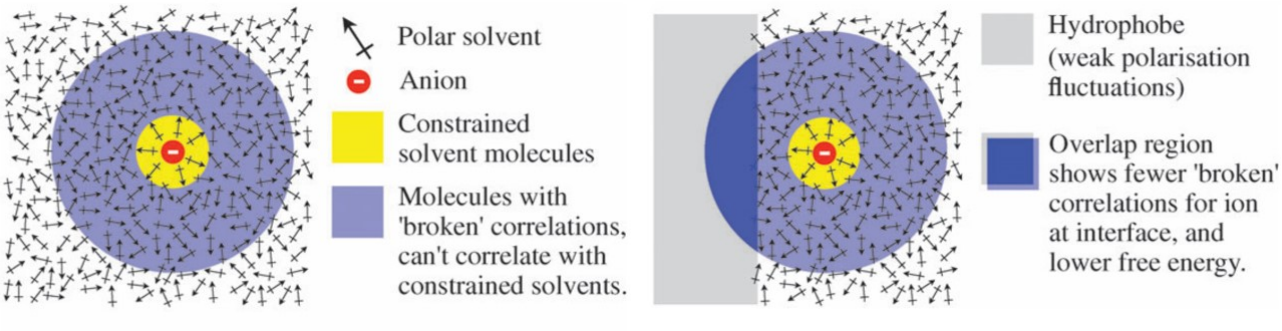


Figure 2.8: *Reason that hydroxide is stabilised at the surface*[64]

The strong adsorption of hydroxide ions at water/non-polar interfaces is a feature specific to hydroxide amongst the anions. This specificity is due to the precise size of the hydration sphere around the hydroxide ion which allows the ion to approach the surface without coming into contact with the non-polar phase.

While initially counter intuitive that the strong adsorption of hydroxide ions at the interface causes acid catalysis, the rationalization becomes clear when considered logically (*Figure 2.9*).

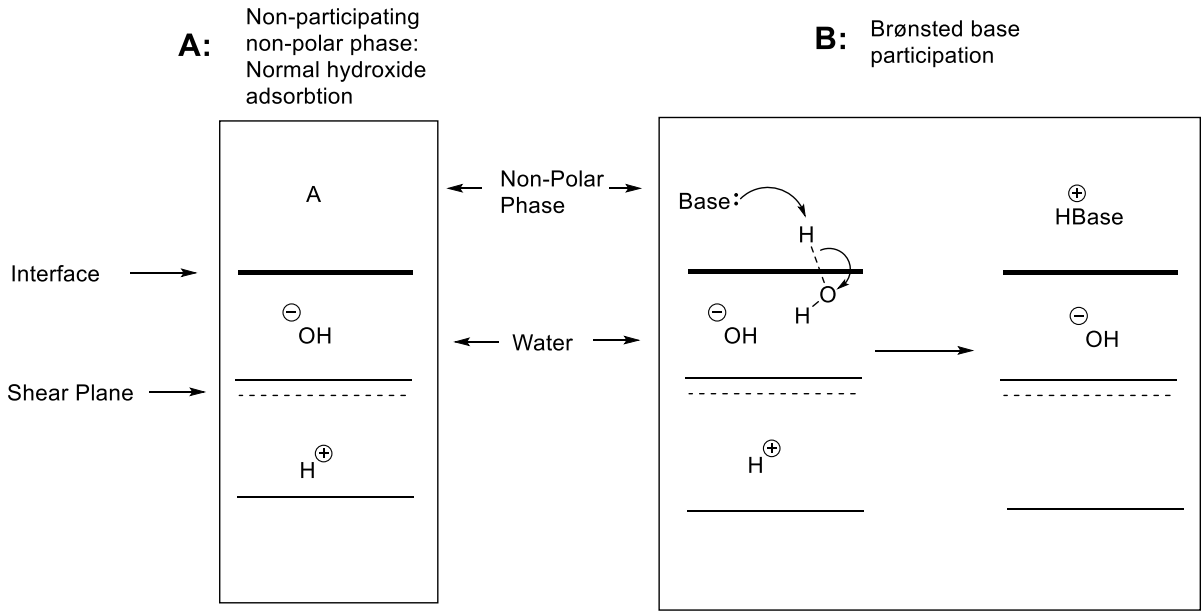


Figure 2.9: *Interfacial water molecules become acidic*

The hydroxide ions are highly stabilised in their position near the interface, therefore are largely immobile and unable to participate in any reaction. In the absence of any participating groups in the non-polar phase the proton counter ion is present in the double layer (*Figure 2.9*, Case A).

In the presence of a Brønsted base in the organic phase the stabilisation of hydroxide at the interface manifests itself as an increase in the acidity of the interfacial water molecules (to a pK_a of 4 to 5[65]) by making hydroxide a good leaving group (*Figure 2.9*, Case B).

Having satisfactorily explained how acid can be generated as a result for hydroxide adsorption in neutral water, it is readily apparent how this can result in acid catalysis in the organic phase (*Figure 2.10*). A suitable Brønsted base can be protonated by the interfacial water and will be activated toward reaction. Consequently, we have proposed that simple acid catalysis could explain the observed phenomena.

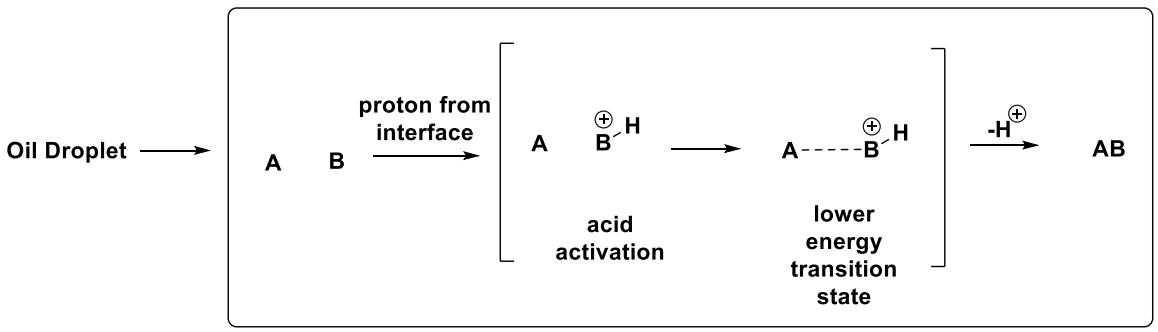
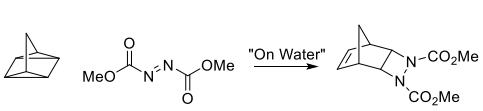


Figure 2.10: *Mechanism of acid catalysis during on-water catalysis*



In essence, this mechanism describes a means of stabilisation and immobilisation of hydroxide ions at the interface which renders interfacial water molecules acidic and able to participate in reactions. This theory also reconciles the ostensibly conflicting facts in the literature that the surface of water is negatively charged[63, 66] (suggesting adsorption of hydroxide) but acidic[65, 67] (which would ordinarily suggest adsorption of hydronium).

2.7.3 Consistency of the acid-catalysis theory with existing observations

This is a simple and general theory to explain on-water catalysis but to test the validity of this theory we need to compare it to the six points previously discussed.

1. The need for an interface: The acid catalysis theory is consistent with this observation. Hydroxide is concentrated and stabilised at the oil/water interface.

2. The need for the interface to be with water: The acid catalysis theory is consistent with this observation. The adsorbed hydroxide is generated from the deprotonation of water and is stabilised by the unique properties of water. Hydroxide has unique mobility and hydration properties in water, so cannot be replaced by other anions.

3. Methanol does not affect the rate "until dissolution occurs": The acid catalysis theory is consistent with this observation. Addition of up to 50% ethanol or methanol does not significantly change the surface properties or surface charge of water.[68] After dissolution, there is no longer a driving force for the stabilisation of hydroxide near the organic molecules so the catalysis will cease.

4. Kinetic isotope effect (KIE): The acid catalysis theory is consistent with this observation. To justify this result a mechanism which involves breaking an OD or OH is required because the oxygen-deuterium bond in heavy water is 8 kJ mol^{-1} stronger than the oxygen-hydrogen bond in normal water. Uniquely among theories for on-water catalysis, our theory can offer an explanation why the rate of reaction is slower on-D_2O than on-H_2O.

This increase in bond strength will have complex and superimposed effects on the properties of D_2O and the deuterons released. The primary effect of the increased bond strength will be the greater amount of energy required to removing a deuteron from the interfacial water thereby increasing the pK_a and reducing the rate of catalysis (*Figure 2.11*).

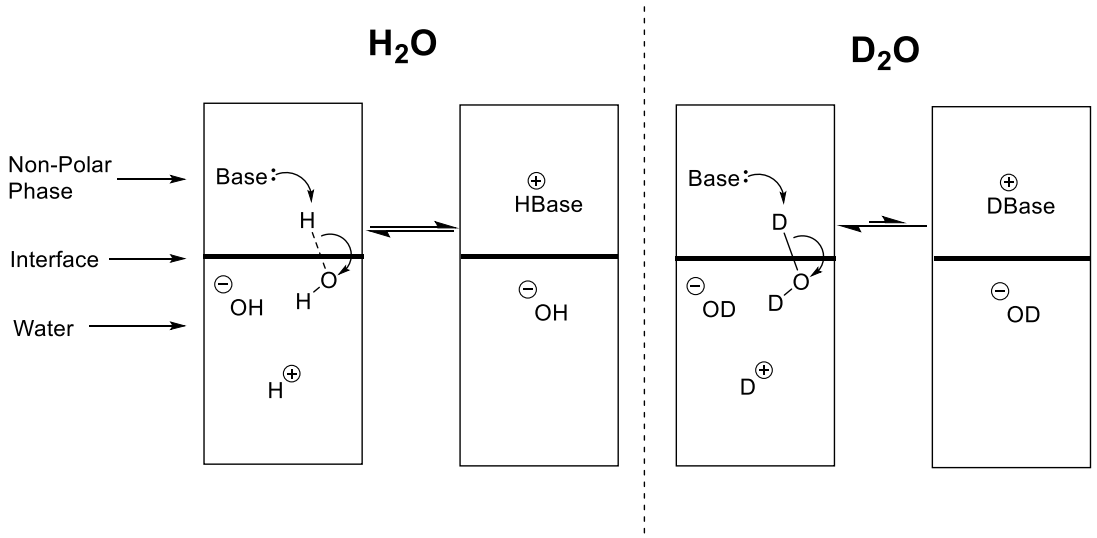


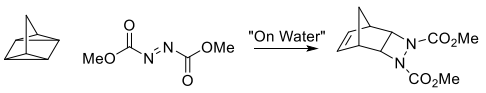
Figure 2.11: *The catalysis will be reduced in heavy water*

Another important effect is the change in autoionisation constant; K_w. The pK_w of H_2O at 25 °C is 13.995 whereas the pK_w of D_2O at 25 °C is 14.951.[69] This difference in pK_w represents an order of magnitude fewer ions present in D_2O than H_2O.

This direction of the kinetic isotope effect in on-water reactions shows these reactions are subject to general acid catalysis, where protonation of the substrate is the rate determining step (c.f. specific acid catalysis where protonation is not involved in the rate determining step). For general acid catalysis the rate of catalysis is proportional to the strength of the acid used.

5. Reactions slowed on-water. The acid catalysis theory is consistent with this observation. The mechanism of 1,3-dipolar cycloadditions is best understood using FMO theory as they are able occur in three ways (type I, II and III) depending on the relative energy of the HOMO and LUMO of both the dipolar and dipolarophile.[70] While the exact mechanisms of the 1,3-dipolar cycloadditions reported by Engberts (see *Scheme 2.10*) are difficult to determine without detailed modelling of the orbital interactions involved, we hypothesise protonation of the dipole under the on-water conditions changes the mechanism of the cycloaddition from type II to type III (*Figures 2.12* and *2.13*).

Nitrile oxides are considered ambiphilic dipoles and consequently undergo type II dipolar cycloadditions where the HOMO and LUMO of both components lie at similar levels (*Figure 2.12*). That is, the HOMO of the dipole can interact with LUMO of the dipolarophile or the HOMO of the dipolarophile can interact with LUMO of the dipole. The rates of type II 1,3-dipolar cycloadditions show little dependence on the electronic nature of the dipolarophile because of the subtle balance of relative energy levels.[71]



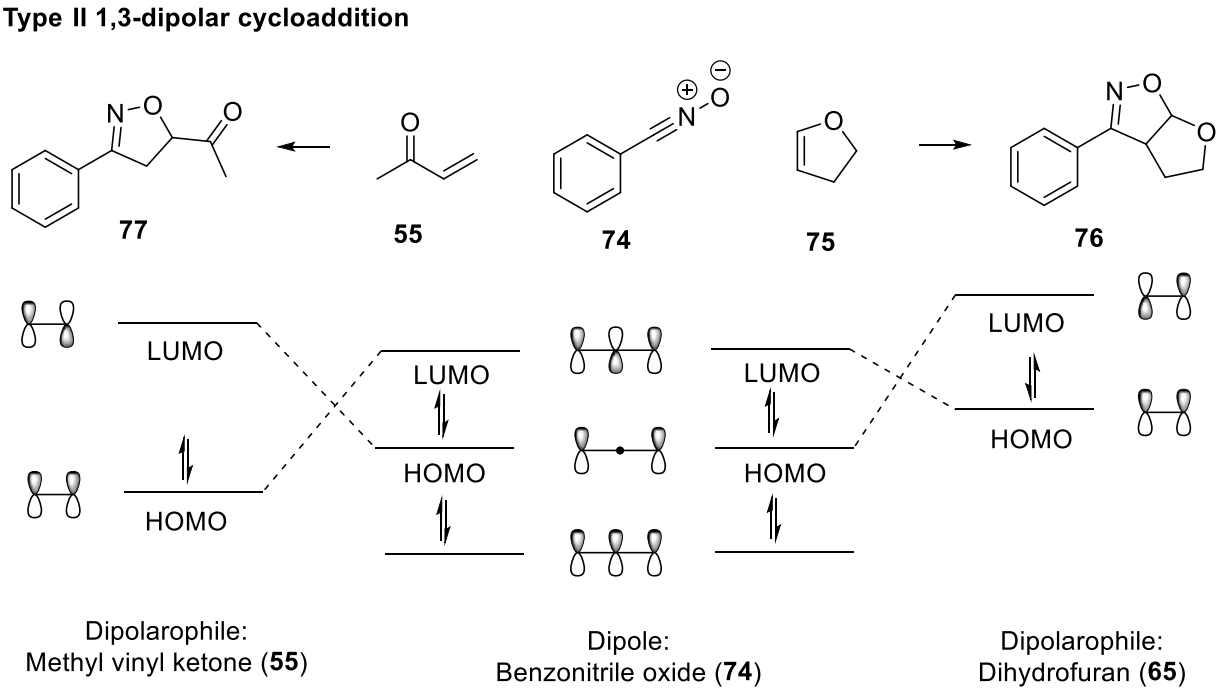
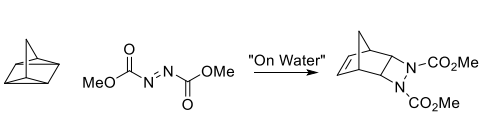


Figure 2.12: *Type II 1,3-dipolar cycloaddition*

Protonation of the nitrile oxide will leave a formal positive charge on the nitrile (**81**), making it more resemble a nitrilium (*Figure 2.13*). Nitrilium ions are highly electrophilic, that is, will have a lower LUMO than the neutral nitrile oxide. 1,3-Dipolar cycloadditions which occur via a low lying LUMO on the dipole overlapping with the HOMO of the dipolarophile are known as type III 1,3-dipolar cycloadditions (*Figure 2.13*). Type III 1,3-dipolar cycloadditions show a strong rate dependence on the electronic nature of the dipolarophile, with electron withdrawing groups on the dipolarophile decelerating the reaction and electron donating groups accelerating the reaction.[72]



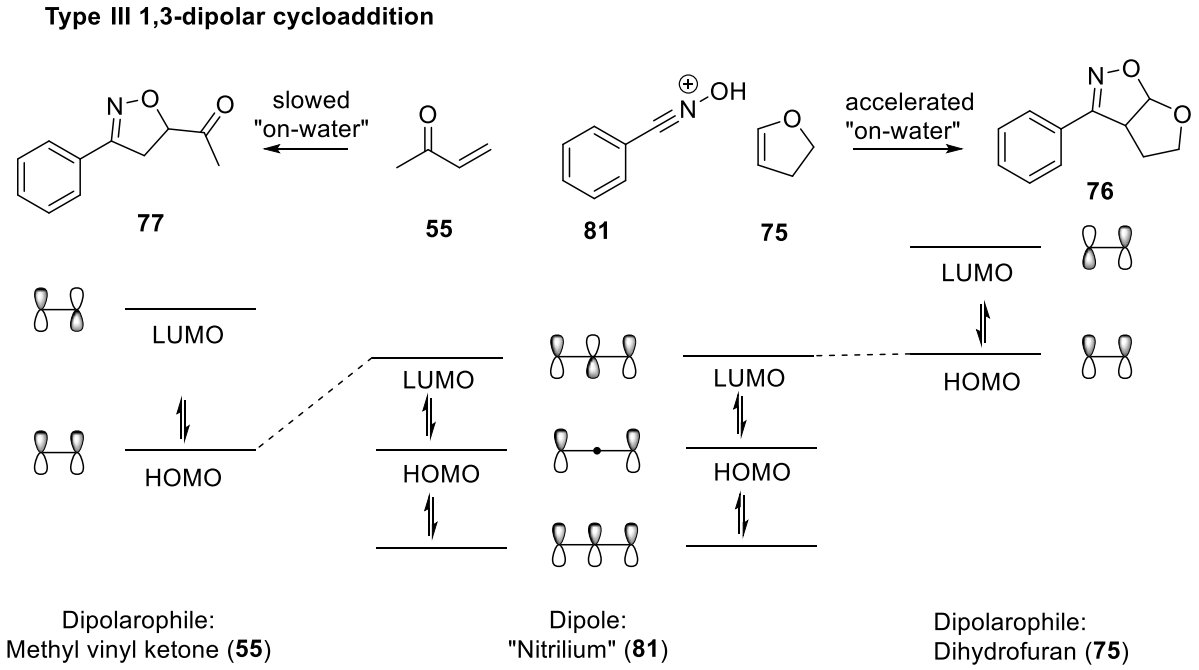


Figure 2.13: *Type III 1,3-dipolar cycloaddition*

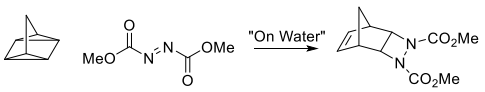
By invoking protonation of the nitrile oxide under on-water conditions we are able to justify why 1,3-cycloadditions with electron-poor dipolarophiles (**55**) are slowed on-water whereas 1,3-dipolar cycloadditions with electron-rich dipolarophiles (**75**) are accelerated. This justification is consistent with the observations reported by Engberts (see *Scheme 2.10*).

6. All on-water reactions are also known to be acid-catalysed. The acid catalysis theory is consistent with this observation. This theory intrinsically explains why all on-water catalysed reactions are also known to be acid catalysed.

The acid-catalysis theory is also consistent with Monte Carlo simulations of aqueous Diels-Alder reaction performed by Jorgensen who states:

> *"Water can be viewed as acting as a weak Brønsted acid catalyst in analogy to the well-known Lewis acid catalysis of Diels-Alder reactions."*[60]

This simple theory of acid catalysis is therefore consistent with all currently reported experimental evidence.



2.8 Testing the new Theory

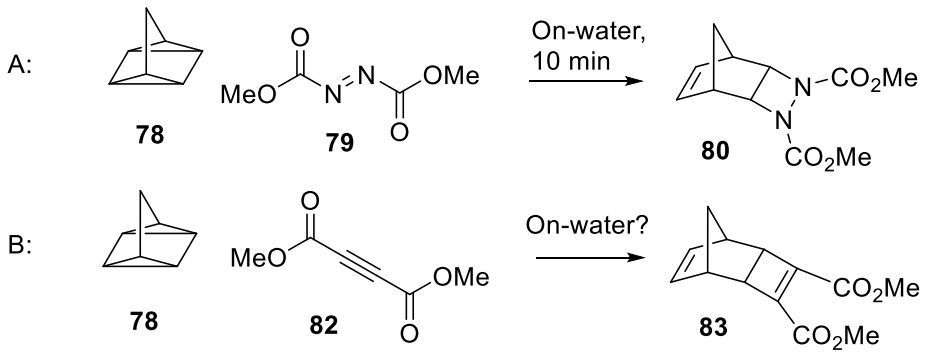
2.8.1 Introduction

The acid catalysis theory for on-water catalysis is consistent with all the existing data, however scientific theories also need to be able explain future results and provide predictions. We propose to perform experimental studies in an attempt to provide further validation for the acid catalysed nature of on-water catalysis. We will perform a series of rate studies for an on-water catalysed reaction to determine the influence of additives in the aqueous phase.

2.8.2 Choice of reactants

Although the theory proposed by Marcus and Jung was irredeemably flawed from the outset, they did provide a falsifiable prediction which would give evidence for or against their theory (*Figure 2.14*). Marcus and Jung state:

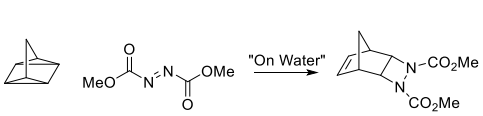
> *"The cycloaddition reaction of quadricyclane with dimethyl acetylenedicarboxylate on water is predicted to show very little or no catalysis, and so experiments on this system would be desirable."*[52]



Scheme 2.14: *Marcus and Jung's Prediction*

Marcus and Jung made this prediction as their results suggested that hydrogen-bonding to the nitrogen of the dimethyl azodicarboxylate was critical (despite their transition state structures), so replacement of this nitrogen with carbon would remove this mode of catalysis.

Despite this prediction it can be seen from *Scheme 2.14* that the reaction between quadricyclane (**78**) and dimethyl azodicarboxylate (**79**) is not closely comparable to the reaction between quadricycle (**78**) and dimethyl acetylenedicarboxylate (**82**). The most apparent dissimilarity is

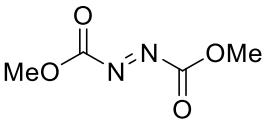


the hybridisation of the atoms participating in the cycloaddition, and the corresponding hybridisation in the product. The change in bond angle for the sp hybridised acetylene (**82**) from 180° to 120° in the product (**83**) is much greater than that for the sp^2 hybridised azo-substrate (120° to 109°) which will result in entirely different transition states for these reactions (Hammond's Postulate). The reaction with the acetylene (*Scheme 2.14*, B) will result in a cyclobutene (**83**) which has much higher ring strain than the 1,2-diazetidine product for the azo-compound (**80**). The azodicarboxylate moiety is also dynamic and not fixed in the *cis*- or *trans*-confirmation; if any change in confirmation is involved in the catalysis the carbon analogue will be significantly disadvantaged regardless of hydrogen bonding ability.

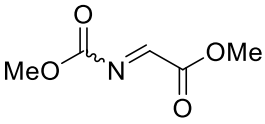
The experiment proposed by Marcus and Jung has the further complication in that very little can be changed in this reaction without drastically affecting the catalysis (see *Section 2.6.3*) and the nucleophile (quadricyclane, **78**) cannot be modified at all. The short reaction time also makes this reaction unamenable to accurate rate measurement.

As the reaction proposed by Marcus and Jung is problematic we propose to study a different but related set of reactions. We will persist with carbon centred electrophiles as any electrophile lacking nitrogen will validate or invalidate Marcus and Jung's prediction.

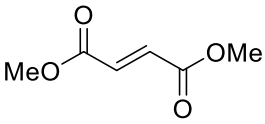
The most significant weakness pertaining to the use of dimethyl acetylenedicarboxylate (**82**) was the change in hybridisation, so we focused on electrophiles in the same sp^2 hybridisation as dimethyl azodicarboxylate (*Figure 2.14*).



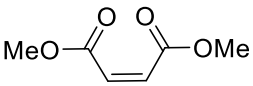
dimethyl azodicarboxylate (**79**)



methyl 2-((methoxycarbonyl)imino)acetate (**84**)



dimethyl fumarate (**85**)

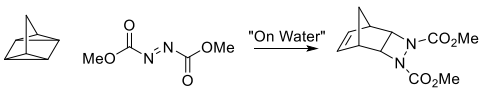


dimethyl maleate (**86**)

Figure 2.14: *Analogous electrophiles*

It would be ideal to compare the rate of the reaction involving methyl 2-((methoxycarbonyl)imino)acetate (**84**) to that of the azodicarboxylate (**79**) but unfortunately this compound is not stable to water. We also cannot employ dimethyl maleate (**86**) as it is highly water soluble (87 g/L[69]). The remaining choice is dimethyl fumarate, which is ideal; dimethyl fumarate (**85**) is stable to water, insoluble in water, non-volatile, and commercially available.

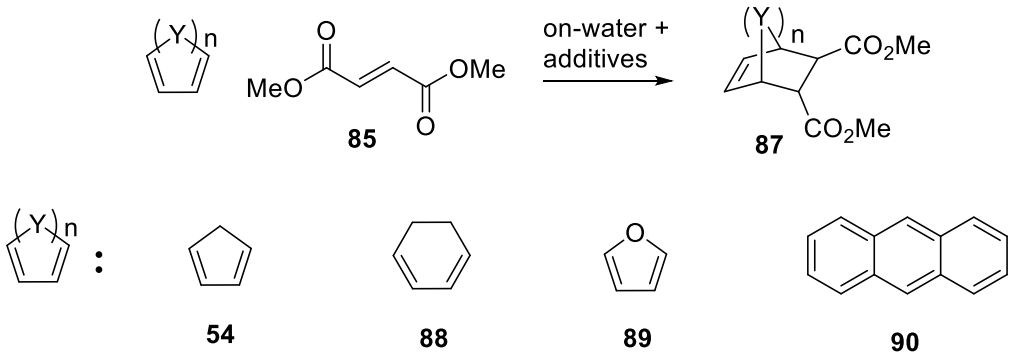
We also sought a more representative and slower reaction that has a greater capacity for



variation. For this purpose we decided upon the Diels-Alder reaction as these reactions indisputably occur on-water[73] was the first known class of on-water catalysed reaction, and is the most well precedented of on-water reactions. The Diels-Alder reaction is also advantageous as there are countless dienes and dienophiles available, so modification of the reaction will be straightforward. Dimethyl fumarate complements this reaction as the *trans*-configuration about the double bond eliminates complications due to the production of *endo/exo* isomers.

2.8.3 Proposed reactions

A series of Diels-Alder reactions will be screened using dimethyl fumarate (**85**) as the dienophile, so that a suitable system for rate measurement could be determined (*Scheme 2.15*).

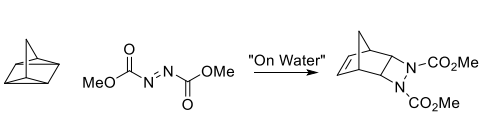


Scheme 2.15: *Survey of dienes for the Diels-Alder reaction*

The rate of the chosen reaction will first be measured on-water to obtain a baseline. The rate of the reaction performed on-water with the addition of additives such as salts, acid or base, will then be measured and compared to the baseline on-water reaction. This will allow for investigations into how the properties of the bulk water influence the catalysis at the interface. The rate will also be measured on-D_2O to establish the magnitude of kinetic isotope effect.

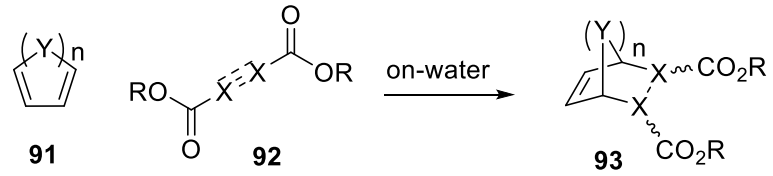
Although not the exact reaction proposed by Marcus, we will derive the same mechanistic data from this study. Both the proposed Diels-Alder reaction and the cycloaddition between quadricyclane and dimethyl acetylenedicarboxylate are pericyclic reactions between a completely non-polar nucleophile and a carbon centred electrophile.*

* Although the quadricyclane reaction may proceed by two step polar mechanism under certain conditions (see *Section 2.6.3*).

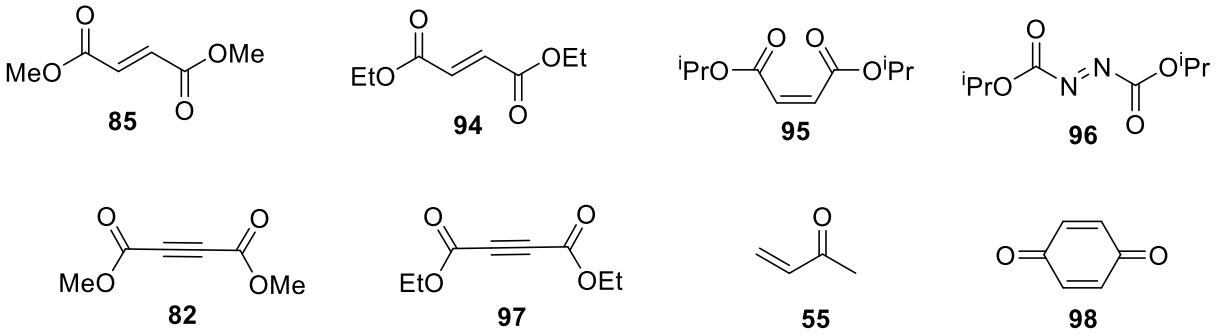


2.8.4 Variation of dienophile

In addition to dimethyl fumarate, we will screen a range of dienophiles against the previously highlighted dienes to elucidate any trends relating to the relative reactivity of both components (*Scheme 2.16*).



Dienophiles:



Scheme 2.16: *Range of electrophiles*

We will screen alkenes (**85**, **94**, **95**) and alkynes (**82**, **97**) with different esters, azo-compounds (**96**) and cyclic compounds (**98**) as the dienophile in on-water catalysed Diels-Alder reactions (*Scheme 2.16*).

2.8.5 At-water reactions

In a review of on-water catalysis, Fokin (who was also an author on Sharpless original on-water catalysis paper) stated; *"In many cases, it is impossible to ascertain whether the reaction is occurring in or on water"*.[42] This statement is true under the methods used for assessing on-water catalysis which were employed at the outset of this project. The only comparison routinely performed was between the on-water reaction and the neat reaction. Using this comparison it *is impossible* to determine if the reaction is occurring on the oil/water interface or in dilute aqueous solution. To remedy this shortcoming we propose to introduce "at-water" reactions as the standard means to distinguish whether the catalysis is occurring in water or on-water (*Figure 2.15*).

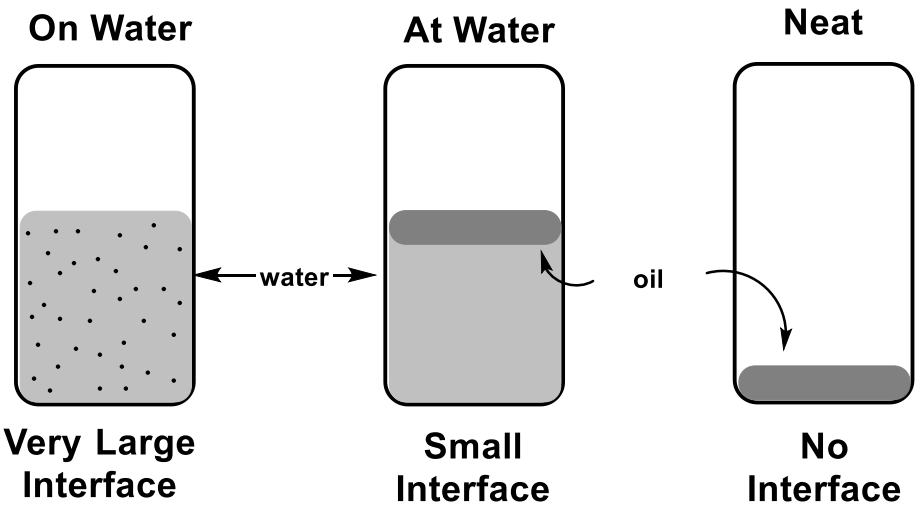


***Figure 2.15**: At-water reaction*

At-water reactions are reactions performed under identical conditions to on-water reactions but with minimal stirring. The minimal stirring will maintain discrete phases and minimise the interfacial area. That is, the only difference between the on-water and at-water reaction is the amount of oil/water interface.

Comparison of the neat reaction and on-water reaction enables us to determine whether water is important for the rate of reaction, whereas comparison of the on-water and at-water reactions allows us to determine whether the oil/water interface is important for the reaction. Comparison to the at-water reaction is the most useful means to determine if a reaction is on-water catalysed because it controls for the small amount of organic material that will be dissolved in the water and the high heat capacity of water. To decisively establish that a reaction is catalysed on-water, the on-water reaction should be faster than the at-water reaction. The rate difference between the at-water reaction and the neat reaction will vary depending on the relative solubility of the components and the role of the water in the reaction.

2.8.6 Summary of new theory

We have proposed a new theory for the mechanism of on-water catalysis based on simple Brønsted acid catalysis. This theory posits interfacial water molecules become acidic as a result of hydroxide adsorption at the oil/water interface (*Figure 2.16*). As such, we predict that any reaction that can be catalysed by weak acid will also be catalysed on-water. This theory is consistent with all the existing evidence. We will test this theory (as well as the hydrogen bonding theory of Marcus and Jung) by performing a series of rate studies on Diels-Alder reactions occurring on-water. We will use the at-water reaction to determine which phase the reaction is occurring in.

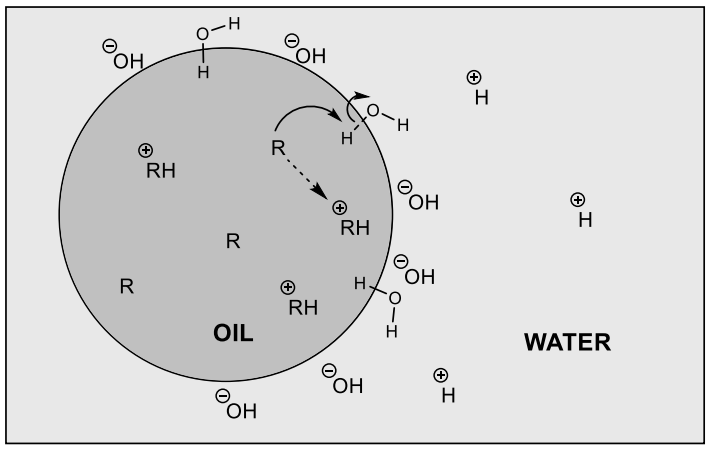


Figure 2.16: *The Beattie and McErlean model for on-water catalysis*

With this information available we will be able to provide significant evidence for either the theory of Beattie and McErlean or Marcus and Jung. With a consistent and comprehensive theory for on-water catalysis we will be able to use this theory predictively and identify unrecognised reactions which should be subject to this form of catalysis. This will transform on-water catalysis into a useful and general tool in organic chemistry.

2.9 Mechanism of on-water catalysis - Aims:

1. Confirm the Diels-Alder reaction involving dimethyl fumarate is on-water catalysed.

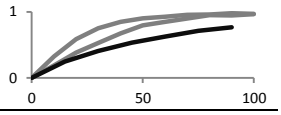
2. Study the effects of ionic strength and pH on the rate of an on-water catalysed Diels-Alder reaction involving dimethyl fumarate.

3. Study other related on-water catalysed Diels-Alder and cycloaddition reactions to uncover trends and corroborate previous findings.

Chapter 2

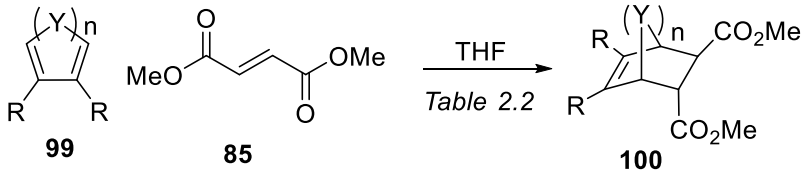
Studies into the Mechanism of On-Water Catalysis

Results and Discussion



2.10 Diels-Alder reactions with dimethyl fumarate

The first goal was to find a Diels-Alder reaction involving dimethyl fumarate (**85**) as the dienophile which was amenable to convenient rate measurement.



Scheme 2.17: *Diels-Alder reactions*

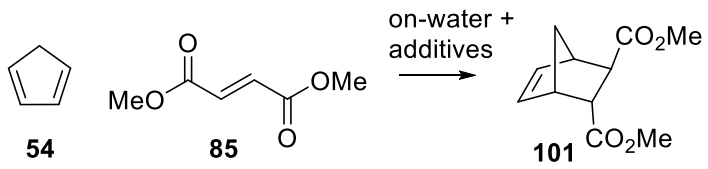
Diene	Diene equiv.	Result
cyclopentadiene (54)	1	complete in 3 h
1,3-cyclohexadiene (88)	2	NR
furan (89)	0.25 - 4	NR
anthracene (90)	0.5 - 3	NR

Table 2.2: *Screening dienes in the Diels-Alder reaction*

Of the four simple dienes screened only cyclopentadiene (**54**) participated in a Diels-Alder reaction with dimethyl fumarate. Furan (**89**), 1,3-cyclohexadiene (**88**) and anthracene (**90**) failed to undergo reaction at room temperature. It would be undesirable to raise the temperature to induce the reaction to occur as this would introduce more variables and significantly complicate the setup of the reaction.

Fortunately the cycloaddition between cyclopentadiene and dimethyl fumarate is ideal for our purposes. This reaction is complete within a matter of hours, making the rate convenient to measure. Cyclopentadiene is highly volatile (boiling point: 39 °C) and can be easily removed, thereby stopping the reaction while leaving the non-volatile fumarate and cycloaddition adduct for analysis. This reaction appeared to be suited to our needs so we proceeded to the detailed study of the on-water catalysed Diels-Alder reaction.

2.10.1 Preliminary studies



Scheme 2.18: *Diels-Alder reaction to be studied*

The Diels-Alder reaction between dimethyl fumarate (**85**) and cyclopentadiene (**54**) was stopped after fixed periods by evaporation of the diene and the conversion was determined by ^{1}H NMR analysis of the crude mixture. This allowed a direct comparison of the ratio of remaining fumarate to Diels-Alder adduct (**101**) by integration of the proton resonances. The clear base line separation of the dienophile and product signals negated the need for an internal standard and made analysis simple, reliable and easy to interpret (*Figure 2.17*).

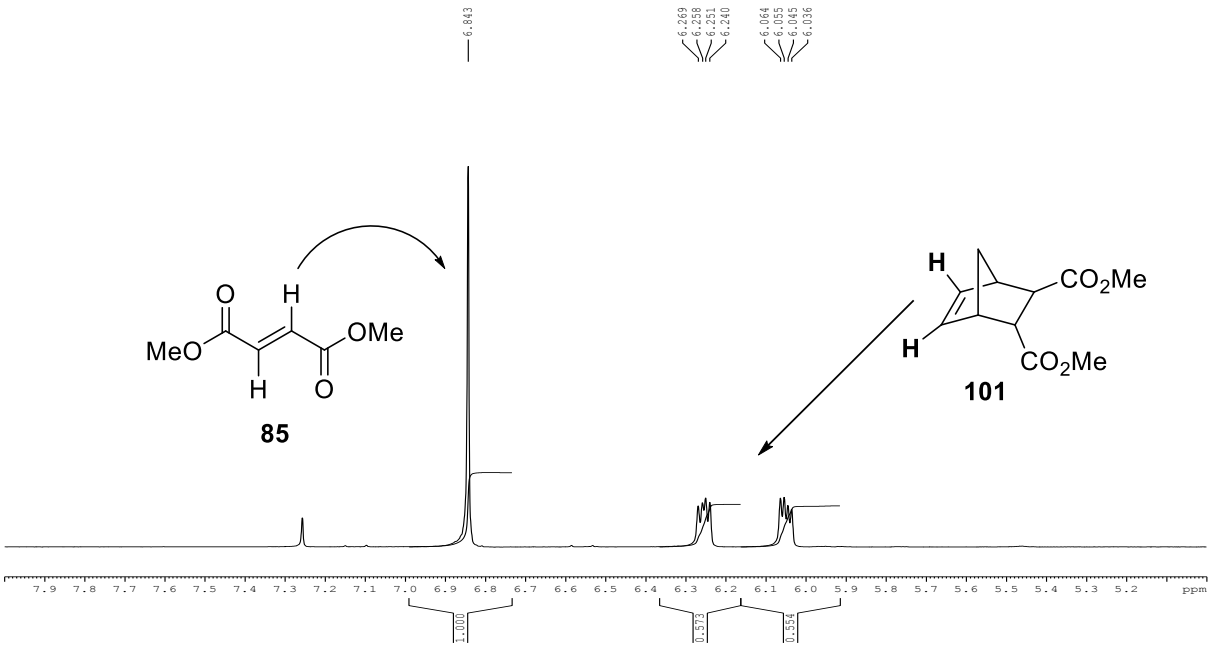


Figure 2.17: *Clear baseline separation of starting material and product in ^{1}H NMR*

All on-water reactions were performed in 21 mL scintillation vials containing 4 mL of water and stirred, off-centre, at greater than 1500 rpm with a magnetic stirrer (*Figure 2.18*). Off-centre positioning of the reaction vessel was found to be important to ensure thorough mixing. After a fixed time, the reaction was halted through dilution with ethyl acetate and subsequent evaporation of the volatile cyclopentadiene using a rotary evaporator.

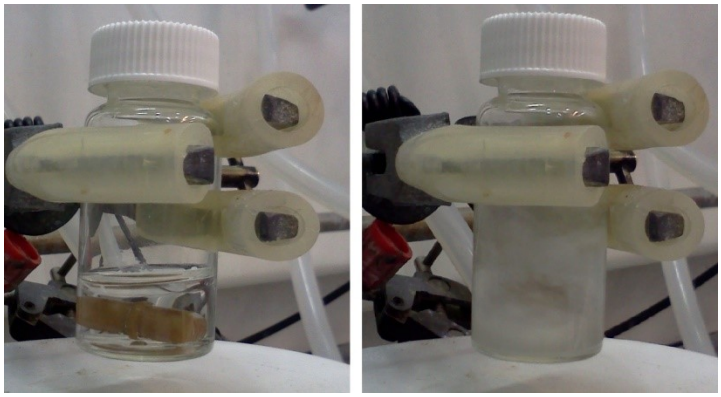


Figure 2.18: *On-water reaction set up (left: unmixed, right: stirring to form emulsion)*

To firmly establish that this reaction was on-water catalysed, we applied our newly established procedure; comparison of the on-water, at-water and neat reactions after a fixed period of time (30 minutes, *Figure 2.19*). The reaction occurred more quickly on-water (75% conversion, *Figure 2.19*, entry 1) than at-water (40% conversion, *Figure 2.19*, entry 2) and more quickly on-water than neat (45% conversion, *Figure 2.19*, entry 3). This result confirmed the Diels-Alder reaction between dimethyl fumarate and cyclopentadiene is on-water catalysed. This result alone invalidates Marcus and Jung's theory of hydrogen bond assistance as the cause of on-water catalysis.

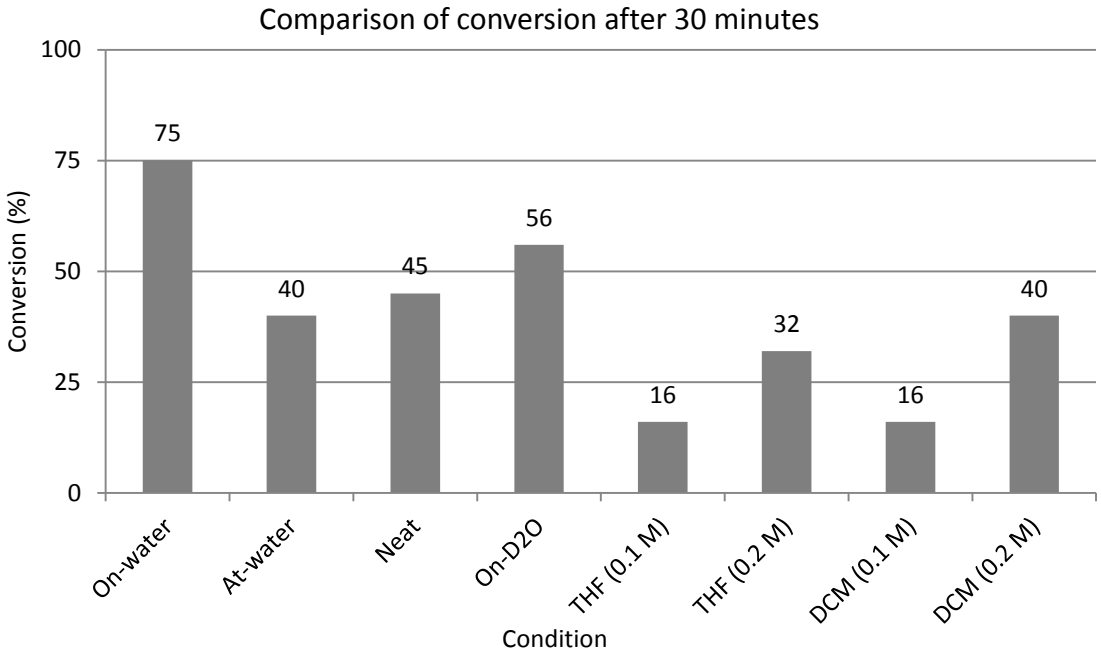
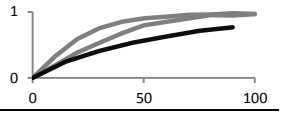


Figure 2.19: *Conversion after 30 minutes*

In addition to confirming that the reaction was catalysed on-water we also measured the conversion of the on-D_2O reaction after 30 minutes. The result was consistent with previously reported results; the reaction is slower on-D_2O than on-water, but faster than the at-water reaction. The relative



conversion of the on-D_2O reaction shows the heavy water interface is definitely catalytic but to a lesser degree than normal water. We also found the rate of reaction on-water was greater than that in common organic solvents.

All of the preliminary data is consistent with the data reported by Sharpless. This indicated the Diels-Alder reaction between cyclopentadiene and dimethyl fumarate was a representative on-water catalysed reaction and we could proceed with our intention to gather quantitative data from this reaction.

2.10.2 Rate measurement

Having developed a qualitative picture of the model reaction, quantitative rate data was obtained (*Figure 2.20*).

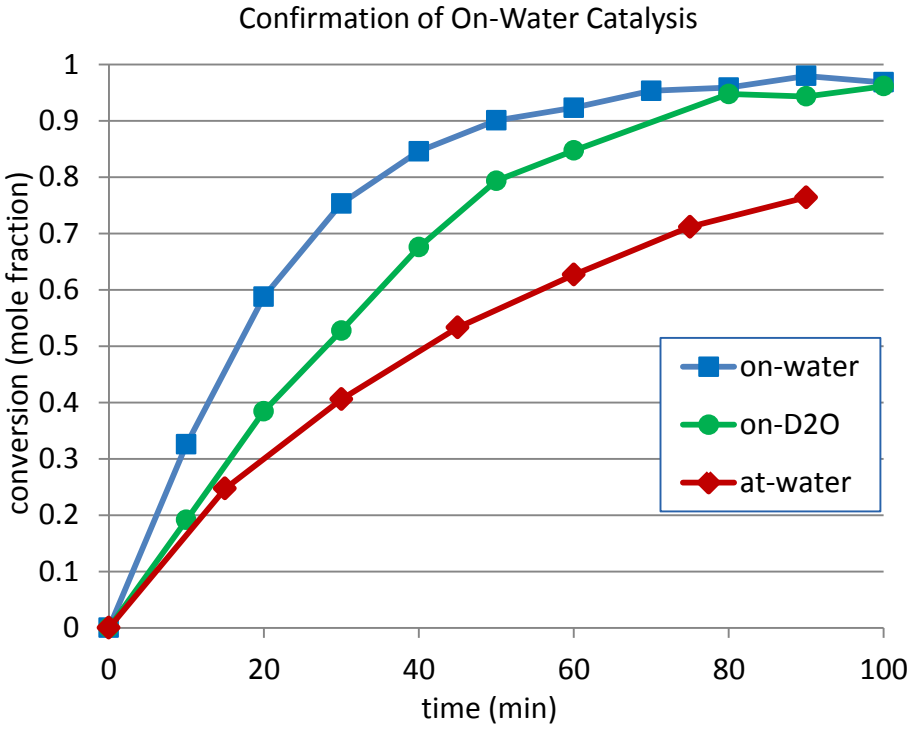


Figure 2.20: *Conversion of on-water, at-water and on D_2O Diels-Alder reaction*

The relative rates of the on-water, on-D_2O and at-water Diels-Alder reactions (*Figure 2.20*) were found to be consistent with the data from the single data points shown in *Figure 2.19*. These measurements allowed us to gain quantitative measure of the kinetic isotope effect. The kinetic isotope effect is simply the rate constant of the protonated reaction (k_H) divided by the rate constant of the deuterated reaction (k_D), that is;

$$KIE = \frac{k_H}{k_D}$$

For the Diels-Alder reaction being studied the kinetic isotope effect was found to have a value of 1.4 which is in accordance to previously reported results.[52]

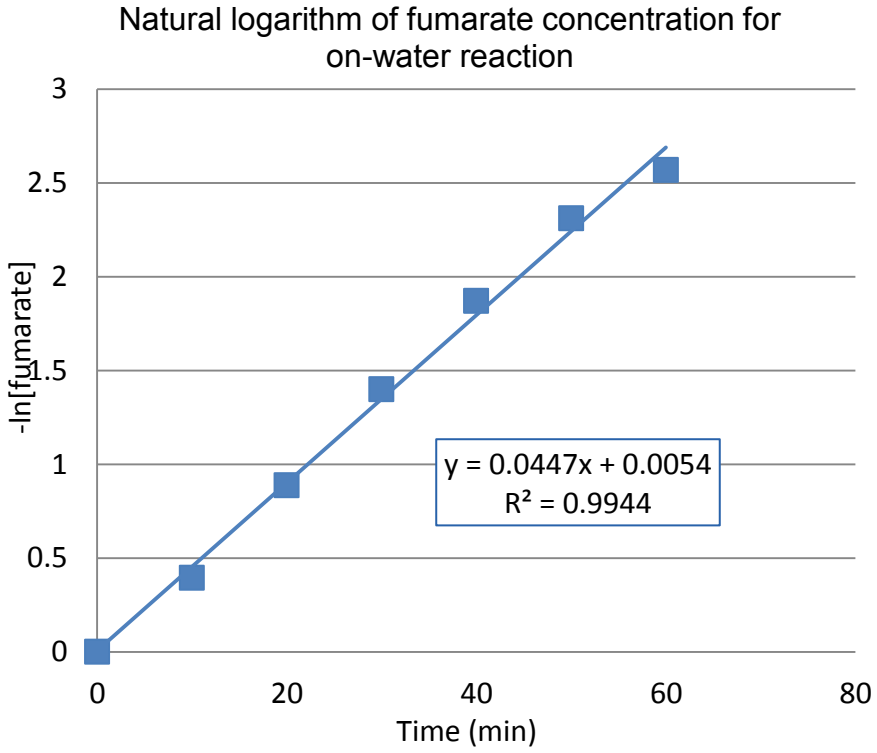
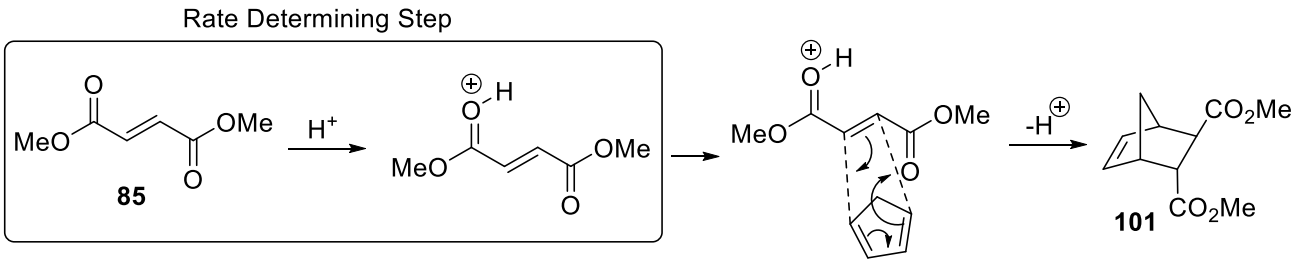


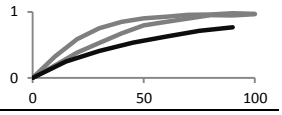
Figure 2.21: *Plot of -ln[fumarate] versus time from the on-water reaction, showing first order kinetics*

Bimolecular reactions ordinarily display second order rate equations, however the deuterium isotope effect observed for this reaction indicates water is also involved in the rate determining step. The natural logarithm of the concentration of fumarate plotted over time reveals a linear trend (R^2 = 0.99, *Figure 2.21*), demonstrating that the reaction is first order in fumarate.

The first order rate equation along with the sign of the kinetic isotope effect shows the catalysis is the rate determining step. In our proposed theory this would indicated the protonation of the fumarate is the rate determining step (*Scheme 2.19*).



Scheme 2.19: *First order kinetics show protonation to be the RDS*



Considering the kinetic isotope effect and the first order kinetics of the fumarate we can confirm on-water catalysis is an example of general acid catalysis rather than specific acid catalysis. Reactions subject to general acid catalysis have protonation involved in the rate determining step and so are sensitive to the strength of the acid used. Our model predicts interfacial D_2O will be a weaker acid than interfacial H_2O leading to the slower rate of reaction for the on-D_2O reaction.

To gain a better understanding of the role of acid in this reaction we performed another study (*Figure 2.22*).

We attempted to determine the role of the reaction occurring in-water and the strength of the acid catalysis on-water. We did this by performing a series of at-water reactions where the water had been replaced by aqueous hydrochloric acid. The previously measured on-water and at-water reactions were used as a guide to determine the relative acceleration. Acid concentrations of between 1 mM and 1 M caused acceleration in the reaction relative to the neutral at-water reaction, presumably through a combination of increasing the rate of the dilute aqueous reaction and additional acid diffused into the organic phase. Under no conditions did the rate of reaction approach that of the on-water reaction. Moving to acid concentrations of greater than 1 M caused decomposition of the reagents. This result shows the great strength of on-water catalysis in that it can give an acceleration which could only otherwise be attained using highly acidic medium, but only uses neutral water.

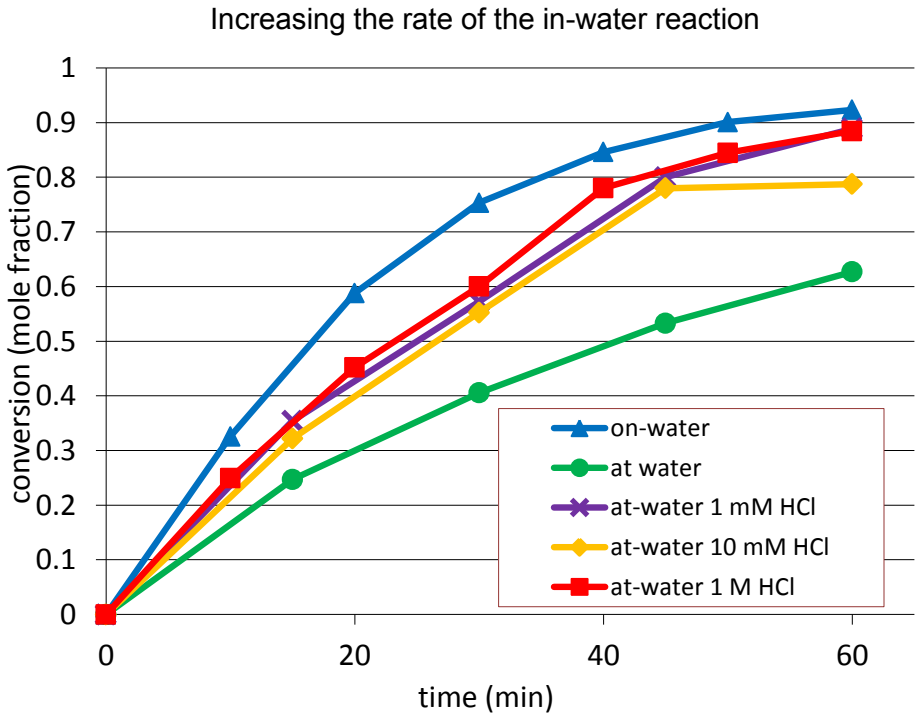
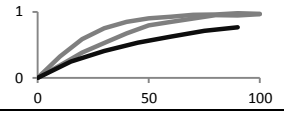


Figure 2.22: *Determining the role of the in-water reaction*

The first outcome to note from these results was that the reaction becomes faster in the



presence of hydrochloric acid, clearly demonstrating this is an acid-catalysed reaction. The small increase in acceleration observed for the at-acidic-water reaction is also in-line with our proposed theory for on-water catalysis, as pH is a property of the bulk water phase, not the interface where the majority of the reaction is occurring. As both the diene and dienophile are largely insoluble in water the rate of reaction is relatively insensitive to the nature of the water.

It is possible the small increase in rate observed in the at-HCl reactions relative to the at-water reactions was due to either the minimal increase in the acid concentration in the oil droplets by diffusion or an increase in the rate of the reaction occurring in dilute aqueous solution. It is highly likely to be the former as the 1 mM HCl and 1 M HCl reactions display effectively the same relative acceleration (*Figure 2.22*). This indicates the extra acid in the non-polar phase quickly saturates (*Figure 2.23*). If the rate increase was due to reactants in the aqueous phase we would expect a rate increase in proportion to the acid concentration.

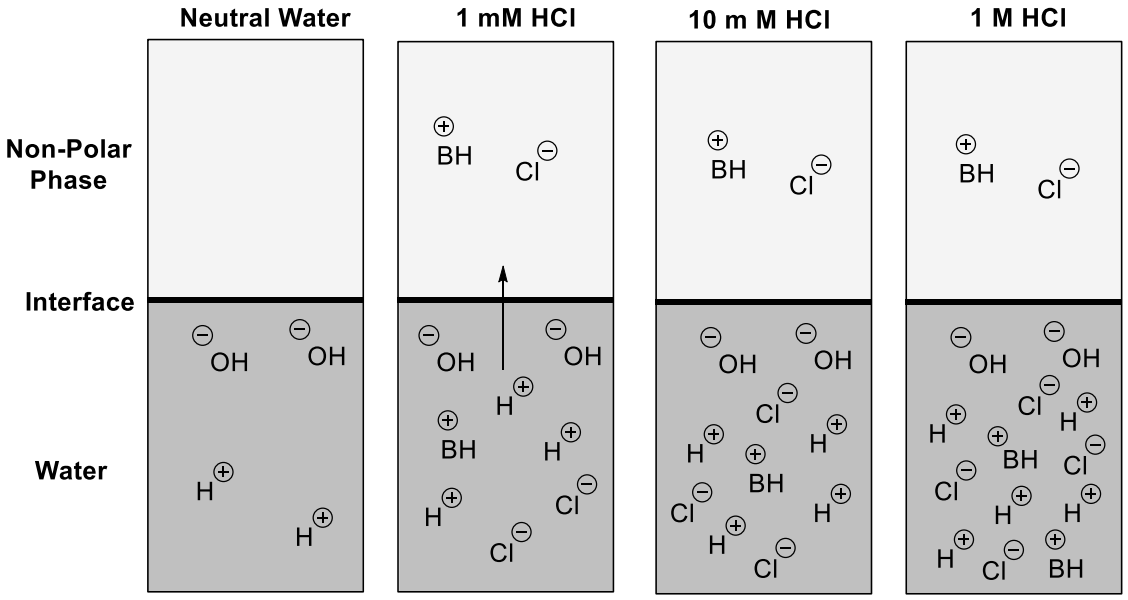


Figure 2.23: *Some acceleration is observed with at-water + HCl reactions*

This result confirmed to us that, not only was the Diels-Alder reaction acid catalysed, but also that on-water catalysis was occurring at the organic phase and certainly not due to the dilute reagents in solution. So the acid-catalysed reaction was not taking place in the bulk aqueous solution, however there remained the possibility that the acceleration was occurring in the double layer surrounding the oil droplets (*Figure 2.24*). That is, in the water near the interface.

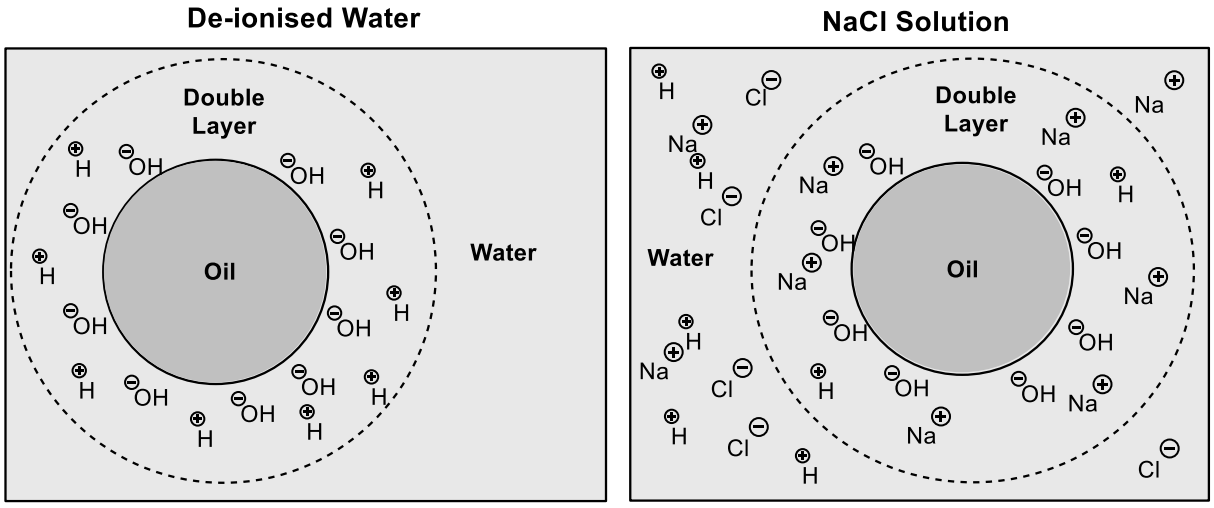


***Figure 2.24**: The charged double layer around an oil droplet*

To exclude this possibility we performed a rate study in the presence of sodium chloride (*Figure 2.25*).

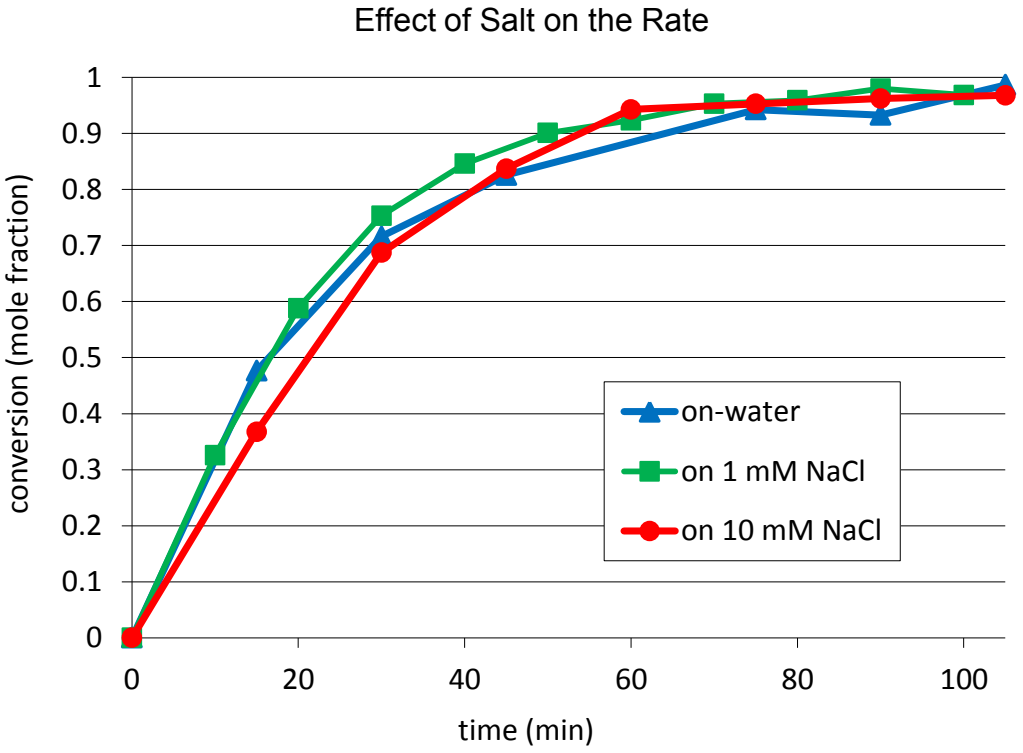
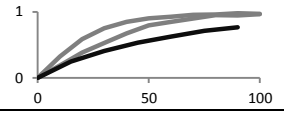


***Figure 2.25:** Dependence on mM concentration of sodium chloride on rate*

The rate of the Diels-Alder reaction between cyclopentadiene and dimethyl fumarate was measured with millimolar concentrations of sodium chloride added to the water (*Figure 2.25*). At these concentrations there would be more than enough sodium ions to displace all the protons in the double



layer.

No difference in rate was observed between the reaction on-[10 mM NaCl] and on-[deionised water]. As depicted in *Figure 2.26*, there will be few protons in the double layer so no acid catalysis will occur here. Given the rate of this reaction was identical to the reaction with pure water this indicates little catalysis was occurring in the double layer even with protons present. If catalysis were occurring in the double layer the displacement of the protons would retard the rate of reaction.

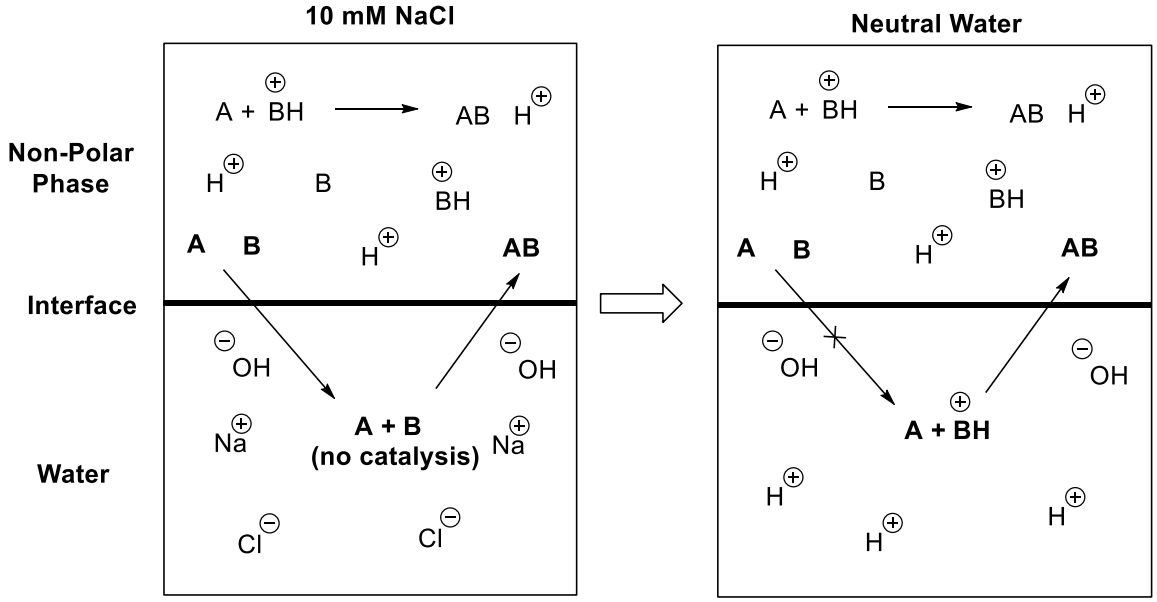


Figure 2.26: *The rate of reaction is identical in deionised water and 10 mM NaCl water*

Water which has been exposed to air for any extended period of time will be at pH 5.6 due to the dissolution of carbon dioxide. All of our previous work was conducted with water which had been open to the air, so we performed an experiment to exclude the possibility that the dissolved carbon dioxide was contributing to the catalysis (*Figure 2.27*).

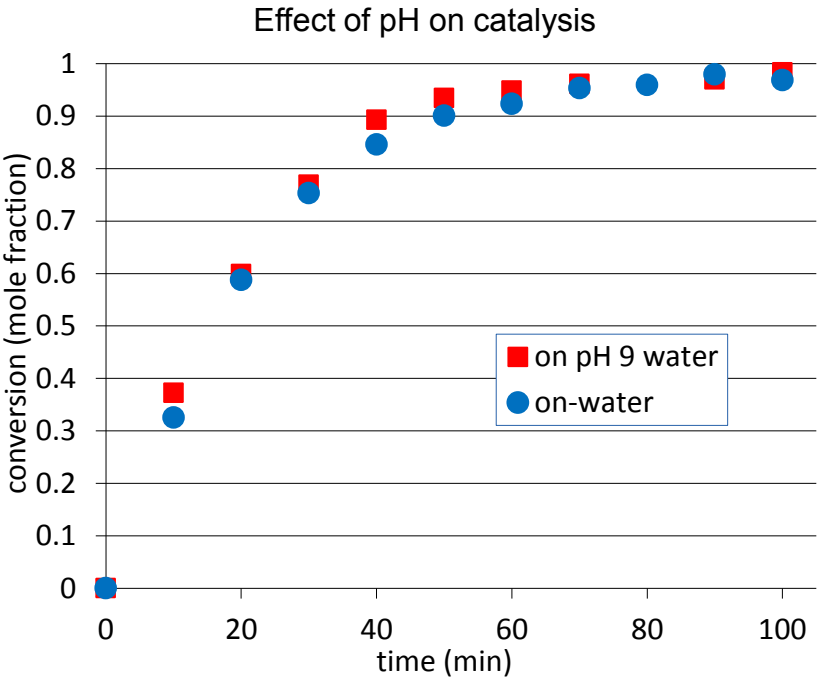


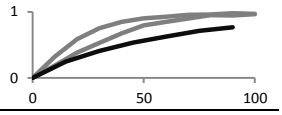
Figure 2.27: *Rate dependence on pH*

The rate of the on-water reaction at pH 5.6 was compared to an on-water reaction with a pH 9 solution obtained with sodium hydroxide[†] (*Figure 2.27*). We chose to do the measurement at pH 9 as the nature of the oil/water interface is unaffected at this pH.[63] It is apparent from these results that the rate is completely unaffected by this variation pH. This indicated that the dissolved carbon dioxide was not contributing to the rate of reaction. This result also indicated the catalysis is insensitive to the nature of the bulk water and only the nature of the interface is important.

Our theory of on-water catalysis is that the acceleration occurs by acid catalysis due to increased acidity of the interfacial water. This result is of great significance as we have shown *we can perform acid catalysis in the presence of alkaline water*. The tolerance of on-water catalysis to modification of the aqueous phase points to further applications of this mode of catalysis, particularly in tandem and co-catalytic systems.

The use of a non-ionic base would also be of interest, however attempts to perform on-water reactions with dilute ammonia (1 - 10 mM) solution caused destabilisation of the emulsion and as such, efficient mixing could not be obtained and no meaningful rates could be measured.

[†]We have shown above the presence of sodium ions will not change the rate of reaction



2.10.3 Summary of rate studies with dimethyl fumarate

We have performed a series of Diels-Alder reactions between cyclopentadiene and dimethyl fumarate, this reaction was chosen to be a convenient version of the experiment suggested by Marcus and Jung. We have also developed the at-water reaction as a method of determining whether acceleration is occurring due to the presence of water, or due to the presence of the interface.

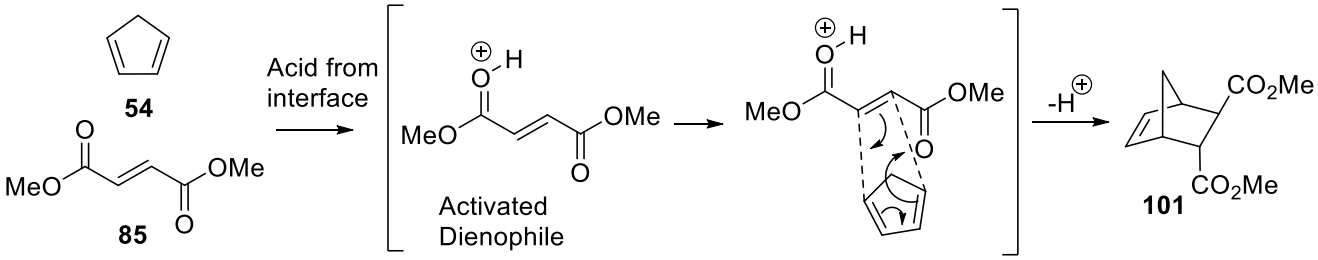
Initially, we showed that the model reaction was catalysed on-water. This contradicts the prediction by Marcus and Jung. Next we performed a series of experiments to probe the mechanism of on-water catalysis.

The first order kinetics and kinetic isotope effect showed protonation of the fumarate to be the rate determining step and confirmed on-water catalysis to be an example of general acid catalysis.

The small and plateauing acceleration found for at-HCl reactions demonstrated that the majority of the reaction is occurring inside the oil droplets. Sodium chloride did not affect the rate of reaction, thereby confirming the catalysis was occurring at the interface, not in the double layer.

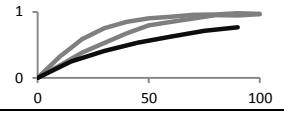
Finally we obtained identical rate data for reactions performed at pH 5.6 (acidic) and pH 9 (alkaline) showing the acid catalysis was insensitive to the nature of the bulk water and was not due to dissolved carbon dioxide.

These findings lead us to *Scheme 2.20* as the description of the origin of the acceleration of the Diels-Alder reaction between cyclopentadiene and dimethyl fumarate when performed on-water.



Scheme 2.20: *Proposed mechanism of on-water catalysis*

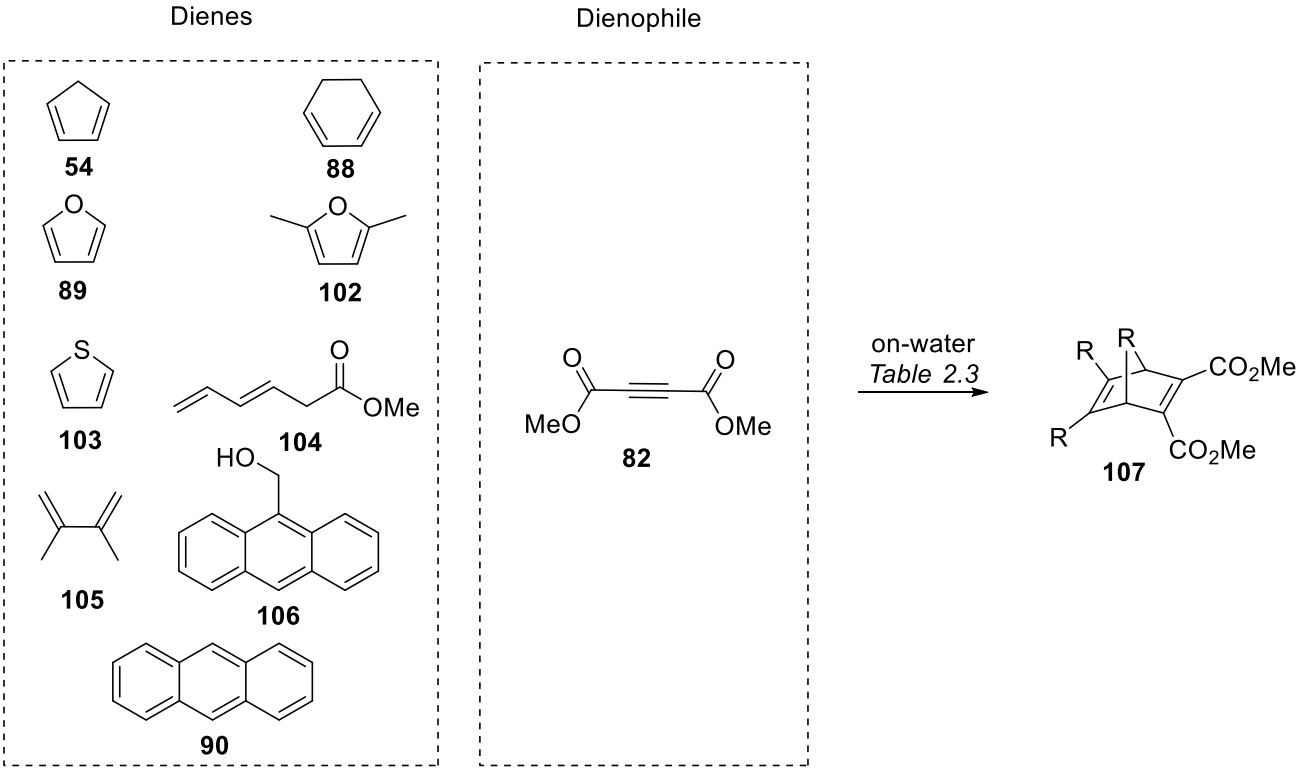
All of our measurements were found to be consistent with our proposed model for on-water catalysis (*Figure 2.10*).



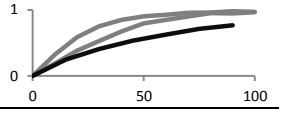
2.11 Acetylenedicarboxylate as the dienophile

Given the success of the rate studies using dimethyl fumarate as the dienophile in the Diels-Alder reaction we sought to extend our experiments to the electrophile originally suggested by Marcus; dimethyl acetylenedicarboxylate. We considered these experiments unlikely to result in measurable acceleration due to on-water catalysis. Acetylenedicarboxylates are known to be amongst the most active dienophiles and react so quickly they unlikely to be subject to any form of catalysis. However given the protocols developed over the course of our previous experiments, if Diels-Alder reactions with acetylenecarboxylate dienophiles are subject to on-water catalysis we will be in a position to observe it.

In a similar fashion to our initial studies with dimethyl fumarate, we screened a range of dienes with dimethyl acetylenedicarboxylate (**82**) to determine reaction time and ease of analysis (*Scheme 2.21*).



Scheme 2.21: *Diels-Alder reactions with dimethyl acetylenedicarboxylate*



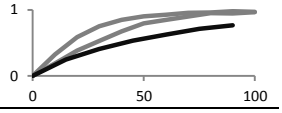
	Diene (equiv.)	Temp. (°C)	Internal Standard (10% w/w)	On-Water Catalysis	TFA Catalysis	Comments
1	**cyclopentadiene (1)**	RT	naphthalene	no	no	-
2	**1,3-cyclohexadiene (1)**	RT	hexamethylbenzene	no	no	-
3	**furan (0.2-5)**	RT	naphthalene	no	no	erratic
4	**furan (0.2-5)**	4	naphthalene	no	yes	-
5	**2,5-dimethylfuran (2)**	RT	-	no	no	-
6	**thiophene (2)**	RT	hexamethylbenzene	no	no	NR
7	**anthracene (1)**	100	-	no	no	NR
8	**9-anthracenemethanol (0.5)**	RT	hexamethylbenzene	no	decomp.	NR
9	**2,3-dimethyl-buta-1,4-diene (2)**	RT	hexamethylbenzene	no	no	-
10	**methyl 3,5-hexadienoate (1)**	RT - 60	-	no	no	-

Table 2.3: *Attempts to find an on-water catalysed reaction with dimethyl acetylenedicarboxylate*

The reaction between cyclopentadiene (**54**) and dimethyl acetylenedicarboxylate (**82**) was extremely fast and extremely exothermic.[74] As was expected no on-water catalysis was observed (*Table 2.3*, entry 1). The reaction appears to have such a small activation barrier that there is no gain to be had from catalysis. To determine whether the reaction was subject to acid catalysis at all we also performed the reaction in the presence of trifluoroacetic acid and again no acceleration was observed. The lack of catalysis even with a very strong acid indicates the reaction is not acid-catalysed. Given this results our theory predicts no Diels-Alder reactions involving dimethyl acetylenedicarboxylate will show an acceleration on-water. It also means acetylenedicarboxylates are unlikely to be a useful substrate to probe Marcus' theory. To confirm this was the case we moved to less active dienes which are more likely to provide reactions with rates amenable to measurement.

1,3-Cyclohexadiene (**88**) is a less active diene as it has less ring strain than cyclopentadiene. Cyclohexadiene (**88**) reacted slowly with dimethyl acetylenedicarboxylate (**82**) but did not show any acceleration under on-water conditions or acid catalysis.

Furan (**89**) is generally considered a poor diene due to aromaticity and consequently was much slower to undergo the Diels-Alder reaction with dimethyl acetylenedicarboxylate (**82**) than cyclopentadiene (**54**). Unfortunately the results of the Diels-Alder reaction were erratic at room temperature due to volatility of furan (boiling point: 31°C) and we were unable to obtain consistent



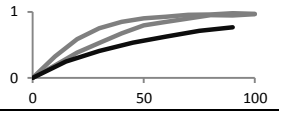
measurements even using a sealed tube reactor and water bath *(Table 2.3*, entry 3). To obtain reproducible data the reaction was cooled to 4°C. At this temperature the reaction was sluggish, but consistent. The slow reaction at 4°C presented further problems as furan is not suitable for long reactions as it can polymerise. No on-water catalysis was observed, but at 4°C trifluoroacetic acid did accelerate this reaction (*Table 2.3*, entry 4).

Furan had proved to be impractical as a diene for our purposes. To negate the problems we had experienced with volatility of furan we experimented with the higher boiling 2,5-dimethylfuran (**102**, boiling point: 94°C). Unlike unsubstituted furan, dimethylfuran (**102**) gave consistent results at room temperature, but at an even slower rate. No on-water catalysis was observed for the Diels-Alder reaction between 2,5-dimethylfuran (**102**) and dimethyl acetylenedicarboxylate (**82**). Interestingly, the Diels-Alder reaction with 2,5-diemethylfuran was *not* accelerated by trifluoroacetic acid (*Table 2.3,* entry 4), in contrast to furan. This suggests the acceleration observed with furan may not have occurred due to activation of the dienophile but possibly by activation of the diene by protonation which removed aromaticity. This mode of catalysis would be entirely outside our theory for on-water catalysis as it would require a very strong acid.

Following the potential shown by the furans we also studied thiophene (**103**, *Table 2.3*, entry 6). Thiophene (**103**) has greater aromatic stabilisation than furan and did not react with dimethyl acetylenedicarboxylate (**82**) under any circumstances.

The next class of dienes studied were anthracenes (*Table 2.3,* entries 7 and 8). Anthracene can be a competent diene in the Diels-Alder as there is greater aromatic stabilisation in the two phenyl rings in the Diels-Alder adduct. The reaction between anthracene (**90**) and dimethyl acetylenedicarboxylate (**82**) occurred slowly. The larger problem with this reaction was that as with many polycyclic aromatic compounds anthracene (**90**) is very insoluble in most organic solvents. Anthracene (**90**) did not mix with the dienophile, **82** so an emulsion could not be formed and without an acceptable emulsion on-water catalysis cannot occur. 9-Anthracenemethanol (**106**) is ostensibly more soluble than unsubstituted anthracene due to disruption of the π-stacking and has been reported to participate in aqueous reactions via the hydrophobic effect.[38] We found 9-anthracenemethanol (**106**) did not participate in the Diels-Alder reaction with dimethyl acetylenedicarboxylate (**82**) and was not stable to trifluoroacetic acid (*Table 2.3*, entry 8).

All of the cyclic dienes which had been studied had been unproductive. So focus turned to acyclic dienes. Dimethylbutadiene (**105**) reacted at a measurable rate but the reaction was not catalysed on-water or with TFA. Similarly, methyl 3,5-hexadienoate (**104**), which has been shown to



participate in aqueous Diels-Alder reactions,[39] was not accelerated on-water or under regular acid catalysis.

2.11.1 Summary of acetylenedicarboxylate reactions

None of the Diels-Alder reactions involving dimethyl acetylenedicarboxylate studied were found to be catalysed on-water. This is consistent with the proposed acid catalysis theory as the dienophile is so reactive it is unlikely to be further activated by protonation. Of all the reactions tested only the reaction between furan and dimethyl acetylenedicarboxylate was found to be accelerated by TFA. This suggests the acceleration observed in this case was due to activation by a means other than protonation of the dienophile.

Overall these results mean acetylenedicarboxylates are unlikely to be a useful substrate to probe Marcus' theory and validates our initial choice of dimethyl fumarate.

2.12 Quantum mechanism calculations

Quantum mechanical calculations of the transition states for both the uncatalysed and acid-catalysed Diels-Alder reactions were kindly performed by Dr Bun Chan. The calculations were performed at the M06-2X/6-311+G(3df,2p)//B3-LYP/6-31+G(d,p) level of theory with the inclusion of solvation effects using the SMD continuum model.

Calculations for the Diels-Alder reaction between cyclopentadiene and dimethyl fumarate showed the transition state for the acid-catalysed process to be 7.6 kJ mol^{-1} lower in energy than the uncatalysed process (*Figure 2.28*). This result clearly shows this Diels-Alder reaction is acid-catalysed is consistent with the observations describe above.

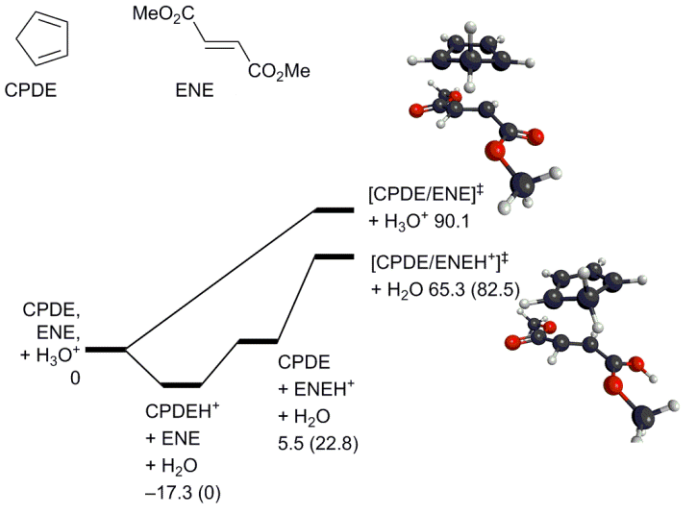


Figure 2.28: *Calculated schematic energy profiles (kJ mol^{-1}) for the acid-catalysed vs non-catalysed Diels-Alder reaction of cyclopentadiene with dimethyl fumarate*

In contrast to this, the Diels-Alder reaction between cyclopentadiene and dimethyl acetylenedicarboxylate was found to essentially have no difference in energy between the two processes. The calculations showed the transition state [CPDE/YNE]‡ to have an energy of 92.9 6 kJ mol^{-1} for the uncatalysed process and for the acid-catalysed process the transition state [CPDE/YNEH]‡ was found to have an energy of 94.0 kJ mol^{-1} from the lowest energy state (*Figure 2.29*). This is also consistent with our observations that none of the reactions involving dimethyl acetylenedicarboxylate were catalysed on-water nor were they found to be subject to acid-catalysis in general.

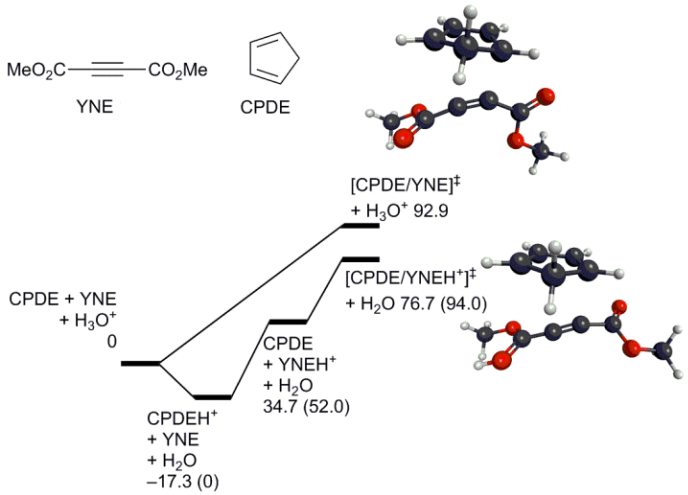
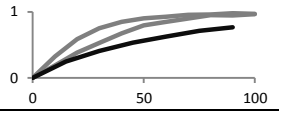


Figure 2.29: *Calculated schematic energy profiles (kJ mol^{-1}) for the acid-catalysed vs non-catalysed Diels–Alder reaction of cyclopentadiene with dimethyl acetylenedicarboxylate*

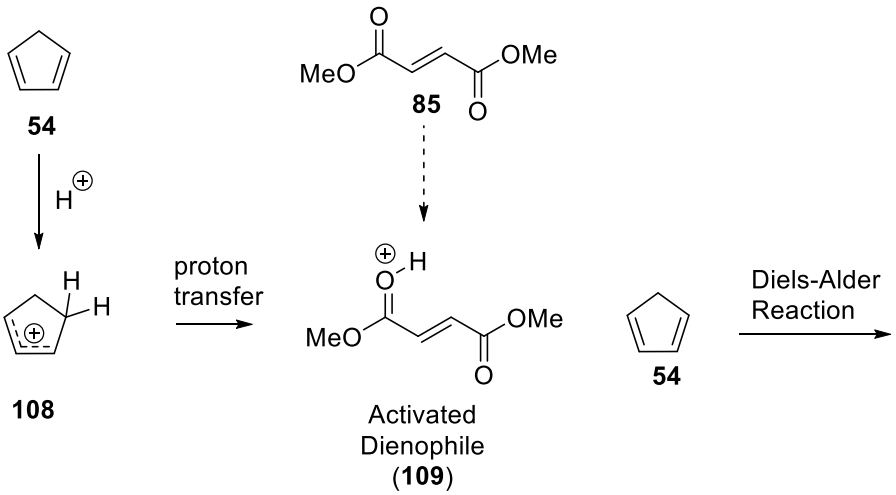
The lack of catalysis in the case of acetylenedicarboxylate dienophiles could be because only one of the carbonyl units is in conjugation with each olefin, reducing the effect of protonation.

Overall, these calculations are consistent with our predictions and experimental data. The calculations for the reaction between cyclopentadiene and dimethyl acetylenedicarboxylate are consistent with Marcus' prediction, but not for the reasons he stated, whereas the calculations for the fumarate reaction are contrary to Marcus predictions. These calculations, in conjunction with our experimental results, demonstrate that acetylenedicarboxylate is not a suitable substrate to probe the mechanism of on-water catalysis.



2.13 Effect of additives

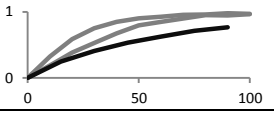
The calculations above were performed using gas phase approximations and under these conditions an unusual outcome was observed. It can be seen from *Figure* 2.28 and *Figure 2.29* that protonation is predicted to first occur on cyclopentadiene followed by proton transfer to the dienophile. (*Scheme 2.22*). The gas phase calculations found cyclopentadiene to be the most basic molecule in the reaction (no experimental pK_b values are available to validate this hypothesis), so we hypothesised cyclopentadiene could be acting as the initial base that gains the proton from the interface and then shuttles it to the fumarate (*Scheme 2.22*).

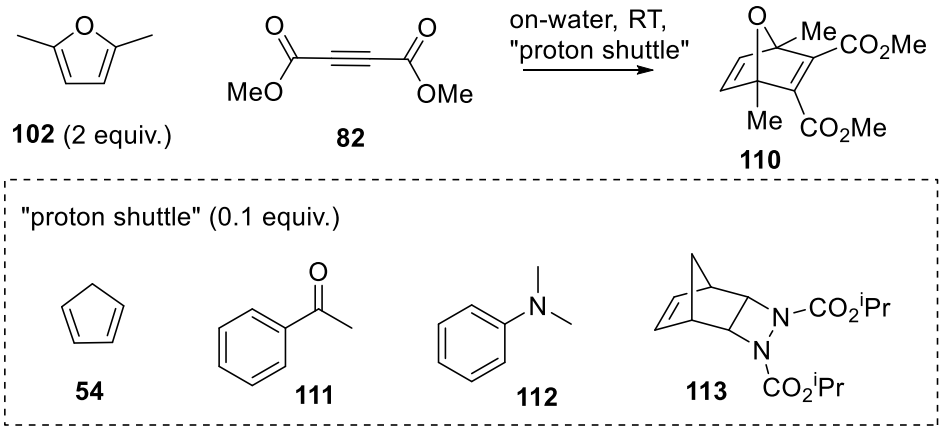


Scheme 2.22: *Proton shuttle hypothesis*

The less active dienes which were subsequently tested may be less basic and may disable this mode of acid transfer catalysis.

Although this effect is likely to be an artefact of the gas phase calculations it was important to fully investigate this outcome. To investigate this hypothesis we added a series of "proton transfer agents" to the reaction between dimethylfuran (**102**) and dimethyl acetylenedicarboxylate (**82**) (*Scheme 2.23*). This reaction was chosen as we still wished to determine if dimethyl acetylenedicarboxylate could be subject to any form of catalysis and 2,5-dimethylfuran was the most unproblematic diene found in the previous studies.

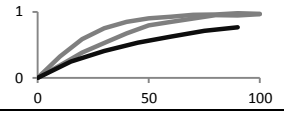




Scheme 2.23: *Effect of additives*

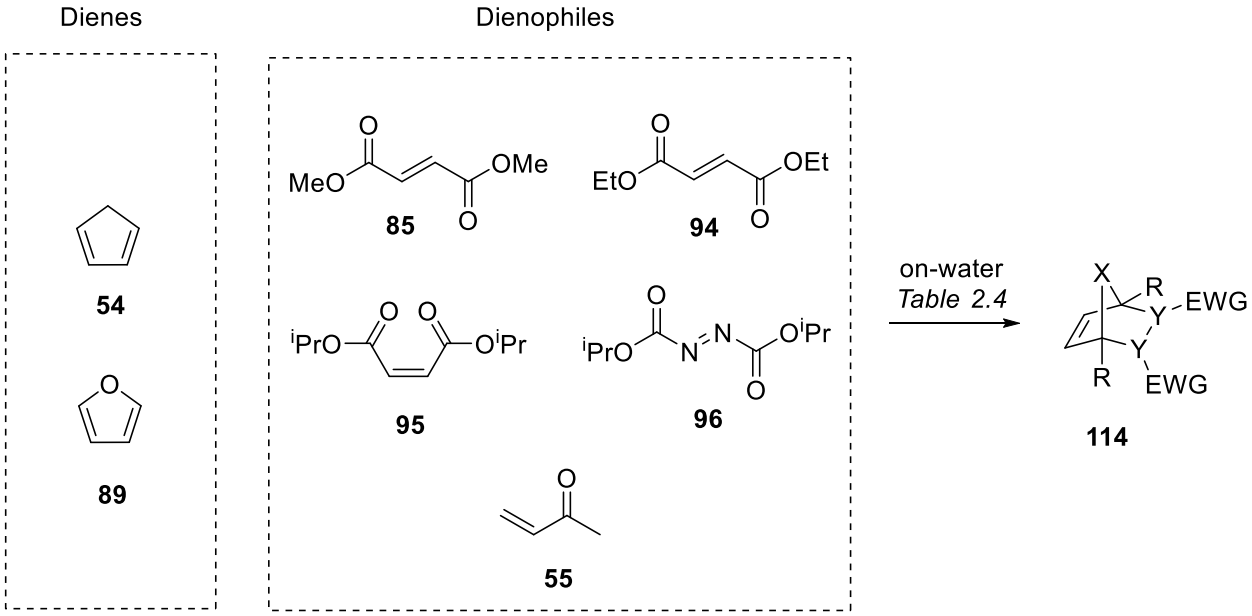
Our proton transfer hypothesis had originated with cyclopentadiene (**54**) as the proton shuttle so this was the natural first choice of proton transfer agent. Unsurprisingly the catalytic quantity of cyclopentadiene (**54**) was consumed almost instantaneously in this case so could not fulfil the role of the proton transfer agent. Although pK_a are widely published pK_b values are not commonly measured. Nonetheless, we opted for acetophenone (**111**) because it has a similar pK_a to cyclopentadiene. Acetophenone also did not cause acceleration of the reaction on-water. Amine bases such as *N,N*-dimethylaniline (**112**) and the adduct of the cycloadditions between quadricyclane and DIAD (**113**, see *Section 2.15*) also did not facilitate on-water catalysis. We did not pursue further proton transfer agents as we lacked any physical evidence to guide our choice.

These finding do not negate the possibilty a proton transfer agent is needed for some on-water reactions, but in this case it is likely to be an artefact of the gas phase calculations performed. These finding did however give further evidence to suggest dimethyl acetylenedicarboxylate is unlikely to be subject to on-water catalysis.



2.14 Other dienophiles

Having examined the range of dienes which can participate in on-water catalysed Diels-Alder reactions we then explored the range of compatible dienophiles (*Scheme 2.24*). For the survey of dienophiles we used cyclopentadiene (**54**) and furan (**89**) as the diene as they provided the most convenient rates of reaction in the previous studies.

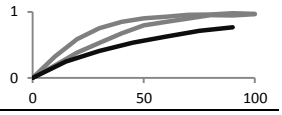


Scheme 2.24: *Other Diels-Alder reactions*

Diene	Diene equiv.	Dienophile	Dieneophile equiv.	On-Water Catalysis	Comments
cyclopentadiene	1	DIAD	2	no	very fast
cyclopentadiene	1.1	diisopropyl maleate	1	-	NR
furan	1	DIAD	1	-	product not water stable
furan	4	dimethyl fumarate	1	no	NR
furan	4	diethyl fumarate	1	no	NR
furan	1	methyl vinyl ketone	1	no	multiple products

Table 2.4: *Other Dienophiles in the Diels-Alder reactions*

Sharpless has shown azodicarboxylates to be highly activated by on-water catalysis so we began by testing the hetero-Diels-Alder reaction between cyclopentadiene (**54**) and diisopropyl



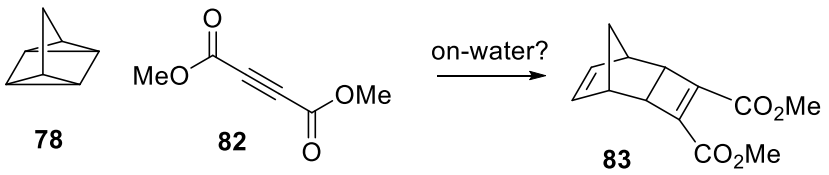
azodicarboxylate (DIAD, **96**). Azodicarboxylates are problematic for on-water rate studies they are not stable to water and can be explosive. In this case however, the problem was that the reaction was complete almost instantaneously, making the rate of reaction difficult to measure.

As discussed above (see *Section 2.8.2*) maleates are generally incompatible with on-water catalysis due to their high water solubility. We synthesised diisopropyl maleate (**95**) in an attempt to make an insoluble but small maleate. Diisopropyl maleate (**95**) was found to be insoluble in water but no reaction occurred between cyclopentadiene (**54**) and diisopropyl maleate (**95**).

We then changed the diene to furan (**89**) in an attempt to slow down the reactions which were too fast to measure with cyclopentadiene. The hetero-Diels-Alder between furan (**89**) and DIAD (**96**) appeared to proceed at an appropriate rate but the product was not stable to water and subsequently decomposed into multiple products. Furan was not active enough to react with either dimethyl or diethyl fumarate. Finally, Breslow has shown the reaction between methyl vinyl ketone (**55**) and cyclopentadiene (**54**) to be catalysed on-water.[38] With this is mind we attempted the reaction between furan (**89**) and methyl vinyl ketone (**55**), this reaction gave multiple products as a result of the conjugate addition of furan to methyl vinyl ketone. This rendered this reaction unusable for our purposes.

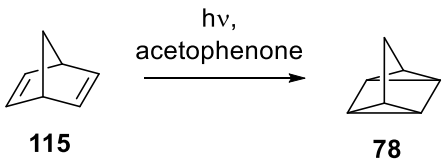
2.15 Marcus and Jung's model reaction

We have previously noted our misgivings with the cycloaddition between quadricyclane (**78**) and dimethyl acetylenedicarboxylate (**82**) as well as our doubts that any reactions with dimethyl acetylenedicarboxylate (**82**) would be catalysed on-water. Despite this we were curious to see how this reaction would respond to on-water conditions (*Scheme 2.25*).



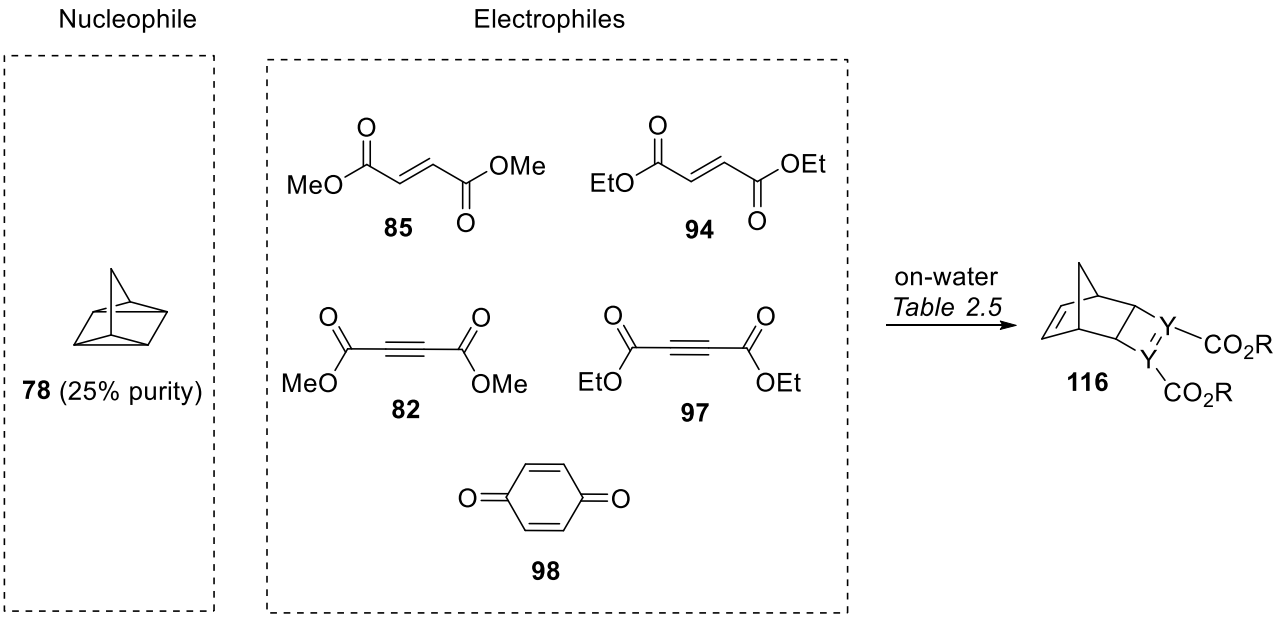
Scheme 2.25: *Marcus and Jung's test reaction*

While dimethyl acetylenedicarboxylate is readily available, quadricyclane (**78**) is not commercially available, even from specialist suppliers. Quadricyclane (**78**) is however ostensibly simple to prepare in a single step *via* a photo-catalysed isomerisation of norbornadiene (**115**) using a well-established procedure published in *Organic Syntheses (Scheme 2.26)*.[75]

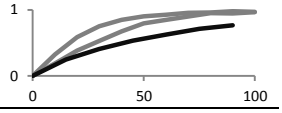


Scheme 2.26: *Synthesis of quadricyclane*

We attempted the photoisomerization reaction using the established procedure. After 7 days of irradiation the reaction had only reached approximately 25% conversion. The long reaction time had also resulted in significant polymerisation of the reactants which formed a coating on the quartz reaction vessel. The increase in opacity associated with the decomposition and polymerisation rendered longer reaction times unfeasible. Quadricyclane (**78**) and norbornadiene (**115**) are very closely related isomers and despite many attempts, could not be separated by any conventional means. Although unable to obtain pure samples of quadricyclane, we attempted several experiments using the impure sample we had obtained (approximately 25% quadricyclane in norbornadiene) (*Scheme 2.27*).



Scheme 2.27: *Marcus' test reaction*



Electrophile	equiv.	Temp.	Internal Standard	On-Water Catalysis	TFA Catalysis	comments
dimethyl acetylenedicarboxylate	1	RT	naphthalene	no	no	slow
diethyl acetylenedicarboxylate	1	RT	naphthalene	no	no	slow
dimethyl fumarate	1	RT	-	no	-	NR
diethyl fumarate	1	RT	-	no	-	NR
benzoquinone	1	RT	-	no	-	NR

Table 2.5: *Reactions with quadricyclane*

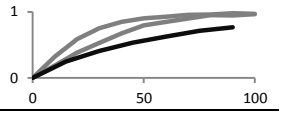
Sharpless reported the neat reaction between quadricyclane (**78**) and dimethyl azodicarboxylate (**79**) was complete after 48 hours (see *Table 2.1, Section 2.5*). Dimethyl acetylenedicarboxylate (**82**) is much less reactive than dimethyl azodicarboxylate (**79**) and only reached approximately 20% conversion after 48 hours. The reaction was still incomplete after one week, at which time analysis of the results was complicated by decomposition and polymerisation. Consistent with Marcus' prediction and our knowledge of acetylene dicarboxylate reactions, we did not observe any acceleration on-water. Mindful of the stark rate difference observed with dimethyl azodicarboxylate (**79**) compared to diethyl azodicarboxylate we also examined diethyl acetylenedicarboxylate (**97**), which gave identical results to the methyl ester. With so many confounding factors, little weight can be placed on this finding and we cannot rule out the norbornadiene (**115**) also participating in the reaction.

We also attempted the cycloaddition between quadricyclane (**78**) and dimethyl fumarate (**85**) and diethyl fumarate (**94**) but neither reacted with quadricyclane (**78**). The same was observed for benzoquinone (**98**).

2.15.1 Summary of quadricyclane reactions

We have carried out a range of Diels-Alder reactions using dimethyl acetylenedicarboxylate (**82**) as the dienophile. None of these reactions were found to be subject to on-water catalysis. This outcome was consistent with the predictions we have made about the nature of on-water catalysis and was supported by high level quantum mechanical modelling of the reaction.

We have performed the cycloaddition between dimethyl acetylenedicarboxylate (**82**) and quadricyclane (**78**) recommended by Marcus and Jung as a test for the mechanism of on-water catalysis, albeit with low purity quadricyclane. We did not observe acceleration of this reaction but



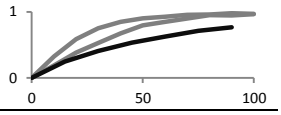
were confounded by technical difficulties obtaining a pure sample of the unusual nucleophile, so little weight can be placed on the findings.

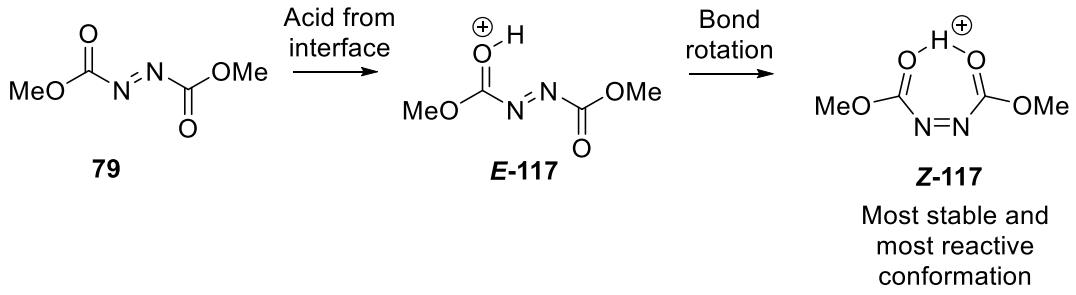
Despite those problems, we have gathered some important information about the nature of this reaction. Both dimethyl azodicarboxylate (**79**) and quadricyclane (**78**) are highly reactive chemicals, but even so the reaction takes 48 hours to reach completion when neat. Dimethyl azodicarboxylate (**79**) is amongst the most reactive molecules available for pericyclic reactions, so it is obvious other reagents will react more slowly. It is nonetheless surprising how much slower the reaction is with diethyl azodicarboxylate and dimethyl acetylenedicarboxylate (**82**) and that no reaction at all occurs with highly active reagents such as dimethyl fumarate (**85**). The slow reaction with carbon centred electrophiles gives credence to the modelling performed by Domingo which suggested this reaction proceeds via a two-step polar mechanism.[53] This suggests the reaction between dimethyl azodicarboxylate and quadricyclane is highly specific and general trends cannot be discerned from it so it should be abandoned as a test case for on-water catalysis.

2.15.2 An alternative acid-catalysed explanation for Sharpless' observations

The remarkable rate enhancement shown by the reaction between quadricyclane and dimethyl azodicarboxylate still requires an explanation and this explanation must also explain why the acceleration is only notable with the methyl variant.

It has been experimentally measured that protonated dimethyl fumarate is two orders of magnitude more acidic that protonated dimethyl maleate due to bidentate coordination of the proton by the maleate.[76] Unlike fumarates and maleates, azodicarboxylates are conformationally flexible and can interconvert between the *E* and *Z* isomers. The *trans*-configuration is the most thermodynamically stable geometry for both steric and electronic reasons, however protonation of dimethyl azodicarboxylate (**79**) by the interface may encourage it to adopt the *Z* configuration to stabilise the nascent positive charge (*Scheme 2.28*). The *Z* configuration of dimethyl azodicarboxylate (***Z*-117**) will be the more reactive conformation for both steric and electronic reasons and it will be further activated by the protonation.





Scheme 2.28: *Acid catalysed explanation for Sharpless' observation*

In contrast to *dimethyl* fumarate, it has been found that protonated *diethyl* fumarate is only one order of magnitude more acidic than protonated diethyl maleate.[77] Given the contrast in measured acidity, we hypothesise the larger ester groups of the azodicarboxylate will retard the adoption of the reactive *Z* confirmation, justifying why the 3000-fold acceleration is *only* observed for the methyl ester. Obviously this mode of activation will be unavailable to dimethyl fumarate and dimethyl acetylenedicarboxylate. Unfortunately we were unable to test this hypothesis with dimethyl maleate as it is too water soluble.

2.16 Summary and Conclusions

The first significant outcome of our studies into on-water catalysis has been the development of the at-water reaction. With this test in place we can, for the first time, conclusively determine whether a reaction is catalysed on-water or in dilute solution.

After determining the Diels-Alder reaction between cyclopentadiene and dimethyl fumarate was catalysed on-water we performed a series of rate studies with additives in the aqueous phase. These studies allowed us to thoroughly investigate mechanism of the catalysis operating in this reaction. We were able to show that protonation is the rate determining step and conclusively determine that catalysis was occurring at the interface rather than in the double layer. On-water catalysis was found to be insensitive to the nature of the aqueous phase, so acid-catalysis can be performed at the interface with both acid and basic solutions.

In addition to understanding the influence of the aqueous phase on the rate of catalysis the purpose of our experiments was to test the predictions made by Marcus and Jung. The mere fact that the Diels-Alder reaction with fumarate showed acceleration is contrary to Marcus and Jung's prediction (*Figure 2.30*).

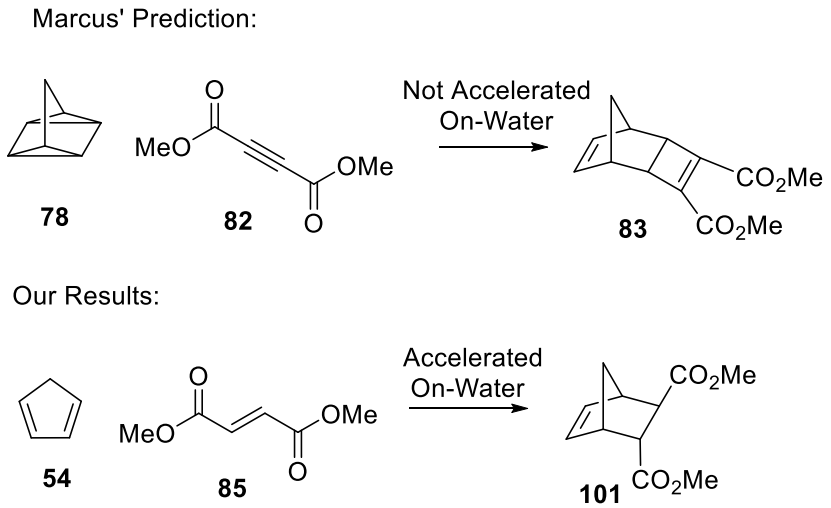
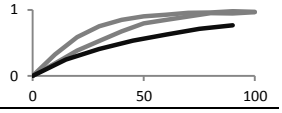


Figure 2.30: *Comparison of results*

We explored many other Diels-Alder reactions, but the stringent requirements of our reaction meant that most reactions were not amenable to convenient rate measurement. None of the Diels-Alder reactions involving dimethyl acetylenedicarboxylate showed any acceleration on-water, which was consistent with our predictions and the computer modelling performed for us. These results



showed dimethyl acetylenedicarboxylate is unlikely to be activated by on-water catalysis so it is not a suitable substrate for investigation of this phenomenon.

We attempted the specific reaction recommended by Marcus and Jung but were hampered by technical difficulties in obtaining of one of the reagents.

None of the data we have gathered or any recently published results have been inconsistent with our theory and predictions.

We have developed a rational and consistent theory for on-water catalysis based on all of the available experimental evidence. From this theory we can predict that any reaction that can be catalysed by mild acid will be subject to on-water catalysis. With this knowledge the full potential of on-water catalysis will be able to come to fruition. The utility of this mode of catalysis will be highlighted in the following chapters.

Several preliminary results from this work were published in *Chemistry – A European Journal* and this report has attracted 31 citations (Scopus).[1]

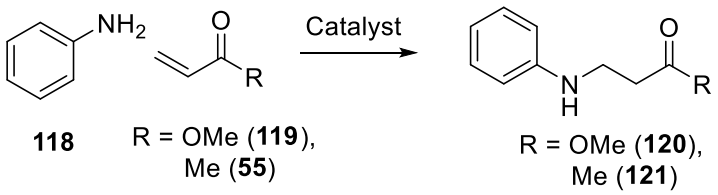
Chapter 3

Introduction to the Conjugate Additions of Anilines

3.1 "Un-catalysed" Michael additions with aniline

The critical test for any scientific theory is the ability to anticipate and predict unknown results. To test our theory for on-water catalysis, we sought to predict which reactions should be subject to on-water catalysis. This would simultaneously provide further evidence for the acid catalysed nature of on-water catalysis and increase the scope and utility of this phenomenon.

Anilines are usually considered poor nucleophiles, and are often overlooked as coupling partners in reactions such as the conjugate addition depicted in *Scheme 3.1*. Despite this perception, experimental measurements by Mayr have shown the nucleophilicity of aniline to be comparable to other primary amines.[78] As such, the generally poor reactivity of anilines can be attributed to steric hindrance from the aryl ring. Given the poor reactivity of anilines under practical conditions, their use in conjugate addition reactions is normally considered a difficult transformation and a range of quite forcing catalytic systems have been developed to increase the rate of reaction.

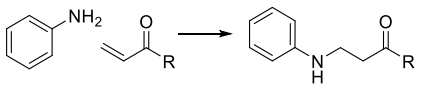


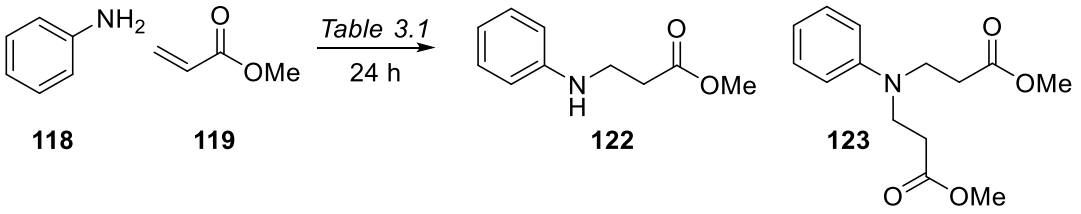
Scheme 3.1: *Conjugate addition of aniline to simple Michael acceptors*

Catalysts for the conjugate addition of aniline (**118**) to methyl acrylate (**119**) (*Scheme 3.1*) include sulphuric acid,[79] *o*-benzenedisulfonimide,[80] vanadyl(IV) acetate,[81] methanesulfonic acid,[82] tungstophosphoric acid,[83] aluminium chloride[84] and heated acetic acid.[85] Notably, many of these reports use strong protic acid catalysis to facilitate this reaction.

Despite the usually forcing conditions required to perform conjugate addition reactions with aniline an examination of the literature uncovered several reports of "un-catalysed" Michael additions of anilines to simple Michael acceptors using water as the solvent.[86] In none of these reports could the authors offer a plausible explanation for these outcomes.

The most thorough study was that of Legros, Crousse and co-workers[87] who reported the "solvent assisted" addition of anilines onto methyl acrylate in alcoholic solvents (*Scheme 3.2*, *Table 3.2*).





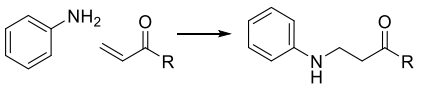
118 **119** **122** **123**

Scheme 3.2: *Reaction reported by Legros and Crousse*

Solvent	Methyl acrylate (equiv)	T (°C)	Conversion (%)	122:123
water	1	80	15	100:0
water	3	80	40	100:0
water/TFE	3	80	100	96:4
TFE	1	80	50	80:20
TFE	3	80	77	71:29
HFIP	1	58	50	37:63
HFIP	3	58	95	37:63
CH_2Cl_2	1-3	40	0	-
ethanol	1-3	78	0	-

Table 3.1: *Results from Legros and Crousse*[87] *(TFE: trifluoroethanol, HFIP: hexafluoroisopropanol)*

As shown in *Table 3.1,* the 1,4-addition of aniline (**118**) onto methyl acrylate (**119**) did not proceed in ethanol at reflux which discounts a simple hydrogen bond donor role for the solvent. The reaction gave 40% of the addition product (**122**) when the reaction was performed with water. When the solvent was changed to 1,1,1-trifluoroethanol at reflux (80°C) the conversion was increased to 77%, and in the even more acidic 1,1,1,3,3,3-hexafluoropropan-2-ol at reflux (54°C) the conversion was further increased to 95%.



Solvent	pK_a	Conversion (%)
ethanol	15.9	0
water	15.7	40
TFE	12.5	77
HFIP	9.3	95

Table 3.2: *Correlation between conversion and* pK_a[87]

The apparent correlation between pK_a of the solvent and conversion indicates these reactions are likely to be acid-catalysed rather than the purported "un-catalysed" process (*Table 3.2*). The small difference in pK_a between ethanol and water contrasted with the large difference in conversion also indicates other factors are influencing the outcome of the reaction. Given these results the Michael addition of aniline to enones and enoate equivalents was an ideal candidate for our investigation of the scope of on-water catalysis.

The use of on-water catalysis may enable these traditionally difficult reactions to be developed into a protocol that is general and could help overcome the negative perception of the nucleophilicity of aniline.

3.2 On-water catalysed conjugate addition reactions with anilines

The conjugate addition of anilines onto methyl acrylate (**118**) and methyl vinyl ketone (**55**) is the most common reaction of this class, so we chose to first focus our attention on these reactions. Studying this process will not only give insight into the mechanism of on-water chemistry, but it will also lead to a simple and efficient synthesis of biologically relevant compounds.

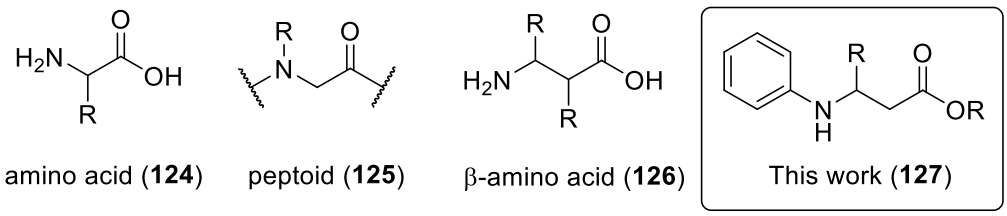
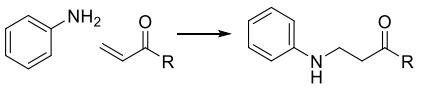


Figure 3.1: *Related compounds*

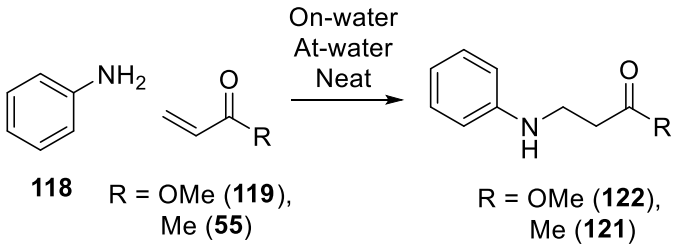
Amino acids (**124**) and peptides are some of the fundamental building blocks of nature and as such it is unsurprising that analogues of these are highly useful. Peptoids (**125**), where the side chain is attached to the nitrogen, are achiral peptide mimics and have demonstrated a wide variety of useful



biological properties (*Figure 3.1*).[88] Due to the absence of the N-H bond peptoids have altered solubility and generally do not form secondary structures. Another useful peptide mimic are peptides which incorporate β-amino acids, known as β-peptides (**126**). β-Peptides are useful as they can form secondary structures[89] and have been used to kill antibiotic resistant bacteria[90] and as anti-fungal agents.[91] As these peptide analogues are not naturally occurring they can avoid problems associated with medicinal peptides such as metabolism, and help overcome drug resistance. This synthetic methodology will allow access to the β-amino acid structure (**127**) in a simple and "green" manner.

3.2.1 Mechanistic investigation

We will first establish the role of the solvent in the conjugate additions of anilines by comparison of the rate of the reaction in the presence and absence of aqueous emulsion using the protocol established in *Section 2.8.5* (*Scheme 3.3*).

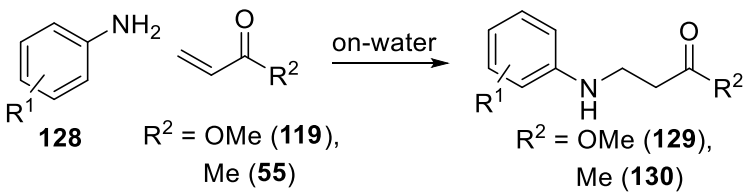


Scheme 3.3: *Investigation of mechanism*

After exploring the mechanism of the reaction we will examine the scope of this reaction by systematically varying both the nucleophile and electrophile component.

3.3 Conjugate addition of anilines to α,β-unsaturated esters and ketones

We will first explore the range of anilines compatible with this reaction by testing a range of electron-rich, electron-poor and sterically hindered anilines (**128**) (*Scheme 3.4*). Published reports[87] show that methyl acrylate (**119**) and methyl vinyl ketone (**55**) participate in this type of reaction so we will use these as our test substrates.



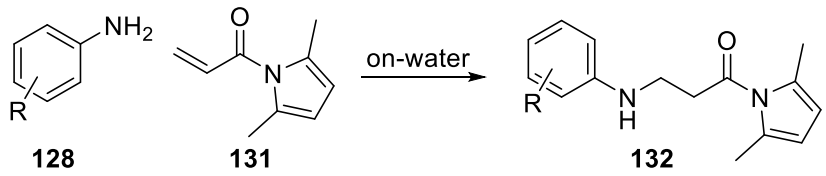
Scheme 3.4: *Testing range of nucleophiles*

Previous reports of this reaction have shown the conjugate addition of aniline (**118**) to methyl acrylate (**119**) to be very slow. The rate of reaction can be increased by using methyl vinyl ketone (**55**) which is inherently more electrophilic. The corollary to the enhanced electrophilicity is that there is a more limited range of reaction which can be performed on the resulting ketone.

To develop this conjugate addition reaction into a useful protocol we require a highly electrophilic Michael acceptor which can also be transformed into a range of other functional groups. The functional group which can fulfil this role is the *N*-acylpyrrole.

3.3.1 Conjugate addition of anilines to α,β-unsaturated N-acylpyrroles

Although *N*-acylpyrroles are highly versatile groups they have been neglected by synthetic chemists. The use of *N*-acylpyrroles will help to overcome some of the limitations previously highlighted (*Figure 3.5*).



Scheme 3.5: *Conjugate addition of unsaturated N-acylpyrrole*

This study will not only improve the scope of the on-water conjugate addition reaction of aniline, it will also highlight the many advantages of *N*-acylpyrrole units.

3.4 Introduction to N-acylpyrroles

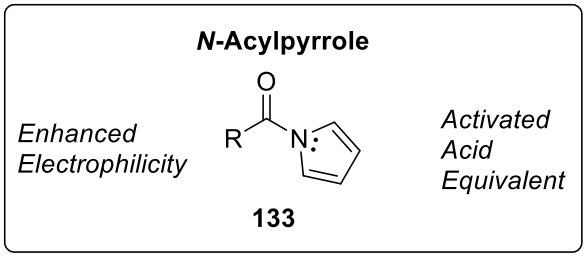


Figure 3.6: *N-Acylpyrroles and their properties*

Protecting groups, activating groups and functional group surrogates are cornerstones of modern organic synthesis. An underutilised functional group which can fulfil all these roles is the 1-acyl-1*H*-pyrrole, commonly known as an *N*-acylpyrrole (**133**).[92] *N*-Acylpyrroles display unusual reactivity because the delocalisation of the nitrogen lone pair in the aromatic pyrrole ring prevents

substantial donation of electron density into the putative amide bond (*Figure 3.7*). This has two principal effects; increased electrophilicity of the carbonyl, and the ability to undergo acyl-substitution reactions (*vide infra*).

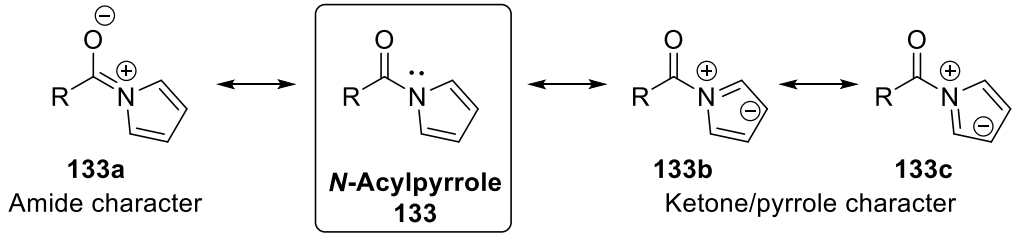


Figure 3.7: *Resonance contributions to N-acylpyrroles*

3.4.1 Increased electrophilicity

The delocalisation of the nitrogen lone pair has profound effects on the reactivity of *N*-acylpyrroles during and after nucleophilic attack. The nitrogen-carbon "amide" bond of *N*-acylpyrroles displays lower bond order than what is normally observed in amides due to the electron withdrawing effects of the pyrrole. The reduced electron density in this bond results in a more electrophilic carbonyl. The small amount of amide character remaining renders the electrophilic character of *N*-acylpyrroles somewhere between ketones and esters (*Figure 3.8*).[93]

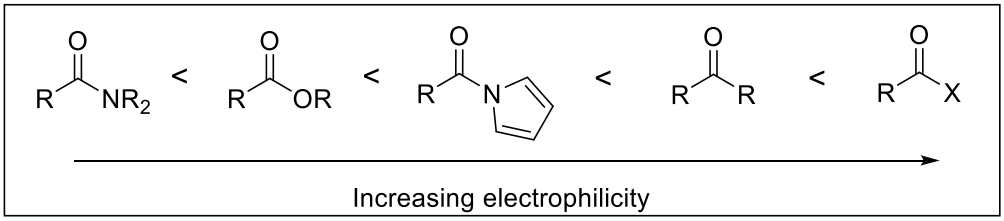
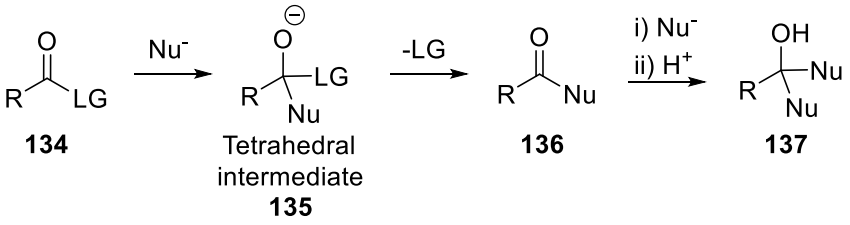


Figure 3.8: *Relative electrophilicity of common carbonyl compounds*

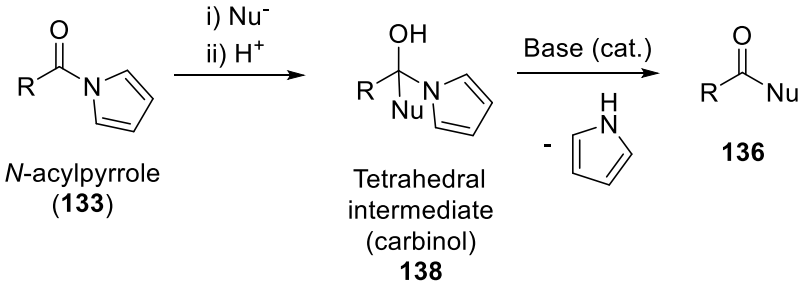
3.4.2 Tetrahedral intermediates and substitution reactions

It is a fundamental principle in chemistry that nucleophilic attack onto a carbonyl gives a tetrahedral intermediate (**135**, *Scheme 3.6*). Tetrahedral intermediates which are able to eliminate a leaving group will lead to the formation of a new carbonyl unit (**136**) thus introducing a new electrophile. It is possible for another equivalent of the nucleophile to add to the new carbonyl (**137**). Hence nucleophilic substitution reactions of activated ester equivalents often give mixtures of products (**134**, **136** and **137**).



Scheme 3.6: *Normal reactivity of carbonyl compounds*

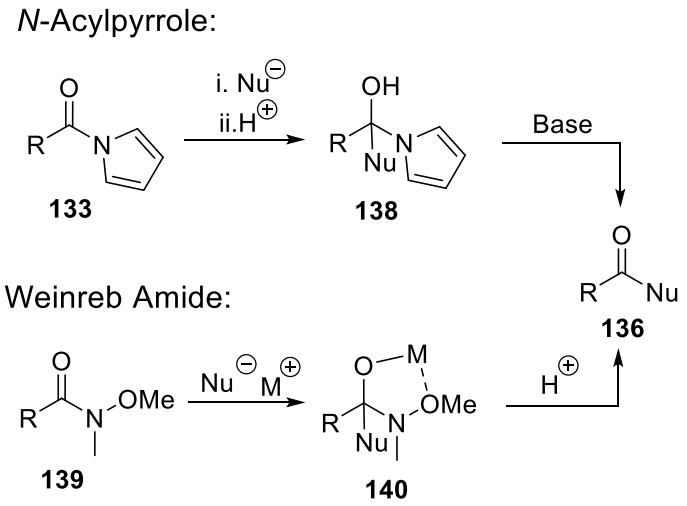
The most notable consequence of the electron withdrawing nature of the pyrrole on *N*-acylpyrrole units is the ability to form *stable* tetrahedral intermediates upon the addition of a nucleophile (*Scheme 3.7*).[94] The addition of a nucleophile to the carbonyl of an *N*-acylpyrrole results in a tetrahedral "carbinol" intermediate **138**. The relative stability of the carbinol signifies that the pyrrole will not be immediately eliminated and *N*-acylpyrrole derived carbinols are often stable enough to be isolated. As no new carbonyl is formed, addition of the nucleophile can only occur once. Later, under controlled conditions, it is possible to eliminate the pyrrole and yield the desired carbonyl compound, **136**.[94]



Scheme 3.7: *Substitution of an N-acylpyrrole*

3.4.3 Comparison to other activated acid equivalents

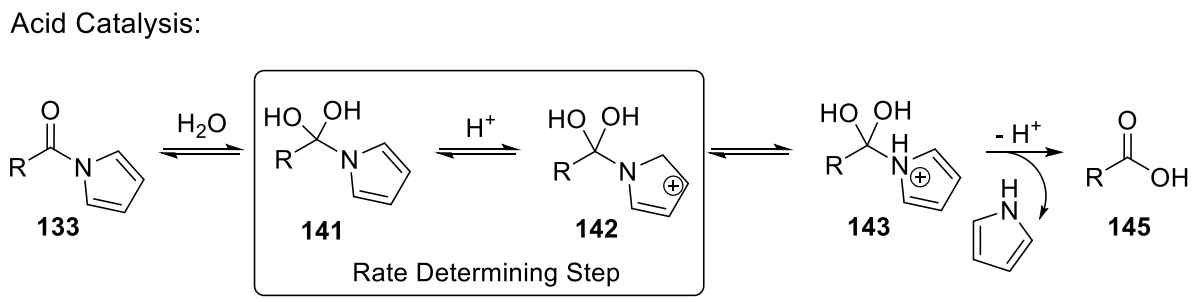
With regard to the formation of stable tetrahedral intermediates *N*-acylpyrroles (**133**) have much in common with Weinreb amides (*N*-methyl-*N*-methoxy amides, **139**). *N*-Acylpyrroles possess significant advantages over Weinreb amides due to the mechanism by which the intermediate is stabilised (*Scheme 3.8*). Weinreb amides (**139**) can also form stable tetrahedral intermediates (**140**) by virtue of chelation of metal ions with the methoxy group (*Scheme 3.8*). The stability of the chelate and the poor nucleofugacity of the methoxyamine prevent Weinreb amides from collapsing during the reaction. The methoxyamine is a good base so upon acidic workup the amine will be protonated and eliminated, thus forming the carbonyl product, **136**.



Scheme 3.8: *Comparison of reactivity*

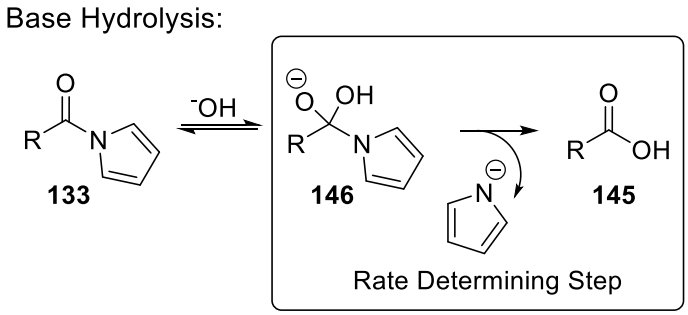
Weinreb amides (**139**) require the use of organometallic reagents to form stable tetrahedral intermediates for two reasons. Firstly, amides are inherently unreactive, so only highly reactive nucleophilic reagents can add to them. Secondly, chelation of a metal ion by the methoxy group is required to prevent elimination (**140**). In contrast, *N*-acylpyrroles (**133**) are ketone-like so a greater range of nucleophiles including weaker nucleophiles such as amines and alkoxides can be added to *N*-acylpyrroles. The greater range of nucleophiles available with *N*-acylpyrroles also often negates the requirement for rigorously anhydrous and anoxic conditions normally associated with the addition of organometallic reagents to Weinreb amides.

The *N*-acylpyrrole can form stable tetrahedral intermediates because the pyrrole anion is a poor leaving group but at the same time the pyrrole ring in carbinol **138** is a weak base that cannot easily be protonated to give neutral pyrrole. In the formation of the new carbonyl from an *N*-acylpyrrole the rate determining step is the elimination of pyrrole under both acidic[95] and basic[96] conditions (*Schemes 3.9 and 3.10*). Pyrrole is a poor nucleophile so the elimination will be irreversible. The mechanism of hydrolysis of *N*-acylpyrroles in both acidic and basic solution has been thoroughly studied and is instructive in demonstrating the unique nature of *N*-acylpyrroles.[95-96]



Scheme 3.9: *Mechanism of Acid Catalysed N-acylpyrrole hydrolysis*

In acidic aqueous solution the carbonyl of the *N*-acylpyrroles is substantially hydrated (**141**) due to its high electrophilicity (*Scheme 3.9*). From tetrahedral intermediate **141** the pyrrole will only be eliminated when it can leave as a neutral molecule, that is, when it is protonated (**142** and **143**). As pyrrole is a weak base the protonation will happen slowly hence protonation is the rate determining step.



Scheme 3.10: *Base catalysis hydrolysis of N-acylpyrrole*

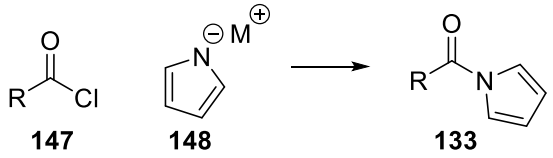
During base hydrolysis, hydroxide will add to the carbonyl (**146**), but as the pyrrole anion is a poor nucleofuge the elimination of pyrrole from the tetrahedral intermediate (**146**) will be the rate determining step (*Scheme 3.10*). In all but the most basic solutions the pyrrole anion will be protonated, the result of which is a relatively poor nucleophile so the reaction will also be irreversible.[97]

From the cases depicted in *Schemes 3.9* and *3.10*, it can be seen that due to the unique chemistry of pyrrole, the loss of pyrrole from a carbinol intermediate is always rate determining. This property can be exploited for selective formation of carbonyl compounds.

3.4.4 Preparation of N-acylpyrrole compounds

The difficulty installing *N*-acylpyrroles in complex molecules is often seen as the major impediment to their use in synthesis. Despite this notion there are a multitude of simple and efficient methods to form *N*-acylpyrroles which can be tailored to suit the demands of any substrate.

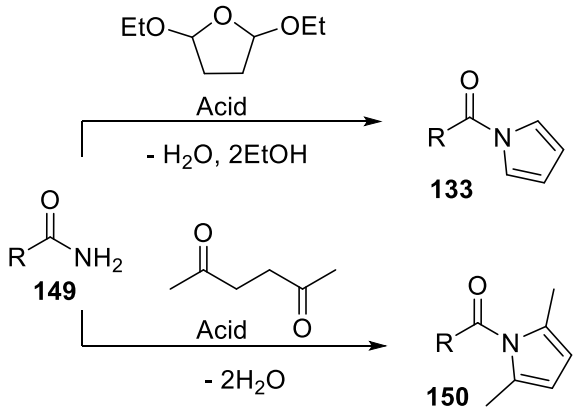
The addition of an *N*-metalated pyrrole into an acyl chloride is a traditional method for generating *N*-acylpyrroles (*Scheme 3.11*).[98]



Scheme 3.11: *N-metalated pyrrole and acyl chloride*

This method is a simple means to generate *N*-acylpyrrole from easily available precursors; however the pyrrole anion (**148**) is highly basic and can be incompatible with base sensitive substrates, especially enolisable carbonyl compounds. *N*-Metalated pyrrole (**148**) can also undergo a rearrangement, leading to substitution at the 2-position of pyrrole.[93] As discussed above it can also be difficult to obtain single products from additions to acyl chloride reagents.

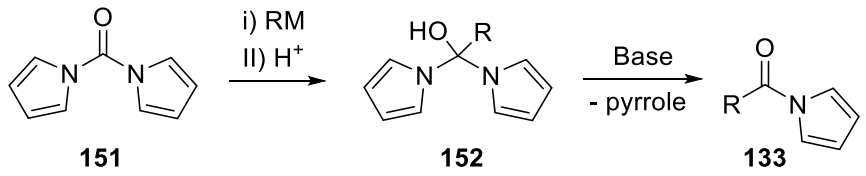
Amides are readily available and stable functional groups so the Paal-Knorr reaction is often an attractive method for forming *N*-acylpyrroles (*Scheme 3.12*).



Scheme 3.12: *Paal-Knorr reaction*

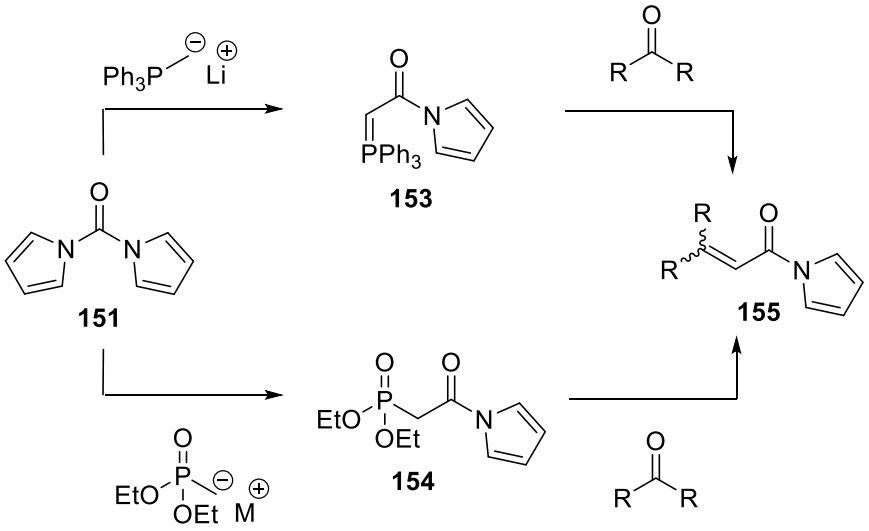
While the Paal-Knorr reaction is facile with amines it can be difficult with amides as the delocalisation of the nitrogen lone pair makes them less nucleophilic. The Paal-Knorr reaction with amides often requires prolonged heating in strongly acidic reagents such as thionyl chloride,[99]

phosphorus pentoxide,[100] acetic acid[101] or toluene sulfonic acid,[102] which reduces its compatibility with many substrates.



Scheme 3.13: *Carbonyl dipyrrole*

Another common method utilises the inherent reactivity of *N*-acylpyrroles by using 1,1′-carbonyl dipyrrole, **151** (*Scheme 3.13*).[93-94] Addition of an organometallic reagent will result in a pyrrolic carbinol (**152**). One of the pyrroles can be eliminated from **152** to yield an *N*-acylpyrrole (**133**).



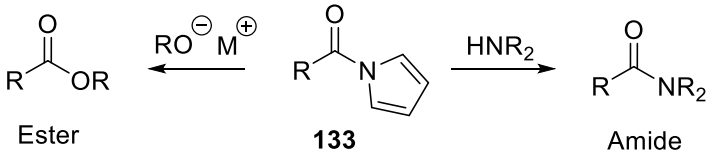
Scheme 3.14: *Olefination to introduce an N-acylpyrrole*

From 1,1′-carbonyl dipyrrole it is also possible to synthesise phosphorus reagents capable of performing Wittig (**153**) or Horner-Wadsworth-Emmons (**154**) olefination reactions (*Scheme 3.14*). This is a mild and efficient method of generating unsaturated *N*-acylpyrroles (**155**).[93, 103]

3.4.5 N-Acylpyrroles as acylating agents

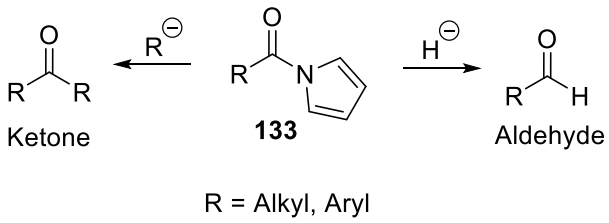
The properties of *N*-acylpyrroles during substitution reactions render them extremely useful as acylating reagents in organic synthesis. *N*-Acylpyrrole can be envisaged as an acid chloride, but more stable and selective. Most *N*-acylpyrroles are indefinitely stable to air and water, and require no special handling or storage. The enhanced electrophilicity at the carbonyl renders them highly capable coupling partners so they are straightforward to incorporate.

N-Acylpyrroles can react with amines to form amides and alkoxides to form esters (*Scheme 3.15*).[104] The high electrophilicity of the carbonyl means the substitution reactions occur under mild conditions.[104]



Scheme 3.15: *Heteroatom nucleophiles with N-acylpyrroles*

N-Acylpyrroles also react with organometallic reagents to form ketones (*Scheme 3.16*).[94] However, possibly the most useful reaction of *N*-acylpyrroles is reduction with hydride to form aldehydes (*Scheme 3.16*).[94, 104-105]

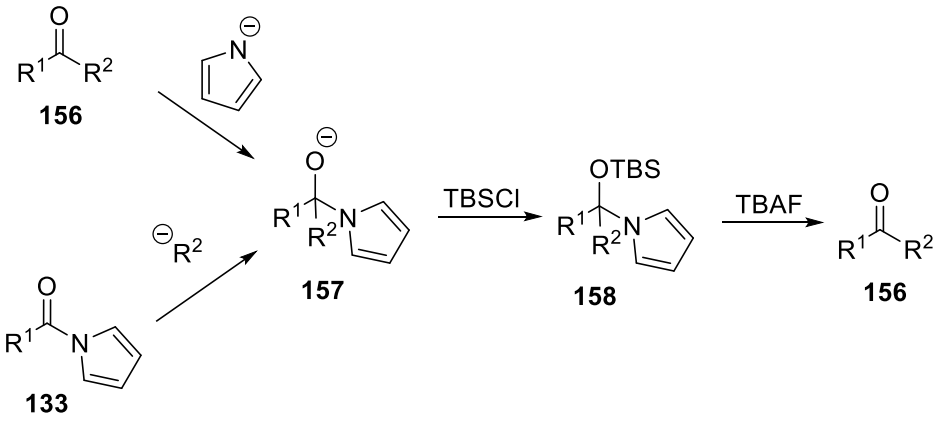


Scheme 3.16: *Organometallic nucleophiles*

Aldehydes are extremely useful functional groups as they can easily be transformed into many other functional groups. However, this utility is a consequence of their high reactivity. As a result, the incorporation of aldehydes into a molecule during a multi-step synthesis will often lead to side reactions and consequently they must be protected. Concurrently, it is often desirable to maintain the carbonyl functionality due to the electronic influence it exerts, and yet, it is often difficult to chemoselectively reduce an ester or amide to give an aldehyde. In such instances the benefits of *N*-acylpyrroles are clear; they maintain the electron withdrawing nature of the carbonyl, but can be selectively transformed into an aldehyde under mild reaction conditions ($NaBH_4$ or $LiBH_4$).[104]

3.4.6 N-Acylpyrroles as a protecting group

As a result of their unique reactivity carbinols derived from *N*-acylpyrroles can also be employed as a protecting group for carbonyl compounds (*Scheme 3.17*).[106] Starting from either an *N*-acylpyrrole (**133**) or a carbonyl compound (**156**) a tetrahedral intermediate (**157**) can be obtained and the carbinol can subsequently be protected as the silyl ether (**158**) in the usual manner. This functional group, **158**, will be susceptible to the same reactions as a conventional silyl ether, but when the silyl ether is removed from **158** it will yield a carbonyl (**156**) through loss of the pyrrole.

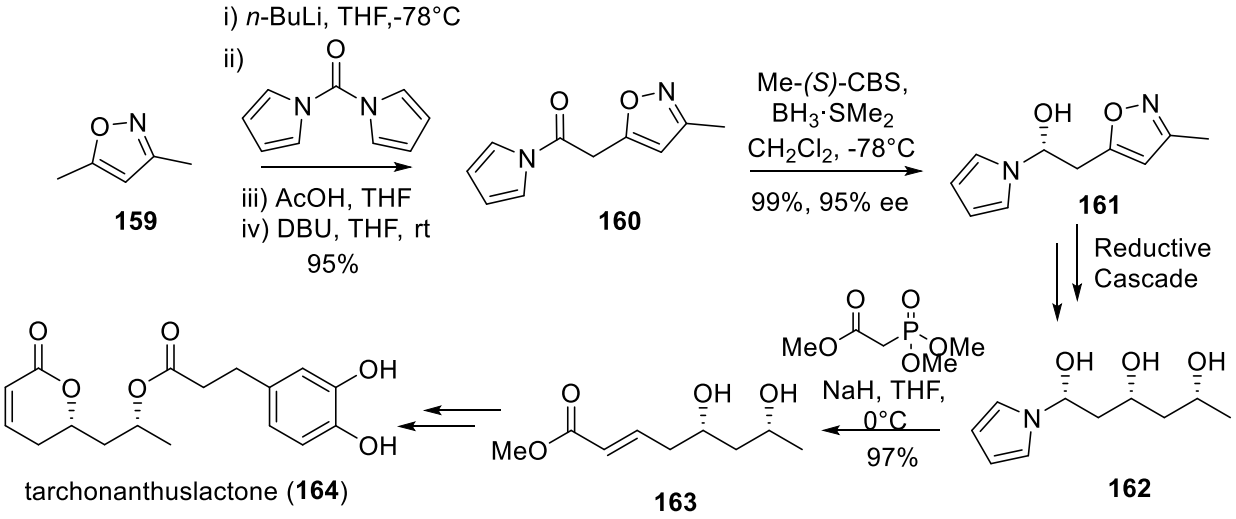


Scheme 3.17: *N-acylpyrrole as a protecting group*[106]

3.4.7 N-Acylpyrroles in total synthesis

The useful properties of *N*-acylpyrroles have been utilised in total syntheses. In the following examples the use of an *N*-acylpyrrole was paramount to the success of the syntheses and no other functional group could have sufficed.

The Dixon group used the Corey-Bakshi-Shibata (CBS) reduction of a *N*-acylpyrrole as the stereo-controlling element in the asymmetric synthesis of tarchonanthuslactone (**164**) (*Scheme 3.18*).[107]



Scheme 3.18: *Key steps in the synthesis of tarchonanthuslactone*

The CBS reduction is generally specific to ketones so the greater electrophilicity of the carbonyl of *N*-acylpyrrole **160** was central to the success of this reduction to alcohol **161**. Compound **161** underwent a series of diastereoselective reductions controlled by the carbinol stereocentre. The pyrrole was then eliminated *in situ* to form an aldehyde and a Horner-Wadsworth-Emmons olefination

was performed to give **163**. Intermediate **163** was then elaborated to yield tarchonanthuslactone, **164**. The *N*-acylpyrrole was indispensable in this synthesis as it was uniquely suited to perform key steps. Any other functional group would have required many more manipulations.

The Trost group have also utilised the unique reactivity of *N*-acylpyrroles in the synthesis of the "northern fragment" of laulimalide (**165**) (*Scheme 3.20*).[108] The key step to synthesis this fragment was to be a Trost Bis-ProPhenol (**166**) catalysed asymmetric aldol reaction (*Figure 3.9*).

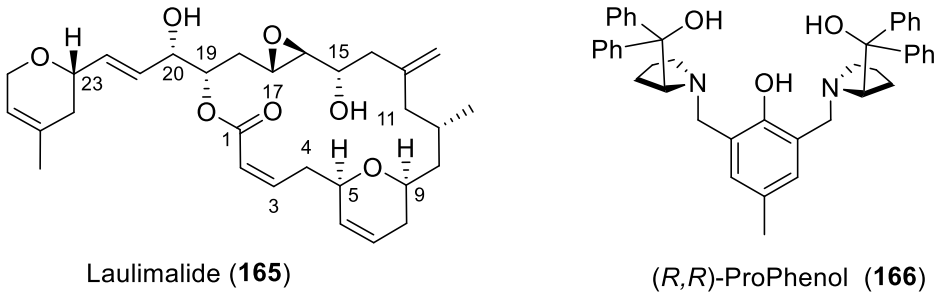
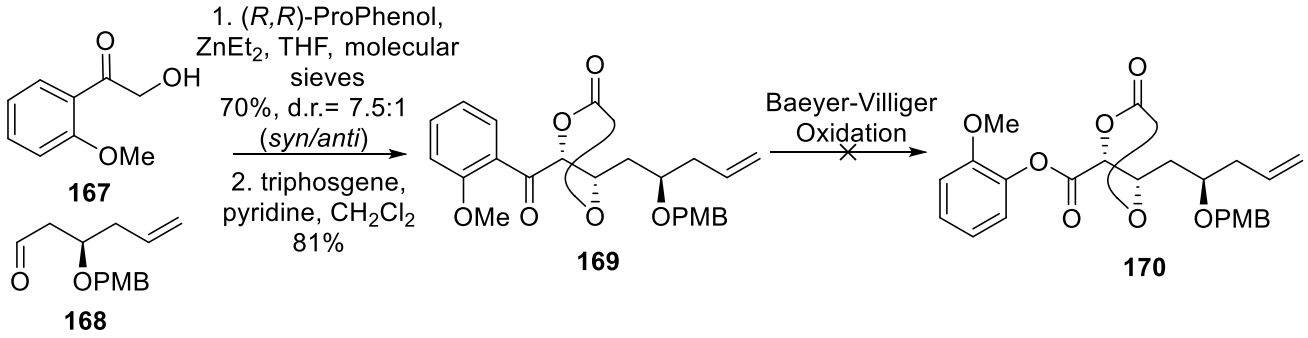


Figure 3.9: *Target and catalyst*

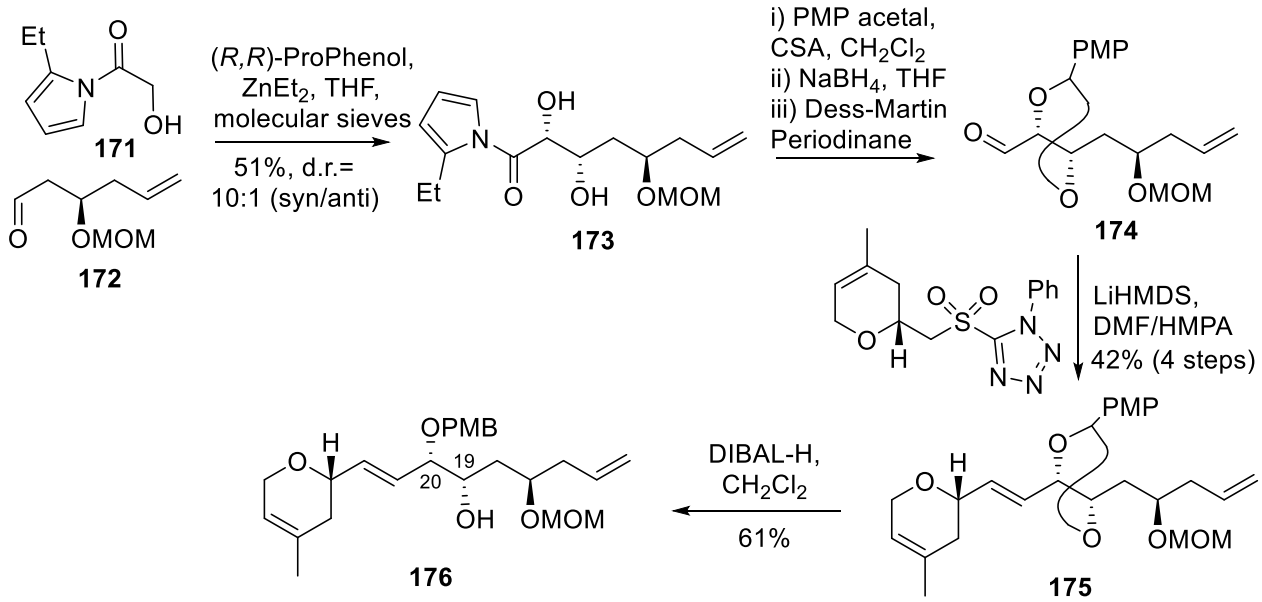
The ProPhenol catalyst requires an enolate derived from an aromatic ketone to induce asymmetry in the aldol reaction. In the initial methodological studies a phenyl ketone (**167**) was used, which successfully underwent the aldol reaction with high selectivity to give **169** (*Scheme 3.19*). All attempts to perform the necessary Baeyer-Villiger oxidation to facilitate the removal of the phenyl group failed.



Scheme 3.19: *Asymmetric aldol reaction and attempted Baeyer-Villiger oxidation*

The corresponding *N*-acylpyrrole (**171**) also underwent the asymmetric aldol reaction (**173**) with higher selectivity than the phenyl ketone (*Scheme 3.20*). *N*-Acylpyrrole **173** was reduced to the alcohol with sodium borohydride then re-oxidised to aldehyde (**174**). Aldehyde **174** underwent the Julia–Kocienski olefination, and PMP acetal **175** was chemoselectively reduced to PMB ether **176** with DIBAL-H.

The conditions required to produce compound **175** chemoselectively also highlight the selectivity imparted by the *N*-acylpyrrole unit. The mild hydride source (sodium borohydride) used to form compound **174** did not affect the PMP acetal, which was subsequently removed with a strong hydride reagent (DIBAL-H). The *N*-acylpyrrole could not have been replaced with any other functional group as any reducing agent capable reducing an ester or amide would have also reduced the PMP acetal.



Scheme 3.20: *Synthesis of the "Northern" fragment of laulimalide*[108]

This synthesis again demonstrates the value of *N*-acylpyrroles. In this case the *N*-acylpyrrole succeeded where more conventional functional groups had failed.

Although *N*-acylpyrroles performed well in these examples, there are few examples of their use in synthesis.

3.4.8 Summary and Outlook of N-Acylpyrroles

Although *N*-acylpyrroles are versatile functional groups and have been demonstrably advantageous in organic synthesis they remain underutilised. The lack of applications of *N*-acylpyrroles in synthesis can be attributed in part to the lack of established compatibility with common reaction conditions. We intend to remedy this situation by performing studies into several reactions which utilise *N*-acylpyrroles and applying them to total synthesis.

3.5 Conjugate addition of anilines to α,β-unsaturated N-acylpyrroles

To conduct a study of unsubstituted Michael acceptors we required an *N*-acryloylpyrrole Michael acceptor. *N*-Acryloylpyrrole would be an extremely useful synthon which could be considered equivalent to methyl acrylate, acryloyl chloride or acrolein, but which would be stable and relatively non-volatile. The low water solubility of this compound would also enhance its on-water reactivity.

The published syntheses of *N*-acryloylpyrrole[94] are low yielding and require multiple steps from uncommon starting materials. We preferred to synthesise *N*-acryloyl-2,5-dimethylpyrrole (**131**) to prevent side reaction at the nucleophilic 2- and 5-positions of the pyrrole ring and as well as to reduce volatility (*Figure 3.10*).

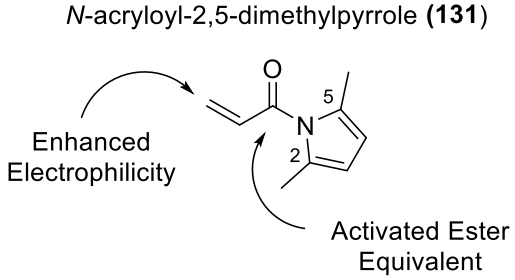
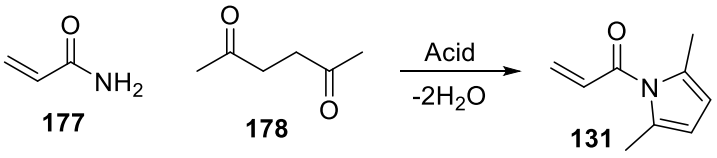


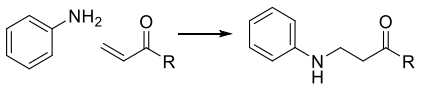
Figure 3.10: *The properties of α,β-unsaturated N-acylpyrroles*

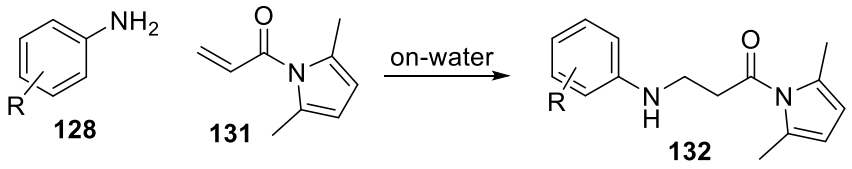
To this end we planned to synthesise *N*-acryloyl-(2,5-dimethyl)pyrrole (**131**) in a single step using the Paal-Knorr pyrrole condensation between acrylamide (**177**) and 2,5-hexanedione (**178**) (*Scheme 3.21*). This would give our desired compound (**131**) in a single step from readily available starting materials.



Scheme 3.21: *Proposed Paal-Knorr synthesis*

Once we have synthesised *N*-acryloyl-(2,5-dimethyl)pyrrole (**131**) we will subject it to the on-water conjugate addition conditions (*Scheme 3.22*). The enhanced electrophilicity will increase the rate of the reaction and the use of an α,β-unsaturated *N*-acylpyrrole will expand the synthetic utility of this reaction.



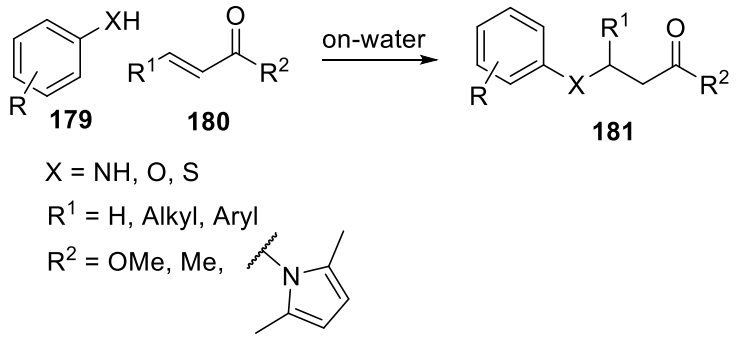


Scheme 3.22: *Conjugate addition of unsaturated N-acylpyrrole*

This study will conclude our investigation into on-water catalysed conjugate addition reactions of anilines to unsubstituted Michael acceptors and we will move on to studies of other nucleophiles and substituted Michael acceptors.

3.6 Conjugate addition with other nucleophiles and Michael acceptors

The incorporation of *N*-acylpyrroles into these conjugate addition reactions was intended to expand the scope of the reaction. As such, we will determine the range of nucleophiles and Michael acceptors which are compatible with his reaction (*Scheme 3.23*). We will attempt the conjugate addition with aniline, phenols and thiophenols as the nucleophile, and a range of substituted esters and *N*-acylpyrroles as the Michael acceptor.

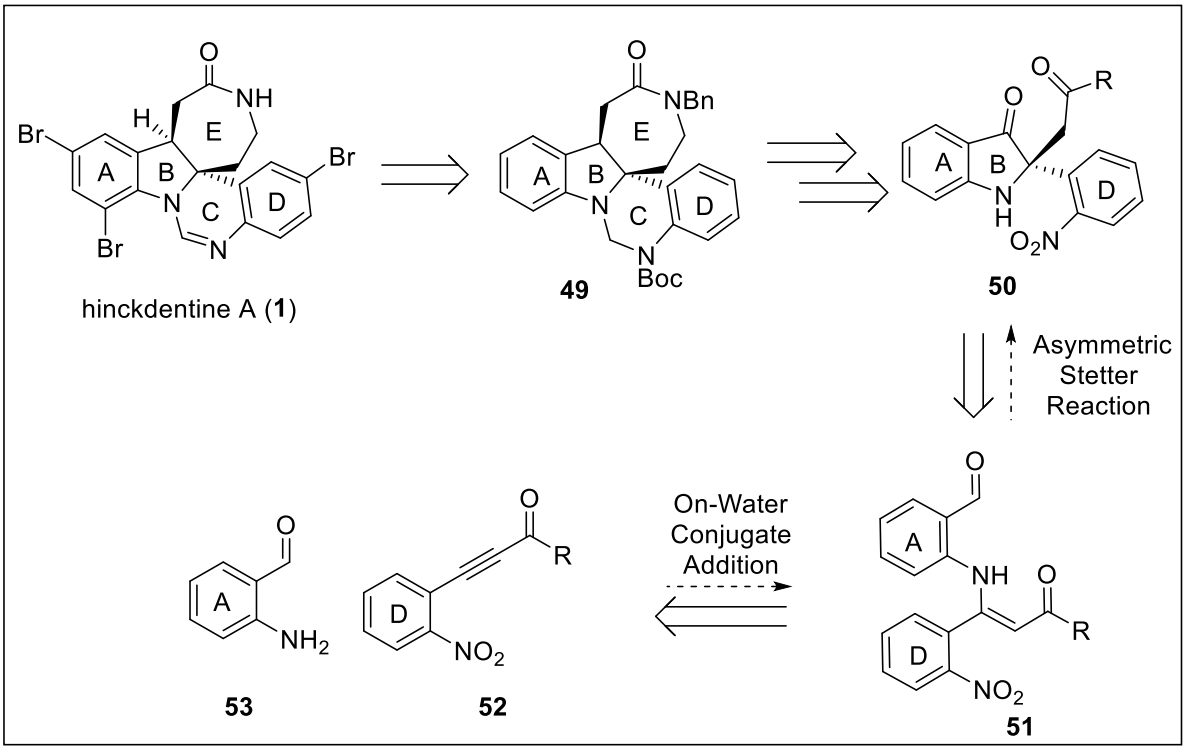


Scheme 3.23: *Testing range of reaction partners*

An inspection of the literature reveals conjugate addition reactions with β-substituted Michael acceptors to be relatively easy with ketones, but very difficult with esters. As such the reactivity of the *N*-acylpyrrole substrates will be illuminating.

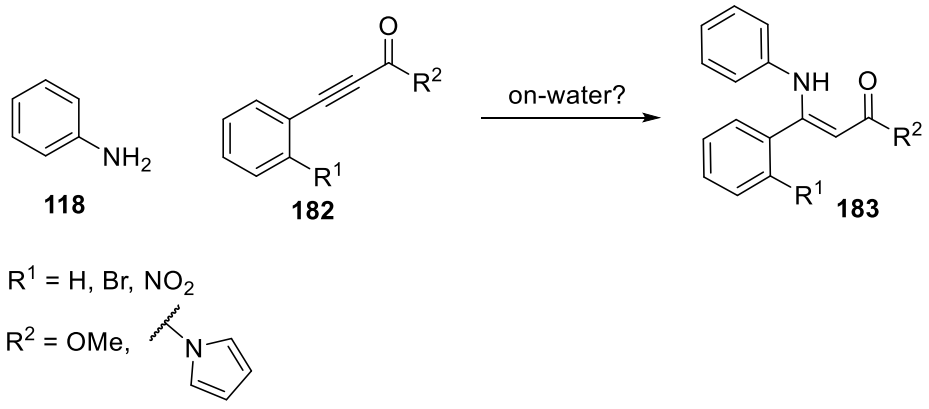
3.7 Conjugate addition of anilines to phenylpropiolate Michael acceptors

Finally we will investigate on-water catalysed conjugate addition reactions of anilines which have direct relevance to our proposed synthesis of hinckdentine A (*Scheme 3.24*).

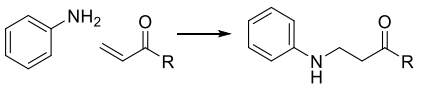


***Scheme 3.24**: Retrosynthesis of hinckdentine A*

With the proposed synthesis of hinckdentine A (**1**) in mind we will perform a study of the on-water catalysed conjugate addition of aniline (**118**) onto phenylpropiolate Michael acceptors (**182**) (*Scheme 3.25*).

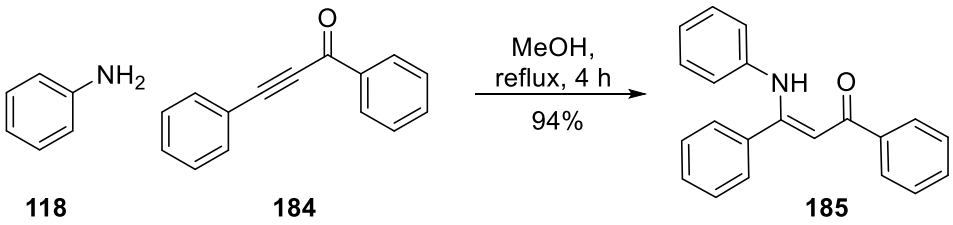


***Scheme 3.25:** Addition of anilines to phenylpropiolate Michael acceptors*



The synthesis of hinckdentine A will require an *o*-nitrogen on the Michael acceptor so our study will include Michael acceptors which are appropriately functionalised to install this nitrogen at a later stage of the synthesis (**182**, R^1 = Br, NO_2). We will also incorporate *N*-acylpyrroles into this study as the increased electrophilicity and unique reactivity of *N*-acylpyrroles will be likely to assist the synthesis.

Conjugate additions of this class are known to work well for 3-phenylpropiolyl ketones (**184**)[109] (*Scheme 3.26*) but are unknown for esters.



Scheme 3.26: *Example of reported conjugate addition reaction*[109a]

There are a handful of examples of this transformation with esters but these are not in fact conjugate additions but π-Lewis acid catalysed hydroamination reactions and use catalysts such as silver(I) triflimide,[110] silver(I) tetrafluoroborate[111] or the Gagosz catalyst (triphenylphosphino gold(I) triflamide).[112] Previous work in the group indicated these π-Lewis acid catalysed reactions are incompatible with the required substrate.

Although there were no reports of anilines adding to phenylpropiolate Michael acceptors it was felt this would be a test for the strength of the methodology and if the ester failed to undergo conjugate addition it is likely the ketone-like *N*-acylpyrrole would participate.

3.8 Conjugate Addition of Anilines - Aims

A discrete set of goals for this section of the thesis was formulated as follows:

1. Determine the role of water in the conjugate additions of aniline to simple acyclic Michael acceptors.
2. Determine the range of aniline nucleophiles compatible with this reaction.
3. Synthesise α,β-unsaturated-*N*-acylpyrrole Michael acceptors and perform conjugate additions of heteroatom nucleophiles.
4. Determine the range of heteroatom nucleophiles compatible with the conditions.
5. Determine the range of β-substituted Michael acceptors compatible with this reaction.
6. Investigate the conjugate addition of anilines to phenylpropiolate Michael acceptors in preparation for the proposed synthesis of hinckdentine A.

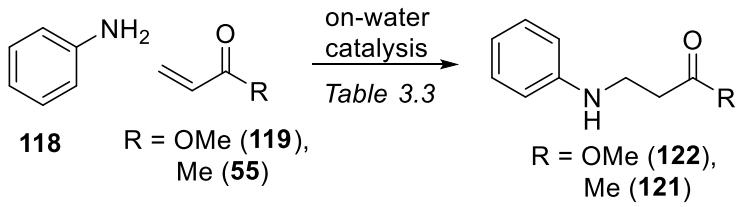
Chapter 3

On-Water Conjugate Additions of Anilines

Results and Discussion

3.9 Mechanistic investigation with methyl acrylate and butenone

We needed to unambiguously establish whether conjugate additions of the type published by Legros and Crousse could be catalysed on-water. Using the protocol we had previously established, we compared the conversion of the neat reaction, the at-water reaction and the on-water reaction after a fixed time (*Table 3.3*). We chose the simplest reactions possible as our test cases, the reaction between methyl acrylate (**119**) or methyl vinyl ketone (**55**) and aniline (**118**, *Scheme 3.27*).



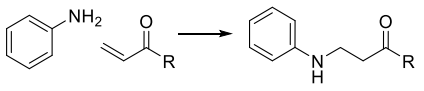
Scheme 3.27: *Test for on-water catalysis*

	Methyl acrylate (119)		Methyl vinyl ketone (55)	
	Time (h)	Yield 122 (%)	Time (h)	Yield 121 (%)
Neat	24	0	1	66
At-Water	24	12	1	89
On-Water	24	21	1	100

Table 3.3: *Evidence that Michael additions are catalysed on-water*

The data in *Table 3.3* clearly shows that, for both methyl acrylate (**119**) and methyl vinyl ketone (**55**), the conjugate addition of aniline (**118**) was faster on-water than neat. In fact the reaction between methyl acrylate (**119**) and aniline (**118**) does not occur at all in the absence of water. In both cases the on-water reaction was faster than the at-water reaction. As we had predicted, these results confirm that the conjugate addition of anilines to enoate and enone acceptors display all of the characteristics associated with on-water catalysis. The relatively high conversion at-water suggests that there is likely to be a significant contribution to the overall conversion from the reaction occurring in water. Regardless, the rate of reaction benefits substantially from the presence of water. The comparison between the two Michael acceptors is also illuminating. It is immediately apparent that water is critical to the success of this reaction with methyl acrylate (**119**), but the more reactive ketone Michael acceptor (**55**) will react quickly even without catalysis.

The on-water reaction between aniline and methyl acrylate had reached 21% conversion after

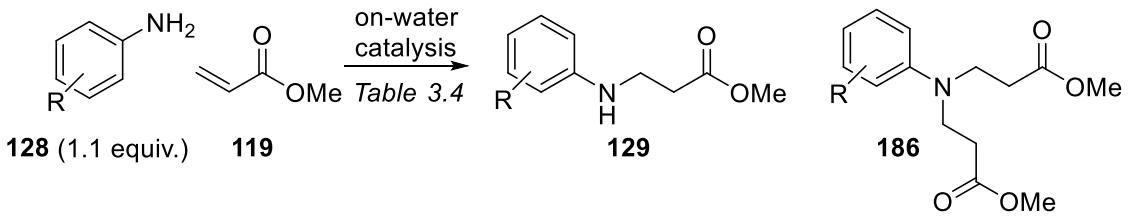


24 hours at room temperature. This is considerably higher conversion than Legros and Crousse observed (15% after 16h at 80°C) despite a much lower reaction temperature. The lower yield at the higher temperature is likely to be due to a combination of the increased solubility decreasing the amount of acrylate in the oil droplets and the greater interfacial area in our case.

These results verify that the conjugate addition of anilines was an unrecognised example of on-water catalysis and demonstrate the predictive power of our model. These results also show the value of possessing a consistent theory for the mechanism of on-water catalysis.

3.10 Range of anilines nucleophiles

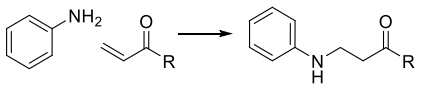
Having fulfilled our first goal by ascertaining that the reactions were occurring under on-water conditions, we next sought to determine the range of anilines which can participate in this reaction (*Scheme 3.28, Table 3.4*).



Scheme 3.28: *Testing range of anilines with methyl acrylate*

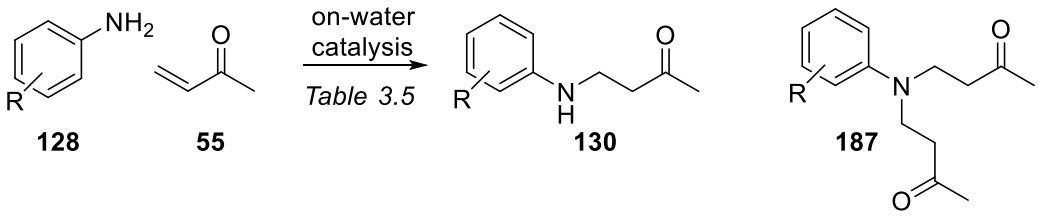
		RT		50°C	
	Nucelophile	**Time (h)**	**Yield 186 (%)**	**Time (h)**	**Yield 129 (Yield 186) (%)**
1	**aniline**	24	21	24	35
2	**4-methoxyaniline**	24	46	24	94
3	**4-aminophenol**	24	16	24	55 (25)
4	**4-methylaniline**	24	18	24	45
5	**2,4-dimethylaniline**	24	6	24	8
6	**4-bromoaniline**	24	NR	24	10
7	**2,4,5-trichloroaniline**	48	NR	24	NR
8	**4-nitroaniline**	48	NR	-	-

Table 3.4: *On-water Michael additions of anilines*



At room temperature a range of electron-rich anilines (*Table 3.4,* entries 1–4) added into methyl acrylate (**119**) in moderate yield. Electron-poor and hindered (*ortho*-substituted) anilines performed poorly or did not react at all (*Table 3.4,* entries 5–8). These results were consistent with other published reports.[87] By raising the reaction temperature from room temperature to 50°C most substrates could be obtained in synthetically useful yield. The electron-poor 4-bromoaniline (*Table 3.4,* entry 6) now participated in the reaction. However, the hindered but electron-rich 2,4-dimethylaniline (*Table 3.4,* entry 5) still gave a poor yield and the hindered and electron-poor 2,4,5-trichloroaniline (*Table 3.4,* entry 7) did not react at all at the elevated temperature.

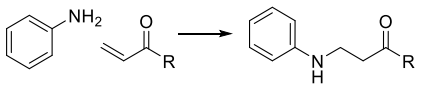
These results were obtained using just 1.1 equivalents of the aniline, rather than the three-fold excess of the Michael acceptor Legros and Crousse required to obtain good conversion. The stoichiometric quantities we have used are more synthetically relevant and portend to the application of this reaction in synthesis.



Scheme 3.29: *Testing range of anilines with methyl vinyl ketone*

	Nucelophile	Time (h)	Yield 130 (Yield 187) (%)
1	**aniline**	1	100
2	**4-methoxyaniline**	1	70 (30)
3	**4-aminophenol**	1	75 (25)
4	**4-methylaniline**	1	80 (10)
5	**2,4-dimethylaniline**	1	100
6	**4-bromoaniline**	1	85
7	**2,4,5-trichloroaniline**	2	14
8	**4-nitroaniline**	24	NR

Table 3.5: *On-water Michael additions of anilines*



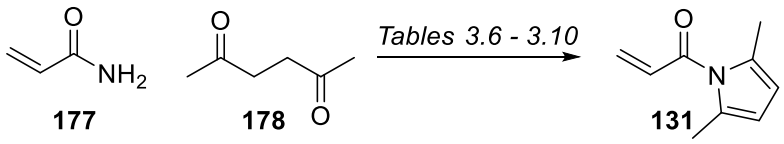
The addition of anilines to the more electrophilic methyl vinyl ketone (**55**) was much more facile (*Scheme 3.29, Table 3.5*). All anilines, both electron-rich and electron-poor resulted in conversion into the desired product at room temperature after only one hour. The hindered 2,4-dimethylaniline gave quantitative conversion (*Table 3.5,* entry 5) and even the highly electron-poor and hindered 2,4,5-trichloroaniline (*Table 3.5,* entry 7) underwent slow addition. For the electron-rich anilines some bis-alkylation was also observed (*Table 3.5,* entries 2-4).

Although 4-nitroaniline did not react with either Michael acceptor, it seems this is due to low solubility rather than low nucleophilicity (*Tables 3.4* and *3.5,* entry 8). This compound did not mix with the Michael acceptor and upon stirring 4-nitroaniline formed a foam rather than an emulsion. This again indicates the interface is important in these reactions.

It is also appears bis-alkylation in the case of 4-aminophenol (*Tables 3.4* and *3.5,* entry 3) is due to a secondary process as the mono-alkylated product converted into the bis-alkylated compound upon standing in chloroform.

Having determined which anilines participate in on-water catalysed conjugate additions with methyl acrylate and methyl vinyl ketone we were ready to incorporate *N*-acylpyrroles into the reaction. With the results from the ester and ketone we had set ourselves a standard against which we could compare our *N*-acylpyrrole Michael acceptor. We had anticipated that *N*-acylpyrrole should be as activated as the ketone but possess more synthetic versatility than the ester. The *N*-acylpyrrole will also be less water soluble.

3.11 N-Acylpyrrole Michael acceptors

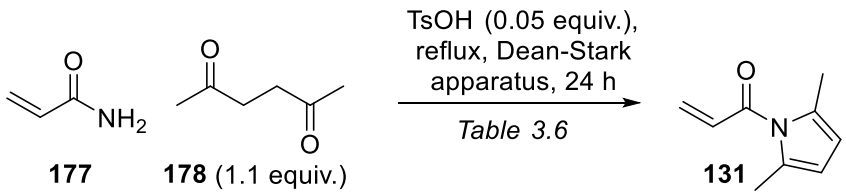


177 178 131

Scheme 3.30: *Synthesis of N-acylpyrrole Michael acceptor*

We began the synthesis of *N*-acryloyl-2,5-dimethylpyrrole (**131**) by heating acrylamide (**177**) and 2,5-hexanedione (**178**) with catalytic *p*-toluenesulfonic acid in toluene under reflux, using a Dean-Stark condenser (*Scheme 3.31*, *Table 3.6).* This method gave the desired *N*-acylpyrrole (**131**), albeit in the somewhat low yield of 24%. For related compounds we had found substitution of benzene for toluene in the Paal-Knorr condensation gave less decomposition and higher yields due to the lower boiling point of benzene. In this instance the yield of Michael acceptor **131** using benzene as the solvent was all but identical to using toluene (*Table 3.6*) so we persisted with toluene due to its lower toxicity. The low yield of this reaction can be largely attributed to the formation of polyacrylamide

which was observed in the reaction mixture soon after the reaction had started.



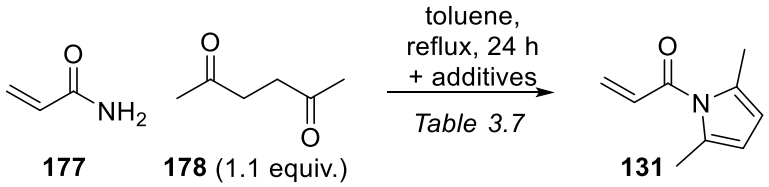
Scheme 3.31: *Synthesis of an N-Acylpyrrole Michael acceptor*

Solvent	Temp. (°C)	Result
toluene	110	26%
benzene	80	24%

Table 3.6: *Effect of solvent*

As we were not content with these low yields further methods to improve the efficiency of the reaction were explored.

It was clear that a large amount of polyacrylamide was being formed during the reaction, so we turned our attention to the use of additives in the reaction to inhibit this polymerisation (*Scheme 3.32, Table 3.7*).



Scheme 3.32: *Additives for the synthesis of N-Acylpyrrole Michael acceptor*

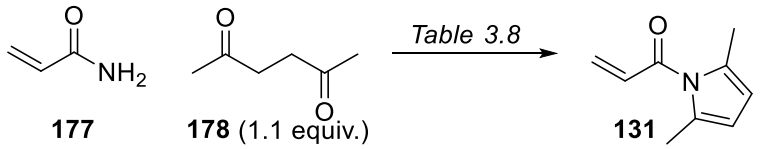
	Acid (equiv.)	Additive (equiv.)	Other	Result
1	TsOH (0.1)	hydroquinone (0.1)	azeotropic distillation	**131** (5%)
2	ascorbic acid (0.2)	ascorbic acid (0.2)	azeotropic distillation	decomp.
3	TsOH (0.05)	-	$CaCl_2$	polymerisation

Table 3.7: *Effect of additives*

Polyacrylamide is formed by radical polymerisation so we first added hydroquinone as a

radical inhibitor, but this significantly decreased the yield of the reaction (*Table 3.7,* entry 1). We next tested ascorbic acid, which would have the dual role of being both a radical scavenger and acid catalyst. The presence of ascorbic acid appeared to prevent polymerisation but did not give the desired condensation product (*Table 3.7,* entry 2). We were aware that the high rate of reflux associated with the use of a Dean-Stark apparatus may have been adding to the amount of polymerisation, so we added a drying agent which would allow for more control over the temperature of the reaction. Performing the formerly successful Paal-Knorr condensation in the presence of anhydrous calcium chloride did not facilitate the reaction but in fact increased the amount of polymerisation due to the additional nucleation sites.

As toluenesulfonic acid was a successful catalyst for the reaction we screened further Brønsted and Lewis acids to determine if these could improve the yield of compound **131** (*Scheme 3.33, Table 3.8*).



177 **178** (1.1 equiv.) **131**

Scheme 3.33: *Screening acid catalysts for the synthesis of N-Acylpyrrole Michael acceptor*

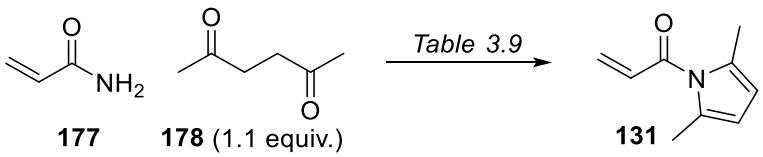
	Acid/ Lewis acid (equiv.)	Time	Temp. (°C)	Solvent	Other	Result
1	TsOH (0.05)	24 h	110	Toluene	Azeotropic distillation	26%
2	AcOH	24 h	100	AcOH	-	NR
3	$Bi(NO_3).5H_2O$ (0.5)	24 h	RT	CH_2Cl_2	-	NR
4	$Ti(O^iPr)_4$ (1.1)	24 h	RT	Toluene	-	NR
5	$SnCl_4$ (1.1)	24 h	110	Toluene	-	NR
6	$BF_3.Et_2O$ (1.1)	24 h	RT	THF	-	6%

Table 3.8: *Acid catalysis*

A common method for the Paal-Knorr condensation employs acetic acid as the solvent, catalyst and dehydrating agent. In this instance, acetic acid was found to be ineffective, giving none of the desired product (*Table 3.8*, entry 2). Given that protic acids had not improved the situation, a range of oxo-philic Lewis acids were screened (*Table 3.8*, entries 3-6). Reports in the literature had indicated that bismuth nitrate[113] and titanium(IV) isopropoxide[114] were able to catalyse Paal-Knorr

condensations. These were found to be unsuccessful for our synthesis. Boron trifluoride gave a small yield (6%) of the product but had consumed all of the starting material, so it appeared the product was not stable to this reagent.

We then sought to utilise the numerous recent reports of microwave assisted Paal-Knorr reactions (*Scheme 3.34, Table 3.9*).[115]



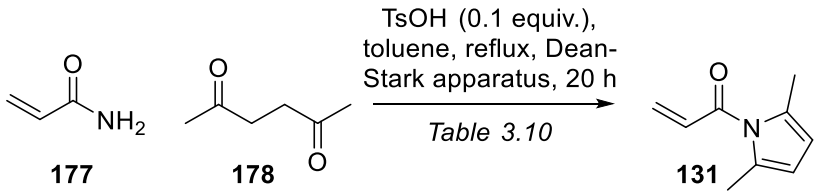
Scheme 3.34: *Synthesis of N-Acylpyrrole Michael acceptor under microwave irradiation*

Catalyst (equiv.)	Time	Temp. (°C)	Solvent	Other	Result
TsOH (0.05)	10 min	170	Neat	μW (150 W)	trace product/ polymerisation
AcOH	10 min	170	AcOH	μW (150 W)	polymerisation
Ascorbic acid (0.2)	10 min	170	Neat	μW (150 W)	decompostion
TsOH	10 min	170	Neat	μW (150W)/ Hydroquinone (0.1)	decompostion
$Bi(NO_3).5H_2O$ (0.5)	30 min	100	THF	μW (150W)	NR

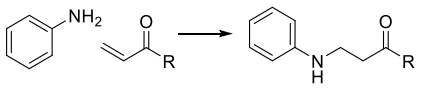
Table 3.9: *Influence of microwave irradiation*

Under a range of conditions, with a range of catalysts under microwave irradiation no significant yield of the pyrrole was obtained (*Table 3.9*).

Finally, given that polymerisation of acrylamide appeared to be the largest problem we decided to modify the stoichiometry and use an excess of the amide, contrary to traditional practice (*Scheme 3.35, Table 3.10*).



Scheme 3.35: *Synthesis of N-Acylpyrrole Michael acceptor*



Acrylamide (equiv.)	2,5-hexandione (equiv.)	Yield
1	1.1	26%
4	**1**	**45 – 58%**
5	1	45%
10	1	30%

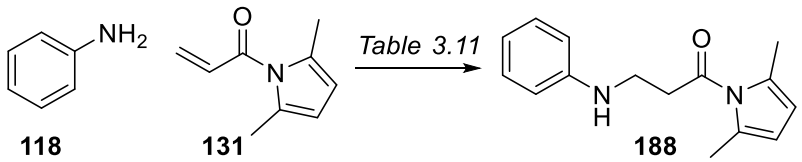
Table 3.10: *Effect of stoichiometry*

All of the previous reactions had used a 10% excess of dione **178**, which conventionally gives the highest conversion to the heterocycle. Using a four to one ratio of acrylamide to 2,5-hexanedione a vastly improved yield of up to 58% was obtained (*Table 3.10*). Further increasing the quantity of acrylamide did not improve the yield. When performed under air rather than nitrogen the yield was consistently higher, presumably due to radical inhibition by oxygen. Although the yield was still only moderate, this was acceptable due to the ease of operation and low cost of the reagents.

Having uncovered a simple method for the synthesis of an *N*-acryloylpyrrole Michael acceptor (**131**) we were ready to attempt the on-water conjugate addition reaction with a range of anilines and compare the results to those obtained with the ester and ketone substrates (see *Section 3.10*).

3.11.1 On-water catalysis with N-acylpyrrole Michael acceptors

The first objective was to confirm that, like the previous Michael additions, the conjugate addition of anilines to unsaturated *N*-acylpyrroles was catalysed on-water (*Scheme 3.37, Table 3.11*).

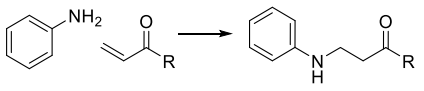


118 **131** **188**

Scheme 3.37: *Test for on-water catalysis*

	Time (min)	Yield (%)
Neat	15	51
At-Water	15	63
On-Water	15	70

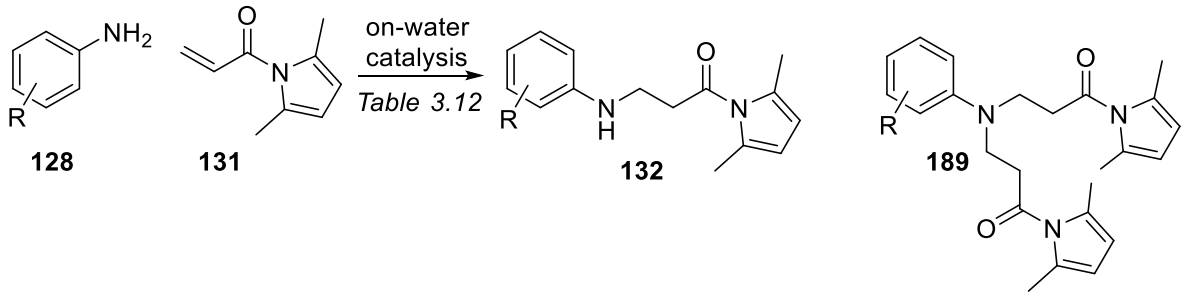
Table 3.11: *Conversion after 15 minutes*



Performing the standard yield comparison of the neat, at-water and on-water reactions after a fixed period of time (*Table 3.11*), showed that the reaction is on-water catalysed, but the rate enhancement is less pronounced than with either of the previous Michael acceptors. On-water catalysis will nonetheless be useful with less nucleophilic anilines.

3.11.2 Conjugate addition of anilines with N-acylpyrrole Michael acceptors

Having confirmed the addition of aniline (**118**) to *N*-acylpyrrole Michael acceptors is catalysed on-water we proceeded to determine how this reaction performed in comparison to the previously studied conjugate addition reactions (*Scheme 3.39, Table 3.12*).



Scheme 3.39: *Addition of aniline to unsaturated N-acylpyrrole*

		RT		50°C	
	Nucelophile	**Time (h)**	**Yield 132 (Yield 189) (%)**	**Time (h)**	**Yield 132 (%)**
1	**aniline**	4	96	-	-
2	**4-methoxyaniline**	4	98	-	-
3	**4-aminophenol**	4	75 (25)	-	-
4	**4-methylaniline**	4	98	-	-
5	**2,4-dimethylaniline**	16	70	24	100
6	**4-bromoaniline**	4	20	24	98
7	**2,4,5-trichloroaniline**	24	30	24	65
8	**4-nitroaniline**	24	NR	-	-

Table 3.12: *N-Acylpyrrole Michael acceptors*

Like the reaction with methyl vinyl ketone, all of the anilines tested reacted with *N*-acryloyl-2,5-dimethylpyrrole (**131**) at room temperature with vigorous stirring (*Table 3.12*). The

only exception was 4-nitroaniline (*Table 3.12,* entry 8), which again did not form an emulsion. Unlike the conjugate additions onto methyl vinyl ketone bis-alkylation was only observed for 4-aminophenol (*Table 3.12,* entry 3). The electron-poor and hindered substrates reacted slowly at room temperature but when heated to 50°C the reaction gave the conjugate addition products in good yield, even the hindered and extremely electron-poor 2,4,5-trichloroaniline participated in the reaction (*Table 3.12,* entry 7).

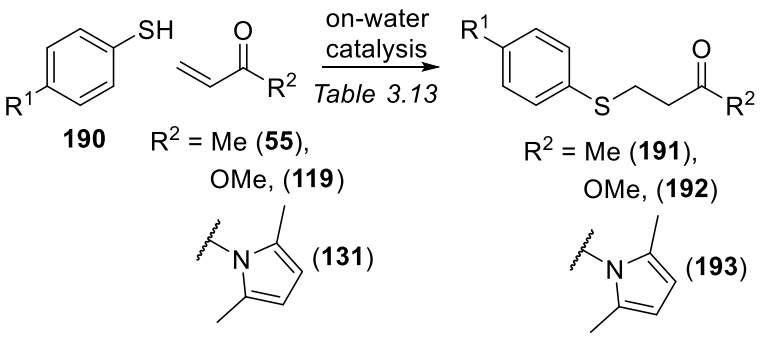
In comparison to the previously tested Michael acceptors, *N*-acryloyl-2,5-dimethylpyrrole (**131**) reacted more quickly and with more sterically encumbered and electronically deactivated anilines than methyl acrylate (**119**) and gave only mono-alkylation products unlike methylvinyl ketone (**55**). This demonstrates that acceptors *N*-acryloyl-2,5-dimethylpyrrole (**131**) possess all of the reactivity benefits of a ketone, but with the synthetic utility of an ester or Weinreb amide.

With the success of anilines as nucleophiles in the conjugate addition reaction, we moved on to the next goal of determining the range of heteroatom nucleophiles which would participate in the reaction.

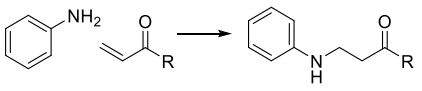
3.12 Thiol and phenol nucleophiles

3.12.1 Thiophenol nucleophiles

Anilines are traditionally considered poor nucleophiles (see *Section 3.1*) but the use of on-water catalysis has facilitated their addition to enoate equivalents. Given this result we moved on to investigate how strongly nucleophilic thiophenols would respond to these conditions (*Scheme 3.40*). Determining the range of nucleophiles which participate in the reaction will open up opportunities for tandem and cascade reactions.



Scheme 3.40: *Michael addition of thiophenols*



	Methyl acrylate		Methyl vinyl ketone		*N*-Acryloyl-2,5-dimethylpyrrole	
Nucleophile	**Time (h)**	**Yield (%)**	**Time (h)**	**Yield (%)**	**Time (h)**	**Yield (%)**
thiophenol	4	46	1	95	1	95
4-bromothiophenol	4	45	1	95	1	96
4-methylthiophenol	4	38	1	92	1	94

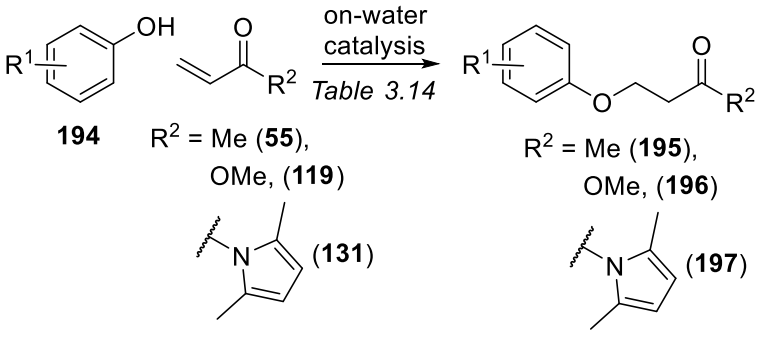
Table 3.13: *Conjugate addition of thiophenols*

Thiophenols are strong nucleophiles and the conjugate addition of thiols is sometimes referred to as a "click reaction".[116] As such thiophenols were expected to add to all Michael acceptors quickly. Representative electron-rich, electron-neutral and electron-poor thiophenols were screened against the three Michael acceptors (*Table 3.13*).

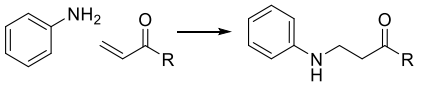
In the case of methyl acrylate (**119**) the desired conjugate addition products were obtained in moderate yield along with numerous uncharacterised by-products which appeared to be the result of Baylis-Hillman-type reactions. All thiophenols added to methyl vinyl ketone (**55**) in high yield, with none of the by-products observed. The α,β-unsaturated-*N*-acylpyrrole (**131**) was equally as reactive as the ketone, but unlike the ester no by-products were observed. Again this demonstrated the advantages *N*-acylpyrroles.

3.12.2 Phenol nucleophiles

Thiophenol had participated in the conjugate addition reaction well so we moved on to study the much less nucleophilic phenol nucleophiles (*Scheme 3.41*).



Scheme 3.41: *On-water Michael addition of phenols*



	Methyl acrylate		Methyl vinyl ketone		*N*-Acryloyl-2,5-dimethylpyrrole	
Nucleophile	**Time (h)**	**Yield (%)**	**Time (h)**	**Yield (%)**	**Time (h)**	**Yield (%)**
phenol	24	NR	24	NR	24	NR
4-methylphenol	24	NR	24	NR	24	NR
naphthol	24	NR	24	NR	24	NR
2-methoxylphenol	24	NR	24	NR	24	NR

Table 3.14: *Attempted on-water Michael addition of phenols*

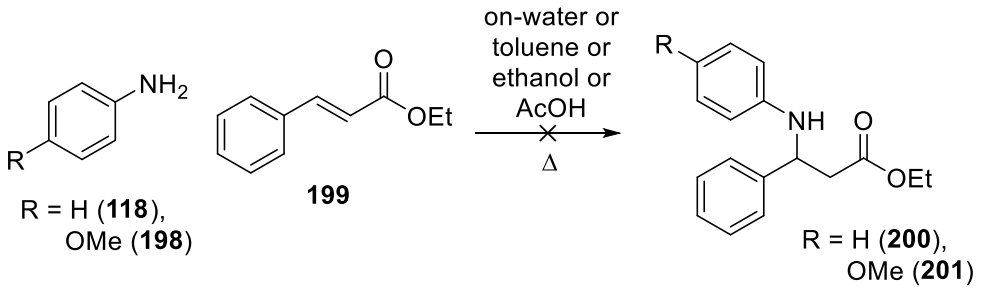
Although anilines and thiophenols had proved to be competent coupling partners, it was found that phenols could not be added to any Michael acceptors, even to the highly active methyl vinyl ketone (*Table 3.14*). An examination of the literature revealed that the only examples of Brønsted acid catalysed Michael additions of phenols employs highly acidic and forcing conditions such as heated triflimide or fluoroboric acid.[117] Such strongly acidic conditions indicate that these reactions are likely to be occurring by a mechanism other than protonation of the carbonyl. It is probable that the few published acid catalysed conjugate additions of phenols occur by an S_N1 mechanism with protonation of the alkene followed by nucleophilic attack of the resulting carbocation.

Our inability to perform Michael additions with phenols (*Scheme 3.41, Table 3.14*) provided further evidence for the acid-catalysed nature of on-water catalysis. The Michael addition of anilines and thiophenols (which are known to be acid catalysed) could be accomplished (see *Sections 3.10, 3.11* and *3.13*). However the conjugate addition of phenol, which (except under specific conditions) is only known to be base catalysed, could not be accomplished. Marcus's hydrogen bonding model does not account for the acceleration seen in these Michael addition reactions. According to the modelling published by Marcus and Jung, nitrogen atoms will hydrogen bond to the "dangling" hydroxyl groups at the surface. For the case of the conjugate additions, this would deactivate the aniline toward reaction. Consequently Marcus's hydrogen bond model predicts the greater stabilisation of the starting material, which would slow this reaction.

3.13 Variation of electrophile

Having successfully demonstrated the efficacy of the on-water catalysed conjugate addition of aniline to unsubstituted Michael acceptors we next explored substituted Michael acceptors.

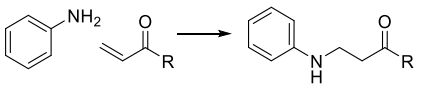
We began our studies by testing the reactivity of aniline (**118**) with a simple ester Michael acceptor, ethyl cinnamate (**119**, *Scheme 3.42*).

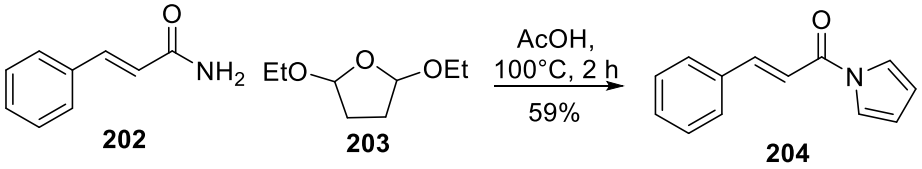


Scheme 3.42: *Conjugate addition to cinnamate*

Aniline (**118**) did not react with ethyl cinnamate (**199**) under on-water conditions, even when heated to 80°C. The reaction also failed to occur under any of the more conventional conditions employed. With the lack or reaction with aniline we moved to the much more nucleophilic *p*-anisidine (**198**), but again no reaction occurred under any conditions. Given no reaction occurred between *p*-anisidine (**198**) and ethyl cinnamate (**199**) there appears to be an intrinsic limit in reactivity of cinnamate Michael acceptors with aniline nucleophiles. It is pertinent to note that there are no published accounts of this type of conjugate addition occurring. This lack of reaction is likely to be due to the perturbation of the electronic nature of the α,β-unsaturated system.

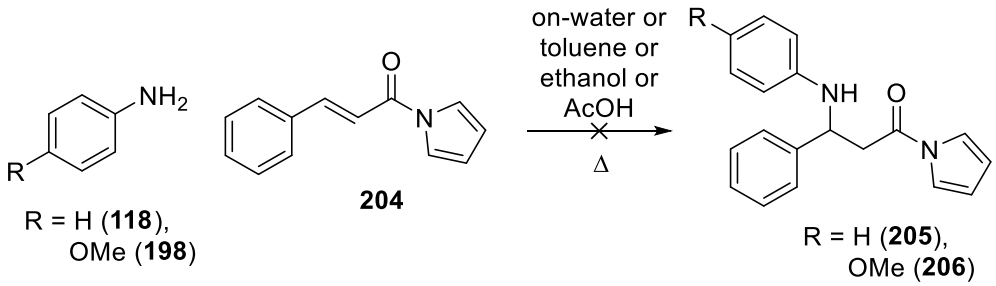
Although there are no reports of conjugate additions to cinnamates there are many reports of Michael additions of anilines to chalcones, but these are non-trivial and require catalysis from ionic liquids,[118] squaric acid,[119] TMSI[120] and N-heterocyclic carbenes,[121] amongst others. There are also some encouraging reports of anilines being added to chalcones in heated glycerol.[122] The contrasting reactivity of the ester and ketone substrates made it fitting to examine the reactivity of *N*-cinnamoylpyrroles and determine if they were ketone-like enough to overcome the reactivity problems, while retaining the utility of the ester.





Scheme 3.43: *N-cinnamoylpyrrole*

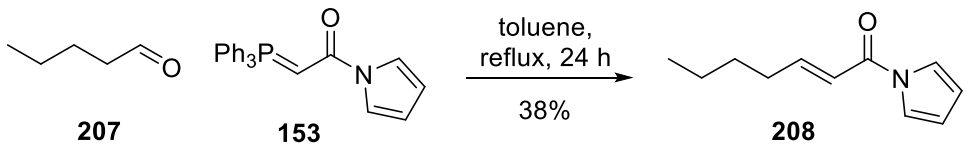
N-Cinnamoylpyrrole (**204**) was easily prepared in good yield using a Paal-Knorr condensation between cinnamamide (**202**) and 2,5-diethyoxytetrahydrofuran (**203**, *Scheme 3.43*).



Scheme 3.44: *Attempted conjugate addition with N-cinnamoylpyrrole*

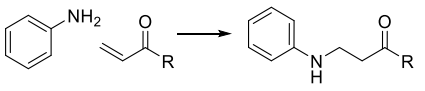
Unfortunately, we observed the same reactivity pattern with the *N*-acylpyrrole Michael acceptor **204** as with the ester substrate (**199**). Neither aniline (**118**) nor *p*-anisidine (**198**) reacted with *N*-cinnamoylpyrrole (**204**) under on-water conditions up to 80°C, or in toluene, ethanol or acetic acid at reflux.

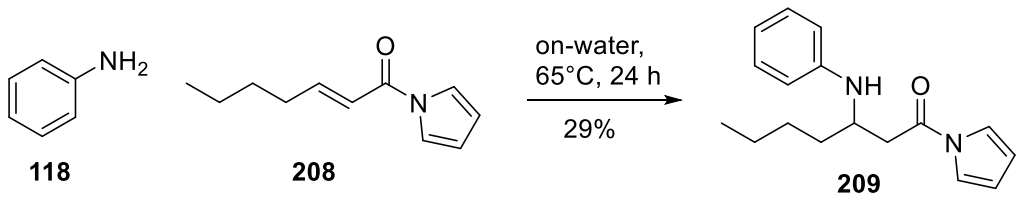
Unsubstituted Michael acceptors had participated in the on-water conjugate additions of anilines, whereas the phenyl substituted Michael acceptors did not participate all. To determine whether this contrasting reactivity was due to steric or electronic effects we synthesised an *N*-acylpyrrole Michael acceptor with a non-aromatic β-substituent (*Scheme 3.45*).



Scheme 3.45: *Wittig reaction to form alkyl-substituted N-acylpyrrole*

As shown in *Scheme 3.45*, the alkyl-substituted *N*-acylpyrrole (**208**) was formed through a Wittig reaction of pentanal (**153**) in acceptable yield.





118 **208** **209**

Scheme 3.46 *Conjugate addition with substituted Michael acceptor*

Under on-water conditions *N*-acylpyrrole **208** did not react with aniline (**118**) at room temperature. At 50°C, a trace amount of product could be seen after 24 hours. At 65°C considerable amounts of decomposition occurred but 29% of the product (**209**) was formed after 24 hours. Comparing the conversion of the on-water reaction to the neat reaction revealed no significant difference, so it appears this reaction is not subject to on-water catalysis.

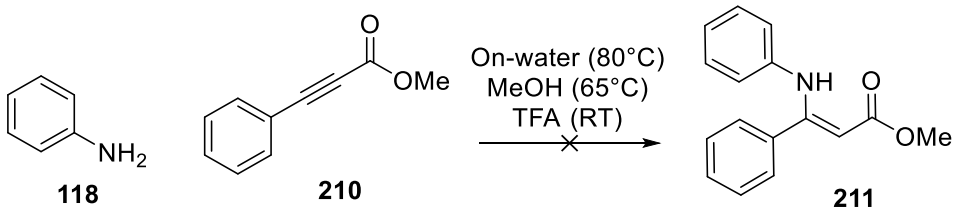
Experimental evidence in conjunction with examination of the literature showed α,β-unsaturated esters with large β-substituents are not subject to conjugate additions by anilines. Even α,β-unsaturated esters with small β-substituents do not readily participate in conjugate addition reactions with aniline. The only examples in the literature are of crotonates and require Lewis acid catalysis.[123]

Given the lack of published results for the conjugate addition of anilines to substituted ester Michael acceptors, even the poor yield of conjugate addition product **209** represents an improvement to the current the state-of-the-art. This also shows α,β-unsaturated *N*-acylpyrroles have some similarity to α,β-unsaturated ketones, which are known to participate in this type of reaction.[122, 124]

It appears β-substituted Michael acceptors are inherently unreactive toward the addition of aniline and this reactivity limitation cannot be overcome using on-water catalysis. As such we did not pursue these reactions any further.

3.14 Phenylpropiolate Michael acceptors

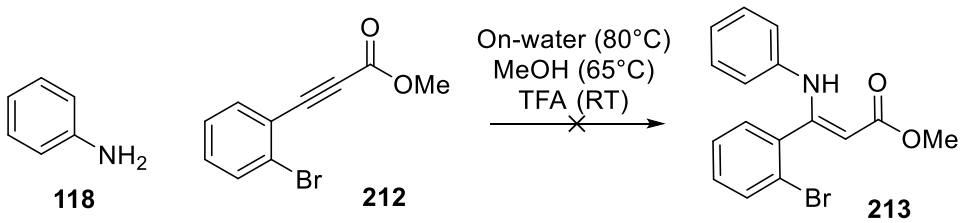
We finally turned our attention to the class of on-water catalysed conjugate additions that was to be used for the total synthesis of hinckdentine A (see *Scheme 3.24*). We began this study with the most simple substrates available; methyl phenylpropiolate (**210**) and aniline (**118**, *Scheme 3.47*). Methyl phenylpropiolate (**210**) was obtained using a literature procedure.[125]



Scheme 3.47: *Attempted Michael addition of aniline to methyl phenylpropiolate*

Aniline (**118**) did not reaction with methyl phenylpropiolate (**210**) under on-water catalysis up to 80°C or when heated in methanol. Nor did any reaction occur under the influence of a strong protic acid.

The lack of reaction between these simple substrates was concerning, but we moved to Michael acceptors which could be of potential use in our proposed synthesis of hinckdentine A (*Scheme 3.48*). To this end we investigated the conjugate addition onto methyl 2-bromophenylpropiolate (**212**). The aryl bromide could easily be transformed into an aryl amine by a Buchwald-Hartwig coupling, should the conjugate addition occur.

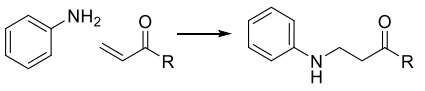


Scheme 3.48: *Attempted conjugate addition with o-bromophenylpropiolate*

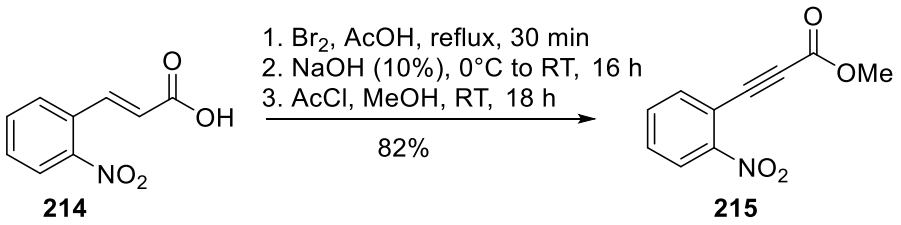
As was the case with the unsubstituted phenylpropiolate, no reaction occurred with methyl 2-bromophenylpropiolate under any circumstances (*Scheme 3.48*).

Although these results appeared discouraging they were not entirely unexpected as this mode of reactivity is not precedented in the literature.

Regardless, we moved to the preferred substrate for the synthesis of hinckdentine A. Methyl

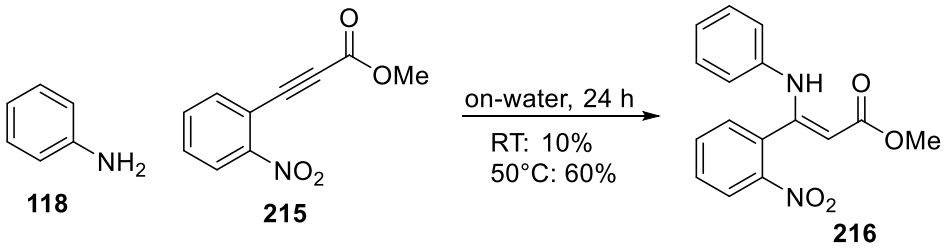


o-nitrophenylpropiolate (**215**) was synthesised in high yield three steps starting with *o*-nitrocinnamic acid[126] (**214**, *Scheme 3.49*). This synthesis required no purification and could be performed on large scale (up to 20 g). It would also possible to produce ester **215** in a single step *via* Sonogashira coupling between methyl propiolate and *o*-nitroiodobenzene,[127] however the cross coupling suffers from poor yields and requires high palladium loadings and excess methyl propiolate. Therefore, the longer but more robust, atom efficient and cost effective route was followed.



Scheme 3.49: *Synthesis of propiolate Michael acceptor*

Aniline (**118**) was stirred vigorously with methyl 3-(2-nitrophenyl)propiolate (**215**). After 24 hours at room temperature 10% of the desired conjugate addition product (**216**) was isolated as a single isomer (*Scheme 3.50*). When the temperature of the reaction was raised to 50°C a 60% yield of the conjugate addition (**216**) product was isolated.



Scheme 3.50: *On-water conjugate addition to phenylpropiolate*

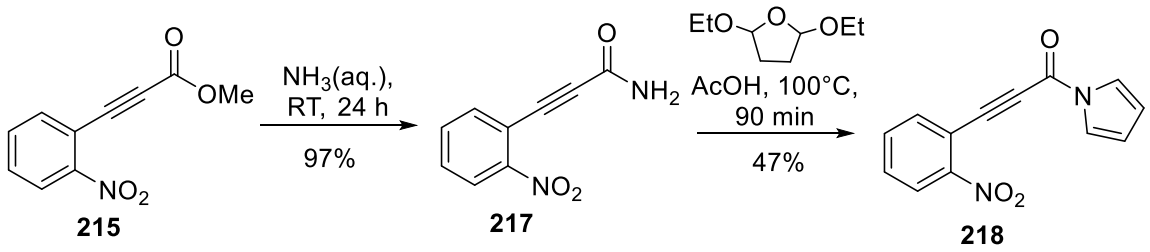
This represented a significant result as it was the first conjugate addition of an aniline to a phenylpropiolate, the only previous reports of similar reaction were π-Lewis acid catalysed hydroamination reactions.[110-112]

To determine the role of the water in the reaction we repeated the reaction in a range of solvents. The conjugate addition did not occur in toluene (a non-polar solvent) at reflux, nor did the reaction occur in DMSO (polar aprotic) at 100°C. The reaction did proceed in good yield in methanol, a polar protic solvent. The reaction also failed to occur with water in the absence of vigorous stirring, indicating the interface is necessary for reaction.

Regardless of the role of water these results confirmed our synthetic strategy for the synthesis

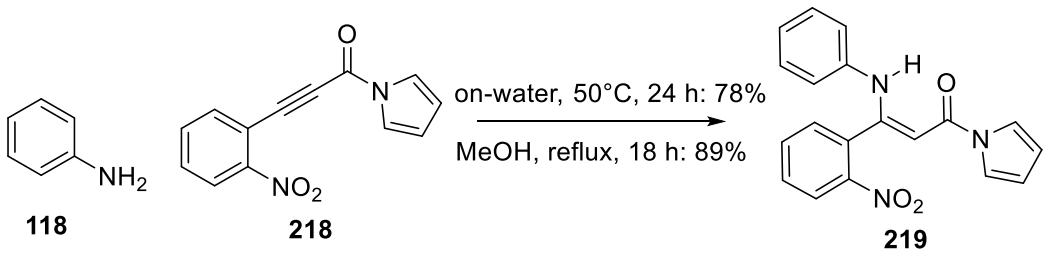
of hinckdentine A was viable.

The synthesis of ester **215** was easily extended to give *N*-acylpyrrole **218.** Amidation of ester **215** with aqueous ammonia gave the primary amide **217** in high yield and in sufficient purity to negate the need for chromatography. The amidation was followed by the Paal-Knorr reaction with 1,4-diethoxytetrahydrofuran which gave *N*-3-(4-nitrophenyl)propiolylpyrrole (**218**) in 47% yield (*Scheme 3.51*). These reactions could be performed on large scale to give compound **218** in multigram quantities.



Scheme 3.51: *Formation of N-acylpyrrole Michael acceptor*

N-Acylpyrrole **218** was reacted on-water with aniline (**118**) to give conjugate addition product **219** in 78% yield (*Scheme 3.52*). The coupling reaction occurred in higher yield than the corresponding ester, demonstrating the greater electrophilicity of the *N*-acylpyrrole substrate. This reaction also occurred in very good yield when the reagents were heated in methanol at reflux (64°C). This observation is consistent with Sharpless' original description of on-water catalysis, who found on-water reactions also occurred quickly in methanol.



Scheme 3.52: *Nucleophilic addition to N-acylpyrrole Michael acceptor*

In view of the changes made to the Michael acceptor we performed further experiments to determine the role of water in this reaction (*Table 3.15*).

Solvent	Temp. (°C)	Yield (%)
On-water	50	78
At-water	50	trace
PhMe	100	NR
PhMe/AcOH	100	NR
DMSO	100	NR
MeOH	64	89

Table 3.15: *Examination of the role of water*

Only a trace amount of product could be observed under at-water conditions and no reaction occurred with heating in toluene, toluene/acetic acid or DMSO (*Table 3.15*). This again confirms this reaction fulfils all the requirements for on-water catalysis.

Unlike ester **216** the *N*-acylpyrrole derivative (**219**) was a crystalline solid. Compound **219** was crystallised in sufficient quality to obtain a single crystal X-ray diffraction structure. The X-ray structure shown in *Figure 3.11* was obtained by Dr. Peter Turner of the School of Chemistry Crystal Structure Analysis Facility.

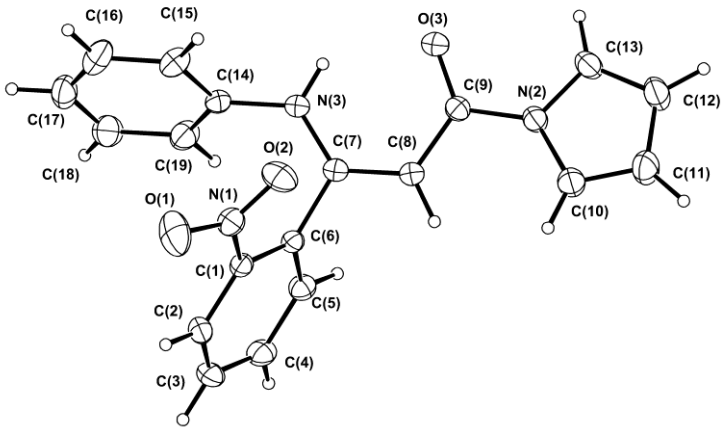
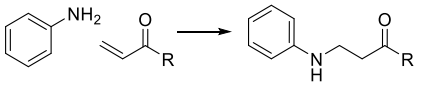


Figure 3.11: *Crystal structure of compound* ***219***

The crystal structure unambiguously shows a *Z* configured double bond. The preference for this configuration is due to an intramolecular hydrogen bond between the N-H and the carbonyl of the *N*-acylpyrrole. The measured bond distance between O(3) of the carbonyl and the hydrogen atom on N(3) is 2.0271 Å and 2.7084 Å between O(3) and N(3), these distances are correct for a medium



strength hydrogen bond. By analogy we presume the same interaction results in the same geometry for all analogous compounds. It is likely only the *Z*-isomer is obtained due to the reversibility of Michael additions leading to the thermodynamic product.

We have successfully performed an on-water conjugate addition of an aniline onto a phenylpropiolate Michael acceptor. This is the first example of this class of reaction in the absence of a π-Lewis acid. The *o*-nitro group, which was necessary for our proposed synthesis of hinckdentine A appears to be important to the success of this conjugate addition reaction. The conjugate addition reactions with functionalised anilines pertinent to the proposed synthesis will be discussed in chapter 6.

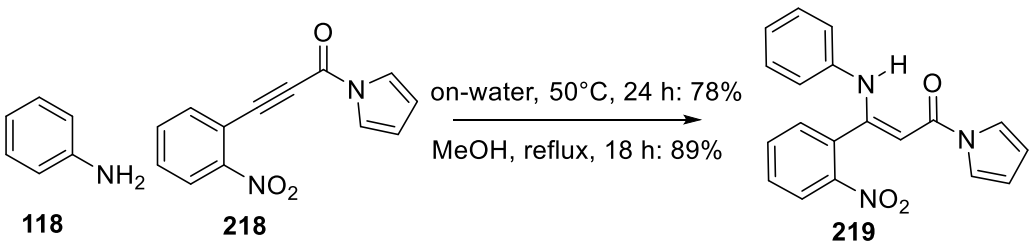
3.15 Summary and Conclusions

We have shown that the conjugate addition of anilines to unsubstituted Michael acceptors is catalysed on-water. The reaction with methyl acrylate (**119**) was found to be slow, which restricted the range of anilines which could participate in the reaction. We have overcome this problem by using *N*-acylpyrrole **131** which reacted quickly with all of the aniline tested, without giving rise to by-products.

Thiophenols were also found to add to the unsubstituted Michael acceptors tested. Again the *N*-acylpyrrole **131** was found to be advantageous as it did not result in the by-products that were formed when using methyl acrylate (**119**). Phenols did not participate in the conjugate addition, which is consistent with our theory of the acid catalysed nature of on-water catalysis.

Experimental evidence in conjunction with examination of the literature, showed α,β-unsaturated ester with large β-substituents do not participate in conjugate additions with anilines. Although α,β-unsaturated ketones are able to participate in this type of reaction, the use of *N*-acylpyrroles was not able to overcome this lack of reactivity.

Importantly we have shown aniline can participate in conjugate addition reactions to phenylpropiolate Michael acceptors under on-water conditions (*Scheme 3.53*). This result has laid the groundwork for the utilisation of this reaction in the synthesis of hinckdentine A (see *Scheme 3.24*).



118 **218** **219**

Scheme 3.53: *Nucleophilic addition to N-acylpyrrole Michael acceptor*

These results expand the scope of on-water catalysis by demonstrating a new class of reactions which can be accelerated by interfacial water. These results also demonstrate the utility of *N*-acylpyrroles and show how they can be advantageously applied in situations where esters are insufficiently electrophilic.

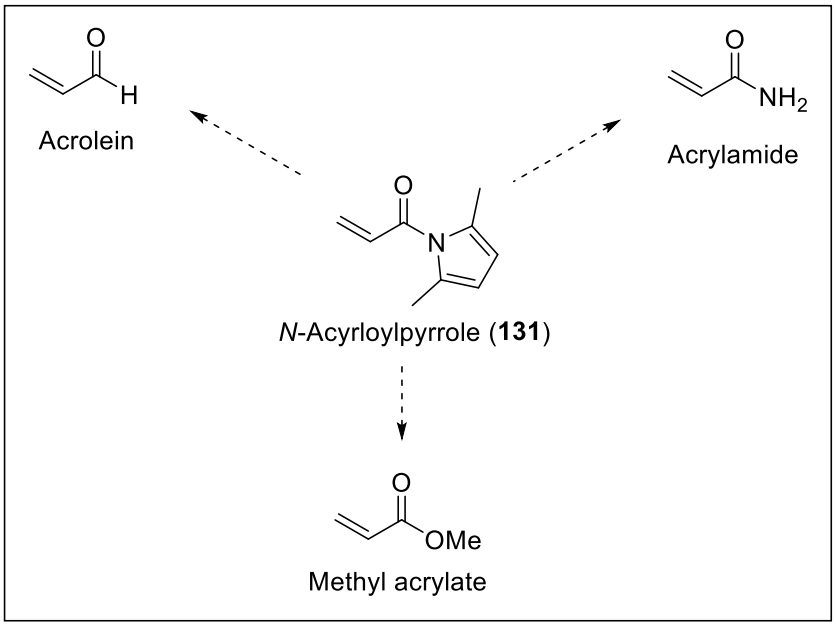


Figure 3.12: *Reactivity of N-acryloylpyrrole*

Another major outcome of this research has been a simple method for the synthesis of *N*-acryloylpyrrole **131**. This compound possesses all of the advantages of methyl acrylate, acrylamide and acrolein (*Figure 3.12*) but is stable to storage for long periods without the need for a radical inhibitor. It is very non-polar and is non-volatile. These properties suggest *N*-acyryol-2,5-(dimethyl)pyrrole (**131**) will be useful building block for organic synthesis.

Aspects of this work have been published in *Chemical Communications*[2] and have attracted 17 citations.

Chapter 4

Aqueous Synthesis of Thiazesim

Having developed a successful model for the acid catalysed nature of on-water catalysis and subsequently used this model to improve a previously difficult class of reactions we now sought to probe the strength of the acid catalysis which can be performed with this catalytic system. The investigation was to be performed in conjunction with the synthesis of a pharmaceutically important scaffold, which would allow us to concurrently illustrate the utility of *N*-acyryol-2,5-(dimethyl)pyrrole (**131**) as a building block for organic synthesis.

4.1 Introduction to 1,5-benzothiazepines

1,5-Benzothiazapines are a valuable scaffold in medicinal chemistry and are found in drugs with many billions of dollars of sales per year (*Figure 4.1*). Examples of successful 1,5-benzothiazepines include the antipsychotic Quetiapine (trade name: Seroquel, **220**) and the calcium channel blockers Diltiazem (**221**) and Clentiazem (**222**).

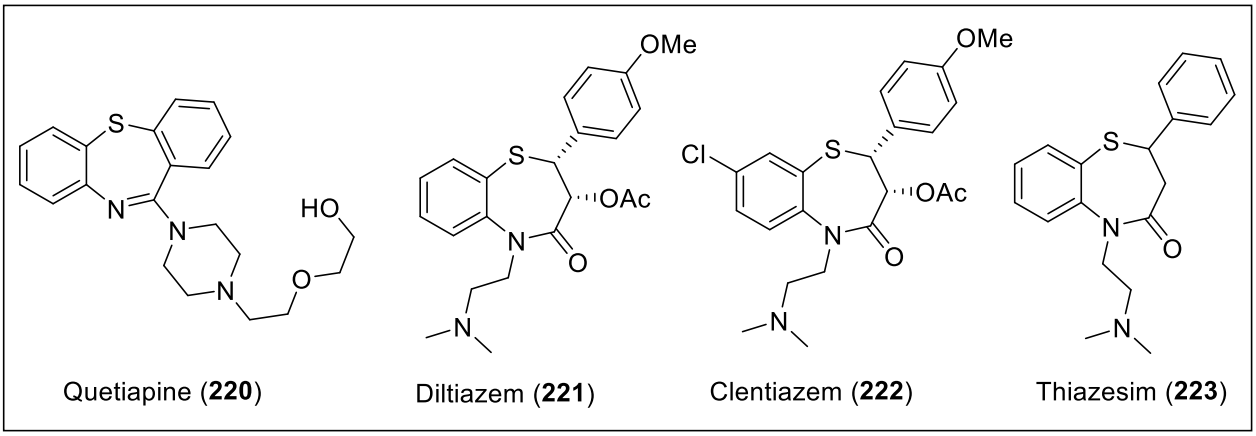


Figure 4.1: *Common benzothiazepines*

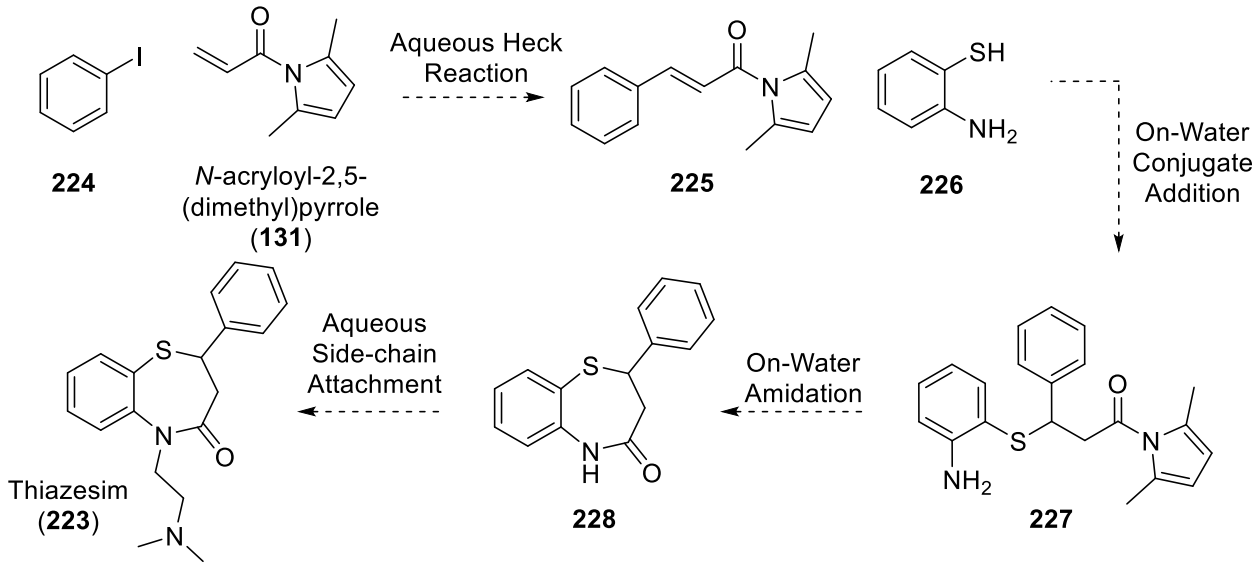
One of the first 1,5-benzothiazepine to be marketed as a pharmaceutical was Thiazesim (*Figure 4.1,* **223**). Thiazesim (**223**) was first marketed in 1966 as an anti-depressant and was sold in racemic form under the brand name Altinil. Although thiazesim (**223**) is a relatively simple member of the 1,5-benzothiazepine family it contains all of the important structural features so it is an ideal test case for exploring the synthesis of this group of compounds.

Despite the prevalence of 1,5-benzothiazepines in top-selling drugs this moiety can be difficult to synthesise. With these issues in mind, we sought to develop a synthetic pathway to this scaffold which utilised *N*-acylpyrroles and on-water catalysis and resulted in a sequence that was simple and versatile. This would also address the growing need for ecologically sustainable and energy efficient syntheses in the pharmaceutical industry, as aqueous and water-tolerant chemistry is seen as an

opportunity to reduce waste organic solvents and improve sustainability.

4.2 Proposed synthesis of thiazesim

We envisioned the construction of thiazesim occurring in 4 steps, all of which involved water (*Scheme 4.1*).

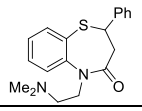


Scheme 4.1: *Proposed thiazesim synthesis*

N-Cinnamoyl-2,5-(dimethyl)pyrrole (**225**) was to be obtained using a aqueous Heck coupling of *N*-acryloyl-2,5-(dimethyl)pyrrole (**131**) and iodobenzene (**224**).[128] Although compound **225** could also be obtained through a condensation with commercially available cinnamamide (see *Section 3.14*), this methodology would allow for the generation of a large range of structural analogues by using different aryl halides in the Heck reaction.

Guided by our previous research we then planned to perform an on-water Michael addition onto the newly formed cinnamic Michael acceptor **225**. We had shown anilines do not participate in conjugate additions with cinnamates so choosing 2-aminothiophenol (**226**) as the nucleophile would result in selective coupling through the more nucleophilic sulfur atom without the need for protecting groups.

This will leave the aniline in close proximity to the *N*-acylpyrrole (**227**), positioning it to perform the intramolecular amidation. It was envisioned that the trans-amidation would be spontaneous under the acidic conditions of on-water catalysis to give compound **228**. The success or failure of this amidation under on-water conditions will give measure of the acid strength of interfacial water as previous reports of reactions such as this required high temperatures and harsh conditions, and the formation of 7-membered rings is traditionally difficult.[129] Conventionally lactamisations to



form 1,5-benzothiazepines require strong acid at high temperature to occur.[130]

The final step in the synthesis would be *N*-alkylation, which is well known in the literature using wet ethyl acetate or acetone as the solvent, and would give thiazesim (**223**).[131]

This approach is not only short and ecologically sustainable; it is also modular and could give rise to many analogues by variation of the aryl halide in the Heck reaction, variation of the aminothiophenol or by changing the substituent on the nitrogen atom.

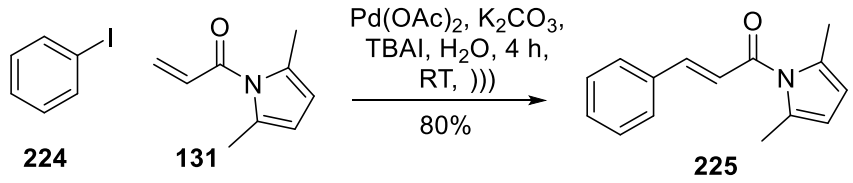
4.3 Synthesis of thiazesim - Aims

1. Synthesise thiazesim using *N*-acryloyl-2,5-(dimethyl)pyrrole (**131**) as the starting material.
2. Focus on aqueous and air/water tolerant steps to complete the synthesis.

4.4 *Synthesis of thiazesim - Results*

Palladium catalysed cross coupling reactions are well known to occur with water as the solvent or as a cosolvent.[132] We were interested by a report by Zhou and co-workers who described an aqueous Heck cross-coupling under phase transfer conditions. The authors of this report used ultrasonic irradiation to accelerate the reaction, ostensibly through the generation of palladium(0) nanoparticles.[128]

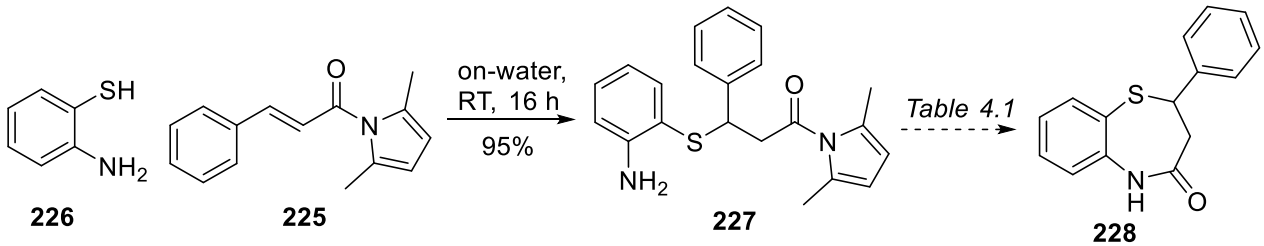
Using the sonication conditions which had been optimised by Zhou the Heck reaction between *N*-acryloyl-2,5-(dimethyl)pyrrole (**131**) and iodobenzene (**224**) proceeded to give *N*-cinnamoyl-2,5-(dimethyl)pyrrole (**225**) in 80% yield at room temperature (*Scheme 4.2*).



Scheme 4.2: *Aqueous Heck coupling*

This constitutes the first example of a Heck coupling on an α,β-unsaturated *N*-acylpyrrole. We wished to probe the role of sonication in this reaction and determine whether vigorous stirring could affect the same acceleration. Using the same reaction conditions, but with vigorous stirring, rather than sonication the coupling product (**225**) was obtained in 14% yield after 6 hours and 50% after 24 hours. These yields are comparable to those reported by Zhou. By raising the temperature the yield could be raised to 28% in 6 hours. These results suggest sonication is likely to be a source of heat, rather than generating highly active palladium(0) nano-particles as proposed by Zhou. Nonetheless simple stirring was a highly energy efficient and green method of generating the desired compound.

Vigorously stirring a 1.5:1 ratio of 2-aminothiophenol (**226**) and Michael acceptor **225** with water at room temperature for 16 hours gave the expected conjugate addition product **227** in high yield (*Scheme 4.3*).



Scheme 4.3: *Michael addition of thiophenol*

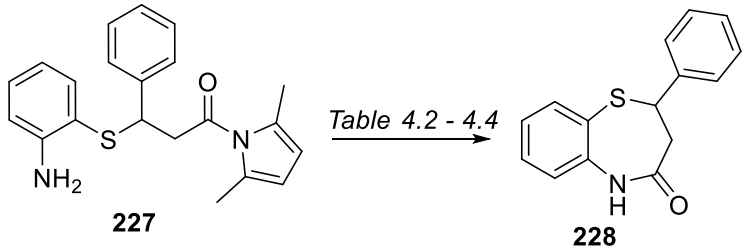
Consistent with our previously observations, the aniline did not participate in the conjugate addition reaction. It is instructive to note that the desired lactamisation reaction to give lactam **228** had not occurred spontaneously at room temperature (*Scheme 4.3*) and raising the reaction temperature as high as 80°C also did not affect the cyclisation (*Table 4.1*). At higher temperature we began to observe the elimination of thiophenolate, reforming the starting materials. The lactamisation also did not occur with heating in organic solvents even in xylene at reflux.[133]

Solvent	Catalyst	Temp. (°C)	Time	Result
neat	on-water	RT	24 h	NR
neat	on-water	50	24 h	NR
neat	on-water	80	24 h	β-elimination
THF	-	66	24 h	NR
xylenes	-	140	16 h	β-elimination/ decomposition

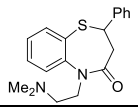
Table 4.1: *Attempts at spontaneous cyclisation*

It appears that the interfacial water at the surface of the oil droplets is not acidic enough to catalyse this transformation. The isoelectric point of oil-in-water emulsions has been experimentally measured to correspond to a pH of between 3 and 4 and the rate of hydrolysis of *N*-acylpyrroles has been experimentally measured to be fastest at approximately pH 2.37[134] and is lower for more hindered substrates such as dimethylpyrrole. Consequently trans-amidation did not occur under on-water conditions and this result provides evidence the interfacial water has similar acidity to a carboxylic acid.

Given the substrate did not spontaneously cyclise under on-water conditions we moved to more conventional Lewis and Brønsted acids, and nucleophilic catalysts to perform the reaction (*Scheme 4.4, Table 4.2-4.4*).



Scheme 4.4: *Lactamisation to form benzothiazepine core*



Solvent	Catalyst	Temp. (°C)	Time	Result
neat	on-water/4-DMAP	RT	24 h	NR
CH_2Cl_2	4-DMAP	RT	24 h	β-elimination
THF	4-DMAP	66	16 h	β-elimination
THF	NaOMe	66	24 h	NR
toluene	NaOMe	110	16 h	NR
THF	NEt_3	66	16 h	β-elimination
THF	NaOH	RT	1 h	β-elimination

Table 4.2: *Nucleophilic catalysis*

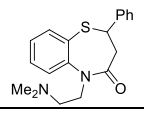
Nucleophilic catalysts are known to facilitate the use of *N*-acylpyrroles as acylating agents. Although 4-(dimethylamino)-pyridine (4-DMAP),[135] sodium methoxide,[106] and triethylamine[136] have been shown to result in substitution of *N*-acylpyrroles, in this instance these reagents did not affect the desired lactamisation (*Table 4.2*), but rather exposure of compound **227** to these basic reagents resulted in elimination of the β-thiophenol. Sodium hydroxide, which is also known to catalyse lactamisations of 1,5-benzothiazepines,[137] also gave the eliminated product.

Solvent	Catalyst	Temp. (°C)	Time	Result
toluene	$AlMe_2Cl$	0	3 h	NR
toluene	$AlMe_2Cl$	RT	16 h	β-elimination/ decomposition
toluene	$AlMe_2Cl$	110	3 h	decompostion
water	$CeCl_3$	RT	24 h	NR
$MeOH/CH_2Cl_2$	$CeCl_3$	40	16 h	β-elimination
xylenes	$CeCl_3$	140	24 h	β-elimination

Scheme 4.3: *Lewis acid catalysis*

As the substrate had proven to be sensitive to base we attempted Lewis acid catalysis, first with dimethylaluminium chloride,[138] then cerium(III) chloride but again only retro-Michael reactions were detected (*Table 4.3*).

Finally we returned our attention to protic acids (*Table 4.4*).

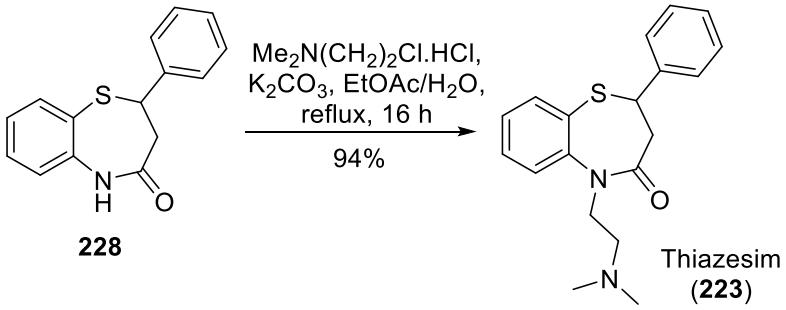


Solvent	Catalyst	Temp. (°C)	Time	Result
acetone/water	HCl	RT	4 h	NR
acetone/water	HCl	56	4 h	multiple products
THF/water	HCl	66	5 h	NR
THF/water	HCl	66	16 h	decompostion
Water	HCl (pH 3)	100	4 h	hydrolysis
THF	TsOH	66	16 h	22%
THF	TsOH	100 (μW 300 W)	30 min	trace
toluene	TsOH	110	30 min	86%

Table 4.4: *Brønsted acid Lactamisation conditions*

We wished to incorporate as many aqueous reactions as possible into our synthesis so we began with acetone and water with catalytic hydrochloric acid, this gave a complex mixture of hydrolysis and condensation products, but none of the desired cyclised product was obtained (*Table 4.4*). Substituting acetone for THF removed many by-products which were the result of condensation but still did not give the desired product.

Removing the water and changing the acid from aqueous hydrochloric acid to *p*-toluenesulfonic acid gave the desired product **228**, albeit in modest yield. Raising the reaction temperature to 100°C through microwave irradiation did not give any further improvement. As the reaction precursor contained three aromatic rings we reasoned that the slow rate of cyclisation could be due to conformational effects and employing an aromatic solvent may overcome this. When the cyclisation was attempted in toluene at reflux we were pleased to find our reasoning validated as we obtained an 86% yield of compound **228** in only 30 minutes. This reaction did not require any special preparation or protection from air or water. This expedient cyclisation shows the strong electrophilicity of the acylpyrrole and is a vast improvement on the previous methods which often involved xylenes at reflux for extended periods.[130a, 130c] This results also demonstrated that the trans-amidation requires a strong acid to catalyse the transformation.

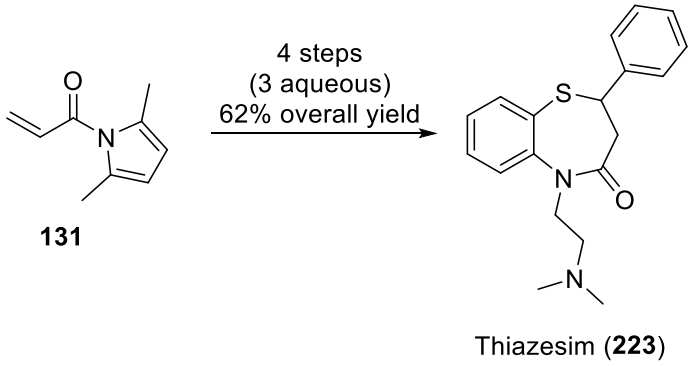


Scheme 4.5: *N-Alkylation to complete the synthesis of thiazesim*

Having constructed the benzothiazepine core (**228**) the final step required to complete the synthesis of thiazesim (**223**) was to append the *N,N*-dimethylaminoethyl side chain (*Scheme 4.5*). This was completed using a known procedure[32] utilising wet ethyl acetate to give the desired compound (**223**) in high yield.

4.5 Summary and Conclusions

We have synthesised the pharmaceutical thiazesim (**223**) in 4 steps (62% overall yield), 3 of which involved water as a catalyst, solvent or co-solvent (*Scheme 4.6*). The cyclisation also represents a significant improvement on published syntheses and could be performed open to the atmosphere. All steps were catalytic and high yielding and the synthesis used no protecting groups. This methodology for the synthesis of 1,5-benzothiazepines was practical, modular and environmentally friendly.



Scheme 4.6: *Overall synthesis of Thiazesim*

Through this study we have shown some of the usefulness of *N*-acryloyl-2,5-(dimethyl)pyrrole (**131**, *Figure 4.2*) as a starting material and many of the advantages of *N*-acylpyrroles. We demonstrated how advantageous on-water catalysis and other aqueous reaction can be while also testing the limits of on-water catalysis. We have determined that interfacial water is not as acidic as a sulfonic acid, but rather, has similar acidity to a carboxylic acid.

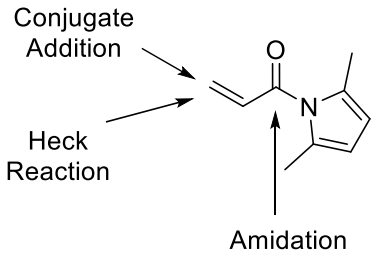
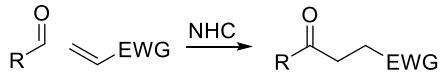


Figure 4.2: *Reactions performed on N-acryloyl-2,5-(dimethyl)pyrrole (**131**) as part of this synthesis*

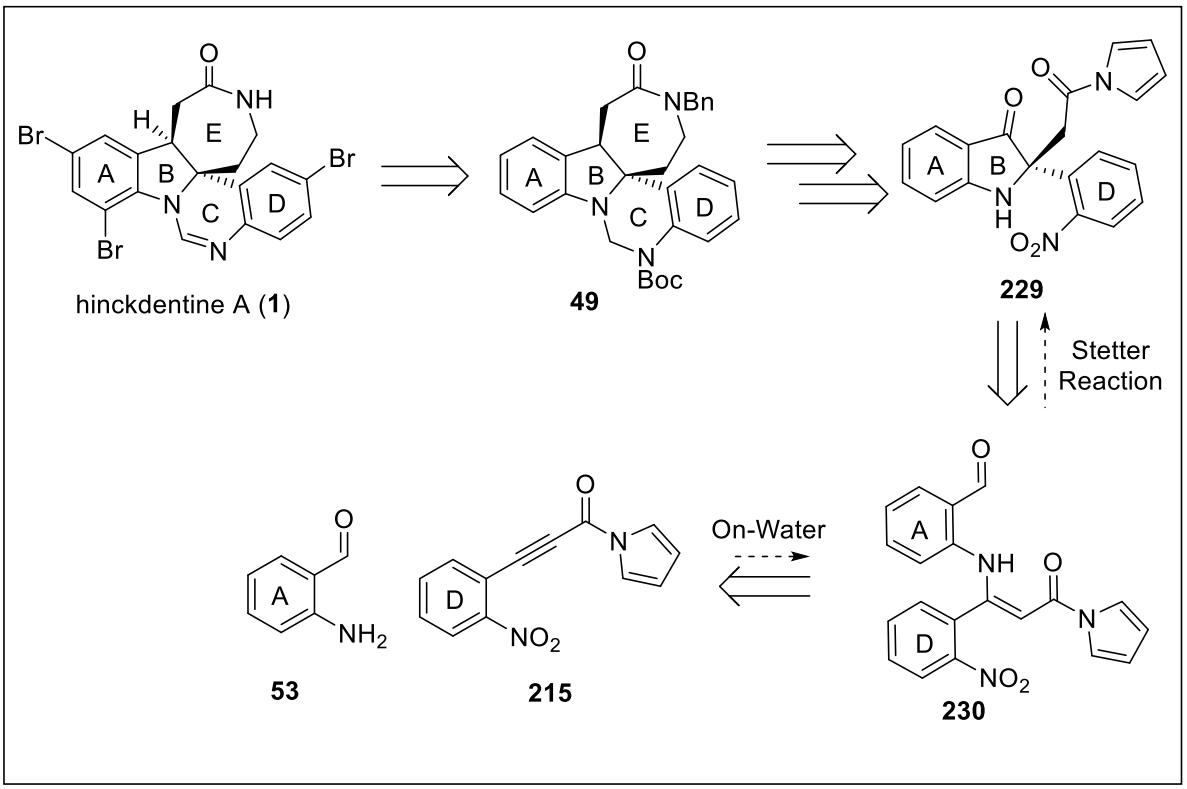
This work has been published in *Tetrahedron Letters*.[139]

Chapter 5

Introduction to the Stetter Reaction



Having demonstrated that the use of an on-water catalysed conjugate addition was a viable step toward the hinckdentine A scaffold (see *Section 3.14*) we turned our attention to the second key step in our proposed synthesis of hinckdentine A; the Stetter reaction of *N*-acylpyrroles (*Scheme 5.1*).



***Scheme 5.1**: Retrosynthesis of hinckdentine A*

The understanding of *N*-acylpyrrole Michael acceptors which we have gained from our previous studies would assist us in the development of the Stetter reaction which is an organocatalytic conjugate addition reaction.

5.1 The Stetter reaction

The Stetter reaction is the conjugate addition of an aldehyde onto a Michael acceptor, catalysed by cyanide or an N-heterocyclic carbene (NHC). The Stetter reaction generates a new carbon-carbon bond and usually results in a 1,4-dicarbonyl compound (*Figure 5.1*). In contrast to conventional reactivity, the aldehyde component of the Stetter reaction reacts as a nucleophile; this reversal of reactivity is termed "umpolung", literally "reversal of polarity" in German.[140]

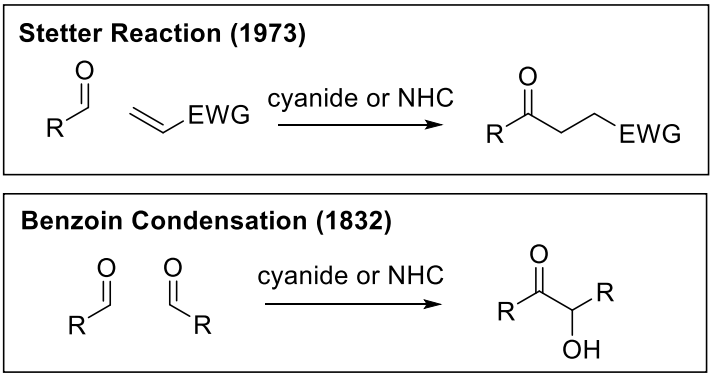
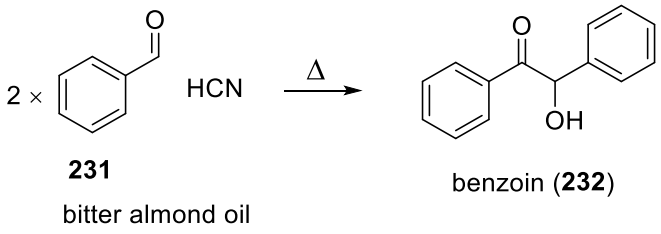


Figure 5.1: *Benzoin and Stetter reaction*

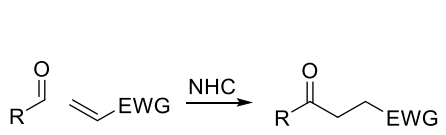
The Stetter reaction is closely related to the benzoin condensation, which is the umpolung addition of one aldehyde to another (*Figure 5.1*). In essence, the Stetter reaction is a vinylogous benzoin condensation.

5.1.1 History of the Stetter reaction

The benzoin condensation is amongst the oldest known organic reactions. It was first described by Stange in 1824[141] and first examined in depth in 1832 by Liebig and Wöhler.[142] They both observed the formation of benzoin (**232**) upon heating bitter almond oil, which contains benzaldehyde (**231**) and hydrogen cyanide (*Scheme 5.2*).[142] As little was known of the chemistry occurring the reaction was erroneously termed a condensation and for historical reasons this name is still used.

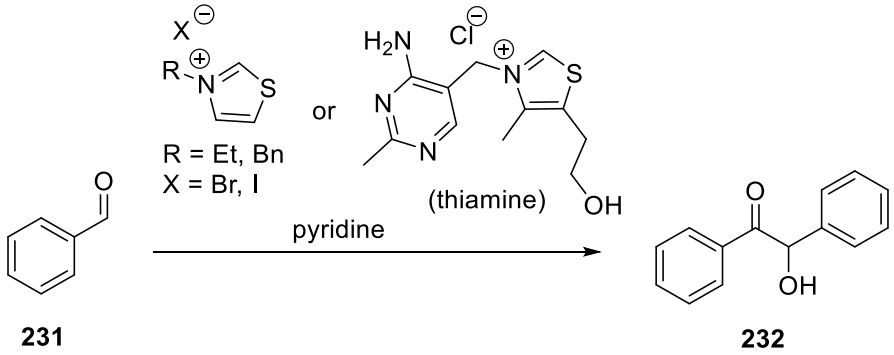


Scheme 5.2: *The first report of the benzoin condensation*



Using cyanide as the catalyst limited the scope of the benzoin reaction. Only aromatic aldehydes could tolerate the reaction conditions without decomposition and side reactions. The condensation was also limited to homo-coupling as cross-benzoin condensations usually led to statistical mixtures of products.

In 1943, more than 100 years after the initial report of the benzoin reaction, Ukai found the benzoin condensation could also be catalysed by a thiazolium salt and a base (*Scheme 5.3*).[143] Ukai demonstrated a range of thiazolium salts in combination with a base could catalyse the benzoin reaction, as could thiamine (vitamin B_1).

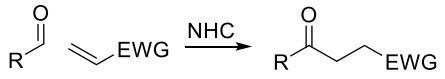


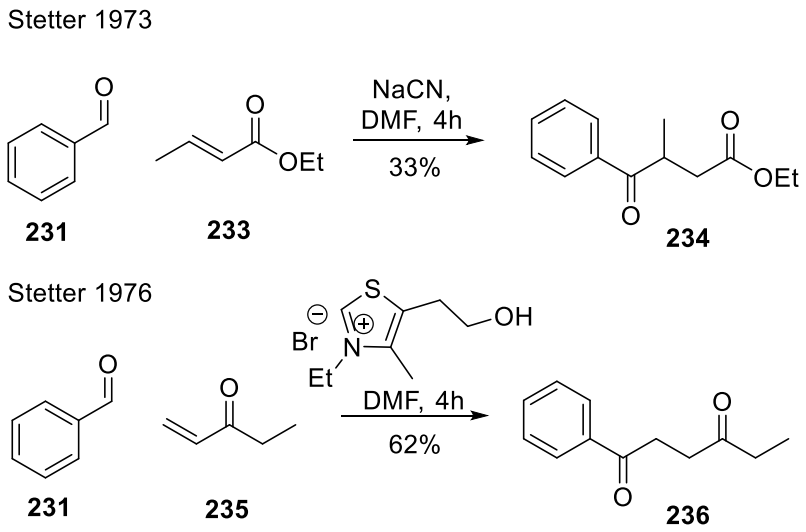
Scheme 5.3: *NHC catalysed benzoin condensation performed by Ukai*[143]

The use of thiazolium derived carbenes significantly enhanced the scope of the benzoin condensation, as these catalysts were more compatible with aliphatic aldehydes. The pre-catalysts were also non-toxic, air stable, easily handled, and the reactions often occurred at ambient temperature.

Rather than performing a 1,2-addition of the nucleophilic aldehyde, Hermann Stetter performed a 1,4-conjugate addition reaction under the same conditions as the benzoin condensation. The umpolung addition of an aldehyde to a Michael acceptor subsequently became eponymous with Stetter.

The cyanide catalysed Stetter reaction was first reported in 1973 (*Scheme 5.4*).[144] This reaction, like the cyanide catalysed benzoin condensation, could only tolerate aromatic aldehydes and suffered the additional problem of competition with the benzoin condensation. Stetter's report of the thiazolium salt catalysed Stetter reaction in 1976 (*Scheme 5.4*)[145] again allowed for the use of aliphatic aldehydes and a greater range of Michael acceptors.





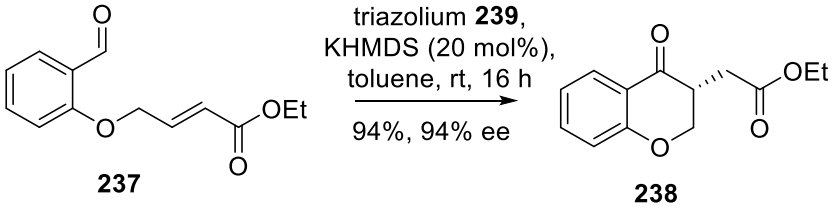
Scheme 5.4: *Representative Stetter reactions*

Despite spending his career developing what would become his eponymous reaction, Stetter never published an example of an intramolecular Stetter reaction. The first study into intramolecular Stetter reactions was reported in 1995 by Ciganek.[146] This report precipitated a renewed interest in the Stetter reaction as the intramolecular reaction was facile, high yielding and did not suffer from competing reactions.

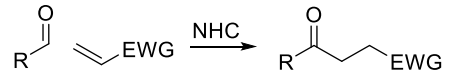
Intermolecular Stetter reactions are now considered to be the more challenging variant as they must compete with the benzoin condensation, carbene dimerization and for aliphatic aldehydes, aldol-type reactions. Hence they require greater optimisation and generally suffer from lower yields.

5.1.2 Asymmetric Stetter reactions

Asymmetric *intramolecular* Stetter reactions were first developed 1996 by Enders[147] using a triazolinylidene carbene. Since then Rovis has made significant progress in catalyst design, achieving high enantiomeric excess (usually greater than 95%) with a range of substrates (*Scheme 5.5*).[148] Crucial to this success has been the development of fused polycyclic 1,2,4-triazolium salt precatalysts (*Figure 5.2*) which are now commercially available as both enantiomers. The asymmetric Stetter reaction has been particularly successful at creating quaternary stereocentres, which are traditionally difficult to construct, with high enantiomeric excess.



Scheme 5.5: *A representative asymmetric Stetter reaction*[148a]



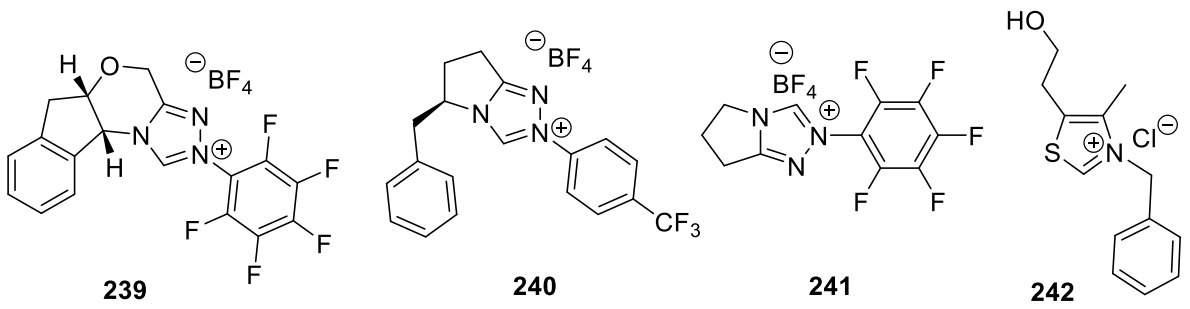
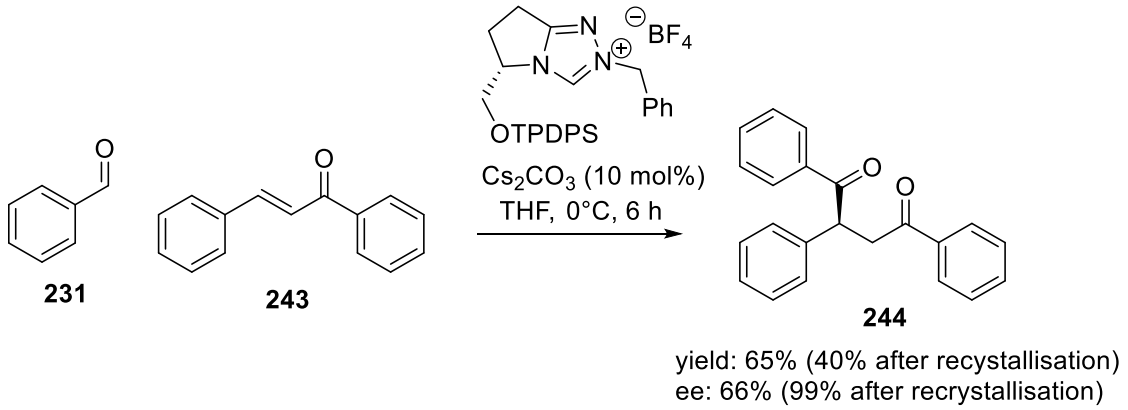


Figure 5.2: *Common azolium pre-catalysts*

Enders had been attempting asymmetric *intermolecular* Stetter reactions with chiral thiazolium salts since the early 1990's with only minor success.[149] Since 2008 Enders,[150] Rovis[151] and Glorius[152] have made significant progress on the asymmetric intermolecular Stetter reaction with a range of new catalysts (*Scheme 5.6*). These reactions now work well albeit on a restricted range of substrates.

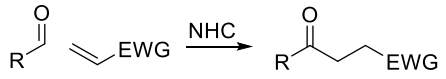


Scheme 5.6: *An asymmetric intermolecular Stetter reaction*[150a]

5.2 Mechanism of the Stetter reaction

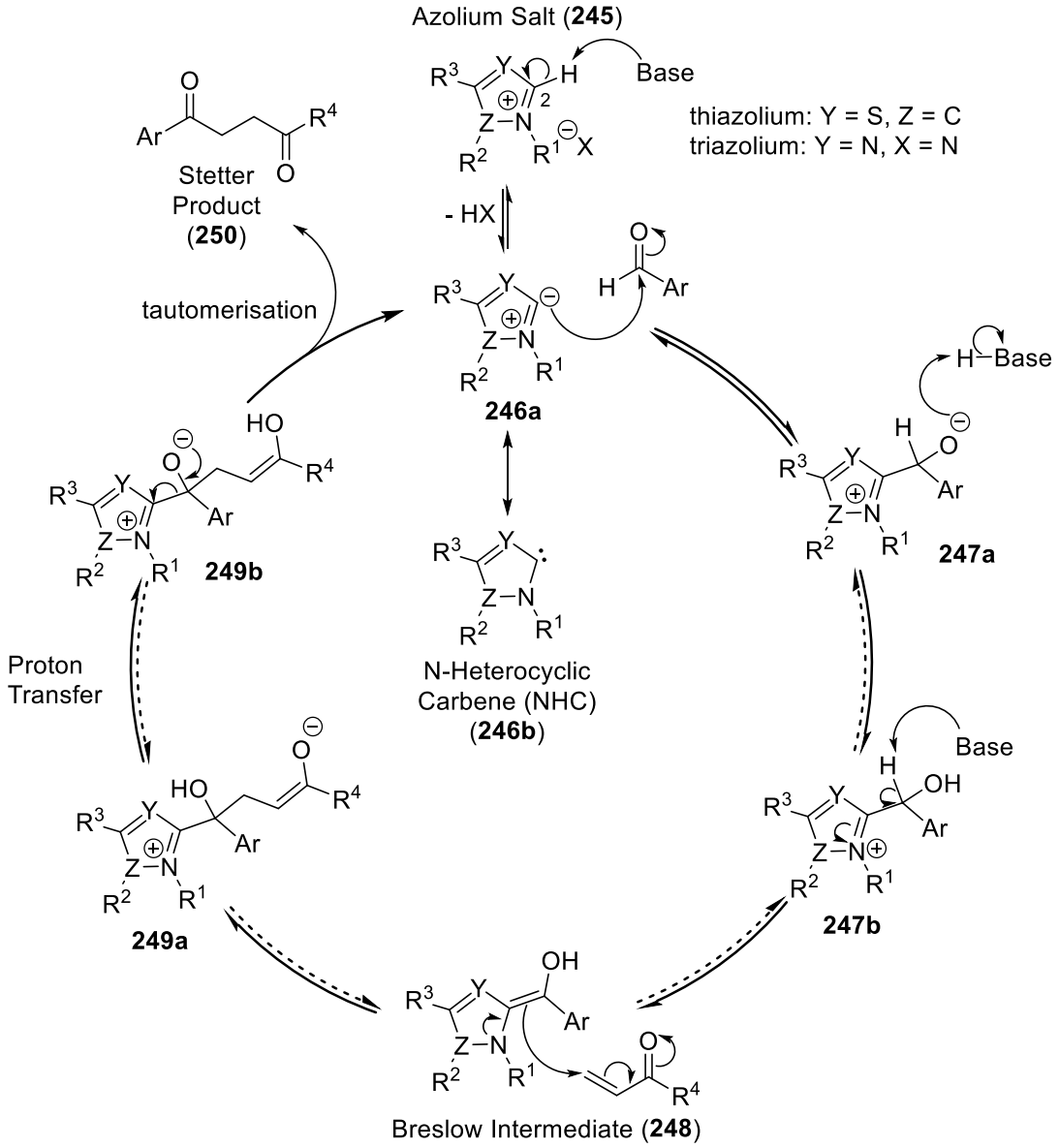
The mechanism for cyanide catalysed benzoin condensation was proposed by Lapworth in 1903[153] and mechanism of thiazolium catalysed benzoin reaction was elucidated by Breslow in 1958 when determining the mechanism of action of thiamine (vitamin B_1), a naturally occurring thiazolium salt.[154] There have been numerous experimental and computational studies into the mechanism of the benzoin condensation. Experimental evidence has often been difficult to interpret as several steps are partially rate determining.[155]

It has been assumed the mechanism of the Stetter reaction (*Scheme 5.7*) is analogous to the benzoin condensation, but there is no experimental evidence to support this assumption. In 2011 Rovis stated:



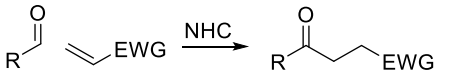
"To the best of our knowledge a detailed study probing the mechanism of the Stetter reaction has not been reported. In the absence of such a study the working model of the Stetter reaction is based on the Breslow mechanism for the thiamine-catalyzed benzoin reaction"[156]

The only significant difference between the benzoin condensation and the Stetter reaction that has been noted is that the benzoin condensation is reversible[157] whereas the Stetter reaction is not. The proposed mechanism of the Stetter reaction is shown in *Scheme 5.7*.



Scheme 5.7: *Proposed Mechanism of the Stetter reaction*

The generally accepted mechanism of the Stetter reaction and benzoin condensation begins with the formation of an N-heterocyclic carbene (NHC, **246**, *Scheme 5.7*). The C2 proton of the azolium salt (**245**) is acidic due to its proximity to electronegative heteroatoms. The removal of the C2-



proton leads to the NHC which can be represented by two resonance forms, ylide **246a** or carbene **246b**. The availability of these two resonance structures, as well as the inductive stabilisation of the proximal heteroatoms explains the relative persistence of these carbenes.[158] There are a variety of azolium salts which can form NHCs the most common being thiazolium, (Y = S, Z = C), triazolium (Y = N, Z = N) and imidazolium (Y = N, Z = C) salts. Due to the different heteroatoms, these heterocycles display different pK_a, nucleophilicity and nucleofugacity properties which are all important during the catalytic cycle. The electronic nature (electron donating or withdrawing) of the R^1 group on the invariant nitrogen also significantly affects the reaction by changing the pK_a of the C2 proton.[159]

The newly formed carbene (**244**) attacks an aldehyde and proton transfer (**247**) results in the "Breslow intermediate" (**248**). Rovis has determined that with *some* catalysts this proton transfer is irreversible.[156] Formation of the Breslow intermediate is common to both the benzoin condensation and the Stetter reactions. Analogues of the Breslow intermediate resulting from carbene addition to an iminium are isolable[160] and the Breslow intermediate has recently been unambiguously characterised and studied by NMR.[161] It is because of the formation of the Breslow intermediate (**248**) that the aldehyde can undergo "umpolung" reactivity; the Breslow intermediate (**248**) is an enaminol and reacts as an enamine, as such it is nucleophilic at the formerly electrophilic aldehydic position. In the benzoin condensation the Breslow intermediate attacks another aldehyde but in the Stetter reaction it reacts with a Michael acceptor. For the Stetter reaction it is usually suggested this attack and protonation occurs in a stepwise manner (as shown in *Scheme 5.7*). However, it is also possible this occurs via a concerted "hydroacylation" mechanism, as shown in *Figure 5.4*.[162]

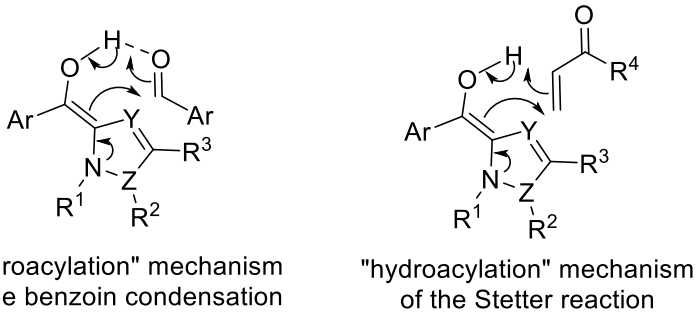
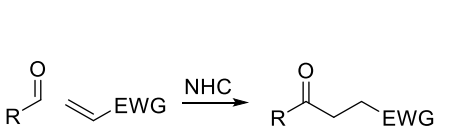


Figure 5.4: *Alternate mechanism*

The benzoin reaction was originally proposed to be concerted by Breslow[154] and calculations have predicted it to be concerted.[163] In the concerted mechanism concomitant hydrogen bonding from the "enol" may activate the incoming aldehyde toward nucleophilic attack (*Scheme 5.4*). For the Stetter reaction there is an absence of experimental evidence for either pathway, but the attack and proton transfer has been predicted to occur in a single step by computer modelling.[164] It has been suggested this step could be concerted but asynchronous[162a] and has been proposed to resemble a



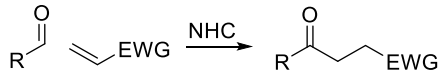
reverse cope rearrangement[162b] or a Conia-ene reaction.[162c] The concerted mechanism is supported by Glorius' reports of NHC catalysed hydroacylation of unactivated alkenes.[162a, 165]

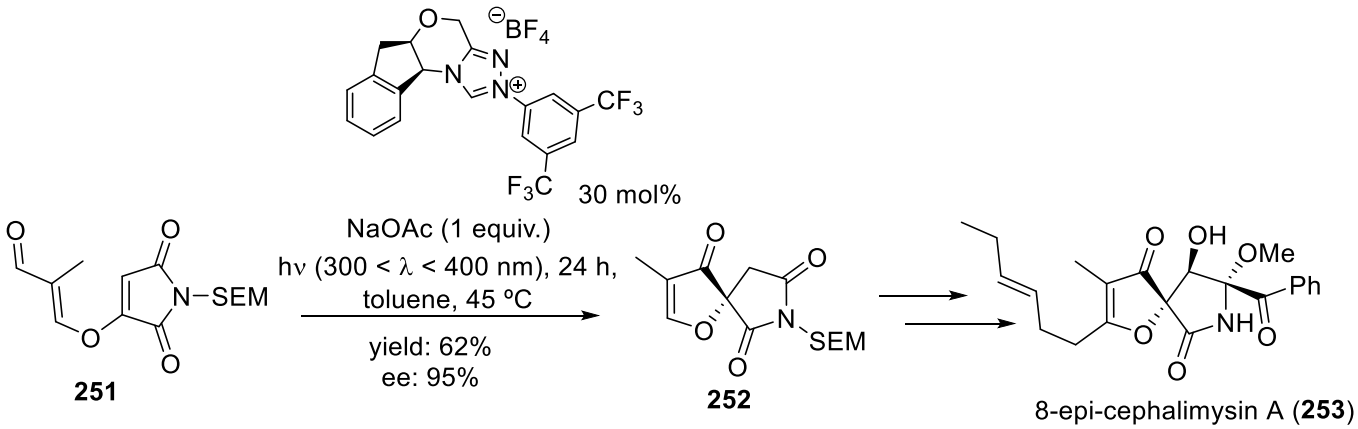
Regardless, after the umpolung attack and proton transfer (**249**), the catalyst is eliminated resulting in the 1,4-dicarbonyl product (**250**) and regeneration of the NHC (**246**). It can be seen that the NHC performs many roles in this reaction and choosing the most appropriate catalyst; is a subtle balance between sterics, acidity, nucleophilicity and nucleofugacity. At this time, there is no rule-of-thumb to suggest the most appropriate catalyst for a given system, and the process remains one of trial-and-error.

5.3 The Stetter reaction in total synthesis

The umpolung character of the Stetter reaction renders it useful in obtaining compounds which would be otherwise difficult to synthesise, such as 1,4-dicarbonyl compounds. The reaction also possesses many other desirable attributes; it is catalytic, occurs under mild conditions and can achieve high enantioselectivity. The catalysts do not contain heavy metals and are also non-toxic. The Stetter reaction is effective with a range of Michael acceptors such as esters, ketones, nitriles, dicarbonyl compounds,[145] nitroalkenes,[151a] phosphine oxides,[166] phosphonates[166] and sulfones.[167]

Accordingly, the Stetter reaction has been used as a key step in many total syntheses;[168] these include hirsutine,[169] roseophilin,[170] CI-981,[171] (±)-*trans*-sabinene hydrate,[172] haloperidol,[173] (±)-platensimycin[174] and (-)-englerin A.[175] Remarkably, despite the high levels of enantiocontrol attainable with the asymmetric Stetter reaction, it has only been used as the stereo-inducing reaction on two occasions, both by Rovis. The first was in studies toward the total synthesis of FD-838[176] which were eventually abandoned. This leaves the 2013 total synthesis of (-)-cephalimysin A (**253**) as the only published and successful utilisation of the asymmetric Stetter reaction in total synthesis (*Scheme 5.8*).[177]

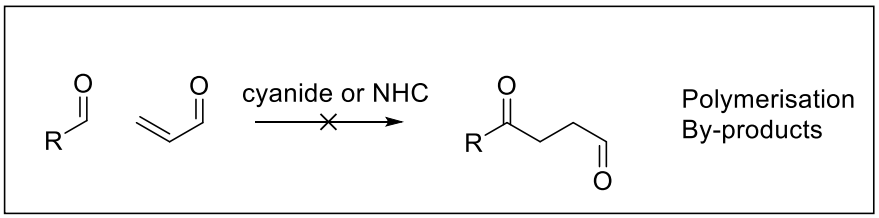




***Scheme 5.8**: Photoisomerization-coupled asymmetric Stetter reaction for the total synthesis of (-)-cephalimysin A*

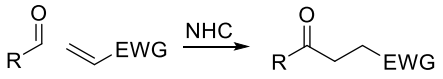
The dearth of successful applications of the asymmetric Stetter reaction compared to its readily apparent advantages demonstrates how underutilised the Stetter reaction is in modern synthesis. One of the obstacles limiting the application of the asymmetric Stetter reaction to total synthesis is the current incapacity to use two key Michael acceptors – namely α,β-unsaturated aldehydes and amides.

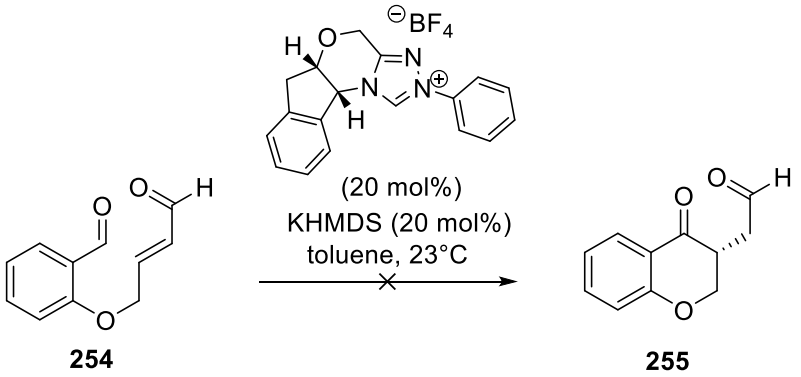
α,β-Unsaturated aldehydes such as acrolein are highly desirable substrates for the Stetter reaction as they can subsequently be transformed into many other functional groups. The obvious problem which arises is that the Stetter reaction is the umpolung addition of an *aldehyde*; if the Michael acceptor contains an aldehyde the product will contain an aldehyde and the reaction will lead to polymerisation and by-products (*Scheme 5.9*).[178]



***Scheme 5.9**: First limitation of the Stetter reaction*

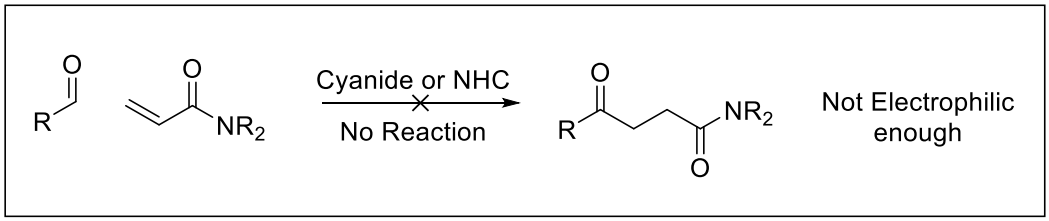
Rovis has reported that even simple intramolecular Stetter reactions onto α,β-unsaturated aldehydes (**254**) fail to give the desired product (**255**) despite the consumption of the starting material (*Scheme 5.10*).[178]





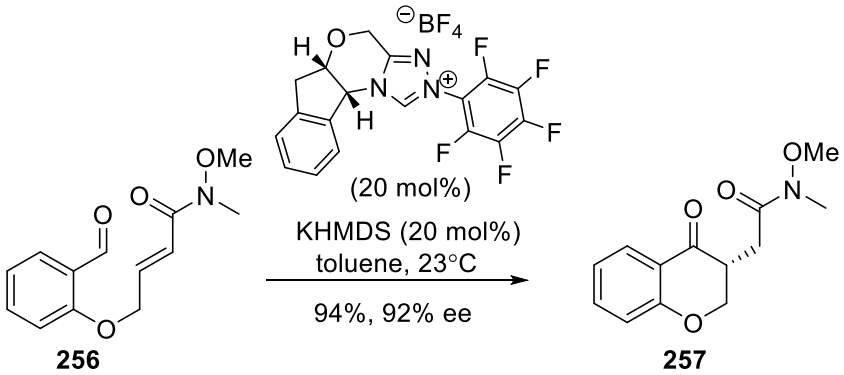
***Scheme 5.10**: An attempted Stetter reaction reported by Rovis[178]*

One of the most common aldehyde surrogates is the Weinreb amide. This raises the second major limitation of the Stetter reaction (*Scheme 5.11*). The electron withdrawing group on the Michael acceptor must be strongly electron withdrawing and α,β-unsaturated amides are generally not electrophilic enough to participate in the Stetter reaction. *In the forty year history of the Stetter reaction there has only been a single report of the successful use of an amide Michael acceptor.*[148a]

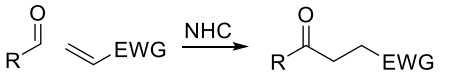


***Scheme 5.11**: Second limitation of the Stetter reaction*

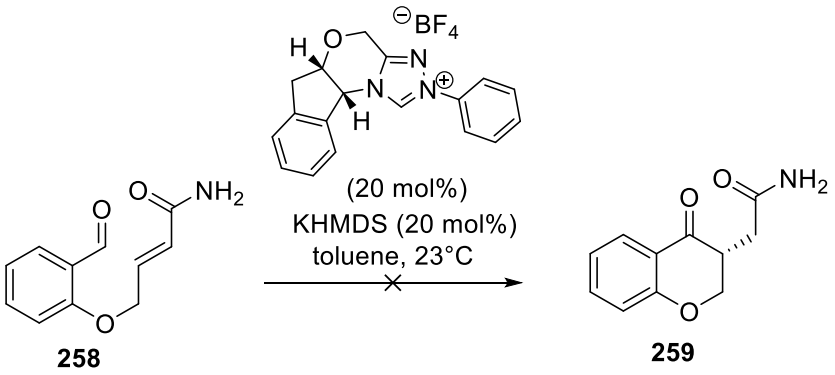
In 2008 Rovis[148a] reported the simple intramolecular Stetter reaction onto an amide (**256**), as shown in *Scheme 5.12*.



***Scheme 5.12:** The only reported Stetter reaction onto an amide*



The specificity of this reaction is exemplified by the fact that Rovis has also reported that no reaction occurs with the primary amide substrate (**258**) under almost identical conditions (*Scheme 5.13*).[178]



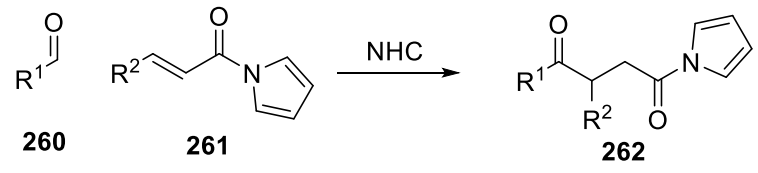
Scheme 5.13: *An attempted Stetter reaction reported by Rovis*[178]

This limitation precludes the widespread use of Weinreb amides as aldehyde equivalents in the Stetter reaction. It also prevents the straightforward use of simple amides which is disadvantageous due to their abundance in natural products and pharmaceuticals.

The two limitations highlighted above are especially true for intermolecular Stetter reactions, which already suffer from competing side reactions.

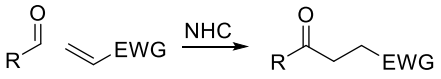
5.4 Stetter reactions of N-acylpyrroles

We intend to increase the utility of the Stetter reaction by utilising a new Michael acceptor - the α,β-unsaturated *N*-acylpyrrole (**261**, *Scheme 5.14*). Although it is well established that α,β-unsaturated *N*-acylpyrroles (**261**) are good Michael acceptors[93] there are no reports of Stetter reactions onto these substrates. The potential benefits that *N*-acylpyrroles can bring to the Stetter reaction are clear; they are electrophilic enough to participate in the Stetter reaction and able to be transformed into many other functional groups (see *Section 3.4*), especially amides and aldehydes.



R^1 = aromatic, heteroaromatic, alkyl

Scheme 5.14: *Proposed Stetter reaction of α,β-unsaturated N-acylpyrrole*



We aim to demonstrate the utility of the *N*-acylpyrrole as a Michael acceptor by performing a range of intra- and intermolecular Stetter reactions onto *N*-acylpyrroles (**261**, *Scheme 5.14*) with a range of aldehydes (**260**). This reaction will then be used as the key stereo-defining step in our proposed total synthesis of hinckdentine A (see *Figure 5.1*).

5.5 Stetter reactions of N-acylpyrroles - Aims

1. Perform a range of intramolecular Stetter reactions to form fused heterocyclic systems.
2. Investigate the intermolecular Stetter reaction of *N*-acylpyrrole Michael acceptors.

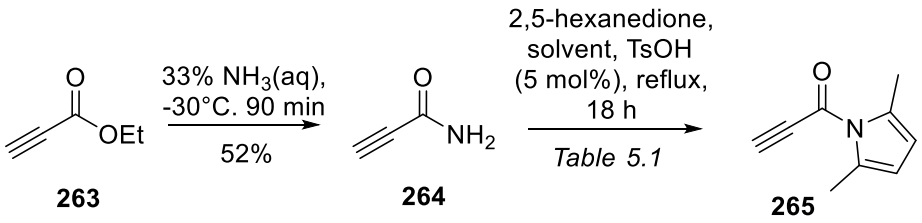
Chapter 5

Stetter Reactions of α,β-Unsaturated *N*-Acylpyrroles

Results and Discussion

5.6 Intramolecular Stetter reactions of N-acylpyrroles

We intended to synthesise a range of α,β-unsaturated *N*-acylpyrroles for intramolecular Stetter reactions by conjugate addition onto *N*-propioloylpyrrole (**265**). We have previously performed extensive experimentation toward the synthesis compound **265** and had determined that the Paal-Knorr reaction to be the most expedient route, despite suffering from low yields (*Scheme 5.15*).



Scheme 5.15: *Synthesis of an N-propioloylpyrrole*

Readily available ethyl propiolate (**263**) was amidated with aqueous ammonia to give propiolamide (**264**) in good yield on large scale. We directed our syntheses at the 2,5-dimethylpyrrole to prevent side reactions at the nucleophilic 2- and 5-positions of the pyrrole ring and also to reduce volatility of the reagent. Condensation reactions to form heterocycles are often facile, but in this case two factors make the reaction challenging: firstly, the low nucleophilicity of amides; and secondly, the high reactivity associated with the alkyne unit of both the starting material and product.

Solvent	Temp. (°C)	Maximum Yield (%)
Toluene	111	24
Benzene	80	47 (after two iterations)
Fluorobenzene	84	28

Table 5.1: *Paal-Knorr condensation*

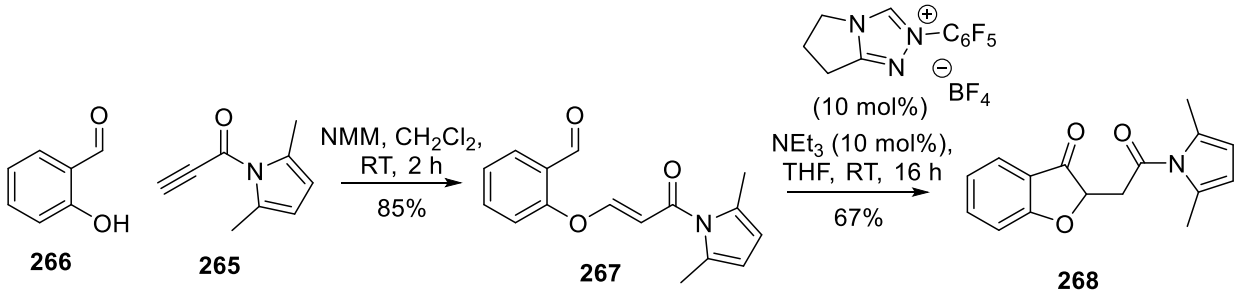
To facilitate this condensation continuous azeotropic distillation using Dean-Stark apparatus was performed. Conventionally benzene or toluene is used for this purpose with toluene often preferred by others due to its lower toxicity. In this case, toluene gave the product in moderate yield (*Table 5.1*), but due to the high temperature, a large amount of charring was also observed which led to complications in product isolation. Switching to the lower boiling but much more hazardous benzene gave a similar yield, but no charring. After isolation of the product and resubjecting the residue to the reaction conditions a good yield of **265** could be achieved (*Table 5.1*). Due to the hazards associated with benzene the reaction was also attempted in the unconventional solvent fluorobenzene

(boiling point: 84°C). Under these conditions the desired *N*-acylpyrrole (**265**) was obtained in slightly higher yield (28%) than in either toluene or benzene (after a single iteration), and with none of the charring associated with toluene. We thereafter settled on the use of fluorobenzene as the solvent of choice for this reaction due to its lower toxicity and slightly higher yield.

5.6.1 Intramolecular Stetter reactions of N-acylpyrroles – Oxygen tether

We began our investigation into the Stetter reactions of α,β-unsaturated *N*-acylpyrroles with the benchmark intramolecular reaction to form a dihydrobenzofuran. Addition of salicylaldehyde (**266**) onto the *N*-propioloylpyrrole (**265**) using *N*-methylmorpholine as a nucleophilic catalyst gave the desired α,β-unsaturated *N*-acylpyrrole **267** as a single diastereomer in high yield (*Scheme 5.16*).

Having prepared an *N*-acylpyrrole Michael acceptor appended to an aldehyde (**267**) we were ready to attempt the Stetter reaction. We chose the electron-poor pentafluorophenyltriazolium precatalyst and triethylamine as the base, as these conditions had been successful in our laboratory.

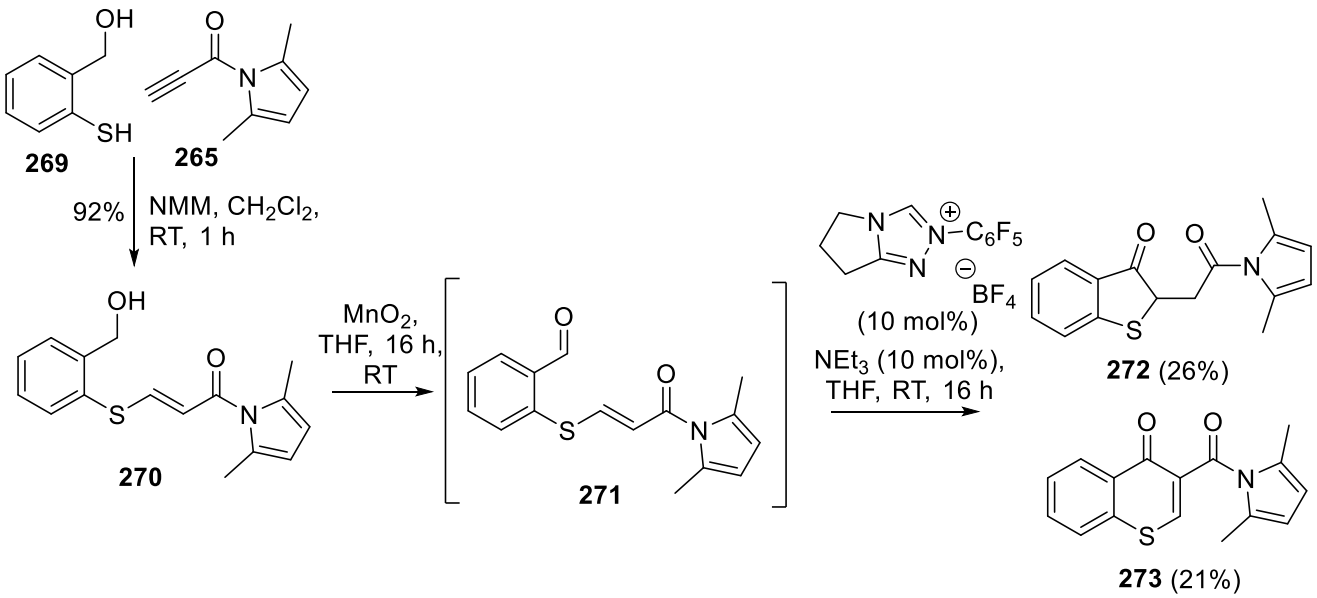


Scheme 5.16: *Intramolecular Stetter reaction of a salicylaldehyde derivative*

Under these conditions the Stetter reaction occurred to give compound **268** (*Scheme 5.16*) in a yield comparable to the corresponding ester.[148a, 179] This represents the first Stetter reactions onto an α,β-unsaturated *N*-acylpyrrole. This reaction also demonstrates the *N*-acylpyrrole unit is stable to the presence of N-heterocyclic carbenes, which indicated Stetter reactions of α,β-unsaturated *N*-acylpyrrole substrates is likely to be a reaction which is applicable to total synthesis.

5.6.2 Intramolecular Stetter reactions of N-acylpyrroles – Sulfur tether

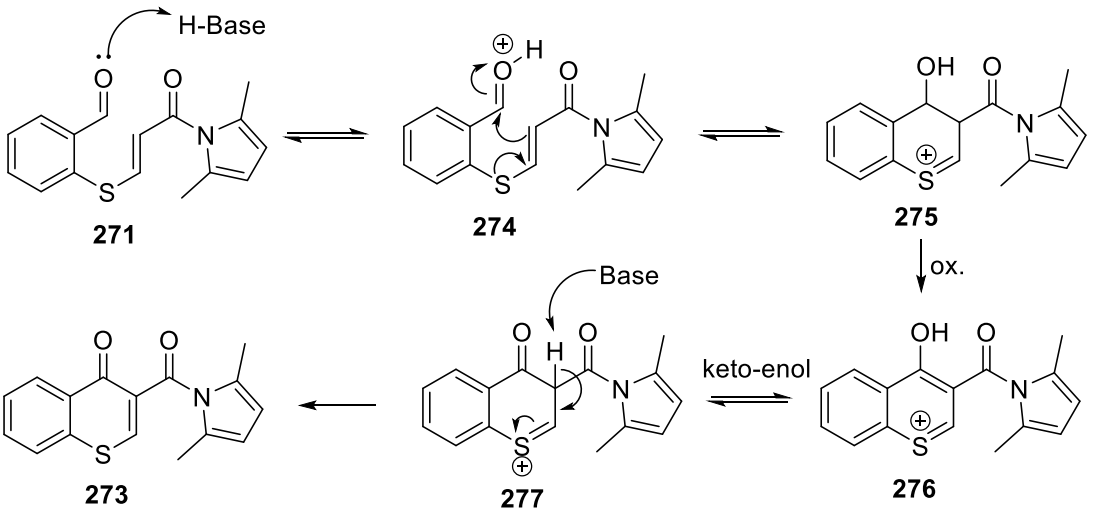
Having demonstrated that the Stetter reaction on unsaturated *N*-acylpyrroles was a viable process we moved to determine the range of heterocycles which can be formed in this process. With the success of the oxygen substrate we moved to the next group 16 element: sulphur. 2-Mercaptobenzaldehyde is not stable, so the synthesis of the analogous thioether compound, **271**, began with 2-mercaptobenzylalcohol (**269**, *Scheme 5.17*).



Scheme 5.17: *Stetter reaction to form a dihydrothiophene derivative*

2-Mercaptobenzylalcohol (**269**) underwent conjugate addition to the *N*-propioloylpyrrole (**265**) to give exclusive formation of the thioether, **270**, as a single double bond isomer in 92% yield (*Scheme 5.17*). Both the Swern oxidation and Parikh-Doering oxidation failed to give aldehyde **271**. Exposure of benzylalcohol **270** to manganese dioxide in dichloromethane overnight led to clean conversion the aldehyde **271**, however all attempts to concentrate the solution of the aldehyde led to decomposition. As the oxidation appeared to proceed very cleanly the reaction was repeated in THF and the crude mixture was filtered to remove the heterogeneous oxidant, and the solution of compound **271** was then exposed to the successful N-heterocyclic carbene conditions as shown in *Scheme 5.16*.

This gave the Stetter product (**272**) in moderate yield, but also a 4*H*-thiochromen-4-one (**273**) in approximately the same yield. Although the intermediate aldehyde (**271**) was not characterised, it is certain that the 4*H*-thiochromen-4-one **273** was formed after exposure to the Stetter reaction conditions as it is highly coloured and could also be easily visualised using thin layer chromatography. Compound **273** may be formed as described in *Scheme 5.18*.



Scheme 5.18**: Plausible mechanism for formation of compound **273

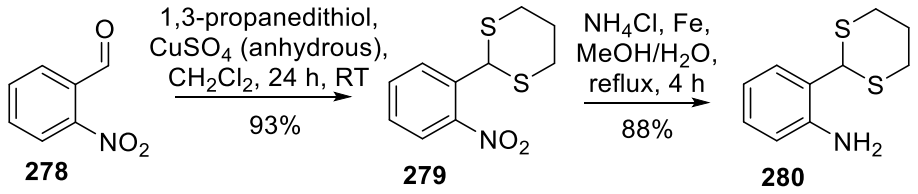
The thioenol ether present in compound **271** could attack the aldehyde, with additional activation by protonation (**274**). This mode of attack prevents the carbene adding to the aldehyde. Oxidation of intermediate **275** would lead to an aromatic compound and is likely to be irreversible. It is unclear what causes this oxidation to occur, but as it did not occur in the presence of the Swern reagent or manganese dioxide, the well-known redox activity of NHCs may be responsible. The low yield of both compound **272** and **273** does not eliminate the possibility of disproportionation. Intermediate **276** could undergo keto-enol tautomerisation (**277**) followed by removal of the acidic proton between the carbonyl units. This deprotonation would be highly favourable as it would result in a neutral and aromatic molecule, compound **273**. An analogous mode of reactivity has previously been observed in enaminones.[180]

Nonetheless, the isolation of benzothiophenone **272** shows that *N*-acylpyrrole Stetter reaction is possible with sulfur as the heteroatom tether.

5.6.3 Intramolecular Stetter reactions of N-acylpyrroles – Nitrogen tether

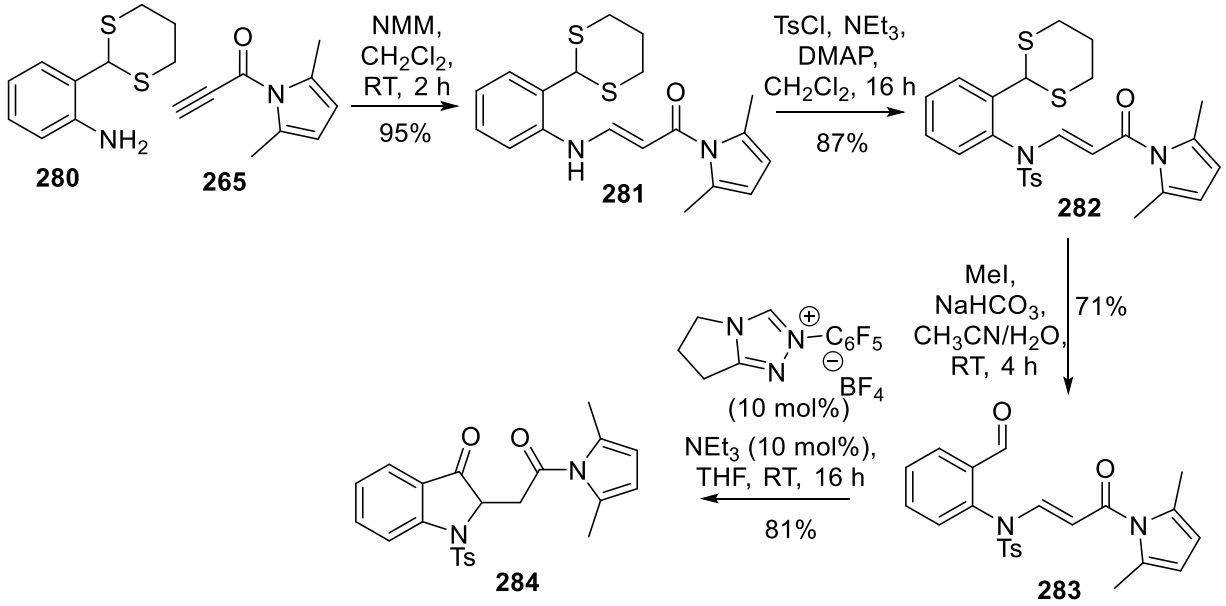
Given the abundance of alkaloid natural products, we next focused on the synthesis of an indolone (*Scheme 5.19*).

Beginning with 2-nitrobenzaldehde (**278**), the aldehyde was protected as a dithiane using anhydrous copper(II) sulfate and 1,3-propanedithiol[181] to give the dithiane (**279**) in high yield (*Scheme 5.19*). The nitro group was then reduced to the amine (**280**) using a modified Bechamp reduction, where hydrochloric acid was replaced with the weakly acidic ammonium chloride to prevent removal of the acid labile dithiane.[182]



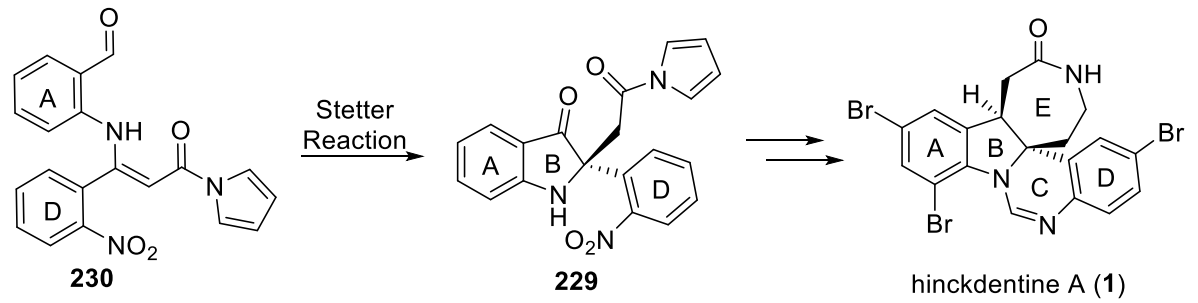
***Scheme 5.19**: Preparation of aniline nucleophile*

The aniline (**280**) was added to the *N*-propioloylpyrrole in an analogous manner to the oxygen and sulfur substrates, to give **281** in high yield as a single diastereomer (*Scheme 5.20*). It was requisite that an electron withdrawing protecting group be used on the new secondary amine (**281**) to prevent the possibility of Friedländer-type quinoline synthesis occurring. We first attempted to form an amide by acylation but exposure to acetyl chloride and acetic anhydride led only to decomposition, possibly due to reactions with a sulphur atom of the dithiane. We then successfully protected the amine as a toluenesulfonamide (**282**) under standard conditions in high yield. This was followed by alkylative hydrolysis of the dithiane to give the aldehyde **283**. The Stetter reaction was performed under identical conditions to those depicted in *Schemes 5.16* and *5.17*, and gave indolone **284** in 81% yield (*Scheme 5.20*).



***Scheme 5.20**: Stetter reaction to form an indolone*

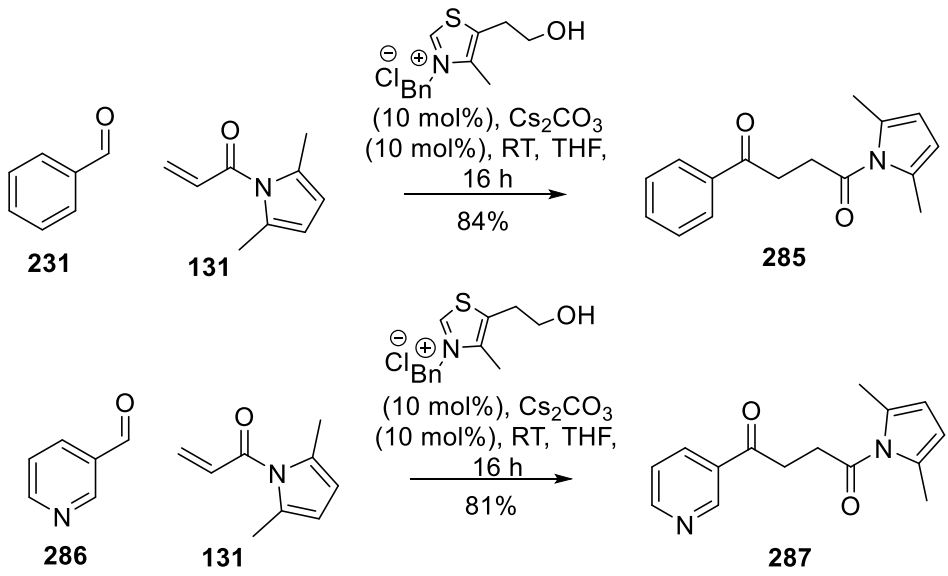
Therefore, we have shown that 5-membered heterocycles with oxygen, sulfur and nitrogen can be formed using the intramolecular Stetter reaction with *N*-acylpyrroles. The later example is directly applicable to our proposed synthesis of hinckdentine A (*Scheme 5.21*).



***Scheme 5.21**: Proposed synthesis of hinckdentine A*

5.7 Intermolecular Stetter reactions of N-acylpyrroles

Intermolecular Stetter reactions are much more difficult than intramolecular Stetter reactions but given the success described above we felt justified in attempting them with *N*-acylpyrrole substrates. A recent report had disclosed conditions for intermolecular Stetter reactions which were successful on esters and apparently general so these conditions were used.[183] We began with the less challenging non-enolisable aldehydes (*Scheme 5.22*).



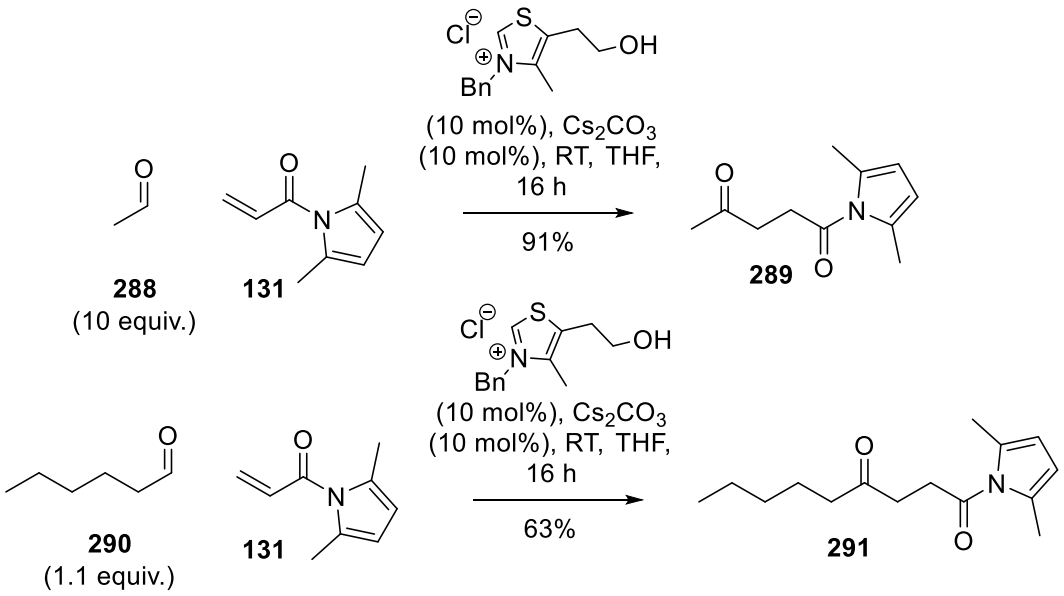
***Scheme 5.22:** Intermolecular Stetter reaction of non-enolisable aldehydes*

We found that we could achieve high yields with no need for optimisation for intermolecular Stetter reactions between *N*-acryloylpyrrole **131** and both aromatic (**231**) and heteroaromatic (**286**) aldehydes (*Scheme 5.22*). Negligible benzoin condensation products were formed. The benzoin condensation is usually competitive with intermolecular Stetter reactions, so the lack of benzoin in these instances demonstrates that the enhanced electrophilicity of the unsaturated *N*-acylpyrrole (**131**) was overcoming the problems which are usually associated with this reaction. The high isolated yields

of the desired products (**285** and **287**) were obtained using just 1.1 equivalents of the aldehyde.

Intermolecular Stetter reactions of enolisable aldehydes are considered the most challenging Stetter reactions. This is especially true when using less electrophilic acceptors such as unsaturated esters. There are very few examples and even these require very specific conditions.[152a, 173, 183] For these reactions the enhanced electrophilicity of *N*-acylpyrroles ought to be advantageous.

We first performed the reaction between *N*-acryloylpyrrole (**131**) and acetaldehyde (**288**, *Scheme 5.23*). Due to the high volatility of acetaldehyde (**288**, boiling point: 20°C) we used ten equivalents of this aldehyde. Pleasingly, this gave 91% yield of the desired Stetter product (**289**). The reaction could also be performed with longer aliphatic aldehydes, such as hexanal (**290**, *Scheme 5.23*). The intermolecular Stetter reaction between *N*-acryloylpyrrole **131** and hexanal (**290**) with a more conventional 1.1 equivalents of the aldehyde also gave the Stetter product (**291**) in good yield.

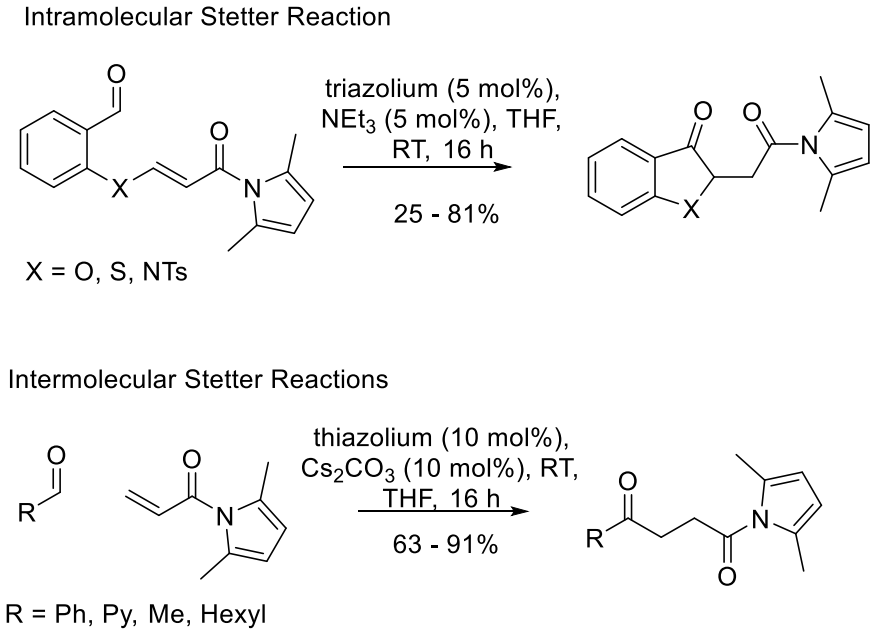


***Scheme 5.23**: Intermolecular Stetter reaction of enolisable aldehydes*

The trouble free nature of these usually challenging Stetter reactions demonstrates the strength of this methodology. We obtained good yields of the most challenging intermolecular Stetter reactions under mild conditions in an operationally simple manner, and without the need for optimisation.

The success of the intermolecular Stetter reactions is a significant improvement to the published methodology. The success of these reactions, particularly those with enolisable aldehydes, would not have been possible without the added electrophilicity of the *N*-acylpyrrole. Not only does the *N*-acylpyrrole facilitate the Stetter reaction, it also enables further transformations to be performed.

5.8 Summary and Conclusions



***Scheme 5.24**: Stetter reactions of N-acylpyrroles*

We have demonstrated the utility of *N*-acylpyrroles in the Stetter reaction. We have shown that the *N*-acylpyrrole unit is not only compatible with the N-heterocyclic carbene conditions, but that they are also highly efficient Michael acceptors in the Stetter reaction. We have formed a range of fused heterocycles in high yields using this protocol (*Scheme 5.24*). We have also demonstrated that *N*-acylpyrroles participate in intermolecular Stetter reactions with both aromatic and enolisable aldehydes (*Scheme 5.24*). These results will significantly enhance the utility of the Stetter reaction by broadening the range of Stetter reaction possible, and also expand the range of subsequent transformations. This work provided confidence that incorporating a Stetter reaction of an *N*-acylpyrrole into the total synthesis of the natural product hinckdentine A would be productive.

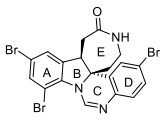
Aspects of this work have been published in *The European Journal of Organic Chemistry*.[3]

With the completion of this study into the Stetter reaction of *N*-acylpyrroles we had investigated both key steps in our proposed total synthesis of hinckdentine A and we were ready to assemble these to complete the synthesis.

Chapter 6

Studies Toward the Synthesis of Hinckdentine A

Results and Discussion

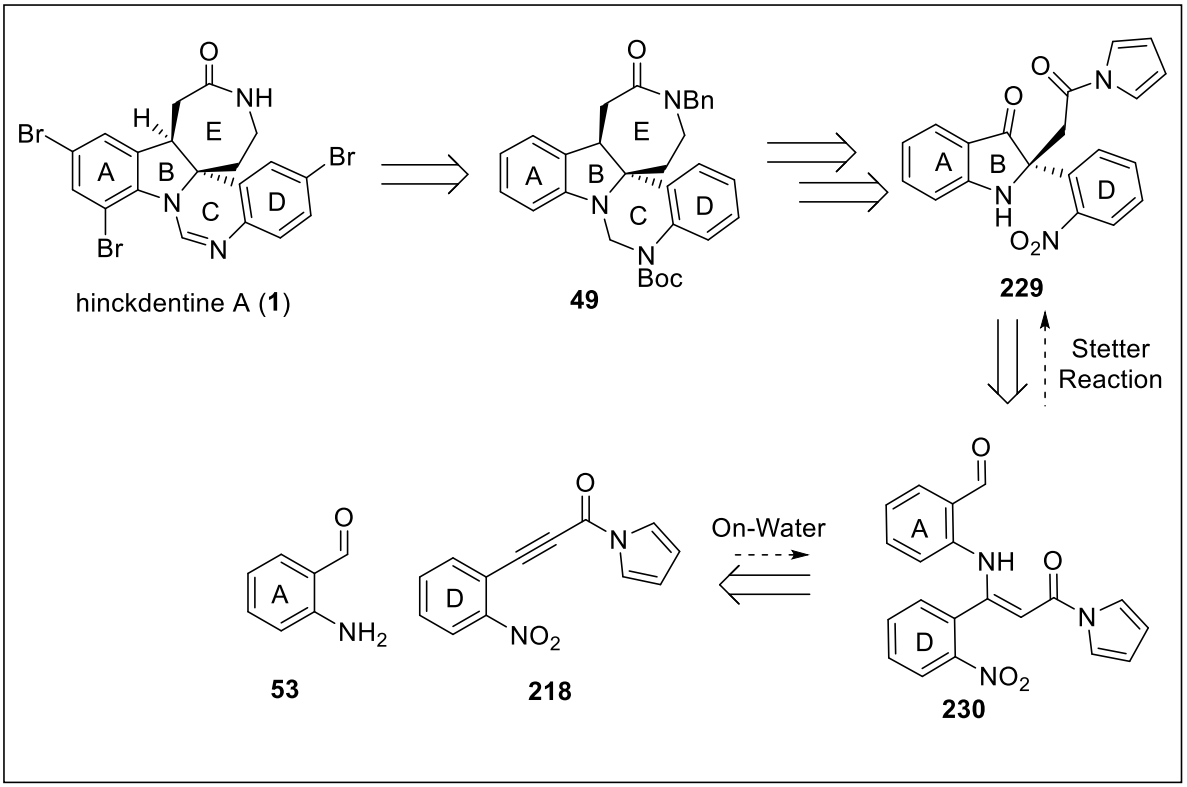


6.1 Proposed synthesis of hinckdentine A

We undertook these studies into underutilised reactions with the goal of developing them so that they can be used in synthesis. We have demonstrated that on-water catalysis is powerful and can be beneficial in a synthetic setting. Similarly we have demonstrated *N*-acylpyrroles participate in reactions in an analogous fashion to a ketone or ester, but with latent synthetic versatility. We propose to construct hinckdentine A by utilising the two previously studied reactions; an on-water conjugate addition reaction and a Stetter reaction, both utilising an *N*-acylpyrrole. The advantages of this strategy will be that we learn additional information about these reactions while simultaneously synthesising a potentially useful molecule. Total synthesis is an ideal testing ground for these goals due to the strict requirements of the molecular architecture and obvious benchmarks of success.

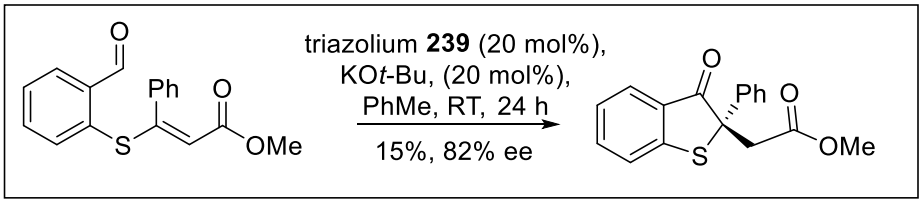
We have demonstrated the key steps of the synthesis are entirely viable, so the synthesis should be achieved by applying the knowledge of the reactions we have developed.

6.1.1 Retrosynthesis of hinckdentine A



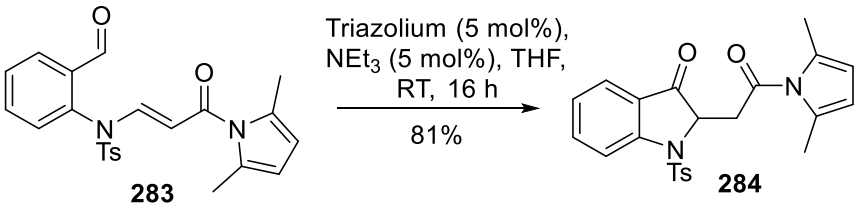
***Scheme 6.1**: Retrosynthesis of hinckdentine A*

This proposed synthesis will utilise the previously studied reactions as key bond forming steps (*Scheme 6.2*). We planned our synthesis to target a similar intermediate to Kawasaki (**49**), as he had demonstrated conditions for successful electrophilic tribromination of the hinckdentine A core (see *Section 1.2.3*),. Installation of a 2-carbon unit and condensation of the pyrimidine ring would lead to pentacycle **49** from **229**. Compound **229** would be the product of an asymmetric Stetter reaction with aldehyde **230**. This Stetter reaction is closely related to examples of asymmetric Stetter reactions published by Rovis (*Scheme 6.2*)[184] although there are relatively few examples as the precursors are difficult to synthesise.



***Scheme 6.2:** Example of asymmetric Stetter reaction by Rovis*

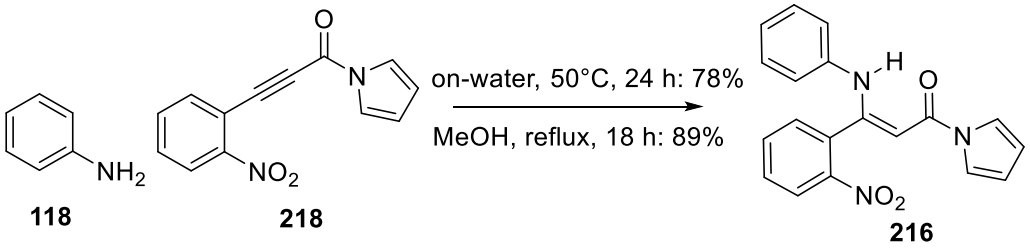
The Stetter reaction required for the synthesis of hinckdentine A (*Scheme 6.1*) is directly comparable to the Stetter reactions to form an indolone which was detailed in Chapter 5 (*Scheme 6.3*).



Scheme 6.3: *Example of a Stetter reaction to form an indolone*

Given the well precedented reliability of the asymmetric intramolecular Stetter reaction to create quaternary stereocentres[148b] the synthesis should easily be elaborated into an asymmetric synthesis. Quaternary stereocentres are difficult to synthesise enantioselectivity; the asymmetric Stetter reaction is one of the few general methods to make quaternary stereocentres in high enantiomeric excess and this synthesis will highlight the utility of the Stetter reaction in creating these challenging stereocentres.

The Stetter reaction substrate, **230** (*Scheme 6.1*), would be obtained by an on water conjugate addition of a suitable aniline (**53**) into an alkynyl Michael acceptor **218**.



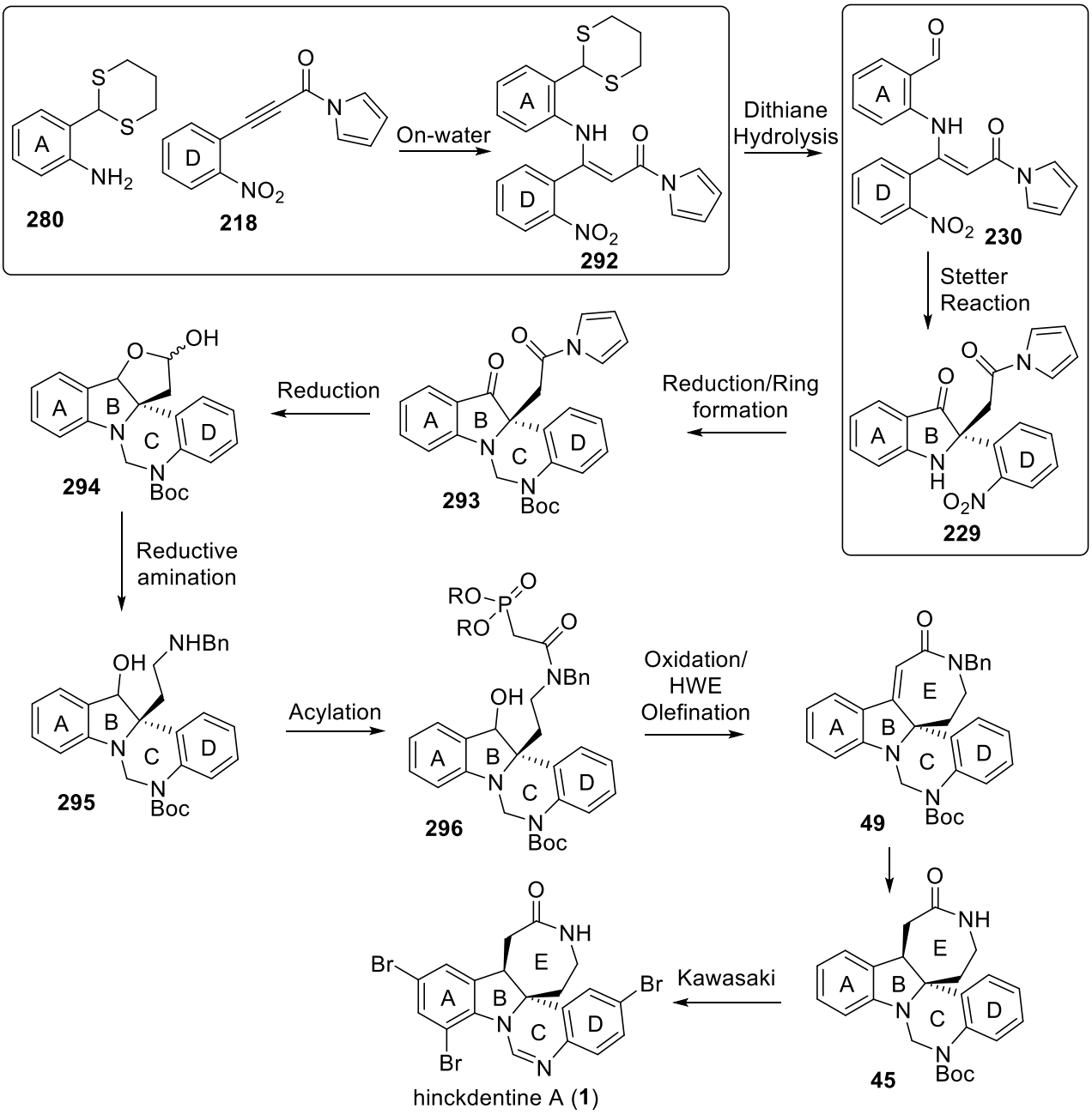
Scheme 6.4*: Nucleophilic addition to N-acylpyrrole Michael acceptor*

This conjugate addition also has precedence in our own work, being analogous to the on-water catalysed conjugate addition reactions of anilines described in chapter 3 (*Scheme 6.4*). The conjugate addition reaction will synthesise a highly functionalised molecule which would be difficult to prepare by other means.

All of the published strategies for the total synthesis of hinckdentine A began at indole system which consequently required a difficult de-aromatisation to begin the synthesis (see *Section 1.2*). The Stetter reaction allows entry into the hinckdentine a scaffold without having to break aromaticity, and will enable the synthesis of the quaternary stereocentre. The Stetter reaction also facilitates the installation of the ε-lactam through the functional groups it introduces. We anticipated that our synthetic strategy would demonstrate the improvements which can be made by utilising neglected reactions.

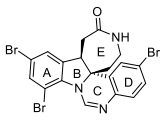
6.1.2 Synthetic strategy to hinckdentine A

With the understanding we had acquired of on-water conjugate addition reactions and the Stetter reaction, we were able to plan a detailed synthetic sequence (*Scheme 6.5*).



***Scheme 6.5**: Proposed synthetic sequence to hinckdentine A*

The conjugate addition reaction between compounds **280** and **218** would be modelled off the successful on-water conjugate additions described in Chapter 3 (see *Section 3.14*). It is necessary to use a protected aldehyde, such as dithiane **280**, rather than the parent compound 2-aminobenzaldehyde (**53**) as 2-aminobenzaldehyde is relatively unstable and would be unlikely to survive the reaction



conditions. Hydrolysis of the dithiane (**292**) would give an aldehyde (**230**) which is ready for a Stetter reaction to give key intermediate **229**. As the Stetter reaction is not often used in synthesis, there are many gaps in the knowledge of compatible substrates. There are no reports of Stetter reactions occurring in the presence of secondary amines, however, should this be a problem it should simply be a matter of choosing a suitable protecting group.

Reduction of the nitrobenzene group (**229**) to the aniline under any of the multitude of conditions available, followed by insertion of a methylene unit in an S_N2 reaction with methylene bromide would give the ABCD tetracycle (**293**) of hinckdentine A. Requisite protection of the secondary amine as the *tert*-butylcarbamate would allow for the necessary manipulations to make the D ring and complete the synthesis.

We will use the previous syntheses to guide our strategy for the synthesis of the 7-membered D ring. McWhorter's aldol strategy (see *Section 1.2.2*) was both shorter than Kawasaki's (see *Section 1.2.3*) and did not suffer from *syn*- and *anti*-selectivity problems. Therefore we can determine that reduction after lactamisation is the more efficient strategy.

At this point the benefits of the Stetter reaction become clear. Aside from forming the quaternary stereocentre enantioselectively the Stetter reaction also produces reactive functionality which will enable the synthesis of the remainder of hinckdentine A. Reduction of the *N*-acylpyrrole and phenyl ketone would result in a lactol (**294**). Reductive amination of the aldehyde with benzylamine will install the final nitrogen atom (**295**). The newly installed pendant nitrogen will be acylated with a phosphonate containing group (**296**) in preparation for a Horner-Wadsworth-Emmons (HWE) olefination.

In McWhorter's eventual successful synthesis they found the aldol reaction to form the ε-lactam worked with an *N*-benzyl amide but not an *N*-carbamoylamide, as such we chose the benzyl protection group. In preparation for the HWE olefination an oxidation of the benzyl alcohol to phenylketone will be performed. Others have found that intramolecular Horner-Wadsworth-Emmons reactions to form 7-membered rings are not trivial, but have succeeded with careful choice of solvent[185], additives[186] and base.[187]

After the cyclisation to form compound **49**, reduction of the alkene with concurrent hydrogenolysis of the benzyl group protecting the amide would result in compound **45**. Reaching this compound would constitute a formal total synthesis of hinckdentine A as compound **45** occurs as one of the final intermediates in Kawasaki's synthesis of hinckdentine A (**1**). As our synthesis will be asymmetric is it important to complete the synthesis to confirm the optical data matches that of the authentic sample. As such, repetition of the final three steps performed by Kawasaki will be used to complete the synthesis of hinckdentine A (**1**).

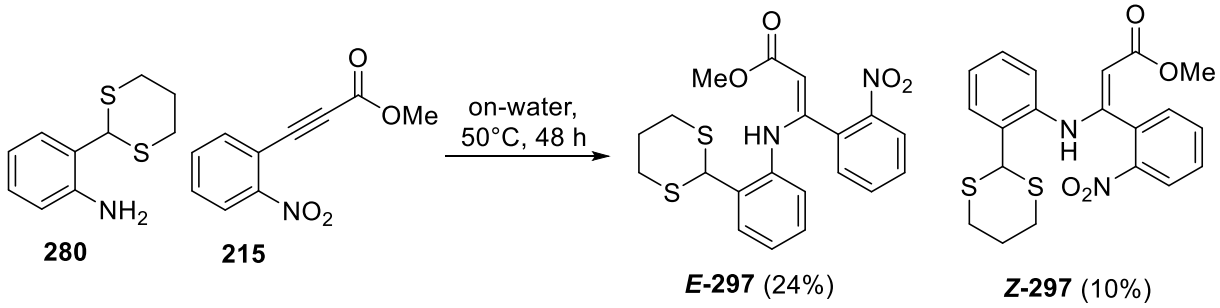
6.1.3 Synthetic strategy for model study

We planned to begin our studies into the total synthesis of hinckdentine A using a model system, starting with simple and known starting materials (*Scheme 6.6*). For this preliminary study the *N*-acylpyrrole would be replaced by an ester in the Michael acceptor (**215**). This model study would allow for the identification of any obvious problems before applying the synthesis to the *N*-acylpyrrole substrate and allow us to analyse the benefits of the *N*-acylpyrrole unit.

The synthesis was to begin with the on-water catalysed conjugate addition between 2-(2'-1,3-dithianyl)-aniline (**280**) and 3-(2-nitrophenylpropiolate) (**215**), which had both been synthesised for earlier work.

6.2 Ester Michael acceptor - Results

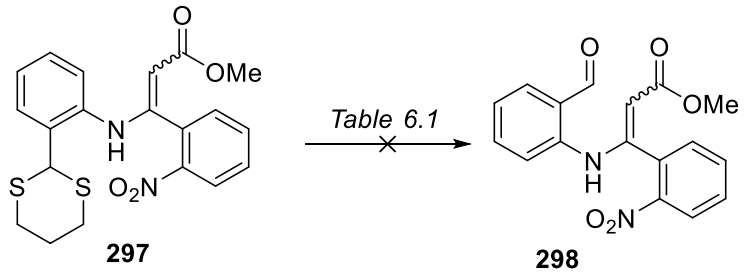
Having previously synthesised 2-dithianylaniline (**280**, see *Section 5.6*) and methyl *o*-nitrophenylpropiolate (**215**, see *Section 3.14*) we were immediately ready to begin the synthesis with an on-water conjugate addition reaction (*Scheme 6.6*).



Scheme 6.6: *On-water addition of dithiane containing nucleophile*

We subjected these reactants to the previously successful on-water conditions (*Scheme 6.7*). This gave the desired conjugate addition product (**297**) as a 2:1 mixture of separable *E/Z* isomers in combined yield of 34%. This yield is somewhat lower than that with unsubstituted aniline and also displayed much less selectivity (see *Section 3.14*). This can be attributed to the very large group *ortho*- to the nucleophilic amine (**280**).

Having quickly obtained the on-water product we sought to hydrolyse the dithiane in preparation for the Stetter reaction (*Scheme 6.7, Table 6.1*).



Scheme 6.7: *Attempted dithiane hydrolysis*

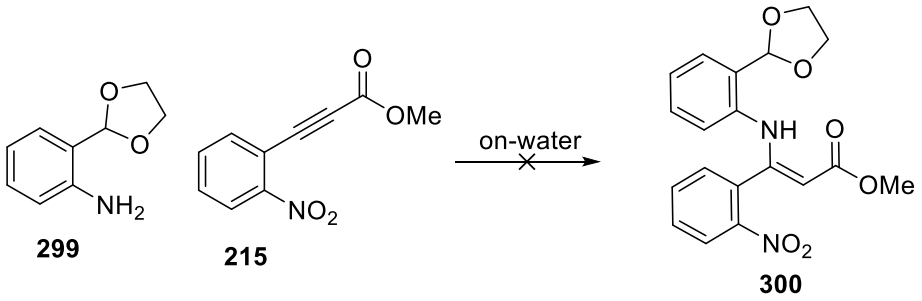
Catalyst	Solvent	Temp. (°C)	Time (h)	Result
$MeI/NaHCO_3$	$MeCN/H_2O$	RT	24	NR
$MeI/NaHCO_3$	$MeCN/H_2O$	50	4	decomposition
$MeI/NaHCO_3$	THF/H_2O	RT	24	NR
HIO_4	THF	0	1	decomposition
$Bi(NO_3)_3.5H_2O$	$toluene/H_2O$	RT	24	decomposition
$HgCl_2/CaCO_3$	$MeCN/H_2O$	RT	2	decomposition

Table 6.1*: Conditions attempted to hydrolyse dithiane*

The plethora of methods available to remove dithiane protecting groups reflects the inherent unpredictability of their performance. This is what we found when attempting this hydrolysis (*Table 6.1*). We first attempted the often reliable alkylative deprotection with iodomethane in aqueous acetonitrile. At room temperature no reaction was observed and when the temperature was raised decomposition resulted, even after short reaction times. Next we tried oxidative deprotection using periodic acid, but this again resulted in decomposition. We then turned our attention to Lewis acid mediated deprotection. Under the action of wet bismuth nitrate[188] none of the desired aldehyde was observed. Under the influence of mercury the dithiane (**297**) was removed but none of the desired aldehyde (**298**) was recovered. As compound **297** contains many reactive functional groups (secondary amine, enamine, Michael acceptor, nitro group) many side reaction can occur, especially in the presence of a Lewis or protic acid. It appears these reactive groups were giving rise to complex aromatic by-products. Given the poor yield and mixture of isomers obtained in the conjugate addition it was decided to find an alternate protecting group.

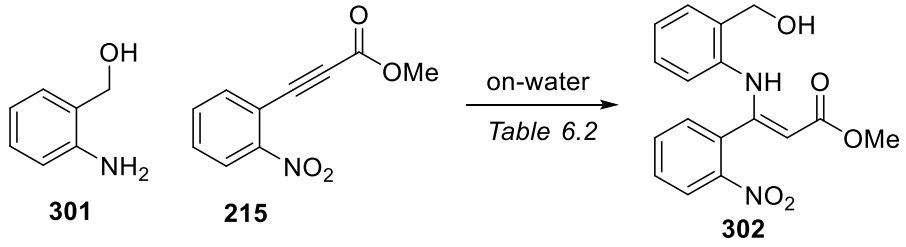
The dioxolane protected 2-aminobenzaldehyde (**299**) was synthesised in two steps from *o*-nitrobenzaldehyde using a literature procedure.[189] When this nucleophile was subjected to the on-water reaction with methyl 2-nitrophenylpropiolate (**215**) no addition product (**300**) was observed but

decomposition of the nucleophile was noted due to hydrolysis of the dioxolane (*Scheme 6.8*).



Scheme 6.8: *Attempted conjugate addition with dioxolane protecting group*

As starting with a protected aldehyde had proved unproductive we changed to the lower oxidation state, introducing this group as an alcohol with the intention of oxidising it to the aldehyde later in the synthesis. It had previously been demonstrated that alcohols do not participate in on-water catalysed conjugate addition reactions (see *Section 3.13*), as such, we attempted the addition of commercially available 2-aminobenzyl alcohol (**301**, *Scheme 6.9*). It was also hoped this smaller group would avoid the formation of double bond isomers.



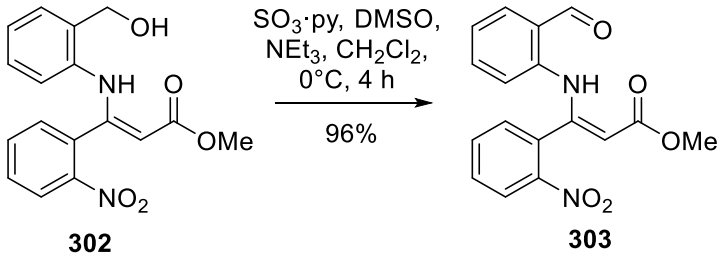
Scheme 6.9: *On-water addition of 2-aminobenzylalcohol*

Equiv. 301	Temp. (°C)	Time (h)	Yield (%)
1	50	48	10
3	50	48	22
3	55	60	44
4	**50**	**72**	**66**
8	50	72	31

Table 6.2*: Stoichiometry of on-water aniline addition*

When using a 1:1 ratio of aniline (**301**) to Michael acceptor (**215**) the addition product (**302**) was obtained in low yield (10%) after 48 hours at 50˚C (*Scheme 6.9, Table 6.2*). This could be improved to 44% when using a 3:1 ratio, and further improved to 66% when using a 4:1 ratio. The requirement

for an excess of the nucleophile is likely to be due to the reversible nature of Michael additions. Additional equivalents of the aniline only hindered the formation of an emulsion and hence did not increase the yield (*Table 6.2*). This pathway was greatly advantageous over the use of the dithiane **280** as the nucleophile due to the much higher yield of compound **302** and as the conjugate addition product (**302**) was obtained as a single isomer.



302 **303**

Scheme 6.10: *Parikh-Doering oxidation*

Having obtained the addition product (**302**) the alcohol was oxidised to the aldehyde (**303**) under Parikh-Doering conditions (*Scheme 6.10*), although this reaction was found to be extremely unreliable. Under apparently identical conditions the result of the oxidation varied from complete decomposition to 96% isolated yield. A number of alternate oxidations methods were tested, all of which were even less productive than the Parikh-Doering oxidation (*Table 6.3*).

Oxidant	Solvent	Temp. (°C)	Time	Result
Parick-Doering	CH_2Cl_2/DMSO	0	2 h	0 - 96%
Swern	CH_2Cl_2	-78	1 h	decomposition
Dess-Martin	MeCN	70	1 h	decomposition
MnO_2	CH_2Cl_2	RT	1 h	decomposition
TPAP/NMO	CH_2Cl_2	RT	30 min	decomposition

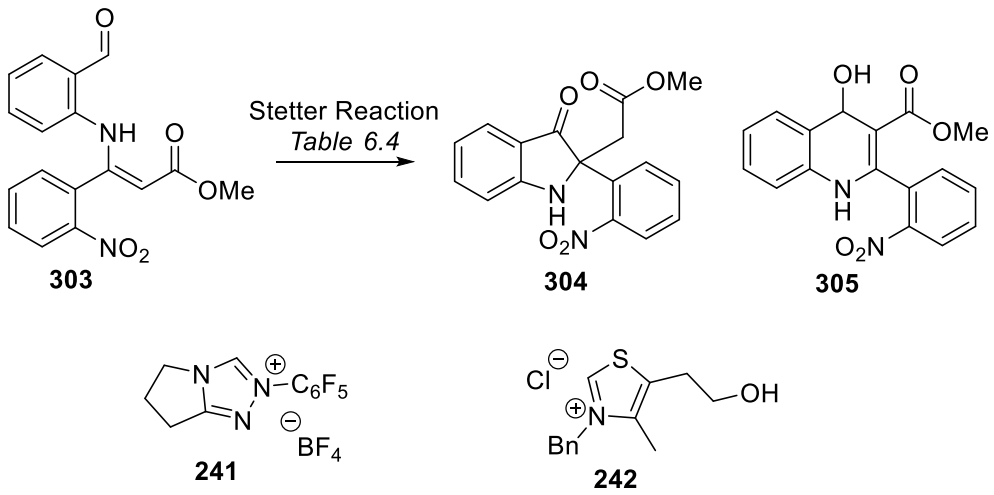
Table 6.3*: Attempted oxidation conditions*

Despite the capricious nature of the oxidation we had successfully synthesised a substrate that was ready to undergo a Stetter reaction (**303**, *Scheme 6.11*).

We initially used achiral NHC catalysts to perform the Stetter reaction. Once successful reaction conditions had been found we would switch to a chiral NHC catalyst to form the quaternary stereocentre as a single enantiomer.

Starting with the mild conditions of a thiazolium based NHC and triethylamine as the base in

tetrahydrofuran at room temperature, no reaction was observed (*Table 6.4*). When the base was changed to the stronger DBU at higher temperature, decomposition ensued. When the catalyst was changed to the more nucleophilic pentafluorophenyl triazolium NHC the desired Stetter product (**304**) was not observed, instead there was quantitative conversion to the intramolecular enamine addition product (**305**, *Scheme 6.11*), formed in a reaction reminiscent of an interrupted Friedländer quinoline synthesis.



***Scheme 6.11**: Attempted Stetter reaction*

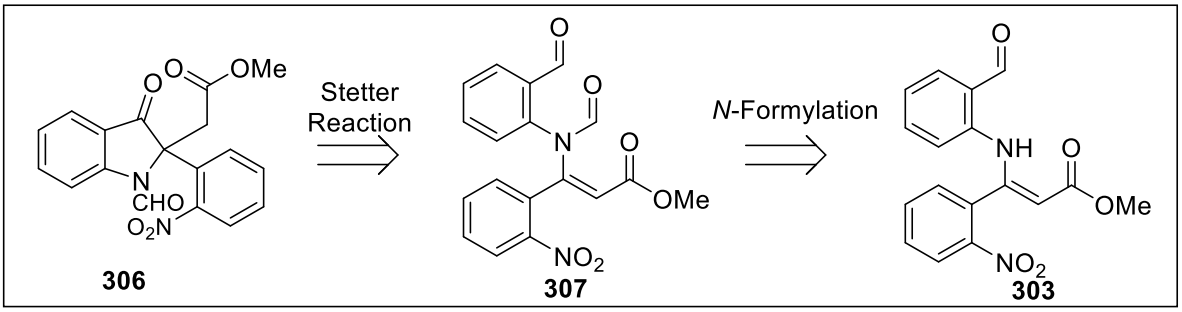
Precatalyst	Base	Solvent	Temp. (°C)	Time (h)	Result
242 (20 mol%)	NEt_3 (20 mol%)	THF	RT	24	NR
242 (20 mol%)	DBU (20 mol%)	THF	66	24	decomp.
241 (10 mol%)	NEt_3 (10 mol%)	THF	RT	16	**305** (100%)

***Table 6.4**: Stetter reaction conditions*

It was clear this unwanted reaction was due to the presence of the triazolium based carbene, as no reaction occurred in the presence of the triethylamine and the thiazolium derived carbene. This is likely to be a result of the differing nucleophilicities[190] and basicities[191] of the respective carbenes.

There is no precedent for a Stetter reaction to form heterocycle containing a secondary amine. The few examples of Stetter reactions to form nitrogen containing heterocycles all employ withdrawing groups such as amides[184] and sulfonamides[192] on the nitrogen atom. As the Stetter reaction has seldom been used in a synthetic setting it was impossible to know how it would behave in complex molecule synthesis, consequently all of these results added to the knowledge about Stetter reactions.

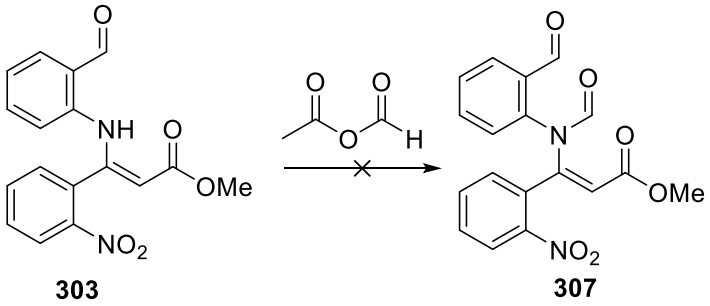
As it appeared an electron withdrawing group was necessary on the nitrogen atom to allow the Stetter reaction to occur a new strategy was developed (*Scheme 6.12*).



***Scheme 6.12**: Formylation protection strategy*

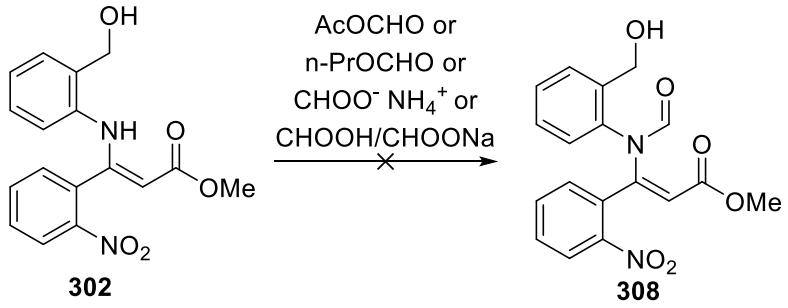
In this modified strategy, the problematic nitrogen atom was to be formylated (**307**) immediately before the Stetter reaction (**306**). The formyl group would first serve as a protecting group for the amine and later it would be condensed to form the pyrimidine ring of the natural product. Formylation reactions are not as trivial as other acylations as formyl chloride and formic anhydride cannot be prepared due to their facile decomposition into carbon monoxide. As such, formylation is usually performed with mixed anhydrides, catalytic carbonylation with carbon monoxide or amidation from a formyl ester.

We attempted to formylate the amine (**303**) with acetic formic anhydride (which was prepared according to the *Organic Syntheses* preparation[193]). This reaction failed to give the formamide product (**307**) and only led to decomposition (*Scheme 6.13*).



***Scheme 6.13**: Attempted formylation*

Given the erratic nature of the oxidation to form the aldehyde intermediate (**303**) it would have been unproductive to attempt further formylation reactions. We supposed if the protecting group was installed before the oxidation it might make subsequent oxidation more reliable, in addition to facilitating the aforementioned Stetter reaction.



***Scheme 6.14**: Attempted formylation*

Unfortunately under all of the formylation conditions either no reaction or decomposition was observed (*Scheme 6.14*).

Due to the problems accumulating in this synthetic sequence it appeared to be an ideal time to begin the originally proposed synthetic plan with an *N*-acylpyrrole Michael acceptor. Despite the setbacks, we had already demonstrated that the conjugate addition route was a viable strategy to reach the Stetter reaction precursor (**303**). We had also learned smaller *ortho* groups on the aniline nucleophile gave better selectivity and the nitrogen atom requires an electron withdrawing protecting group to be appended before the Stetter reaction was performed. As such we incorporated these lessons into our new synthetic plan with the *N*-acylpyrrole Michael acceptor.

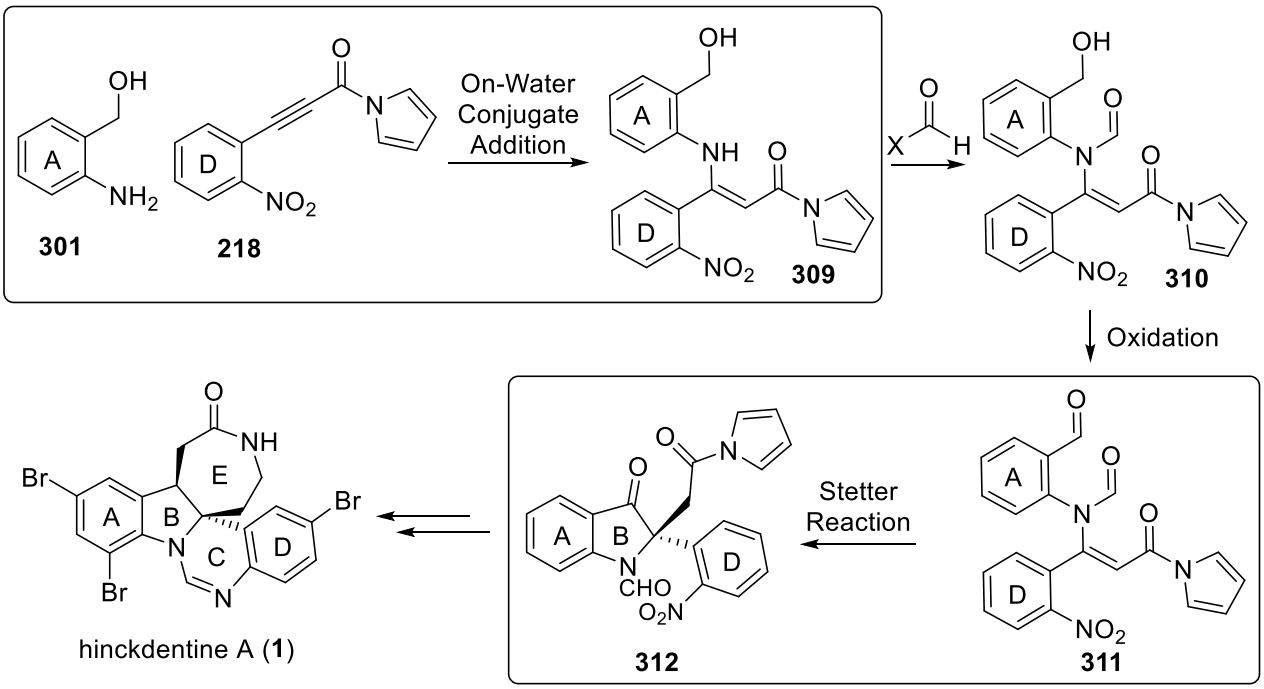
6.3 Revised synthesis plan and incorporation of *N*-acylpyrroles

6.3.1 Key changes from model study

The first of our key reactions, the conjugate addition, had worked well so only minor changes were required to this reaction. The most significant modifications required were those to allow the Stetter reaction to occur as desired.

We sought to change the initial synthetic plan in three ways;

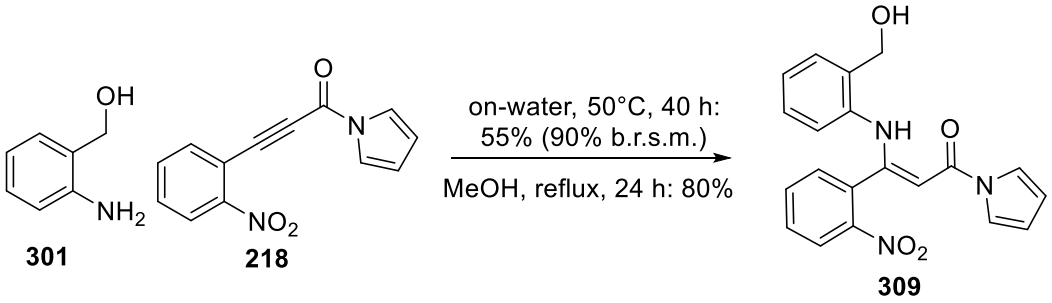
1. Replace the dithiane protected aldehyde (**280**) with a benzylic alcohol (**301**). The smaller ortho-group had been found to give higher yields and a single double bond isomer during the conjugate addition. 2-Aminobenzyl alcohol (**301**) is commercially available so even with protection and oxidation it does not add steps to the overall synthesis.
2. Replace the ester (**215**) with an *N*-acylpyrrole. Synthesis of the appropriate *N*-acylpyrrole Michael acceptor (**218**) was described in Chapter 3 (see *Section 3.14*). The *N*-acylpyrrole will result in a more electrophilic Michael acceptor and will be more easily reduced.
3. Use a protecting group on the nitrogen. This will remove the reactivity problems in the oxidation the aldehyde and in the Stetter reaction. For this a formyl group was selected, as discussed above. Forming this formamide early in the synthesis should give us more options than formerly available.



***Scheme 6.15**: Key steps in the synthesis of hinckdentine A*

6.4 *Incorporation of N-acylpyrrole - Results*

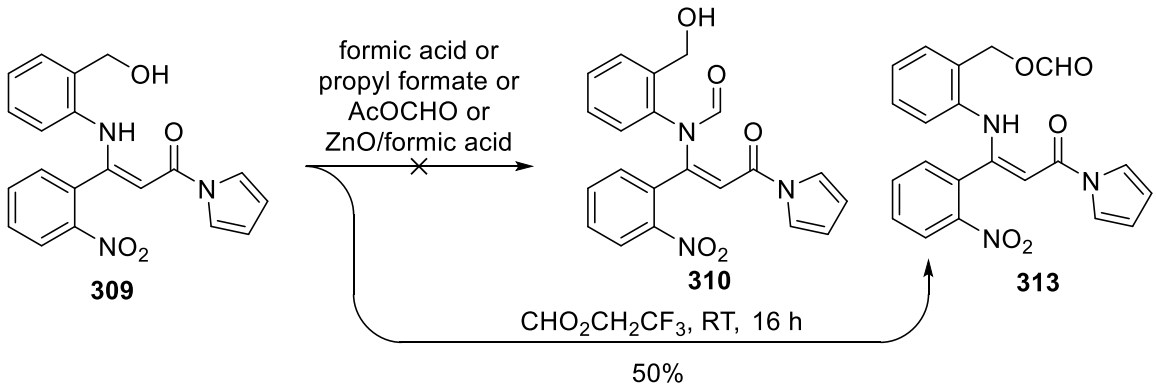
With the incorporation of the lessons we had learned from the model study, we began the synthesis with the *N*-acylpyrrole Michael acceptor (*Scheme 6.16*).



***Scheme 6.16**: On-water conjugate addition*

As was the case with the propiolate (**215**), a fourfold excess of the aniline (**301**) gave the best yield for the on-water conjugate addition to *N*-acylpyrrole **218** (*Scheme 6.16*). As had occurred with unsubstituted aniline in Chapter 3, compound **218** reacted more quickly than the corresponding ester (**215**). To obtain a similar yield with the ester a reaction time of 72 hours was required (see *Table 6.2*).

This reaction is effective when performed on-water but the on-water reaction was impeded as both reactants are solids. Consequently the reaction was superior when performed in methanol (*Scheme 6.16*). We wished to design a synthesis which was an efficient route to hinckdentine A. Regardless of how we performed the conjugate addition reaction, our novel route was inspired by the intention to explore an underutilised reaction.

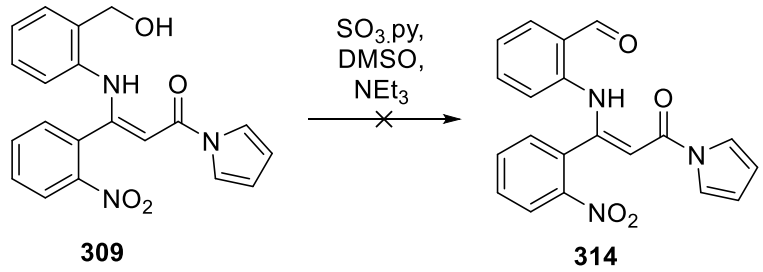


***Scheme 6.17**: Attempted formylation*

With compound **309** in hand, the next step necessary was protection of the nitrogen. Selective formylation of an amine over an alcohol would ordinarily be trivial as amines are generally more nucleophilic. For the reaction depicted in *Scheme 6.17* that was not the case. Common formylation reagents such as acetic formic anhydride or buffered formic acid led to complete decomposition. With propyl formate at reflux slow decomposition was observed so we switched to the more active

trifluoroethyl formate[194] at room temperature. In this case we obtained a good yield of *O*-formylated product (**313**). Under no conditions could we obtain the compound with both the alcohol and amine formylated. The cause of this altered reactivity was the delocalisation of the lone pair of electrons on the nitrogen thereby reducing its nucleophilicity.

Protection of the nitrogen had become problematic due to reversal of conventional reactivity trends, however the nucleophilic benzyl alcohol was only present as a proxy for an aldehyde which would be essential later in the synthesis. If the nucleophilicity of the benzyl alcohol could be removed by transforming it into an aldehyde now the reactivity problems could be circumvented (*Scheme 6.18*).

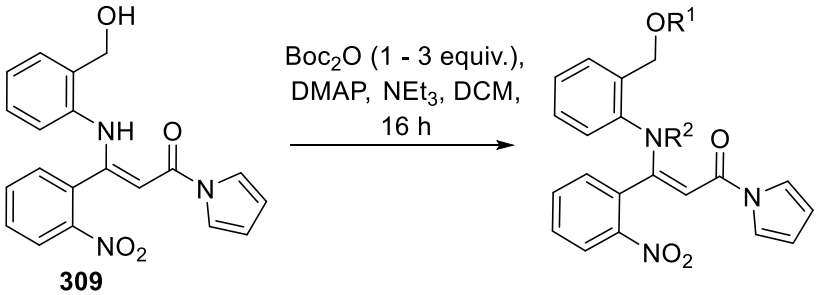


309 **314**

***Scheme 6.18**: Attempted oxidation*

We attempted the Parikh-Doering oxidation which had given erratic results with the analogous ester. The oxidation also failed to give the aldehyde (**314**) with *N*-acylpyrrole **309**, demonstrating that the reliability problems were not specific to the ester. As this was the most reliable oxidation on the closely related substrate it was unlikely that we would obtain superior results with other oxidation methods.

From these results it was clear that not only was a protecting group necessary for the nitrogen, but a protecting group was also necessary for the benzyl alcohol. As a result of the lack of success with formylation we moved on to more conventional protecting groups.

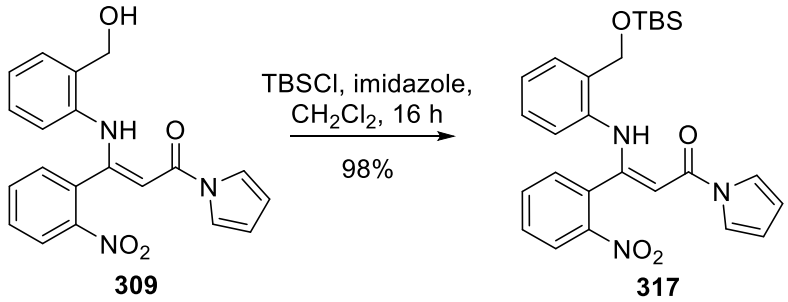


309

1 equiv. Boc_2O: R^1 = Boc, R^2 = H (**315**, 95%)
3 equiv. Boc_2O: R^1 = R^2 = Boc (**316**, 64%)

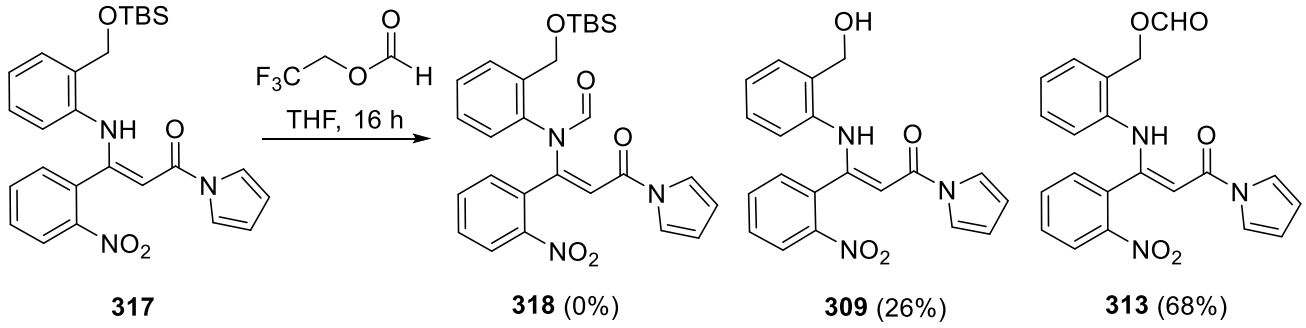
***Scheme 6.19**: Carbamate protection*

We first studied the *tert*-butylcarbamate protecting group, which is a well precedented nitrogen protecting group ubiquitous in peptide synthesis. When using one equivalent of di-*tert*-butylcarbonate we again observed exclusive formation the *O*-protected product (**315**, *Scheme 6.19*). The formation of the *tert*-butyl*carbonate* occurred despite the existence of many references to the selective formation of tert-butylcarbamate groups in the presence of alcohols.[195] We could confirm the formation of the carbonate rather than carbamate due to the drastic change in the ^{1}H NMR of the benzylic protons (4.83 ppm in **309** and 5.24 ppm in **315**) and the persistence of a distinctive hydrogen bonded NH signal in the ^{1}H NMR spectrum (11.83 ppm). With two additional equivalents of the anhydride we were able to obtain compound **316** which possessed both a carbonate and carbamate group (*Scheme 6.19*), but all attempts at selectively removal of the carbonate over the carbamate led to decomposition. Although this di-protected compound had proven to be a dead end we were encouraged that we had successfully installed an electron withdrawing protecting group on the amine, albeit unselectively and without orthogonality.



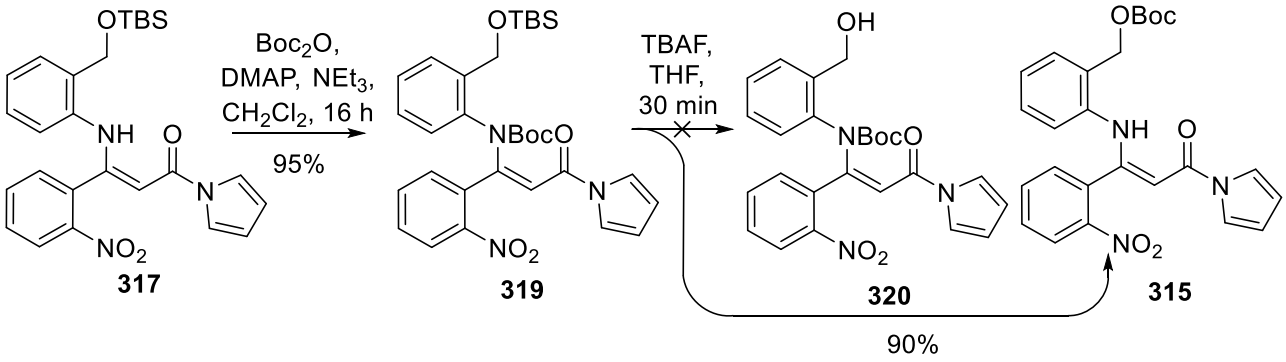
***Scheme 6.20**: Silylation of benzyl alcohol*

To facilitate orthogonal protection of the alcohol and amine in compound **309** we first silylated the benzyl alcohol under standard conditions and obtained the *tert*-butyldimethylsilyl ether, **317**, in excellent yield (*Scheme 6.20*).



***Scheme 6.21**: Attempted nitrogen formylation*

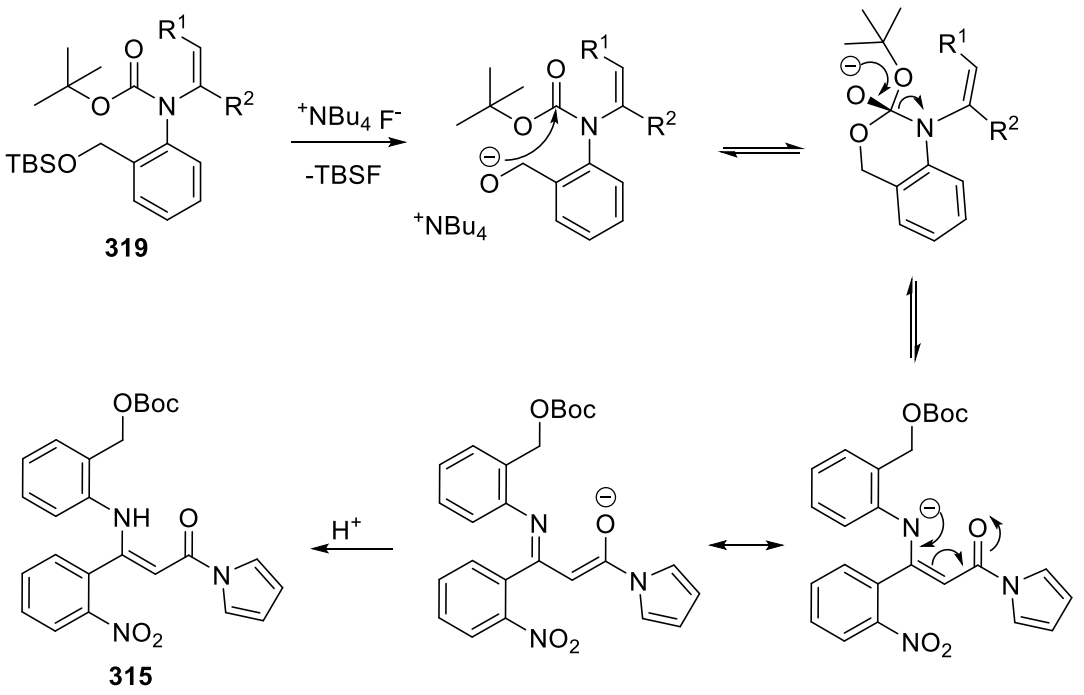
Attempts to formylate silyl protected compound **317** again gave decomposition, except in the case of trifluoroethyl formate (*Scheme 6.21*). Trace amounts of formic acid and trifluoroethanol slowly removed the silyl ether to return compound **309**. Once the benzyl alcohol was free it was again possible to form the *O*-formylated product (**313**).



***Scheme 6.22**: Carbamate protection strategy*

Installation of the preferred formamide protecting group on the nitrogen atom (**318**) had again failed so we returned to the carbamate which had, at least, reacted with the amine. Compound **317** was easily protected as the *tert*-butylcarbamate under the influence of 4-dimethylaminopyridine as a nucleophilic catalyst, to give compound **319** (*Scheme 6.22*). At this point the intense yellow colour of the compound disappeared, indicating the loss of long range conjugation and the characteristic downfield hydrogen bonded resonance disappeared from the ^{1}H NMR.

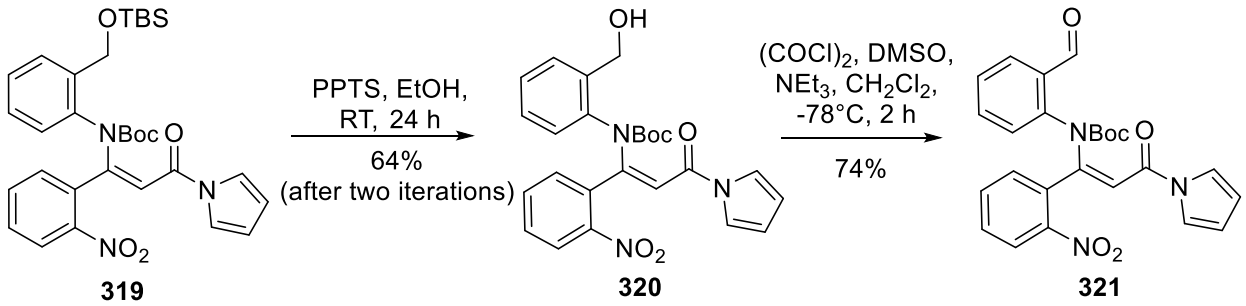
Compound **319** possessed differentially protected heteroatoms, so it was now a case of choosing appropriate conditions to selectively remove the oxygen-protecting group. Removal of the silyl ether with fluoride did not give the desired compound (**320**) but again gave the *carbonate* product, **315**, in high yield. This product is very likely to arise from an intramolecular acyl transfer via a six-membered ring transition state (*Scheme 6.23*). This again highlights the high electron delocalisation of the enamine system. This reactivity is extremely uncharacteristic of nitrogen under such mild conditions.



***Scheme 6.23**: Proposed mechanism for carbamate transfer*

From the proposed mechanism it can be seen the reason the acyl shift can occur is the alkoxide generated by fluoride cleavage of the silyl ether. Under acidic conditions the oxygen would never be an alkoxide and will not be nucleophilic enough to attack the carbonyl of the proximal carbamate.

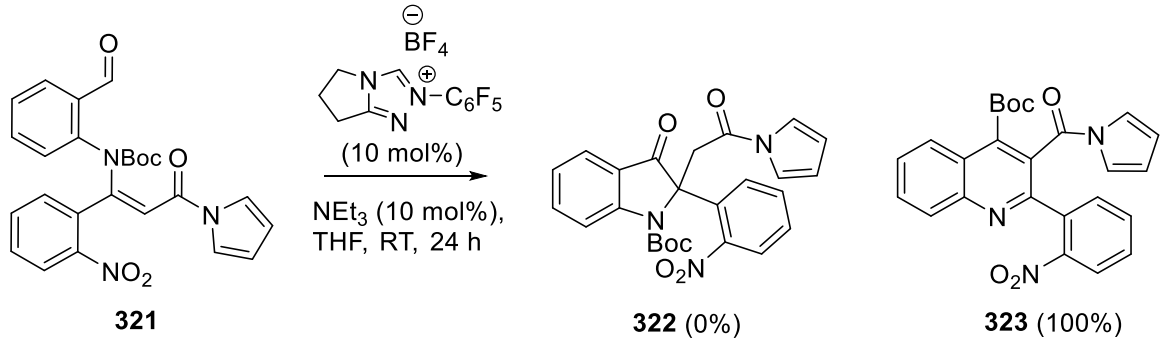
Ethanolysis of compound **319** with catalytic pyridinium *p*-toluenesulfonate gave the desired benzyl alcohol (**320**) in good yield, with most of the remaining material being unreacted starting material (*Scheme 6.24*).



***Scheme 6.24**: Synthesis of Stetter substrate*

Having exposed the benzyl alcohol we next needed to oxidise this functional group to an aldehyde. Parikh-Doering conditions resulted in the formation of aldehyde **321**, but very slowly and the reaction was incomplete even after stirring overnight at room temperature. The Swern oxidation worked well to give the aldehyde (**321**) in 74% yield (*Scheme 6.24*). After recurrent problems with

protecting group manipulations we had uncovered an efficient route to compound **321**, which contained an *N*-acylpyrrole Michael acceptor with an aldehyde and electron withdrawing group to prevent enamine reactivity, that is, compound **321** was a suitable substrate for the Stetter reaction.



321 **322** (0%) **323** (100%)

***Scheme 6.25**: Attempted Stetter reaction*

The Stetter reaction was attempted on compound **321** using the conditions we had found to be successful for related substrates in Chapter 5. Surprisingly, under these conditions none of the desired Stetter product (**322**) was formed but instead a quinolone, **323**, was observed (*Scheme 6.25*). The identity of this product was unambiguously determined from the spectroscopic data (*Table 6.5* and *6.6, Figures 6.1-6.3*).

The high resolution mass spectrum clearly indicated a dehydration reaction had occurred as the mass of compound **323** differed by 18 mass units, relative to the starting material (**321**, *Table 6.5*).

Formula	Required	Found
321 (Starting Material): $C_{25}H_{23}N_3O_6Na$ $[M + Na]^+$	484.14846	484.14791
323 (Observed Product): $C_{25}H_{21}N_3O_5Na$ $[M + Na]^+$	466.13734	466.13745

Table 6.5**: HRMS of compound **323

Inspection of the ^1H NMR spectrum of compound **323** obtained from the attempted Stetter reaction immediately revealed this compound lacked an aldehyde but also lacked any upfield resonances diagnostic of hydrogen atoms alpha to the carbonyl of the *N*-acylpyrrole (*Figure 6.1*). This clearly indicated the reaction which had occurred was not the desired Stetter reaction.

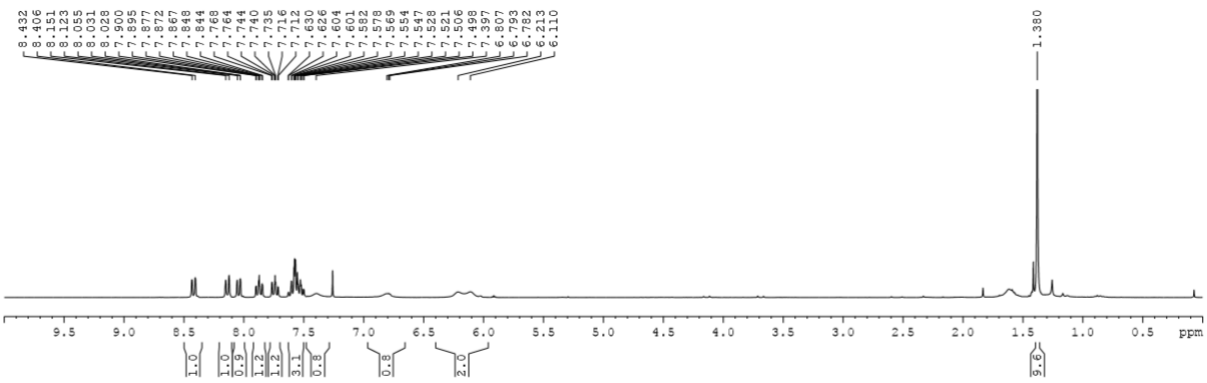


Figure 6.1**: [1]H NMR spectrum of compound **323

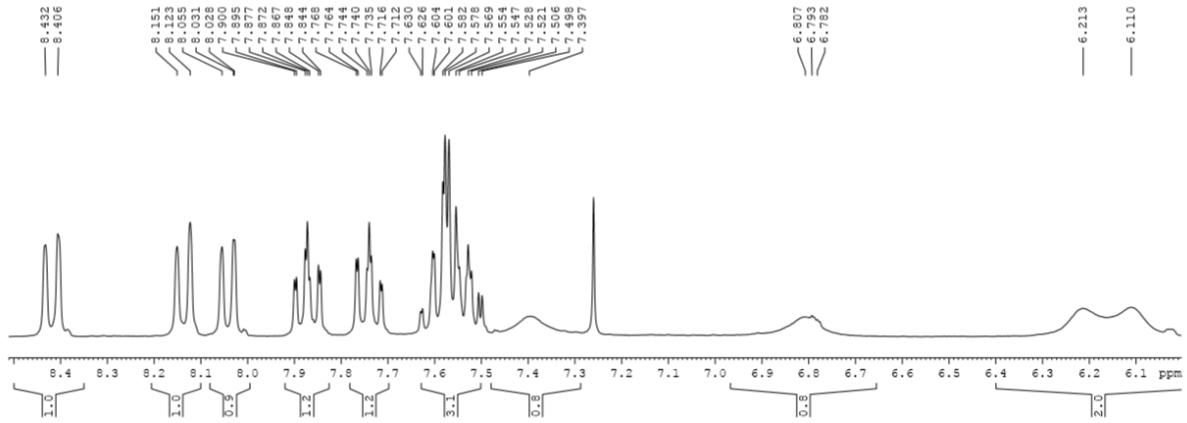


Figure 6.2**: Expansion of aromatic region of [1]H NMR spectrum of **323

From the [1]HNMR spectrum (*Figure 6.1*) it can be see compound **323** is almost entirely aromatic and still has a *tert*-butyl group present (1.38 ppm). It is also worth noting that the usually symmetric pyrrole protons have become diastereotopic and very broad (7.39, 6.79, 6.21 and 6.11 ppm, *Figure 6.2*), which is likely to indicate conformational isomerism due to restricted rotation. Aside from the pyrrole signals there are eight further aromatic signals which show the coupling pattern of *o*-disubstituted benzene rings (8.43 – 7.39 ppm, *Figure 6.2*).

The [13]C NMR spectrum provided the most constructive information to determine the structure of compound **323** (*Figure 6.3, Table 6.6*).

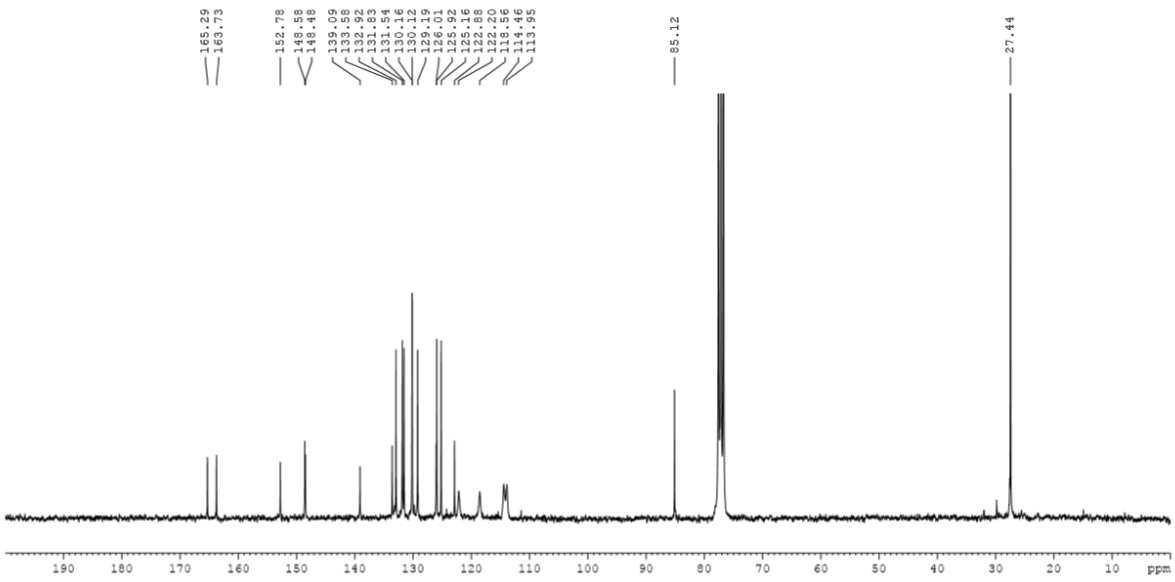


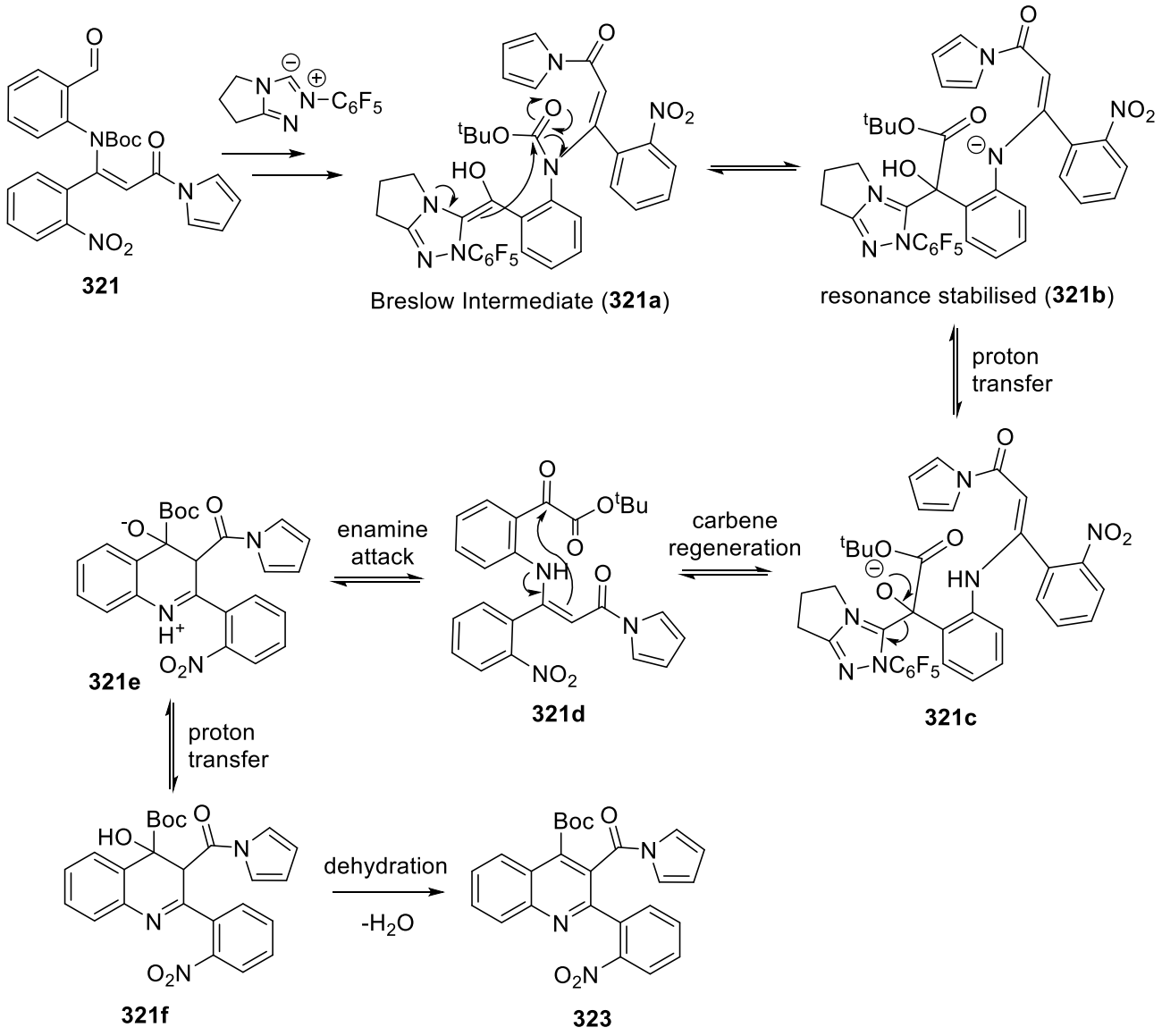
Figure 6.3**: [13]C NMR spectrum of compound **323

Shift (ppm)	165.3	163.7	152.8	148.6	148.5	139.1	133.6	132.9	131.8	131.5	130.1	130.1
DEPT	C	C	C	C	C	C	C	CH	CH	CH	CH	CH
Other	carbonyl	carbonyl	-	-	-	-	-	-	-	-	-	-
Shift (ppm)	129.1	126.0	125.9	125.2	122.9	122.2	118.6	114.5	112.9	85.5	27.4	
DEPT	CH	C	CH	CH	C	CH	CH	CH	CH	C	CH_3	
Other	-	-	-	-	-	pyrrole	pyrrole	pyrrole	pyrrole	*t*-butyl	*t*-butyl	

***Table 6.6**:* [13]C NMR data of compound **323**

Compound **323** possessed two [13]C resonances in the carbonyl region. The peak at 165.3 was characteristic of an *N*-acylpyrroles and the chemical shift of the second carbonyl was above 160 ppm. This relatively high chemical shift indicated the *tert*-butyloxy group was no longer part of a carbamate or carbonate, but rather an ester. There are only eight aromatic tertiary carbon signals (excluding those due to the pyrrole) and there are seven quaternary aromatic signals (*Table 6.6*), which is consistent with the information from the proton spectrum. This suggests the presence of a highly substituted aromatic system. Also consistent with the [1]H NMR spectrum the carbon atoms associated with the pyrrole group display individual and very broad resonances. Broad resonances in the [13]C NMR such as these strongly suggested restricted movement.

This information in conjunction with knowledge of the operation of NHCs led us to compound **323** as the product of the reaction. A proposed mechanism by which this product forms is depicted in *Scheme 6.26.*



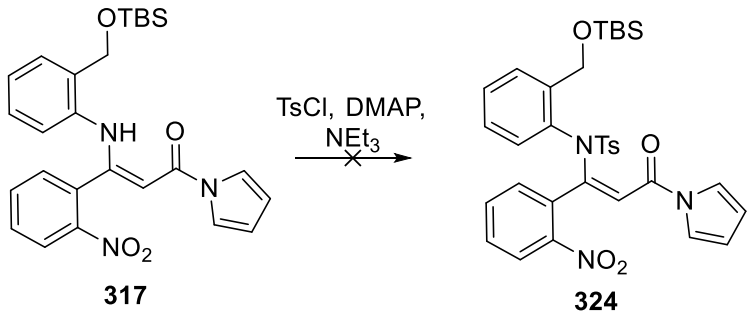
Scheme 6.26**: Proposed mechanism for formation of quinoline **323

After formation of the Breslow intermediate (**321a**) there are two sites for nucleophilic attack to occur; the Michael acceptor to form a 5-membered ring as desired, or the carbonyl of the carbamate. As observed previously the lone pair on the "carbamate" nitrogen is already highly delocalised so will not be contributing significantly to the carbamate character of this group and it will behave more like an ester (which is more electrophilic than a carbamate). The electron donating capacity of this nitrogen will also reduce the electrophilicity of the Michael acceptor and the steric hindrance of the large nitrophenyl group will slow the desired addition. From the observed result it is evident the Breslow intermediate exclusively attacks the carbamate to form resonance stabilised intermediate **321b**. Proton transfer (**321c**) followed by elimination and regeneration of the carbene (**321d**) proceeds in the usual manner. Once the nitrogen protecting group is removed (**321d**) it displays enamine

reactivity, as it did in the first instance. Enamine attack on the highly active α-ketoester (**321e**) and proton transfer (**321f**) is followed by a favourable dehydration due to the gain of aromaticity, which leads to the observed product **323**. It is worth noting this is a very similar mode of reactivity to that observed formerly when the *tert*-butyloxy group was transferred from the nitrogen to the oxygen in the presence of TBAF (see *Scheme 6.23*) and also the reactivity when the Stetter reaction was performed without an *N*-protecting group (see *Scheme 6.11*).

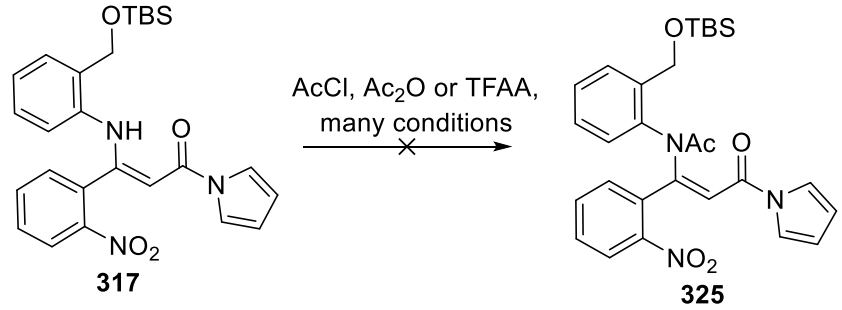
The only plausible mechanism for the formation of this undesired product involves formation of the Breslow intermediate so it was anticipated other NHC catalysts would suffer from the same problems. There did not appear to be any potential for progress using this protecting group so we moved onto an alternate protecting group strategy.

As the carbamate protecting group had proven to be incompatible with the conditions we required a new electron withdrawing protecting group for the nitrogen. Toluenesulfonyl groups had been demonstrated to be compatible with the Stetter reaction in the Chapter 5 (see *Section 5.6.3*), although they can be difficult to subsequently remove.

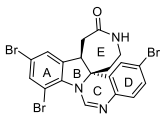


***Scheme 6.27**: Attempted tosylation*

We attempted to sulfonylate compound **317** using the conditions which had previously been successful in our study of the Stetter reaction (see *Section 5.6.3*). Under these conditions no reaction was observed and under a range of more forcing conditions, decomposition was observed (*Scheme 6.27*).



***Scheme 6.28**: Attempted acylation*



Another common electron withdrawing group for amines is the amide. We had previously and unsuccessfully tried to install a formamide on compound **317** but we now tried more conventional amides. However, acylation or trifluoroacylation under a multitude of conditions resulted in decomposition (*Scheme 6.28*).

We had successfully performed an on-water conjugate addition to the new *N*-acylpyrrole substrate and after some experimentation synthesised the desired substrate for the Stetter reaction. An unforseen reaction pathway had dominated under the NHC conditions. To circumvent this we tried to use several different electron withdrawing nitrogen protecting groups but with little success. We repeatedly observed unusual reactivity involving delocalisation of electrons from the nitrogen.

The proposed synthetic pathway still appeared to be robust, however it was apparent we needed a new nitrogen protecting group strategy. The new protecting group must be electron withdrawing to prevent the Friedländer-type reactivity observed, but also have low electrophilicity to avoid nucleophilic attack by the Breslow intermediate.

6.5 Nitrobenzenesulfonamide protecting group strategy

Using the previous synthetic strategy we had successfully synthesised a molecule with the required functionality to perform a Stetter reaction however unforseen problems with a protecting group had caused the Stetter reaction to give rise to a by-product. Other electron withdrawing protecting groups had proven impossible to install. At this point we did not wish to make significant changes to our strategy so an electron withdrawing protecting group was still required on the nitrogen. To circumvent the reactivity observed with the carbamate it was also necessary for this electron withdrawing protecting group to have low electrophilicity. The protecting group which was chosen for this role was the nitrobenzenesulfonyl group or "nosyl" group (*Figure 6.4*).

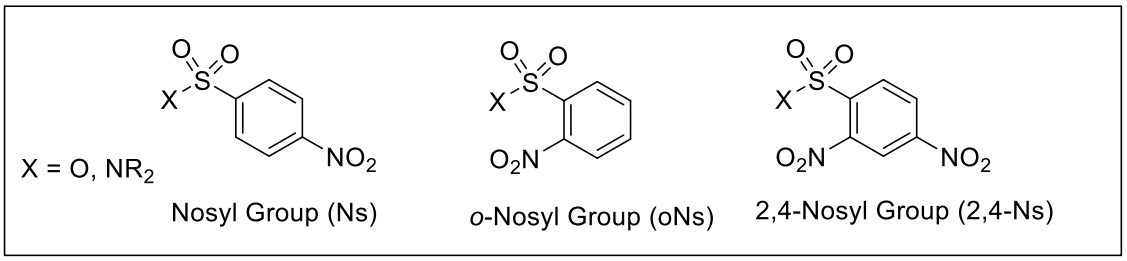
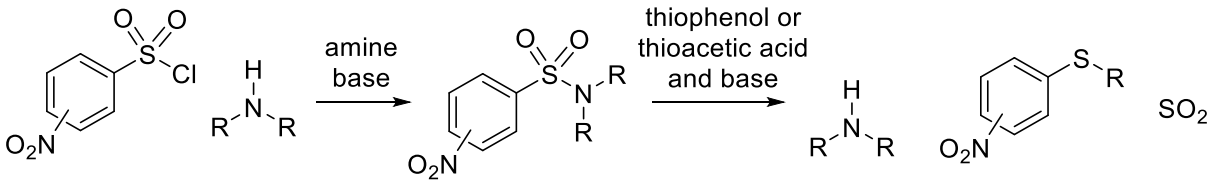


***Figure 6.4**: The nosyl group*

The nitrobenzenesulfonyl group is a sulfonyl protecting group for amines and alcohols.[196] Like all sulfonyl groups it is electron withdrawing, and this property is enhanced by the inductive effect of the nitro group/s. Nosyl groups are advantageous over other sulfonyl groups in that they can be easily removed (*Scheme 6.29*). Three variants of the nosyl group are commonly used; *para*-nitrobenzenesulfonyl groups (Ns),[196a] *ortho*-nitrobenzenesulfonyl groups (*o*-Ns)[196b] and 2,4-dinitrobenzenesulfonyl groups (2,5-Ns) (*Figure 6.4*).[196c] The different nosyl groups offer different relative stability so can be chosen depending on the requirements of the synthesis.



***Scheme 6.29**: Addition and removal of nosyl groups*

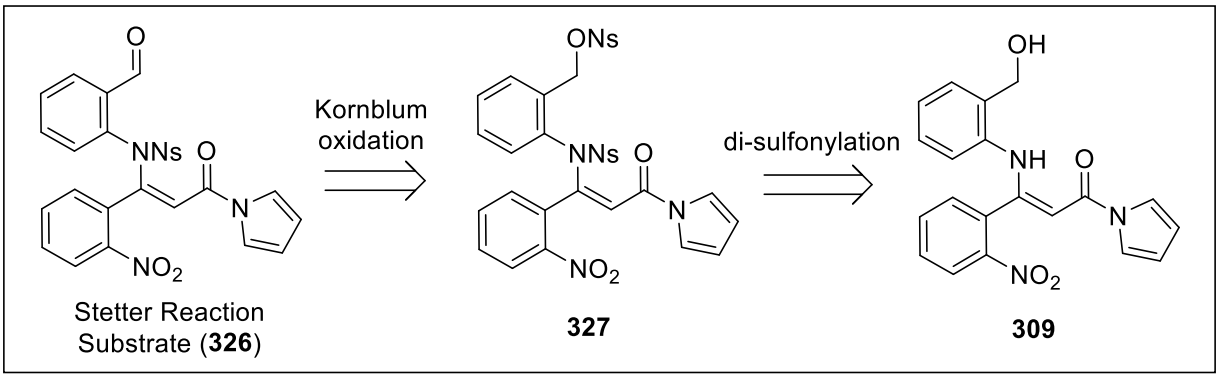
Nosyl groups can installed in an identical manner to tosyl groups or other sulfonyl groups, such as exposure to an amine base (*Scheme 6.29*). Removal of a nitrobenzenesulfonamide is accomplished through exposure to thiophenolate or thioacetate.[196] The removal conditions are not

only mild, but are orthogonal to most other functional groups.

For our purposes we have chosen the 4-nitrobenzenesulfonyl group as it is the most common, and the presence of the characteristic *para*-disubstituted ^{1}H NMR pattern would be diagnostic in our molecules which already possessed two other *ortho*-substituted aromatic rings.

6.5.1 Retrosynthesis incorporating the nosyl protecting group

With the intention to incorporate sulfonyl protecting groups into our synthesis from the beginning we were able to make changes to our synthetic plan which would reduce the overall number of operations required (*Scheme 6.30*).



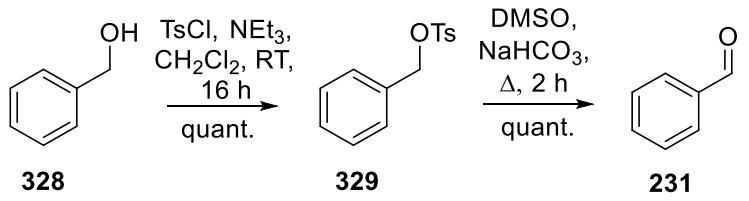
***Scheme 6.30**: Retrosynthesis of sulfonylation strategy*

The use of a sulfonyl group opened up new possibilities for reactivity which could be incorporated into the synthesis targeted at Stetter reaction substrate **326**. Where we had previously performed the Swern oxidation to form the aldehyde, we could now use the Kornblum oxidation from compound **327**. The Kornblum oxidation is ordinarily performed on a benzylic halide but pseudohalides are also known to participate in this reaction.[197]

With a sulfonyl group required on both the nitrogen and oxygen there would be no need for the differential protection used in the previous synthetic sequence. The di-sulfonyl compound **327** would be the result of sulfonylation of compound **309**, which is identical to the intermediate in our previous synthesis. This strategy was more efficient and succinct than the first sequence attempted.

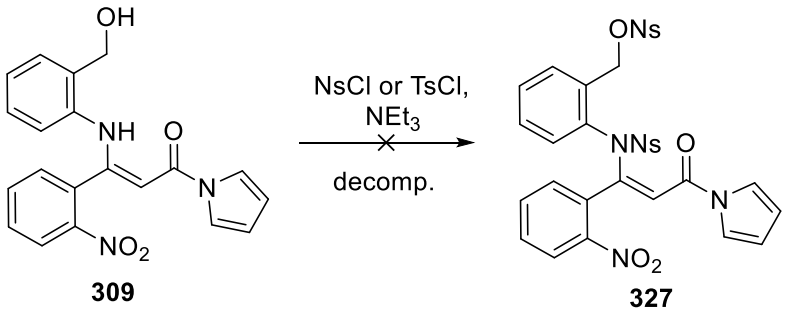
6.5.2 Incorporation of nosyl group - Results

Although the Kornblum reaction is known to proceed with pseudo-halides there are no reports of it occurring with a benzylic benzenesulfonate. Before we began this strategy we needed to be sure it was a viable transformation.



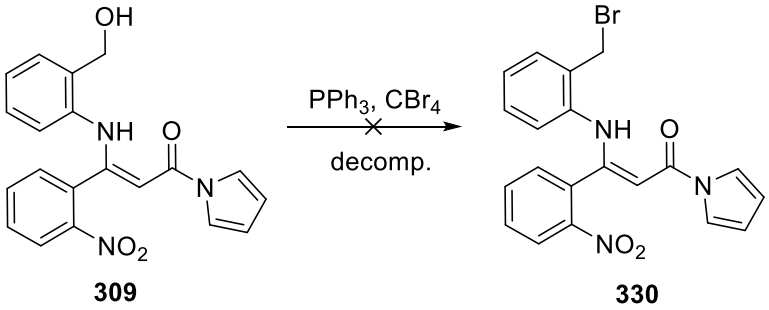
***Scheme 6.31**: Confirmation of the Kornblum oxidation*

Toluenesulfonyl chloride was reacted with benzyl alcohol (**328**) to give the tosyl protected alcohol (**329**) in quantitative yield (*Scheme 6.31*). Exposing compound **329** to the standard conditions for the Kornblum oxidation benzaldehyde (**231**) was obtained, again quantitatively. This shows the Kornblum oxidation can work very well on benzylic pseudo-halides, although it will undoubtedly be more challenging on a more complicated substrate. Having shown our strategy was viable we were in a position to apply it to the necessary substrates.



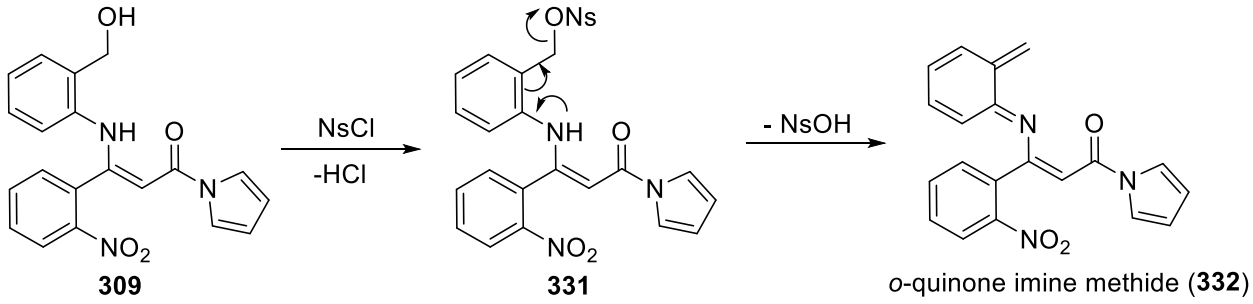
***Scheme 6.32**: Attempted di-sulfonylation*

Unfortunately, all attempts to perform either a di-nosylation or di-tosylation of compound **327** resulted in decomposition across a range of temperatures (*Scheme 6.32*). To determine the cause of this undesired reactivity we sought to eliminate each of the variables. To that end we sought to perform an Appel reaction to convert the alcohol (**309**) into a bromide (**330**). This would allow us to experiment with conditions to install the sulfonyl group on the nitrogen in the absence of the complicating di-sulfonylation but still allow us to proceed with the synthesis.



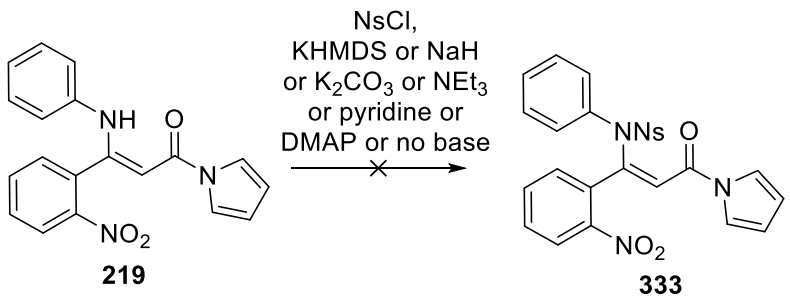
***Scheme 6.33**: Attempted Appel reaction*

Much like the attempts at sulfonylation, attempts at the Appel reaction resulted in decomposition of the starting material (*Scheme 6.33*). Consideration of the likely reactivity of compounds **327** and **330** made it simple to justify these results (*Scheme 6.34*).



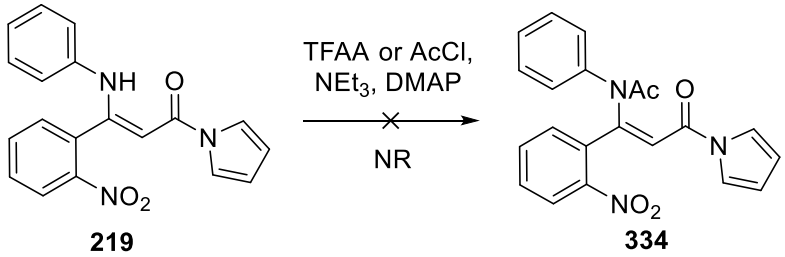
***Scheme 6.34**: Likely decomposition pathway*

Based on prior results it is likely that sulfonylation would occur first on the oxygen to give **331**. The nitrogen lone pair can aid elimination of the sulfonate, which is a good nucleofuge. This reaction path would result in an *ortho*-quinone imine methide (**332**) as well as hydrogen chloride and 4-nitrobenzenesulfonic acid (*Scheme 3.34*). *ortho*-Quinone imine methides (**332**) are highly reactive species whose reactivity is difficult to control even under ideal conditions. *ortho*-Quinone imine methides are known to react as both the diene and dienophile in the Diels-Alder reaction, in many other cycloadditions and as Michael acceptors, among other modes of reactivity. This reactivity, in the presence of the other functional groups likely leads to polymerisation. This outcome would only be exacerbated by the strongly acidic nitrobenzenesulfonic acid also produced. This mode of decomposition could also occur after the Appel reaction, which also places a good leaving group at the benzylic position. Having developed a hypothesis as to why the di-sulfonylation had not worked we sought to investigate whether the nitrogen atom could be sulfonylated in the absence of the reactive benzylic sulfonate (*Scheme 6.35*).



***Scheme 6.35**: Attempted sulfonylation of simplified substrate*

In an attempt to find conditions to successfully sulfonylate the amine we employed the simplified substrate (**219**) which lacked any substitution on the aniline ring. This removes the possibility of side reactions and allows us to investigate the effects of steric hindrance from the *ortho*-position. With a range or strong bases, weak bases and nucleophilic catalysts at a range of temperatures no sulfonamide product was observed. As the conditions became more forcing decomposition was observed (*Scheme 6.35*). This result suggests steric hindrance from the *ortho*-substituent of the aniline is not significant but that the nitrogen atom is simply not nucleophilic enough to engage in the desired reaction.



219 **334**

Scheme 6.36 *Attempted acylation*

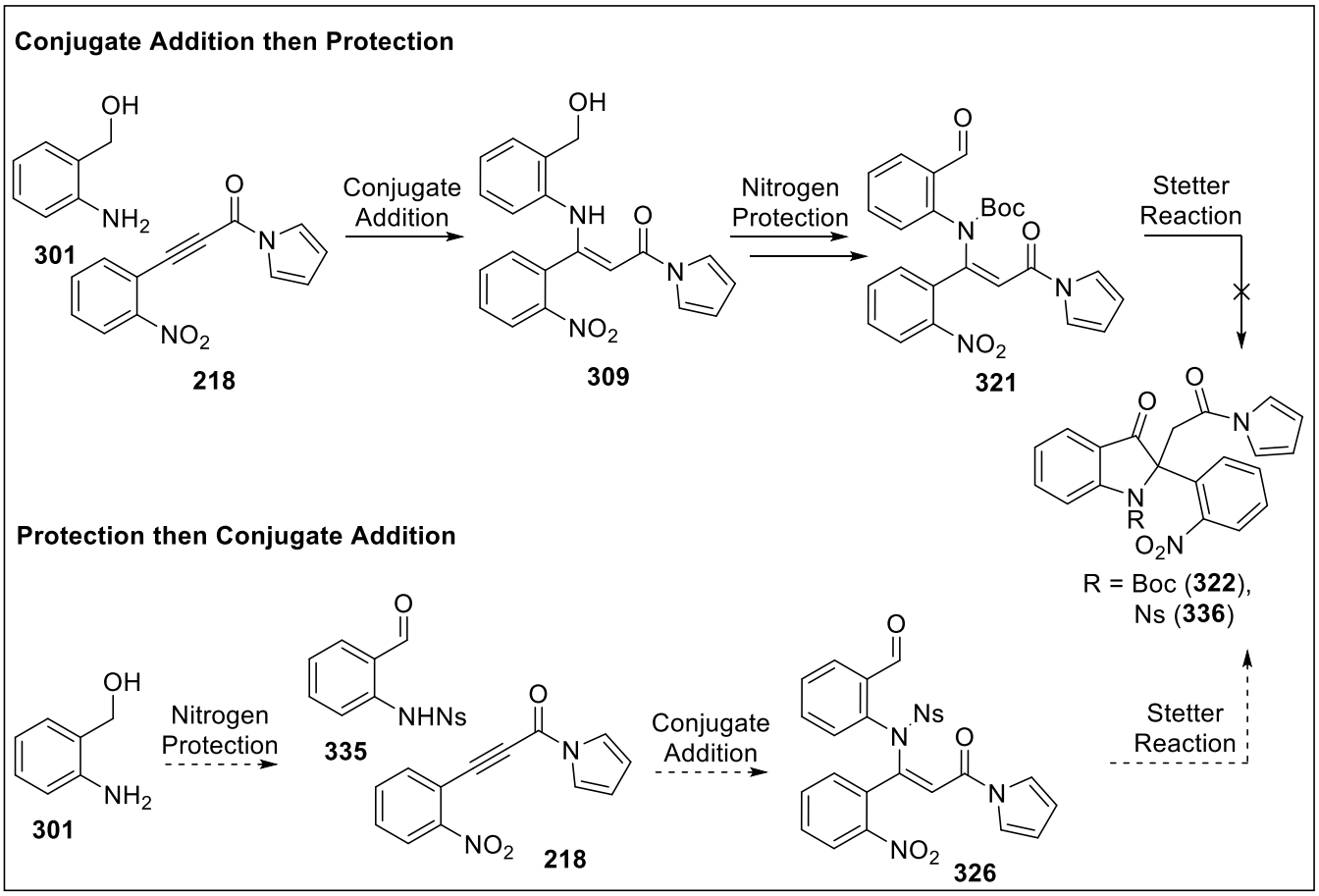
To determine if this problem was specific to sulfonylation reactions we attempted acylation with acetyl chloride and trifluoroacetic anhydride, but no reaction occurred (*Scheme 6.36*). The difficulty performing sulfonylation and acylation reaction with the amine in compound **219** is entirely consistent with the reactivity observed previously (see *Schemes 6.14* and *6.28, Section 5.6.3*).

These results, in conjunction with those described earlier tell us the nitrogen atom in these substrates is highly delocalised and essentially non-nucleophilic. This makes the requisite protection of the nitrogen atom extremely difficult. Our promising synthetic strategy was again hampered by protecting group manipulations.

By now it was evident the electron withdrawing protecting group was unlikely to be installed after the conjugate addition so we moved to a strategy which still targeted the same intermediate but which installed the protecting group before the conjugate addition reaction.

6.6 Conjugate addition with a protected amine

We still held that the nosyl group was the most appropriate protecting group available. To circumvent the problematic reactivity we decided to persist with conjugate additions to phenylpropiolate Michael acceptors but change the order of the transformations. That is, protect the nitrogen before the conjugate addition (*Scheme 6.37*).

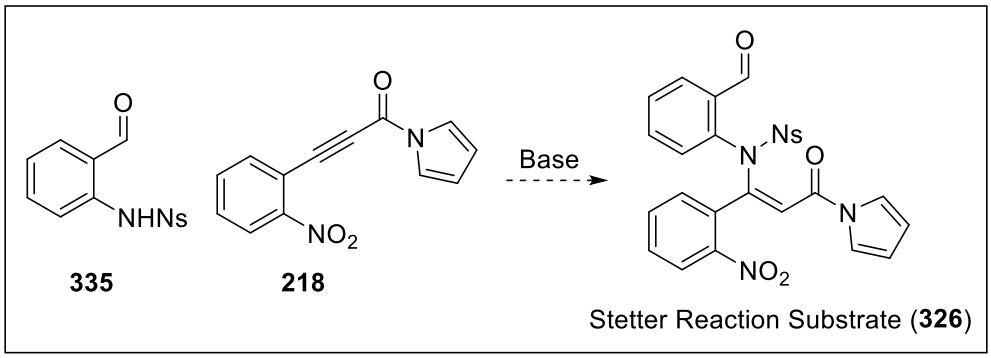


***Scheme 6.37**: Changing the order of transformations*

This new strategy involved the synthesis of an *N*-protected 2-aminobenzaldehyde (**335**) which would be added to Michael acceptor **218** (*Scheme 6.37*). This would circumvent the problems described above and lead to compound **326**, which could undergo the Stetter reaction to form compound **336**.

6.6.1 Proposed synthesis using a pre-protected amine

Our new synthetic plan was to keep all of the steps after the Stetter reaction the same as initially discussed, but target the Stetter reaction substrate using an amine already protected as a sulfonamide prior to the conjugate addition reaction (*Scheme 6.38*).



***Scheme 6.38**: Proposed synthesis with sulfonamide*

Due to the electron withdrawing nature of the sulfonyl group sulfonamides are not ordinarily nucleophilic however in the presence of a weak base the sulfonamide will be deprotonated and will become nucleophilic in an analogous manner to a phenolate. This deprotonation is possible under mild conditions as sulfonamides are quite acidic (*Figure 6.5*), in contrast to amines which are most often seen as bases. This inversion of conventional nitrogen reactivity allows for contrasting synthetic approaches.

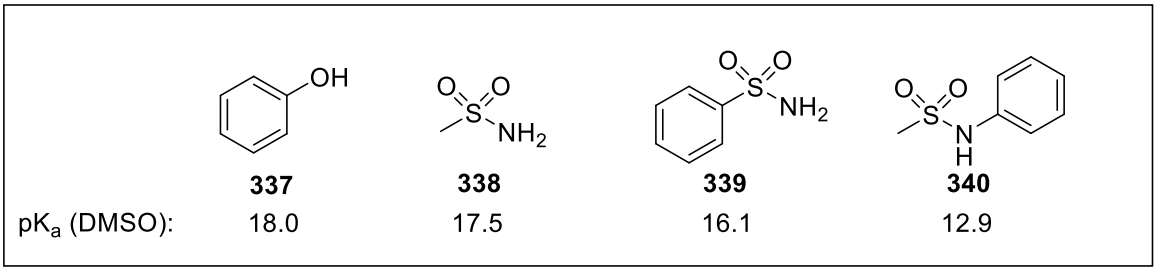


***Figure 6.5**: Acidity of sulfonamides and phenol*

The pK_a values of some representative sulfonamides are shown in *Figure 6.5*. Phenol (**337**), which is usually considered an acid, has a pK_a of 18.0 in DMSO.[198] Most sulfonamides are more acidic than phenol (**337**). For example, the pK_a values methanesulfonamide (**338**) and benzenesulfonamide (**339**) are 17.5[199] and 16.1[200] respectively in DMSO. The pK_a of *N*-phenyl methanesulfonamide (**340**) is again much lower at 12.9[199] due to the additional electron withdrawing group. As a result if the high acidity and high electronegativity sulfonamides are analogous to phenols in terms of the reactions and transformations they will participate in.

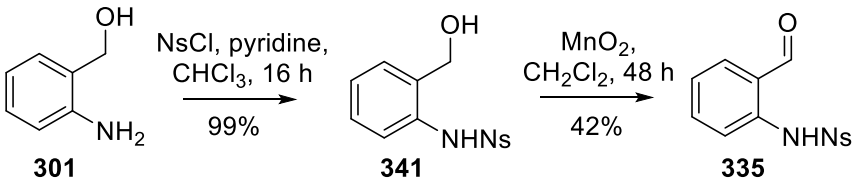
The sulfonamides used in our work (**335**) will be considerably more acidic than the examples shown in *Figure 6.5* due to the cumulative effects of the *p*-nitrophenylsulfonamide and phenyl groups. Another beneficial effect is that sulfonyl protected aminobenzaldehydes such as compound **335** are

perfectly stable (c.f. salicylaldehyde and 2-aminobenzaldehyde).

This strategy is shorter than the original proposal and will reduce the number of steps in the longest linear sequence.

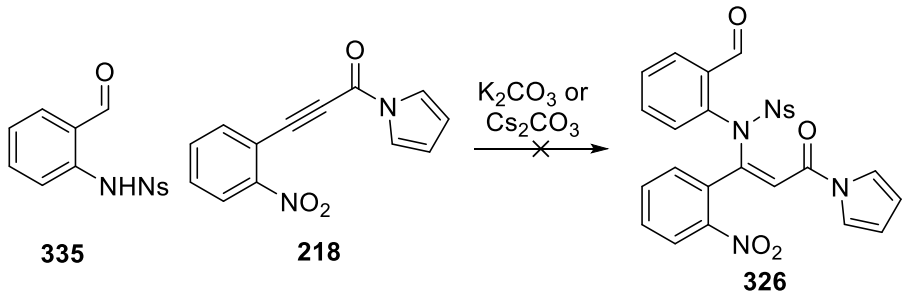
6.6.2 Synthesis using a pre-protected amine - Results

Synthesis of the protected aminobenzaldehyde derivative was achieved through modification of a literature procedure in which tosyl chloride was replaced with nosyl chloride (*Scheme 6.39*).[165]



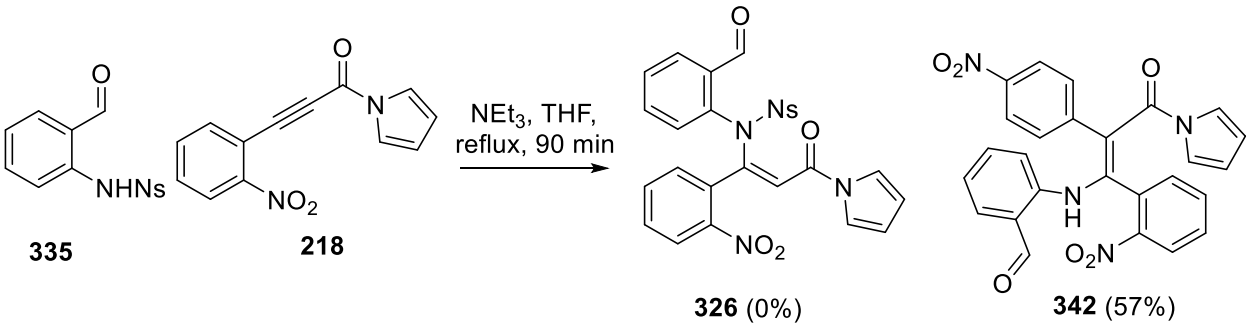
Scheme 6.39: *Synthesis of aldehyde partner*

2-Aminobenzyl alcohol (**297**) was selectively sulfonylated at the nitrogen in quantitative yield (**341**, *Scheme 6.39*). This was followed by exposure to manganese dioxide which cleanly converted the benzyl alcohol to the corresponding aldehyde (**335**). The moderate isolated yield of the aldehyde is largely due to difficulty separating the product from the heterogeneous oxidant because of the insolubility of compound **335**.



Scheme 6.40*: Attempt to use inorganic bases*

In our first attempts at the conjugate addition between compound **335** and **218** we used weak inorganic bases in THF as the solvent, but these led to decomposition (*Scheme 6.40*).



***Scheme 6.41**: Attempted sulfonamide conjugate addition*

Switching to an amine base resulted in a 57% yield of a compound which appeared to have undergone a conjugate addition (**342**, *Scheme 6.41*). The remainder of the starting materials had decomposed.

Analysis of the ^{1}H NMR revealed that compound **342** contained an aldehyde and *para*-substituted aromatic ring along with an *N*-acylpyrrole and many further overlapping aromatic signals (*Figure 6.6*). This unambiguously showed the nucleophile had been incorporated into the Michael acceptor but significantly, compound **342** lacked a characteristic vinylic proton resonance and showed a downfield resonance at 10.9 ppm, due to a hydrogen bonded proton (*Figure 6.7*).

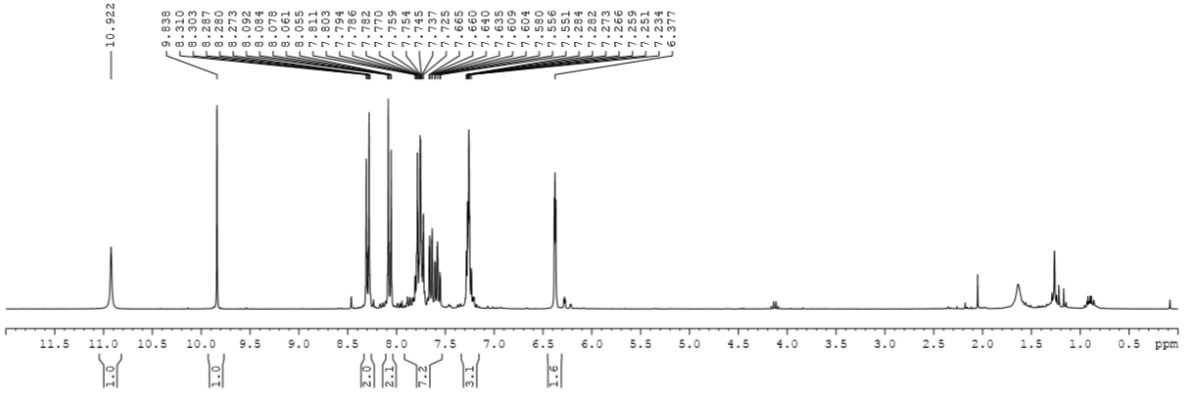


Figure 6.6**: ^{1}H NMR spectrum of compound **342

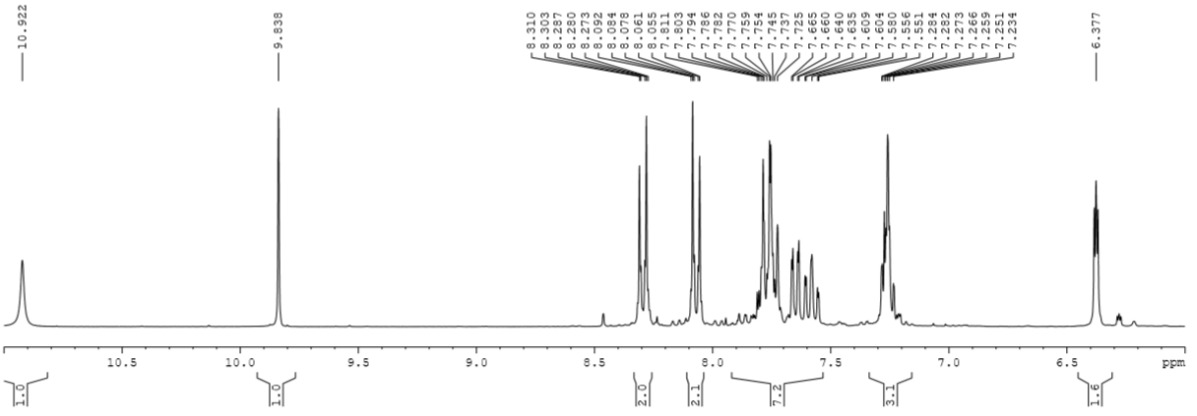


Figure 6.7**: Expansion of ^{1}H NMR spectrum of compound **342

The ^{13}C NMR spectrum showed 22 resonances, which indicated all of the carbon atoms of both the electrophile and nucleophile had been incorporated (*Figure 6.8*). There were no resonances in the alkyne region, which showed a reaction had occurred at the position as desired.

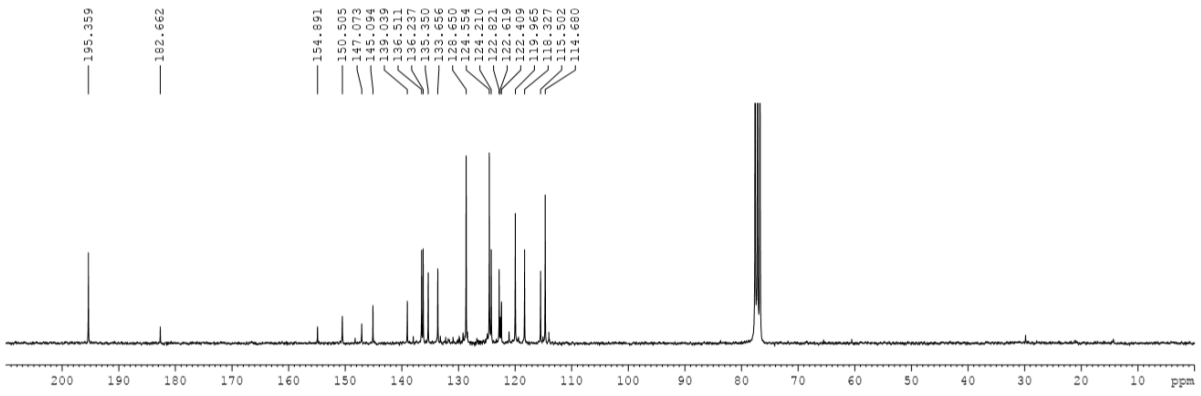


Figure 6.8**: ^{13}C NMR spectrum of compound **342

The DEPT spectrum showed twelve resonances due the tertiary aromatic carbon environments (*Figure 6.9*). This number corresponds to the number of environments in the starting materials, again indicating the reaction had occurred at the Michael acceptor, not on the aromatic rings.

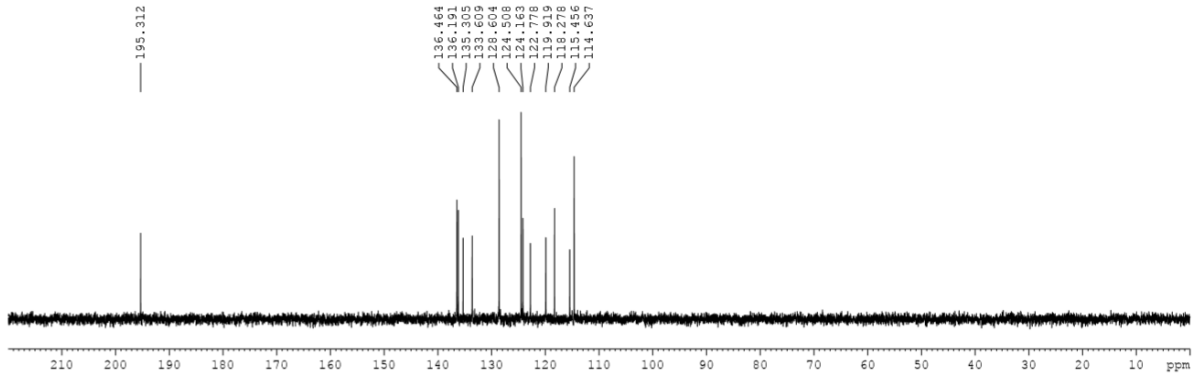


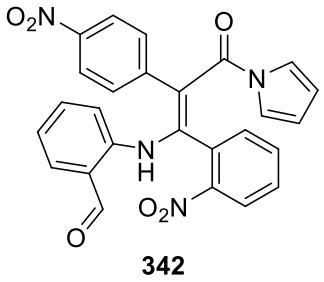
Figure 6.9**: DEPT spectrum of compound **342

Finally, analysis of the HRMS indicated the loss of sulfur dioxide from compound **342** compared to the desired product (**326**) (*Table 6.7*).

Formula	Required	Found
326 (Expected Product): $C_{26}H_{18}N_4O_8S$	546.08453	-
342 (Observed Product): $C_{26}H_{18}N_4O_6Na$ $[M + Na]^+$	503.09621	503.09614

Table 6.7**: HRMS of compound **342

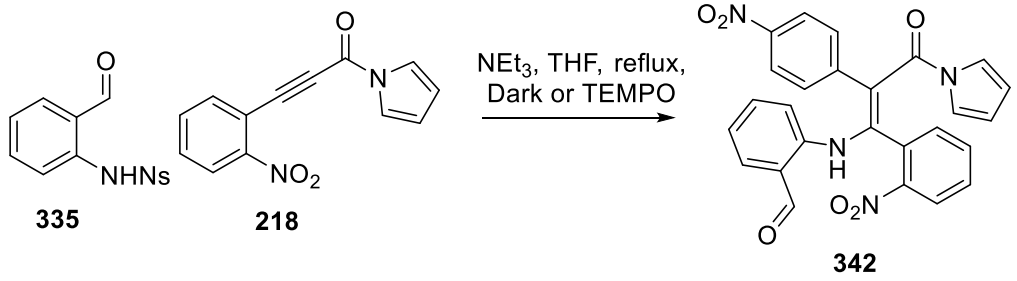
This spectroscopic data suggests the identity of product **342** is as depicted in *Figure 6.10*. The double-bond geometry of compound **342** was assigned based on the proposed mechanism shown in *Scheme 6.44*.



342

Figure 6.10: *Compound* ***342***

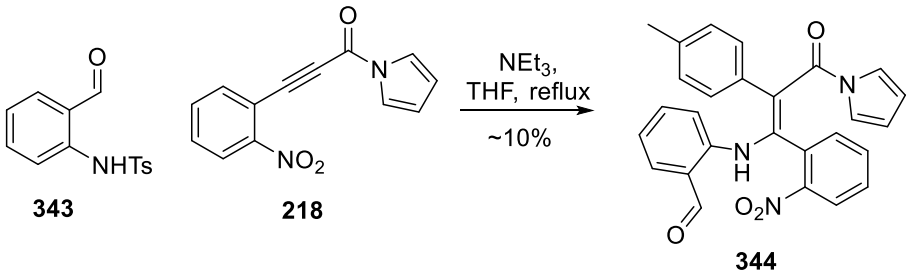
Due to the unexpected nature of this product we performed some further experiments to provide evidence for the mechanism by which it is occurring.



335 **218** **342**

Scheme 6.42*: Investigation of radical mechanism*

We first performed some experiments to confirm the rearrangement was not occurring by a radical pathway (*Scheme 6.42*). The rearrangement reaction still occurred in the dark and in the presence of TEMPO. This makes it highly unlikely that the reaction is occurring by a radical mechanism.



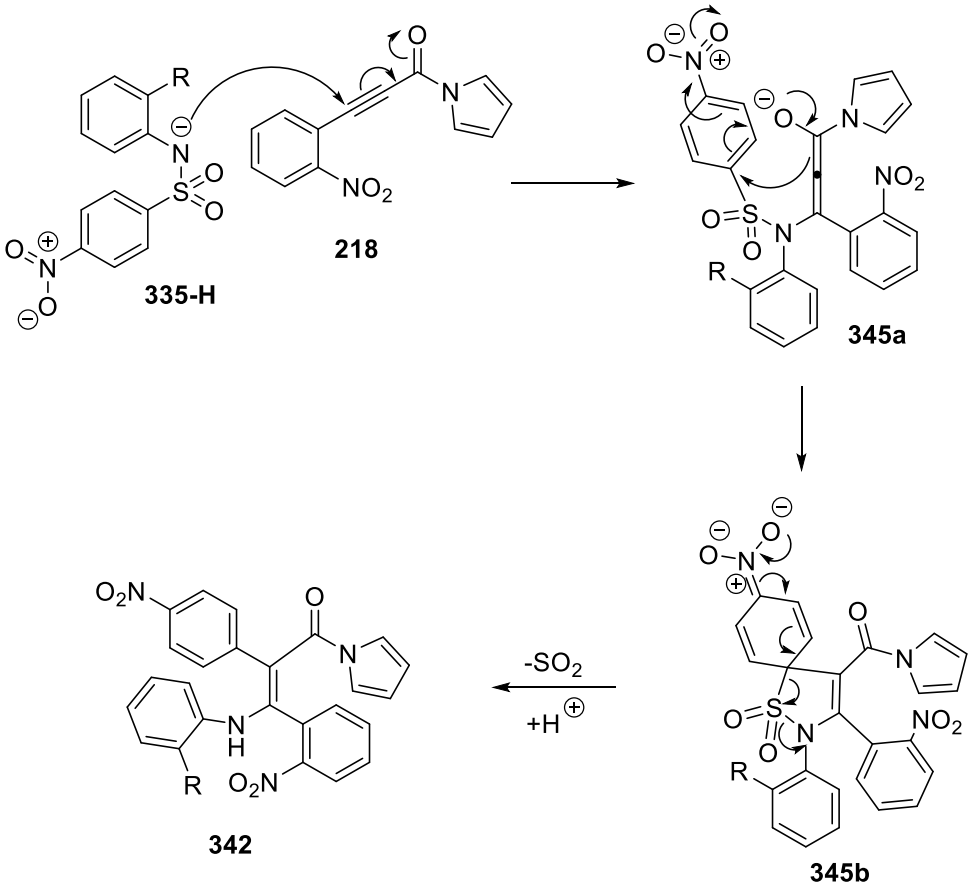
343 **218** **344**

Scheme 6.43*: Rearrangement with tosyl group*

To find whether the reaction is specific to the properties of the nosyl group we synthesised the equivalent tosyl protected compound (**343**, *Scheme 6.43*). In this case the reaction still occurred, albeit in low yield and purity, with significant amounts of decomposition.

The elimination reaction also occurred in low yield for the reaction between sulfonamide **335** and the methyl ester Michael acceptor (**315**).

With these results we were able to provide a plausible mechanism for the transformation observed (*Scheme 6.44*).



***Scheme 6.44**: Plausible mechanism for aryl migration reaction*

As the aniline is incorporated in the product, the most likely reaction pathway is one in which the deprotonated sulfonamide (**335-H**) first adds into the Michael acceptor (**218**) as desired (*Scheme 6.44*). The Michael addition will however result in an enolate (**345a**) which can add to the electrophilic position on the nitrobenzene ring. This mode of attack is analogous to the reactivity which allows for the thiol deprotection of nitrobenzene sulfonamide groups. Expulsion of sulfur dioxide from intermediate **345b** and re-protonation will give the observed product (**342**).

6.6.3 Other sulfur (VI) protecting groups for nitrogen

The strategy of protecting the nitrogen atom before conjugate addition had come close to succeeding. The required conjugate addition had occurred, but this was followed by an unforeseeable rearrangement. With the understanding we had gained of how the elimination reaction was taking place we felt we may still be able to find an electron withdrawing sulfur (VI) protecting group which would not undergo the elimination reaction. As such, the new protecting group we applied to this conjugate addition strategy was the sulfamoyl group (*Figure 6.11*).

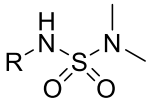
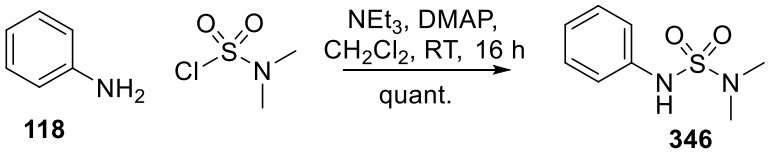


Figure 6.11: *The N,N-dimethylsulfamoyl protecting group*

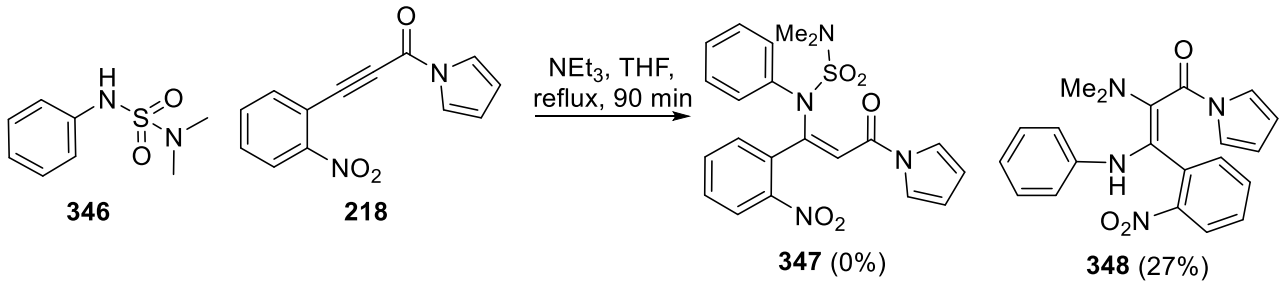
The sulfamoyl group is an uncommon protecting group which possesses many of the features of a sulfonyl group but has no sulfur-carbon bond. The most common variety is the *N,N*-dimethylsulfamoyl group (*Scheme 6.11*), with the precursor, *N,N*-dimethylsulfamoyl chloride, being commercially available. This protecting group is removed by acid hydrolysis[201] or transamination.[202] The nitrogen of the dimethylamine portion of the sulfamoyl group should be much less electrophilic that the carbon centres of sulfonyl groups and may prevent the unwanted sulfur dioxide elimination reaction from occurring.



118 **346**

Scheme 6.45: *Synthesis of sulfamoyl protected aniline*

Given the unexpected reactivity we had previously observed we began our investigations of the sulfamoyl group with a simplified substrate (*Scheme 6.45*). Aniline (**118**) reacted with *N,N*-dimethylsulfamoyl chloride under the influence of nucleophilic catalysis to give *N,N*-dimethylsulfamoyl aniline (**346**) is quantitative yield.



Scheme 6.46: *Conjugate addition of sulfamoyl protected aniline*

N,N-Dimethylsulfamoyl aniline (**346**) was deprotonated with triethylamine and added into the propiolate Michael acceptor (**218**, *Scheme 6.46*). Remarkably, we observed the same rearrangement occurring with the sulfamoyl group, albeit in modest yield (**348**, *Scheme 6.46*). This suggests our proposed mechanism for this transformation is correct (*Scheme 6.44*). Despite this rearrangement being unproductive for our proposed synthesis, this mode of reactivity is of potential interest, as these tetrasubstituted alkenes would be difficult to synthesise by other means.

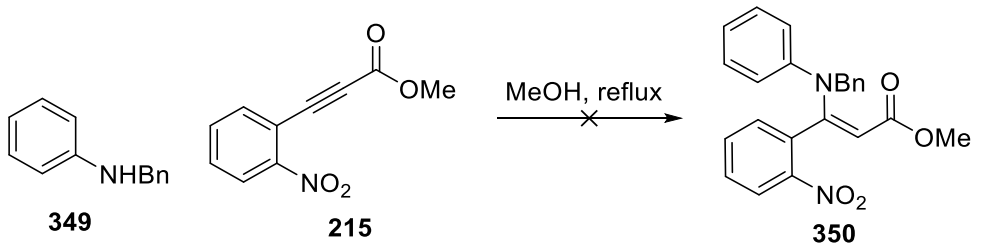
The conjugate additions we had performed with sulfonyl groups already present on the aniline were suffering from persistent side reactions as a result of the protecting group. Despite these setbacks we were encouraged that the identity of the products confirmed the conjugate addition was occurring. These results suggested the conjugate addition strategy remained a viable route to quickly introduce complexity, so to remain consistent with our approach we attempted some further conjugate addition strategies.

6.7 Other conjugate addition approaches

6.7.1 Benzyl protecting group

Most protecting groups for nitrogen which are electron withdrawing are electron withdrawing due to resonance stabilisation of the nitrogen lone pair. This also has the effect of reducing the nucleophilicity and reduces the potential of using protected nitrogen compounds in conjugate additions. Protecting groups which are electron withdrawing through inductive effects have the potential to be modified to suit the synthesis in question. A protecting group which does not ordinarily change the character of nitrogen is the benzyl group. Benzyl groups can be made electron withdrawing through halogen substitution on the phenyl ring. In *Section 3.14* we had shown primary anilines add to the phenylpropiolate Michael acceptors. As secondary amines are more nucleophilic

than primary amines it seemed likely benzyl-protected anilines would also participate in the conjugate addition reaction.

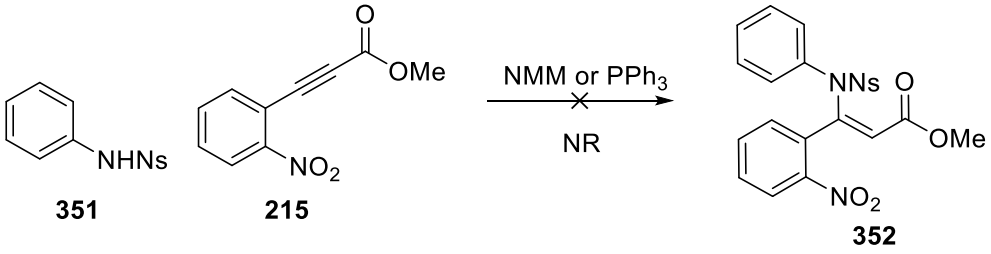


Scheme 6.47: *Attempted conjugate addition of N-benzylaniline*

To determine if this route was feasible we began our studies with commercially available *N*-benzylaniline (**349**, *Scheme 6.47*). If the conjugate addition with *N*-benzylaniline (**349**) was successful we could repeat the experiment with electron-poor benzyl groups such as *N*-(4-chlorobenzyl)-aniline. To this end, *N*-benzylaniline (**349**) was heated to reflux in methanol with methyl *o*-nitrophenylpropiolate (**315**). Although these conditions were successful for unsubstituted aniline, in this instance, the reaction gave multiple products, none of which were the desired conjugate addition product (*Scheme 6.47*).

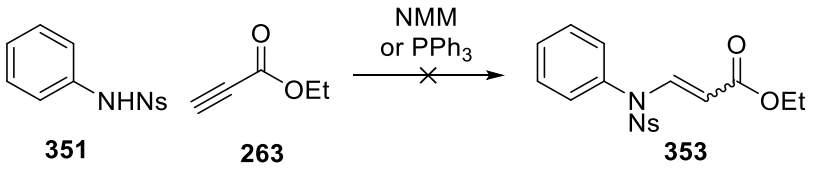
6.7.2 Nucleophilic catalysis

The similarities between sulfonamides and phenols mean that sulfonamides should be subject to nucleophilic catalysis.



Scheme 6.48: *Nucleophilic catalysis*

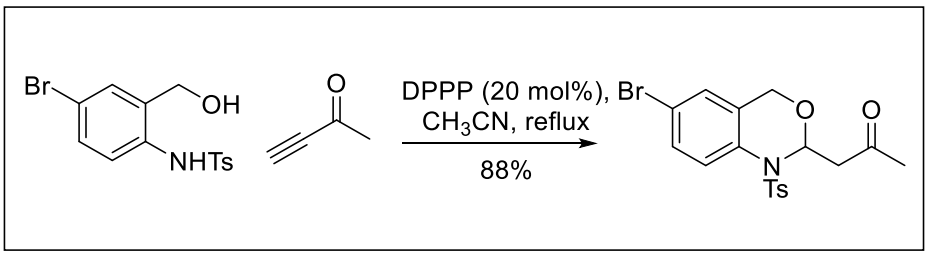
Unfortunately, using *N*-methylmorpholine or triphenylphosphine as a catalyst for the addition of a simple sulfonamide (**351**) to methyl *o*-nitrophenylpropiolate (**215**) did not result in any reaction (*Scheme 6.48*).



Scheme 6.49: *Nucleophilic catalysis with ethyl propiolate*

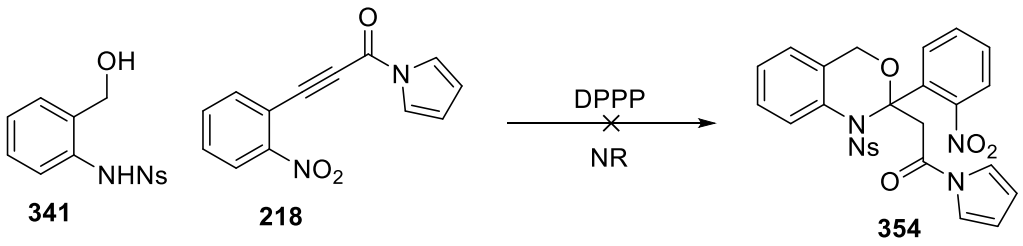
To determine whether the substituent at the 3- position of the propiolate was preventing the conjugate addition from occurring we attempted to add sulfonamide **351** to ethyl propiolate (**263**) using nucleophilic catalysis (*Scheme 6.49*). In the event of this reaction working, we should be able to elaborate this to a suitable intermediate. Although we had previously added salicylaldehyde (**266**) to ethyl propiolate (**263**) in good yield, applying the same reaction conditions to sulfonamides resulted in an intractable and uncharacterised product mixture, none of which appeared to be the desired conjugate addition product (**353**). It appears the phenyl substitution was in fact preventing the reaction shown in *Scheme 6.48* from occurring, but no useful improvement could be made with an unsubstituted propiolate.

After the failure of mono-functional catalysts to effect this transformation we tried to use bi-functional catalysis. There are reports in the literature of diphosphine catalysis to add sulfonamides into propioloyl groups *(Scheme 6.50)*.[203]



Scheme 6.50: *Conjugate addition by Sriramurthy and co-workers*[203]

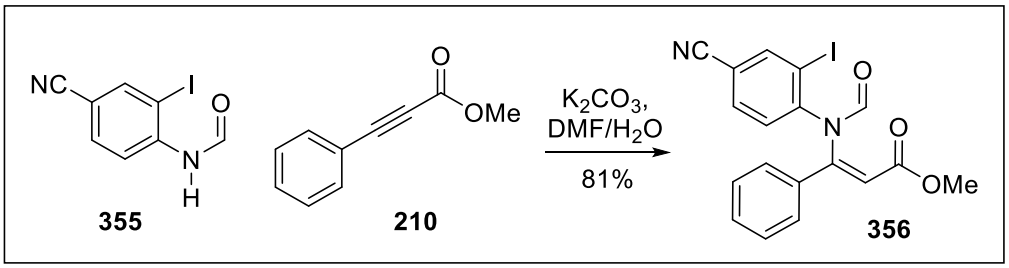
We replicated the conditions described in this paper with our substrates but no reaction occurred which was unsurprising given the structural differences (*Scheme 6.51*).



Scheme 6.51: *Attempt to generalise diphosphine catalysis*

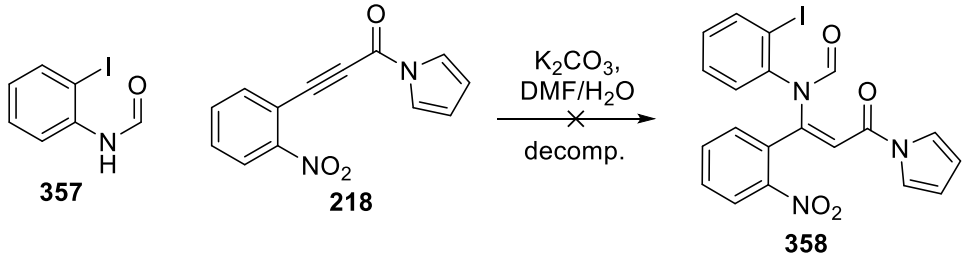
6.7.3 Formanilide nucleophile

During our investigations Back and co-workers published a conjugate addition reaction which yielded a product (**356**) similar to the intermediate required in our synthesis. This report revealed a case where a formanilide (**355**) was added to methyl phenylpropiolate (**210**) using potassium carbonate in DMF/Water (*Scheme 6.52*).[204]



Scheme 6.52: *Formanilide conjugate addition reported by Back*[204]

Given the obvious similarities between the reaction shown in *Scheme 6.52* and the conjugate additions we had been investigating we performed an experiment to determine if this reaction was applicable to our substrates.



Scheme 6.53: *Attempt to imitate the reaction reported by Back*

To keep our reaction as similar as possible to the literature reaction we used 2-iodoformanilde (**357**) as the nucleophile and compound **218** as the Michael acceptor. Should the reaction work it would be possible to later transform the aryl halide into an aldehyde. Under identical conditions to those reported none of the desired conjugate addition product (**358**) was formed, instead complete decomposition occurred (*Scheme 6.53*).

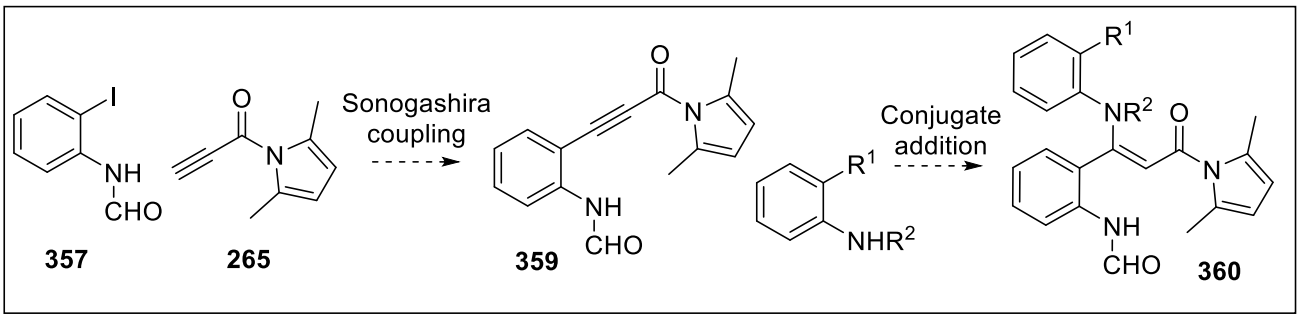
6.7.4 Other Michael acceptors

We suspected the major cause of the unexpected reactions we had repeatedly encountered was resonance stabilisation of anionic intermediates. The stabilisation was particularly significant due to the resonance contributions from the nitro substituent. The nitro group was present as it was a convenient and stable protected amine. Our synthetic strategy mandated reduction of this group to an amine later in the synthesis.

Although we had previously found that the conjugate addition of *anilines* to phenylpropiolate Michael acceptors required an *o*-nitro group to proceed (see *Section 3.14*), we had subsequently uncovered a range of new conditions and nucleophiles which may not suffer from this limitation.

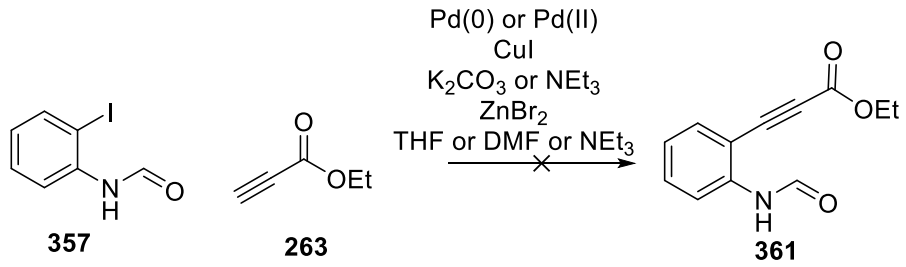
Given the nitro group was initially present as a convenient protected amine we felt we could avoid the resonance stabilisation from the nitro group if we reduced this problematic group to an amine before the conjugate addition. Reduction of the nitrobenzene to an aniline would necessitate an additional protecting group as it would introduce another aniline which could otherwise undergo conjugate addition.

For reasons discussed above we opted for the formyl group as the protecting group. We envisioned synthesising this Michael acceptor (**359**) through a Sonogashira coupling of readily available starting materials (**357** and **265**, *Scheme 6.54*).



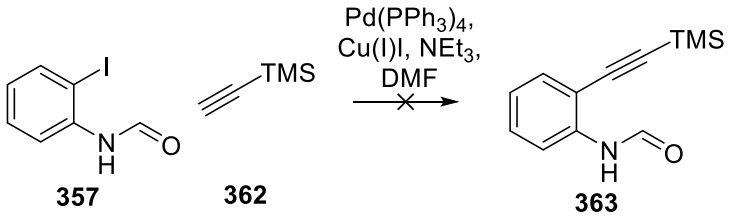
Scheme 6.54: *Conjugate addition strategy with pre-reduced amine*

Although we ultimately desired the *N*-acylpyrrole Michael acceptor we began our investigations into the Sonagashira coupling with ethyl propiolate (**263**) as the alkyne coupling partner as it is readily available (*Scheme 6.55*).



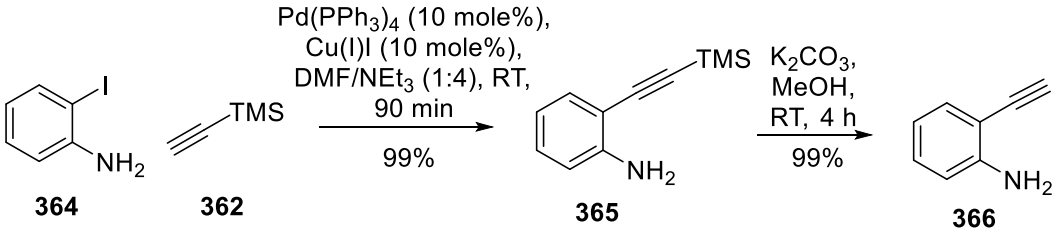
Scheme 6.55: *Attempted Sonogashira reaction*

A range of solvents, bases, palladium sources and additives were screened to facilitate the coupling between compounds **357** and **263**. In each case none of the Sonagashira coupling product (**361**) was obtained, instead numerous indole products were formed (*Scheme 6.55*).



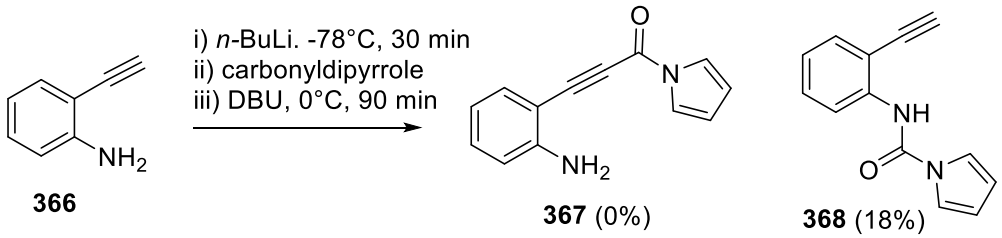
Scheme 6.56: *Attempted Sonogashira reaction with TMS-acetylene*

Suspecting the electron-poor nature of the alkyne coupling partner was contributing to the reactivity problems, we attempted the same coupling reaction with trimethylsilylacetylene (**262**), but no coupling to the aryl halide was observed (*Scheme 6.56*).



Scheme 6.57: *Synthesis of 2-ethynylaniline*

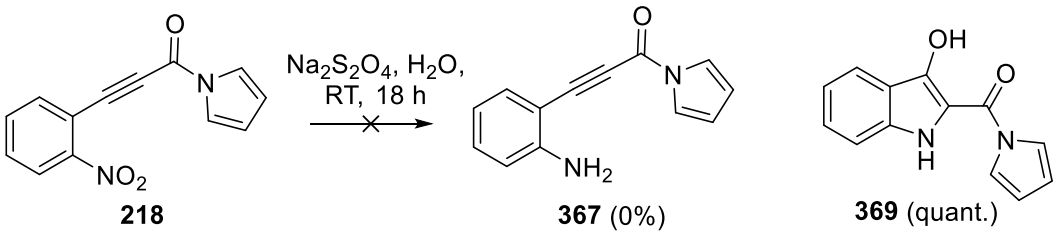
As the Sonagashira coupling had been unsuccessful with the formyl group present we synthesised 2-ethynylaniline (**366**) in two steps from 2-iodoaniline (**364** *Scheme 6.57*).[205] The success of this coupling reaction demonstrated the problem with the reactions shown in *Schemes 6.55* and *6.56* was the presence of the formyl group.



Scheme 6.58: *Attempt to acylate 2-ethynylaniline*

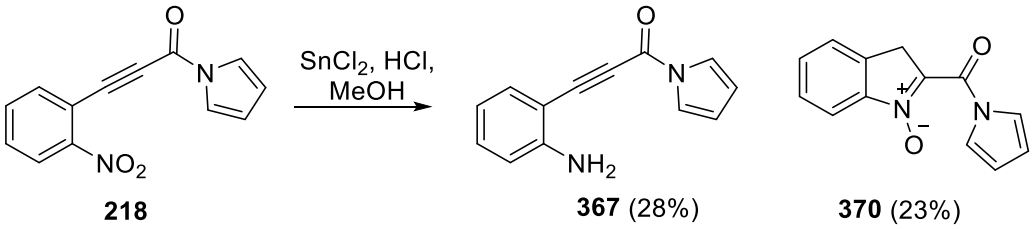
With alkyne **366** in hand we attempted to perform an acylation to reach the amine substituted Michael acceptor (*Scheme 6.58*). Deprotonation of the terminal alkyne (**366**) with n-butyllithium followed by addition of carbonyl dipyrrole did not yield the expected acylated alkyne product (**367**), instead the reaction gave amide product **368** in low but reproducible yield. We could not formylate the aniline prior to the deprotonation to prevent this unexpected acylation as the nucleophilic n-butyllithium would add to the electrophilic carbonyl.

We had initially shied away from direct reduction of the nitro-substituted Michael acceptors already at hand (**215** and **218**) as this route would require many linear steps from *o*-nitrocinnamic acid to reach the desired substrate. However, given the complications described above, we decided to follow this longer route as we had previously synthesised the precursors in good yield. There are many procedures available to reduce nitrobenzene moieties to anilines. We were constrained in our choice of reducing conditions by the need to leave the alkyne and Michael acceptor intact, and the possibility of forming indoles in the presence of transition metals.



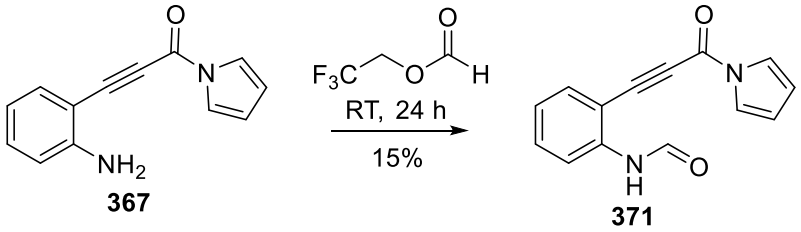
Scheme 6.59: *Attempt at reduction of nitro group*

The first reduction we attempted was with sodium dithionite as these conditions have been shown to be compatible with 2-ethynylanlines.[206] In our case this did not give the aniline product (**367**), rather we obtained quantitative yield of indole **369** (*Scheme 6.59*).



Scheme 6.60: *Reduction with stannous chloride*

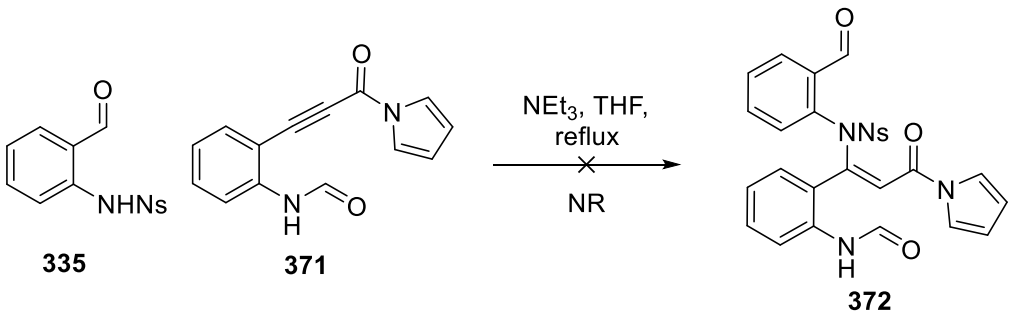
We next tried to reduce the nitro group with stannous chloride and hydrochloric acid as this reaction has been applied successfully to methyl 2-nitrophenylpropiolate (**215**).[207] Applying the literature conditions to the *N*-acylpyrrole (**218**) did not provide equivalent results (*Scheme 6.60*). The reaction did result in the desired aniline product (**367**), albeit in low yield. However, the reaction also gave an unusual *N*-oxide compound (**370**) in comparable yield. We had, however, synthesised an amine substituted Michael acceptor (**367**) and we could use this to continue our investigations.



Scheme 6.61: *Formylation of the aniline*

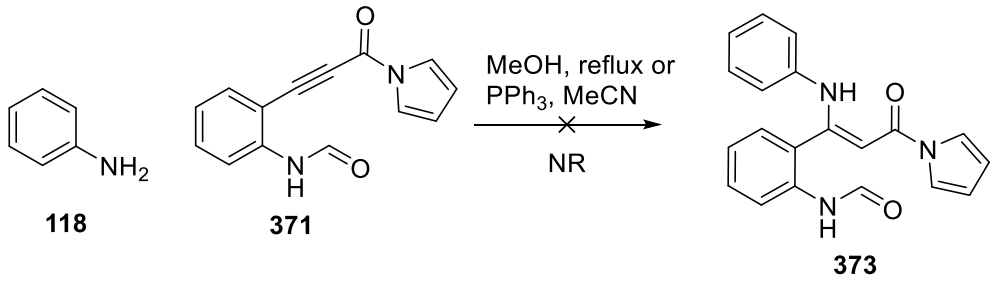
With aniline **367** in hand we attempted a formylation reaction (*Scheme 6.61*). The formylation reagent chosen was trifluoroethyl formate as it is mild and effective at room temperature. Given the small scale of the reaction, this reagent was also used as the solvent. After 24 hours the desired formanilide (**371**) was obtained in low yield. Longer reaction times did not increase the yield, so it appears the reaction had reached an equilibrium point.

Despite the consecutive poor yields we had synthesised a Michael acceptor with a reduced and protected amine group (**371**) and were able to investigate conjugate addition onto these substrates. As a result of the consecutive poor yields, the formamide product (**371**) was only obtained in milligram quantities and a limited number of reactions could be performed.



Scheme 6.62: *Attempted conjugate addition with new Michael acceptor*

Heating a sulfonamide (**335**) and the formanilide Michael acceptor (**372**) to reflux in the presence of triethylamine did not result in any reaction occurring despite these conditions being identical to those which had resulted in conjugate addition (and elimination of sulfur dioxide) (*Scheme 6.62*).

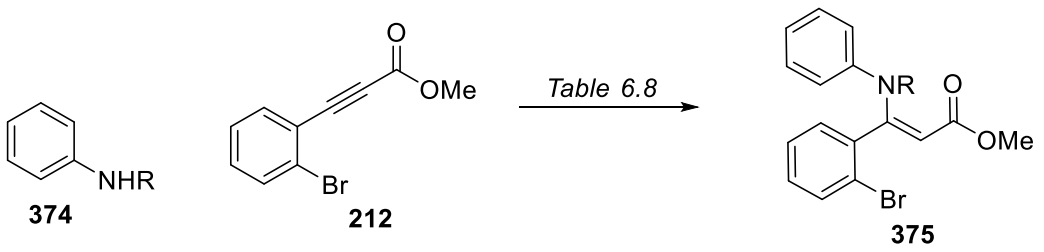


Scheme 6.63: *Attempt at conjugate addition with aniline*

Conjugate addition of aniline (**118**) under conditions which had been successful for the nitro-substituted compounds (see *Section 3.14*) did not result in any reaction (*Scheme 6.63*). Similarly nucleophilic catalysis with triphenylphosphine did not give the desired product (**373**, *Scheme 6.63*).

The lack of reactivity with the amide substituted Michael acceptor again showed conjugate addition reactions to phenylpropiolates are greatly assisted by the presence of an *o*-nitro group. The source of this enhanced reactivity is still largely unknown but it was very likely to be due to the electron withdrawing effect of the nitro group.

We had previously synthesised *o*-bromophenylpropiolate (**212**) and although it did not react with aniline we elected to test some alternate nucleophile with this Michael acceptor. This could further the synthesis of hinckdentine A and give us a more thorough understanding of the limits of the conjugate addition reaction.



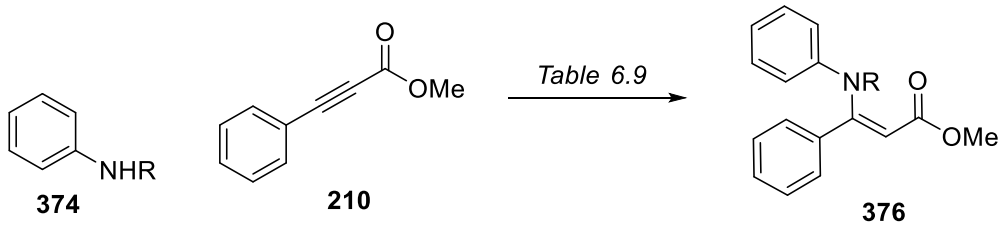
Scheme 6.64: *Conjugate addition with electron withdrawing group*

R	Catalyst	Temp. (°C)	Solvent	Time (h)	Result
Ns	NEt_3	66	THF	24	NR
Ns	DABCO	66	THF	24	NR
CHO	K_2CO_3	RT	DMF/H_2O	16	NR

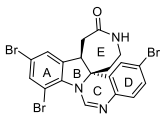
Table 6.8: *Conjugate addition onto 2-bromophenylpropiolate*

Adding deprotonated sulfonamide to the bromine substituted Michael acceptor (**212**) under conditions which had resulted in a reaction with Michael acceptors **215** and **218** did not give any reaction (*Scheme 6.64, Table 6.8*). Similarly with a very strong nucleophilic catalyst (DABCO) no reaction occurred. Formanilide also did not react with ester **212** under the conditions reported by Back[204] despite the apparent similarities between the reactions.

With the complete lack of reactivity of Michael acceptors possessing either an amide (**371**) or a bromide (**212**) we decided to investigate whether any aromatic amines are able add to unsubstituted phenylpropiolate Michael acceptors. We already possessed methyl phenylpropiolate (**210**) from our initial studies and this simple substrate seemed ideal for these experiments (*Scheme 6.65, Table 6.9*).



Scheme 6.65: *Range of Michael addition*



R	Catalyst	Temp. (°C)	Solvent	Time (h)	Result
Ns	NEt_3	66	THF	24	NR
Ns	K_2CO_3	66	THF	24	NR
Ns	NaH	66	THF	24	NR
Ns	PPh_3	82	MeCN	24	NR
Ns	PBu_3	RT	MeCN	24	decomp
Ns	DABCO	66	THF	24	NR
CHO	K_2CO_3	RT	DMF/H_2O	16	NR

Table 6.9: *Conjugate addition onto methyl phenylpropiolate*

Using *N*-phenyl sulfonamide as a nucleophile no reaction occurred with a range of bases and nucleophilic catalysts (*Table 6.9*). This was consistent with what had been observed for substrates other than *o*-nitropropiolates (see *Section 3.14*). The lack of reactivity between sulfonamides and phenylpropiolates is supported by a recent report in which the authors expressed surprise at a similar reaction failing.[208] Formanilide also did not react with ester **210** under the conditions reported by Back.[204]

There are no reports in the literature of generalisable conjugate addition reactions of anilines onto phenylpropiolate Michael acceptors. In our investigations we had found that no conjugate reactions occurred on substrates other than 2-nitropropiolates. It appears the conjugate addition reactions we had performed were specific to *o*-nitropropiolates. This specificity is not inherently problematic, although in our case the nitro group promoted a number of side reactions in subsequent steps.

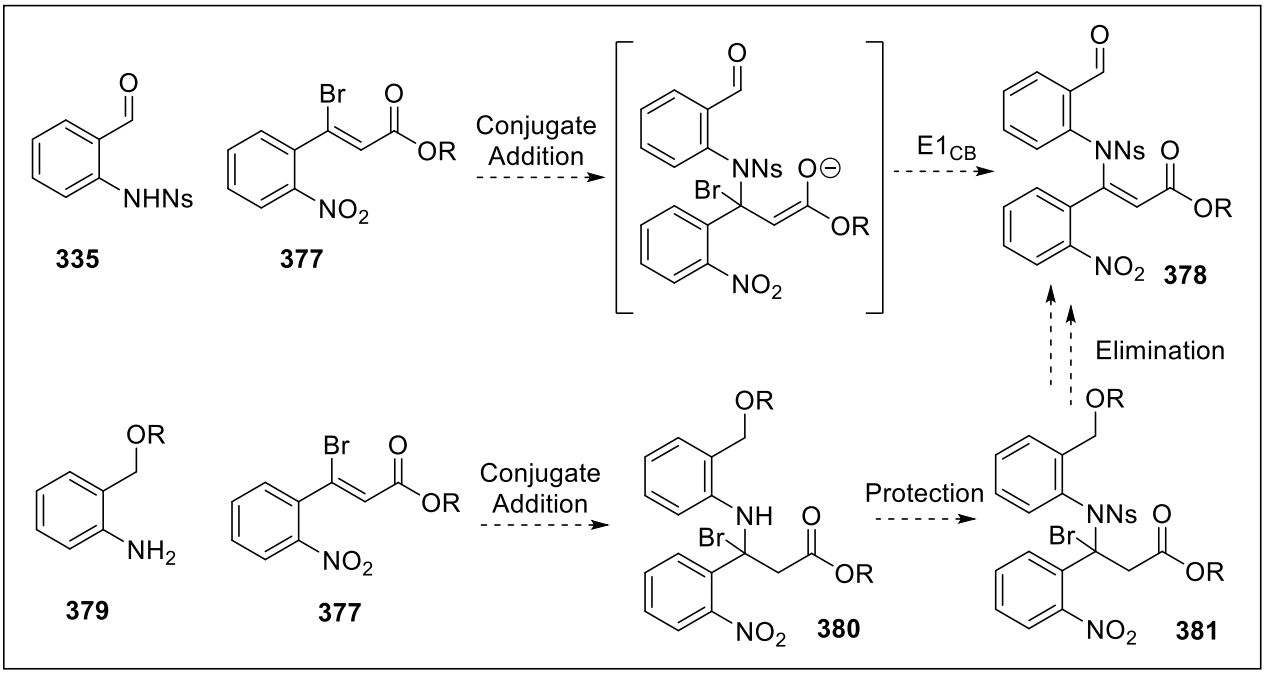
To probe the role of the nitro group in these reactions we would need to perform reactions on related substrates. The most closely related isostere of a nitro group is the carboxylate. Phenylpropiolates with a carboxylate at the ortho position are not trivial to make[209] and would not further our total synthesis so we did not pursue this option.

It is unclear why the Michael addition is so substrate specific, but *o*-nitrophenylalkynes have been noted to display unique reactivity in the past.[210] In the published crystal structure of ethyl 2-nitrophenylpropiolate the alkyne shows a 7° *trans* deviation from the normal alkyne bond angle of 180° due to interaction between the alkyne and nitro group.[211] This bond distortion may also distort the LUMO in a way not available to other substrates.

6.7.5 Conjugate addition/elimination strategy

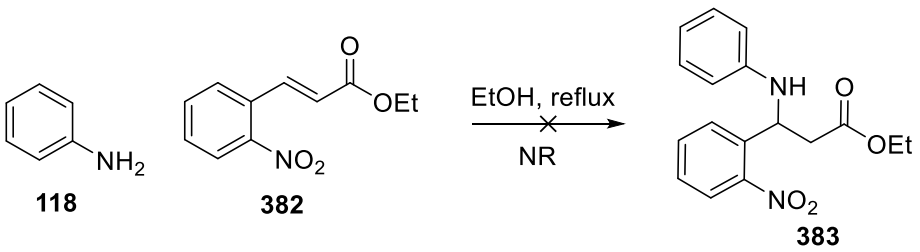
If *trans*-distortion to the alkyne bond is the reason the conjugate addition reaction was successful with the *o*-nitrophenylpropiolate Michael acceptors, it was possible a *trans*-alkene could participate in the conjugate addition. We had shown in *Section 3.14* that anilines do not add to cinnamate Michael acceptors. We had, however, also found anilines do not generally add to propiolate Michael acceptors except in the case of *o*-nitro substitution. As such the unique beneficial effects of the *ortho*-nitro group may extend to *o*-nitrocinnamates.

If the cinnamate Michael acceptor was also functionalised with a leaving group (**377**) the conjugate addition could be followed by an $E1_{CB}$ elimination and lead to the required intermediate (**378**, *Scheme 6.66*). This pathway may render protection of the amine feasible if protection can be performed before the elimination reaction (**380**, *Scheme 6.66*).



Scheme 6.66: *Proposed conjugate addition/elimination sequence*

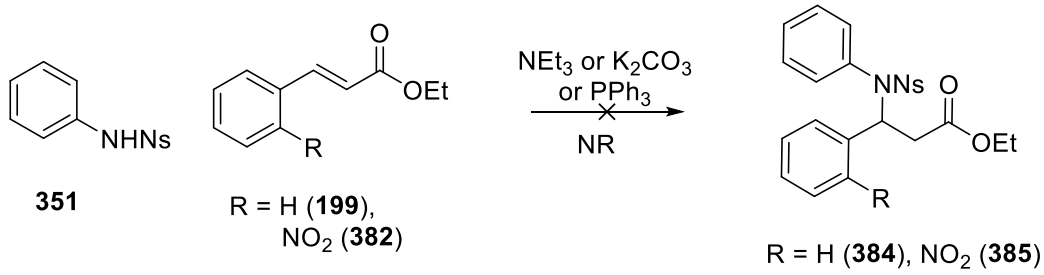
Although halogenated cinnamates are simple to prepare we began our investigations with cinnamates lacking additional substitution as they are readily available. The halogen substitution would only hinder the conjugate addition, but in the event of the test reaction working we would immediately synthesise the appropriate substrate.



Scheme 6.67: *Attempted conjugate addition to ethyl o-nitrocinnamate*

We began by attempting to add aniline (**118**) into ethyl *o*-nitrocinnamate (**382**) but observed no reaction under conditions successful for the analogous alkyne (**215**, *Scheme 6.67*).

The other successful conjugate addition reaction we had developed was the addition of a deprotonated sulfonamide (see *Section 6.7.1*). No reaction was observed with cinnamate Michael acceptors **199** or **382** using conditions which had been successful with *o*-nitrophenylpropiolate Michael acceptors (*Scheme 6.68*).



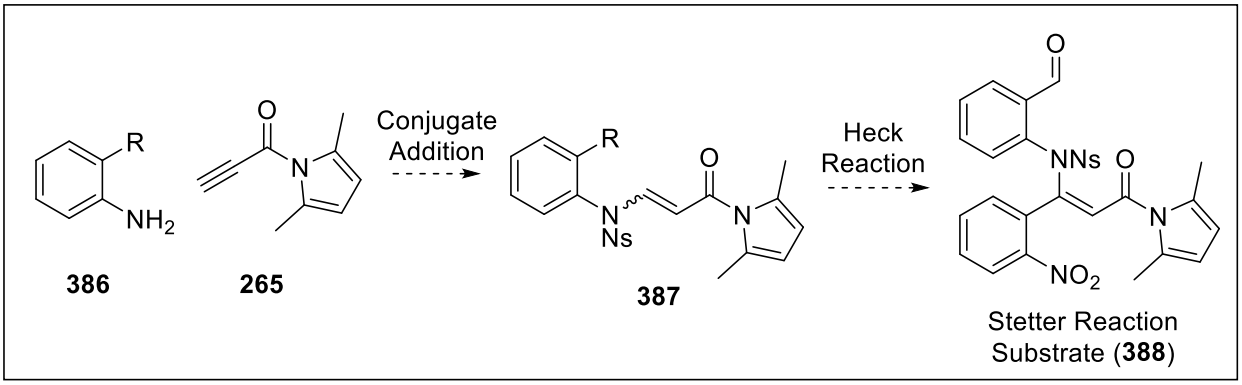
Scheme 6.68: *Attempted conjugate addition of sulfonamide*

Although this strategy mandated halogenation of the Michael acceptor it is unlikely the halogen would improve the reactivity of these Michael acceptors. The added steric hindrance in conjunction with deactivation through inductive effects would render any analogous halogenated Michael acceptors much less competent coupling partners. As such, this strategy was not pursued any further.

The features which had permitted conjugate addition reactions onto *o*-nitrophenylpropiolate Michael acceptors were not transferable to other Michael acceptors, as such to move forward with the conjugate addition strategy we needed to entirely remove the substituent on the propiolate.

6.7.6 Changing the order of bond formation using the Heck reaction

Our investigation into the conjugate addition onto phenylpropiolates revealed that this reaction was specific to substrates containing an *ortho*-nitro group. Unfortunately this group appeared to be the source of subsequent and problematic side reactions. Although conjugate additions onto phenylpropiolates are rare, additions to simple propiolates are common. As such we developed a new synthetic plan which involved adding a nucleophile (**386**) onto an unsubstituted propiolate (**265**) followed by protection to give compound **387** and subsequently appending the additional aryl group through a Heck reaction (*Scheme 6.69*).



Scheme 6.69: *Heck reaction strategy*

Heck reactions onto electron-rich alkenes such as enamines tend to result in poor regioselectivity. The presence of an electron withdrawing sulfonamide group on nitrogen should attenuate the electron donation and allow the usual regioselectivity of the Heck reaction to dominate. Nonetheless, if the selectivity of the Heck reaction became problematic conditions have been reported the enforce substitution alpha to the electron donating group,[212] which would be reinforced by the electron withdrawing carbonyl unit. Regardless of complications with the Heck reaction, protection of the nitrogen needs to be performed before the Heck reaction to avoid reaching an intermediate identical to the one we had formerly had difficulty protecting. We have already synthesised compounds analogous to compound **387** (such as compound **282**) in *Section 5.6.3* (*Figure 6.12*).

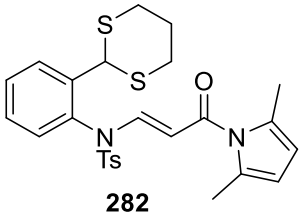
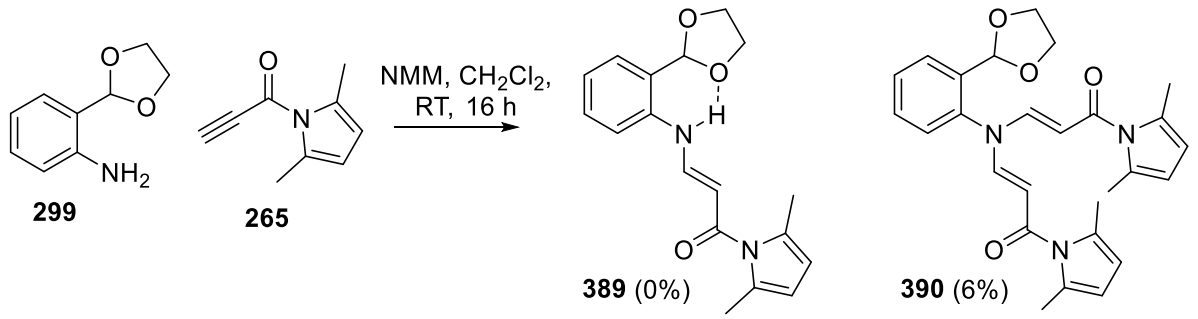


Figure 6.12*: Analogous compound (**282**) prepared in Section 5.6.3*

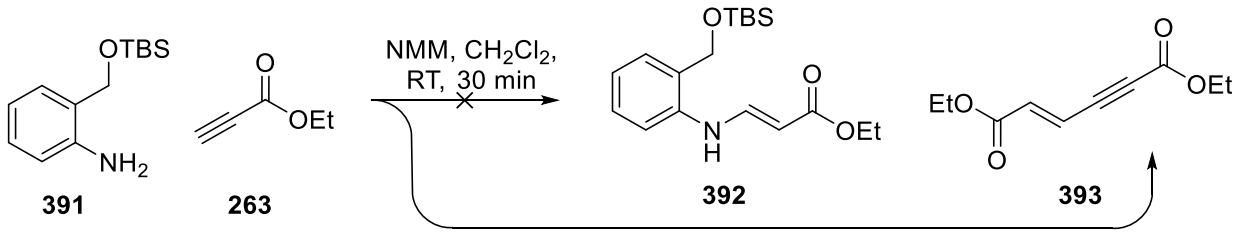
Our previous synthesis utilised a dithiane to protect the aldehyde. In this case we could not use a dithiane as the sulfur would poison the palladium catalyst during the Heck reaction. Therefore, we opted to modify the synthesis by substituting the dithiane for a comparable dioxolane (*Scheme 6.70*).



Scheme 6.70: *Conjugate addition of dioxolane substrate*

The conjugate addition of 2-(1,3-dioxolan-2-yl)aniline (**299**) did not proceed at all like that of the corresponding nucleophile with the dithiane protecting group (**280**, see *Section 5.6.3*). None of the simple conjugate addition product (**389**) was observed and only a very small amount of the di-addition product **390** was obtained. Decomposition accounted for the remainder of the mass balance. This disparate reactivity appears to be because the dioxolane substrate possesses an internal hydrogen bond were the dithiane does not. Compound **299** is not stable to long term storage even at 4°C as the internal hydrogen bonds appears to facilitate opening of the acetal, resulting in decomposition. At room temperature and in the presence of other reactive groups this decomposition is accelerated. It is notable the only compound recoverable from this reaction (**390**) lacks the hydrogen bond donor.

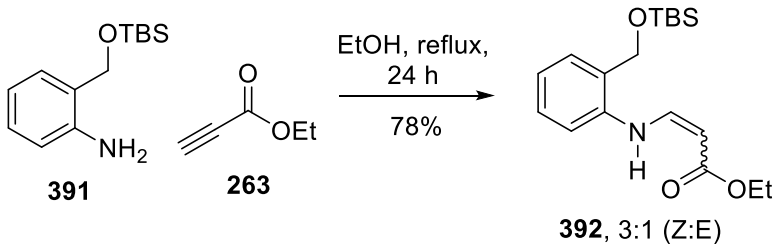
Considering these difficulties with protecting groups we returned to the most reliable protecting group strategy we had hitherto uncovered.



Scheme 6.71: *Attempt to perform conjugate addition*

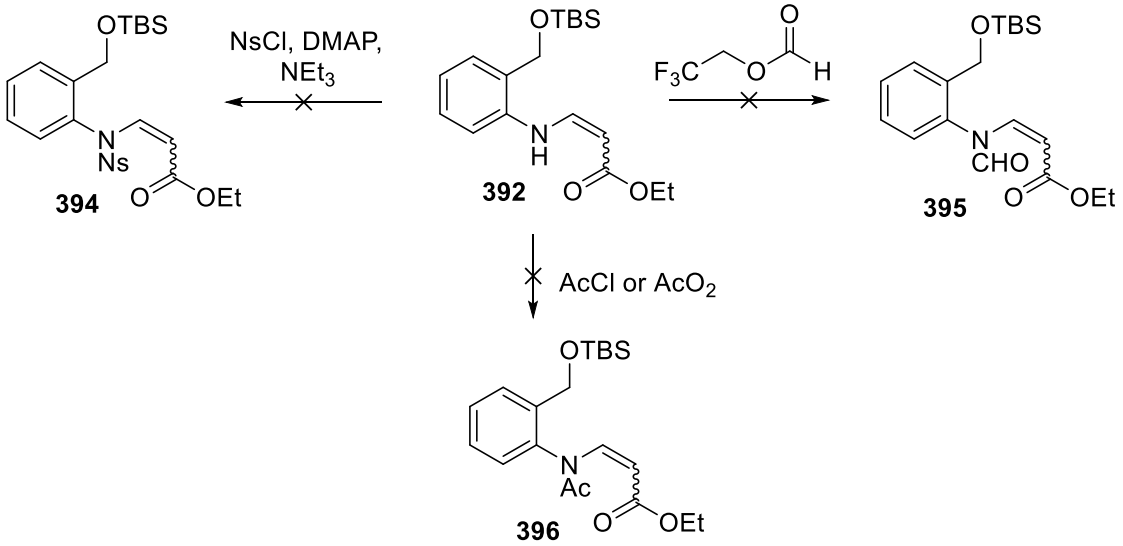
We attempted to add a protected 2-aminobenzylalcohol (**391**) to ethyl propiolate (**263**) using nucleophilic catalysis (*Scheme 6.71*). We used an ester as a Michael acceptor with the intention of reverting to the *N*-acylpyrrole once suitable reaction conditions had been found. Instead of the

conjugate addition product we observed multiple products including a coupling reaction between two molecules of ethyl propiolate (**393**). This coupling reaction is known to occur with all nucleophilic catalysts if the incipient nucleophile is not sufficiently reactive.[213] The basic nature of the conditions generated by the nucleophilic catalyst had resulted in the formation of the dimeric by-product **393**, so we returned to the neutral conditions which had been successful for addition to the phenylpropiolate.



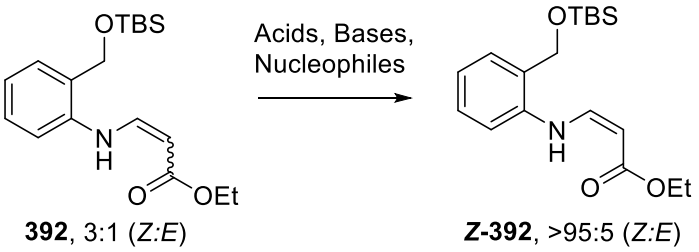
Scheme 6.72: *Conjugate addition with hydrogen bond assistance*

Heating aniline **391** and ethyl propiolate (**263**) to reflux in ethanol yielded the desired product (**392**), but as a mixture of isomers favouring the *Z* isomer due to an internal hydrogen bond (*Scheme 6.72*).



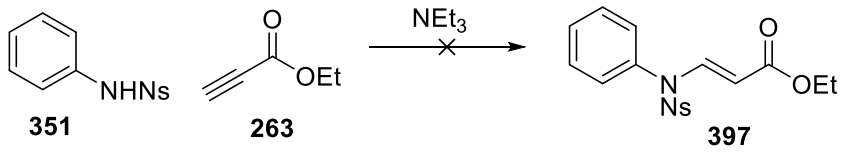
Scheme 6.73: *Attempted protection of amine*

As had occurred before, all attempts at protection of the secondary amine **392** as an amide (**395**, **396**) or sulfonamide (**394**) failed to give the desired product (*Scheme 6.73*), and under increasingly forcing conditions decomposition was observed. This was attributed to the ease at which the alkene can isomerise to the *Z*-configuration (*Scheme 6.74*), which prevented the amine from reacting.



Scheme 6.74: *Isomerisation of alkene*

Attempts to isomerise the mixture of isomers to the ostensibly more suitable *E*-isomer using acid, base or nucleophiles resulted in exclusive formation of the *Z*-isomer. Analysis of the products from the attempted protection reactions also showed the compound was almost entirely in the *Z*-configuration after exposure to the predominantly acidic reaction conditions.



Scheme 6.75: *Attempt to protect first*

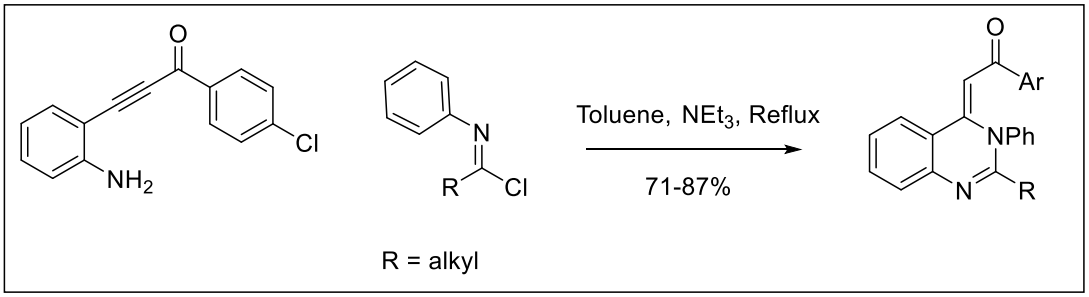
Finally we attempted to add a pre-protected amine (**351**) to ethyl propiolate (**263**, *Scheme 6.75*). Attempts to add a deprotonated sulfonamide into ethyl propiolate led to multiple overlapping products being formed and it was unclear whether the desired product (**397**) was present at all in this complex mixture. The multitude of products formed were likely to be the result of ethyl propiolate dimerization (**393**, *Scheme 6.71*) and subsequent attack of the sulfonamide followed by other Michael additions of enolates.

Our projected strategy relied on the ability to protect the nitrogen before performing the Heck reaction, but the high stability of the *Z*-configured alkene (***Z*-392**) had made this more difficult than was anticipated. As such this synthetic strategy had also become unproductive and we moved on to other strategies to synthesise the key Stetter reaction precursor.

6.7.7 Other applicable conjugate addition reactions

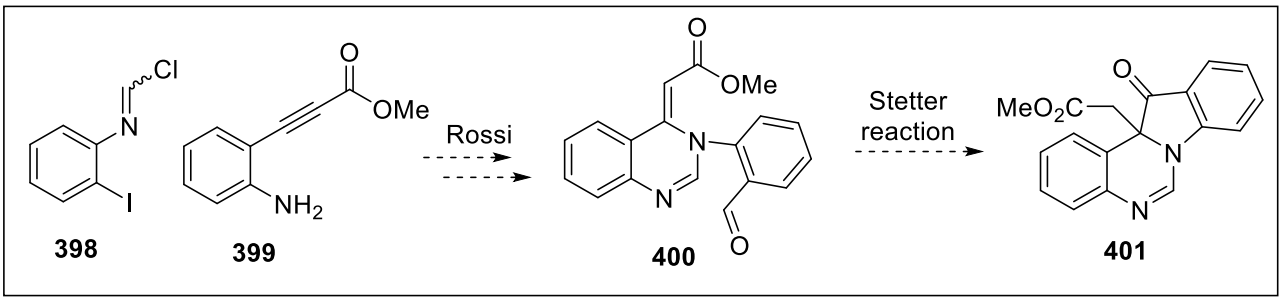
Although there have been few reports directly targeted at the total synthesis of hinckdentine A the literature contained an example of a set of reactions which could potentially be modified to suit our synthetic pathway to hinckdentine A.

Rossi has reported "sequential reactions of β-(2-aminophenyl)-α,β-ynones with nitrogen nucleophiles" to generate quinazoline moieties with appended Michael acceptors (*Scheme 6.76*).[214]



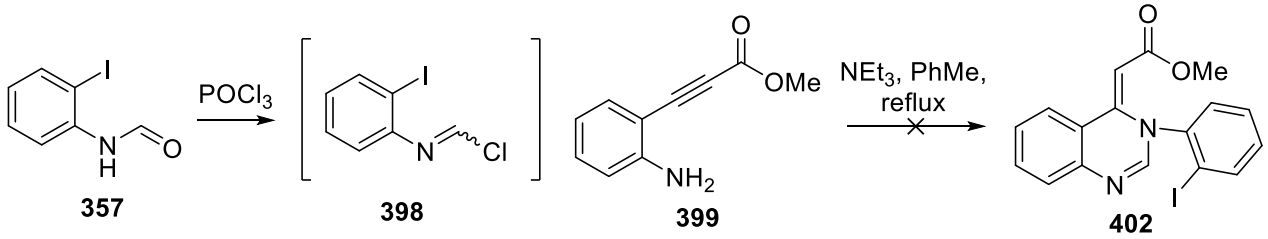
Scheme 6.76: *Reactions reported by Rossi*[214]

We felt we could modify this work to suit our needs by replacing the β-(2-aminophenyl)-α,β-ynone with methyl 2-aminophenylpropiolate (**399**) and using an appropriate chloroimine (**398**) (*Scheme 6.77*). This strategy would also have the consequence that the dihydropyrimidine ring would be formed before the Stetter reaction was performed on substrate **400**.



Scheme 6.77: *Proposed modification of Rossi's work*

This approach described in *Scheme 6.77* still incorporates a conjugate addition reaction, albeit in the cascade reaction after tethering of the nucleophile.



Scheme 6.78: *Attempt to modify Rossi's conditions*

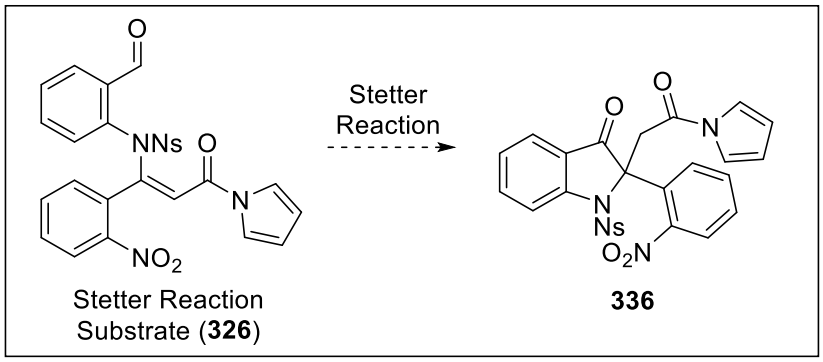
When we attempted our reaction under identical conditions to those reported by Rossi decomposition occurred (*Scheme 6.78*). Several further attempts to modify the conditions also resulted in decomposition. It appears this reaction failed to give similar results to the reactions reported by Rossi as we had made several changes that were beyond the scope of this reaction. In the original report all of the substrates were ynones, whereas we employed esters. Moreover, all the chloro-imines Rossi used originated from amides, but none from a formamide. Unfortunately all of the changes we made were absolutely necessary for our synthesis so it would be unproductive to determine the exact cause of the failure.

As a result of the increasingly poor synthetic outcomes we re-examined our synthetic scheme with the aim of exploring other possible paths that did not involve conjugate addition.

6.8 Synthesis of the Stetter reaction substrate by other means

We have shown the initial conjugate addition strategy was viable but we encountered unforeseeable problems with protecting group manipulations. We have also attempted a number of related conjugate addition strategies, some of which had shown promise but all of which had suffered from insurmountable reactivity problems. The original reason for adopting a conjugate addition as a key step in the strategy was to showcase the utility of on-water catalysis, but this was by no means the only way to synthesise the required Stetter reaction substrate.

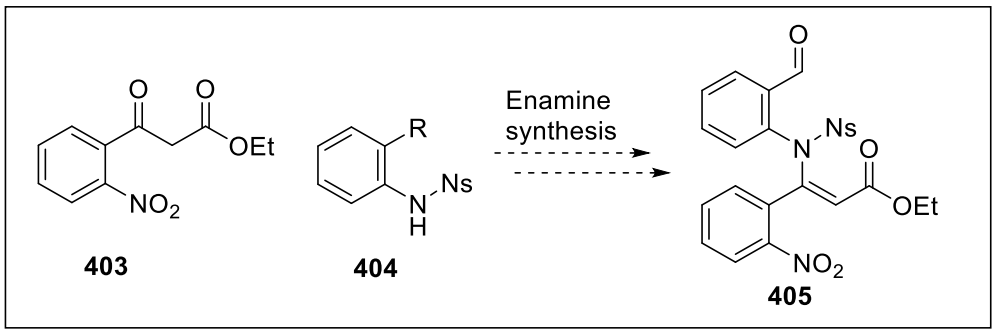
Furthermore the Stetter reaction was the most important step of the synthesis as it would form the quaternary stereocentre (**336**, *Scheme 6.79*). Therefore we endeavoured to synthesise the Stetter reaction substrate (**326**) by means other than conjugate addition.



Scheme 6.79: *Required substrate for intramolecular Stetter reaction*

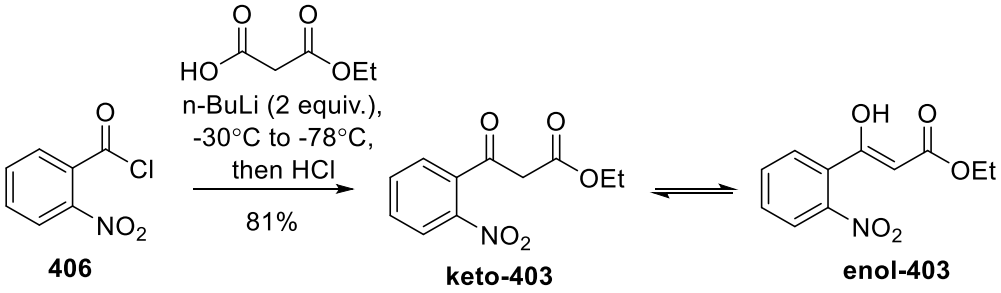
6.8.1 Synthesis of Stetter substrate by enamine formation

The required Stetter reaction precursor (**326**) is an enamine. There are many ways to synthesise simple enamines but our synthesis was complicated by the necessity for an electron withdrawing protecting group.



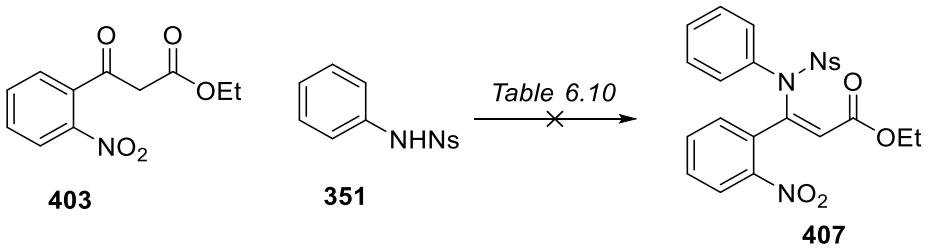
Scheme 6.80: *Proposed enamine synthesis*

In the proposed reaction depicted in *Scheme 6.80* compound **403** was to be a β-ketoester. It must be an ester rather than an *N*-acylpyrrole to allow for differentiation between the two carbonyl units. The amine component (**404**) was to be a sulfonamide, which we hold to be the most appropriate protecting group. Although this reaction seems unlikely with a sulfonamide (which might appear unsuitable for this type of reactivity) there are, in fact, many examples of using sulfonamides to make imines.[215] Obviously the requisite aldehyde cannot be present at this stage, but will be incorporated once the conditions for the enamine synthesis have been developed.



Scheme 6.81: *Synthesis of β-ketoester*

The required β-ketoester, **403**, was synthesised using a literature procedure in good yield (*Scheme 6.81*).[216] When investigating the enamine synthesis we again began with a model sulfonamide (**351**) to eliminate any unnecessary complications (*Scheme 6.82, Table 6.10*).



Scheme 6.82: *Enamine formation*

	Catalyst	Base	Temp. (°C)	Solvent	Time (h)	Result
1	$TiCl_4$	NEt_3	0 to 40	CH_2Cl_2	8	decomp
2	$ZnCl_2$	NEt_3	0 to 40	CH_2Cl_2	8	NR
3	$CeCl_3.7H_2O$	NEt_3	0 to 40	CH_2Cl_2	8	NR
4	AcOH	none	110	AcOH	6	NR
5	TsOH	none	110	toluene	8	decomp
6	none	none	110	toluene	24	NR

Table 6.10*: Results of enamine formation*

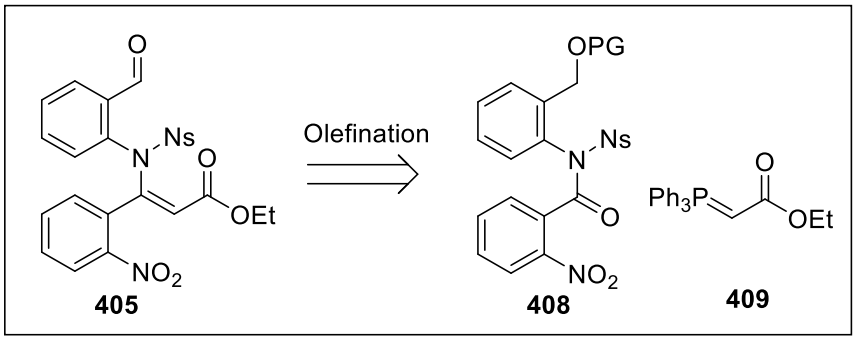
The most common method for the synthesis of enamines from sulfonamides utilises titanium tetrachloride and triethylamine,[217] so we began with these conditions (*Table 6.10,* entry 1). In our case this led to decomposition almost immediately. It is likely chelation of titanium by the 1,3-dicarbonyl compound in the presence of base results in enolization and aldol-type reactions faster than the attack of the sulfonamide. The prompt decomposition of the starting materials indicated that the titanium Lewis acid was too reactive so we turned to other strong oxo-philic Lewis acids. However, with either zinc chloride or cerium chloride and triethylamine no reaction occurred (*Table 6.10,* entries 2 and 3).

Finally we turned to traditional protic acid catalysts, which have been shown to work with sulfonamides. Unfortunately, with neither acetic acid or toluenesulfonic acid[218] did we observe any reaction (*Table 6.10,* entries 4 and 5).

Although there are examples in the literature of the formation of enamines with sulfonamides they all involve primary sulfonamides. There are no reports of the formation of enamine with secondary sulfonamides and our substrate is made even more challenging by the electron withdrawing effect of the phenyl ring. In addition to the problems with the nucleophile there are also no examples of forming enamine with sulfonamides starting from β-ketoesters.

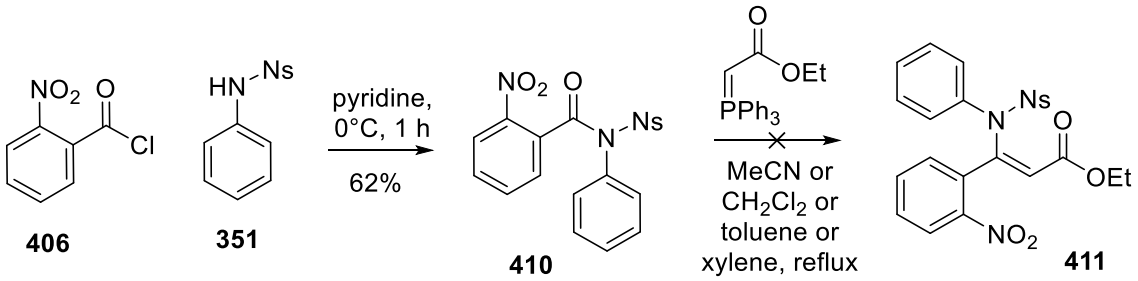
6.8.2 Synthesis of Stetter reaction substrate by olefination

After the failure of the enamine formation we shifted our focus to an entirely different bond forming step. Disconnection of the alkene brings to the fore the possibilty of performing one of the many olefination reactions, of which we chose the Wittig olefination (*Scheme 6.83*).



Scheme 6.83: *Proposed Olefination*

The evident shortcoming of this strategy is that amides do not participate in Wittig reactions. We were speculating the combined electron withdrawing effects of the 4-nitrobenzenesulfonyl group and the *o*-nitrobenzene group would make the "amide" carbonyl electrophilic enough to participate. This strategy could be easily adapted to incorporate *N*-acylpyrrole in the event it was successful.



Scheme 6.84: *Attempted Wittig reaction*

The amide compound (**410**) needed to attempt the Wittig reaction was easily synthesised from compounds **406** and **351** (*Scheme 6.84*). The Wittig reaction with compound **410** was attempted with the preformed ylide in a range of solvents at a range of temperatures. In each case, both starting materials were consumed but none of the olefination product (**411**) was recovered, only highly coloured and highly polar by-products were observed.

Under normal circumstances the Wittig reaction occurs because there is a strong thermodynamic driving force for the reaction in the formation of a strong phosphorus-oxygen bond. In unabbreviated form it can be seen compound **410** (*Scheme 6.84*), on which we attempted the Wittig reaction, possesses several oxygen atoms which are more available than the hindered carbonyl. It is also unlikely that the LUMO of this highly conjugated molecule would lie significantly on the carbonyl. As such it is unsurprising this reaction did not give the desired product.

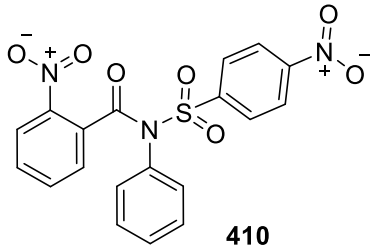


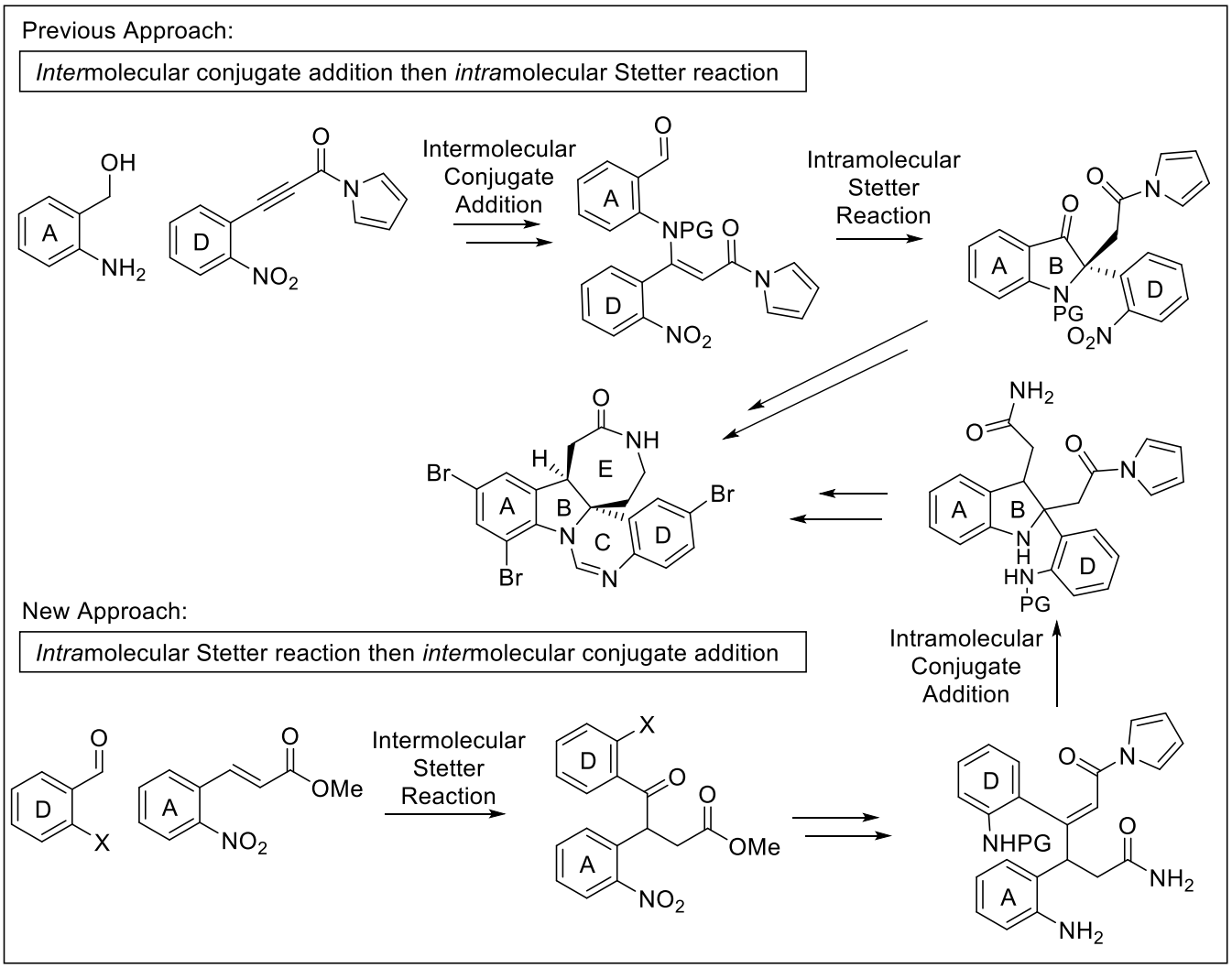
Figure 6.13*: Compound* ***410*** *depicted in full*

At this point we had tried to synthesise the desired substrate for the intramolecular Stetter reaction by a number of routes and bond disconnections. The lack of success caused us to reconsider the synthetic strategy and the order in which we performed the key bond forming steps.

6.9 *Intermolecular Stetter reaction strategy to synthesise hinckdentine A*

The original synthetic plan for hinckdentine A, namely, an *intermolecular* conjugate addition followed by an *intramolecular* Stetter reaction appeared to have hit insurmountable obstructions. Consequently, it was necessary to develop an entirely new synthetic plan. As we did not wish to move away from the reactions we had developed expertise in, we sought only to change the order of the strategic steps in the synthesis. That is, perform a Stetter reaction first followed by a conjugate addition.

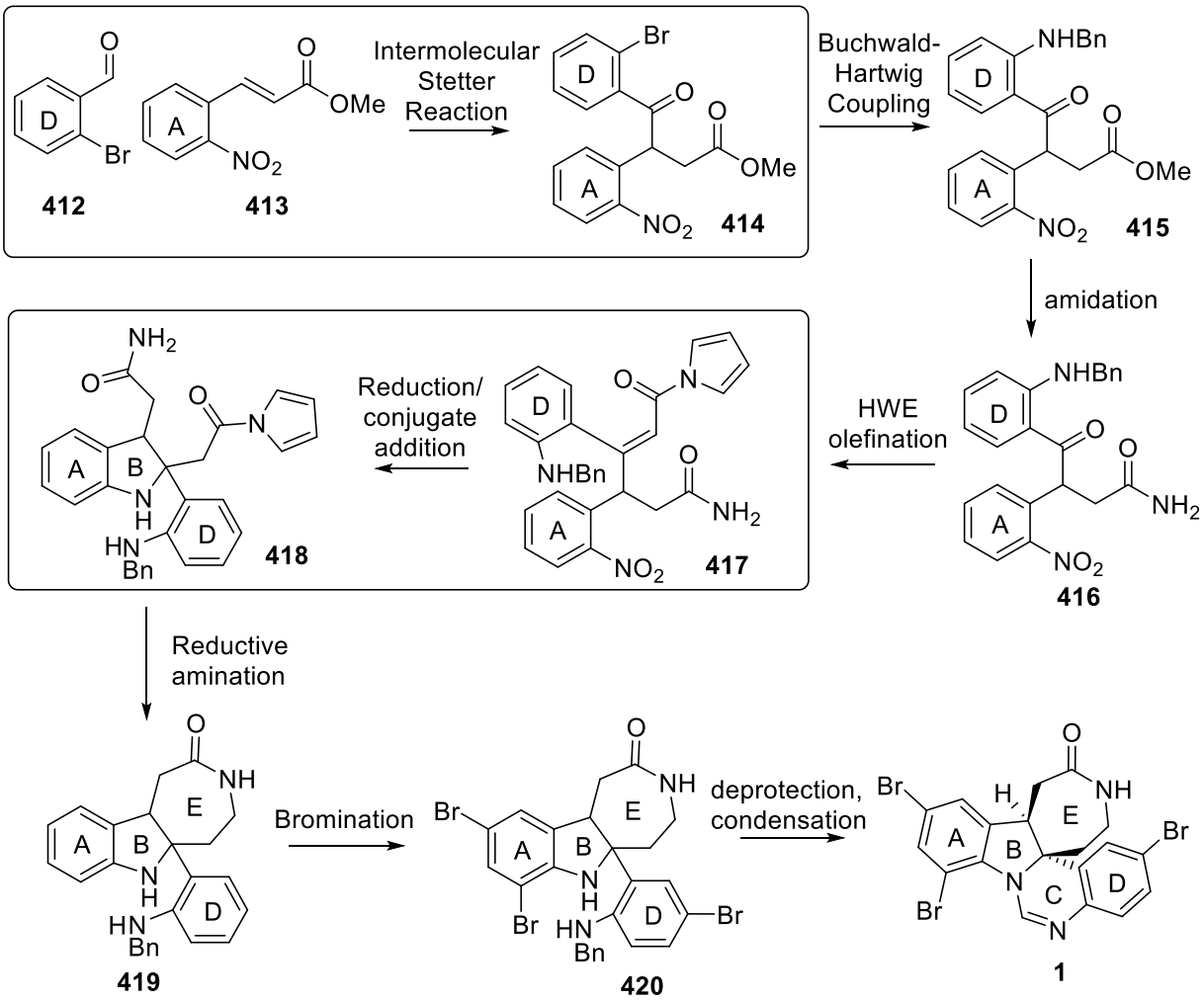
The corollaries of this apparently simple change are significant. The most substantive change was that the synthesis now mandated an *intermolecular* Stetter reaction and an *intramolecular* conjugate addition (*Scheme 6.85*).



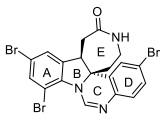
Scheme 6.85: *Comparison of approaches*

Intermolecular Stetter reactions are much less facile than intramolecular Stetter reactions because they often suffer from competing and unproductive side-reactions, such as the benzoin condensation, carbene dimerisation and tautomerisation the Breslow intermediate (see *Section 5.1*).

Performing an intermolecular Stetter reaction meant it would not be possible to begin with a phenylpropionate Michael acceptor as we had done previously. Stetter reactions with alkynes as the Michael acceptor are exceptionally rare and not generalisable due to the high reactivity of the products. There is a single account of an of intramolecular alkynyl Stetter reaction[219] and the only reported intermolecular alkynyl Stetter reaction required tandem gold catalysis to further activate the already highly activated diethyl acetylenedicarboxylate Michael acceptor.[220] As such, our synthesis of hinckdentine A, which relies on the intermolecular Stetter reaction, must begin with a cinnamate (*Scheme 6.86*).



Scheme 6.86: *Proposed intermolecular Stetter reaction strategy*



The planned synthesis would begin with a Stetter reaction between a 2-bromobenzaldehye (**412**) and methyl *o*-nitrocinnamate (**413**, *Scheme 6.86). Ortho*-substituted aromatic aldehydes are acknowledged as being very poor participants in the Stetter reaction due to steric hindrance of the Breslow intermediate. If the bromine became problematic we could replace it with the smaller chlorine although this would make subsequent reactions more challenging. In the first instance we planned to perform the Stetter reaction to give compound **414** as a racemic mixture. Although the stereocentre created in this Stetter reaction would not be intentionally modified, its position alpha to a ketone and at a benzylic position led us to anticipate it could not be prevented from epimerising during the many subsequent steps. With the recent success of Enders performing asymmetric intermolecular Stetter reactions it would be conceivable but challenging to modify this synthesis to be enantioselective.[221, 150b]

The next step was to be a Buchwald-Hartwig-type palladium catalysed animation with benzylamine as an ammonia equivalent, which should be unproblematic.[222] It would not be advisable to begin the synthesis with the protected amine *ortho* to the aldehyde as Stetter reactions are known to be sensitive to large ortho substituents. Although the amination could be performed later it seemed beneficial to perform it early in the synthesis as these reactions often require somewhat forcing conditions to occur.

After amidation of the ester to give compound **416**, the upshot of the reversal of bond formation would be revealed. The 2-carbon unit of the Michael acceptor would be in the correct orientation to form the carbonyl unit present on the E ring of hinckdentine A and would not require a change of oxidation state and deoxygenation. Horner-Wadsworth-Emmons olefination with the known *N*-acylpyrrole phosphonate[103] would be used to install the new Michael acceptor (**417**). This olefination was to form the last of the carbon-carbon bonds and the subsequent steps focus on forming carbon-nitrogen bonds.

Reduction of nitro group should be followed by spontaneous intramolecular conjugate addition to give compound **418**.[223] The unique properties of the *N*-acylpyrrole would then be utilised through reduction to an aldehyde and reductive amination to make the 7-membered E ring (**419**). Bromination at this point should be selective due to the large protecting group on the nitrogen (**420**). The synthesis would be completed by condensation with an ortho-formate and finally hydrogenation to remove the remaining *N*-benzyl group to give hinckdentine A (**1**).

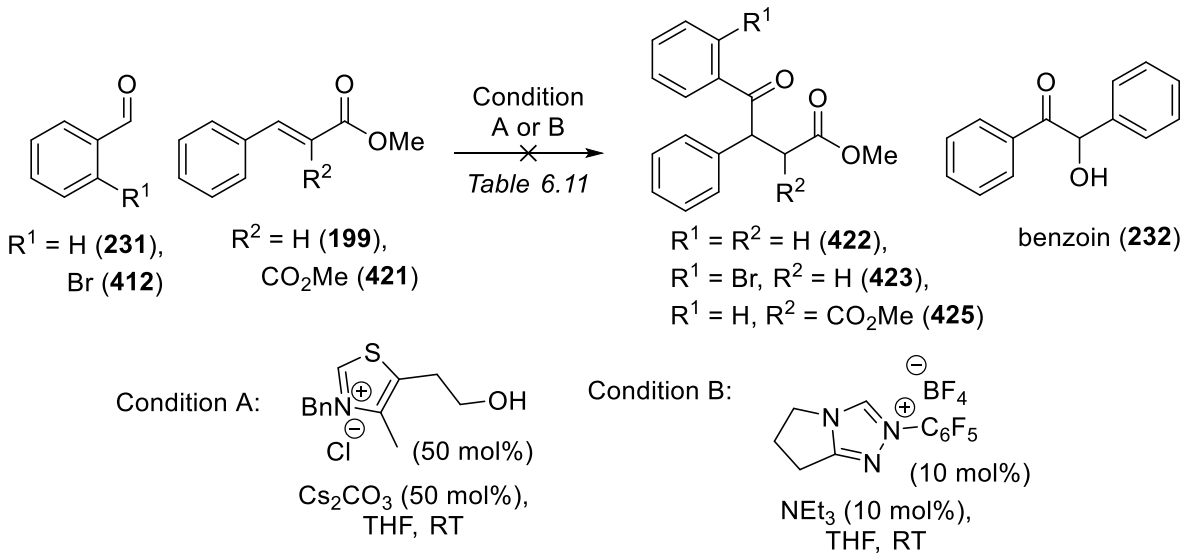
This rearranged synthetic scheme would still be consistent with our original goal of synthesising hinckdentine A using under-utilised reactions and highlight the efficacy of the Stetter reaction and *N*-acylpyrroles.

6.9.1 Intramolecular Stetter reactions - Results

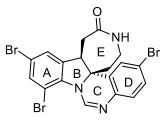
Given that intermolecular Stetter reactions are recognised as difficult, especially onto substituted Michael acceptors, we began with an investigation to establish the limitations of the reaction and find whether any modifications which would be necessary to the synthetic plan.

We focused our attention on thiazolium precatalysts as it has been established by Enders that Stetter reactions onto 4-aryl Michael acceptors are only possible using N-heterocyclic carbenes bearing an alkyl group on the nitrogen atom.[221] Most triazolium salt precatalysts have an aryl group and hence do not catalyse the reaction, whereas the most common thiazolium salt precatalysts bear either a benzyl or ethyl group. Although Enders has been a leader in this field for two decades, he could offer no explanation as to why this is the case.

We began by attempting a Stetter reaction between benzaldehyde (**231**) and methyl cinnamate (**199**) using the *N*-benzylthiazolium precatalyst (*Scheme 6.87, Table 6.11*).



Scheme 6.87: *Intermolecular Stetter reaction*



	R^1	R^2	Condition	Result
1	H	H	A	benzoin
2	H	H	B	benzoin
3	Br	H	A	NR
4	Br	H	B	NR
5	H	CO_2Me	A	benzoin
6	H	CO_2Me	B	benzoin

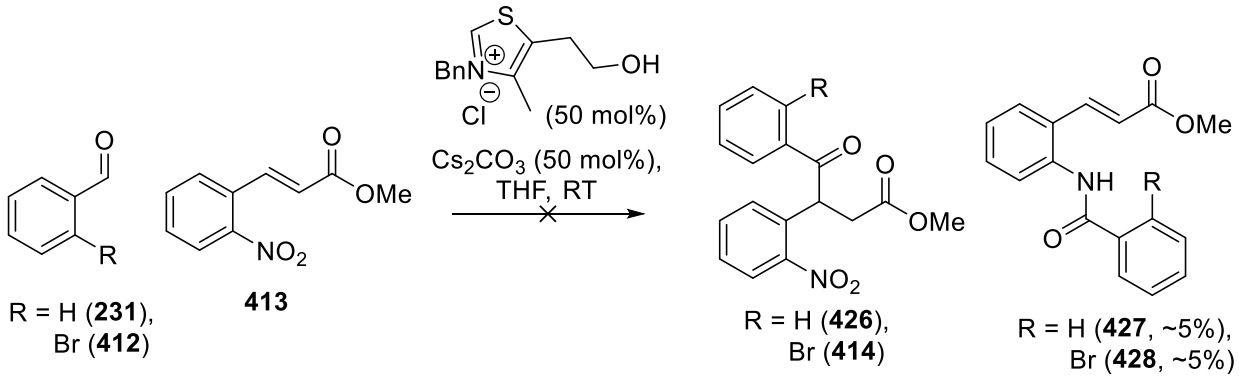
***Table 6.11**: Intermolecular Stetter reaction of esters*

Given the absence of this apparently simple reaction in the literature it is unsurprising this reaction failed to give the 1,4-dicarbonyl product (**422**) and only yielded benzoin (**232**, *Table 6.11*, entry 1). While the formation of benzoin (**232**) was not the desired outcome, it demonstrated the Breslow intermediate was being formed, but that the Stetter reaction could not compete with the benzoin condensation (even though the benzoin condensation is reversible). This reaction also failed with the *N*-pentafluorophenyltriazolium carbene.

Next we tried to perform a Stetter reaction between 2-bromobenzaldehyde (**412**) and methyl cinnamate (**199**) in the hope that the *ortho*-substituent would slow the benzoin reaction and give the Breslow intermediate long enough to undergo the Stetter reaction. Judging from the colour changes observed during the reaction the Breslow intermediate was formed, but no benzoin condensation or Stetter products were observed under either condition (*Table 6.11*, entries 3 and 4).

To determine whether increasing the electrophilicity of the Michael acceptor was advantageous, we changed from a cinnamate to the benzylidene malonate diester (**421**).[224] In the event that this substrate underwent the Stetter reaction it could be decarboxylated to reach a useful intermediate. Unfortunately the diester gave the same result as the cinnamate under both thiazolium and triazolium conditions and only benzoin was observed (*Table 6.11*, entries 5 and 6).

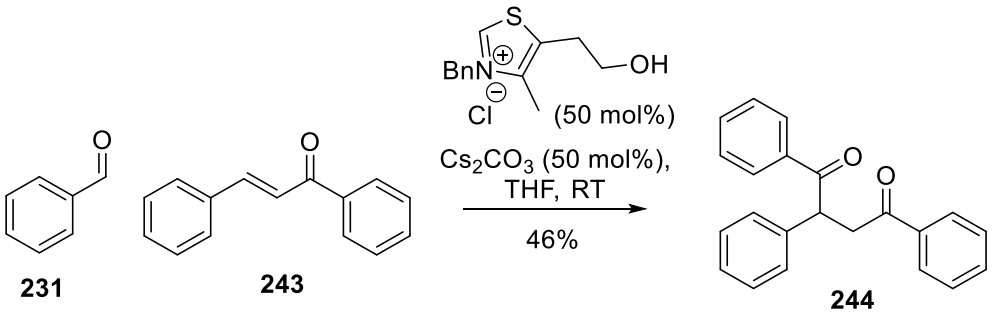
Given that the *o*-nitrophenylpropiolate had displayed unique reactivity toward conjugate addition we next attempted the Stetter reaction with commerically available methyl *o*-nitrocinnamate (**413**) to determine whether the nitro group could again induce a reaction (*Scheme 6.88*).



Scheme 6.88: *Intermolecular Stetter reaction onto nitrocinnamate*

The Stetter reaction with methyl *o*-nitrocinnamate (**413**) failed to give the 1,4-dicarbonyl compound (**426** or **414**) or benzoin when using either benzaldehyde (**231**) or 2-bromobenzaldehyde (**412**, *Scheme 6.88*). Although no benzoin was observed, all of the aldehyde was consumed as was half of the Michael acceptor. Despite the depletion of the reagents the only product recovered in both cases was a very small amount of an amide product (**427** and **428**). Although these amides obviously arose from the redox activity of N-heterocyclic carbenes, it is impossible to determine how it is formed due to the low isolated yield, coupled with the high catalyst loading employed. It can, however, be deduced that nitro groups are not compatible with the N-heterocyclic carbene conditions of the Stetter reaction and our strategy must be modified to reflect this.

The only β-substituted Michael acceptors which generally participate in the intermolecular Stetter reaction are ketones. Of these, the only reaction which has been reproduced to any extent is the reaction between benzaldehyde (**231**) and chalcone (**243**).

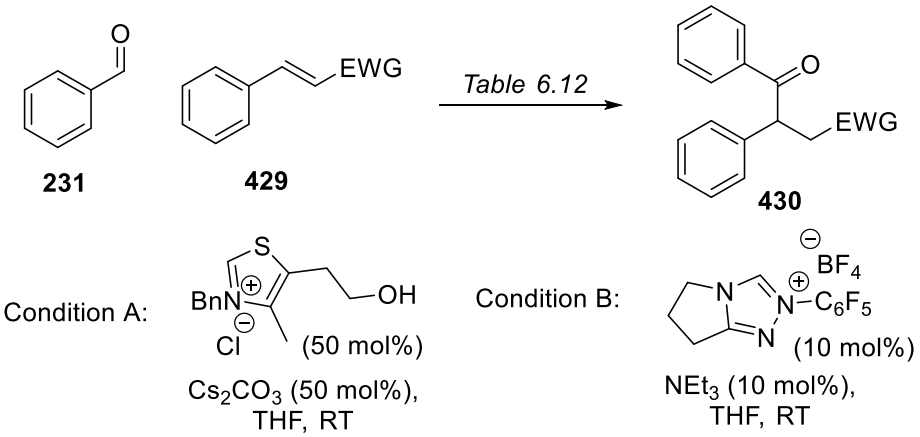


Scheme 6.89: *Intermolecular Stetter reaction of chalcone*

To confirm the conditions we were using to attempt intermolecular Stetter reactions onto cinnamates were efficacious we performed this well precedented Stetter reaction between benzaldehyde (**231**) and chalcone (**243**, *Scheme 6.89*). Under these conditions we obtained the 1,4-dione product (**244**) in comparable yield to the published reports,[150a] although this product is not useful for

the synthesis of hinckdentine A.

Having demonstrated the intermolecular Stetter reaction does indeed work for ketones we attempted to utilise the ketone-like reactivity of *N*-cinnamoylpyrrole (**204**, *Scheme 6.90, Table 6.12*).



Scheme 6.90: *Intermolecular Stetter reaction with other electron withdrawing groups*

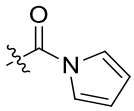
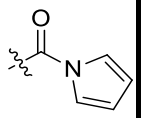
EWG	Condition	Result
	A	by-product
	B	decomp
CN	A	benzoin
CN	B	benzoin
$PO(O^iPr)_2$	A	by-product
$PO(O^iPr)_2$	B	decomp

Table 6.12*: Intermolecular Stetter reactions with other electron withdrawing groups*

Unfortunately it appears the *N*-acylpyrrole is not similar enough to the ketone to participate in the intermolecular Stetter reaction (*Table 6.12*). Under the influence of the thiazolium carbene an uncharacterised by-product which incorporated the catalyst and aldehyde was isolated. With the triazolium carbene only decomposition was observed.

Given the apparent specificity of the intramolecular Stetter reaction we also investigated some other uncommon Michael acceptors. With commercially available cinnamonitrile or with a

phosphonate[225] as the electron withdrawing group no improvement could be made (*Table 6.12*).

Based on these results it was clear only specific substrates would participate and the intermolecular Stetter reaction was not going to be a fruitful reaction for the synthesis of hinckdentine A.

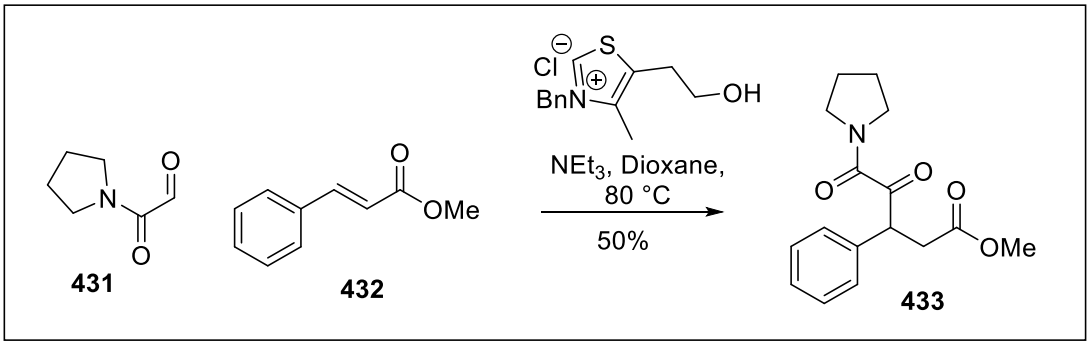
6.9.2 Intermolecular Stetter reaction summary

The lack of success we had encountered when attempting intermolecular Stetter reactions appears to represent several of the inherent restrictions on the currently available methods for performing these reactions.

The currently disclosed examples of intermolecular Stetter reactions of 4-aryl Michael acceptors possess a restricted range of electron withdrawing groups and seem to be restricted to complementary pairs of aldehydes and Michael acceptors. With the increasing popularity of the intermolecular Stetter reaction the absence of a greater range of Michael acceptors in the literature is notable. According to Hermann Stetter, intermolecular Stetter reactions of aromatic and alkyl aldehydes involving β-substituted Michael acceptors must possess a ketone as the electron withdrawing group[226] whether it be a simple ketone, 1,3-dione, β-ketoester[227] or β-ketoamide.[171]

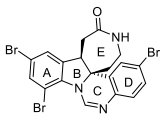
This rule can be bent under certain circumstances for very specific, highly activated aldehydes. Benzylidene malonates will react with the Breslow intermediated derived from furfural, picolinaldehyde[150b] or ethyl glyoxylate,[228] but these aldehydes have been noted by Stetter[145] and Rovis[151a] to be abnormally active for unknown reasons.

There is a single example of a carbene catalysed Stetter reaction occurring onto a cinnamate Michael acceptor (*Scheme 6.91*). This reaction was performed by Stetter himself using an unusual non-enolisable aldehyde (**431**) and is stated to be specific to this aldehyde.[229]



Scheme 6.91: *The only known Stetter reaction to a cinnamate*

Stetter has reported some other Stetter reactions using cinnamate Michael acceptors under the



influence of cyanide catalysis, but there have been no subsequent reports by other authors.[230]

Others who have investigated the scope of intermolecular Stetter reaction have been met with similar results. Fang and co-workers have used enals as the nucleophile in the intermolecular Stetter reaction with substituted Michael acceptors and explicitly stated that only benzylidene diones participate in the reaction.[231]

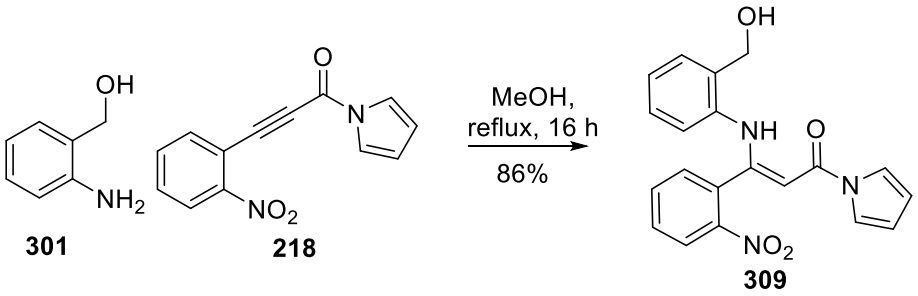
In a similar vein to the restrictions on the range of Michael acceptors, we have found *ortho*-substitution of the benzaldehyde entirely inhibits the occurrence of the Stetter reaction. There are no examples of any intermolecular Stetter reactions using a 2-substituted benzaldehyde occurring with *any* Michael acceptors bearing substitution at the β-position.

Our synthetic strategy had intersected with two inherent limitations of the Stetter reaction and we had no choice but to abandon the synthesis at this point. Despite the failure to use the intermolecular Stetter reaction as a useful step in the synthesis of hinckdentine A we had learned a great deal about this reaction. This information could only be learned through experimentation as there was no way of knowing whether the absence of these reactions in the literature represented a limitation in the chemistry or a lack of experimentation or publication by chemists.

Our intermolecular Stetter reaction strategy was futile and the original intramolecular conjugate addition strategy had encountered continual difficulty with ostensibly simple protecting group manipulations, as such this seemed a fitting time to halt the investigations toward the total synthesis of hinckdentine A.

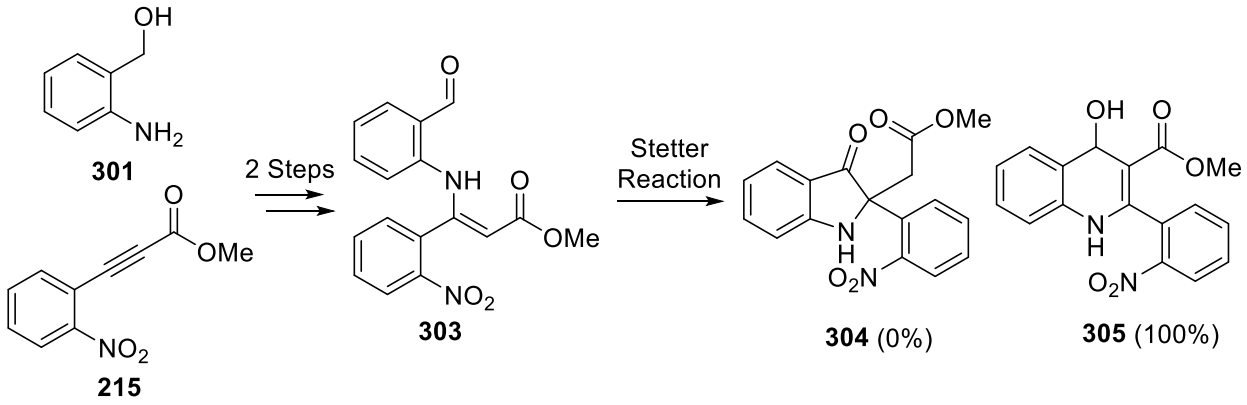
6.10 Summary and Conclusions

We successfully performed a conjugate addition of anilines to phenylpropiolate Michael acceptors, and improved this reaction through the extra electrophilicity introduced by *N*-acylpyrroles (*Scheme 6.92*). This reaction can be performed on-water but is superior when performed in methanol. This conjugate addition was subsequently found to be specific to *o*-nitrophenylpropiolate Michael acceptors.



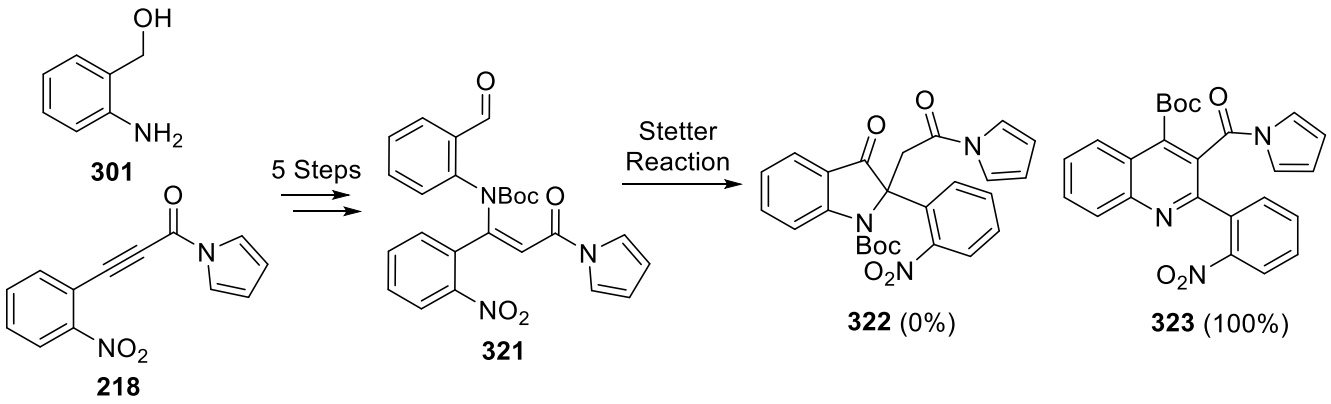
Scheme 6.92: *Conjugate addition to an N-acylpyrrole Michael acceptor*

We attempted a Stetter reaction on a secondary amine and found protection of this nitrogen was necessary to avoid unwanted Friedländer-type reactivity (*Scheme 6.93*).



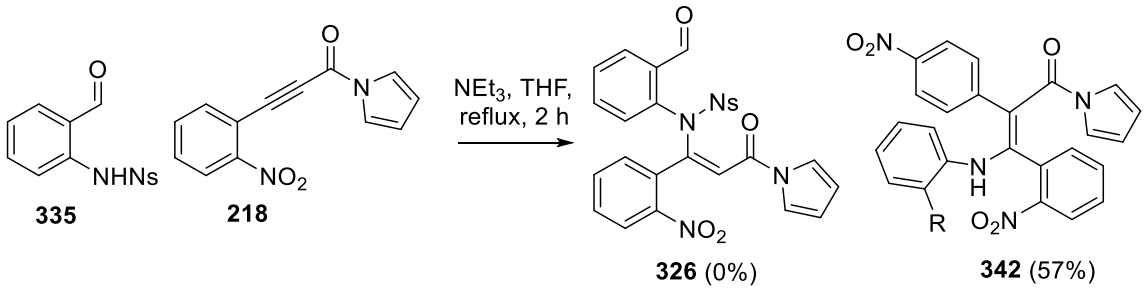
Scheme 6.93: *Attempt at Stetter reaction with secondary amine*

After much experimentation the commonly employed and electron-withdrawing *tert*-butyl carbamate group was installed. Surprisingly, this compound also failed to give the desired Stetter product, but instead underwent a rearrangement to give *tert*-butyl ester product **323** (*Scheme 6.94*).



Scheme 6.94: *Attempt at Stetter reaction with protected amine*

We found the conjugate addition could be performed with a sulfonyl protecting group already present on the nitrogen, but this suffered from an entirely unexpected mode of reactivity (*Scheme 6.96*). A rearrangement with concomitant expulsion of sulfur dioxide to give tetra-substituted alkenes occurred. Even sulfamoyl amides underwent this rearrangement to give the undesired product.



Scheme 6.96: *Conjugate addition of sulfonamide*

We attempted to synthesise the key Stetter reaction substrate by numerous conjugate addition strategies and a number of other pathways, all of which were unproductive. Finally we found inverting the order of our key bond forming steps was not possible due to the inherent limitations of the intermolecular Stetter reaction (*Figure 6.14*).

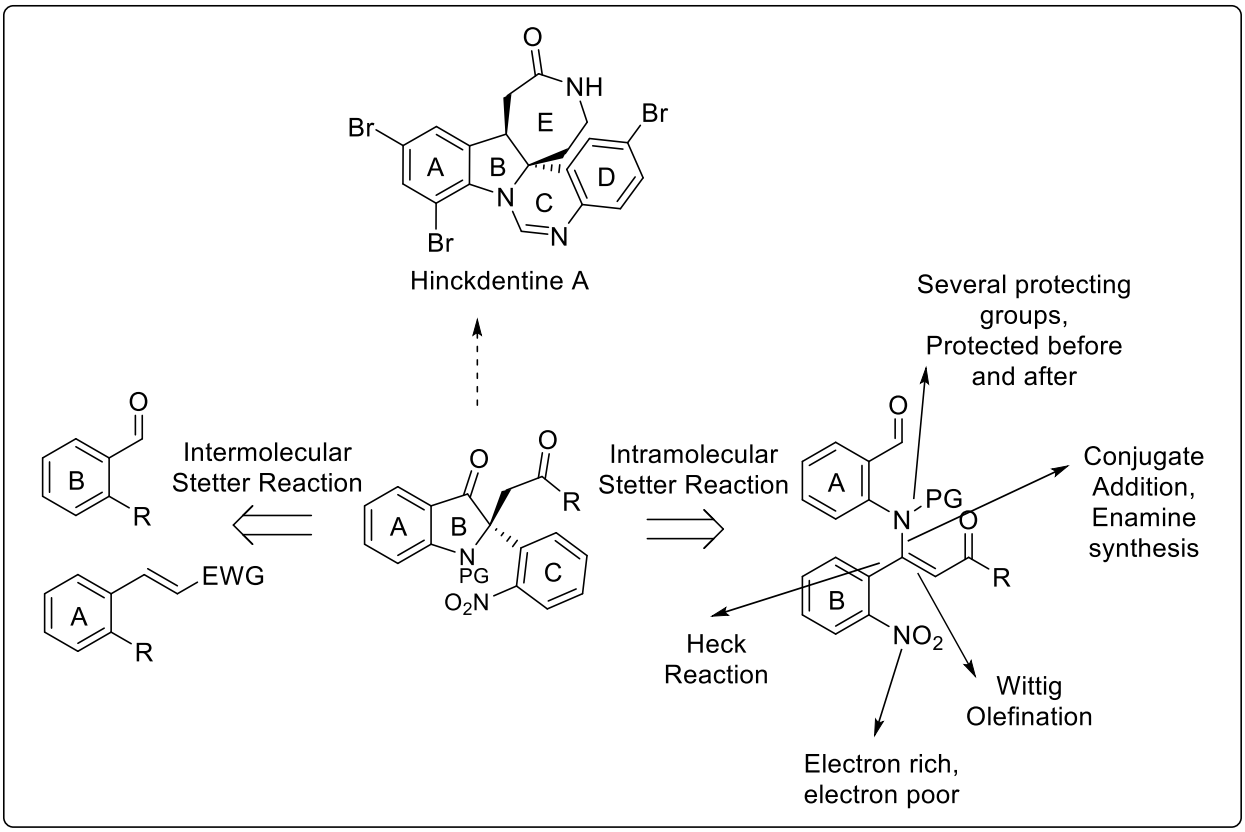


Figure 6.14: *Routes taken to synthesis hinckdentine A*

We had initially set out to perform the total synthesis of hinckdentine A to demonstrate the utility of the reactions and functional groups we had previously explored. We had successfully used on-water catalysed conjugate additions, *N*-acylpyrroles and the Stetter reaction to demonstrate key steps in our planned synthesis. Disappointingly, when applied to the synthesis, the key bond forming steps were hampered by unforeseeable problems with protecting group manipulations. Although we did not synthesise hinckdentine A, in terms of the reasons for originally undertaking the synthesis we had achieved a degree of success. These results show the value of experimentation as these interesting results could not have been predicted.

Conclusion

We set out to investigate the properties several underutilised reactions and functional groups with the aim of subsequently demonstrating the advantages of these reactions in a synthetic setting.

On-Water Catalysis

We began by proposing a new theory for the mechanism of on-water catalysis (*Figure 7.1*).

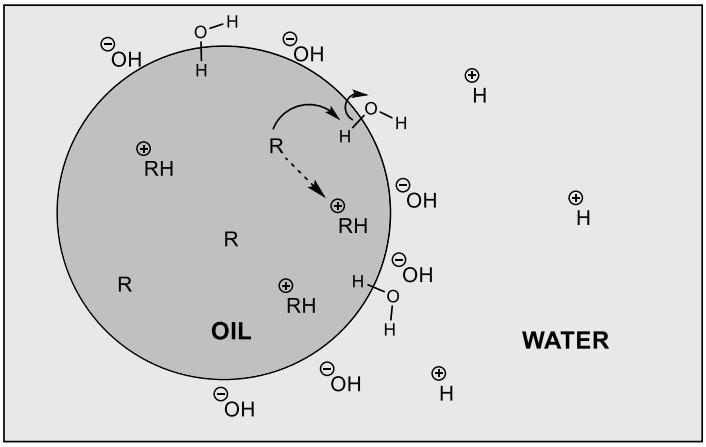


Figure 7.1: *The Beattie and McErlean model for on-water catalysis*

The strong adsorption of hydroxide ions at the oil/water interfaces will render interfacial water acidic, hence leading to the observed acid catalysis with the participation of non-polar Brønsted bases.

We studied a series of Diels-Alder reactions and through these studies provided evidence for the acid-catalysed nature of on-water catalysis. None of the data we have gathered or any recently published results have been inconsistent with our theory and predictions.

We also established the at-water reaction as a test to conclusively determine whether a reaction is catalysed on-water or in dilute solution.

We have developed a rational and consistent theory for on-water catalysis based on all of the available experimental evidence. From this theory we can predict that any reaction that can be catalysed by mild acid will be subject to on-water catalysis. To demonstrate this predictive power we identified an unrecognised example of on-water catalysis; conjugate addition of anilines.

Conjugate addition of anilines

We identified several reports of "uncatalysed" Michael additions of anilines with water as a solvent which we suspected were in fact catalysed on-water. We first demonstrated that the conjugate addition of anilines to Michael acceptors was catalysed on-water. We then proceeded to develop this

class of reactions until it was synthetically useful. Like the examples in the literature the reaction with methyl acrylate was found to be slow which restricted the range of anilines which could participate in the reaction, although the yield on-water was greater than those reported. We improved the rate of reaction, range of nucleophiles and synthetic utility by using *N*-acylpyrroles which reacted quickly with all of the anilines tested, without giving rise to the mixture of products observed with methyl vinyl ketone.

Thiophenols were also found to add on-water to the Michael acceptors tested. Again the *N*-acylpyrrole was found to be advantageous as it did not result in Morita-Baylis-Hillman-type by-products.

Studies into the conjugate addition of aniline to phenylpropiolate Michael acceptors laid the groundwork for the on-water catalysed conjugate addition of anilines that was to be used as a key step toward the total synthesis of hinckdentine A.

These results expand the scope of on-water chemistry by demonstrating a new class of reaction that can be accelerated through this mode of catalysis. These results also demonstrate the usefulness *N*-acylpyrroles and show how they can be advantageous due to their greater electrophilicity and possible subsequent transformations (*Figure 7.2)*.

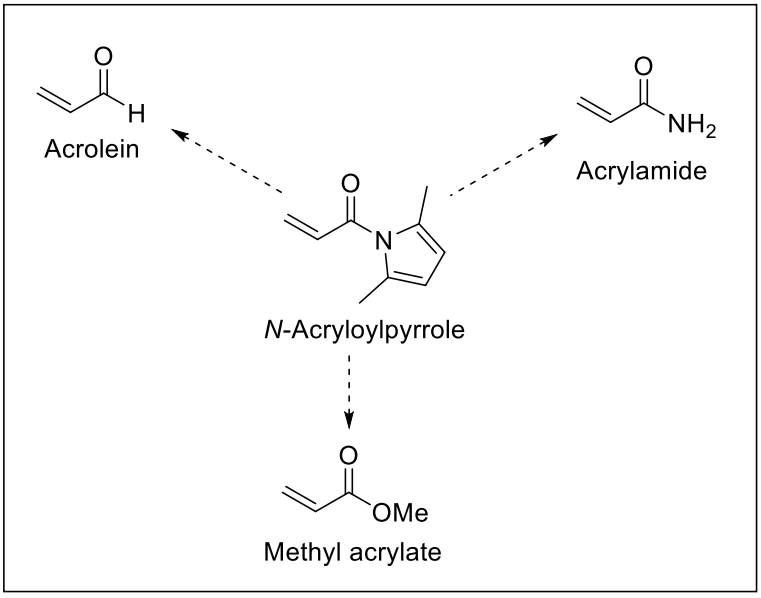


Figure 7.2: *Reactivity of N-acryloylpyrrole*

Another major outcome of this research has been a simple method for the synthesis of *N*-acyryol-2,5-(dimethyl)pyrrole. This inherent reactivity of this compound will render it a useful building block for organic synthesis (*Figure 7.2*).

To demonstrate the convenience of *N*-acyryol-2,5-(dimethyl)pyrrole as well as the on-water

conjugate addition protocol, we utilised this molecule in the synthesis of the pharmaceutical agent thiazesim.

Aqueous synthesis of thiazesim

We have synthesised the pharmaceutical thiazesim in 4 steps (62% overall yield), 3 of which involved water as a catalysis, solvent or co-solvent, with the remaining step utilising the acyl-substitution properties of *N*-acylpyrroles (*Figure 7.3*). All steps were catalytic and high yielding and the synthesis used no protecting groups. This methodology for the synthesis of 1,5-benzothiazepines was practical, modular and environmentally friendly.

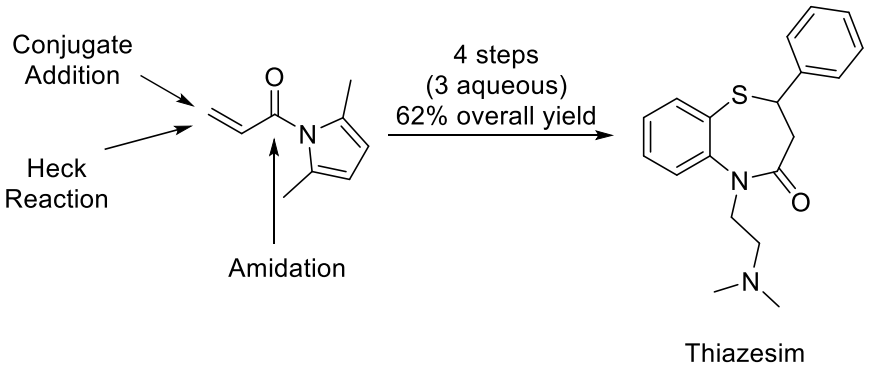


Figure 7.3: *Overall synthesis of Thiazesim*

Through this study we have shown some of the usefulness of *N*-acryloyl-2,5-(dimethyl)pyrrole as a starting material and many of the advantages of *N*-acylpyrroles. We have also gained a measure of the strength of the acid catalysis that can be performed on-water. These studies confirmed interfacial water is of similar pK_a to a carboxylic acid.

Given our success with conjugate addition reactions onto *N*-acylpyrroles we moved our efforts to the Stetter reaction.

Stetter reaction of N-Acylpyrroles

The asymmetric Stetter reaction has not been applied to many syntheses despite its ability to form quaternary stereocentres in high enantiomeric excess. This is due to limitations in the range of Michael acceptors which can be used. We have enabled the Stetter reaction to be used more frequently by showing *N*-acylpyrroles are highly competent electron withdrawing groups for the Stetter reaction (*Figure 7.4*).

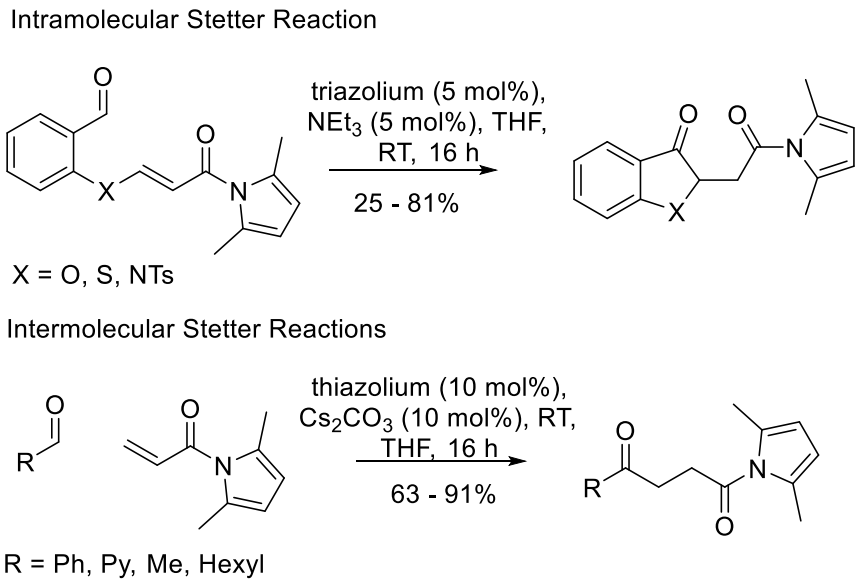


Figure 7.4: *Stetter reactions of N-acylpyrroles*

The intramolecular Stetter reactions of *N*-acylpyrroles performed well, as did intermolecular Stetter reactions with aromatic and even enolisable aldehydes, which are traditionally very challenging. The ability to use an *N*-acylpyrrole as a masked aldehyde or amide will significantly increase the use of the Stetter reaction in total synthesis. In this study we formed an indolone which is directly comparable to the intermediate required in our proposed total synthesis.

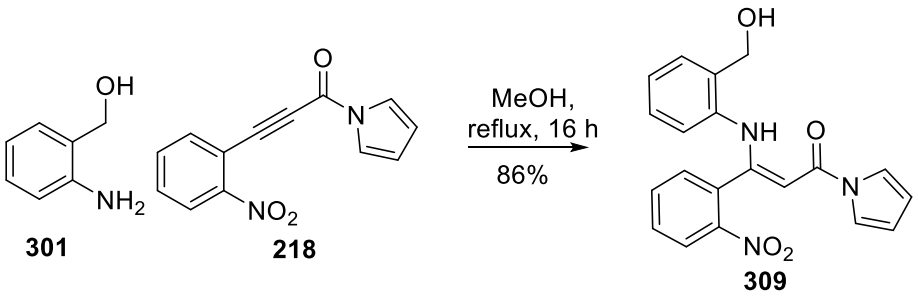
Finally we assembled all of the previously studied components into one total synthesis.

Studies toward the total synthesis of hinckdentine A

We had had developed the two new reactions which were needed in our synthetic strategy toward the synthesis of hinckdentine A and it appeared that these reactions would be easily applied.

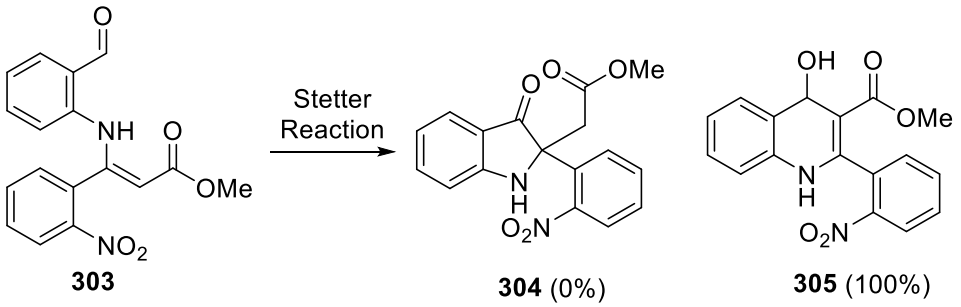
The total synthesis of hinckdentine A was to be a showcase for the benefits and insights which can be gained by applying neglected reactions and functional groups. The reaction we sought to highlight performed well individually, but our synthesis was repeatedly impeded by unforeseeable problems with protecting groups and side reactions.

We successfully performed a conjugate addition of anilines to phenylpropiolate Michael acceptors, and improved this reaction through the extra electrophilicity introduced by *N*-acylpyrroles (*Scheme 7.1*).



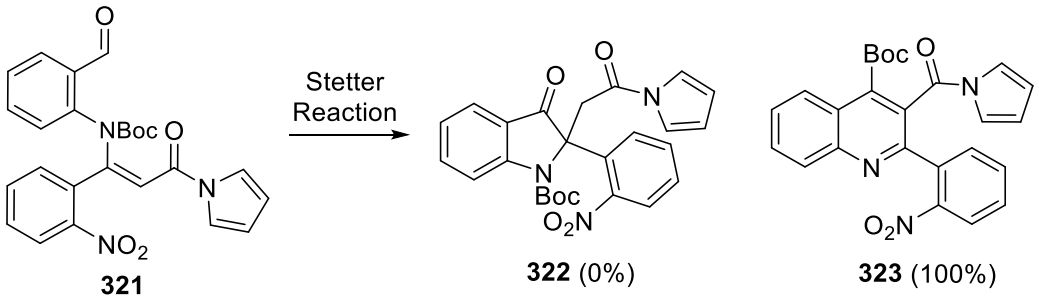
Scheme 7.1: *Conjugate addition to an N-acylpyrrole Michael acceptor*

We attempted a Stetter reaction on a secondary amine and found protection was necessary to permit the Stetter reaction to occur (*Scheme 7.2*).



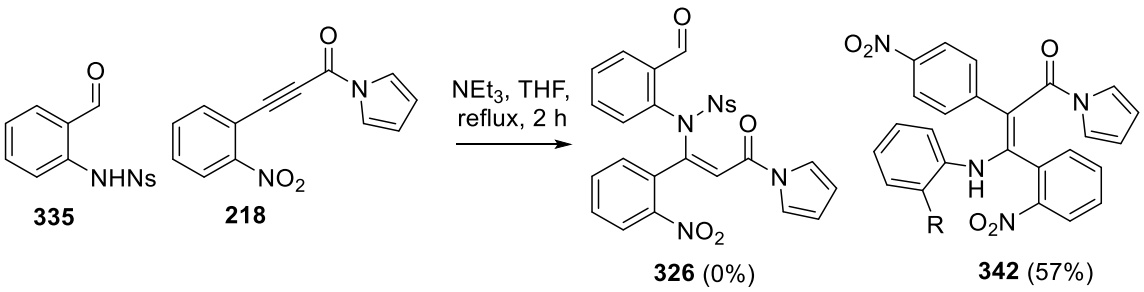
Scheme 7.2: *Attempt at Stetter reaction with secondary amine*

After modifying our synthesis to incorporate the lessons from the initial study we again observed an unexpected by-product resulting from an unprecedented rearrangement (*Scheme 7.3*).



Scheme 7.3: *Attempt at Stetter reaction with protected amine*

Alteration of the protecting group strategy was deemed necessary, but this again suffered from an entirely unexpected mode of reactivity. We observed the elimination of sulfur dioxide to yield tetrasubstituted alkenes such as **342** (*Scheme 7.4*).



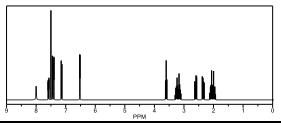
Scheme 7.4: *Conjugate addition of sulfonamide*

We attempted to synthesise the key Stetter reaction substrate by a numerous conjugate addition strategies and a number of other pathways, all of which were unproductive. Finally we found inverting the order of our key bond forming steps was not possible due to the inherent limitations of the intermolecular Stetter reaction.

Conclusion

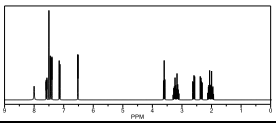
We sought to undertake this work to highlight the merits of uncommon and neglected reactions and functional groups. After investigating on-water catalysis, the on-water conjugate addition of anilines and the Stetter reaction of *N*-acylpyrrole Michael acceptors we attempted to use these transformations as key steps in a total synthesis. The real reason for undertaking a total synthesis is not often the target compound. The value of total synthesis is usually to be found in what was discovered along the way. This sentiment is particularly true for our investigations which focused on drawing attention to useful but neglected chemistry. When these uncommon reactions were applied to synthesis they performed well but we were let down by more conventional chemistry. Our results highlight the great range of chemistry already available but also how much chemistry is left to discover.

Experimental



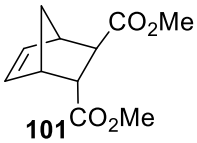
General experimental

All reactions were performed under an inert atmosphere (nitrogen or argon) in oven dried glassware, unless otherwise stated. Dichloromethane, acetonitrile and triethylamine were freshly distilled from calcium hydride. Tetrahydrofuran and ether were freshly distilled from sodium wire/benzophenone. Toluene was freshly distilled from sodium. Dimethylsulfoxide was dried over molecular sieves (4 Å). Dimethylformamide, diethyl ether, toluene, acetonitrile and methanol were also purified and dried by passage through an alumina column with an Innovative Technology PureSolv system. Pyrrole was purified by passage through activated alumina. Water for on-water reactions was purified using a Millipore Milli-Q System (<18.2 MΩ.cm @25°C) or Millipore Elix system (<15 MΩ.cm @25°C). On-water reactions were performed under air in 21 mL scintillation vials and an emulsion was obtained through stirring at greater than 1500 rpm. Melting points were determined using a Stanford Research Systems Optimelt automated melting point system. Infrared spectra were acquired on a Bruker ALPHA FT-IR as thin films, neat. Absorption maxima are expressed in wavenumbers (cm^{-1}). ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$, DMSO-d_6, acetone-d_6, methanol-d_4 or D_2O on a Bruker AVANCE DPX300, or Bruker DPX200 spectrometer (^{1}H frequencies 300, 200 MHz, ^{13}C frequency 75 MHz). ^{1}H chemical shifts are expressed as parts per million (ppm) with residual chloroform (δ 7.26), dimethylsulfoxide (δ 2.50), methanol (δ 3.31) or acetone (δ 2.05) as internal references and are reported as chemical shift (ppm); multiplicity (s = singlet, br = broad, d = doublet, t = triplet, q = quartet, m = multiplet); coupling constants (*J*) reported in Hz; and relative integral. ^{13}C NMR chemical shifts are expressed as parts per million (ppm) with residual chloroform (δ 77.16), dimethylsulfoxide (δ 39.52), methanol (δ 49.00) or acetone (δ 29.84) as internal references; multiplicity was assigned from DEPT experiments. High resolution mass spectra were recorded on a Bruker Apex II FTICR mass spectrometer with a 7.0 T magnet, fitted with an off-axis Analytica electrospray source. Column chromatography was performed using Grace Davison, Scharlau or Merck 40-63 μM (230-400 mesh) silica gel. Analytical thin layer chromatography was performed using preconditioned plates (Merck TLC silica gel 60 F_{254} on aluminium) and visualised using UV light (254 nm and 365 nm), ethanolic anisaldehyde or potassium permanganate solution.



Chapter 2 – Studies into the Mechanism of On-Water Catalysis

Dimethyl bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (101)[232]

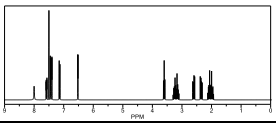


101

Freshly distilled cyclopentadiene (33 μL, 0.40 mmol) was added to a suspension of dimethyl fumarate (50 mg, 0.35 mmol) in deionised water (4 mL) and the suspension was stirred vigorously for 150 minutes. Ethyl acetate (10 mL) was added and the phases were separated, the organic phase was dried over Na_2SO_4 and the solvent was evaporated to give the *title compound* as colourless oil (68.3 mg, 93%). IR (neat): ν_{max} 2953, 1726, 1435, 1265, 1163, 1017 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.22 (dd, J = 3.1, 5.7 Hz, 1 H), 6.02 (dd, J = 3.1, 5.7 Hz, 1 H), 3.66 (s. 3 H), 3.59 (s, 3 H), 3.32 (t, J = 3.9 Hz, 1 H), 3.21 (br s, 1 H), 3.07 (br s, 1 H), 2.63 (dd, J = 1.5, 4.5 Hz, 1 H), 1.57 (m, 1 H), 1.40 (dd, J = 1.8, 8.7 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.0 (C), 173.8 (C), 137.7 (CH), 135.3 (CH), 52.2 (CH_3), 51.9 (CH_3), 48.0 (CH), 47.7 (CH), 47.4 (CH2), 47.2 (CH), 45.7 (CH) ppm. MS (ESI): m/z (%) 443 (100), $[M_2 + Na]^+$, 233 (45) $[M + Na]^+$, 211 (69) $[M + H]^+$.

Standard Conditions for Replicate Reactions

Freshly distilled cyclopentadiene (33 μL, 0.40 mmol) was added to ten identical suspensions of dimethyl fumarate (50 mg, 0.35 mmol) in water (with additives, 4 mL) and stirred vigorously. At ten minute intervals one reaction vessel was removed from the stirrer. Ethyl acetate (10 mL) was added, the phases were separated, the organic phase was dried over Na_2SO_4 and the solvent was evaporated. The ratio of product to starting material in this mixture was determined by analysis of the ^1H NMR spectrum of the crude mixture in $CDCl_3$.

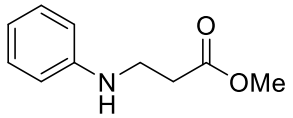


Chapter 3 – On-Water Conjugate Addition of Anilines

General procedure for the addition of anilines to methyl acrylate

Aniline (1.2 mmol) and methyl acrylate (100 μL, 1.1 mmol) were added to deionised water (4 mL) and stirred vigorously for 24 hours. Dichloromethane (10 mL) was added, the phases were separated and the organic phase was dried over Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography.

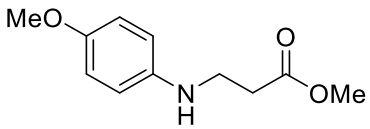
methyl 3-(phenylamino)propanoate (129a)[87]



129a

R_f: 0.60 (50 % ethyl acetate in hexanes). IR (neat): ν_{max} 3403, 2925, 1705, 1602, 1386, 1242, 750 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.17 (dd, J = 8.4, 7.4 Hz, 2 H), 6.71 (dd, J = 7.4, 0.8 Hz, 1 H), 6.62 (dd, J = 8.6, 0.8 Hz, 2 H), 4.00 (br s, 1 H), 3.69 (s, 3 H), 3.45 (t, J = 6.4 Hz, 2 H), 2.62 (t, J = 6.6 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.9 (C), 147.7 (C), 129.4 (CH), 117.9 (CH), 113.1 (CH), 51.8 (CH_3) 39.5 (CH_2), 33.8 (CH_2) ppm.

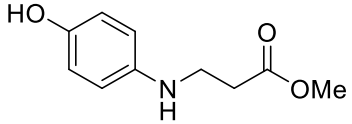
methyl 3-(4-methoxyphenylamino)propanoate (129b)[87]



129b

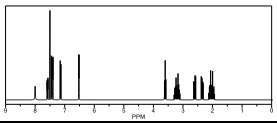
R_f: 0.36 (50% ethyl acetate in hexanes). IR (neat): ν_{max} 3386, 2995, 1730, 1511, 1233, 819 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.78 (d, J = 8.8 Hz, 2 H), 6.59 (d, J = 8.8 Hz, 2 H), 3.74 (s, 3 H), 3.69 (s, 3 H), 3.39 (t, J = 6.4 Hz, 2 H), 2.59 (t, J = 6.4 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.9 (C), 152.5 (C), 141.8 (CH), 115.0 (CH), 114.6 (CH), 55.8 (CH_3), 51.7 (CH_3), 40.6 (CH_2), 33.8 (CH_2) ppm.

methyl 3-(4-hydroxyphenylamino)propanoate (129c)



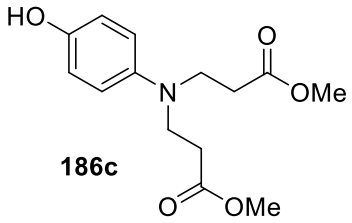
129c

R_f: 0.39 (50% ethyl acetate in hexanes). mp: 93.5 °C. IR (neat): ν_{max} 3305, 2953, 1719, 1514, 1177, 810 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.68 (d, J = 8.8 Hz, 2 H), 6.55 (d, J = 8.8 Hz, 2 H), 4.41 (br s, 2 H), 3.70 (s, 3 H), 3.38 (t, J = 6.4 Hz, 2 H), 2.60 (t, J = 6.4 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.3 (C), 148.5



(C), 141.5 (C), 116.4 (CH), 115.3 (CH), 51.9 (CH_3), 40.6 (CH_2), 33.8 (CH_2) ppm. MS (APCI): *m*/*z* (%) 196 (100) $[M + H]^+$, 122 (11). HRMS (ESI): calcd. for $C_{10}H_{14}O_3N$ $[M + H]^+$: 196.09737; found: 196.09682.

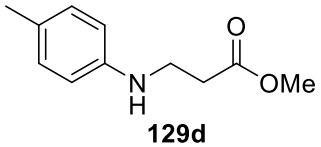
dimethyl 3,3'-(4-hydroxyphenylazanediyl)dipropanoate (186c)



186c

R_f: 0.53 (50% ethyl acetate in hexanes). IR (neat): ν_{max} 3356, 2951, 1717, 1511, 1177, 810 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.76 (d, J = 9.4 Hz, 2 H), 6.69 (d, J = 9.4 Hz, 2 H), 4.81 (br s, 1 H), 3.66 (s, 6 H), 3.51 (t, J = 7.0 Hz, 4 H), 2.52 (t, J = 7.2 Hz, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.9 (C), 148.8 (C), 141.6 (C), 117.2 (CH), 116.4 (CH), 51.8 (CH_3), 48.4 (CH_2), 32.6 (CH_2) ppm. MS (APCI): *m*/*z* (%) 304 (100) $[M + Na]^+$, 282 (77) $[M + H]^+$, 208 (10). HRMS (ESI): calcd. for $C_{14}H_{19}O_5NNa$ $[M + Na]^+$: 304.11609; found: 304.11554.

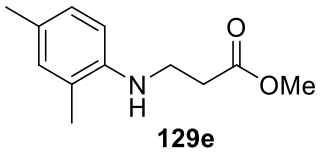
methyl 3-(*p*-tolylamino)propanoate (129d)[87]



129d

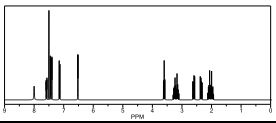
R_f: 0.43 (20% ethyl acetate in hexanes). IR (neat): ν_{max} 3382, 2997, 1730, 1511, 1233, 831 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.05 (d, J = 8.2 Hz, 2 H), 6.59 (d, J = 8.2 Hz, 2 H), 3.83 (br s, 1 H) 3.73 (s, 3 H), 3.46 (t, J = 6.4 Hz, 2 H), 2.64 (t, J = 6.4 Hz, 2 H), 2.29 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.8 (C), 145.3 (C), 129.8 (CH), 126.9 (C), 113.2 (CH), 51.6 (CH_3), 39.8 (CH_2), 33.7 (CH_2), 20.3 (CH_3) ppm.

methyl 3-(2,4-dimethylphenylamino)propanoate (129e)

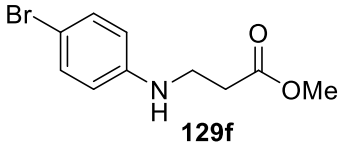


129e

R_f: 0.60 (50% ethyl acetate in hexanes). IR (neat): ν_{max} 3401, 2953, 1735, 1619, 1176, 805 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.92 (m, J = 8.0 Hz, 1 H), 6.88 (s, 1 H), 6.53 (d, J = 8.0 Hz, 1 H), 3.79 (br s, 1 H), 3.68 (s, 3 H), 3.46 (t, J = 6.6 Hz, 2 H), 2.64 (t, J = 6.6 Hz, 2 H), 2.21 (s, 3 H), 2.09 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5 (C), 143.6 (C), 131.3 (CH), 127.6 (CH), 126.7 (C), 123.1 (C), 110.4 (CH), 52.2 (CH_3), 39.9 (CH_2), 33.9 (CH_2), 20.5 (CH_3), 17.5 (CH_3) ppm. MS (APCI): *m*/*z* (%) 209 (100) $[M + H]^+$, 134 (37); *m/z* (ESI): 208 (MH^+, 100%), 134 (35). HRMS (ESI): calcd for $C_{12}H_{18}O_2N$ $[M + H]^+$: 208.13375; found: 208.13321.



methyl 3-(4-bromophenylamino)propanoate (129f)



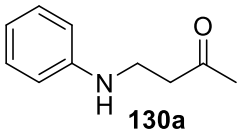
129f

R_f: 0.81 (30% ethyl acetate in hexanes). IR (neat): ν_{max} 3395, 2951, 1731, 1596, 1504, 1195, 815 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.25 (d, J = 7.6 Hz, 2 H), 6.50 (d, J = 7.6 Hz, 2 H), 4.05 (br s, 1 H), 3.70 (s. 3 H), 3.42 (t, J = 4.4 Hz, 2 H), 2.61 (t, J = 4.4 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.8 (C), 146.7 (C), 132.2 (CH), 114.7 (CH), 109.5 (C), 51.9 (CH_3), 39.6 (CH_2), 33.7 (CH_2) ppm. MS (APCI): m/z (%) 258/260 (100) $[M + H]^+$, 184/186 (75). HRMS could not be obtained with the instrumentation available.

General procedure for the addition of anilines to methyl vinyl ketone

Aniline (0.66 mmol) and methyl vinyl ketone (50 μL, 0.6 mmol) were added to deionised water (4 mL) and stirred vigorously for 1 hour. Dichloromethane (10 mL) was added, the phases were separated and the organic phase was dried over Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography.

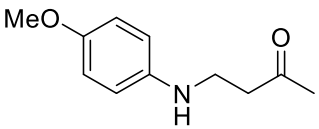
4-(phenylamino)butan-2-one(130a)[87]



130a

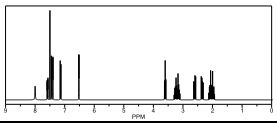
R_f: 0.19 (15% ethyl acetate in hexanes). IR (neat): ν_{max} 3394, 2900, 1708, 1601, 1504, 1168, 749 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.21 (dd, J = 7.4, 8.6 Hz, 2 H), 6.73 (t, J = 7.2 Hz, 1 H), 6.62 (d, J = 1.0, 8.6 Hz, 2 H), 3.98 (br s, 1 H), 3.42 (t, J = 6.2 Hz, 2 H), 2.73 (t, J = 6.2 Hz, 2 H), 2.16 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.1 (C), 147.8 (C), 129.3 (CH), 117.6 (CH), 113.0 (CH), 42.6 (CH_2), 38.4 (CH_2), 30.3 (CH_3) ppm.

4-(4-methoxyphenylamino)-butane-2-one (130b)[87]

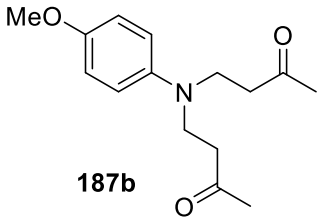


130b

R_f: 0.28 (40% ethyl acetate in hexanes). IR (neat): ν_{max} 3376, 2936, 1708, 1597, 1510, 1233, 820 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.78 (d, J = 8.4 Hz, 2 H), 6.58 (d, J = 8.4 Hz, 2 H), 3.74 (s, 3 H) 3.70 (br s, 1 H), 3.35 (t, J = 5.8 Hz, 2 H), 2.72 (t, J = 5.8 Hz, 2 H), 2.15 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.2 (C), 152.5 (C), 142.0 (C), 115.0 (CH), 114.7 (CH), 55.9 (CH_3), 42.8 (CH_2), 39.6 (CH_2), 30.3 (CH_3) ppm.

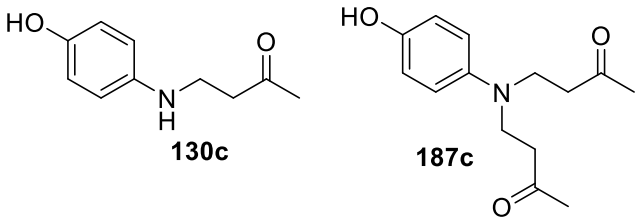


4,4′-(4-methoxyphenylaxanediyl)-dibutan-2-one (187b)[87]



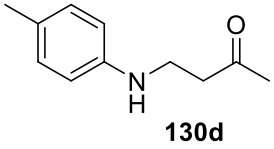
R_f: 0.25 (40% ethyl acetate in hexanes). IR (neat): ν_{max} 2930, 1708, 1597, 1510, 1233, 820 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.84 (d, J = 8.4 Hz, 2 H), 6.72 (d, J = 8.4 Hz, 2 H), 3.76 (s, 3 H), 3.45 (t, J = 6.8 Hz, 4 H), 2.64 (t, J = 6.8 Hz, 4 H), 2.13 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.3 (C), 153.6 (C), 142.3 (C), 117.4 (CH), 115.3 (CH), 56.1 (CH_3), 47.6 (CH_2), 41.7 (CH_2), 30.9 (CH_3) ppm.

4-(4-hydroxyphenylamino)butan-2-one (130c) and **4,4'-(4-hydroxyphenylazanediyl)-dibutan-2-one (187c)**

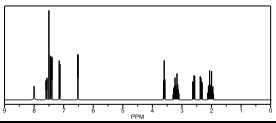


3 : 1 mixture of **130c** and **187c**. R_f: 0.20 (50% ethyl acetate in hexanes). IR (neat): ν_{max} 3347, 1703, 1512, 1219, 823, 725 cm^{-1}. MS (ESI): *m*/*z* (%) 250 (34) $[M + H]^+$, 214 (100), 180 (29) $[M + H]^+$, 122 (15). *4-(4-hydroxyphenylamino)-butan-2-one* (**130c**); ^1H NMR (300 MHz, $CDCl_3$): δ 6.68 (d, J = 6.8 Hz, 2 H), 6.53 (d, J = 6.8 Hz, 2 H), 4.90 (br s, 2 H), 3.32 (t, J = 5.0 Hz, 2 H), 2.69 (t, J = 5.0 Hz, 2 H), 2.15 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.1 (C), 148.4 (C), 141.3 (C), 116.4 (CH), 115.6 (CH), 42.6 (CH_2), 40.1 (CH_2), 30.4 (CH_3). HRMS (ESI): calcd. for $C_{10}H_{14}O_2N$ $[M + H]^+$: 180.10245; found: 180.10191. *4,4'-(4-hydroxyphenylazanediyl)-dibutan-2-one* (**187c**); ^1H NMR (300 MHz, $CDCl_3$): δ 3.40 (t, J = 6.0 Hz, 4 H), 2.61 (t, J = 6.0 Hz, 4 H), 2.11 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.0 (C), 149.0 (C), 141.6 (C), 118.1 (CH), 117.3 (CH), 47.7 (CH_2), 41.4 (CH_2), 30.6 (CH_3). HRMS (ESI): calcd. for $C_{14}H_{19}O_3NNa$ $[M + Na]^+$: 272.12626; found: 272.12572.

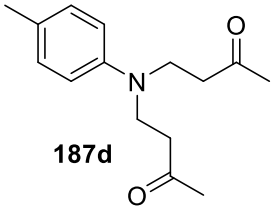
4-(*p*-tolylamino)butan-2-one (130d)[87]



R_f: 0.28 (20% ethyl acetate in hexanes). IR (neat): ν_{max} 3379, 2918, 1708, 1518, 1168, 808 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.01 (d, J = 8.6 Hz, 2 H), 6.56 (d, J = 8.6 Hz, 2 H), 3.64 (br s, 1 H), 3.39 (t, J = 4.8 Hz, 2 H), 2.72 (t, J = 4.8 Hz, 2 H), 2.26 (s, 3 H), 2.16 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.1 (C), 145.4 (C), 129.8 (CH), 126.8 (C), 113.3 (CH), 42.6 (CH_2), 38.8 (CH_2), 30.2 (CH_3), 20.3 (CH_3) ppm.



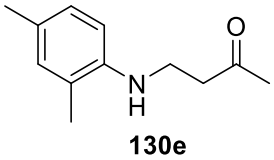
4,4'-(*p*-tolylazanediyl)dibutan-2-one (187d)[87]



187d

R_f: 0.25 (20% ethyl acetate in hexanes). IR (neat): ν_{max} 2918, 1708, 1518, 1168, 808 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.05 (d, J = 8.0 Hz, 2 H), 6.61 (d, J = 8.0 Hz, 2 H), 3.54 (t, J = 6.2 Hz, 4 H), 2.69 (t, J = 6.2 Hz, 4 H), 2.25 (s, 3 H), 2.14 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.0 (C), 145.1 (C), 130.1 (CH), 126.8 (C), 113.8 (CH), 46.3 (CH_2), 41.3 (CH_2), 30.7 (CH_3), 20.3 (CH_3) ppm.

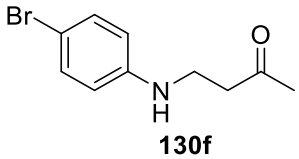
4-(2,4-dimethylphenylamino)butan-2-one (130e)



130e

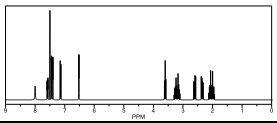
R_f: 0.34 (20% ethyl acetate in hexanes). IR (neat): ν_{max} 3412, 2917, 1709, 1512, 1167, 804 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.99 (d, J = 8.2 Hz, 1 H), 6.94 (s, 1 H), 6.60 (d, J = 8.2 Hz, 1 H), 3.76 (br s, 1 H), 3.48 (t, J = 6.0 Hz, 2 H), 2.80 (t, J = 6.0 Hz, 2 H), 2.29 (s, 3 H), 2.20 (s, 3 H), 2.15 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.2 (C), 143.4 (C), 131.1 (CH), 127.3 (CH), 126.3 (C), 122.7 (C), 110.0 (CH), 42.6 (CH_2), 38.7 (CH_2), 30.2 (CH_3), 20.3 (CH_3), 17.3 (CH_3) ppm. MS (ESI): m/z (%) 192 (100) $[M + H]^+$, 88 (75). HRMS (ESI): calcd for $C_{12}H_{18}ON$ $[M + H]^+$: 192.13884; found: 192.13829.

4-(4-bromophenylamino)-butan-2-one (130f)

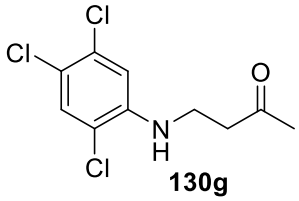


130f

R_f: 0.35 (15% ethyl acetate in hexanes). IR (neat): ν_{max} 3380, 2892, 1702, 1597, 1503, 1313, 814 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.20 (d, J = 9.2 Hz, 2 H), 6.44 (d, J = 9.2 Hz, 2 H), 4.02 (br s, 1 H), 3.31 (t, J = 5.8 Hz, 2 H), 2.68 (t, J = 5.8 Hz, 2 H), 2.12 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.3 (C), 148.5 (C), 141.5 (C), 116.4 (CH), 115.3 (CH), 51.9 (CH_3), 40.6 (CH_2), 33.8 (CH_2) ppm. MS (APCI): m/z (%) 242/244 (100) $[M + H]^+$. HRMS (ESI): calcd. for $C_{10}H_{12}ONBrNa$ $[M + Na]^+$: 242.01750/244.01546; found: 242.01762/244.01557.



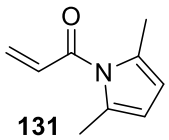
4-(2,4,5-trichlorophenylamino)butan-2-one (130g)



130g

R_f: 0.41 (20% ethyl acetate in hexanes). mp: 71.3–71.8°C. IR (neat): ν_{max} 3382, 2916, 1715, 1596, 1510, 1379 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.31 (s, 1 H), 6.70 (s, 1 H), 4.64 (br s, 1 H), 3.43 (t, J = 5.8 Hz, 2 H), 2.78 (t, J = 5.8 Hz, 2 H), 2.20 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.1 (C), 143.3 (C), 131.8 (C), 130.2 (CH), 119.5 (C), 118.2 (C), 111.9 (CH), 42.3 (CH_2), 38.2 (CH_2), 30.4 (CH_3) ppm. MS (APCI): m/z (%) 265/267 (45) $[M + H]^+$, 201/203 (100). HRMS could not be obtained with the instrumentation available.

***N*-acryloyl-(2,5-dimethyl-pyrrole) (131)**

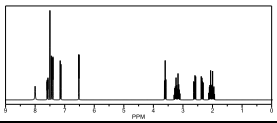


131

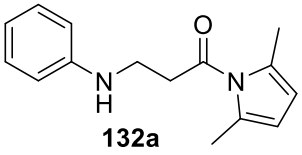
Acrylamide (500 mg, 7.03 mmol), 2,5-hexanedione (180 μL, 1.53 mmol) and *p*-toluenesulfonic acid (0.23 mmol, 39 mg) were dissolved in toluene (60 mL) and heated to reflux for 24 hours under continuous azeotropic distillation. The solution was washed with water (3 × 50 mL), dried over Na_2SO_4 and the solvent was removed. The residue was purified by column chromatography (5% ether in hexanes) to give the *title compound* as a bright yellow oil (125 mg, 55%). R_f: 0.69 (10% ethyl acetate in hexanes). IR (neat): ν_{max} 2927, 1693, 1619, 1401, 1363, 1258, 976, 773 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.69 (dd, J = 10.0, 16.8 Hz, 1 H), 6.45 (dd, J = 1.6, 16.8 Hz, 1 H), 5.94 (dd, J = 1.4, 10.2 Hz, 1 H), 5.84 (s, 2 H), 2.34 (s, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.1 (C), 132.2 (CH), 131.3 (CH), 130.1 (C), 111.2 (CH), 15.7 (CH_3) ppm. MS (APCI): m/z (%) 149 (100) $[M + H]^+$, 94 (62). HRMS could not be obtained with the instrumentation available.

General procedure for the addition of anilines to *N*-acryloyl-(2,5-dimethyl-pyrrole)

Aniline (0.29 mmol) and *N*-acryloyl-(2,5-dimethyl-pyrrole) (40 mg, 0.27 mmol) were added to deionised water (4 mL) and stirred vigorously for 4 hours. Dichloromethane (10 mL) was added, the phases were separated and the organic phase was dried over Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography.



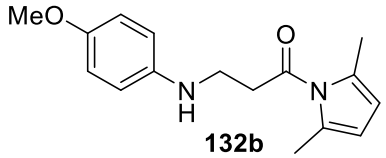
***N*-(3-(2,5-dimethyl-1*H*-pyrrol-1-yl)-3-oxo-prop-1-yl)-aniline (132a)**



132a

R_f: 0.21 (5% ethyl acetate in hexanes). IR (neat): ν_{max} 3403, 2925, 1705, 1602, 1386, 1242, 750 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.16 (t, J = 9.0 Hz, 2 H), 6.70 (t, J = 6.2 Hz, 1 H), 6.61 (d, J = 7.8 Hz, 2 H), 5.81 (s, 2 H), 4.12 (br s, 1 H), 3.58 (t, J = 6.8 Hz, 2 H), 3.04 (t, J = 6.8 Hz, 2 H), 2.37 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5 (C), 147.6 (C), 130.7 (C), 129.5 (CH), 117.9 (CH), 113.2 (CH), 111.9 (CH), 39.5 (CH_2), 38.2 (CH_2), 17.1 (CH_3) ppm. MS (APCI): *m*/*z* (%) 242 (100) $[M + H]^+$, 159 (44), 120 (16), 108 (20). HRMS (ESI): calcd. for $C_{15}H_{19}ON_2$ $[M + H]^+$: 243.14974; found: 243.14919.

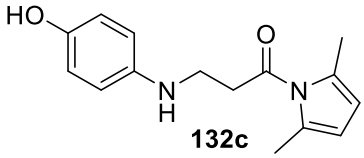
***N*-(3-(2,5-dimethyl-1*H*-pyrrol-1-yl)-3-oxo-prop-1-yl)-*p*-anisidine (132b)**



132b

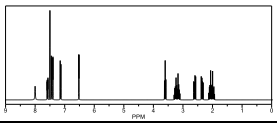
R_f: 0.18 (10% ethyl acetate in hexanes). IR (neat): ν_{max} 3397, 2929, 1705, 1513, 1331, 1239 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.79 (d, J = 9.2 Hz, 2 H), 6.63 (d, J = 9.2 Hz, 2 H), 5.83 (s, 2 H), 3.75 (s, 3 H), 3.55 (t, J = 6.0 Hz, 2 H), 3.06 (t, J = 6.0 Hz, 2 H), 2.40 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6 (C), 152.6 (C), 141.8 (C), 130.6 (C), 115.1 (CH), 114.8 (CH), 111.9 (CH), 55.0 (CH_3), 40.7 (CH_2), 38.3 (CH_2), 17.1 (CH_3) ppm. MS (APCI): *m*/*z* (%) 273 (70) $[M + H]^+$, 136 (100). HRMS (ESI): calcd. for $C_{16}H_{21}O_2N_2$ $[M + H]^+$: 273.16030; found: 273.15975.

***N*-(3-(2,5-dimethyl-1*H*-pyrrol-1-yl)-3-oxo-prop-1-yl)-4-hydroxy-aniline (132c)**

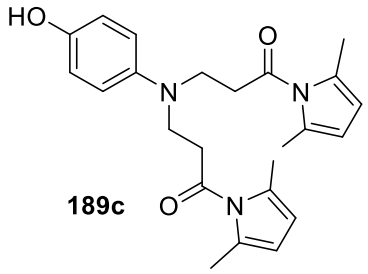


132c

R_f: 0.33 (50% ethyl acetate in hexanes). IR (neat): ν_{max} 3376, 2924, 1703, 1542, 1366, 1242 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.68 (d, J = 8.6 Hz, 2 H), 6.57 (d, J = 8.6 Hz, 2 H), 5.83 (s, 2 H), 4.69 (br s, 2 H), 3.52 (t, J = 6.2 Hz, 2 H), 3.04 (t, J = 6.2 Hz, 2 H), 2.39 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.8 (C), 148.7 (C), 141.2 (C), 130.7 (C), 116.5 (CH), 115.5 (CH), 112.0 (CH), 41.1 (CH_2), 38.0 (CH_2), 17.1 (CH_3) ppm. MS (APCI): *m*/*z* (%) 259 (100) $[M + H]^+$, 162 (15), 122 (24). HRMS (ESI): calcd. for $C_{15}H_{19}O_2N_2$ $[M + H]^+$: 259.14465; found: 259.14520.



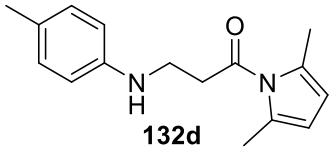
***N,N'*-di-(3-(2,5-dimethyl-1*H*-pyrrol-1-yl)-3-oxo-prop-1-yl)-4-hydroxy-aniline (189c)**



189c

R_f: 0.70 (50% ethyl acetate in hexanes). mp: 136.4 °C. IR (neat): ν_{max} 2987, 1699, 1365, 1241, 777 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.72 (m, 4 H), 5.81 (s, 4 H), 4.76 (br s, 1 H), 3.65 (t, J = 5.8 Hz, 4 H), 2.99 (t, J = 5.8 Hz, 4 H), 2.34 (s, 12 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5 (C), 149.1 (C), 141.8 (C), 130.5 (C), 117.6 (CH), 116.5 (CH), 111.8 (CH), 48.9 (CH_2), 36.9 (CH_2), 16.8 (CH_3) ppm. MS (APCI): m/z (%) 408 (71) $[M + H]^+$, 271 (100), 176 (19). HRMS (ESI): calcd. for $C_{24}H_{30}O_3N_3$ $[M + H]^+$: 408.22872; found: 408.22817.

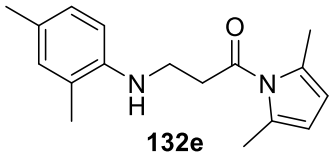
***N*-(3-(2,5-dimethyl-1*H*-pyrrol-1-yl)-3-oxo-prop-1-yl)-*p*-toluidine (132d)**



132d

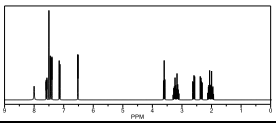
R_f: 0.17 (5% ethyl acetate in hexanes). IR (neat): ν_{max} 3401, 2920, 1703, 1542, 1364, 1255, 980 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.05 (d, J = 9.2 Hz, 2 H), 6.60 (d, J = 9.2 Hz, 2 H), 5.87 (s, 2 H), 3.99 (br s, 1 H), 3.61 (t, J = 5.8 Hz, 2 H), 3.08 (t, J = 5.8 Hz, 2 H), 2.43 (6 H, s), 2.28 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5 (C), 145.3 (C), 130.6 (C), 129.9 (CH), 127.1 (C), 113.4 (CH), 111.8 (CH), 39.8 (CH_2), 38.2 (CH_2), 20.4 (CH_3), 17.0 (CH_3) ppm. MS (APCI): m/z (%) 257 (100) $[M + H]^+$, 173 (12), 138 (29), 120 (100). HRMS (ESI): calcd. for $C_{16}H_{21}ON_2$ $[M + H]^+$: 257.16539; found: 257.16484.

***N*-(3-(2,5-dimethyl-1*H*-pyrrol-1-yl)-3-oxo-prop-1-yl)-2,4-xylidine (132e)**



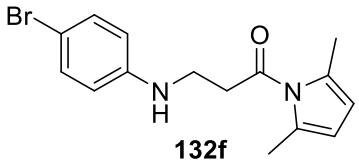
132e

R_f: 0.39 (10% ethyl acetate in hexanes). IR (neat): ν_{max} 3408, 2921, 1704, 1619, 1386, 1245 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.92 (d, J = 7.8 Hz, 1 H), 6.87 (s, 1 H), 6.56 (d, J = 7.8 Hz, 1 H), 5.81 (s, 2 H), 3.61 (t, J = 5.8 Hz, 2 H), 3.04 (t, J = 5.8 Hz, 2 H), 2.38 (s, 6 H), 2.21 (s, 3 H), 2.08 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.7 (C), 143.2 (C), 131.4 (CH), 130.6 (C), 127.5 (CH), 126.6 (C), 122.9 (C), 111.9 (CH), 110.0 (CH), 39.7 (CH_2), 38.2 (CH_2), 20.4 (CH_3), 17.5 (CH_3), 17.0 (CH_3) ppm. MS (APCI): m/z (%) 271 (100) $[M + H]^+$, 213 (19), 174 (25), 134 (87). HRMS (ESI): calcd. for $C_{17}H_{23}ON_2$ $[M + H]^+$: 271.18104; found:



271.18049.

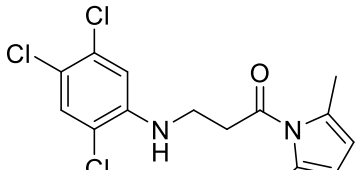
_N_-(3-(2,5-dimethyl-1_H_-pyrrol-1-yl)-3-oxo-prop-1-yl)-4-bromo-aniline (132f)



132f

R_f: 0.14 (5% ethyl acetate in hexanes). IR (neat): ν_{max} 3401, 2924, 1702, 1594, 1497, 1385, 1256, 813; cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.27 (d, J = 9.0 Hz, 2 H), 6.52 (d, J = 9.0 Hz, 2 H), 5.84 (s, 2 H), 4.21 (br s, 1 H), 3.57 (t, J = 6.0 Hz, 2 H), 3.05 (t, J = 6.0 Hz, 2 H), 2.40 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.3 (C), 146.6 (C), 132.2 (CH), 130.7 (C), 114.7 (CH), 112.1 (CH), 109.5 (C), 39.5 (CH_2), 38.0 (CH_2), 17.1 (CH_3) ppm. MS (APCI): m/z (%) 320/322 (65) $[M + H]^+$, 184/186 (100), 138 (70), 108 (11). HRMS (ESI): calcd. for $C_{15}H_{18}ON_2Br$ $[M + H]^+$: 321.06025/323.05820; found: 321.05996/323.0596.

_N_-(3-(2,5-dimethyl-1_H_-pyrrol-1-yl)-3-oxo-prop-1-yl)-2,4,5-trichloro-aniline (132g)

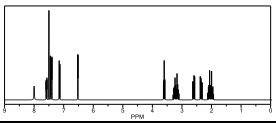


132g

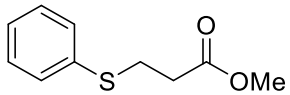
R_f: 0.39 (10% ethyl acetate in hexanes). mp: 103.0 – 105.2°C. IR (neat): ν_{max} 3408, 2921, 1704, 1619, 1386, 1245 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.32 (s, 1 H), 6.75 (s, 1 H), 5.85 (s, 2 H), 4.82 (br s, 1 H), 3.63 (q, J = 6.0 Hz, 2 H), 3.09 (t, J = 6.0 Hz, 2 H), 2.41 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.7 (C), 143.3 (C), 131.9 (C), 130.8 (C), 130.3 (CH), 119.7 (C), 118.3 (C), 112.3 (CH), 111.9 (CH), 39.2 (CH_2), 38.0 (CH_2), 17.2 (CH_3) ppm. MS (APCI): m/z (%) 345/347 (8) $[M + H]^+$, 208/210 (100), 137 (22), 96 (33), 120 (11). HRMS (ESI): calcd. for $C_{15}H_{16}ON_2Cl_3$ $[M + H]^+$: 345.02500/345.02205; found: 345.03282/347.02987.

General procedure for addition of thiophenols to Michael acceptors

Thiophenol (0.66 mmol) and Michael acceptor (0.6 mmol) were added to deionised water (4 mL) and stirred vigorously for 1 hour. Dichloromethane (10 mL) was added, the phases were separated and the organic phase was dried over Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography.



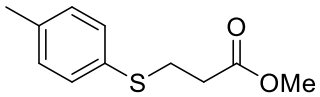
methyl 3-(phenylthio)propanoate (192a)[233]



192a

R_f: 0.37 (10% ethyl acetate in hexanes). IR (neat): ν_{max} 2951, 1733, 1481, 1282, 893 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.34-7.16 (m, 5 H), 3.63 (s, 3 H), 3.12 (t, J = 7.4 Hz, 2 H), 2.59 (t, J = 7.4 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.0 (C), 135.2 (C), 130.0 (CH), 129.0 (CH), 126.5 (CH), 51.7 (CH_3), 34.1 (CH_2), 29.0 (CH_2) ppm.

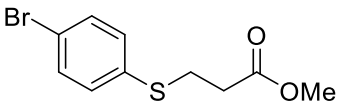
methyl 3-(*p*-tolylthio)propanoate (192b)[233]



192b

R_f: 0.39 (10% ethyl acetate in hexanes). IR (neat): ν_{max} 2951, 1733, 1435, 1282, 804 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.27 (d, J = 8.0 Hz, 2 H), 7.09 (d, J = 8.0 Hz, 2 H), 3.65 (s, 3 H), 3.09 (t, J = 7.4 Hz, 2 H), 2.58 (t, J = 7.4 Hz, 2 H), 2.30 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.3 (C), 136.9 (C), 131.4 (C), 131.1 (CH), 129.9 (CH), 51.8 (CH_3), 34.4 (CH_2), 29.9 (CH_2), 21.1 (CH_3) ppm.

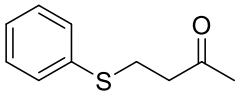
methyl 3-(4-bromophenylthio)propanoate (192c)



192c

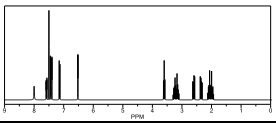
mp: 49.6 °C. IR (neat): ν_{max} 2948, 1728, 1366, 1176, 809 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.25 (d, J = 8.6 Hz, 2 H), 7.06 (d, J = 8.6 Hz, 2 H), 3.52 (s, 3 H), 2.98 (t, J = 7.2 Hz, 2 H), 2.45 (t, J = 7.2 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.0 (C), 134.6 (C), 132.1 (CH), 131.6 (CH), 120.5 (CH), 51.9 (CH_3), 34.1 (CH_2), 29.1 (CH_2) ppm. MS (APCI): m/z (%) 273/275 (15) $[M + H]^+$, 214/216 (100), 188/186 (37), 149 (24), 119 (24). HRMS (ESI): calcd. for $C_{10}H_{11}O_2SBrNa$ $[M + Na]^+$: 296.95608/298.95404; found: 296.95581/298.95380.

4-(phenylthio)butan-2-one (191a)[233]



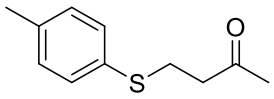
191a

R_f: 0.27 (10% ethyl acetate in hexanes). IR (neat): ν_{max} 2951, 1712, 1480, 1359, 1158, 737 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.33-7.14 (m, 5 H), 3.10 (t, J = 7.0 Hz, 2 H), 2.72 (t, J = 7.0 Hz, 2 H), 2.10 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.4 (C), 135.7 (C), 129.3 (CH), 128.9 (CH), 126.2 (CH), 42.9 (CH_2),



29.9 (CH_3), 27.3 (CH_2) ppm.

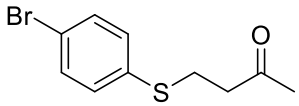
4-(*p*-tolylthio)butan-2-one (191b)[233]



191b

R_f: 0.33 (20% ethyl acetate in hexanes). IR (neat): ν_{max} 2925, 1716, 1493, 1361, 806 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.27 (d, J = 8.0 Hz, 2 H), 7.12 (d, J = 8.0 Hz, 2 H), 3.09 (t, J = 7.2 Hz, 2 H), 2.73 (t, J = 7.2 Hz, 2 H), 2.33 (s, 3 H), 2.14 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.8 (C), 136.6 (C), 131.9 (C), 130.5 (CH), 129.9 (CH), 43.3 (CH_2), 30.1 (CH_3), 28.3 (CH_2), 21.1 (CH_3) ppm.

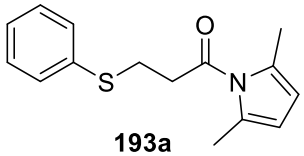
4-(4-bromophenylthio)butan-2-one (191c)



191c

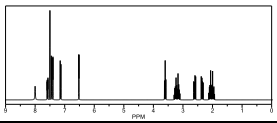
R_f: 0.25 (20% ethyl acetate in hexanes). mp: 62.1°C. IR (neat): ν_{max} 2925, 1712, 1472, 1092, 906, 728; cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.39 (d, J = 8.6 Hz, 2 H), 7.17 (d, J = 8.6 Hz, 2 H), 3.10 (t, J = 7.2 Hz, 2 H), 2.74 (t, J = 7.2 Hz, 2 H), 2.14 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.2 (C), 135.1 (C), 132.0 (CH), 130.9 (CH), 120.1 (C), 42.8 (CH_2), 30.1 (CH_3), 27.5 (CH_2) ppm. MS (APCI): m/z (%) 273/275 (100) $[M + O]^+$, 201/203 (63), 162/164 (17), 122 (24). HRMS (ESI): calcd. for $C_{10}H_{11}O_2SBrNa$ $[M + O + Na]^+$: 296.95608/298.95404; found: 296.95553/298.95372.

***S*-(3-(2,5-dimethyl-1*H*-pyrrol-1-yl)-3-oxo-prop-1-yl)-*p*-thiophenol (193a)**

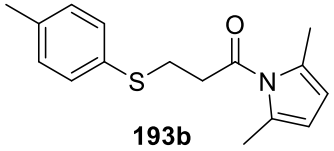


193a

R_f: 0.40 (5% ethyl acetate in hexanes). mp: 53.2 – 54.0°C. IR (neat): ν_{max} 2928, 1709, 1367, 1265, 783 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.37-7.20 (m, 5 H), 5.81 (s, 2 H), 3.29 (t, J = 7.0 Hz, 2 H), 3.08 (t, J = 7.0 Hz, 2 H), 2.34 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.8 (C), 135.3 (C), 130.6 (C), 130.4 (CH), 129.2 (CH), 126.9 (CH), 111.9 (CH), 38.9 (CH_2), 29.5 (CH_2), 16.9 (CH_3) ppm. MS (APCI): m/z (%) 259 (100) $[M]^+$, 232 (95), 187 (39), 96 (30). HRMS (ESI): calcd. for $C_{15}H_{18}ONSNa$ $[M + Na]^+$: 282.09285; found: 282.09231.



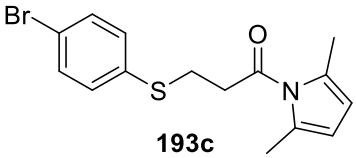
_S_-(3-(2,5-dimethyl-1_H_-pyrrol-1-yl)-3-oxo-prop-1-yl)-_p_-thiocresol (193b)



193b

R_f: 0.46 (5% ethyl acetate in hexanes). mp: 74.7–75.1˚C. IR (neat): ν_{max} 2921, 1698, 1311 1276, 793 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.28 (d, J = 7.8 Hz, 2 H), 7.10 (d, J = 7.8 Hz, 2 H), 5.80 (s, 2 H), 3.26 (t, J = 6.0 Hz, 2 H), 3.03 (t, J = 6.0 Hz, 2 H), 2.33 (s, 6 H), 2.31 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.9 (C), 137.2 (C), 131.4 (C), 131.3 (CH), 130.6 (C), 130.0 (CH), 111.8 (CH), 39.0 (CH_2), 30.2 (CH_2), 21.1 (CH_3), 16.9 (CH_3) ppm. MS (APCI): m/z (%) 273 (100) $[M]^+$, 179 (41), 150 (24), 122 (16), 96 (10). HRMS (ESI): calcd. for $C_{16}H_{20}ONS$ $[M + H]^+$: 274.11873; found: 274.12601.

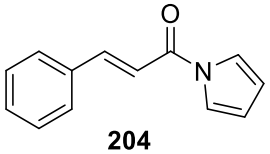
_S_-(3-(2,5-dimethyl-1_H_-pyrrol-1-yl)-3-oxo-prop-1-yl)-4-bromo-thiophenol (193c)



193c

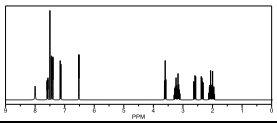
R_f: 0.41 (5% ethyl acetate in hexanes). mp: 68.5–69.0 ˚C. IR (neat): ν_{max} 2924, 1698, 1389 1278, 795 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.40 (d, J = 8.4 Hz, 2 H), 7.20 (d, J = 8.4 Hz, 2 H), 5.81 (s, 2 H), 3.27 (t, J = 6.8 Hz, 2 H), 3.05 (t, J = 6.8 Hz, 2 H), 2.34 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.5 (C), 134.7 (C), 132.2 (CH), 131.7 (CH), 130.6 (C), 120.7 (C), 112.0 (CH), 38.6 (CH_2), 29.5 (CH_2), 16.9 (CH_3) ppm. MS (APCI): m/z (%) 337/339 (100) $[M]^+$, 215/217 (62), 201/203 (20), 150 (18), 112 (18). HRMS (ESI): calcd. for $C_{15}H_{17}ONSBr$ $[M + H]^+$: 338.02142/340.01938; found: 338.02089/340.01878.

_N_-cinnamoylpyrrole (204)[93]

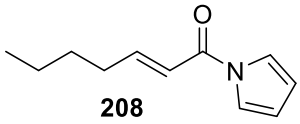


204

Cinnamamide (1.0 g, 5.08 mmol) and 2,5-diethoxytetrahydrofuran (1.22 g, 7.62 mmol) were dissolved in acetic acid (15 mL) and the solution was heated to 100˚C for 2 hours. The reaction was cooled to room temperature and poured onto ether (100 mL). The solution was washed with brine (3 × 50 mL) then saturated aqueous sodium bicarbonate (3 × 50 mL) and dried over Na_2SO_4. The solvent was removed and the residue was purified by column chromatography (5% ethyl acetate in hexanes) to give the *title compound* as a colourless solid (674 mg, 59%). ^1H NMR (300 MHz, $CDCl_3$): δ 8.00 (d, J = 15.3 Hz, 1 H), 7.63 (m, 2 H), 7.48-7.43 (m, 5 H), 7.15 (d, J = 15.3 Hz, 1 H), 6.37 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.1, 147.7, 134.4, 131.1, 129.2, 128.6, 119.4, 115.9, 113.5 ppm.



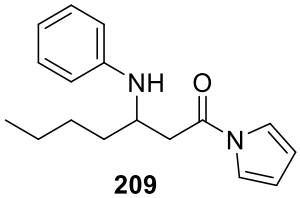
1-(1*H*-pyrrol-1-yl)non-2-en-1-one (208)



208

Pentanal (70 mg, 0.81 mmol) and phosphorane **153** (300 mg, 0.81 mmol) were dissolved in toluene (5 mL) and the solution was heated to reflux for 48 hours. The solvent was then evaporated and the crude product was purified by flash column chromatography (5% ethyl acetate in hexanes) to give the *title compound* as a colourless oil (54 mg, 38%). R_f: 0.54 (20% ethyl acetate in hexanes). IR (neat): ν_{max} 2929, 1697, 1639, 1467, 1350, 1290, 1264, 1119, 740 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.38 (m, 2 H), 7.33–7.23 (m, 1 H), 6.47 (dt, J = 15.0, 1.5 Hz, 1 H), 6.24 (m, 2 H), 2.26 (qd, J = 7.2 0.9 Hz, 2 H), 1.47-1.27 (m, 4 H), 0.86 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.0, 153.1, 119.5, 119.4, 113.3, 32.7, 30.3, 22.4, 14.0 ppm. MS (APCI): m/z (%) 178 (100) $[M + H]^+$. HRMS (ESI): calcd. for $C_{11}H_{15}NONa$ $[M + Na]^+$: 200.10459; found: 200.10464.

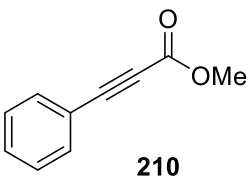
3-(phenylamino)-1-(1*H*-pyrrol-1-yl)heptan-1-one (209)



209

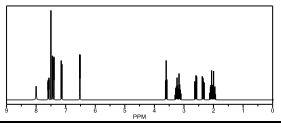
Aniline (21 mg, 0.23 mmol) and *N*-acylpyrrole **208** (40 mg, 0.23 mmol) were added to deionised water (4 mL) and heated to 65°C for 24 hours with vigorous stirring. Dichloromethane (10 mL) was added, the phases were separated and the organic phase was dried over Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography (10% ethyl acetate in hexanes) to give the *title compound* as a colourless oil (13 mg, 28%). IR (neat): ν_{max} 3393, 2929, 1708, 1601, 1505, 1468, 1317, 1264, 1072, 742 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.27 (m, 2 H), 7.17 (m, 2 H), 6.74-6.63 (m, 3 H) 6.28 (m, 2 H), 4.05 (m, 2 H), 3.13 (dd, J = 4.2, 16.2 Hz, 1 H) 2.97 (dd, J = 6.6, 16.2 Hz, 1 H), 1.75-1.26 (m, 5 H), 0.90 (t, J = 6.0 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.2, 146.9, 129.6, 119.1, 118.0, 113.6, 113.4, 50.4, 38.9, 34.6, 28.6, 22.7, 14.1 ppm. MS (ESI): m/z (%) 271 (100) $[M + H]^+$, 162 (35). HRMS (ESI): calcd. for $C_{17}H_{22}N_2ONa$ $[M + Na]^+$: 293.16243; found: 293.16246.

methyl 3-phenylpropiolate (210)[125]



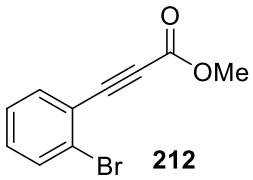
210

Methyl 3-phenylpropiolate was obtained using the procedure published by Ferreira.[125] ^1H NMR (300



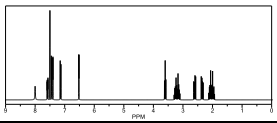
MHz, $CDCl_3$): δ 7.60-7.33 (m, 5 H), 3.84 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.3, 132.8, 130.8, 128.4, 128.6, 96.3, 80.3, 52.4 ppm.

methyl 3-(2-bromophenyl)propiolate (212)[234]

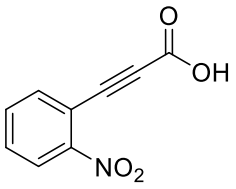


212

2-Bromobenzaldehyde (1.84 g, 10.0 mmol) and ethyl (triphenylphosphoranylidene)acetate (3.48 g, 10.0 mmol) were dissolved in dichloromethane (10 mL) and stirred at room temperature for 24 hours. The solvent was evaporated and the residue was purified by column chromatography (10% ethyl acetate in hexanes) to give ethyl 3-(2-bromophenyl)acrylate (2.41 g, 10.0 mmol) as a mixture of isomers (4/1; *E/Z*).[235] ^1H NMR (300 MHz, $CDCl_3$): δ 8.02 (d, J = 15.9 Hz, 1 H), 7.57-7.43 (m, 2.7 H), 7.30-7.03 (m, 3.2 H), 7.05 (d, J = 12.0 Hz, 0.25 H), 6.35 (d, J = 15.9 Hz, 1 H), 6.03 (d, J = 12.0 Hz, 0.25 H), 4.27 (q, J = 6.9 Hz, 2 H), 4.07 (q, J = 7.2 Hz, 0.5 H), 1.32 (t, J = 6.9 Hz, 3 H), 1.14 (t, J = 7.2 Hz, 0.75 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.9, 142.5, 134.5, 133.4, 132.2, 131.2, 130.8, 129.9, 127.8, 127.7, 126.6, 125.3, 123.1, 121.8, 121.1, 60.7, 60.3, 14.3, 14.0 ppm. Ethyl 3-(2-bromophenyl)acrylate (500 mg, 1.97 mmol) was dissolved in chloroform (5 mL) and bromine (467 mg, 9.85 mmol) was added dropwise. After completion of the addition the mixture was heated to reflux for 2 hours. The reaction mixture was cooled to room temperature and saturate aqueous sodium sulfite solution (10 mL) was added. The phases were separated and the organic phase was washed with water (10 mL) and brine (10 mL) then solvent was evaporated to give ethyl 2,3-dibromo-3-(2-bromophenyl)propanoate as a colourless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.57 (m, 1 H), 7.49 (m, 1 H), 7.35 (m, 1 H), 7.18 (M, 1 H), 5.91 (br s, 1 H), 4.85 (br s, 1 H), 4.34 (q, J = 6.9 Hz, 2 H), 1.35 (t, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.5, 137.1, 133.5, 130.6, 128.8, 128.4, 124.6, 62.9, 48.3, 46.1, 14.0 ppm. The crude 2,3-dibromo-3-(2-bromophenyl)propanoate (600 mg) was dissolved in sodium hydroxide solution (10% w/w, 8 mL) at 0°C. The solution was stirred for 8 hours, being allowed to warm to room temperature. Hydrochloric acid (1 M, 8 mL) was added followed by ethyl acetate (30 mL), the phases were separated, the organic phase was dried over Na_2SO_4 and the solvent was evaporated. The residue was dissolved in methanol then acetyl chloride (500 μL) was added. The solution was stirred for 16 hours then the solvent was removed by evaporation. The crude product was purified by column chromatography (5% ethyl acetate in hexanes) to give the *title compound* as a colourless oil (324 mg, 68%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.63-7.58 (m, 2 H), 7.32-7.26 (m, 2 H), 3.86 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.2, 140.7, 134.9, 132.8, 131.8, 127.3, 126.4, 84.2, 84.0, 53.0 ppm. Spectroscopic data matched that previously reported.[234]

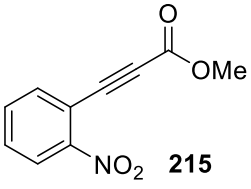


3-(2-nitrophenyl)propiolic acid



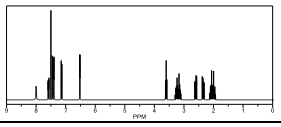
o-Nitrocinnamic acid (10.0 g, 51.7 mmol) was dissolved in acetic acid (40 mL) then bromine (3.9 mL, 75 mmol) was added dropwise. After completion of the addition the mixture was heated to reflux for 30 minutes. The reaction was then cooled to room temperature and poured onto water (250 mL). The precipitated product was collected by filtration and air dried to give 2,3-dibromo-3-(2-nitrophenyl)propanoic acid as a pale yellow solid (18.0 g, 51.5 mmol). mp: 187.0-187.8 °C. IR (neat): ν_{max} 2860, 1722, 1516, 1344, 1268 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 14.05 (br s, 1 H), 8.12 (d, J = 7.8 Hz, 1 H), 7.97 (d, J = 8.1 Hz, 1 H), 7.81 (t, J = 7.5 Hz, 1 H), 7.65 (t, J = 7.5 Hz, 1 H), 5.82 (d, J = 11.7 Hz, 1 H), 5.43 (d, J = 11.7 Hz, 1 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.6, 148.2, 133.9, 131.4, 130.5, 130.3, 124.4, 46.2, 43.2 ppm. MS (ESI): m/z (%) 707/705 (100) [M_2 - H]. HRMS (ESI): calcd. for $C_9H_7NO_4Br_2Na$ [M + Na]$^+$: 375.86136; found: 375.86150. The dibromide was dissolved in sodium hydroxide solution (10% w/w, 150 mL) at 0°C. The reaction mixture was stirred for sixteen hours, being allowed to warm to room temperature. Hydrochloric acid (1 M, 75 mL) was added dropwise until the solution became acidic. The precipitate was collected by filtration then dissolved in ethyl acetate (100 mL) and washed with brine (3 × 50 mL). The organic phase was dried over Na_2SO_4 and the solvent was evaporated to give 3-(2-nitrophenyl)propiolic acid (8.40 g, 85%) as a brown solid. mp: 154.9 - 155.4 °C. IR (neat): ν_{max} 2986, 2227, 1718, 1520, 1341, 1208 cm^{-1}. ^1H NMR (300 MHz, MeOD): δ 8.05 (d, J = 7.8 Hz, 1 H), 7.72-7.56 (m, 3 H) ppm. ^{13}C NMR (75 MHz, MeOD): δ 155.9, 151.3, 136.7, 134.6, 132.4, 126.0, 116.2, 87.8, 81.0 ppm. MS (ESI): m/z (%) 190 (100) [M - H]. HRMS (ESI): calcd. for $C_9H_5NO_4Na$ [M + Na]$^+$: 214.01108; found: 214.01094.

methyl 3-(2-nitrophenyl)propiolate (215)[127]



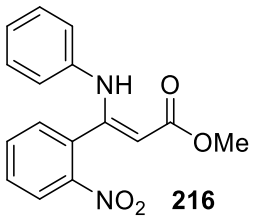
215

3-(2-nitrophenyl)Propiolic acid (1.00 g, 5.24 mmol) was dissolved in methanol (200 mL) and acetyl chloride (500 μL) was added. The solution was stirred for 48 hours then ethyl acetate (200 mL) and brine (100 mL) were added. The phases were separated and the organic phase was washed and saturated aqueous sodium bicarbonate (3 × 100 mL). The organic phase was dried over Na_2SO_4 and the solvent was evaporated to give the *title compound* (962 mg, 90%) as a brown solid. ^1H NMR (300 MHz,



$CDCl_3$): δ 8.15 (dd, J = 1.2, 7.8 Hz, 1 H), 7.76 (d, J = 7.8 Hz, 1 H), 7.69-7.58 (m, 2 H), 3.85 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.9 (C), 150.0 (C), 135.8 (CH), 133.4 (CH), 131.1 (CH), 125.1 (CH), 115.4 (C), 86.5 (C), 80.9 (C), 53.1 (CH_3) ppm. Spectroscopic data matched that previously reported.[127]

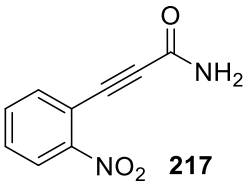
methyl (*Z*)-3-(2-nitrophenyl)-3-(phenylamino)acrylate (216)



216

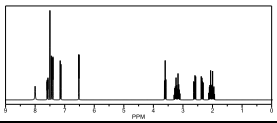
Methyl 3-(2-nitrophenyl)propiolate (20 mg, 67 μmol) and aniline (10 mg, 107 μmol) were added to deionised water (4 mL) and stirred vigorously at 50 ˚C for 24 hours. Dichloromethane (10 mL) was added, the phases were separated and the organic phase was dried over Na_2SO_4 then the solvent was removed by evaporation. The crude product was purified by column chromatography (10% ethyl acetate in hexanes) to give the *title compound* as a yellow oil (18 mg, 61%). R_f: 0.10 (10% ethyl acetate in hexanes). IR (neat): ν_{max} 3402, 2926, 1751, 1725, 1459, 1213, 811 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.74-7.70 (m, 2 H), 7.33 (dd, J = 8.4, 0.9 Hz, 1 H), 7.18 (dd, J = 0.9, 7.5, Hz, 1 H), 7.07 (dd, J = 7.5, 0.8 Hz, 2 H), 6.75 (dd, J = 0.8, 7.2 Hz, 1 H), 6.47 (dd, J = 7.5, 0.9 Hz, 2 H), 6.23 (br s, 1 H), 5.69 (s, 1 H), 3.73 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.5, 159.6, 145.2, 142.5, 138.0, 129.2, 123.8, 122.8, 119.6, 116.1, 114.8, 114.3, 87.7, 53.7 ppm. MS (ESI): m/z (%) 321 (100) $[M + Na]^+$. HRMS (ESI): calcd. for $C_{16}H_{14}N_2O_4Na$ $[M + Na]^+$: 321.08513; found: 321.08520.

3-(2-nitrophenyl)propiolamide (217)



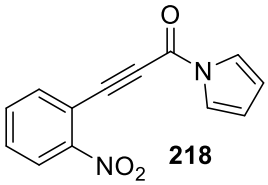
217

Methyl 3-(2-nitrophenyl)propiolate (10.0 g, 48.8 mmol) was dissolved in ether (30 mL) and aqueous ammonia (33%, 200 mL) was added. The biphasic mixture was stirred vigorously for 24 hours then ethyl acetate (100 mL) was added. The phases were separated and the aqueous phase was washed with ethyl acetate (100 mL), the combined organic layers were washed with brine (3 × 50 mL). The organic phase was dried over Na_2SO_4 and the solvent was removed to give the *title compound* (8.99 g, 97%) which was used without further purification. mp: 143-145˚C. IR (neat): ν_{max} 3157, 2216, 1668, 1604, 1518, 1340 cm^{-1}. ^1H NMR (300 MHz, acetone-d_6): δ 8.19-8.16 (m, 1 H), 7.86–7.73 (m, 3 H), 7.55 (br s, 1 H), 7.07 (br s, 1 H) ppm. ^{13}C NMR (75 MHz, acetone-d_6): δ 154.2, 150.9, 136.2, 134.4, 131.8, 125.7, 116.4,



90.3, 78.8 ppm. MS (APCI): *m*/*z* (%) 191 (100) $[M + H]^+$. HRMS (ESI): calcd. for $C_9H_6N_2O_3Na$ $[M + Na]^+$: 213.02706; found: 213.02667.

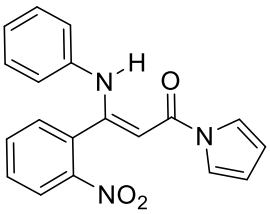
_N_-(3-(2-nitrophenyl)-propioloyl)pyrrole (218)



218

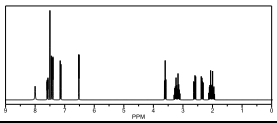
3-(2-nitrophenyl)Propiolamide (1.60 g, 8.42 mmol) and 2,5-diethoxytetrahydrofuran (2.02 g, 12.6 mmol) were dissolved in acetic acid (15 mL) and the solution was heated to 100°C for 16 hours. The reaction was cooled to room temperature and poured onto ether (200 mL). The solution was washed with brine (3 × 100 mL) then saturated aqueous sodium bicarbonate (3 × 100 mL) and dried over Na_2SO_4. The solvent was removed by evaporation and the residue was purified by column chromatography (5% ethyl acetate in hexanes) to give the *title compound* as an orange solid (948 mg, 47%). R_f: 0.69 (33% ethyl acetate in hexanes). mp: 107°C. IR (neat): ν_{max} 3143, 2215, 1669, 1519, 1466, 1340, 1109 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.25-8.22 (m, 1 H), 7.91–7.88 (m, 1 H), 7.75–7.65 (m, 2 H), 7.58 (m, 2 H), 7.37 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.9, 149.7, 136.7, 133.7, 131.8, 125.4, 115.3, 114.7, 114.6, 88.9, 85.8 ppm. MS (APCI): *m*/*z* (%) 241 (100) $[M + H]^+$. HRMS (ESI): calcd. for $C_{13}H_8N_2O_3Na$ $[M + Na]^+$: 263.04271; found: 263.04214.

(*Z*)-3-(2-nitrophenyl)-3-(phenylamino)-1-(1*H*-pyrrol-1-yl)prop-2-en-1-one (219)



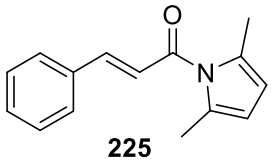
219

Compound **318** (100 mg, 0.42 mmol) and aniline (156 mg, 1.67 mmol) were dissolved in methanol (2 mL) then the solution was heated to reflux for 24 hours. The solvent was removed by evaporation and the crude product was purified by column chromatography (40: 60: 5; toluene: hexane: acetone) to give the *title compound* as an orange solid (112 mg, 80%). IR (neat): ν_{max} 3440, 2932, 1709, 1615, 1465, 1330 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 11.64 (br s, 1 H), 7.96 (d, J = 7.8 Hz, 1 H), 7.63–7.46 (m, 3 H), 7.33 (m, 2 H), 7.11-7.02 (m, 3 H), 6.81-6.79 (m, 2 H), 6.28 (m, 2 H), 5.37 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.6, 159.1, 148.0, 138.3, 133.5, 131.2, 130.9, 130.6, 129.1, 125.3, 124.8, 123.4, 118.5, 112.4, 87.2 ppm. MS (APCI): *m*/*z* (%) 334 (15) $[M + Na]^+$, 300 (30), 267 (100), 221 (52), 204 (17). HRMS (ESI): calcd. for $C_{19}H_{15}N_3O_3$ $[M + H]^+$: 334.11862; found: 334.11849.



Chapter 4 – Aqueous Synthesis of Thiazesim

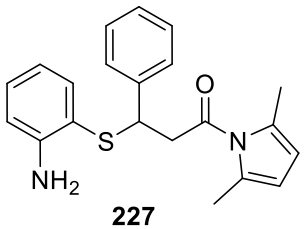
N-cinnamoyl-2,5-dimethylpyrrole (225)



225

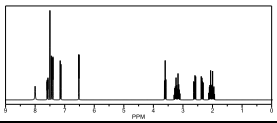
N-Acryloyl-(2,5-dimethyl)pyrrole (149 mg, 1.0 mmol), iodobenzene (112 μL, 1.0 mmol), potassium carbonate (414 mg, 3.0 mmol), palladium(II) acetate (45 mg, 0.2 mmol) and tetrabutylammonium iodide (370 mg, 1 mmol) were added to water (3 mL). The mixture was sonicated for 4 hours then partitioned between ether (20 mL) and water (10 mL). The organic phase was dried over Na_2SO_4, the solvent was removed by evaporation and the crude product was purified by column chromatography (5% ether in hexanes) to give the *title compound* as a yellow oil (180 mg, 80%). R_f: 0.52 (5% ether in hexanes). IR (neat): ν_{max} 2925, 1682, 1617, 1363, 1337, 1247, 1063, 764 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.77 (d, J = 15.6 Hz, 1 H), 7.59 (m, 2 H), 7.44 (m, 3 H), 6.96 (d, J = 15.6 Hz, 1 H), 5.90 (s, 2 H), 2.41 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.5 (C), 145.9 (CH), 134.5 (C), 130.9 (CH), 130.0 (C), 129.1 (CH), 128.4 (CH), 121.9 (CH), 110.9 (CH), 15.5 (CH_3) ppm. MS (APCI): m/z (%) 226 (100) $[M + H]^+$, 207 (20). HRMS (ESI): calcd. for $C_{15}H_{15}NONa$ $[M + H]^+$: 248.10513; found: 248.10459.

3-(2-aminophenylthio)-1-(2,5-dimethyl-1*H*-pyrrol-1-yl)-3-phenylpropan-1-one (227)

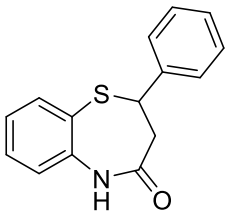


227

Compound **225** (165 mg, 0.73 mmol) and 2-aminothiophenol (138 mg, 1.1 mmol) were added to water (4 mL) and stirred vigorously for 18 hours. Dichloromethane (10 mL) was added, the phases were separated and the organic phase was dried over Na_2SO_4. The solvent was evaporated and the crude product was purified by column chromatography (15 % ethyl acetate in hexanes) to give the *title compound* as a colourless solid (241 mmol, 95%). mp: 117.7-118.0°C. R_f: 0.40 (25% ethyl acetate in hexanes). IR (neat): ν_{max} 3461, 3362, 2925, 1700, 1603, 1474, 1307, 748 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.23-7.07 (m, 7 H), 6.66 (d, J = 7.8 Hz, 1 H), 6.55 (t, J = 7.5 Hz, 1 H), 5.78 (s, 2 H), 4.62 (t, J = 7.5 Hz, 1 H), 4.33 (br s, 2 H) 3.40 (dd, J = 2.1, 7.2 Hz, 2 H), 2.22 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.3 (C), 149.7 (C), 140.7 (C), 137.9 (CH), 131.0 (CH), 130.3 (CH), 128.6 (CH), 127.7 (CH), 127.6 (C), 118.3 (CH), 115.3 (C), 115.1 (CH), 111.5 (CH), 48.3 (CH), 44.8 (CH_2), 16.3 (CH_3) ppm. MS (ESI): m/z (%) 351 (45) $[M + H]^+$, 328 (100), 242 (27). HRMS (ESI): calcd. for $C_{21}H_{23}N_2OS$ $[M + H]^+$: 351.15311; found: 351.15256.



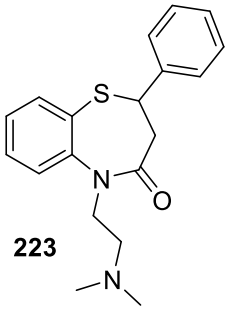
2-phenyl-2,3-dihyrdro-1,5-benzothiazepin-4(*5H*)-one (228)[236]



228

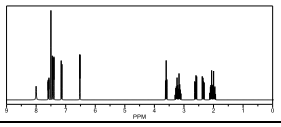
Compound **227** (63 mg, 0.16 mmol) was dissolved in toluene (20 mL) with p-toluenesulfonic acid (14.5 mg, 80 μmol). The solution was heated to reflux for one hour, cooled, washed with saturated aqueous sodium bicarbonate, dried over Na_2SO_4 and the solvent was removed by evaporation. The crude product was purified by column chromatography (30% ethyl acetate in hexanes) to give the *title compound* as a colourless solid (40 mg, 86%). mp: 176.1˚C. R_f: 0.12 (25% ethyl acetate in hexanes). IR (neat): ν_{max} 3176, 3095, 2898, 1700, 1671, 1475, 1382, 756, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.92 (br s, 1 H), 7.67 (dd, J = 8.4, 1.2 Hz, 1 H), 7.43 (dd, J = 1.2, 7.5 Hz, 1 H), 7.32-7.22 (m, 6 H), 4.88 (dd, J = 5.7, 11.1 Hz, 1 H), 2.89 (dd, J = 12.3, 12.4 Hz, 1 H), 2.81 (dd, J = 5.7, 12.6 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.1 (C), 143.6 (C), 141.4 (C), 136.1 (CH), 130.3 (CH), 129.0 (CH), 128.0 (CH), 126.9 (CH), 126.9 (C), 126.6 (CH), 123.4 (CH), 53.3 (CH), 41.6 (CH_2) ppm. MS (ESI): m/z (%) 533 (100) [M_2 + Na]$^+$, 278 (100) [M + Na]$^+$, 256 (20) [M + H]$^+$, 242 (14). HRMS (ESI): calcd. for $C_{15}H_{13}NOSNa$ [M + Na]$^+$: 278.06155; found: 278.06101.

Thiazesim (223)

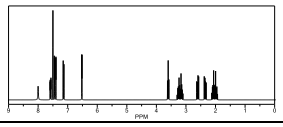


223

Compound **228** (37 mg, 0.15 mmol) and 2-(dimethylamino)-ethyl chloride hydrochloride (95 mg, 0.6 mmol) were dissolved in ethyl acetate (3 mL) and water (100 μL). Finely ground potassium carbonate (190 mg, 1.5 mmol) was added and the mixture was heated to reflux for 16 hours. The remaining solid was removed by filtration and the solvent was removed by evaporation. The residue was purified by column chromatography (20% methanol and 0.5% triethylamine in ethyl acetate) to give *thiazesim* as a colourless oil (44 mg, 94%). R_f: 0.18 (ethyl acetate). IR (neat): ν_{max} 2941, 2771, 1660, 1471, 1390, 757, 697 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.65 (d, J = 7.2 Hz, 1 H), 7.53-7.45 (m, 2 H), 7.30-7.23 (m, 5 H), 7.15-7.12 (m, 1 H), 4.79 (dd, J = 6.0, 12.0 Hz, 1 H), 4.32 (ddd, J = 5.7, 9.6, 15.3 Hz, 1 H), 3.68 (ddd, J = 5.1, 9.6, 14.1 Hz, 1 H), 2.84-2.67 (m, 2 H), 2.45-2.36 (m, 2 H), 2.27 (s, 6 H) ppm. ^{13}C NMR (75 MHz,

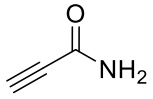


$CDCl_3$): δ 170.5 (C), 146.4 (C), 143.9 (C), 136.5 (CH), 130.6 (CH), 128.9 (CH), 127.8 (CH), 127.7 (C), 127.4 (CH), 126.2 (CH), 124.8 (CH), 56.3 (CH_2), 52.9 (CH), 47.2 (CH_2), 45.5 (CH_3), 42.0 (CH_2) ppm. MS (ESI): *m*/*z* (%) 675 (24) $[M_2 + Na]^+$, 349 (17) $[M + Na]^+$, 327 (100) $[M + H]^+$, 282 (15), 177 (10). HRMS (ESI): calcd. for $C_{19}H_{23}N_2OS$ $[M + H]^+$: 327.15311; found: 327.15256.



Chapter 5 – Stetter Reactions of α,β-Unsaturated *N*-Acylpyrroles

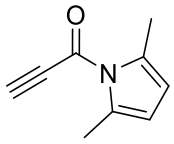
Propiolamide (264)



264

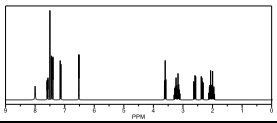
Ethyl propiolate (2.0 mL, 20 mmol) was added to aqueous ammonia (33 % w/w; 50 mL) at 0 °C and the reaction mixture was stirred for 1 hour. The mixture was the poured onto ethyl acetate (50 mL), the phases were separated. The aqueous phase was washed with ethyl acetate (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent and residual starting material was removed by evaporation to give propiolamide as an off-white solid (0.70 g, 52 %). mp: 57°C. IR (neat): ν_{max} 3317, 3122, 2790, 2106, 1659, 1371, 1131 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.32 (br s, 1 H), 5.97 (br s, 1 H), 2.86 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.0, 74.6, 68.1 ppm.

2,5-dimethyl-1-propiolyl-1*H*-pyrrole (265)

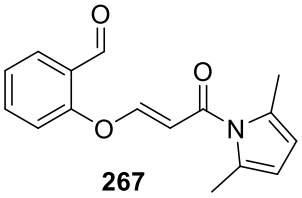


265

Propiolamide (700 mg, 10 mmol) was dissolved in fluorobenzene (50 mL). *p*-Toluenesulfonic acid (90 mg, 0.52 mmol) and 2,5-hexanedione (1.7 mL, 14 mmol) were added and the reaction mixture was heated to reflux under continuous azeotropic distillation for 16 hours. The reaction mixture was cooled to room temperature and saturated aqueous sodium carbonate (20 mL) was added, the phases were separated and the organic phase was washed with brine (20 mL) then dried over Na_2SO_4. The solvent was removed by evaporation and the residue was purified by column chromatography (5% ethyl acetate in hexanes) to give the *title compound* pale-yellow solid (350 mg, 27%). mp: 68.0°C. IR (neat): ν_{max} 3200, 2962, 2923, 2099, 1551, 1361, 1323, 1058 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.85 (s, 2 H), 3.42 (s, 1 H), 2.49 (s, 6 H) ppm.^{13}C NMR (75 MHz, $CDCl_3$): δ 151.2, 131.6, 112.5, 82.3, 78.0, 16.5 ppm. MS (APCI): *m*/*z* (%) 147 (100) $[M + H]^+$, 120 (46). HRMS could not be obtained with the available instrumentation.



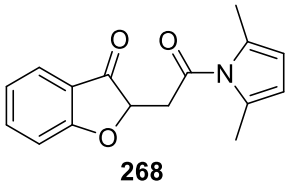
(*E*)-2-[3-(2,5-dimethyl-1*H*-pyrrol-1-yl)-3-oxoprop-1-en-1-yl]oxybenzaldehyde (267)



267

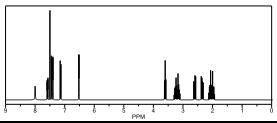
N-Methylmorpholine (64 mg, 0.42 mmol) was added to a solution of salicylaldehyde (42 mg, 0.42 mmol) and *N*-propioloyl-(2,5-dimethyl)-pyrrole (40 mg, 0.27 mmol) in dichloromethane (2 mL). The mixture was stirred for 3 hours. The solvent was evaporated and the residue was purified by column chromatography (15 % ethyl acetate in hexanes) to give the *title compound* as a colourless oil (61 mg, 85 %). IR (neat): ν_{max} 1683, 1627, 1601, 1578, 1368, 1139, 1059, 765 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 10.39 (s, 1 H), 7.98–7.93 (m, 2 H), 7.67 (ddd, J = 8.1, 7.5, 1.8 Hz, 1 H), 7.34 (dd, J = 7.5, 7.5 Hz, 1 H), 7.20 (d, J = 8.1 Hz, 1 H), 6.16 (d, J = 12.0 Hz, 1 H), 5.84 (s, 2 H), 2.34 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.9, 166.8, 159.6, 157.4, 136.2, 129.8, 129.3, 126.7, 125.9, 118.5, 111.0, 108.1, 15.6 ppm. MS (ESI): m/z (%) 292 (65) $[M + Na]^+$, 270 (34). HRMS (ESI): calcd. for $C_{16}H_{15}NO_3Na$ $[M + Na]^+$: 292.09496; found: 292.09441.

2-[2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-2-oxoethyl]benzofuran-3(2*H*)-one (268)

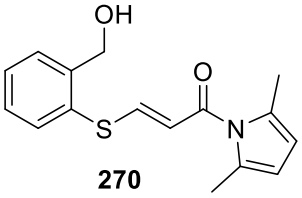


268

Triazolium salt **241** (1.7 mg, 4.7 μmol) was dissolved in THF (1 mL) then triethylamine (0.5 mg, 4.7 μmol) was added. The solution was sparged with argon for 10 minutes. In a separate flask, aldehyde (28 mg, 0.11 mmol) was dissolved in THF (1 mL) and the solution was sparged with argon for 10 minutes. The aldehyde solution was added to the catalyst *via* cannula and the mixture was stirred at room temperature for 24 hours. The solvent was evaporated and the residue was purified by column chromatography (15 % ethyl acetate in hexanes) to give the *title compound* as a colourless oil (19 mg, 67%). IR (neat): ν_{max} 2923, 1699, 1614, 1374, 1259, 757 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.71–7.59 (m, 2 H), 7.13–7.08 (m, 2 H), 5.83 (s, 2 H), 5.11 (dd, J = 8.4, 3.0 Hz, 1 H), 3.53 (dd, J = 17.1, 3.0 Hz, 1 H), 3.21 (dd, J = 17.1, 8.4 Hz, 1 H), 2.39 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.7, 172.6, 170.0, 138.3, 130.8, 124.5, 122.4, 121.0, 113.7, 112.2, 81.2, 40.6, 17.0 ppm. MS (APCI): m/z (%) 286 (100) $[M + H_2O]^+$, 270 (45) $[M + Na]^+$, 175 (32), 147(89). HRMS (ESI): calcd. for $C_{16}H_{17}NO_4$ $[M + H_2O]^+$: 287.10793; found: 286.10738.



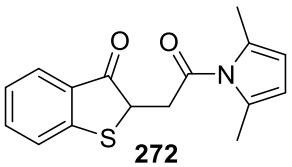
(*E*)-1-(2,5-dimethyl-1*H*-pyrrol-1-yl)-3-((2-(hydroxymethyl)phenyl)thio)prop-2-en-1-one (270)



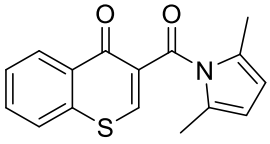
270

N-Methylmorpholine (64 mg, 0.42 mmol) was added to a solution of 2-mercaptobenzyl alcohol (59 mg, 0.42 mmol) and *N*-propioloyl-(2,5-dimethyl)-pyrrole (40 mg, 0.27 mmol) in dichloromethane (2 mL). The mixture was stirred for 24 hours. The solvent was evaporated and the residue was purified by column chromatography (10% ethyl acetate in hexanes) to give the *title compound* as a colourless oil (71 mg, 92%). R_f: 0.27 (10% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88 (d, J = 14.4 Hz, 1 H), 7.61 (d, J = 7.4 Hz, 1 H), 7.55–7.46 (m, 2 H), 7.38 (dd, J = 1.4, 7.4, Hz, 1 H), 5.83 (d, J = 14.5 Hz, 1 H), 5.76 (s, 2 H), 4.80 (s, 2 H), 2.17 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.2, 148.9, 144.0, 135.8, 130.9, 129.9, 129.2, 129.1, 127.3, 119.2, 110.8, 63.2, 15.4 ppm. MS (ESI): *m*/*z* (%) 310 (100) $[M + Na]^+$, 218 (24). HRMS (ESI): calcd. for $C_{16}H_{17}NO_2SNa$ $[M + Na]^+$: 310.08777; found: 310.08722.

2-(2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-2-oxoethyl)benzo[*b*]thiophen-3(2*H*)-one (272),
3-(2,5-dimethyl-1*H*-pyrrole-1-carbonyl)-4*H*-thiochromen-4-one (273)

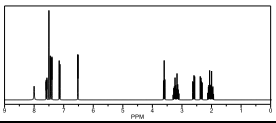


272



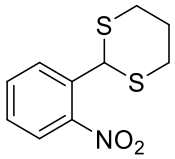
273

Benzyl alcohol **270** (15 mg, 52 μmol) was dissolved in THF (1 mL) and manganese dioxide (100 mg, 1.2 mmol) was added. The mixture was stirred for 4 hours at room temperature then filtered through a plug of silica. The resulting aldehyde solution was sparged with argon for 10 minutes. Triazolium salt **241** (1.0 mg, 2.6 μmol) was dissolved in THF (1 mL) and triethylamine (0.25 mg, 2.6 μmol) was added. The solution was sparged with argon for 10 minutes. The aldehyde solution was added to the catalyst *via* cannula and the mixture was stirred at room temperature for 24 hours. The solvent was evaporated and the residues were subjected to flash column chromatography (3% ethyl acetate in hexanes) to give *3-(2,5-dimethyl-1H-pyrrole-1-carbonyl)-4H-thiochromen-4-one* (**273**) as a yellow solid (3 mg, 24%). IR (neat): ν_{max} 2924, 1684, 1349, 1256, 1075, 746 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90 (d, J = 7.6 Hz, 1 H), 7.63 (m, 1 H), 7.60 (s, 1 H), 7.48 (d, J = 7.8 Hz, 1 H), 7.30 (dd, J = 0.7, 7.8 Hz, 1 H), 5.89 (s, 2 H), 2.43 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.7 (C), 166.3 (C), 148.9 (C), 148.2 (C), 136.9 (CH), 130.5 (CH), 129.3 (C), 127.5 (CH), 126.6 (CH), 124.6 (CH), 119.9 (C), 112.0 (CH), 15.9 (CH_3) ppm. MS (APCI): *m*/*z* (%) 284 (30) $[M + H]^+$, 189 (100). HRMS (ESI): calcd. for $C_{16}H_{14}NO_2S$ $[M + H]^+$: 284.07452; found: 284.07398. The reaction also gave *2-(2-(2,5-dimethyl-1H-pyrrol-1-yl)-2-*



oxoethyl)benzo[b]thiophen-3(2H)-one (**272**) as a colourless oil (3.1 mg, 21%). R_f: 0.65 (10% ethyl acetate in hexanes). IR (neat): ν_{max} 2925, 1698, 1372, 1287, 740 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.81 (d, J = 7.9 Hz, 1 H), 7.58 (dd, J = 1.3, 11.2 Hz, 1 H), 7.42 (d, J = 8.0 Hz, 1 H), 7.21 (t, J = 0.7, 7.2 Hz, 1 H), 5.85 (s, 2 H), 4.37 (dd, J = 3.1, 10.5 Hz, 1 H), 3.85 (dd, J = 3.1, 17.5 Hz, 1 H), 3.17 (dd, J = 10.6, 17.6 Hz, 1 H), 2.42 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ ^{13}C spectrum of this compound could not be obtained as it was highly unstable and decomposed over the course of the acquisition. MS (ESI): m/z (%) 358 (100) $[M + O_2 + H_2O + Na]^+$, 342 (86) $[M + O + H_2O + Na]^+$, 323 (51) $[M + O + Na]^+$. HRMS (ESI): calcd. for $C_{17}H_{19}NO_5SNa$ $[M + O_2 + MeOH + Na]^+$: 372.08816; found: 372.08762.

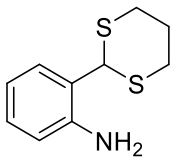
2-(2-nitrophenyl)-1,3-dithiane (279)[182]



279

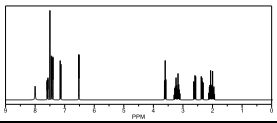
2-Nitrobenzaldehyde (1.00 g, 6.6 mmol) was dissolved in dichloromethane (30 mL), 1,3-propanedithiol (760 mg, 7.0 mmol) was added followed by anhydrous copper sulfate (636 mg, 4.0 mmol). The solution was stirred for one hour, the insoluble material was removed by filtration and the volatile components were removed by evaporation to give the *title compound* as a yellow solid (1.29 g, 93%). mp: 117.2-119.5°C. R_f: 0.54 (25% ethyl acetate in hexane). ^1H NMR (300 MHz, $CDCl_3$): δ 7.92-7.86 (m, 2 H), 7.62 (ddd, J = 1.4, 7.6, 8.8 Hz, 1 H), 7.44 (ddd, J = 1.6, 7.8, 8.8 Hz, 1 H), 5.89 (s, 1 H), 3.21-3.06 (m, 2 H), 2.98-2.87 (m, 2 H), 2.26-2.14 (m, 1 H), 2.06-1.91 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.6 (C), 133.3 (C), 133.2 (CH), 130.6 (CH), 129.0 (CH), 124.6 (CH), 45.8 (CH), 32.1 (CH_2), 24.9 (CH_2) ppm. Spectroscopic data matched that previously reported.[182]

2-(1,3-dithian-2-yl)aniline (280)[182]



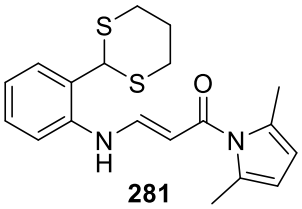
280

2-(1,3-Dithian-2-yl)nitrobenzene (1.00 g, 4.1 mmol) and ammonium chloride (1.09 g, 26 mmol) were dissolved in water and ethanol (1:1, 20 mL). Iron powder (460 mg, 8.2 mmol) was added. The solution was heated to reflux for 4 hours, cooled, diluted with ethyl acetate (40 mL) and washed with water (3 × 20 mL). The organic phase was dried over Na_2SO_4, and the solvent was removed by evaporation to give the *title compound* as a pale yellow solid (767 mg, 88%). mp: 114.0-115.6°C. R_f: 0.33 (25% ethyl acetate in hexane). ^1H NMR (300 MHz, $CDCl_3$): δ 7.32 (dd, J = 1.8, 9.4 Hz, 1 H), 7.11 (ddd, J = 1.2, 7.4, 10.8 Hz, 1 H), 6.77 (ddd, J = 1.4, 7.4, 8.8 Hz, 1 H), 6.69 (dd, J = 1.0, 8.2 Hz, 1 H), 5.30 (s, 1 H), 4.11 (br s, 2 H), 3.15-



2.87 (m, 4 H), 2.22-1.90 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.3, 129.3, 128.5, 123.1, 119.1, 117.0 48.7, 32.0, 25.3 ppm. Spectroscopic data matched that previously reported.[182]

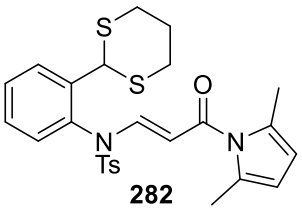
(*E*)-3-[2-(1,3-Dithian-2-yl)phenyl]amino-1-(2,5-dimethyl-1*H*-pyrrol-1-yl)prop-2-en-1-one (281)



281

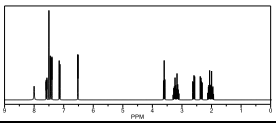
N-Methylmorpholine (64 mg, 0.42 mmol) was added to a solution of compound **280** (89 mg, 0.42 mmol) and *N*-propioloyl-(2,5-dimethyl)-pyrrole (40 mg, 0.27 mmol) in dichloromethane (2 mL). The mixture was stirred for 24 hours then the solvent was removed by evaporation. The residues were purified by column chromatography (25 % ethyl acetate in hexanes) to give the *title compound* as a colourless oil (91 mg, 95 %). IR (neat): ν_{max} 2923, 1643, 1591, 1458, 1367, 1262, 1065, 750 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.57 (br s, 1 H), 7.55 (dd, J = 7.8, 1.2 Hz, 1 H), 7.47 (dd, J = 12.3, 8.1 Hz, 1 H), 7.34 (ddd, J = 8.4, 8.4, 1.2 Hz, 1 H), 7.20–7.12 (m, 2 H), 5.84 (s, 2 H), 5.43 (s, 1 H), 5.37 (d, J = 7.8 Hz, 1 H), 3.27 (m, 2 H), 3.03–2.96 (m, 2 H), 2.41 (s, 6 H), 2.27–2.18 (m, 1 H), 2.08–2.03 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 146.7, 138.0, 129.6, 129.0, 128.7, 128.3, 124.6, 116.6, 109.5, 93.6, 47.7, 32.5, 25.2. 15.1ppm. MS (ESI): *m*/*z* (%) 381 (32) [M + Na]$^+$. HRMS (ESI): calcd. for $C_{19}H_{22}N_2OS_2Na$ [M + Na]$^+$: 381.10712; found: 381.10658.

(*E*)-3- [2-(1,3-dithian-2-yl)phenyl]tosylamino-1-(2,5-dimethyl-1*H*-pyrrol-1-yl)prop-2-en-1-one (282)



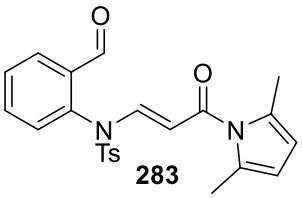
282

Triethylamine (30 μL, 0.21 mmol), 4-(dimethylamino)pyridine (2 mg, 24 μmol) and *p*-toluenesulfonyl chloride (31 mg, 0.16 mmol) were added to a solution of amine **281** (55 mg, 0.15 mmol) in dichloromethane (3 mL). The mixture was stirred for 4 hours at room temperature before aqueous sodium hydroxide (1 M, 10 mL) was added. The phases were separated and the organic phase was washed with water (5 mL), dried with Na_2SO_4 and the solvent was removed by evaporation. The crude product was purified by column chromatography (10 % ethyl acetate in hexanes) to give the *title compound* as a colourless solid (67 mg, 87 %). mp: 180–183°C. IR (neat): ν_{max} 2925, 1682, 1604, 1367, 1246, 1171, 930, 575 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.43 (d, J = 13.2 Hz, 1 H), 7.87 (dd, J = 8.1, 1.2 Hz, 1 H), 7.67 (d, J = 8.4 Hz, 2 H), 7.44 (dd, J = 8.4, 6.9 Hz, 1 H), 7.34 (d, J = 8.4 Hz, 2 H), 7.21 (ddd, J = 7.8, 7.8, 1.2 Hz, 1 H), 6.49 (d, J = 8.1 Hz, 1 H), 5.71 (s, 2 H), 5.31 (s, 1 H), 5.09 (d, J = 13.2 Hz, 1 H), 3.06–



2.81 (m, 4 H), 2.46 (s, 3 H), 2.12 (s, 6 H), 1.96–1.87 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.2, 145.6, 145.5, 139.9, 134.5, 132.8, 131.1, 131.1, 130.3, 129.8, 129.4, 129.4, 128.3, 110.3, 105.8, 46.2, 32.5, 32.2, 25.1, 21.8, 15.6 ppm. MS (ESI): *m*/*z* (%) 535 (100) $[M + Na]^+$. HRMS (ESI): calcd. for $C_{26}H_{28}N_2O_3S_3Na$ $[M + Na]^+$: 535.11597; found: 535.11543.

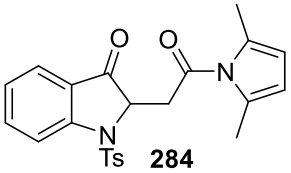
(*E*)-3-[(2-formylphenyl)tosylamino]-1-(2,5-dimethyl-1*H*-pyrrol-1-yl)prop-2-en-1-one (283)



283

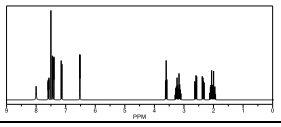
Dithiane **283** (60 mg, 0.15 mmol) was dissolved in a mixture of acetonitrile/water (4/1; 1 mL). Sodium hydrogen carbonate (300 mg, 3.6 mmol) and methyl iodide (220 μL, 3.54 mmol) were added and the mixture was stirred for 24 hours. The mixture was diluted with ethyl acetate (10 mL) and water (10 mL), the phases were separated and the organic phase was washed with brine (10 mL) then dried over Na_2SO_4. The solvent was evaporated and the residue was subjected to flash column chromatography (10 % ethyl acetate in hexanes) to give the *title compound* as a colourless oil (35 mg, 71%). IR (neat): ν_{max} 2925, 1693, 1594, 1367, 1246, 662 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.76 (s, 1 H), 8.54 (d, J = 13.5 Hz, 1 H), 8.07–8.04 (m, 1 H), 7.65–7.59 (m, 4 H), 7.34 (d, J = 8.1 Hz, 2 H), 6.91–6.88 (m, 1 H), 5.72 (s, 2 H), 5.02 (d, J = 13.5 Hz, 1 H), 2.47 (s, 3 H), 2.09 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.8, 166.7, 146.2, 145.6, 137.2, 135.3, 134.3, 133.9, 131.1, 130.7, 130.5, 129.7, 129.6, 128.2, 110.6, 105.1, 21.9, 15.3 ppm. MS (ESI): *m*/*z* (%) 445 (100) $[M + Na]^+$. HRMS (ESI): calcd. for $C_{23}H_{22}N_2O_4SNa$ $[M + Na]^+$: 445.11980; found: 445.11925.

2-[2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-2-oxoethyl]-1-tosylindolin-3-one (284)



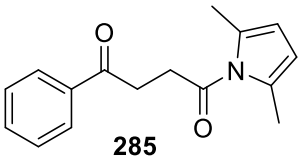
284

Triazolium salt **241** (0.4 mg, 1.1 μmol) and triethylamine (0.1 mg, 1.1 μmol) were dissolved in THF (1 mL) and the solution was sparged with argon for 10 minutes. In a separate flask, aldehyde **283** (10.0 mg, 24 μmol) was dissolved in THF (1 mL) the solution was sparged with argon for 10 minutes. The aldehyde solution was added to the catalyst solution *via* cannula and the mixture was stirred for 24 hours. The solvent was evaporated and the residue was purified by column chromatography (15% ethyl acetate in hexanes) to give the *title compound* as a colourless oil (8 mg, 81%). IR (neat): ν_{max} 2928, 1723, 1604, 1360, 1171, 663, 580 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09 (d, J = 9.0 Hz, 1 H), 7.71–7.67 (m, 4 H), 7.26–7.22 (m, 3 H), 5.83 (s, 2 H), 4.31 (dd, J = 4.8, 3.9 Hz, 1 H), 3.85 (dd, J = 17.4, 4.8 Hz, 1



H), 3.71 (dd, J = 17.4, 3.9 Hz, 1 H), 2.38 (s, 6 H), 2.36 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.6, 170.2, 153.2, 145.4, 137.0, 133.0, 130.8, 130.2, 127.6, 125.2, 124.8, 124.6, 116.7, 112.0, 63.3, 41.2, 21.7, 16.9 ppm. MS (ESI): m/z (%) 445 (100) $[M + Na]^+$. HRMS (ESI): calcd. for $C_{23}H_{21}N_2O_4S$ $[M - H]^+$: 421.12220; found: 421.12165.

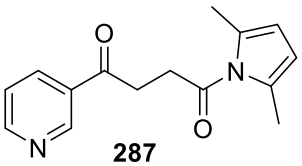
1-(2,5-dimethyl-1*H*-pyrrol-1-yl)-4-phenylbutane-1,4-dione (285)



285

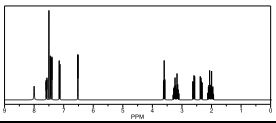
1-Acryloyl-2,5-dimethylpyrrole (50 mg, 0.33 mmol) was dissolved in THF (1 mL) and the solution was sparged with argon for 10 minutes. Benzaldehyde (36 μL, 0.36 mmol) was then added. In a separate flask, caesium carbonate (10 mg, 33 μmol) and 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride (9.0 mg, 33 μmol) were dissolved in THF and the solution was sparged with argon for 10 minutes. The aldehyde solution was added to the catalyst *via* cannula and the mixture was stirred for 24 hours. Water (5 mL) and ethyl acetate (10 mL) were added, the phases were separated, the organic phase was dried over Na_2SO_4, and the solvent was removed by evaporation. The residue was purified by chromatography (10% ethyl acetate in hexanes) to give the *title compound* an off-white solid (68 mg, 84%). mp: 66–67 °C. IR (neat): ν_{max} 2922, 1709, 1698, 1674, 1365, 1239, 1053, 778 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.02 (d, J = 7.5 Hz, 2 H), 7.60–7.45 (m, 3 H), 5.86 (s, 2 H), 3.47 (dd, J = 6.3, 6.0 Hz, 2 H), 3.23 (dd, J = 6.3, 6.0 Hz, 2 H), 2.45 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.1, 173.6, 136.6, 133.3, 130.7, 128.7, 128.1, 111.7, 33.7, 32.9, 17.0 ppm. HRMS (ESI): calcd. for $C_{16}H_{17}NO_2Na$ $[M + Na]^+$: 278.11515; found: 278.11561.

1-(2,5-dimethyl-1*H*-pyrrol-1-yl)-4-(pyridin-3-yl)butane-1,4-dione (287)



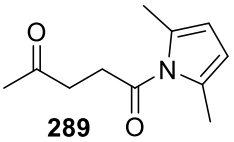
287

1-Acryloyl-2,5-dimethylpyrrole (33 mg, 0.22 mmol) was dissolved in THF (1 mL) and the solution was sparged with argon for 10 minutes. Nicotinaldehyde (23 μL, 0.24 mmol) was then added. In a separate flask, cesium carbonate (7 mg, 22 μmol) 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride (6 mg, 22 μmol) were dissolved in THF and the solution was sparged with argon for 10 minutes. The aldehyde solution was added to the catalyst *via* cannula and the mixture was stirred for 24 hours. Water (5 mL) and ethyl acetate (10 mL) were added, the phases were separated, the organic phase was dried over Na_2SO_4, and the solvent was removed by evaporation. The residue was purified by column chromatography (50% ethyl acetate in hexanes) to give the *title compound* as a colourless oil (45 mg,



81%). IR (neat): ν_{max} 2925, 1685, 1585, 1363, 1249, 993, 783, 702 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 9.23 (d, J = 1.8 Hz, 1 H), 8.78 (dd, J = 1.5, 4.8 Hz, 1 H), 8.26 (dt, J = 8.1, 2.1 Hz, 1 H), 7.42 (ddd, J = 0.6, 4.4, 7.8 Hz, 1H), 5.85 (s, 2 H), 3.45 (dd, J = 5.7, 7.2 Hz, 2 H), 3.26 (dd, J = 5.4, 6.6 Hz, 2 H), 2.44 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.1, 173.2, 153.7, 149.7, 135.5, 132.0, 130.8, 123.8, 111.9, 33.9, 32.7, 17.0 ppm. MS (ESI): m/z (%) 257 (71) $[M + H]^+$, 178 (100), 160 (77). HRMS (ESI): calcd. for $C_{15}H_{16}N_2O_2Na$ $[M + Na]^+$: 279.11040; found: 279.11039.

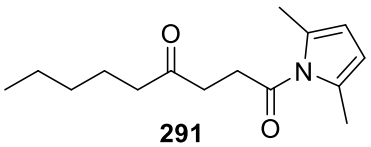
1-(2,5-dimethyl-1*H*-pyrrol-1-yl)pentane-1,4-dione (289)



289

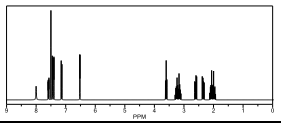
1-Acryloyl-2,5-dimethylpyrrole (66 mg, 0.44 mmol) was dissolved in THF (1 mL) and the solution was sparged with argon for 10 minutes. Acetaldehyde (246 μL, 4.4 mmol) was then added. In a separate flask, cesium carbonate (14 mg, 44 μmol) and 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride (10.5 mg, 44 μmol) were dissolved in THF and the solution was sparged with argon for 10 minutes. The aldehyde solution was added to the catalyst *via* cannula and the mixture was stirred for 24 hours. Water (5 mL) and ethyl acetate (10 mL) were added, the phases were separated, the organic phase was dried over Na_2SO_4 and the solvent was removed by evaporation. The crude product was purified by column chromatography (10 % ethyl acetate in hexanes) to give the *title compound* as a colourless solid (77 mg, 91%). mp: 62–63 °C. IR (neat): ν_{max} 2928, 1704, 1363, 1263, 993, 777 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.82 (s, 2 H), 3.04 (m, 2 H), 2.88 (m, 2 H), 2.41 (s, 6 H), 2.24 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.7, 173.4, 130.7, 111.7, 38.1, 32.8, 30.0, 17.0 ppm. MS (APCI): m/z (%) 194 (100) $[M + H]^+$, 50 (50). HRMS could not be obtained with the available instrumentation.

1-(2,5-dimethyl-1*H*-pyrrol-1-yl)nonane-1,4-dione (291)

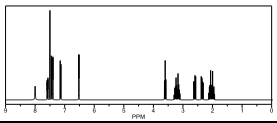


291

1-Acryloyl-2,5-dimethylpyrrole (50 mg, 0.33 mmol) was dissolved in THF (1 mL) and the solution was sparged with argon for 10 minutes. Hexanal (43 μL, 0.36 mmol) was then added. In a separate flask, caesium carbonate (10 mg, 33 μmol) and 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride (9.0 mg, 33 μmol) were dissolved in THF the solution was sparged with argon for 10 minutes. The aldehyde solution was added to the catalyst *via* cannula and the mixture was stirred for 24 hours. Water (5 mL) and ethyl acetate (10 mL) were added, the phases were separated, the organic phase was dried over Na_2SO_4, and the solvent was removed by evaporation. The crude product was purified by

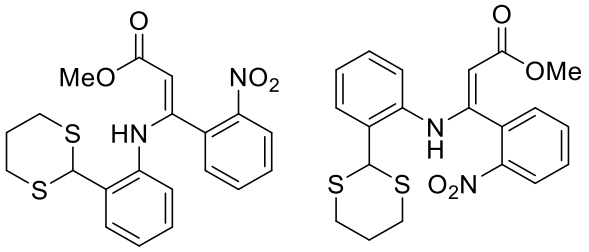


column chromatography (5% ethyl acetate in hexanes) to give the *title compound* as an off-white solid (52 mg, 63%). mp: 38.2–40 °C. IR (neat): ν_{max} 2934, 1703, 1541, 1363, 1255, 1230 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.87 (s, 2 H), 3.05 (dd, J = 6.3, 6.0 Hz, 2 H), 2.85 (dd, J = 6.6, 5.7 Hz, 2 H), 2.50 (dd, J = 7.5, 7.2 Hz, 2 H), 2.40 (s, 6 H), 1.66–1.56 (m, 2 H), 1.38–1.26 (m, 4 H), 0.89 (t, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.2, 173.6, 130.7, 111.6, 42.9, 37.2, 32.8, 31.5, 23.6, 22.5, 16.9, 14.0 ppm. HRMS (ESI): calcd. for $C_{15}H_{23}NO_2Na$ $[M + Na]^+$: 272.16210; found: 272.16257.



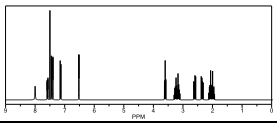
Chapter 6 – Studies Toward the Synthesis of Hinckdentine A

methyl 3-(2-(1,3-dithian-2-yl)phenylamino)-3-(2-nitrophenyl)acrylate (297)

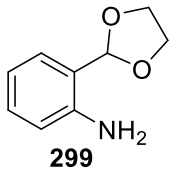


***E*-297** ***Z*-297**

Methyl 3-(2-nitrophenyl)propiolate (49 mg, 0.24 mmol) and 2-(1,3-dithian-2-yl)aniline (50 mg, 0.24 mmol) were added to water (4 mL) with dichloroethane (5 drops) and the mixture was stirred vigorously for 24 hours at 50°C. Dichloromethane (10 mL) was added, the phases were separated and the organic phase was dried over Na_2SO_4. The solvent was removed by evaporation and the crude product was purified by column chromatography (20% ethyl acetate in hexanes) to give (*E*)-methyl 3-(2-(1,3-dithian-2-yl)phenylamino)-3-(2-nitrophenyl)acrylate (***E*-297**) as a yellow oil (10 mg, 10%). R_f: 0.07 (25% ethyl acetate in hexanes). IR (neat): ν_{max} 3402, 2926, 1751, 1725, 1459, 1213, 811 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.72-7.64 (m, 3 H), 7.37 (dd, J = 7.8, 1.4 Hz, 1 H), 7.27 (d, J = 7.4 Hz, 1 H), 7.14 (t, J = 7.6 Hz, 1 H), 6.93 (ddd, J = 1.8, 7.4, 15.2 Hz, 1 H), 6.80 (ddd, J = 1.8, 7.4, 15.2 Hz, 1 H), 6.60 (s, 1 H) 6.38 (br s, 1 H), 6.31 (dd, J = 0.8, 8.2 Hz, 1 H), 5.51 (s, 1 H), 3.73 (s, 1 H), 3.24-3.12 (m, 2 H), 3.02-2.96 (m, 2 H), 2.25-2.20 (m, 1 H), 2.07-1.98 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$; 75 MHz): δ 191.1, 165.9, 159.6, 140.3, 137.9, 129.3, 128.9, 125.5, 124.2, 123.1, 122.6, 121.7, 120.9, 116.6, 53.8, 48.8, 32.4, 32.2, 25.3 ppm. MS (ESI): m/z (%) 855 (62) $[M_2 + Na]^+$, 439 (80) $[M + Na]^+$, 315 (36), 293 (100), 212 (46). HRMS (ESI): calcd. for $C_{20}H_{20}N_2O_4S_2Na$ $[M + Na]^+$: 439.07567; found: 439.07622. The reaction also yielded (*Z*)-methyl 3-(2-(1,3-dithian-2-yl)phenylamino)-3-(2-nitrophenyl)acrylate (***Z*-297**) as a yellow oil (24 mg, 24%). R_f: 0.19 (25% ethyl acetate in hexanes). IR (neat): ν_{max} 3402, 2926, 1751, 1725, 1459, 1213, 811 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.65 (dd, J = 1.0, 7.8 Hz, 1 H), 7.56 (ddd, J = 1.4, 8.2, 9.8 Hz, 1 H), 7.38 (dd, J = 1.2, 7.4 Hz, 1 H), 7.03-6.91 (m, 3 H), 6.82 (ddd, J = 0.8, 7.4, 8.6 Hz, 1 H), 6.42 (d, J = 8.0 Hz, 1 H), 6.13 (s, 1 H) 5.46 (br s, 1 H), 5.43 (s, 1 H), 3.75 (s, 3 H), 3.20-3.08 (m, 2 H), 2.97-2.92 (m, 2 H), 2.28-2.16 (m, 1 H), 2.04-1.93 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.4, 169.0, 160.8, 141.4, 138.8, 129.6, 129.1, 126.6, 125.7, 121.0, 119.8, 115.8, 113.8, 80.2, 54.4, 48.8, 32.5, 32.4, 25.7 ppm. MS (ESI): m/z (%) 855 (95) $[M_2 + Na]^+$, 439 (80) $[M + Na]^+$. HRMS (ESI): calcd. for $C_{20}H_{20}N_2O_4S_2Na$ $[M + Na]^+$: 439.07567; found: 439.07601.



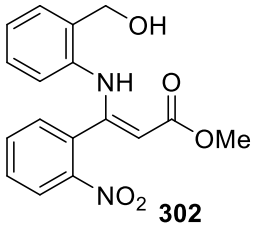
2-(1,3-dioxolan-2-yl)aniline (299)[189]



299

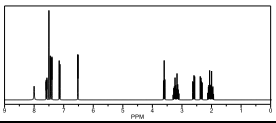
2-Nitrobenzaldehyde (500 mg, 3.3 mmol) was dissolved in toluene (15 mL) with ethylene glycol (1.0 mL) and *p*-toluenesulfonic acid (20 mg). The mixture heated to reflux for 18 hours then cooled to room temperature. Dichloromethane (20 mL) and saturated aqueous sodium bicarbonate solution (20 mL) were added. The organic layer was extracted with further bicarbonate solution (2 × 20 mL). The combined organic fractions were dried over Na_2SO_4 and the solvent was removed by evaporation to give 2-(2-nitrophenyl)-1,3-dioxolane (599 mg, 100%) as a colourless oil. R_f: 0.61 (25% ethyl acetate in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94 (dd, J = 8.0, 1.4 Hz, 1 H), 7.85 (dd, J = 7.9, 1.4 Hz, 1 H), 7.67 (ddd, J = 7.2, 8.6, 1.2 Hz, 1 H), 7.55 (ddd, J = 7.8, 9.2, 1.8 Hz, 1 H), 6.54 (s, 1 H), 4.13-4.06 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.1 (C), 133.5 (C), 133.2 (CH), 129.9 (CH), 127.9 (CH), 124.7 (CH), 99.8 (CH), 65.6 (CH_2) ppm. 2-(2-Nitrophenyl)-1,3-dioxolane (400 mg, 2.2 mmol) was dissolved in isopropanol (4 mL) with triethylamine (100 mg, 1.0 mmol) and 10% palladium on charcoal (30 mg). The mixture was stirred under an atmosphere of hydrogen for 18 hours. The solution was filtered through Celite. The filtrate was dissolved in dichloromethane (10 mL) then extracted with saturated aqueous sodium carbonate (2 × 10 mL), dried over Na_2SO_4 and the solvent was removed by evaporation. The residue was purified by column chromatography (1% triethylamine and 10% ethyl acetate in hexanes) to give the *title compound* as a colourless oil (204 mg, 56%). R_f: 0.52 (25% ethyl acetate in hexanes). IR (neat): ν_{max} 3490, 3389, 1623 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 (dd, J = 7.5, 0.8 Hz, 1 H), 7.22 (dd, J = 7.5, 0.8 Hz, 1 H), 6.69-6.58 (m, 2 H), 5.88 (s, 1 H), 4.20-4.07 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.5 (C), 130.3 (CH), 127.8 (CH), 121.5 (C), 118.2 (CH), 116.8 (CH), 103.6 (CH), 65.1 (CH_2) ppm. Spectroscopic data matched that previously reported.[189]

methyl (*E*)-3-(2-(hydroxymethyl)phenylamino)-3-(2-nitrophenyl)acrylate (302)



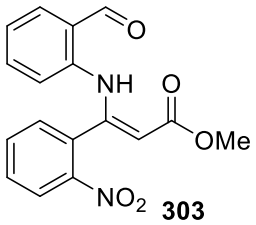
302

Methyl 3-(2-nitrophenyl)propiolate (400 mg, 1.95 mmol) and 2-aminobenzylamine (1.00 g, 9.8 mmol) were added to water (4 mL) and stirred vigorously at 50 °C for 48 hours. Dichloromethane (10 mL) was added, the phases were separated and the organic phase was dried over Na_2SO_4, and the solvent was removed by evaporation. The crude product was purified by column chromatography (40% ethyl



acetate, 1% triethylamine in hexanes) to give the *title compound* as yellow foam (423 mg, 66%). R_f: 0.70 (50% ethyl acetate in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.83 (br s, 1 H), 7.72-7.64 (m, 2 H), 7.24 (d, J = 7.6 Hz, 1 H), 7.13 (t, J = 7.8 Hz, 1 H), 6.99-6.91 (m, 2 H), 6.68 (t, J = 7.2 Hz, 1 H), 6.62 (s, 1 H), 6.17 (d, J = 8.0 Hz, 1 H), 4.88 (d, J = 12.4 Hz, 1 H), 4.52 (d, J = 12.4 Hz, 1 H), 3.69 (s, 3 H), 2.99 (br s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.3, 165.8, 159.7, 142.1, 138.0, 130.0, 129.4, 125.8, 124.1, 122.9, 122.5, 119.5, 114.4, 88.1, 68.1, 64.4, 53.8 ppm. MS (ESI): m/z (%) 679 (40) $[M_2 + Na]^+$, 351 (100) $[M + Na]^+$. HRMS (ESI): calcd. for $C_{17}H_{16}N_2O_5Na$ $[M + Na]^+$: 351.09569; found: 351.09514.

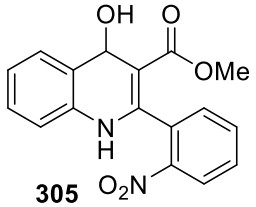
methyl (*E*)-3-(2-formylphenylamino)-3-(2-nitrophenyl)acrylate (303)



303

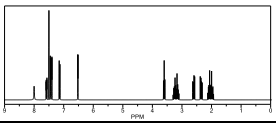
Alcohol **302** (20 mg, 61 μmol) was dissolved in dichloromethane/DMSO (4:1, 2 mL) and cooled to 0°C. Triethylamine (85 mg, 62 mmol) was added followed by sulfur trioxide pyridine complex (60 mg, 0.37 mmol). The solution was stirred at 0°C for two hours. Saturated aqueous sodium bicarbonate solution (5 mL) was added and the mixture was warmed to room temperature and diluted with ether (40 mL). The organic phase was washed with water (5 × 15 mL). The organic layer was dried Na_2SO_4 and the solvent was removed by evaporation. The crude product was purified by column chromatography (20% acetone in hexanes) to give the *title compound* as yellow solid (19 mg, 96%). R_f: 0.33 (50% ethyl acetate in hexanes). ^{1}H NMR (300 MHz, acetone-d_6): δ 9.97 (s, 1 H), 9.53 (s, 1 H) 7.83 (ddd, J = 7.8, 8.0, 1.2 Hz, 1 H), 7.72-7.64 (m, 2 H), 7.42 (d, J = 7.8 Hz, 1 H), 7.26-7.17 (m, 2 H), 6.84 (ddd, J = 7.8, 8.0, 1.2 Hz, 1 H), 6.14 (d, J = 8.4 Hz, 1 H), 3.72 (s, 3 H) ppm. ^{13}C NMR (75 MHz, acetone-d_6): δ 195.3, 166.0, 160.9, 160.7, 146.7, 139.2, 137.8, 136.0, 124.4, 123.8, 123.2, 121.6, 118.4, 115.3, 114.7, 88.2, 54.1 ppm. MS (ESI): m/z (%) 674 (45) $[M_2 + Na]^+$, 349 (100) $[M + Na]^+$. HRMS (ESI): calcd. for $C_{17}H_{14}N_2O_5Na$ $[M + Na]^+$: 349.08004; found: 349.07949.

methyl 1,4-dihydro-4-hydroxy-2-(2-nitrophenyl)quinoline-3-carboxylate (305)



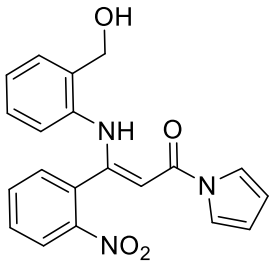
305

Triazolium salt **241** (11 mg, 31 μmol) and triethylamine (6 mg, 62 μmol) were dissolved in THF (1 mL) and the solution was sparged with argon for 10 minutes. Aldehyde **303** (10 mg, 31 μmol) was dissolved



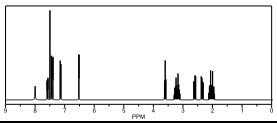
in THF (1 mL) and sparged for 10 minutes with argon. The carbene solution was added to the reactant solution *via* cannula and the reaction was stirred at room temperature for 24 hours, then transferred directly onto a column of silica and purified by column chromatography (40% ethyl acetate in hexanes) to give the *title compound* as a colourless solid (10 mg, 100%). R_f: 0.23 (40% ethyl acetate in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82 (dd, J = 7.8, 2.1 Hz, 1 H), 7.28-7.20 (m, 2 H), 7.03-6.88 (m, 2 H), 6.77 (br s, 1 H), 6.72 (ddd, J = 8.1, 7.8, 0.8 Hz, 1 H), 6.52 (d, J = 8.1 Hz, 1 H), 5.62 (s, 1 H), 4.41 (s, 1 H), 3.74 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.0, 168.4, 151.3, 149.3, 136.6, 131.0, 128.0, 126.8, 123.9, 123.2, 118.6, 115.3, 114.6, 114.2, 89.8, 79.4, 53.2 ppm. MS (ESI): m/z (%) 349 (100) $[M + Na]^+$. HRMS (ESI): calcd. for $C_{17}H_{14}N_2O_5Na$ $[M + Na]^+$: 349.08004; found: 349.08032.

(*Z*)-3-((2-(hydroxymethyl)phenyl)amino)-3-(2-nitrophenyl)-1-(1*H*-pyrrol-1-yl)prop-2-en-1-one (309)

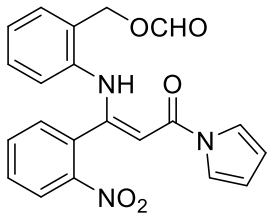


309

Compound **218** (408 mg, 1.7 mmol) and 2-aminobenzylalcohol (627 mg, 5.1 mmol) were added to water (4 mL) and stirred vigorously for 40 hours at 50 °C. Dichloromethane (10 mL) was added, the phases were separated, the organic phase was dried over Na_2SO_4 and the solvent was removed by evaporation. The crude product was purified by column chromatography (25% ethyl acetate in hexanes) to give compound **309** as yellow foam (339 mg, 55%). R_f: 0.34 (30% ethyl acetate in hexanes). IR (neat): ν_{max} 3440, 2932, 1709, 1615, 1465, 1330 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.83 (br s, 1 H), 7.90 (d, J = 11.7 Hz, 1 H), 7.70–7.65 (m, 2 H), 7.59–7.54 (m, 2 H), 7.36 (m, 2 H), 7.28 (m, 1 H), 7.02 (m, 1 H), 6.91 (m, 1 H), 6.43 (d, J = 11.4 Hz, 1 H), 6.28 (m, 2 H), 5.48 (s, 1 H), 4.83 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.8, 158.9, 148.2, 137.7, 133.7, 131.5, 131.3, 130.7, 129.7, 128.3, 125.4, 124.8, 124.0, 119.0, 113.9, 88.4, 63.1 ppm. MS (ESI): m/z (%) 749 (100) $[M_2 + Na]^+$, 386 (21) $[M + Na]^+$, 364 (14). HRMS (ESI): calcd. for $C_{20}H_{17}N_3O_4Na$ $[M + Na]^+$: 386.11168; found: 386.1113.



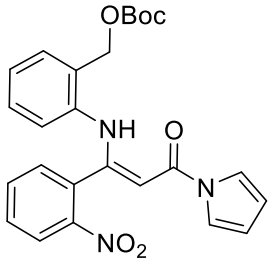
(*Z*)-2-((1-(2-nitrophenyl)-3-oxo-3-(1*H*-pyrrol-1-yl)prop-1-en-1-yl)amino)benzyl formate (313)



313

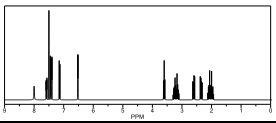
Benzylalcohol **309** (50 mg, 0.14 mmol) was dissolved in methyl *tert*-butyl ether (2 mL) and 1,1,1-trifluoroethyl formate (27 mg, 0.21 mmol) was added. The solution was stirred for 16 hours at room temperature and then the solvent was removed by evaporation. The residue was purified by column chromatography (5% ethyl acetate in hexanes) to give formate **313** as a yellow oil (26 mg, 50%). R_f: 0.71 (25% ethyl acetate in hexanes). IR (neat): ν_{max} 2925, 1723, 1568, 1527, 1464, 1330 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 11.75 (br s, 1 H), 8.27 (s, 1 H), 7.90 (d, J = 7.5 Hz, 1 H), 7.66 (t, J = 7.2 Hz, 1 H), 7.55 (m, 2 H), 7.35 (m, 3 H), 7.05 (t, J = 7.5 Hz, 1 H), 6.98 (t, J = 7.5 Hz, 1 H), 6.54 (d, J = 7.8 Hz, 1 H), 6.29 (m, 2 H), 5.49 (s, 1 H), 5.32 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.7, 161.0, 158.8, 148.1, 138.1, 133.6, 131.4, 131.1, 130.9, 130.8, 129.3, 128.9, 125.6, 124.8, 124.8, 118.7, 112.5, 88.8, 63.4 ppm. MS (ESI): *m*/*z* (%) 805 (46) $[M_2 + Na]^+$, 430 (29), 414 (100) $[M + Na]^+$. HRMS (ESI): calcd. for $C_{21}H_{17}N_3O_5Na$ $[M + Na]^+$: 414.10659; found: 414.10604.

(*Z*)-*tert*-butyl (2-((1-(2-nitrophenyl)-3-oxo-3-(1*H*-pyrrol-1-yl)prop-1-en-1-yl)amino)benzyl) carbonate (315)



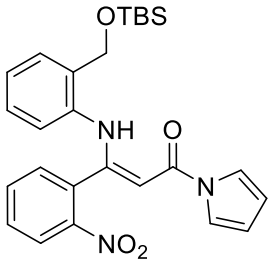
315

Amine **309** (10 mg, 28 μmol) was dissolved in THF (1 mL). Triethylamine (50 μL) was added followed by di-*tert*-butyl dicarbonate (10 mg, 46 μmol) and 4-DMAP (2 mg). The mixture was stirred for 20 hours then saturated aqueous ammonium chloride (5 mL) and ethyl acetate (10 mL) were added. The phases were separated, the organic phase was dried over Na_2SO_4 and the solvent was removed by evaporation. The crude product was purified by column chromatography (15% ethyl acetate in hexanes) to give carbonate **315** as a yellow oil (11 mg, 86%). R_f: 0.75 (25% ethyl acetate in hexanes). IR (neat): ν_{max} 2940, 1741, 1626, 1526, 1422, 1276, 1122 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 11.71 (s, 1 H), 7.91 (d, J = 7.8 Hz, 1 H), 7.62-7.48 (m, 4 H), 7.35-7.26 (m, 3 H), 7.03 (t, J = 7.2 Hz, 1 H), 6.94 (t, J = 7.2 Hz, 1 H), 6.26 (m, 2 H), 5.44 (s, 1 H), 5.24 (br s, 2 H), 1.55 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.6,



158.9, 153.5, 148.3 138.0, 133.5, 131.4, 131.1, 130.8, 130.7, 129.4, 129.2, 125.7, 124.8, 124.8, 118.8, 112.4, 88.6, 82.8, 66.1, 28.0 ppm. MS (ESI): *m*/*z* (%) 949 (100) $[M_2 + Na]^+$, 486 (27) $[M + Na]^+$, 464 (16) $[M + Na]^+$. HRMS (ESI): calcd. for $C_{25}H_{25}N_3O_6Na$ $[M + Na]^+$: 486.16411; found: 486.16356.

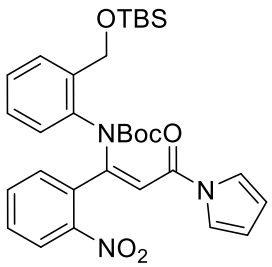
(*Z*)-3-((2-(((*tert*-butyldimethylsilyl)oxy)methyl)phenyl)amino)-3-(2-nitrophenyl)-1-(1*H*-pyrrol-1-yl)prop-2-en-1-one (317)



317

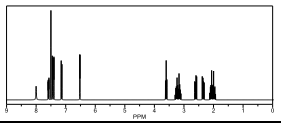
Benzyl alcohol **309** (145 mg, 0.40 mmol) was dissolved in dichloromethane (5 mL) with imidazole (136 mg, 2.0 mmol) and *tert*-butyldimethylsilyl chloride (120 mg, 0.8 mmol). The mixture was stirred at room temperature for 20 hours then saturated aqueous ammonium chloride (10 mL) was added. The phases were separated and the organic phase was washed with water (10 mL) then dried over Na_2SO_4. The solvent was removed by evaporation and the crude product was purified by column chromatography (10% ethyl acetate in hexanes) to give silyl ether **317** as a yellow oil (152 mg, 80%). R_f: 0.81 (25% ethyl acetate in hexanes). IR (neat): ν_{max} 2927, 1568, 1530, 1328, 1122 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 11.63 (br s, 1 H), 7.88 (d, J = 8.1 Hz, 1 H), 7.60-7.49 (m, 3 H), 7.34-7.26 (m, 3 H), 7.02 (t, J = 7.5 Hz, 1 H), 6.86 (t, J = 6.9 Hz, 1 H), 6.53 (d, J = 8.1 Hz, 1 H), 6.28 (m, 2 H), 5.44 (s, 1 H), 4.83 (br s, 2 H), 0.98 (s, 9 H),), 0.17 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.2, 158.7, 148.3, 137.0, 134.5, 133.2, 131.4, 131.4, 130.5, 128.6, 127.6, 125.3, 124.7, 124.4, 118.6, 112.2, 88.2, 63.1, 26.2, 18.5, -5.1 ppm. MS (APCI): *m*/*z* (%) 478 (92) $[M + H]^+$, 361 (100), 343, (40), 328 (46), 311 (55), 296 (51). HRMS (ESI): calcd. for $C_{26}H_{31}N_3O_4SiNa$ $[M + Na]^+$: 500.19760; found: 500.19750.

***tert*-butyl (*Z*)-(2-(((*tert*-butyldimethylsilyl)oxy)methyl)phenyl)(1-(2-nitrophenyl)-3-oxo-3-(1*H*-pyrrol-1-yl)prop-1-en-1-yl)carbamate (319)**



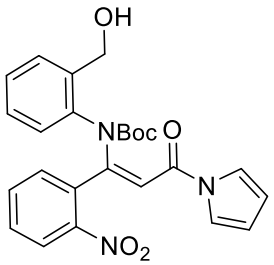
319

Amine **317** (50 mg, 0.10 mmol) was dissolved in dichloromethane (5 mL) followed by triethylamine (500 μL), di-*tert*-butyl dicarbonate (50 mg, 0.23 mmol) and DMAP (5 mg). The mixture was stirred for



20 hours then saturated aqueous ammonium chloride (5 mL) was added. The phases were separated, the organic phase was dried over Na_2SO_4 and the solvent was removed by evaporation. The crude product was purified by column chromatography (20% ethyl acetate in hexanes) to give the carbamate **319** as a colourless oil (48 mg, 80%). R_f: 0.64 (50% ethyl acetate in hexanes). IR (neat): ν_{max} 2929, 1737, 1693, 1526, 1465, 1244, 1147 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) 1:1 Mixture of rotamers: δ 8.08-8.04 (m, 2 H), 7.58-6.91 (m, 14 H), 6.62 (m, 4 H), 5.87 (m, 4 H), 5.33 (s, 1 H), 5.24 (s, 1 H), 4.85-4.56 (m, 4 H), 1.15 (s, 18 H), 0.97 (s, 18 H), 0.16 (s, 12 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) 1:1 Mixture of rotamers: δ 162.0, 161.7, 155.7, 155.3, 151.2, 151.0, 148.6, 147.8, 140.3, 138.4, 136.8, 136.4, 133.6, 133.4, 132.9, 132.7, 129.8, 129.4, 129.4, 129.1, 128.9, 128.6, 128.3, 128.0, 127.7, 127.5, 125.1, 124.8, 124.6, 124.5, 119.0, 119.0, 112.6, 112.6, 101.3, 100.8, 83.5, 83.4, 60.9, 60.5, 27.7, 25.8, 21.2, 21.2, 18.7, -5.1, -5.5 ppm. MS (ESI): *m*/*z* (%) 600 (39) $[M + Na]^+$, 596 (55), 491, (100). HRMS (ESI): calcd. for $C_{31}H_{39}N_3O_6SiNa$ $[M + Na]^+$: 600.25058; found: 600.25003.

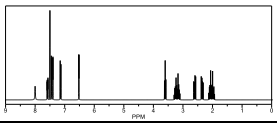
tert-butyl (_Z_)-(2-(hydroxymethyl)phenyl)(1-(2-nitrophenyl)-3-oxo-3-(1_H_-pyrrol-1-yl)prop-1-en-1-yl) carbamate (320)



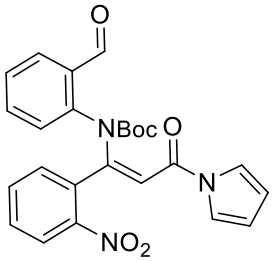
320

Silyl ether **319** (23 mg, 40 μmol) was dissolved in ethanol (1 mL) and PPTS (100 mg, 0.40 mmol) was added. The solution was stirred at room temperature for 24 hours then ethyl acetate (15 mL) and water (15 mL) were added. The aqueous layer was washed with ethyl acetate (3 × 5 mL) then the combined organic layers were washed with brine (5 mL) and dried over Na_2SO_4. The solvent was removed by evaporation and the crude product was purified by column chromatography (50% ethyl acetate in hexanes). The remaining silylated compound was re-exposed to the reaction conditions to obtain the alcohol **320** as a colourless oil (12 mg, 64%). R_f: 0.17 (20% ethyl acetate in hexanes). IR (neat): ν_{max} 3458, 2367, 1717, 1454, 1293, 1153 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.30-8.26 (d, J = 8.1 Hz, 1 H), 7.73-7.26 (m, 7 H), 6.86 (m, 2 H), 6.11 (m, 2 H), 5.54 (d, J = 12.6 Hz, 1 H), 4.85-4.73 (m, 2 H), 1.13 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.9, 155.6, (148.4, 147.9),* 139.3, 138.1, 133.7, 132.8, 130.2, 130.0, 129.8, 129.5, 129.1, 128.9, 128.3, 124.6, 118.9, 112.8, (102.0, 101.6)*, 84.0, (61.7, 61.2)*, 27.7 ppm. MS (ESI): *m*/*z* (%) 486 (100) $[M + Na]^+$, 377 (85), 242, (19). HRMS (ESI): calcd. for $C_{25}H_{25}N_3O_6Na$ $[M + Na]^+$: 486.16411; found: 486.16356.

*peak split due to conformational isomerism



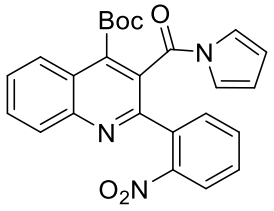
***tert*-butyl (*Z*)-(2-formylphenyl)(1-(2-nitrophenyl)-3-oxo-3-(1*H*-pyrrol-1-yl)prop-1-en-1-yl)carbamate (321)**



321

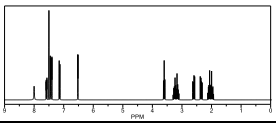
Oxalyl chloride (42 mg, 0.34 mmol) was dissolved in dichloromethane (1 mL) and cooled to -78°C. Dimethyl sulfoxide (33 mg, 0.42 mmol) was added and the solution was stirred for 30 minutes. A solution of benzyl alcohol **320** (9.5 mg, 21 μmol) in dichloromethane was added dropwise and the solution was stirred at -78°C for a further hour. Triethylamine (100 μL) was added and the reaction mixture was stirred for one hour. Saturated aqueous ammonium chloride (2 mL) was added and the mixture was allowed to warm to room temperature. Dichloromethane (10 mL) was added, the phases were separated and the organic phase was washed with water (10 mL). The organic layer was dried over Na_2SO_4 and the solvent was removed by evaporation. The crude product was purified by column chromatography (25% ethyl acetate in hexanes) to give the aldehyde **321** as a colourless solid (7 mg, 74%). IR (neat): ν_{max} 2924, 1728, 1670, 1590, 1454, 1120 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) 1: 2 mixture of rotamers: δ 10.35-10.15 (m, 2 H), 8.29-8.25 (m, 2 H), 8.06-8.03 (m, 2 H), 7.83-7.26 (m, 4 H), 6.98-6.85 (m, 4 H), 6.24-6.12 (m, 4 H), 5.44 (s, 2 H), 1.29-1.22 (m, 18 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.6, 161.8, 156.0, 140.7, 136.0, 133.7, 132.6, 132.2, 130.7, 130.4, 129.8, 129.6, 129.5, 124.9, 124.4, 120.5, 119.0, 112.8, 102.3, 84.1, 27.7 ppm. MS (ESI): *m*/*z* (%) 484 (100) $[M + Na]^+$. HRMS (ESI): calcd. for $C_{25}H_{23}N_3O_6Na$ $[M + Na]^+$: 486.14846; found: 484.14791.

2-(2-nitrophenyl)-3-(1*H*-pyrrole-1-carbonyl)-4-(*tert*-butyloxycarbonyl)quinoline (323)



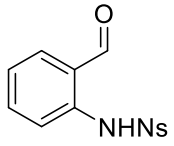
323

Triazolium salt **241** (5 mg, 15 μmol) and triethyl amine (1 μL, 7.5 μmol) were dissolved in THF (1 mL) and the solution was sparged with argon for 10 minutes. Compound **321** (7 mg, 15 μmol) was dissolved in THF (10 mL) and sparged for 10 minutes with argon. The carbene solution was added to the reactant solution *via* cannula and the reaction was stirred at room temperature for 16 hours, then transferred directly onto a column of silica and purified by column chromatography (25% ethyl acetate in hexanes) to give quinoline **323** as a colourless solid (7 mg, 100%). mp: 143-145°C. IR



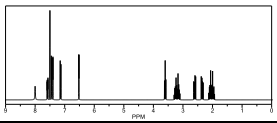
(neat): ν_{max} 2934, 1723, 1531, 1335, 1280, 1154 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.42 (d, J = 8.1 Hz, 1 H), 8.14 (d, J = 8.4 Hz, 1 H), 8.04 (d, J = 7.5 Hz, 1 H), 7.87 (t, J = 6.9 Hz, 1 H), 7.74 (t, J = 8.4 Hz, 1 H), 7.62-7.50 (m, 3 H), 7.40 (br s, 1 H), 6.79 (br s, 1 H), 6.21 (br s, 1 H), 6.11 (br s, 1 H), 1.38 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.3 (C), 163.7 (C), 152.8 (C), 137.0, 148.6 (C), 148.5 (C) 139.1 (C), 133.6 (C), 132.9 (CH), 131.8 (CH), 131.5 (CH), 130.1 (CH), 130.1 (CH), 129.1 (CH), 126.0 (C), 125.9 (CH), 125.2 (CH), 122.9 (C), 122.2 (CH), 118.6 (CH), 114.5 (CH), 112.9 (CH), 85.5 (C), 27.4 (CH_3) ppm. MS (ESI): m/z (%) 909 (21) [M_2 + Na]$^+$, 466 (100) [M + Na]$^+$, 444 (15) [M + H]$^+$. HRMS (ESI): calcd. for $C_{25}H_{21}N_3O_5Na$ [M + Na]$^+$: 466.13734; found: 466.13745.

_N_-nosyl-2-aminobenzaldehyde (335)

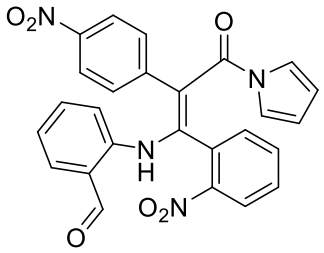


335

2-Aminobenzylalcohol (2.00 g, 16.2 mmol) was dissolved in pyridine (1.2 mL) and chloroform (15 mL). A solution of 4-nitrobenzenesulfonyl chloride (17.9 mmol, 3.94 g) in chloroform (15 mL) was added dropwise to the amine solution and the resulting mixture was stirred at room temperature for 16 hours. The volatiles were removed by evaporation to give crude *N*-nosyl-2-aminobenzylalcohol (5.57 g, 100%). mp: 152.7-153.9°C. IR (neat): ν_{max} 3216, 3109, 1530, 1346, 1153, 1036, 737 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 9.89 (br s, 1 H), 8.39 (d, J = 8.7 Hz, 2 H), 7.92 (d, J = 8.7 Hz, 2 H), 7.43 (d, J = 7.2 Hz, 1 H), 7.23 (t, J = 7.2 Hz, 1 H), 7.15 (td, J = 7.8, 1.2 Hz, 1 H) 6.88 (d, J = 7.2 Hz, 1 H), 5.19 (br s, 1 H), 4.29 (s, 2 H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 149.8, 145.7, 138.6, 132.5, 128.2, 127.6, 127.2, 126.8, 125.7, 124.6, 59.0 ppm. MS (ESI): m/z (%) 615 (95) [M_2 - H]$^-$, 307 (100) [M - H]$^-$. HRMS (ESI): calcd. for $C_{13}H_{12}N_2O_5SNa$ [M + Na]$^+$: 331.03591; found: 331.03591. The crude benzyl alcohol was dissolved in chloroform (11 mL) and manganese dioxide (7.04 g, 80.0 mmol) was added. The suspension was heated to 60°C for 6 hours then cooled to room temperature. The insoluble material was removed by filtration through a plug of Celite and the solvent was removed by evaporation. The crude product was purified by trituration with methyl *tert*-butyl ether to give the *title compound* as a tan solid (2.11 g, 43%). mp: 175.4-176.5°C. IR (neat): ν_{max} 3114, 1656, 1530, 1494, 1347, 1162, 1089, 934, 734 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 10.92 (br s, 1 H), 9.83 (s, 1 H), 8.29 (d, J = 12.6 Hz, 2 H), 8.06 (d, J = 12.6 Hz, 2 H), 7.75-7.54 (m, 3 H), 7.29-7.22 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.4, 150.5, 145.1, 139.1, 136.5, 136.2, 128.7, 124.6, 124.2, 122.4, 118.3 ppm. MS (ESI): m/z (%) 305 (100) [M - H]$^-$. HRMS (ESI): calcd. for $C_{13}H_{10}N_2O_5SNa$ [M + Na]$^+$: 329.02026; found: 329.02030.



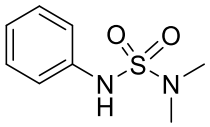
(*E*)-2-((1-(2-nitrophenyl)-2-(4-nitrophenyl)-3-oxo-3-(1*H*-pyrrol-1-yl)prop-1-en-1-yl)amino)benzaldehyde (342)



342

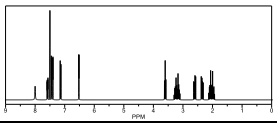
N-Nosyl-2-aminobenzaldehyde (12 mg, 37 μmol) and compound **318** (12 mg, 50 μmol) were dissolved in THF (1 mL) and triethylamine (30 μL) was added. The solution was heated to reflux for four hours then the volatiles were removed by evaporation. The residue was purified by column chromatography (15% ethyl acetate in hexanes) to give the *title compound* as an orange solid (14 mg, 57). R_f: 0.23 (20% ethyl acetate in hexanes). IR (neat): ν_{max} 3104, 2919, 1723, 1606, 1531, 1349, 1172 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 10.91 (br s, 1 H), 9.83 (s, 1 H), 8.28 (d, J = 8.7 Hz, 1 H), 8.07 (d, J = 8.7 Hz, 1 H), 7.80-7.72 (m 4 H), 7.63 (d, J = 6.3 Hz, 1 H), 7.59 (t, J = 7.2 Hz, 1 H), 7.27-7.22 (m, 4 H), 6.37 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.4 (CH), 182.7 (C), 154.9 (C), 150.5 (C), 147.1 (C), 145.1 (C), 139.0 (C), 136.5 (CH), 136.2 (CH), 135.4 (CH), 133.7 (CH), 128.7 (CH), 124.6 (CH), 124.2 (CH), 122.8 (CH), 122.6 (CH), 122.4 (C), 120.0 (CH), 120.0 (C), 118.3 (CH), 115.5 (CH), 114.7 (CH) ppm. MS (ESI): *m*/*z* (%) 503 (100) $[M + Na]^+$, 242 (90). HRMS (ESI): calcd. for $C_{26}H_{16}N_4O_6Na$ $[M + Na]^+$: 503.09621; found: 503.09614.

***N,N*-dimethylsulfamoyl-aniline (346)**[237]

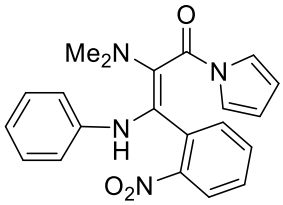


346

Aniline (93 mg, 1.0 mmol) was dissolved in dichloromethane (4 mL) with triethylamine (500 μL) and 4-dimethylaminopyridine (10 mg). *N,N*-Dimethylsulfamoyl chloride (171 mg, 1.2 mmol) was added and the solution was stirred for 24 hours. Saturated aqueous sodium hydrogen carbonate solution (10 mL) was added and the phases were separated. The organic phase was washed with further saturated aqueous sodium hydrogen carbonate solution (10 mL) and brine (10 mL). The organic phase was dried over Na_2SO_4 and the solvent was removed by evaporation to give the *title compound* as a colourless oil (200 mg, 100%). R_f: 0.35 (15% ethyl acetate in hexanes). IR (neat): ν_{max} 3272, 2892, 1600, 1496, 1338, 1144, 954, 708, 561 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.35 (br s, 1 H), 7.30-7.18 (m, 4 H), 7.08 (m, 1 H), 2.81 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.5, 129.0, 124.4, 120.1, 38.2 ppm. MS (ESI): *m*/*z* (%) 199 (100) $[M - H]^-$. HRMS (ESI): calcd. for $C_8H_{12}N_2O_2SNa$ $[M + Na]^+$: 223.05117; found: 223.05124.



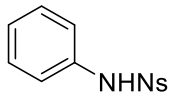
(*E*)-2-(dimethylamino)-3-(3-nitrophenyl)-3-(phenylamino)-1-(1*H*-pyrrol-1-yl)prop-2-en-1-one (348)



348

N-(*N*,*N*-dimethylsulfamoyl)-aniline (30 mg, 0.15 mmol) and compound **318** (30 mg, 0.13 mmol) were dissolved in THF (2 mL) and triethylamine (50 μL) was added. The solution was heated to reflux for 3 hours then cooled to room temperature. The solvent was removed by evaporation and the residue was purified by column chromatography to give the *title compound* as an orange oil (16 mg, 27 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80-7.75 (m, 4 H), 7.34-7.29 (m, 2 H), 7.28 (m, 2 H), 7.20-7.13 (m, 2 H), 6.75 (br s, 1 H), 6.38 (m, 2 H), 2.85 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 182.7 (C), 154.9 (C), 147.0 (C), 137.5 (C), 135.3 (CH), 133.6 (CH), 129.5 (CH), 124.7 (CH), 122.8 (CH), 122.6 (C), 120.3 (CH), 120.0 (CH), 120.0 (C), 115.5 (CH), 114.7 (CH), 38.3 (CH_3) ppm. MS (ESI): *m*/*z* (%) 354 (88), 326 (51), 273 (57), 240 (51), 213 (66), 197 (100). HRMS could not be obtained with the available instruments.

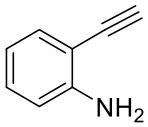
***N*-nosyl-aniline (351)**[238]



351

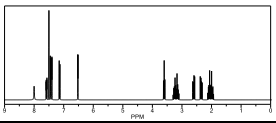
Aniline (930 mg, 1.0 mmol) was dissolved in pyridine (1.0 mL) and dichloromethane (10 mL). A solution of 4-nitrobenzenesulfonyl chloride (2.21 g, 1.0 mmol) in dichloromethane (10 mL) was added dropwise to the amine solution and the resulting mixture was stirred at room temperature for 16 hours. Hydrochloric acid (1 M, 20 mL) was added and the phases were separated. The organic phase was washed with water (30 mL) and the volatiles were removed by evaporation to give the *title compound* as a pink solid (2.94 g, 100%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.60 (br s, 1 H), 8.36 (d, J = 8.7 Hz, 2 H), 7.99 (d, J = 8.7 Hz, 2 H), 7.25 (m, 2 H), 7.11-7.04 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.8, 144.9, 136.9, 136.5, 129.3, 128.2, 124.8, 124.6, 120.7 ppm. Spectroscopic data matched that previously reported.[238]

2-ethynylaniline (366)[205b]



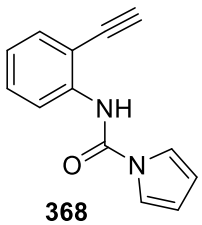
366

Compound **366** was synthesised according to the procedure published by Saá.[205b] ^{1}H NMR (300 MHz,



$CDCl_3$): δ 8.42 (d, J = 8.1 Hz, 1 H), 7.34 (d, J = 6.9 Hz, 1 H), 7.14 (t, J = 7.8 Hz, 1 H), 6.71-6.67 (m, 1 H), 4.26 (br s, 2 H), 3.40 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.6, 132.7, 130.2, 117.9, 114.4, 106.7, 82.6, 80.7 ppm. Spectroscopic data matched that previously reported.[205b]

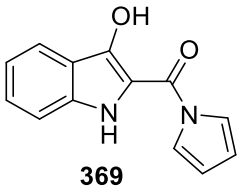
_N_-(1_H_-pyrrole-1-carbonyl)-2-ethynylaniline (368)



368

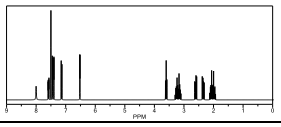
2-Ethynylaniline (42 mg, 0.36 mmol) was dissolved in THF (2 mL) and cooled to -78°C. n-Butyllithium (2.5 M in hexanes, 144 μL, 0.36 mmol) was added dropwise and the solution was stirred for one hour. A solution of 1,1-carbonyldipyrrole (86 mg, 0.54 mmol) in THF (1 mL) was added over 30 minutes. The reaction mixture was stirred for a further two hours at -78°C then saturated aqueous ammonium chloride (5 mL) was added and the solution was allowed to warm to room temperature. Ethyl acetate (15 mL) was added and the phases were separated. The aqueous phase was washed with ethyl acetate (10 mL) and the organic phase was washed with brine (10 mL). The organic phase was dried over Na_2SO_4 and the solvent was removed by evaporation. The residue was purified by column chromatography (5% ethyl acetate in hexanes) to give the *title compound* as a colourless oil (15 mg, 18%). R_f: 0.57 (20% ethyl acetate/hexanes). IR (neat): ν_{max} 3446, 3217, 1718, 1529, 1314 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.34 (d, J = 8.2 Hz, 1 H), 8.26 (br s, 1 H), 7.52-7.47 (m, 2 H), 7.38 (m, 2 H), 7.09 (t, J = 7.6 Hz, 1 H), 6.34 (m, 2 H), 3.61 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.9 (C), 139.1 (C), 132.3 (CH), 130.6 (CH), 123.7 (CH), 118.9 (CH), 118.6 (CH), 112.9 (CH), 111.1 (C), 85.1 (CH), 79.3 (C) ppm. MS (APCI): m/z (%) 211 (100) $[M + H]^+$, 116 (18). HRMS (APCI): calcd. for $C_{13}H_{11}N_2O$ $[M + H]^+$: 211.08659; found: 211.08689.

(3-hydroxy-1_H_-indol-2-yl)(1_H_-pyrrol-1-yl)methanone (369)



369

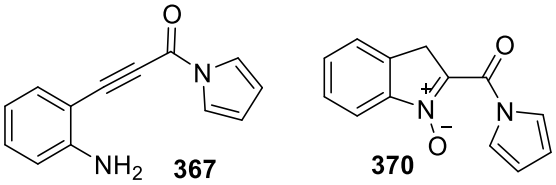
Compound **318** (50 mg, 0.21 mmol) was dissolved in acetone/water (4:1, 2 mL) and sodium dithionite (108 mg, 1.0 mmol) was added. The solution was heated to 50°C for two hours then cooled to room temperature. Ethyl acetate (10 mL) and water (10 mL) were added. The phases were separated, the organic phase was dried over Na_2SO_4 and the solvent was removed by evaporation to give the *title*



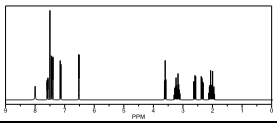
compound as a colourless solid (46 mg, 99%). IR (neat): ν_{max} 3390, 3151, 1626, 1531, 1445, 1334, 1075 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 9.75 (br s, 1 H), 7.80 (d, J = 8.1 Hz, 1 H), 7.68 (br s, 1 H), 7.52 (m, 2 H), 7.55 (t, J = 8.1 Hz, 1 H), 7.32 (d, J = 8.4 Hz, 1 H), 7.16 (t, J = 7.5 Hz, 1 H), 6.44 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.8 (C), 154.4 (C), 138.1 (C), 129.2 (CH), 120.9 (CH), 120.9 (C), 119.9 (CH), 118.4 (CH), 113.8 (CH), 112.7 (CH), 110.0 (C) ppm. MS (APCI): *m*/*z* (%) 225 (80) $[M - H]^+$, 197 (100), 160 (66); (ESI) 227 (62) $[M + H]^+$, 160 (100). HRMS (ESI): calcd. for $C_{13}H_{11}N_2O_2$ $[M + H]^+$: 227.08152; found: 227.08150.

3-(2-aminophenyl)-1-(1*H*-pyrrol-1-yl)prop-2-yn-1-one (367)

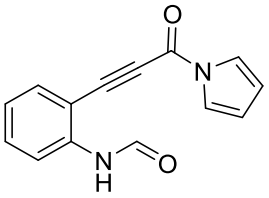
2-(1*H*-pyrrole-1-carbonyl)-3*H*-indole 1-oxide (370)



N-(3-(2-Nitrophenyl)-propioloyl)pyrrole (200 mg, 0.80 mmol) was dissolved in methanol (15 mL) and tin(II) chloride hydrate (756 mg, 4.0 mmol) was added followed by hydrochloric acid (33%, 500 μL). The mixture was stirred for 18 hours then neutralised with saturated aqueous sodium hydrogen carbonate. The reaction mixture was poured onto ethyl acetate (50 mL) and the phases were separated. The organic phase was washed with brine (2 × 20 mL) then dried over Na_2SO_4 and the solvent was removed by evaporation. The residue was purified by column chromatography (15% ethyl acetate in hexanes) to give amine **367** as a colourless oil (55 mg, 28%). R_f: 0.48 (20% ethyl acetate in hexanes). IR (neat): ν_{max} 3400, 3207, 2180, 1652, 1470, 1348, 1254, 1104 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.52 (m, 2 H), 7.42 (d, J = 7.5 Hz, 1 H), 7.26 (t, J = 7.5 Hz, 1 H), 6.72 (m, 2 H), 6.36 (m, 2 H), 4.52 (br s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.7 (C), 150.5 (C), 133.7 (CH), 133.1 (CH), 120.0 (CH), 118.1 (CH), 114.9 (C), 114.0 (CH), 102.9 (C), 90.7 (C), 87.2 (C) ppm. MS (ESI): *m*/*z* (%) 210 (90) $[M + Na]^+$, 144 (100). HRMS (ESI): calcd. for $C_{13}H_{10}N_2ONa$ $[M + Na]^+$: 233.06883; found: 233.06851. The reaction also gave oxide **370** as a yellow oil (45 mg, 23%). R_f: 0.35 (20% ethyl acetate in hexanes). IR (neat): ν_{max} 3147, 2923, 2194, 1714, 1469, 1343, 1113, 911 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.53 (d, J = 9.0 Hz, 1 H), 7.47 (d, J = 9.0 Hz, 1 H), 7.38 (m, 2 H), 7.28 (dd, J = 6.6, 9.3 Hz, 1 H), 6.98 (dd, J = 6.3, 8.7 Hz, 1 H), 6.34 (m, 2 H), 4.70 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.7 (C), 159.4 (C), 157.5 (C), 131.2 (CH), 124.5 (CH), 119.5 (CH), 119.5 (CH), 117.0 (C), 115.3 (CH), 114.4 (CH), 33.8 (CH_2) ppm. MS (ESI): *m*/*z* (%) 249 (100) $[M + Na]^+$. HRMS (ESI): calcd. for $C_{13}H_{1o}N_2O_2Na$ $[M + Na]^+$: 249.06345; found: 249.06353.



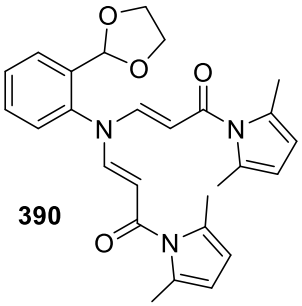
_N_-(2-(3-oxo-3-(1_H_-pyrrol-1-yl)prop-1-yn-1-yl)phenyl)formamide (371)



371

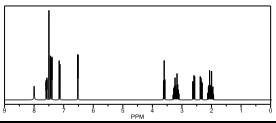
Amine **367** (55 mg, 0.26 mmol) was dissolved in 1,1,1-trifluoroethyl formate (500 μL). The solution was stirred for 16 hours at room temperature and then the solvent was removed by evaporation. The residue was purified by column chromatography (5% ethyl acetate in hexanes) to give the *title compound* as a colourless oil (8 mg, 15%). ^{1}H NMR (300 MHz, $CDCl_3$) mixture of *cis* and *trans* amides (3/1): δ 8.83 (d, J = 11.1 Hz, 0.26 H), 8.54 (s, 0.82 H), 8.48 (d, J = 8.4 Hz, 1 H), 8.10 (br s, 1 H), 7.69-7.53 (m, 2 H), 7.49 (m, 2 H), 7.32 (d, J = 78.2 Hz, 0.25 H), 7.26-7.15 (m, 1 H), 6.39 (m, 2 H) ppm. MS (ESI): m/z (%) 499 (64) $[M_2 + Na]^+$, 261 (100) $[M + Na]^+$. HRMS (ESI): calcd. for $C_{14}H_{10}N_2O_2Na$ $[M + Na]^+$: 261.0345; found: 261.06358.

(2_E_,2'_E_)-3,3'-((2-(1,3-dioxolan-2-yl)phenyl)azanediyl)bis(1-(2,5-dimethyl-1_H_-pyrrol-1-yl)prop-2-en-1-one) (390)

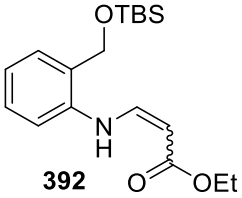


390

2-(1,3-Dioxolan-2-yl)aniline (530 mg, 3.22 mmol) and *N*-propioloyl-(2,5-dimethyl)pyrrole (400 mg, 2.68 mmol) were dissolved in dichloromethane (10 mL) and *N*-methylmorpholine (460 mg, 4.55 mmol) was added. The mixture was stirred for sixteen hours then the solvent was removed by evaporation. The residue was purified by column chromatography (20% ethyl acetate in hexanes) to give the *title compound* as a colourless oil (50 mg, 6%). R_f: 0.19 (20% ethyl acetate in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94 (d, J = 12.9 Hz, 2 H), 7.80 (m, 1 H), 7.56 (m, 2 H), 7.15 (m, 1 H), 5.83 (s, 4 H), 5.68 (s, 1), 5.18 (d, J = 12.9 Hz, 2 H), 4.09-3.93 (m, 4 H), 2.17 (s, 12 H). ^{13}C NMR (75 MHz, $CDCl_3$): could not be obtained due to instability. MS (APCI): m/z (%) 460 (21) $[M + H]^+$, 399 (22), 379 (29), 365 (46), 321 (100), 270 (69), 244 (65), 172 (31). HRMS (ESI): calcd. for $C_{27}H_{29}N_3O_4Na$ $[M + Na]^+$: 482.20558; found: 482.20592.



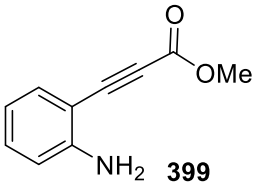
ethyl 3-((2-(((*tert*-butyldimethylsilyl)oxy)methyl)phenyl)amino)acrylate (392)



392

2-(((*tert*-Butyldimethylsilyl)oxy)methyl)aniline (200 mg, 0.84 mmol) and ethyl propiolate (71 mg, 0.72 mmol) were dissolved in ethanol (5 mL) and heated to reflux for 24 hours. The solvent was removed by evaporation and the residue was purified chromatography (15% ethyl acetate in hexanes) to give compound **392** as a colourless oil (173 mg, 71 %) in a mixture of diastereomers (3/1, *Z*/*E*). R_f: 0.79 (ethyl acetate/hexanes, 1/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.19 (br s, 0.68 H), 8.21 (br s, 0.22 H), 7.28–6.93 (m, 4 H), 5.21 (d, J = 13.2 Hz, 0.23 H), 4.84 (dd, J = 8.4 Hz, 0.62 H), 4.71 (m, 2 H), 4.19 (m, 2 H), 1.29 (t, J = 6.9 Hz, 2 H), 0.92 (s, 9H), 0.09 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ *Z* isomer: 169.6, 143.4, 140.2, 128.9, 128.8, 128.6, 122.2, 114.4, 88.3, 63.7, 59.2, 26.0, 18.5, 14.7, -5.1; *E* isomer: 169.1, 143.1, 141.1, 129.4, 128.6, 127.3, 122.9, 114.9, 93.1, 65.5, 59.5, 25.9, 18.2, 14.6, -5.2 ppm. HRMS (ESI): calcd. for $C_{18}H_{29}NO_3SiNa$ $[M + Na]^+$: 358.18144, found: 358.18159.

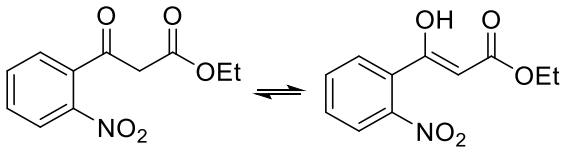
methyl 3-(2-aminophenyl)propiolate (399)[239]



399

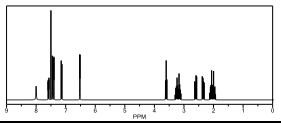
Compound **399** was synthesised according to the procedure published by Sakamoto[207] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43–7.37 (m, 2 H), 7.30–7.21 (m, 2 H), 3.87 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.5, 150.2, 133.8, 132.4, 117.9, 114.6, 103.1, 86.3, 84.4, 52.4 ppm. Spectroscopic data matched that previously reported.[239]

ethyl 3-(2-nitrophenyl)-3-oxopropanoate (403)[216]



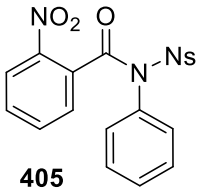
keto-403 **enol-403**

Compound **403** was synthesised according to the procedure published by Nammalwar.[216] ^{1}H NMR (300 MHz, $CDCl_3$) (5/1; keto/enol): δ 12.28 (s, 0.2 H), 8.15 (d, J = 8.4 Hz, 1 H), 7.86 (d, J = 8.1 Hz, 0.2 H), 7.75 (t, J = 7.5 Hz, 1 H), 7.62-7.49 (m, 2.6 H), 5.40 (s, 0.2 H), 4.24 (q, J = 7.2 Hz, 0.4 H), 4.14 (q, J = 7.2 Hz, 2 H), 3.86 (s, 2 H), 1.32 (t, J = 7.2 Hz, 0.6 H), 1.21 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.8,



172.3, 170.0, 166.7, 145.5, 136.9, 134.7, 132.8, 131.2, 130.1, 129.6, 128.3, 124.5, 124.4, 92.2, 61.7, 60.9, 49.1, 49.1, 14.3, 14.1 ppm. Spectroscopic data matched that previously reported.[216]

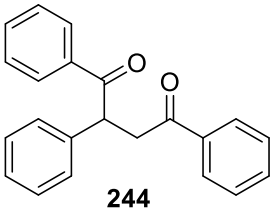
2-nitro-*N*-((4-nitrophenyl)sulfonyl)-*N*-phenylbenzamide (405)



405

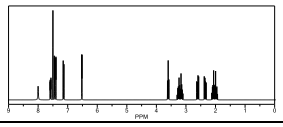
N-Nosyl aniline (500 mg, 1.85 mmol) was dissolved in dichloromethane/pyridine (10 mL, 4:1) and cooled to 0°C. A solution of *o*-nitrobenzoyl chloride (334 mg, 1.8 mmol) in dichloromethane (1 mL) was added dropwise. The solution was stirred for 16 hours, being allowed to warm to room temperature then hydrochloric acid (1 M, 10 mL) was added. The phases were separated and the organic phase was washed with hydrochloric acid (1 M, 2 × 10 mL), saturated sodium carbonate solution (10 mL) and brine (10 mL). The organic phase was dried over Na_2SO_4 and the solvent was removed by evaporation. The crude product was purified by column chromatography (ethyl acetate) to give the *title compound* as a tan solid (477 mg, 62%). mp: 149.4-150.9°C. IR (neat): ν_{max} 1656, 1597, 1526, 1440, 1345, 1323, 740, 702 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.45 (d, J = 9.0 Hz, 2 H), 8.31 (d, J = 9.0 Hz, 2 H), 8.09 (m, 1 H), 7.92 (dd, J = 0.9, 7.5 Hz, 1 H), 7.85 (m, 1 H), 7.74-7.50 (m, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.5, 146.5, 137.4, 134.1, 132.7, 132.6, 130.9, 130.5, 129.9, 129.3, 128.8, 125.4, 124.9, 124.2, 120.1 ppm.

1,2,4-triphenylbutane-1,4-dione (244)[240]



244

Chalcone (100 mg, 0.48 mmol) and benzaldehyde (102 mg, 0.96 mmol) were dissolved in THF (1 mL) and the solution was sparged with argon for 10 minutes. In a separate flask, caesium carbonate (78 mg, 0.24 mmol) and 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride (65 mg, 0.24 mmol) were dissolved in THF and the solution was sparged with argon for 10 minutes. The aldehyde solution was added to the catalyst solution *via* cannula and the resulting mixture was stirred for 24 hours. The reaction mixture was transferred directly to a silica column and purified by column chromatography (10 % ethyl acetate in hexanes) to give the *title compound* a colourless solid (69 mg, 46%). ^1H NMR (300 MHz, $CDCl_3$): δ 8.06-8.03 (m, 4 H), 7.56–7.23 (m, 11 H), 5.33 (dd, J = 3.6, 10.4 Hz, 1 H), 4.22 (dd, J =



10.3, 18.0 Hz, 1 H), 3.31 (dd, J = 3.6, 18.0 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.9, 198.0, 138.6, 136.5, 136.5, 133.2, 132.9, 129.1, 128.9, 128.6, 128.5, 128.2, 128.2, 127.3, 48.7, 43.9 ppm. Spectroscopic data matched that previously reported.[240]

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