Reaction Discovery in Phosphine Organocatalysis via the β-Phosphonium Ylide

A thesis submitted for the degree of Doctor of Philosophy (Chemistry)

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Declaration

I declare that, to the best of my knowledge, the material presented in this thesis represents the result of original work carried out by me during the period 2015–2019 and has not been presented for examination for any degree. This thesis is less than 100,000 words in length. Established methodologies have been acknowledged, wherever possible, by citation of the original publication from which they are derived.

Jhi Ametovski
November 2019

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Publications and Presentations

Publications

- Ametovski, J.; Dutta, U.; Burchill, L.; Maiti, D.; Lupton, D.W.; Hooper, J.F. Phosphine catalysed (5 + 1) annulation of ynone-cinnamates with primary amines. *Chem. Commun.* **2017**, 53, 13071–13074.

Presentations

- Poster presentation: "Enantioselective (3 + 2) annulation of allenoates and allylic amines under via the β-phosphonium ylide", *43rd Annual Synthesis Symposium, Melbourne, Australia,* **2018**.

- Poster presentation: "Enantioselective synthesis of pyrrolidines under phosphine organocatalysis", *Belgian Organic Synthesis Symposium*, *Brussels, Belgium,* **2018**.

- Poster presentation: "Phosphine catalysed (5 + 1) annulation of ynone/cinnamates with primary amines" *42nd Annual Synthesis Symposium, Melbourne, Australia, 2017*.

Abstract

Phosphine organocatalysis with α,β-unsaturated carbonyl compounds lead to host of reactive intermediates which may exhibit the typical reactivity of enolates, or as is the case with activated alkynes and allenes, intermediates which react with inverted polarity at the α- and γ-positions. Under the right conditions such intermediates may lead to the β-phosphonium ylide. At the commencement of my doctoral studies, there were only several reactions which exploited the β-phosphonium ylide, none of which occurred catalytically.

The first chapter of this thesis provides an introduction to normal polarity and umpolung reactions enabled by phosphines. In particular, reactions that proceed via umpolung at the β-position are examined.

The second chapter reports the discovery and development of an annulation of primary amines with ynone/cinnamates that proceeds via interception of an intermediate that is encountered following α-addition of an amine to activated alkynes. Scope studies revealed this process to be useful for the synthesis of isoquinolinones, pyrrolidinones and pyrrolopiperazines. The development of an enantioselective reaction was attempted though selectivity was poor.

In the third chapter, our focus returned to accessing the β-phosphonium ylide. This was ultimately achieved via addition of phosphines to allenoates, which eventually leads to the β-phosphonium ylide in the presence of a bifunctional donor acceptor. Our studies uncovered an enantioselective (3 + 2) annulation that provides enantioenriched pyrrolidines, in many cases, with excellent enantioselectivity. Unfortunately diastereoselectivity was a challenge and our attempts to rectify this are reported. Our efforts to determine the scope of this reaction led to the serendipitous discovery of a related (4 + 2) annulation that leads to functionalised piperidines. Early experiments suggest that an enantioselective variant of this reaction is viable.

The final chapter contains the experimental procedures employed for the experiments conducted throughout this thesis, in addition to the spectral and X-ray crystallography data of the respective compounds.

Glossary

Ac	Acetyl
Ar	Aryl
Bn	Benzyl
Boc	*t*-Butoxycarbonyl
Bu	Butyl
Bz	Benzoyl
Cat.	Catalyst
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIPEA	Diisopropylethyl amine
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMP	Dess-Martin Periodinane
DMSO	Dimethyl sulfoxide
dr	Diastereomeric ratio
E	Electrophile
EWG	Electron withdrawing group
ee	Enantiomeric excess
er	Enantiomeric ratio
eq.	Equation
equiv.	Equivalents
ESI	Electrospray ionization
Et	Ethyl

h	Hours
HFIP	Hexafluoroisopropanol
HPLC	High-performance liquid chromatography
HRMS	High-resolution mass-spectrometry
IBX	2-Iodoxybenzoic acid
i-Pr	*iso*-propyl
IR	Infrared
J	Coupling constant
KO*t*-Bu	Potassium *tert*-butoxide
LRMS	Low resolution mass spectroscopy
Me	Methyl
Mes	Mesityl (2,4,6-trimethylphenyl)
min	Minutes
mp	Melting point
Ms	Methanesulfonyl
MS	Molecular sieves
NHC	N-heterocyclic carbene
NMR	Nuclear magnetic resonance
Nu	Nucleophile
PCC	Pyridinium chlorochromate
Pg	Protecting group
Ph	Phenyl
PivOH	Pivalic acid
Pr	Propyl
PMP	*para*-methoxyphenyl

ppm	Parts per million
PPTS	Pyridinium p-toluenesulfonate
p-TsOH	*p*-Toluenesulfonic acid
R_f	Retardation factor
rt	Room temperature
TBS	*tert*-butyldimethylsilyl
TBSCl	*tert*-butyldimethylsilyl chloride
t-Bu	*tert*-butyl
t-BuOH	*tert*-butanol
temp.	Temperature
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	N,N,N′,N′-Tetramethylethylenediamine
TMS	Trimethylsilyl
TMSCl	Trimethylsilyl chloride
Tol	Tolyl
Ts	*p*-Toluenesulfonyl

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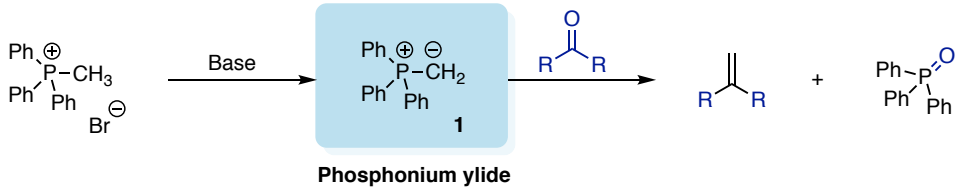
Chapter 1

Introduction to phosphines in organocatalysis

1.1 Introduction

1.1.1 Introduction to phosphorus in organic chemistry

Organophosphorus compounds are used widely in organic synthesis and have numerous applications as reagents and in catalysis. Most commonly, they are known for their role as ligands in transition metal catalysis, or stoichiometric reagents in the Wittig and Mitsunobu reactions, with the former two discoveries leading to Nobel prizes (Wittig, 1979 & Noyori and Knowles, 2001). Perhaps most famously in the context of organic chemistry, organic phosphonium salts are known for their ability to form ylides (i.e. **1**) when reacted with strong bases and their subsequent reactions with ketones and aldehydes leads to the formation of alkenes, as first demonstrated by Wittig & Schöllkopf in 1957 (Scheme 1.1).[1]



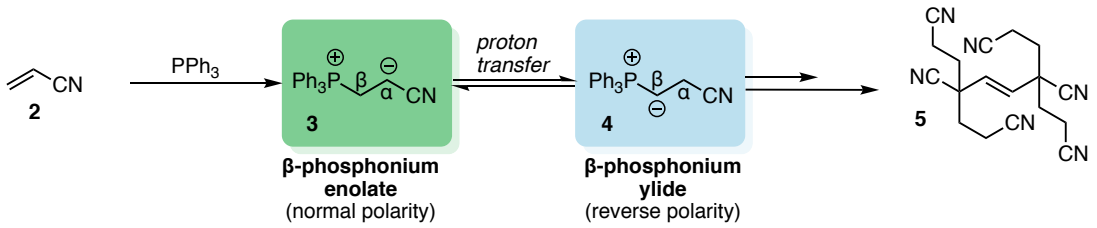
Scheme 1.1: Wittig olefination of benzophenone via a phosphonium ylide.

In addition to their aforementioned uses they are also known to be effective Lewis base organocatalysts. In the latter role they have driven the discovery of a range of interesting

carbon–carbon and carbon–heteroatom bond forming reactions most of which involve α,β-unsaturated carbonyl compounds.[2]

1.1.2 Origins of phosphines as organocatalysts

The first known report of a carbon–carbon bond forming reaction catalysed by a phosphine was disclosed by Takashina and Price who discovered that triphenylphosphine could effect the hexamerisation of acrylonitrile in alcoholic solvents (Scheme 1.2).[3] They proposed that the reaction proceeds via conjugate addition of triphenylphosphine to acrylonitrile **2** to provide phosphonium enolate **3** with subsequent tautomerisation then giving β-phosphonium ylide **4**. This intermediate exhibits inverted polarity at the β-position and reacts with additional equivalents of acrylonitrile **2** to eventually furnish hexamer **5**.

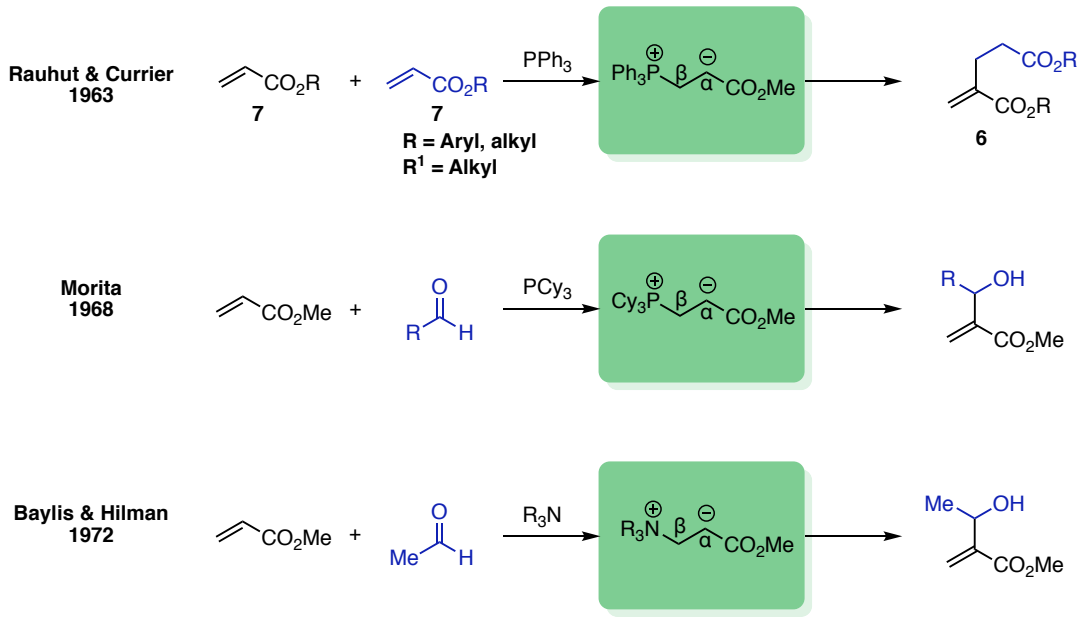


Scheme 1.2: Hexamerisation of acrylonitrile catalysed by triphenylphosphine.

Interestingly, this report is an example of umpolung reactivity at the β-position of electron deficient alkenes and surprisingly, remains one of the few examples of this type of reactivity to this day. Since this original publication, methodology development in the phosphine catalysis with alkenes has primarily focused on chemistry proceeding via normal polarity intermediates (i.e. enolates).

Perhaps most well known is the pioneering work communicated of Rauhut and Currier in a 1963 patent that describes the preparation of dialkyl 2-methyleneglutarates

(i.e. **6**) via dimerisation of acrylate esters (i.e. **7**) under phosphine catalysis (Scheme 1.3).[4] This represented the first example of a carbon–carbon bond forming reaction of this type catalysed by phosphines. In 1968, some five years after this important report, Morita extended the scope of the reaction to include aldehydes as the electrophile.[5] Later, Baylis and Hillman were able to demonstrate that Morita's reaction could also be catalysed by tertiary amines.[6]



Scheme 1.3: Catalysis of acrylate esters proceeding via normal polarity intermediates.

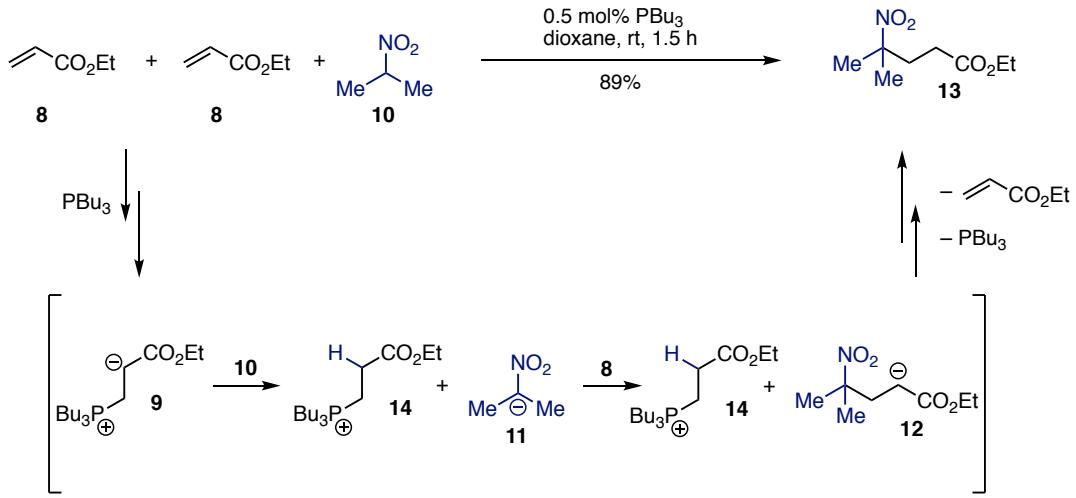
1.2 Phosphine organocatalysis with alkenes

1.2.1 Conjugate addition to alkenes

In addition to reactions proceeding via phosphonium enolates, it is known that addition of nucleophiles such as oximes, alcohols and carbon nucleophiles to α,β-unsaturated carbonyl compounds can be facilitated by phosphine catalysts.[7] Given that phosphines are known to be weak Brønsted bases when compared to amines, this suggests that reactions

catalysed by phosphines must be driven by their Lewis basic character, rather than their Brønsted basicity.[8]

For example, in 1973, Baizer and White reported the Michael addition of carbon nucleophiles to α,β-unsaturated esters (i.e. **8**) catalysed by phosphines (Scheme 1.4).[7b] Mechanistically, it was proposed that although tertiary phosphines are relatively weak Brønsted bases, their high nucleophilicity leads to facile formation of β-phosphonium enolates (i.e. **9**), thereby generating a strong base *in situ*. The reaction is initiated via conjugate addition of tri-*n*-butylphosphine to ethyl acrylate to form phosphonium enolate **9**. This β-phosphonium enolate then deprotonates 2-nitropropane **10**, generating nitronate **11**. Finally, nitronate **11** undergoes conjugate addition to a second equivalent of ethyl acrylate **8** to give enolate **12**, which upon protonation furnishes Michael adduct **13** in excellent yield. Deprotonation and elimination of phosphonium adduct **14** regenerates the catalyst.

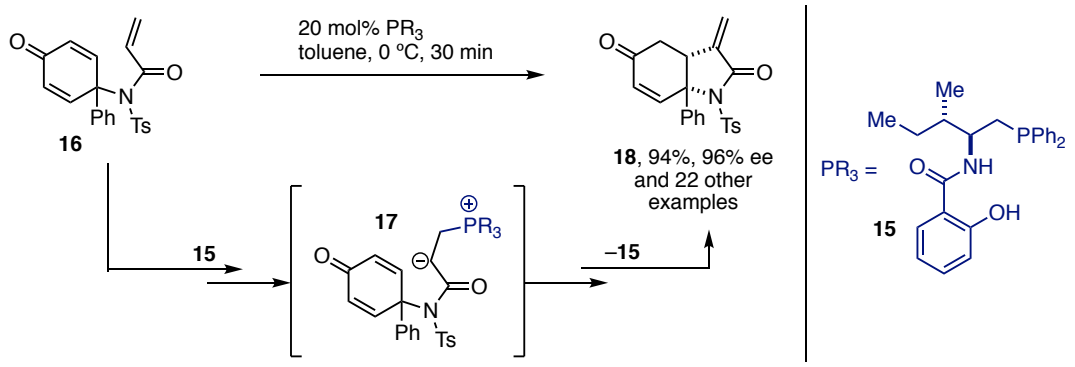


Scheme 1.4: Phosphine catalysed 1,4-addition of nitropropane to acrylates.

1.2.2 Enantioselective reactions proceeding via phosphonium enolates

Phosphine catalysis with alkenes via phosphonium enolates has undergone significant development since the pioneering discoveries discussed previously. In particular, the Rauhut-Currier and Morita-Baylis-Hillman reactions have received significant attention with many enantioselective variants developed.

A recent example was reported by Huang et al. who developed an enantioselective synthesis of hydroindoles via a Rauhut-Currier sequence catalysed by bifunctional phosphine **15**. They postulate that addition of phosphine **15** to acrylamide **16** leads to enolate **17** which then undergoes stereoselective cyclisation to yield, after elimination of the catalyst, hydroindole **18** in excellent yield and enantiopurity (Scheme 1.5).



Scheme 1.5: Enantioselective synthesis of hydroindoles via intramolecular RC reaction.

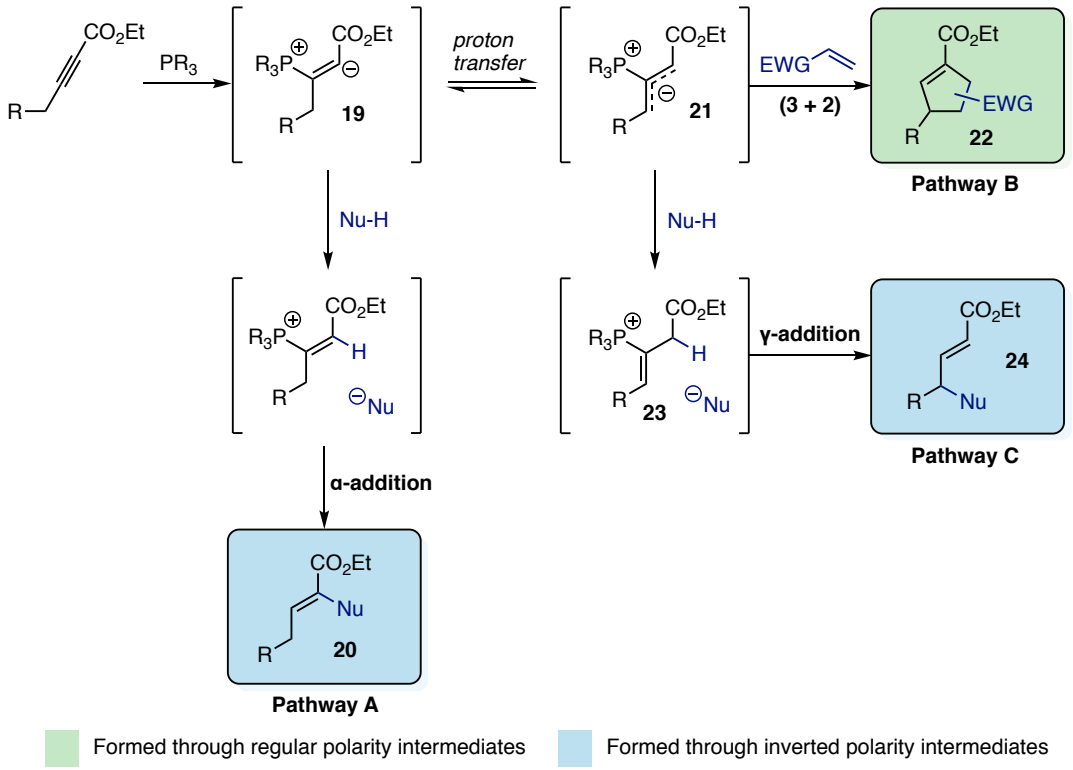
1.3 Phosphine organocatalysis with alkynes and allenes

1.3.1 Typical reactions with allenes and alkynes

In addition to activated alkenes; activated alkynes and allenes when exposed to phosphine catalysts undergo reactions via normal polarity intermediates (i.e. characterised by

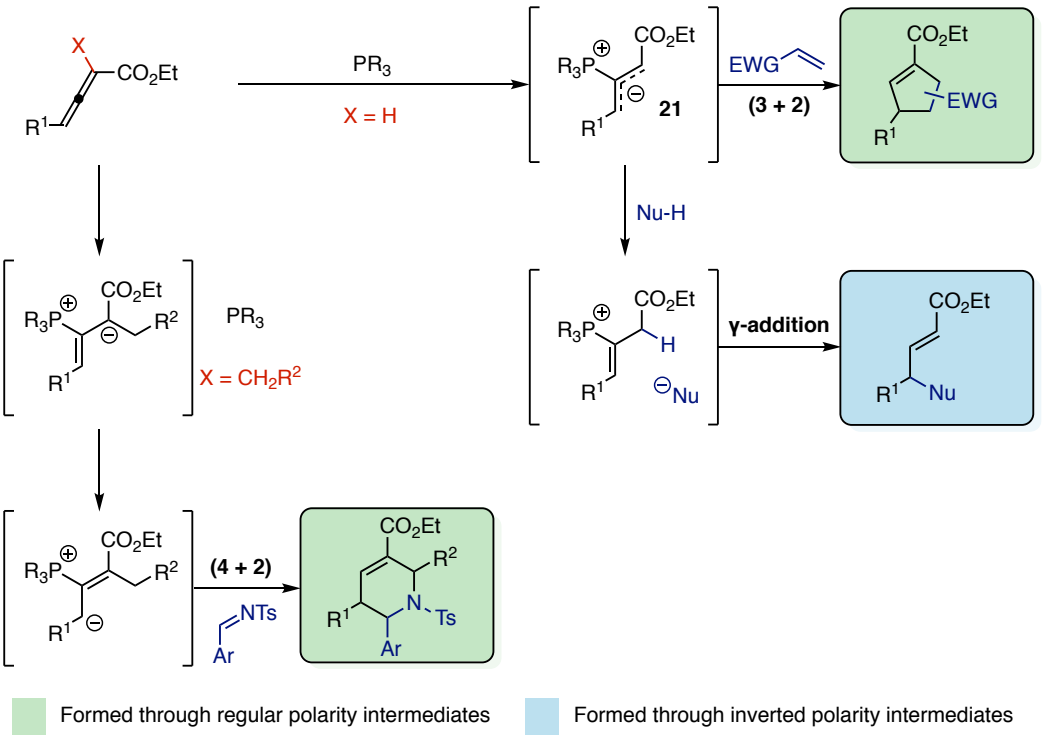
nucleophilicity at the α- and γ-positions, and electrophilicity at the β-position). In addition to this and perhaps more remarkably, such substrates have been shown to engage in α- and γ-umpolung additions, allowing such substrates to react as α- and γ- electrophiles.[9]

Illustrated below are typical events in phosphine catalysis with alkynes (Scheme 1.6). Conjugate addition of a phosphine to an alkynoate leads to vinyl anion **19**, which in the presence of an appropriate pronucleophile (**Nu-H**) can provide α-functionalised products (i.e. **20**) via an α-umpolung addition pathway (Pathway A). Alternatively, tautomerisation affords the extended enolate **21**, which can engage in (3 + 2) annulations with activated alkenes to form cyclopentenes (i.e. **22**) (Pathway B). Alternately, in the presence of a pronucleophile vinyl phosphonium **23** can form en route to the γ-addition product **24**, a product of umpolung reactivity (Pathway C).



Scheme 1.6: Typical reactions of alkynes in nucleophilic phosphine catalysis.

Although in some instances reactions of activated allenes and alkynes lead to unique outcomes, reactions generally proceed through common phosphonium extended enolate intermediates (i.e. **21**) which allows either substrate to undergo similar transformations, most commonly, γ-addition and (3 + 2) annulations (Scheme 1.7). Although beyond the scope of this thesis, substitution of allenes at the α-position gives access to a host of other reactive pathways (i.e. (4 + 2), (4 + 3) and (4 + 4) annulations), and as a result, allenes generally lead to more diverse outcomes in comparison to alkynes, which cannot bear such a substituent.[2b]

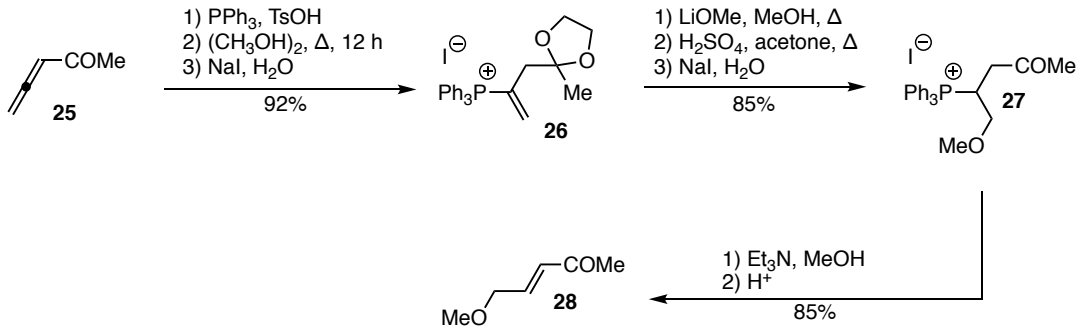


Scheme 1.7: Typical reactions of allenes in nucleophilic phosphine catalysis.

1.3.2 γ-Umpolung addition to alkynoates

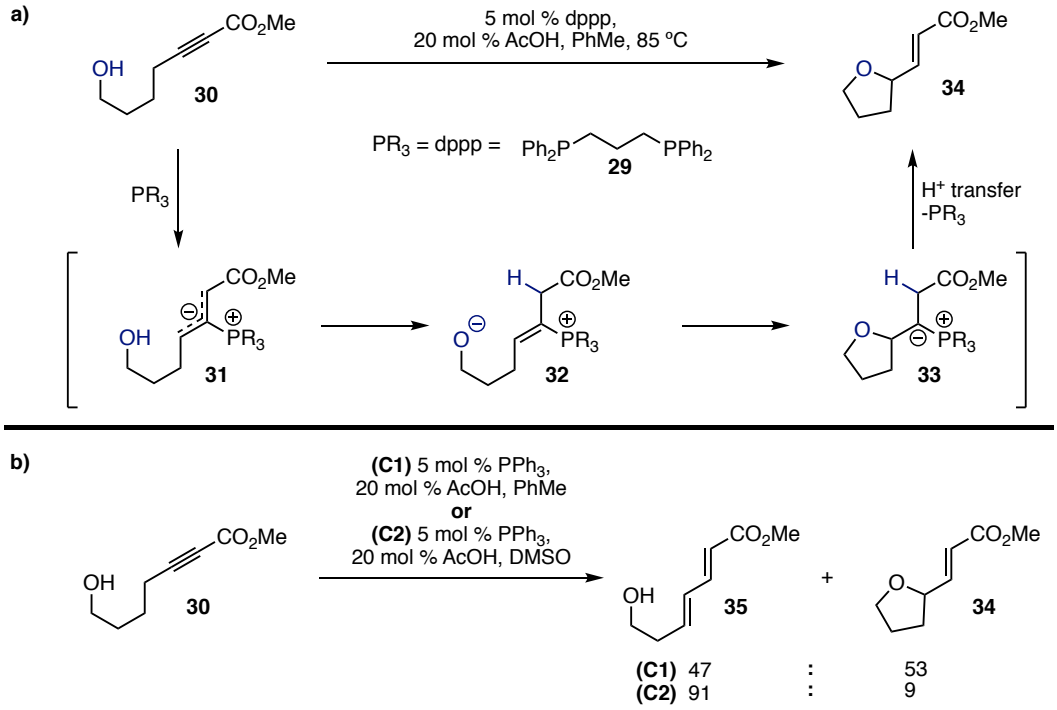
The first example of a γ-umpolung addition was reported by Cristau in a 1982 publication that describes the γ-addition of methanol to allenes, albeit in a non-catalytic fashion

(Scheme 1.8).[10] Treatment of allenone **25** with triphenylphosphine and subsequent tautomerisation and acetal protection of the resultant ketone leads to vinyl phosphonium iodide **26** upon treatment with sodium iodide. This species, which is now rendered electrophilic at the γ-position undergoes addition of lithium methoxide over three steps to yield phosphonium iodide **27**. Elimination of triphenylphosphine is achieved via treatment with triethylamine to furnish the γ-functionalised enone **28**.



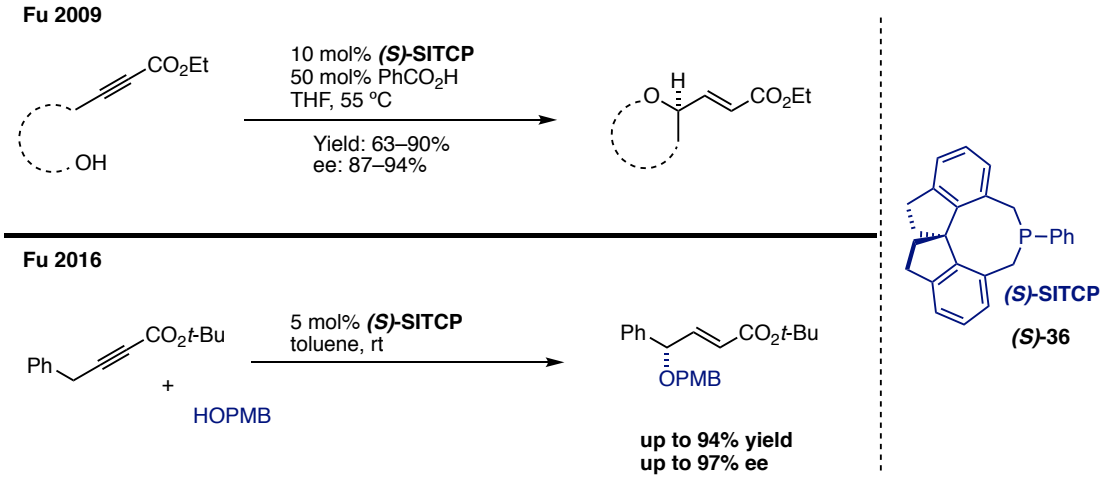
Scheme 1.8: Stepwise γ-addition of methanol to allenone **25**.

A catalytic variant of this type of reaction was first realised by Trost and Dake who reported the intramolecular γ-addition of alcohols to alkynoates catalysed by 1,3-bis(diphenylphosphino)propane **29** (Scheme 1.9a).[9b, 9c] Mechanistically, they propose that the reaction proceeds via conjugate addition of the phosphine to the alkynoate **30** and subsequent tautomerisation to generate the extended enolate **31**. Deprotonation of a tethered alcohol provides, vinyl phosphonium **32**. This intermediate, which now exhibits electrophilicity at the γ-position is attacked by a tethered alcohol to afford β-phosphonium ylide **33**. A final tautomerisation followed by elimination affords tetrahydrofuran **34** and regenerates the catalyst. Under certain conditions, isomerisation of the alkynoate to the corresponding 2,4-dienoate **35** was favoured (Scheme 1.9b).



Scheme 1.9: Trost's catalytic intramolecular γ-umpolung addition to alkynes.

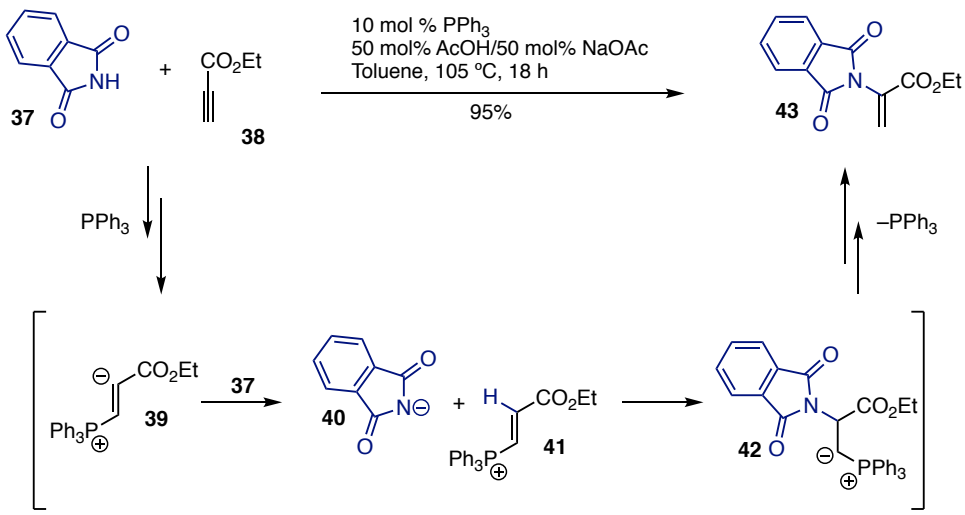
In the years following this report, this concept has been developed into a multitude of methodologies that enable γ-functionalisation of alkynoates with nitrogen, oxygen, phosphorus and carbon nucleophiles, in many cases with excellent enantioselectivity.[11] For example, in 2009 Fu et al. (Scheme 1.10) reported an enantioselective intramolecular γ-addition of alcohols to alkynoates using the homochiral phosphine *(S)*-SITCP *(S)*-**36**,[9d] while more recently, an improved intermolecular variant of this reaction was reported.[12]



Scheme 1.10: Enantioselective C–O bond formation by γ-addition to alkynoates.

1.3.3 α-Umpolung addition to alkynoates

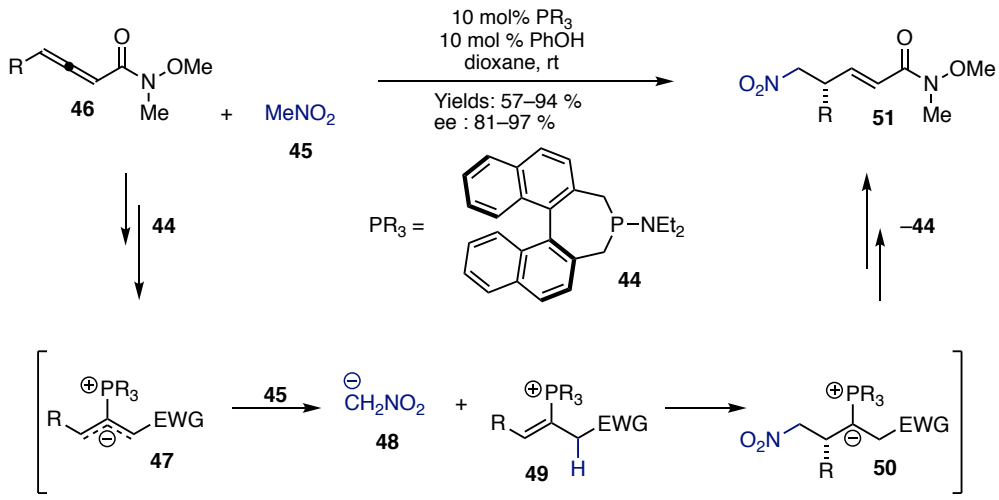
Additionally, phosphine catalysis of activated alkynes facilitates α-umpolung addition of nucleophiles. The Trost group first demonstrated this concept in a 1997 publication describing the α-addition of electron deficient amines (i.e. **37**) to ethyl propynoate **38** catalysed by triphenylphosphine (Scheme 1.11).[9a] They propose a mechanism which proceeds via a similar pathway to their previously reported γ-umpolung addition (Scheme 1.9). Specifically, 1,4-addition of the catalyst leads to the formation of vinyl phosphonium anion **39**, which deprotonates phthalimide **37** to give phthalimide anion **40** and vinyl phosphonium **41**. The vinyl phosphonium species **41** now exhibits electrophilicity at the α-position, allowing addition of the phthalimide anion to afford β-phosphonium ylide **42**, tautomerisation and elimination of the catalyst then provides dehydroamino acid **43** in excellent yield.



Scheme 1.11: Trost's α-umpolung addition of amines to alkynes.

1.3.4 γ-Umpolung addition to activated allenes

Recently, Fu and coworkers have explored the use of homochiral phosphines (i.e. **44**) as catalysts in related transformations with allenes. Specifically, they reported an enantioselective variant of the γ-addition of nitromethane **45** to allenic Weinreb amides **46** (Scheme 1.12).[9d] In this transformation conjugate addition of phosphepine **44** to allene **46** leads directly to phosphonium extended enolate **47**. From this intermediate, deprotonation of nitromethane **45** forms nitronate **48** and vinyl phosphonium **49**. γ-Addition of the nitronate leads to β-phosphonium ylide **50** which affords Weinreb acrylamide **51** upon elimination of the catalyst.



Scheme 1.12: Fu's asymmetric γ-addition of nitromethane to allenic Weinreb amides.

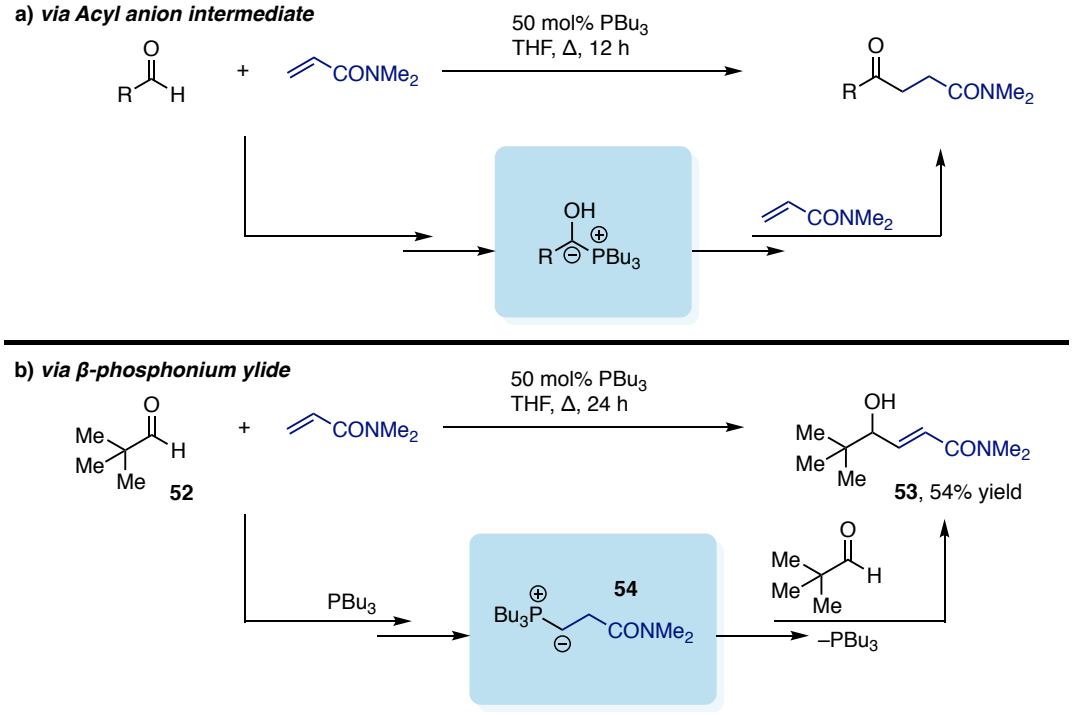
In all of the reactions discussed involving α- or γ-umpolung addition to allenes and alkynes, a common β-phosphonium ylide intermediate (i.e. **50** in Scheme 1.12) is encountered at the end of the catalytic cycle, prior to the elimination of the catalyst. Yet, we observed that there was a clear absence of transformations that took advantage of this intermediate to develop novel reaction cascades. In a non-catalytic context, phosphonium ylides are well known and have been used to develop a host of methodologies.

1.4 Organic reactions proceeding via phosphonium ylides

1.4.1 Phosphonium ylides generated from alkenes

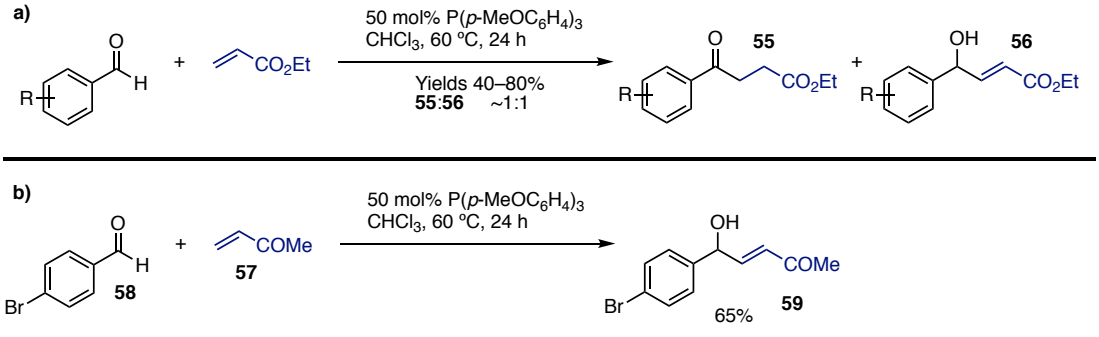
Since Takashina and Price's report (Scheme 1.2, *vide supra*), only two other reactions proceeding via phosphonium ylide intermediates have been reported to this day. Firstly, the tri-*n*-butylphosphine catalysed Stetter reaction of *N,N*-dimethylacrylamide and aldehydes (itself a rare example of the phosphine-catalysed umpolung of aldehydes) for the synthesis of γ-ketoamides was reported in 2002 by Kim et al. (Scheme 1.13a).[13] The

authors noted that use of pivaldehyde **52** unexpectedly gave allylic alcohol **53**, which is likely formed via β-phosphonium ylide **54** (Scheme 1.13b).



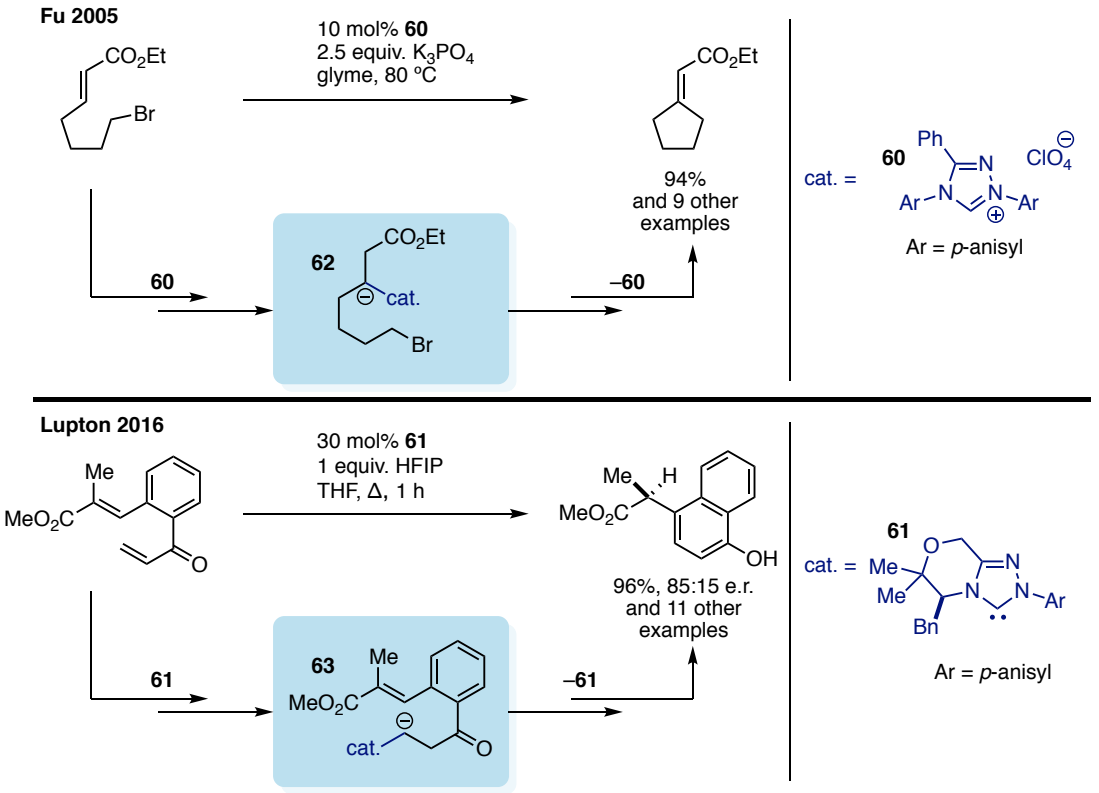
Scheme 1.13: Stetter reaction and β-umpolung reaction catalysed by phosphines.

The Teng group explored this concept further by increasing the scope of Kim's study to allow the coupling of electron deficient aldehydes with ethyl acrylate catalysed by tris(*p*-methoxy)phenylphosphine (Scheme 1.14a).[14] In most cases, this resulted in mixtures of the γ-ketoester **55** and allylic alcohol product **56**, however, when methyl vinyl ketone **57** was used as the alkene component and reacted with 4-bromobenzaldehyde **58**, the β-umpolung product **59** was produced exclusively (Scheme 1.14b).



Scheme 1.14: Stetter reaction and β-umpolung reaction catalysed by phosphines.

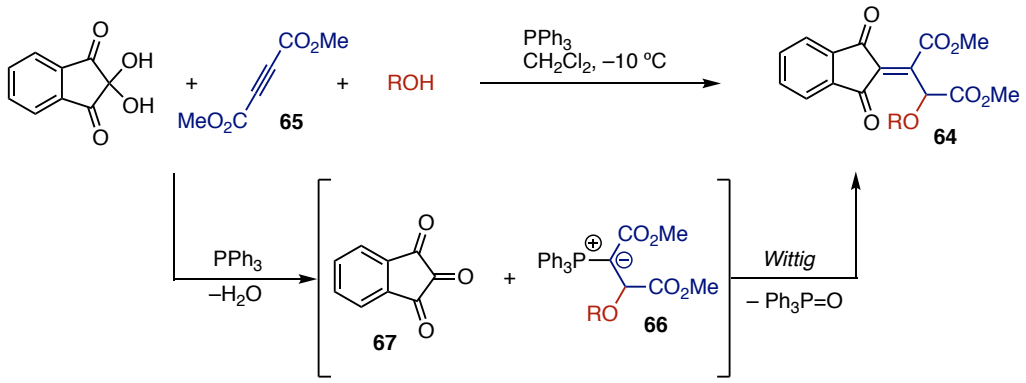
Analogous modes of reactivity have also been discovered using N-heterocyclic carbene catalysis with α,β-unsaturated alkenes. In 2006, Fu and coworkers reported the umpolung of Michael acceptors catalysed by NHC's (i.e. **60**) and more recently, an enantioselective example was reported by Lupton and Nakano using homochiral NHC **61** (Scheme 1.15).[15] Presumably, both transformations occur via formation and interception of β-anions **62** and **63**.



Scheme 1.15: Umpolung of alkenes catalysed by N-heterocyclic carbenes.

1.4.2 Phosphonium ylides generated from alkynes and allenes

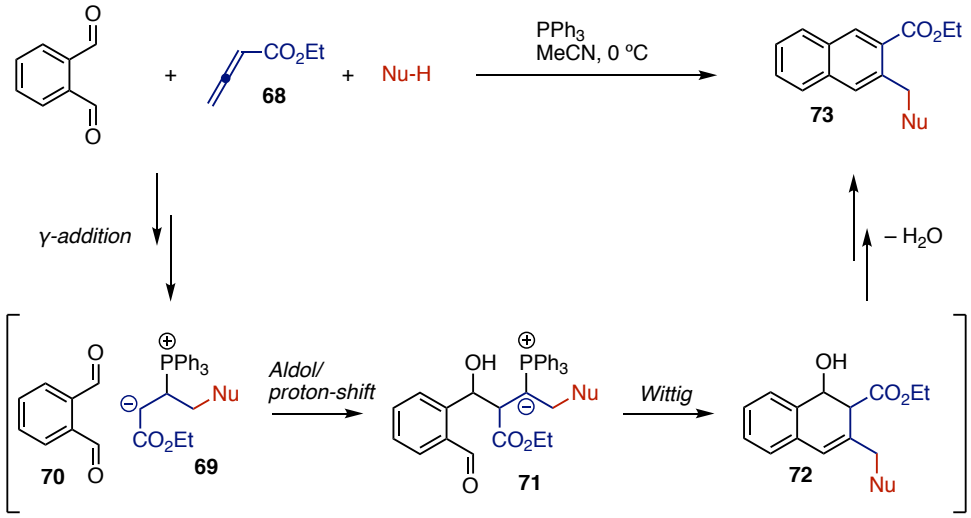
In addition to umpolung reactions at the β-position of alkenes, phosphonium ylides can be generated via nucleophilic addition of phosphines to allenes and alkynes, the vast majority of these reports feature Wittig-type cascade reactions.[2b] For example, in 2000, Ramazani and Bodaghi disclosed a synthesis of indane diones (i.e. **64**) from acetylenedicarboxylates and ninhydrin, mediated by triphenylphosphine (Scheme 1.16).[16] The reaction is initiated by addition of triphenylphosphine to acetylenedicarboxylate **65**, which eventually leads to phosphonium ylide **66** via γ-addtion of an alcohol. This species then undergoes Wittig olefination with indanetrione **67** to provide the indane dione product **64**.



Scheme 1.16: Homologation of arenes via aldol/γ-addition/Wittig cascade.

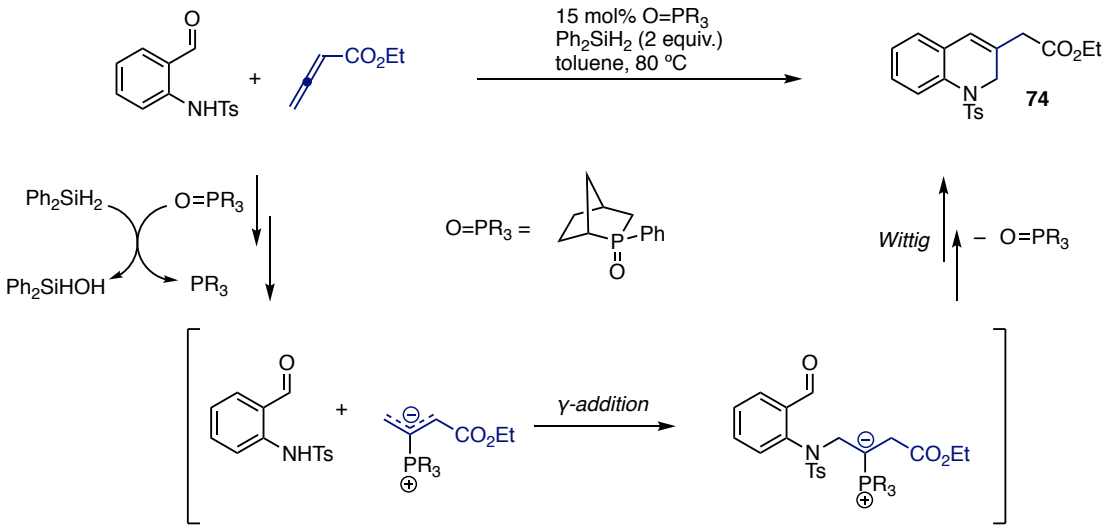
More recently, Kwon and coworkers were able to achieve the phosphine-mediated homologation of arenes with allenes via a novel γ-addition/aldol/Wittig/dehydration cascade (Scheme 1.17).[17] Addition of triphenylphosphine to allene **68** and subsequent γ-addition affords the phosphonium enolate **69**, which undergoes aldol addition to phthalaldehyde **70** and tautomerisation then affords β-phosphonium ylide **71**. Wittig

olefination of β-phosphonium ylide **71** provides alcohol **72** which yields naphthalene **73** upon dehydration.



Scheme 1.17: Homologation of arenes via aldol/γ-addition/Wittig cascade.

In a subsequent report from the Kwon group, 1,2-dihydroquinolines (i.e. **74**) are prepared via Wittig reactions catalysed by phosphines. Although the reaction is catalytic with respect to the phosphine, stoichiometric quantities of silane are required to facilitate catalyst turnover (Scheme 1.18).[18] Mechanistically, this occurs via a γ-addition/Wittig cascade that is related conceptually to the reaction discussed previously (Scheme 1.17).

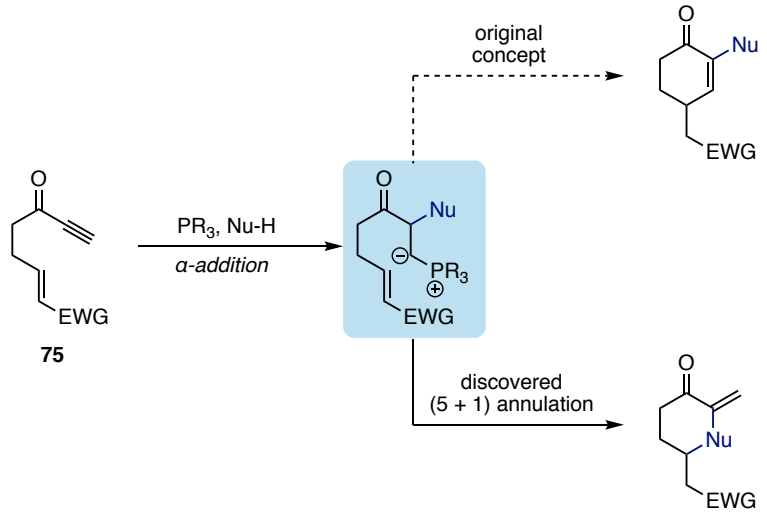


Scheme 1.18: Synthesis of 1,2-dihydroquinolines via phosphine catalysed Wittig reaction.

1.5 Objectives of this thesis

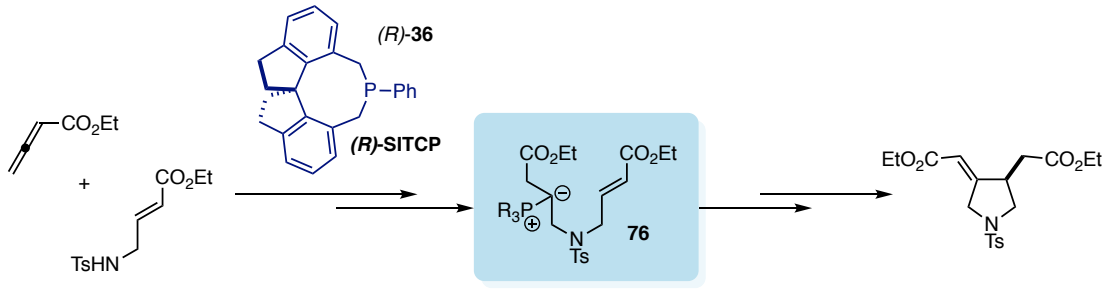
As discussed in the previous section, a number of reactions proceeding via phosphonium ylides have been reported in the literature, yet at the time that I commenced my doctoral studies there had been no reports of a catalytic variant of this kind of reactivity with allenes or alkynes. We found this surprising given the abundance of literature reports describing phosphine catalysed organic reactions in which the β-phosphonium ylide is seemingly encountered. In this, we saw the perfect opportunity for reaction discovery, and consequently, we set out with the aim of discovering and developing catalytic enantioselective reactions exploiting the β-phosphonium ylide.

Reported in Chapter 2 are our attempts to discover such reactivity with ynone/cinnamates (i.e. **75**, Scheme 1.19). While efforts to realise this particular transformation were ultimately unsuccessful, in the course of our endeavours we unexpectedly discovered a new phosphine catalysed (5 + 1) annulation that is the major focus of the chapter.



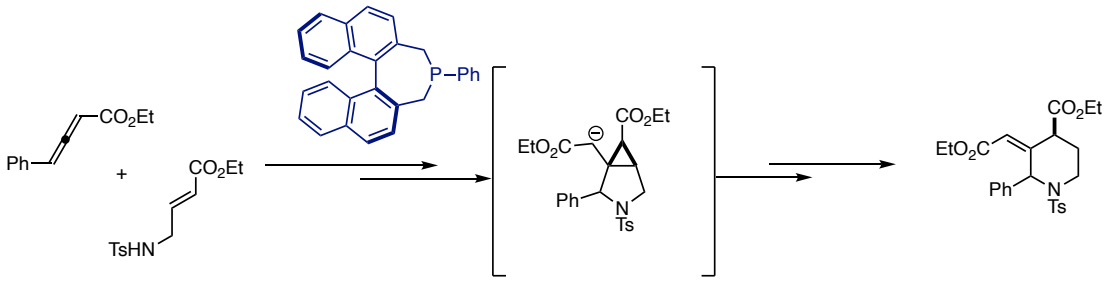
Scheme 1.19: (5 + 1) annulation of ynone/cinnamates via α-umpolung addition.

In Chapter 3, we once again focus on the discovery of a catalytic reaction that proceeds via the β-phosphonium ylide (i.e. **76**, Scheme 1.20). This was ultimately achieved with a reaction design utilising allenoates and allylic amines. Outlined are the reaction design, early attempts at reaction discovery, enantioselective reaction optimisation, scope studies and product derivatisations.



Scheme 1.20: (3 + 2) annulation via the β-phosphonium ylide.

Later in Chapter 3, we report the discovery of another novel annulation which might proceed through rearrangement following (3 + 2) annulation via the β-phosphonium ylide. Early studies of this transformation are discussed (Scheme 1.21).



Scheme 1.21: Formal (4 + 2) annulation via the β-phosphonium ylide.

1.6 References

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Chapter 2

Phosphine Catalysed (5 + 1) Annulation of Ynone/Cinnamates with Primary Amines

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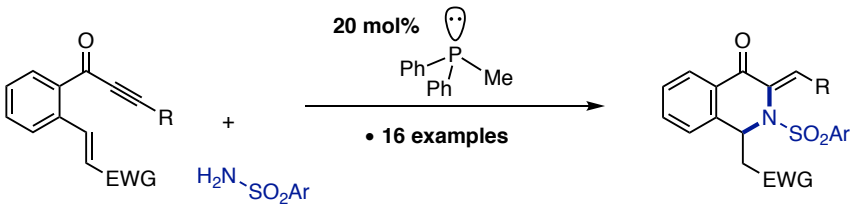
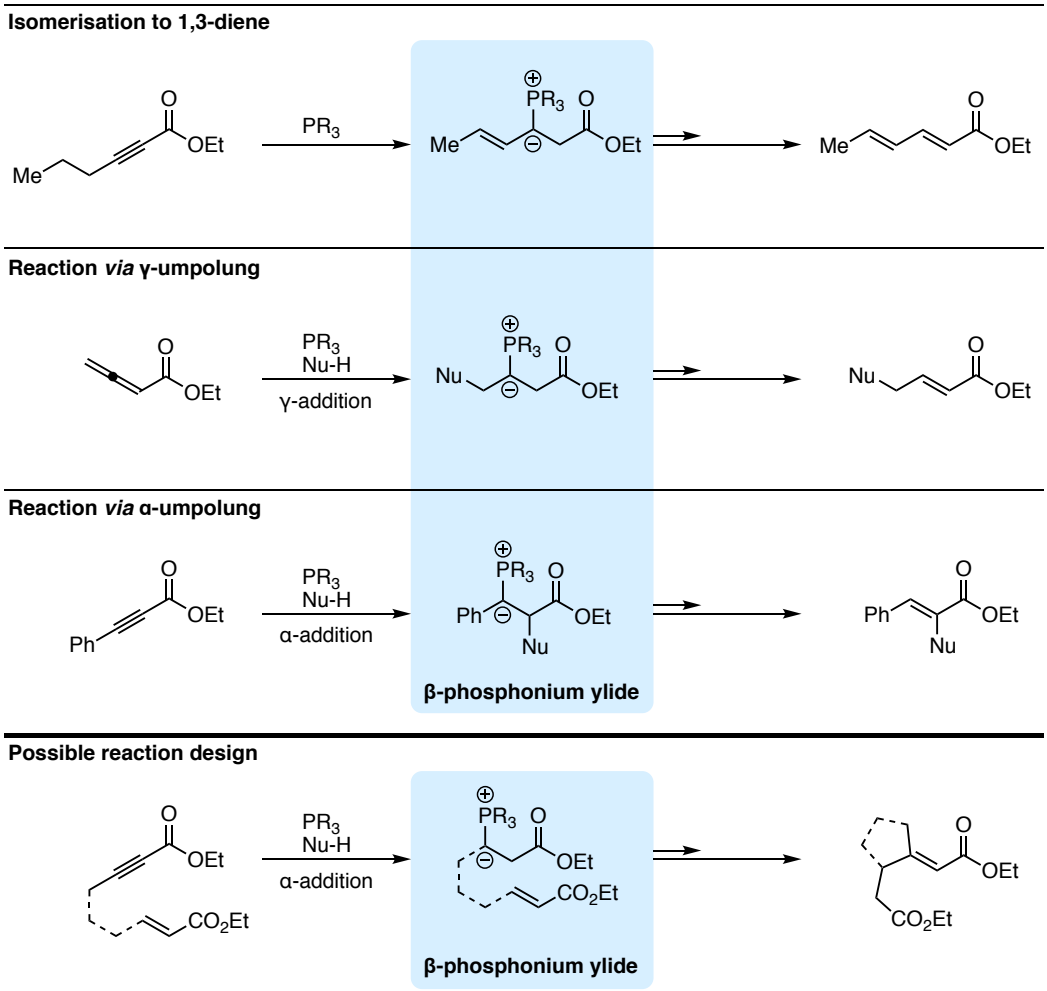
In this chapter the discovery and development of a novel annulation catalysed by phosphines that proceeds through interception of an intermediate generated by α-addition to alkynes is reported. Studies covered include initial reaction discovery, an attempted enantioselective variant, optimisation, scope studies and product derivatisations.



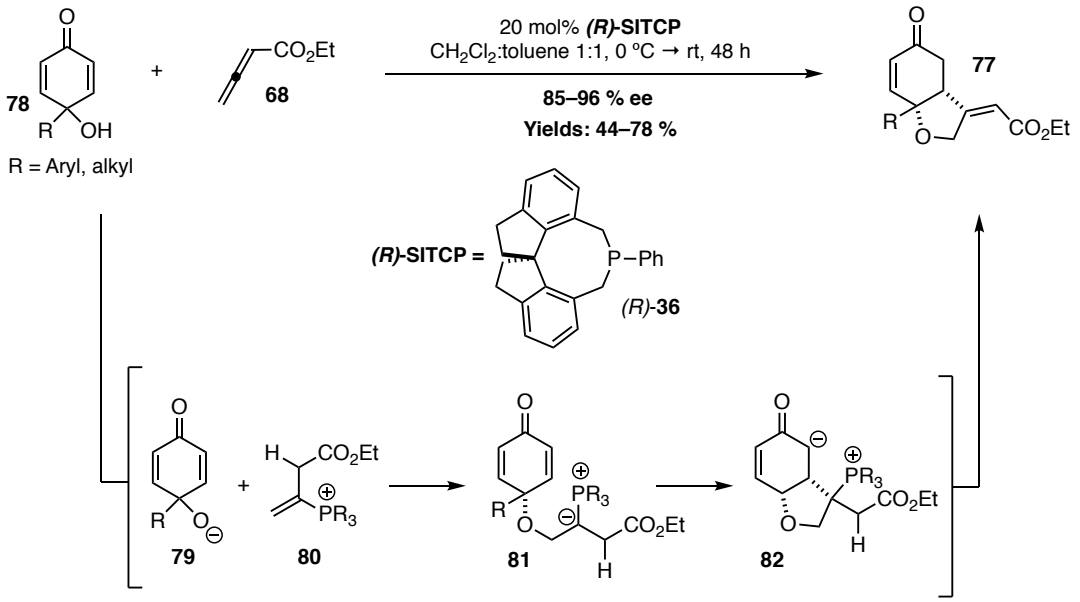
2.1 Background

As introduced in Chapter 1, typical reactions of alkynes and allenes under phosphine organocatalysis include α- and γ-umpolung addition of nucleophiles, while alkynes bearing protons at the γ-and δ-positions are also known to undergo isomerisation to 1,3-dienes.[1-4] Common to all of these pathways is the formation of the β-phosphonium ylide, an intermediate which though hypothesised had not been exploited in organic synthesis when our studies commenced. Due to interest in umpolung reactivity, we wished to design reaction cascades that would exploit formation of the β-phosphonium ylide in cascades involving new carbon–carbon bonds and the β-position (Scheme 2.1).



Scheme 2.1: Formation of the β-phosphonium ylide under phosphine catalysis.

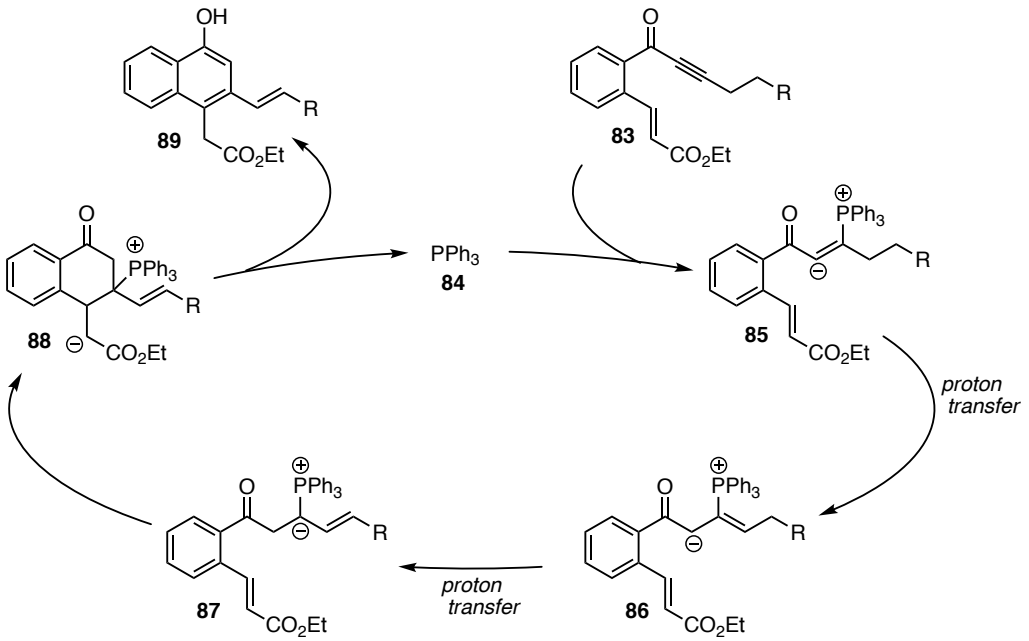
While the β-phosphonium ylide is seemingly implicated in many modes of reactivity under phosphine organocatalysis, it was not reported in synthesis until late 2015, 6-months after our studies commenced, when Sasai et al. disclosed the first enantioselective β,γ-umpolung domino reaction of allenoates with cyclohexadienones, representing a substantial discovery in the field (Scheme 2.2).[5] Using their methodology they were able to prepare a range of functionalised tetrahydrofuranones (ie. **77**) in good to high yields and with excellent enantioselectivity. Mechanistically, it is proposed that the reaction is initiated by conjugate addition of catalyst *(R)*-**36** to allenoate **68**, which following deprotonation of cyclohexadieneone **78** yields the ion pair **79** and **80**. Subsequent γ-addition of the deprotonated cyclohexadieneone **79** into the vinyl phosphonium intermediate **80** affords β-phosphonium ylide **81**. This intermediate then undergoes an intramolecular conjugate addition to yield enolate **82**, which gives tetrahydrofuranone **77** following proton transfer catalyst elimination.



Scheme 2.2: Sasai's phosphine catalysed β,γ-umpolung domino reaction.

2.1.1 Reaction discovery

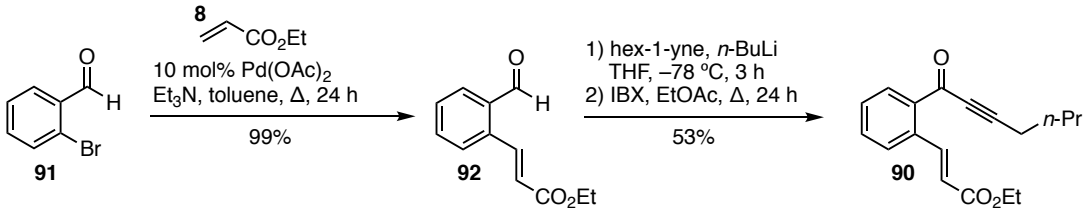
Our studies commenced prior to the report of Sasai et. al. and focused on a similar concept, however exploring ynone-cinnamates such as **83** (Scheme 2.3). Related studies within the Lupton group had exploited similar substrates in N-heterocyclic carbene catalysed annulations.[6] Specifically, we felt that constraining the activated alkyne and Michael acceptor in an S-*cis* configuration should favour the desired reaction. Namely a cascade reaction in which conjugate addition of phosphine **84** to ynone **83** affords enolate **85**, a proton transfer provides the extended enolate **86**, which undergoes tautomerisation to yield the β-phosphonium ylide **87**, now poised to undergo cyclisation and provide enolate **88**. Elimination of the phosphine would then furnish the corresponding dihydronaphthalenone and ultimately the aromatised phenol **89**.



Scheme 2.3: Proposed reaction cycle intercepting the β-phosphonium ylide.

Thus, studies commenced with the synthesis of ynone **90**. This was achieved in three steps from 2-bromobenzaldehyde **91**, beginning with Heck-coupling with ethyl acrylate **8**, as

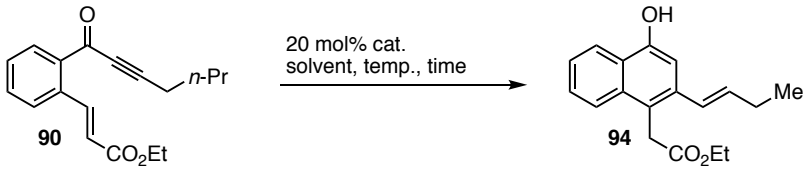
previously reported, to afford aldehyde **92** in excellent yield.[7] This was followed by 1,2-addition of lithium hexynylacetylide using an adapted procedure to provide the corresponding alcohol, which was then oxidised by 2-iodoxybenzoic acid to provide **90** in 53% yield over 2-steps (Scheme 2.4).[8]

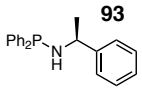


Scheme 2.4: Synthesis of ynone **90** from aldehyde **91**.

With ynone-cinnamate **90** in hand, it was subjected to various conditions for phosphine catalysis (Table 2.1). When treated with PBu_3 at room temperature the starting material was consumed within 8 hours but a complex reaction mixture resulted that could not be purified further (Table 2.1, entry 1). While reducing the reaction temperature to –78 °C led to decreased conversion, a complex mixture of products still formed (Table 2.1, entry 2). When PPh_3 and P-N phosphine **93** were employed as the catalyst in various solvents the results were unchanged (Table 2.1, entries 3-6). Unfortunately the desired phenol **94** was not observed in the reaction mixture in all cases.

Table 2.1: Attempted cycloisomerisation of ynone-cinnamates.



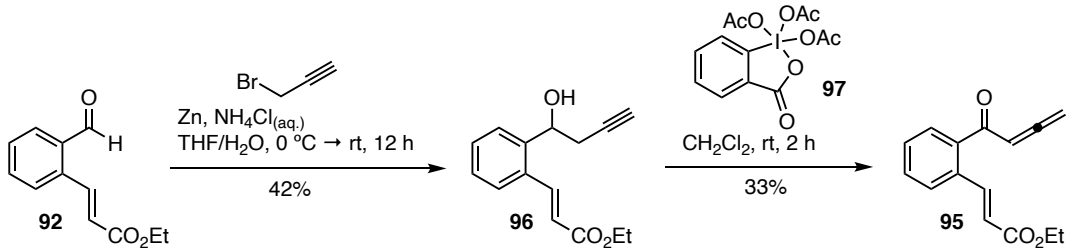
Entry	Cat.	Solvent	Temp.	Time	Yield[a]
1	PBu_3	toluene	rt	8 h	complex
2	PBu_3	toluene	−78 °C	16 h	complex, 91% **90**
3	PPh_3	toluene	rt	24 h	complex
4	PPh_3	THF	0 °C	16 h	complex
5	PPh_3	CH_2Cl_2	0 °C	16 h	complex
6		toluene	rt	48 h	complex

[a]Isolated yield following flash column chromatography.

These initial observations suggested that numerous reaction pathways were operating under the reaction conditions likely arising due to the sequential proton transfers required to access the desired intermediate.

In order to uncover the desired reaction cascade it was hoped that substituting the ynone for an allenone would allow γ-addition of a nucleophile, an established reactivity pattern that could provide a more reliable route to the β-phosphonium ylide. So studies focused on examining the benzannulated allenone **95** in place of ynone **90**. This substrate was synthesised in two steps from aldehyde **92**, itself prepared in the previously described route to ynone **90**. Alcohol **96** was prepared via a zinc-promoted Barbier-type reaction with propargyl bromide in moderate yields, with subsequent oxidation-isomerisation with Dess-Martin periodinane **97** yielding the desired allenone **95** in 33% yield (Scheme 2.5).[9]

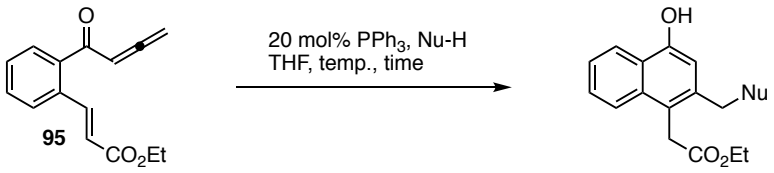
Allenone **95** was found to be unstable at room temperature and was stored in a freezer and used impure for further experiments.



Scheme 2.5: Synthesis of allenone **95** from acrylate **92**.

Upon treatment of allenone **95** with 20 mol% PPh_3 and nitromethane in THF at room temperature, complete decomposition of the starting material was observed after one hour (Table 2.2, entry 1). When the reaction was cooled to –78 °C, the result was unchanged (Table 2.2, entry 2). Other nucleophiles were trialled but unfortunately also led to decomposition of the allenone (Table 2.2, entries 3 and 4).

Table 2.2: Attempted reaction design with allenone **95**.



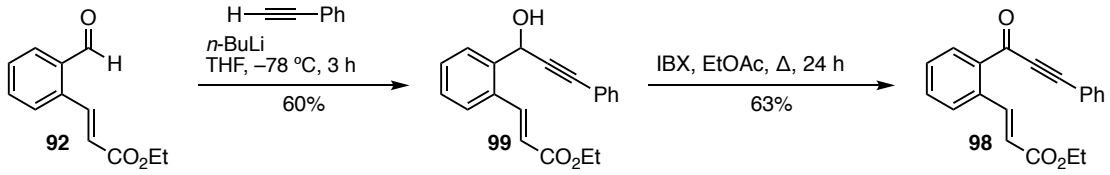
Entry	Nu-H	Temp.	Time	Yield[a]
1	$MeNO_2$	rt	1 h	Decomp.
2	$MeNO_2$	–78 °C	16 h	Decomp.
3	MeOH	–78 °C	16 h	Decomp.
4	*t*-BuOH	–78 °C	16 h	Decomp.

[a]Isolated yield following flash column chromatography.

2.1.2 (5 + 1) annulation of alkynones and sulfonamides

Since our previous attempts to trap the β-phosphonium ylide were unsuccessful, an alternate approach was required. We envisaged that the β-phosphonium ylide could be accessed via an α-umpolung addition of a electron deficient amines to conjugated alkynes as reported by Trost and Dake (Scheme 1.11, *vide supra*).[10] In addition we decided to alter our previously used substrate, by exchanging hexynyl ketone **90** for phenylethynyl ketone **98**. This was undertaken to provide greater control of substrate reactivity by preventing undesired reactions that occur as a result of protons at the γ-position and δ-position, such as redox isomerisation, or γ-umpolung addition of nucleophiles.[11,12]

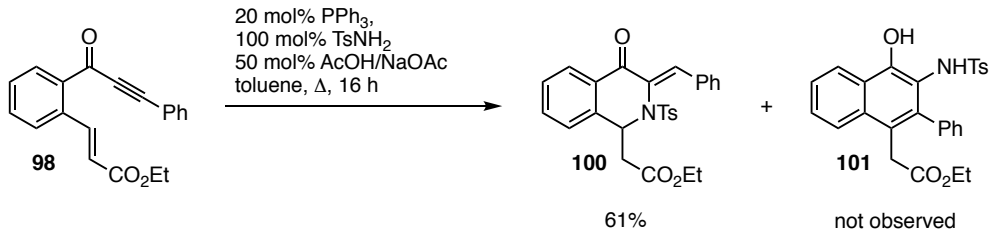
The substrate was synthesised utilising the same sequence as the hexynyl ketone **90**. Beginning with aldehyde **92**, subsequent 1,2-addition of lithium phenylacetylide gave alcohol **99** which was oxidised using IBX to give the desired ynone **98** in 63% yield (Scheme 2.6).



Scheme 2.6: Synthesis of ynone **98** from aldehyde **92**.

With ynone-cinnamate **98** in hand we examined conditions reported by Trost and Dake (Scheme 2.7). Thus, ynone **98** was treated with 20 mol% PPh_3 and *p*-toluenesulfonamide in toluene in the presence of buffered acid. Unexpectedly, isoquinolinone **100** was the major product isolated from the reaction mixture in 61% yield as a single olefin isomer, which was observed to isomerise over the course of a few days to a mixture of the *E* and *Z*

olefin. Unfortunately, the desired product **101** was not observed in the ^{1}H NMR spectrum of the crude residue, nor isolated as a minor product.



Scheme 2.7: Reaction of ynone **98** to form isoquinolinone **100**.

2.1.3 Structural confirmation of isoquinolinone 100

The structure of isoquinolinone **100** was determined by NMR spectroscopy which indicated the disappearance of the two doublets in the ^{1}H NMR spectrum corresponding to the *trans* alkene in the starting material, comparatively the ^{1}H NMR spectrum of the pure reaction product displayed formation of new signals which signified incorporation of the sulfonamide, in addition to signals consistent with an α,β-unsaturated ketone and a methylene unit adjacent to a chiral centre (Figure 2.1).

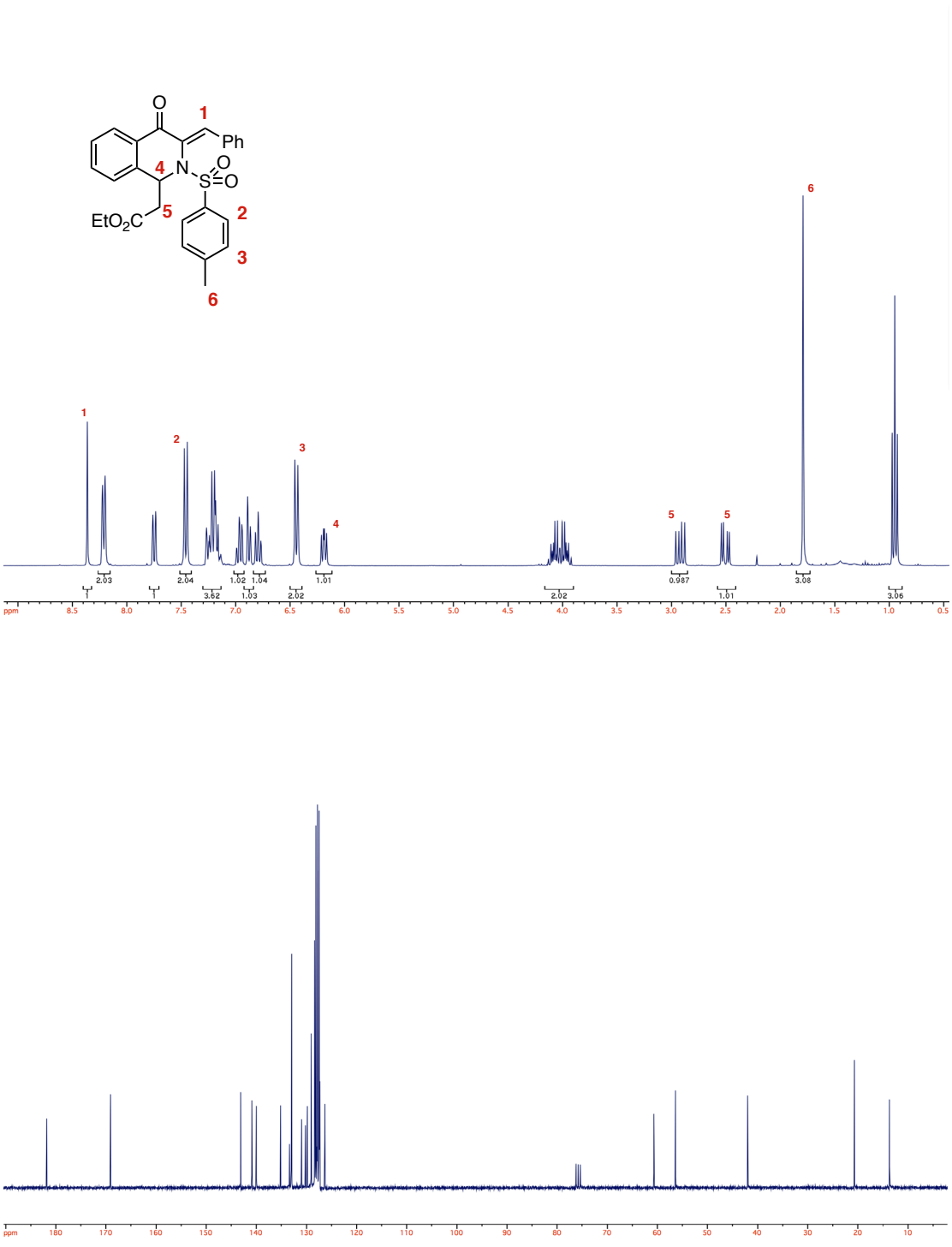


Figure 2.1: ^{1}H and ^{13}C NMR spectrum of isoquinolinone **100** in C_6D_6 at 600 MHz.

Subsequently, a crystal of isoquinolinone **100** formed in MeOH and the structure was elucidated via single crystal X-ray diffraction which confirmed our NMR based assignment while indicating that the olefin geometry was the *(Z)*-isomer (Figure 2.2).

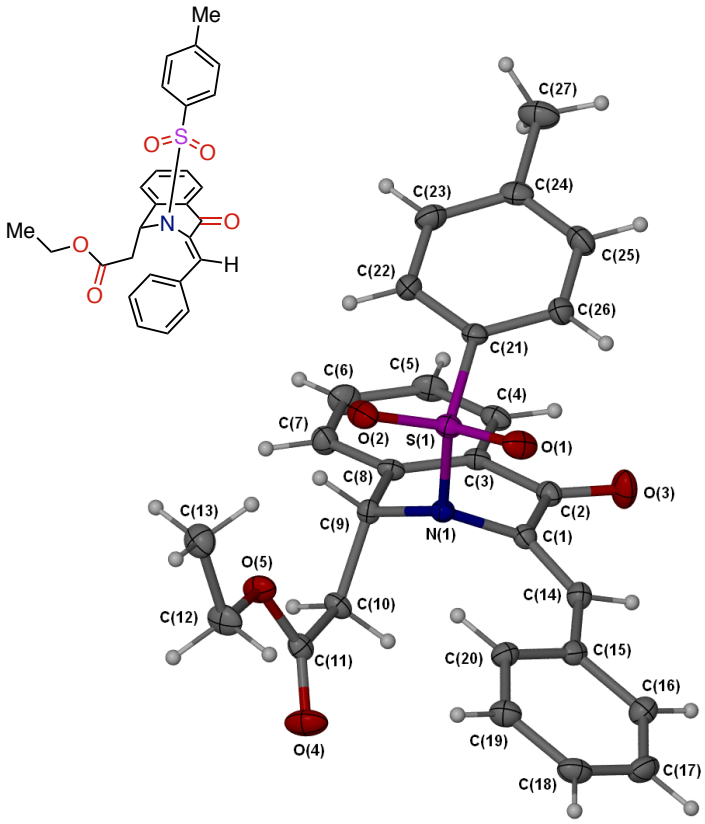
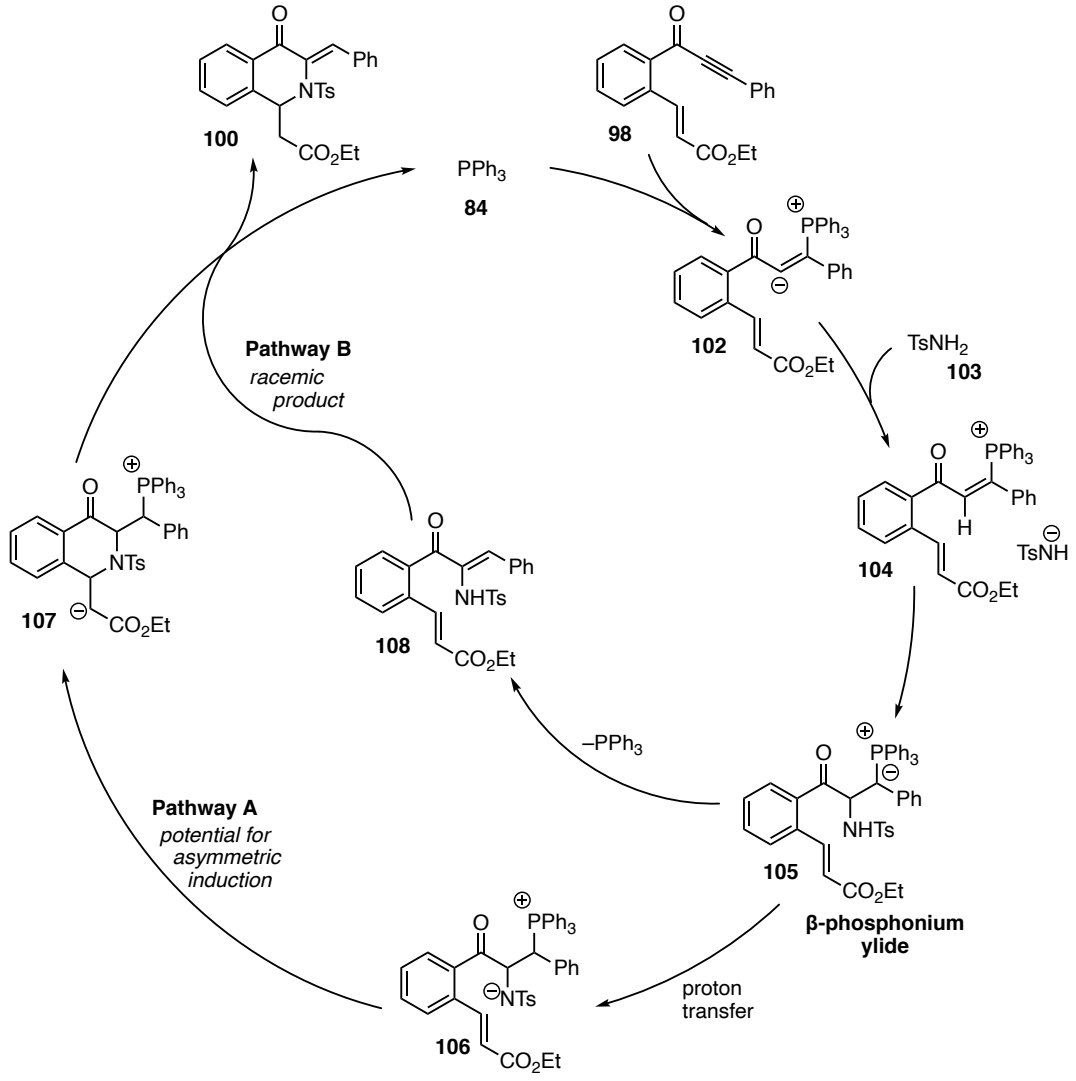


Figure 2.2: Structure of **100** as determined by X-ray crystallography.

It was postulated that isoquinolinone **100** could be formed via a number of pathways (Scheme 2.8). In all cases the reaction is initiated by conjugate addition of catalyst **84** to ynone **98** to afford vinyl enolate **102**. Deprotonation of the sulfonamide **103** gives ion pair **104**, followed by α-umpolung addition to provide β-phosphonium ylide **105**. The reaction could then follow two potential pathways: tautomerisation could provide aza-anion **106** via pathway A, which can undergo intramolecular aza-Michael addition to yield enolate **107**, which following a proton transfer and elimination of the catalyst provides the isoquinolinone product **100**. Since the catalyst is present during formation of the stereocenter, this pathway provides the possibility for asymmetric induction if a homochiral phosphine was employed. Alternatively, following pathway B, the catalyst is eliminated from intermediate **105** to yield the uncyclised α-umpolung addition product **108** which may then undergo base mediated cyclisation with the tethered enoate to form

isoquinolinone **100**, however, since the phosphine catalyst is not present when the carbon–nitrogen bond is formed, this would lead to a racemic product. The two pathways could, presumably, be distinguished through studies with homochiral phosphines.



Scheme 2.8: Proposed mechanism for the observed (5 + 1) annulation of ynone **98** with *p*-toluenesulfonamide.

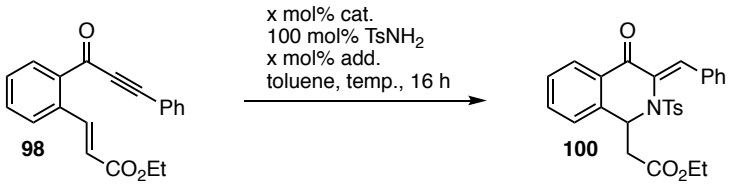
2.2 Reaction optimisation

Having established the α-umpolung aspect of the reaction design, optimisations were performed to either increase the yield of the novel isoquinolinone **100** or alternatively uncover the originally designed reaction. Early optimisations were catalysed with

triphenylphosphine to allow the impact of additives and temperature to be determined (Table 2.3).

The initial reaction conditions are provided for reference (Table 2.3, entry 1). When the reaction temperature was lowered to room temperature the product was generated in only 10% yield (Table 2.3, entry 2). Phenol was also trialled to aid proton transfer, however this also provided inferior results (Table 2.3, entry 3). The best outcome was achieved when all additives were removed entirely, with the product being isolated in an increased yield of 69% (Table 2.3, entry 4).

Table 2.3: Initial reaction optimisation.



Entry	x mol% cat.	x mol% add.	Temp.	Yield[a]
1	10 mol% PPh_3	50 mol% AcOH/50 mol% NaOAc	Δ	60%
2	10 mol% PPh_3	50 mol% AcOH/50 mol% NaOAc	rt	10%
3	10 mol% PPh_3	10 mol% PhOH	Δ	37%
4	10 mol% PPh_3	-	Δ	69%

[a]Isolated yield following flash column chromatography.

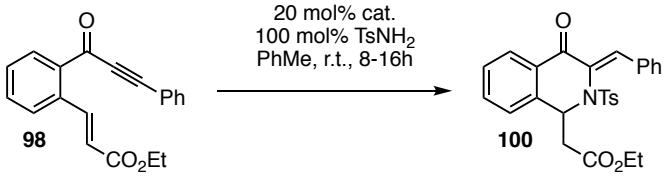
2.2.1 Homochiral catalyst screen

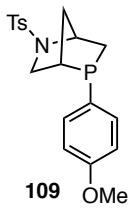
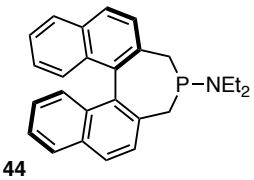
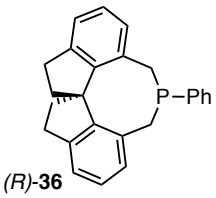
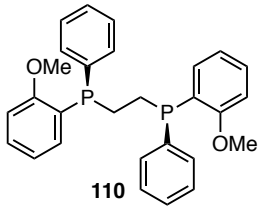
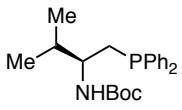
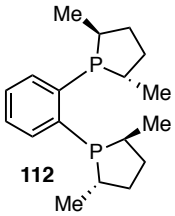
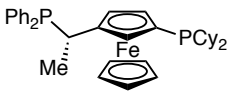
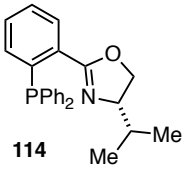
Following our initial studies, we synthesised or purchased several homochiral phosphines to determine if an enantioselective variant of the reaction could be developed. Thus, alkynone **98** was treated with a range of homochiral phosphines and *p*-toluenesulfonamide using conditions taken from Table 2.3, entry 4. In cases where

isoquinoline **100** was formed the enantiomeric excess was determined via HPLC on a chiral stationary phase. The results are presented in Table 2.4.

The first catalyst trialled was phosphine **109** developed by Kwon,[13] which generated isoquinolinone **100** with very low yield, but with moderate enantioselectivity (3% yield, 60% ee). When the reaction was repeated with a shorter reaction time the yield increased slightly, however enantioselectivity decreased significantly (20% yield, 11% ee). This suggested that the initial result was due to selective decomposition of one enantiomer of the product in a type of kinetic resolution. Spiroindane derived phosphine *(R)*-SITCP *(R)*-**36** generated isoquinolinone **100** efficiently at room temperature in high yield but with poor enantioselectivity (79% yield, 10% ee). When the reaction was conducted at 0 °C a small increase in both the yield and enantiopurity of isoquinoline **100** was observed (85%, 14% ee). Unfortunately, attempts to exploit the effect of cooling further were unsuccessful with the reaction failing at –40 °C. DIPAMP **110** and leucine derived phosphine **111** were also trialled but provided isoquinolinone **100** in only modest yields, and with little enantioenrichment (54% yield, 5% ee) and (46% yield, 1% ee) respectively. P-N phosphepine **44**, DUPHOS **112**, ferrocenium **113** and the Pfaltz ligand **114** were also trialled, however, neither of these catalysts afforded the reaction product.

Table 2.4: Attempts towards an enantioselective (5 + 1) annulation.



 **109**	 **44**	 ***(R)*-36**	 **110**
16h, 3% yield, 60% ee 8h, 20% yield, 11% ee	N/R	r.t., 79% yield, 10% ee 0 °C, 85% yield, 14% ee –40 °C, N/R	r.t., 54% yield, 5% ee
 **111**	 **112**	 **113**	 **114**
r.t., 46% yield, 1% ee	N/R	reflux, N/R	reflux, N/R

Isolated yield following flash column chromatography. Enantiomeric excess determined by HPLC on a chiral stationary phase.

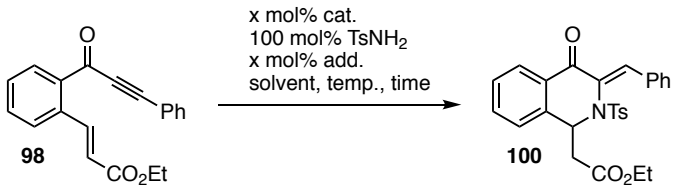
Although the enantioselectivity observed under the trialled conditions was only modest at best, the fact that enantioselectivity was observed in any case suggests that the reaction proceeds, at least to some extent, via an intermediate where the catalyst is able to influence addition of the amine to the Michael acceptor (ie. Pathway A, Scheme 2.8, *vide supra*). If the catalyst were eliminated before the bond forming event (ie. Pathway B, Scheme 2.8, *vide supra*) then the product would be racemic. With this in mind, the most likely explanation is that both pathways are operative, resulting in low enantioselectivity.

As only modest enantioselectivity was observed in our initial catalyst screen, attempts to optimise an enantioselective variant of the reaction were abandoned. Thus, we continued our studies via optimisation of the reaction with achiral phosphine catalysts.

2.2.2 Non-enantioselective reaction optimisation

It was previously observed that the reaction between ynone **98** and sulfonamide **103** catalysed by 20 mol% triphenylphosphine in toluene at reflux provided the product in 73% yield (Table 2.5, entry 1). When the more electron rich PBu_3 was employed, a lower yield was obtained, while the yield of the reaction increased to 83% when PPh_2Me was used (Table 2.5, entries 2 and 3). We then trialled $PPhMe_2$ as the catalyst which also decreased the yield slightly (Table 2.5, entry 4). Lowering the reaction temperature to –40 °C with PPh_2Me inhibited the reaction completely (Table 2.5, entry 5), and when other solvents were trialled at room temperature this also led to inferior yields in comparison to toluene (Table 2.5, entries 6–7).

Table 2.5: Selected reaction optimisation



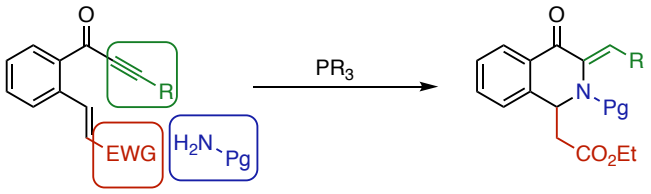
Entry	x mol% cat.	Temp.	Time	Solvent	Yield[a]
1	20 mol% PPh_3	Δ	16 h	toluene	73%
2	20 mol% PBu_3	rt	8 h	toluene	67%
3	20 mol% PPh_2Me	rt	6 h	toluene	83%
4	20 mol% $PPhMe_2$	rt	8 h	toluene	72%
5	20 mol% PPh_2Me	–40 °C	48 h	toluene	N/R
6	20 mol% PPh_2Me	rt	6 h	CH_2Cl_2	35%
7	20 mol% PPh_2Me	rt	6 h	THF	78%

[a]Isolated yield following flash column chromatography.

2.3 Scope of the phosphine catalysed (5 + 1) annulation

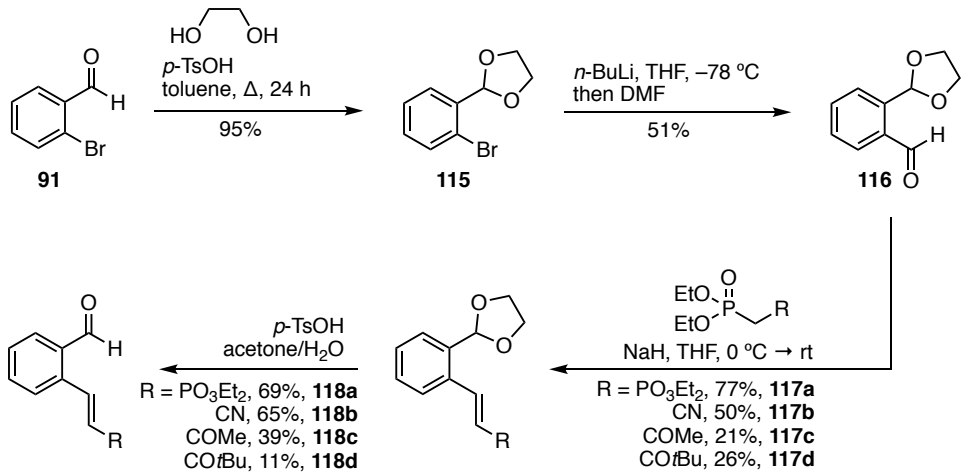
2.3.1 Preparation of ynone-cinnamate substrates

With the optimised conditions in hand, scope studies were undertaken to determine the generality of the reaction. Initially we wished to examine the effect of the substituent at the alkyne position (R), the electron withdrawing group (EWG), and various protected amines (Scheme 2.9).



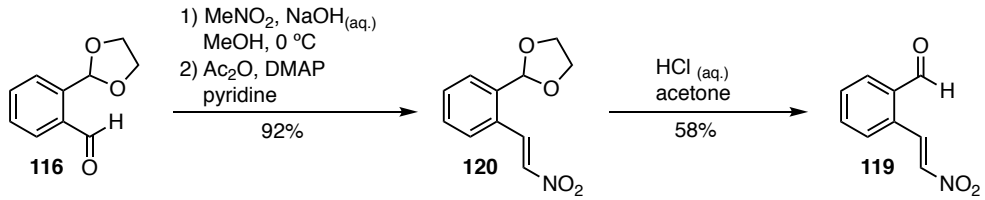
Scheme 2.9: Initial approach to scope studies.

The synthesis of substrates containing an acrylate as the electron withdrawing group was previously described from 2-bromobenzaldehyde **91** (Scheme 2.4, *vide supra*).[7] To synthesise substrates containing other Michael acceptors, a different approach was undertaken (Scheme 2.10). This sequence began with acetal protection of 2-bromobenzaldehyde **91**, to form ethylene glycol acetal **115**, formylation of **115** was then achieved via lithium-halogen exchange and subsequent reaction with *N*,*N*-dimethylformamide to afford aldehyde **116**.[14] Horner-Wadsworth-Emmons olefination of aldehyde **116** with the corresponding phosphonate-stabilised carbanion provided acetals **117a–d** and subsequent acetal hydrolysis afforded alkenes **118a–d**.



Scheme 2.10: Preparation of aldehydes from 2-bromobenzaldehyde.

Nitrostyrene **119** was prepared via a Henry reaction of aldehyde **116** with nitromethane to provide acetal **120** in excellent yield. Subsequent acetal hydrolysis with aqueous HCl afforded the desired nitrostyrene **119** in good yield (Scheme 2.11).[15,16]

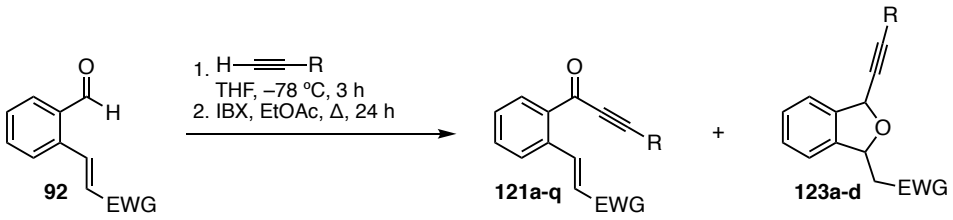


Scheme 2.11: Preparation of nitrostyrene **119**.

Ynones **121a–q** were then accessed via 1,2-addition of the corresponding lithium acetylide to the various benzaldehydes bearing *ortho*-Michael acceptors to afford the corresponding alcohols. The resultant alcohols were then oxidised using IBX to afford the targeted substrates (Table 2.6). While this method was successful for acrylates **92**, **122** and acrylonitrile **118b** (Table 2.6, entries 1–19), reactions of nitrostyrene **119**, vinylphosphonate **118a** and enones **118c** and **118d** under the same conditions led to the formation of the corresponding dihydroisobenzofurans **123a–d** (Table 2.6, entries 20–23). Presumably these are formed via an oxy-Michael addition pathway. It was notable that

substrates either produced the desired ynone product or the dihydrobenzofuran exclusively, and attempts to remedy this via the use of other organometallics reagents failed.

Table 2.6: Synthesis of substrates via 1,2-addition of acetylenes.



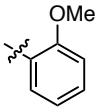
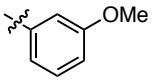
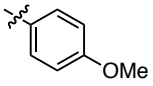
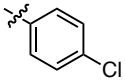
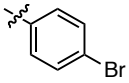
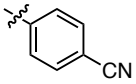
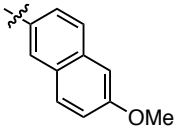
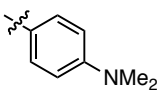
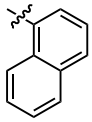
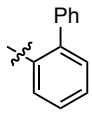
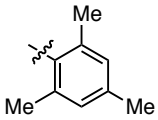
Entry	Substrate	EWG	R	Yield **121**[a]	Yield **123**[a]
1	**92**	CO_2Et		**121a**, 60%	0%
2	**92**	CO_2Et		**121b**, 71%	0%
3	**92**	CO_2Et		**121c**, 77%	0%
4	**92**	CO_2Et		**121d**, 61%	0%
5	**92**	CO_2Et		**121e**, 43%	0%
6	**92**	CO_2Et		**121f**, 62%	0%
7	**92**	CO_2Et		**121g**, 39%	0%
8	**92**	CO_2Et		**121h**, 66%	0%

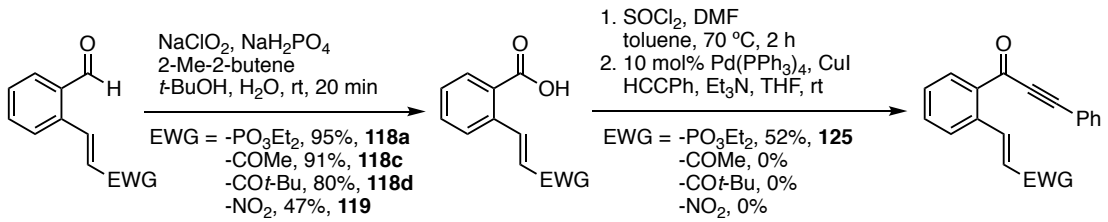
Table 2.6 cont.

9	**92**	CO_2Et		**121i**, 76%	0%
10	**92**	CO_2Et		**121j**, 80%	0%
11	**92**	CO_2Et		**121k**, 55%	0%
12	**92**	CO_2Et		**121l**, 63%	0%
13	**92**	CO_2Et		**121m**, 69%	0%
14	**92**	CO_2Et		**121n**, 75%	0%
15	**92**	CO_2Et		**121o**, 68%	0%
18	**122**	CO_2t-Bu	Ph	**121p**, 55%	0%
19	**118b**	CN	Ph	**121q**, 53%	0%
20	**119**	NO_2	Ph	0%	**123a**, 33%
21	**118a**	PO_3Et_2	Ph	0%	**123b**, 56%
22	**118c**	COMe	Ph	0%	**123c**, 51%
23	**118d**	CO*t*-Bu	Ph	0%	**123d**, 40%

Isolated yield following flash column chromatography.

As a result of the occasional failure of the previously introduced route, an alternative method for the synthesis of ynones **124a–d** was devised (Scheme 2.12). It was envisaged

that Pinnick oxidation of aldehydes **118a**, **118c**, **118d**, and **119** would provide the corresponding carboxylic acids **124a–d**.[17] The acids could then be converted to the corresponding acid chlorides via treatment with thionyl chloride and a subsequent palladium catalysed cross-coupling with phenylacetylene would provide the target substrates.[18] Thus, aldehydes **118a**, **118c**, **118d**, and **119** were reacted according to the literature procedure to provide the corresponding acids **124a–d** in very high yields, however, only vinylphosphonate **124a** was successfully converted to the desired ynone **125** under the reported conditions with the other substrates **124b-d** leading to decomposition under the reaction conditions.



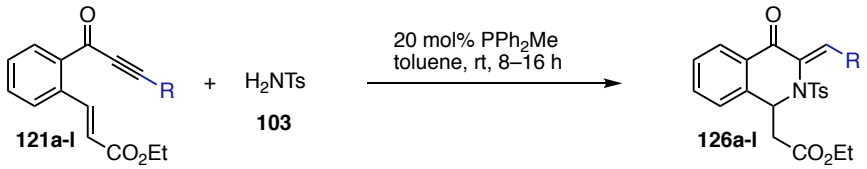
Scheme 2.12: Synthesis of ynones via Pd-catalysed cross coupling.

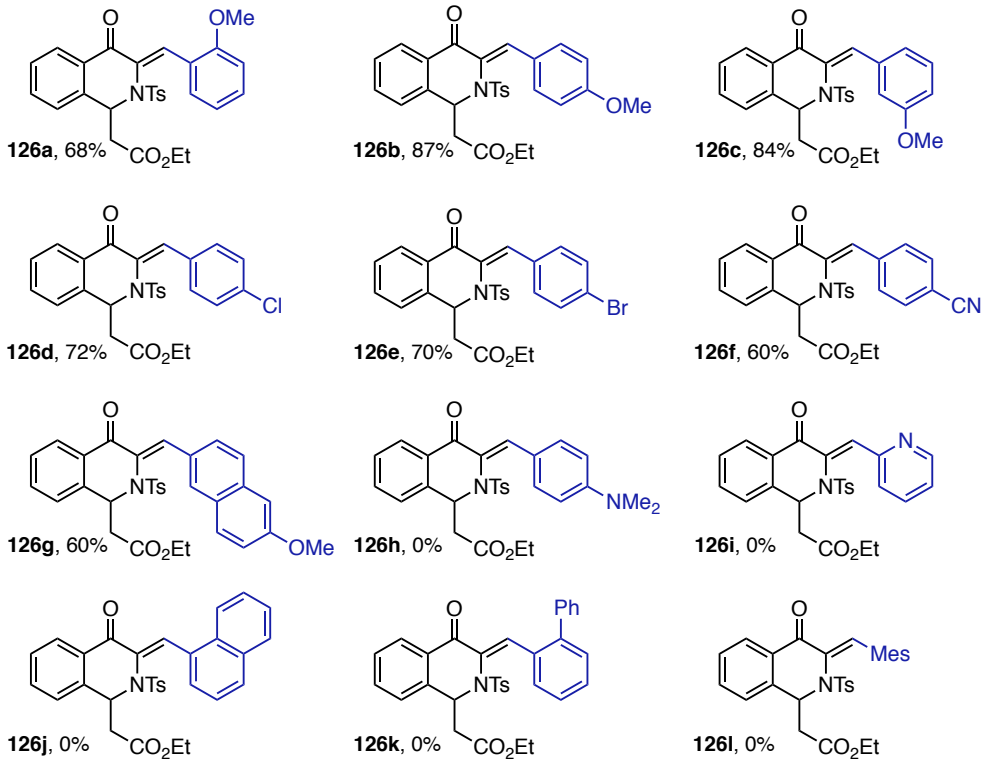
2.3.2 Phosphine catalysed (5 + 1) annulation of ynone-cinnamates

With our target substrates in hand, aryl substituted ynones **121a–l** were reacted under the optimised conditions using *p*-toluenesulfonamide **103** as the coupling partner (Table 2.7). Substrates bearing electron rich alkynes converted to the corresponding isoquinolinones **126a**, **126b** and **126c** in excellent yields, although decreased yield was observed for **126a**, presumably due to steric effects. The efficiency of the transformation decreased for electron deficient substrates providing isoquinolinones **126d**, **126e** and **126f**, though yields were still moderate to good. Pyridinyl and 4-(dimethylamino)-substituted ynones

121h and **121i** failed to react. More sterically hindered ynones such as **121j, 121k** and **121l** did not afford the desired product.

Table 2.7: (5 + 1) annulation with substituted acetylenes.

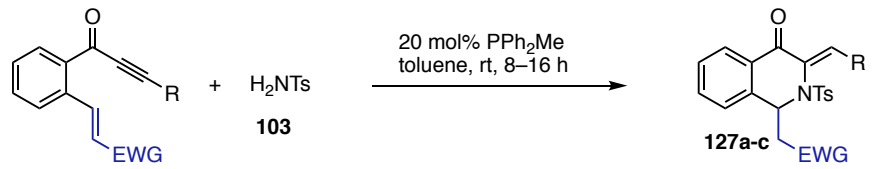


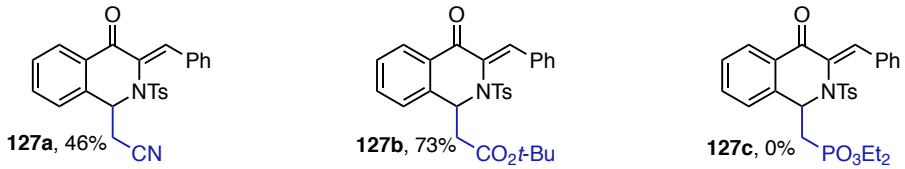


Isolated yield following flash column chromatography. Scope was undertaken in conjunction with visiting PhD student Uttam Dutta.

The effect of the Michael acceptor on the reaction yield was examined next by reaction of substrates **118a, 118b** and **122** under the optimised conditions (Table 2.8). Substitution of the acrylate for an acrylonitrile provided the product **127a** in moderate yield. The *tert*-butyl acrylate **122** provided the corresponding isoquinolinone **127b** with decreased yield in comparison to the parent example, while substitution with a vinylphosphonate prevented formation of the product altogether.

Table 2.8: (5 + 1) annulation with substituted Michael acceptors.

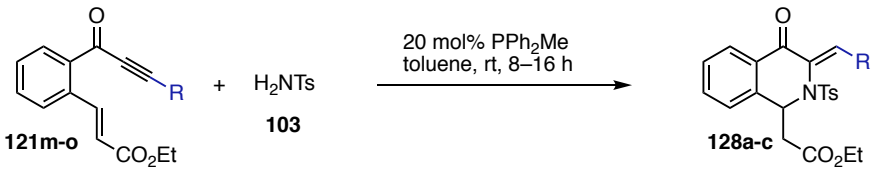


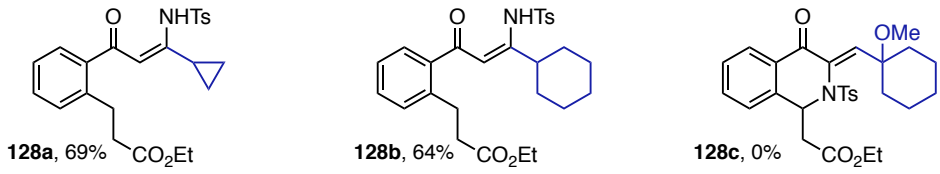


Isolated yield following flash column chromatography.

Thus far only aryl substituted acetylenes had been investigated. So ynones **121m–o** were reacted under the optimised conditions (Table 2.9). Interestingly, cyclopropyl and cyclohexyl substituted ynones **121m** and **121n** did not afford an isoquinolinone product, but instead the conjugate addition products **128a** and **128b** were isolated. Ynone **121o** failed to produce any product under the conditions.

Table 2.9: (5 + 1) annulation with alkyl substituted acetylenes.



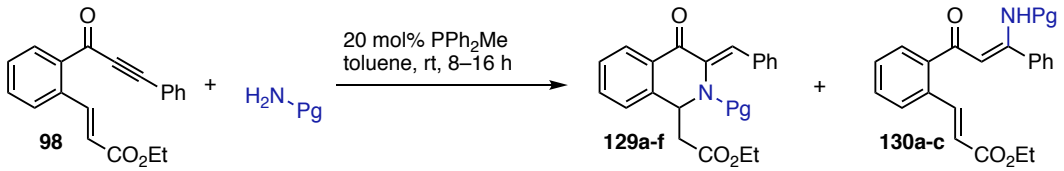


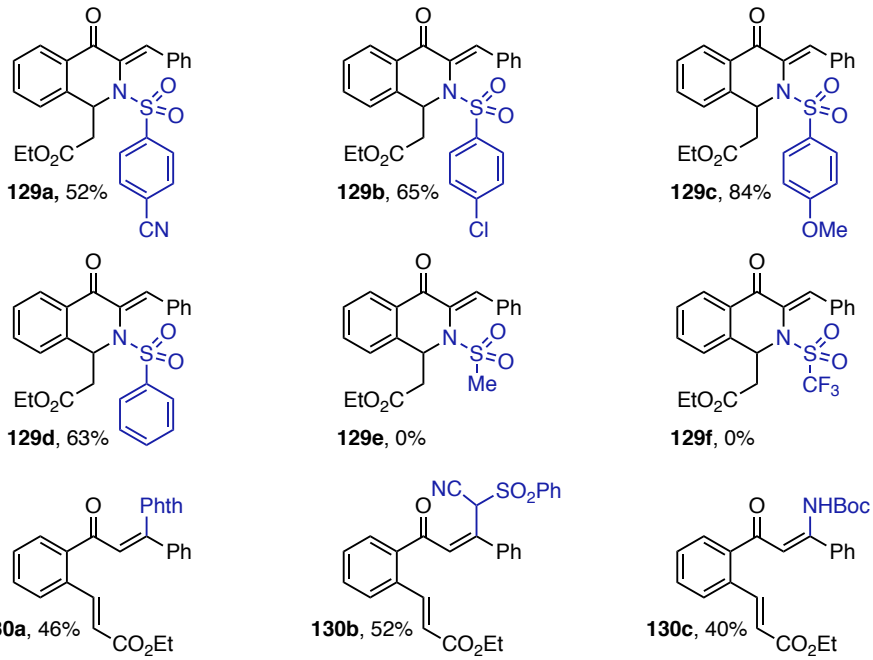
Isolated yield following flash column chromatography.

Next, an array of electronically differentiated aryl sulfonamides were coupled to ynone **98**. Electron deficient aryl sulfonamides decreased the reaction yield slightly, whereas the more electron rich 4-methoxybenzenesulfonamide resulted in greater conversion to the

product (Table 2.10, **129a–d**). Alkyl sulfonamides were also trialled however no reaction was found to occur (Table 2.10, **129e–f**). Trost and Dake had previously observed that phthalimide could participate in α-additions under phosphine catalysis and since it is a disubstituted amine, it was hoped that this could uncover the originally desired reactivity via the β-position as a proton transfer is not possible following addition to the ynone. Unfortunately, when trialled under the reaction conditions, only the conjugate addition product **130a** was isolated (Table 2.10, **130a**). Coupling of carbon derived nucleophiles and carbamates was attempted but these also led to conjugate addition products (Table 2.10, **130b** and **130c**).

Table 2.10: (5 + 1) annulation trialled with various nucleophiles.

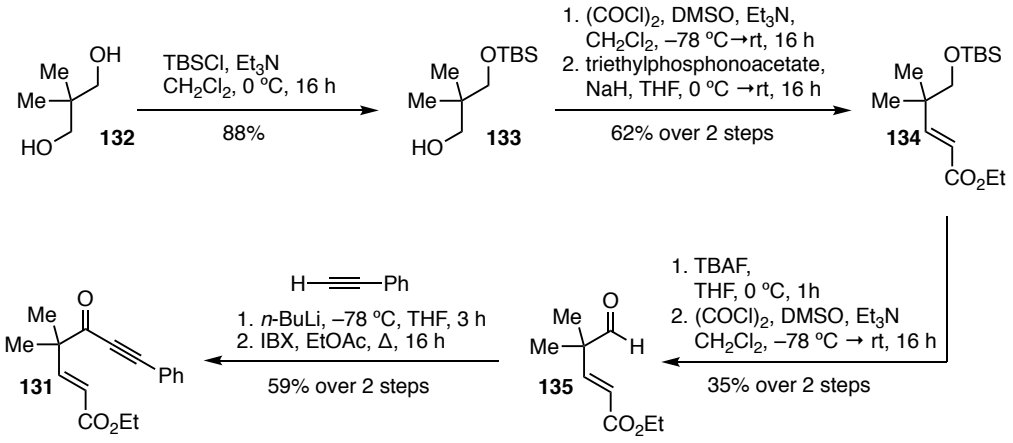




Isolated yield following flash column chromatography.

2.3.3 Non-benzannulated substrates

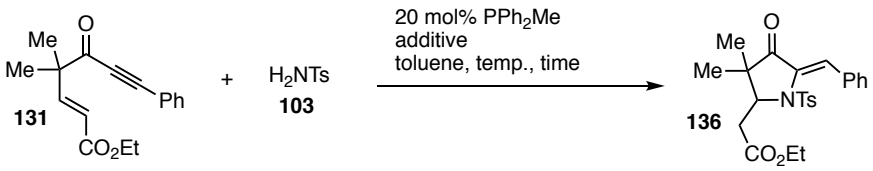
In addition to benzannulated substrates, we were interested in trialling aliphatic linkers, thus ynone **131** was synthesised via the following sequence (Scheme 2.13). Starting from neopentyl glycol **132**, treatment with TBSCl afforded silyl ether **133**, which was then converted to acrylate **134** by oxidation and Horner-Wadsworth-Emmons olefination.[19] Subsequent deprotection with TBAF and oxidation under Swern conditions yielded aldehyde **135**. Addition of lithium phenylacetylide and oxidation with IBX provided the desired ynone **131** in 59% yield over two steps.



Scheme 2.13: Synthetic sequence used to access aliphatic ynone **131**.

With the substrate in hand, it was subjected to the optimised reaction conditions. We were disappointed to discover that while the reaction did proceed, poor conversion was observed and the desired product **136** was isolated in low yield (Table 2.11, entry 1). When the reaction was conducted at increased temperatures, the yield decreased (Table 2.11, entry 2). We suspected that alcoholic additives might facilitate proton transfers, thus *t*-BuOH was employed as an additive and the yield was significantly improved (Table 2.11, entry 3).

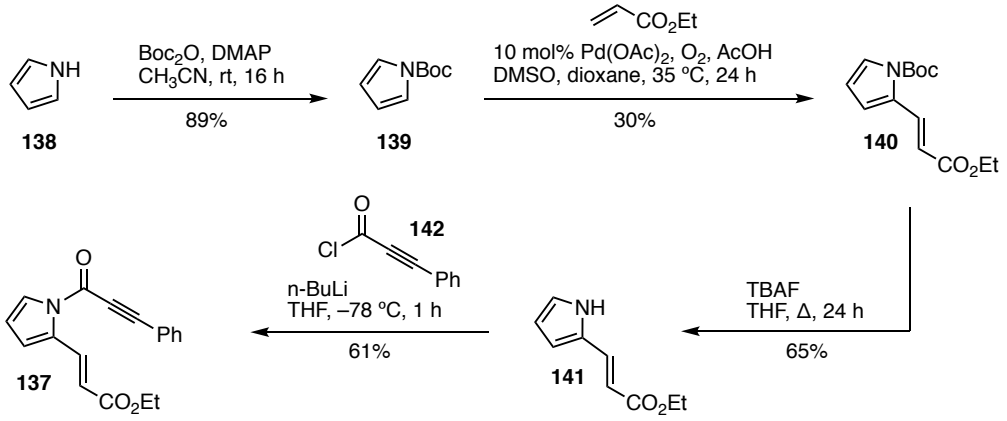
Table 2.11: (5 + 1) annulation with an aliphatic linker.



Entry	Additive	Temp.	Time	Yield[a]
1	-	r.t.	16 h	11%
2	-	Δ	48 h	9%
3	5 mol% t-BuOH	r.t.	16 h	34%

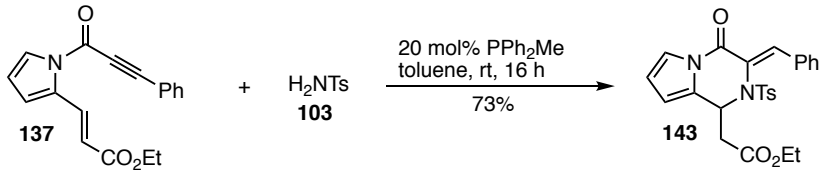
[a]Isolated yield following flash column chromatography.

Perhaps the lower yields are potentially a result of the phenylpropiolyl- and acrylate-moieties no longer being restricted to the S-*cis* configuration that is present in the benzannulated scaffold. Heterocyclic scaffolds were also examined using *N*-phenylpropiolyl pyrrole **137**. This substrate was prepared by first protecting pyrrole **138** to give *N*-Boc pyrrole **139**,[20] before aerobic palladium catalysed C-H functionalisation was employed to install the acrylate moiety as reported previously by Kim et. al..[21,22] Deprotection of **140** was achieved with TBAF to provide pyrrole acrylate **141**,[23] while acylation with phenylpropiolyl chloride **142** afforded the desired substrate **137** in moderate yield (Scheme 2.14).



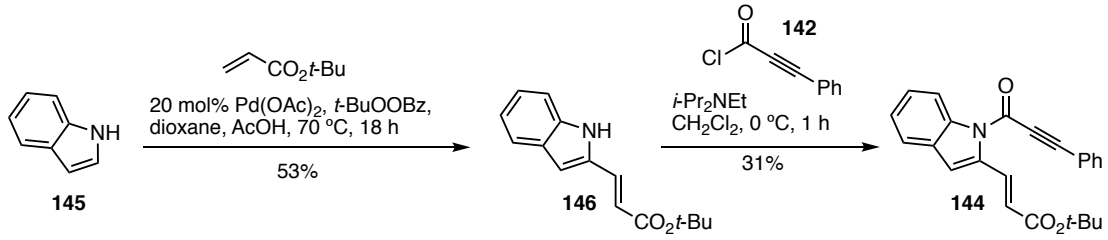
Scheme 2.14: Synthesis of *N*-phenylpropiolyl pyrrole **137**.

Gratifyingly, when trialled under the standard conditions, *N*-phenylpropiolyl pyrrole **137** was converted to pyrrole-fused piperazinone **143** in 73% yield (Scheme 2.15).



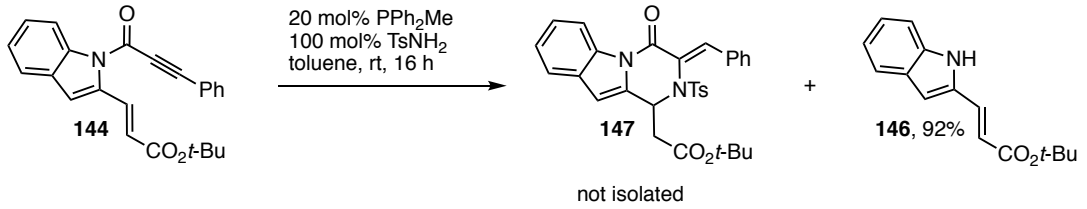
Scheme 2.15: (5 + 1) annulation of pyrrole **137** afforded piperazinone **143**.

As *N*-phenylpropiolyl pyrrole **137** proved to be a successful substrate, *N*-phenylpropiolyl indoles became the next logical substrate to examine. *N*-Phenylpropiolyl indole **144** was synthesised in two steps from indole **145**. Following a procedure of Gaunt et. al., direct palladium catalysed C-H functionalisation of indole **145** provided acrylate **146** in moderate yield.[24] Subsequent acylation of acrylate **146** with phenylpropiolyl chloride **142** gave the desired product **144** in acceptable yield (Scheme 2.16).



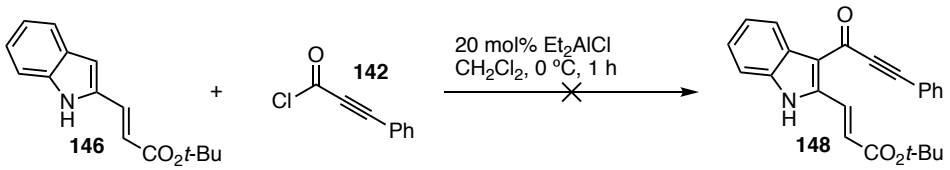
Scheme 2.16: Synthesis of *N*-phenylpropionyl indole **144**.

Unfortunately, when subjected to the optimised reaction conditions the desired product **147** was only observed in trace amounts. Indole **146** was isolated as the major reaction product which is presumably formed via deacylation of the starting material **144** (Scheme 2.17).



Scheme 2.17: Attempted (5 + 1) annulation of *N*-phenylpropiolyl indole **144**.

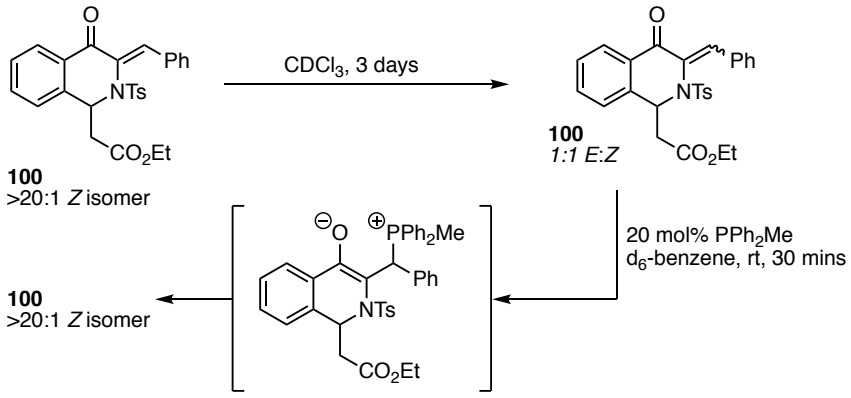
Since indole acrylate **146** was also a suitable precursor for the potential synthesis of C3-acylated indole **148**, we attempted the acylation of this substrate utilising conditions reported previously by Yoshino et. al..[25] Unfortunately, this proved to be unsuccessful and resulted in decomposition of the starting material (Scheme 2.18).



Scheme 2.18: Attempted synthesis of indole **148**.

2.4 Mechanistic observations

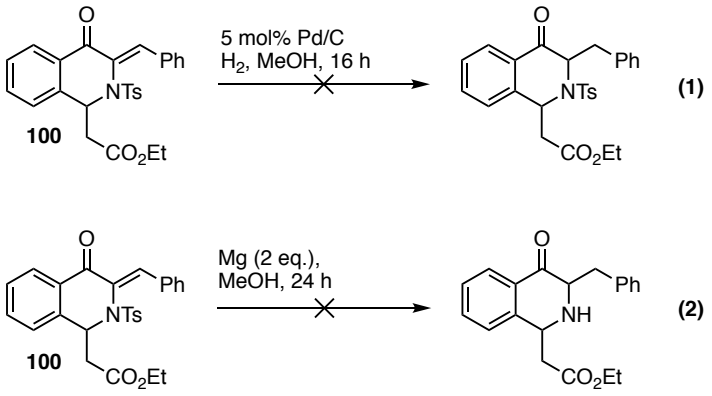
Over the course of our studies it was observed that the isoquinolinone product **100**, isolated as a single olefin isomer *(Z)*, isomerised significantly over the course of several days. Presumably this mixture is the thermodynamic product, with the *Z*-isomer formed under kinetic control. To test this, a 1:1 d_6-benzene solution of isoquinolinone *(E)*-**100** and *(Z)*-**100** was treated with 20 mol% PPh_2Me and the reaction was analysed directly via ^1H NMR spectroscopy. This confirmed that resubjection to the catalyst facilitated 100% conversion to the *(Z)*-isomer **100**, supporting the conclusion that the *(Z)*-isomer is the kinetic reaction product (Scheme 2.19).



Scheme 2.19: Conversion of E/Z isomers to single Z isomer.

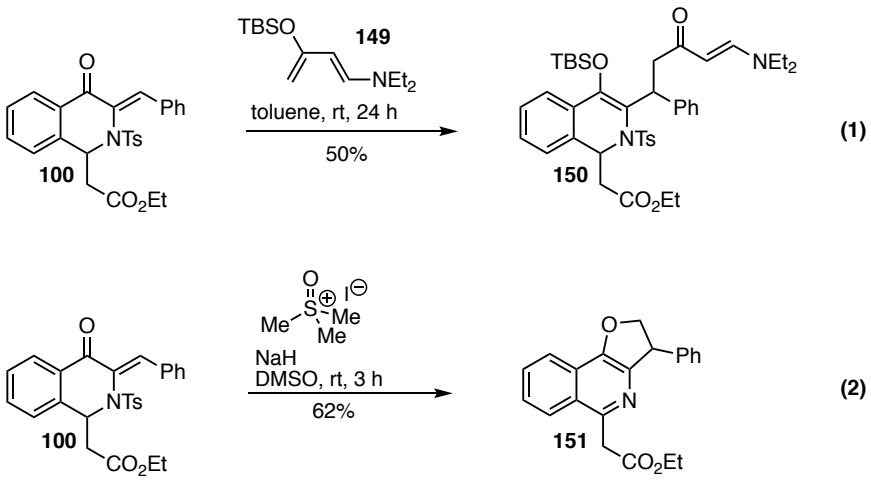
2.5 Derivatisation studies

In order to assess the reactivity of the isoquinolinone product, several transformations were attempted (Scheme 2.20). These were focused on deprotection of the amine and functionalisation of the olefin. Firstly, when reduction of the α,β-unsaturated system was attempted via hydrogenation with palladium on charcoal, no reaction was observed and only starting material was recovered (Scheme 2.20, eq. 1). It has been reported that an Mg/MeOH reducing system is effective in reducing enoates as well as for the deprotection of sulfonamides, however, this proved to be ineffective for our substrate (Scheme 2.20, eq. 2).[26,27]



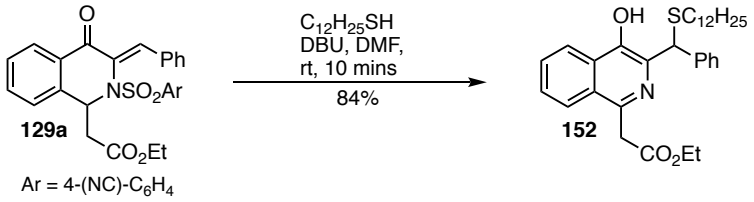
Scheme 2.20: Attempted reduction of isoquinolinone **100**.

Having failed to reduce the olefin, studies focused on its potential as a dienophile. Thus, isoquinolinone **100** was exposed to Rawal's diene **149** in toluene at room temperature. Rather than the expected Diels-Alder product, a Mukaiyama-type Michael addition product was observed providing dihydroisoquinolone **150** in moderate yield as a single diastereomer (Scheme 2.21, eq. 1). Other nucleophiles could also be added to this olefin. Specifically, when isoquinolinone **100** was treated with a Corey-ylide, dihydrofuran-fused isoquinolinone **151** was isolated as the reaction product in moderate yield (Scheme 2.21, eq. 2). Its formation is thought to have occurred via conjugate addition followed by etherification. Such reactions have been previously reported in the literature.[28]



Scheme 2.21: Conjugate additions to isoquinolinone **100**.

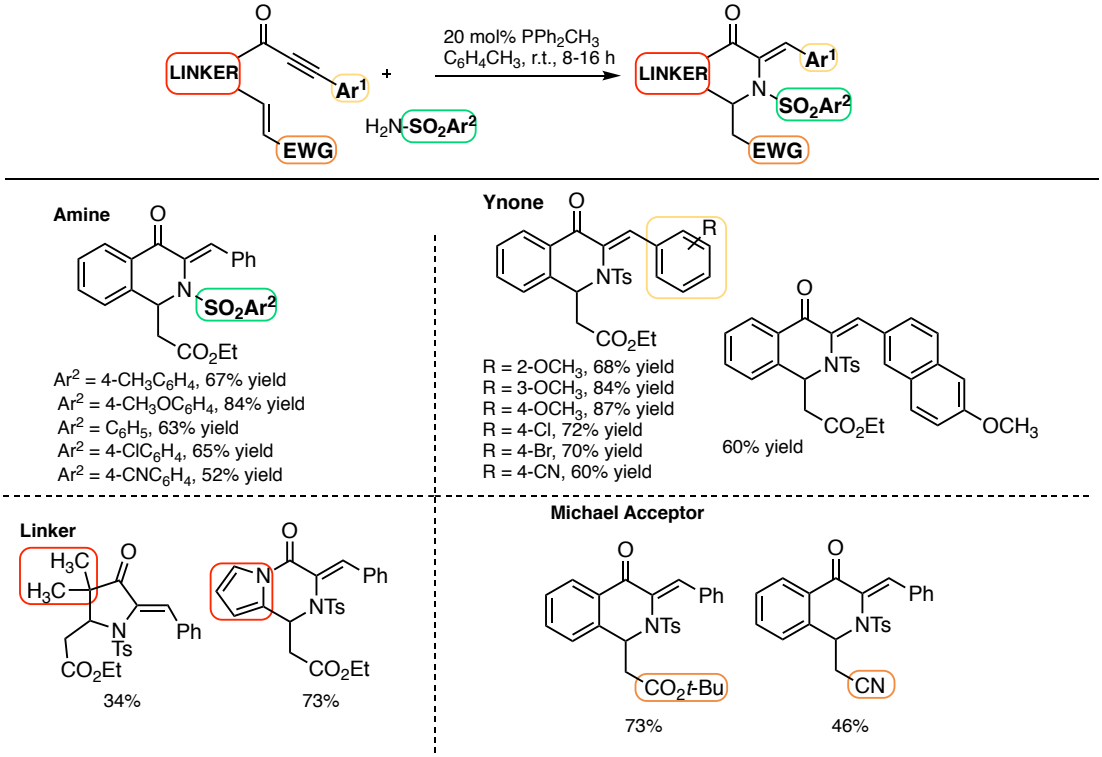
Finally we examined the deprotection of the sulfonyl group. In studies reported by Schmidt et al. it was found that deprotection of 4-cyanobenzenesulfonyl substituted amines could be affected by treatment with dodecanethiol.[29] When isoquinolinone **129a** was subjected to the reported reaction conditions the protecting group was removed, along with introduction of the dodecanethiol group by conjugate addition to afford isoquinolinol **152** in good yield (Scheme 2.22).



Scheme 2.22: Synthesis of isoquinolinol **152** via treatment with dodecanethiol.

2.6 Conclusions

To conclude, our attempts to develop a methodology that exploits the proposed β-phosphonium ylide were unsuccessful, however, these studies led to the discovery of a novel (5 + 1) annulation of ynone/cinnamates with sulfonamides via the rare interception of intermediates from an α-addition to ynones. The methodology was useful for the synthesis of isoquinolinones, pyrrolidinones and pyrrolopiperazines, with the products obtained being amenable to various synthetic transformations via conjugate addition of nucleophiles. Unfortunately, although an enantioselective reaction appears to be viable, this was only achieved with low selectivity in our hands.



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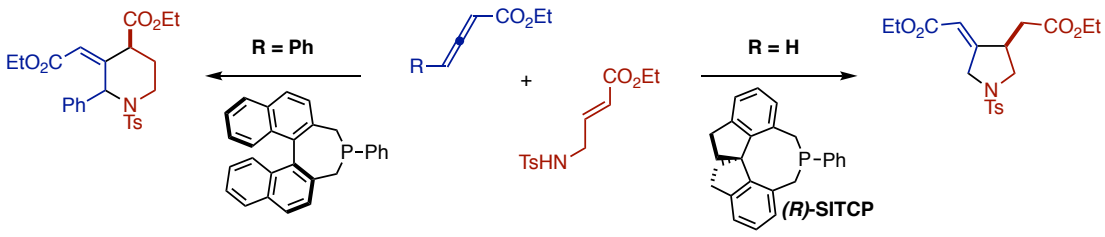
Chapter 3

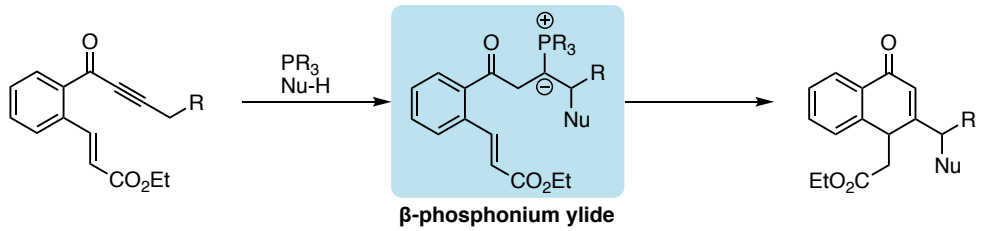
Enantioselective (3 + 2) annulation of allenes and allylic amines via the β-phosphonium ylide

Herein the development of a novel methodology for the synthesis of enantioenriched pyrrolidines via a (3 + 2) annulation of allylic amines with activated allenes is reported. This reactions development from the conceptual stage and reaction discovery, through optimisation, followed by initial scope studies, is discussed. Furthermore, these studies led to the discovery of a novel (4 + 2) annulation that is able to produce chiral piperidines with modest levels of enantiopurity, and initial investigations into this process are also disclosed.



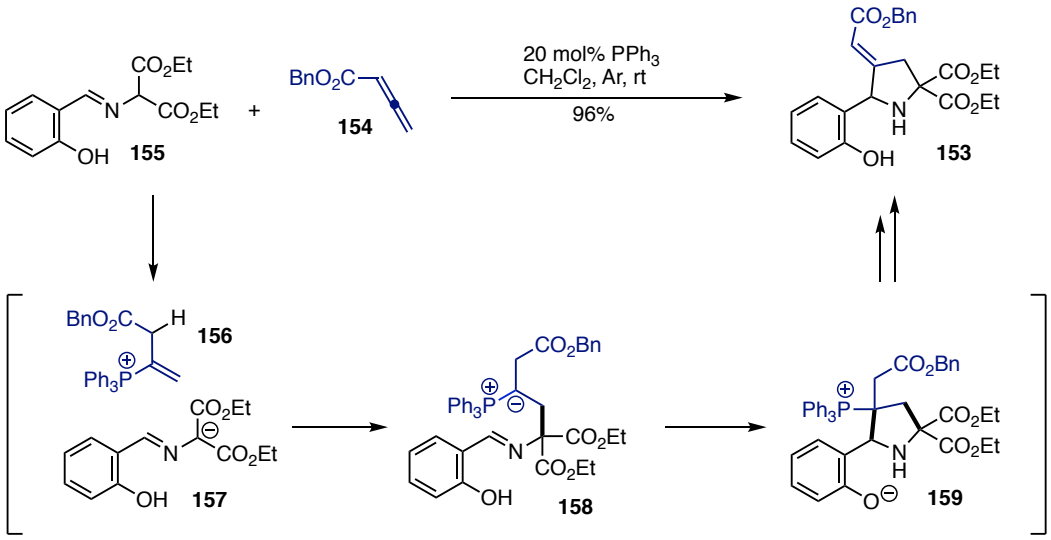
3.1 Introduction

Following discovery of the phosphine catalysed (5 + 1) annulation reported in the previous chapter, our focus returned to originally envisioned reaction designs that sought to exploit the β-phosphonium ylide (Scheme 3.1).



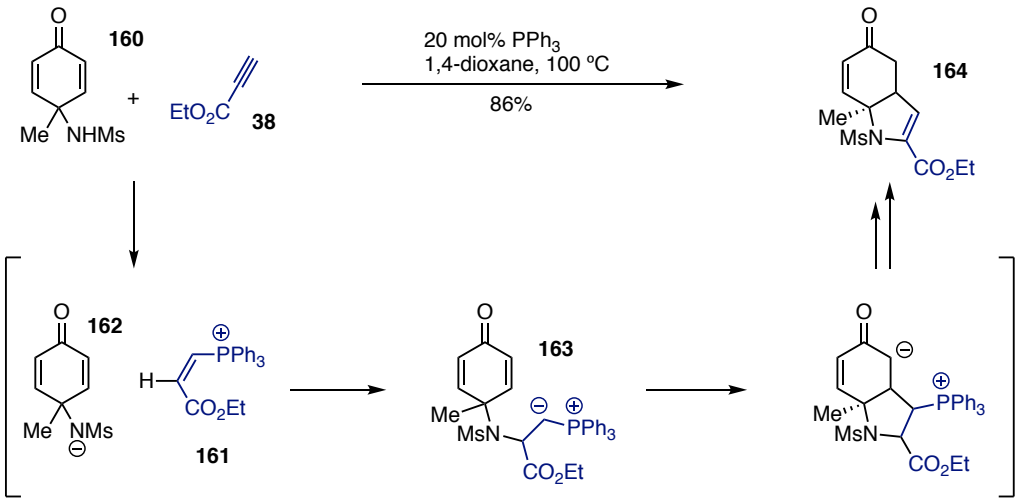
Scheme 3.1: Proposed reaction design discussed in chapter 2.

In the period since the initial studies of Sasai et. al.,[1] two further reports which exploited the β-phosphonium ylide were published. The first was a hydroxy-assisted synthesis of 4-methylenepyrrolidine derivatives (i.e. **153**) via (3 + 2) annulation of allenes and azomethine ylides as reported by the Zhou group.[2] The postulated mechanism for this transformation involves conjugate addition of triphenylphosphine to allenoate **154** which deprotonates azomethine ylide **155** to form vinylphosphononium **156** and enolate **157**. Enolate **157** then undergoes γ-addition to vinylphosphonium **156** to form the β-phosphonium ylide **158** followed by cyclisation into the pendant imine and subsequent tautomerisation to yield phenolate **159**. Finally, tautomerisation and elimination of the phosphine then affords pyrrolidine **153**. Interestingly, it was observed that the reaction only proceeds for 2-hydroxyphenyl derivatives, suggesting that the phenol is required for activation of the imine (Scheme 3.2).



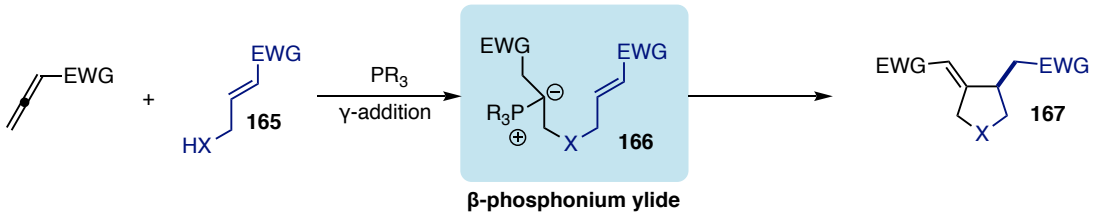
Scheme 3.2: Zhou's (3 + 2) annulation of allenoates and azomethine ylides.

In 2018, Sasai et al. reported the synthesis of hydroindoles via a dual umpolung domino reaction of alkynes with aminocyclohexadienones (i.e. **160**) in a reaction reminiscent of their earlier chemistry with oxygen containing substrates.[3] In this case, addition of triphenylphosphine to alkynoate **38** affords an enolate species which deprotonates amine **160** to provide vinylphosphonium **161** and aza-anion **162**. Subsequent α-addition yields the β-phosphonium ylide **163** which undergoes cyclisation and elimination of the phosphine to provide hydroindole **164** (Scheme 3.3).



Scheme 3.3: Sasai's dual umpolung domino Michael reaction of alkynes.

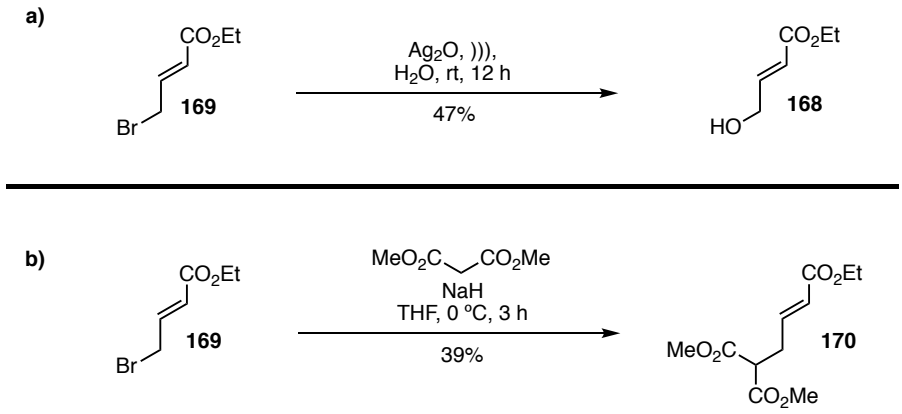
As the ynone-cinnamate substrates trialled previously (Chapter 2) were not amenable to the desired transformation, a new reaction design was conceived. Based on literature reports in which allenoates have proven to be more amenable to β,γ-reactivity, we moved away from alkynes in favour of more reactive allenes. Various nucleophiles have been reported to undergo γ-umpolung addition to allenoates under phosphine catalysis, including amines, alcohols, thiols, malonates, enolates, nitroalkanes and others.[4] It was anticipated that reaction of an activated allene with a suitable nucleophile tethered to a Michael acceptor (i.e. **165**) under phosphine catalysis could successively elicit formation of β-phosphonium ylide **166** that would then undergo intramolecular cyclisation to form five membered rings such as **167** (Scheme 3.4). Furthermore, by using a homochiral catalyst an enantioselective variant of the reaction should be possible.



Scheme 3.4: (3 + 2) annulation exploiting the β-phosphonium ylide.

3.1.1 Reaction discovery

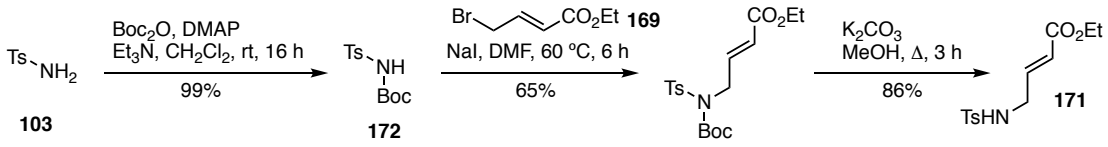
With the reaction design in place the nature of the bifunctional donor-acceptor (i.e. **165**) had to be determined. To this end three different pro-nucleophilic domains were identified as worthy of investigation. In 2016, Ziegler and Fu reported the γ-addition of alcohols to alkynoates and given the similar reactivity of allenoates we reasoned that related oxygen containing substrates might be viable in this reaction design.[5] To this end, allylic alcohol **168** was prepared via overnight sonication of ethyl 4-bromocrotonate **169** in the presence of Ag_2O to provide ethyl 4-hydroxycrotonate **168** in moderate yield, in accordance with the literature (Scheme 3.5a).[6] In a related vein, Fu and coworkers reported that malonates were suitable pronucleophiles in γ-umpolung additions of allenoates,[7] and so allyl malonate **170** was synthesised in one step by direct substitution of ethyl 4-bromocrotonate **169** with dimethyl malonate (Scheme 3.5b).[8]



Scheme 3.5: Synthesis of bifunctional donor-acceptors.

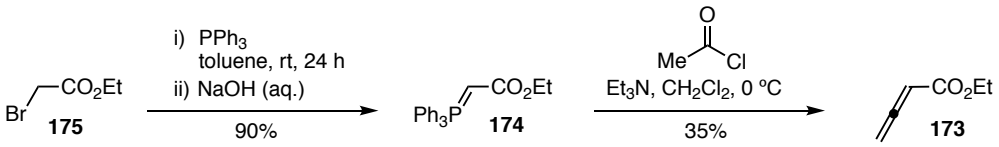
Finally, previous studies by Kwon et al. reported the γ-addition of sulfonamides to allenoates and it was thought that an allyl amino derivative of this substrate might allow the desired reaction.[9] Thus, allyl amine **171** was synthesised according to a literature procedure in three steps.[10] Specifically, Boc-protection of *p*-toluenesulfonamide **103**

proceeded in quantitative yield to provide Boc-amine **172**, which was then reacted with ethyl 4-bromocrotonate **169** at 60 °C in DMF. Removal of the Boc-protecting group was achieved via treatment with K_2CO_3 in MeOH heated to reflux to provide allyl amine **171**.



Scheme 3.6: Synthesis of allyl amine **171**.

Allenoate **173** was prepared in two steps from ethyl bromoacetate (Scheme 3.7) according to the procedure of Zhou.[11] Ylide **174** was synthesised via quarternisation of triphenylphosphine with ethyl bromoacetate **175** and subsequent deprotonation with NaOH in excellent yield. Wittig olefination of in situ generated ketene with ylide **174** provided the desired allenoate **173** in 35% yield.

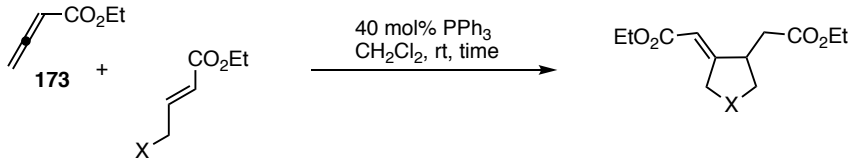


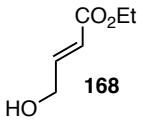
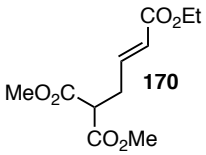
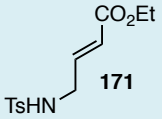
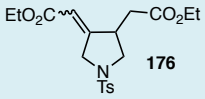
Scheme 3.7: Preparation of ethyl 2,3-butadienoate **173**.

With potential substrates in hand, their reactions with allenoate **173** in the presence of triphenylphosphine were examined (Table 3.1). Dichloromethane was chosen as a solvent as it is commonly used in phosphine organocatalysis. Ethyl 4-hydroxycrotonate **168** underwent full conversion under the reaction conditions, however, this resulted in a complex mixture of products with none successfully isolated (Table 3.1, entry 1). When allyl malonate **170** was employed, complete consumption of the starting materials was observed, and purification of the crude reaction residue resulted in a pure but inseparable

mixture of compounds (Table 3.1, entry 2). In contrast, when allyl amine **171** was employed, the desired β,γ-umpolung product, pyrrolidine **176**, was isolated from the reaction mixture in 34% yield (Table 3.1, entry 3).

Table 3.1: Reaction of ethyl 2,3-butadienoate with allylic nucleophiles.



Entry	Substrate	Time	Yield[a]
1		5 h	decomp.
2		5 h	complex
3		16 h	 34%, dr 5:1

[a]Isolated yield following flash column chromatography.

The structure of **176** was determined by ^{1}H and ^{13}C NMR spectroscopy. In particular, signals corresponding to the alkenyl protons in the allyl amine and the terminal allenic protons were absent in the ^{1}H NMR spectrum of the product, however, new signals corresponding to two methylene units and a methine unit were observed which were consistent with the proposed structure (Figure 3.1).

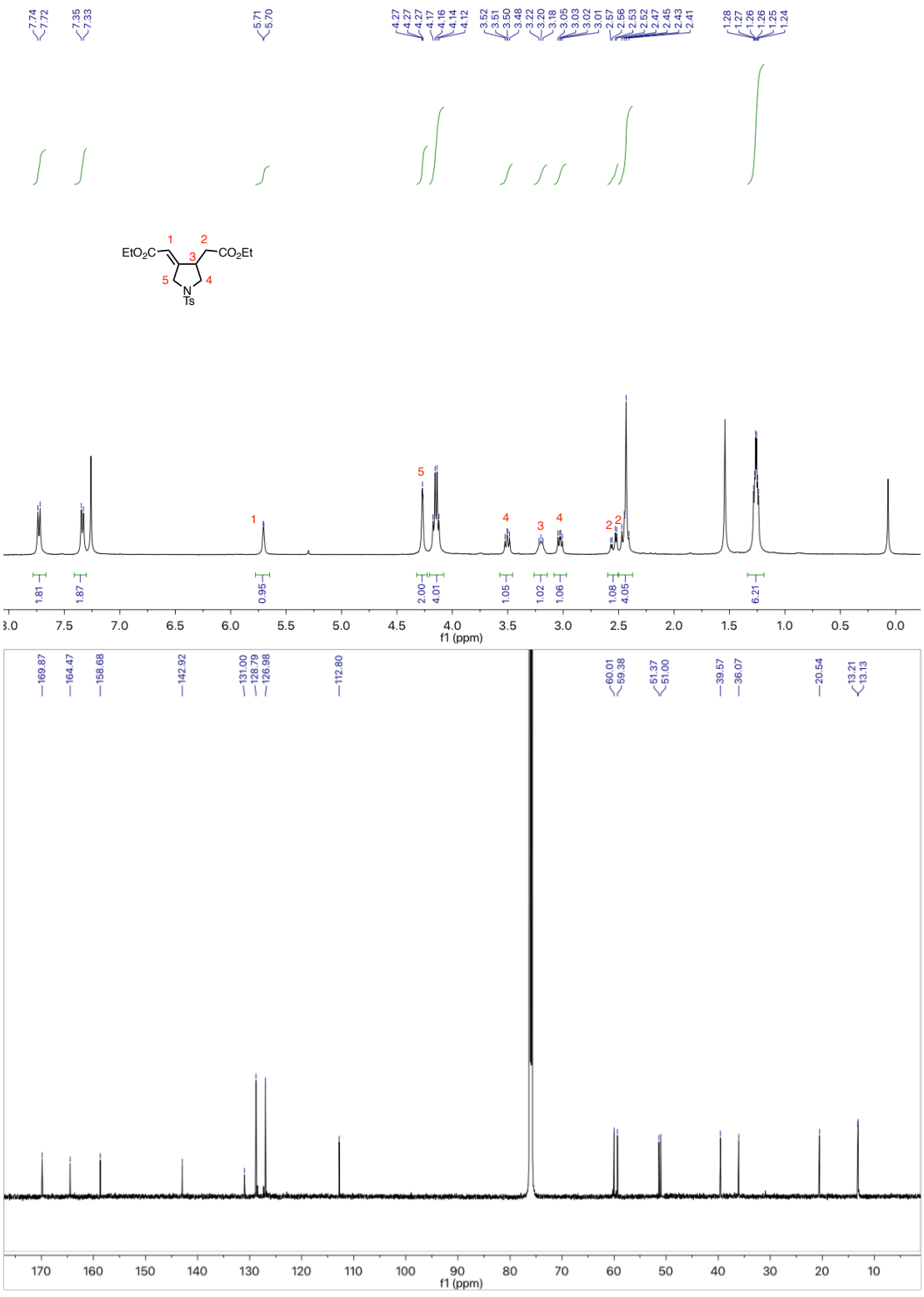


Figure 3.1: ^{1}H and ^{13}C NMR spectra of pyrrolidine **176** conducted in $CDCl_3$ at 600 MHz.

Crystallisation of the pyrrolidine **176** was attempted to determine the olefin geometry however this was unsuccessful. The benzyl ester variant **177**, which was synthesised

during a later stage of the project (Table 3.5, *vide infra*) produced crystals of sufficient quality for crystallography. Thus, analysis by XRD confirmed that the structure was indeed the *(Z)*-isomer of pyrrolidine **177** (Figure 3.2).

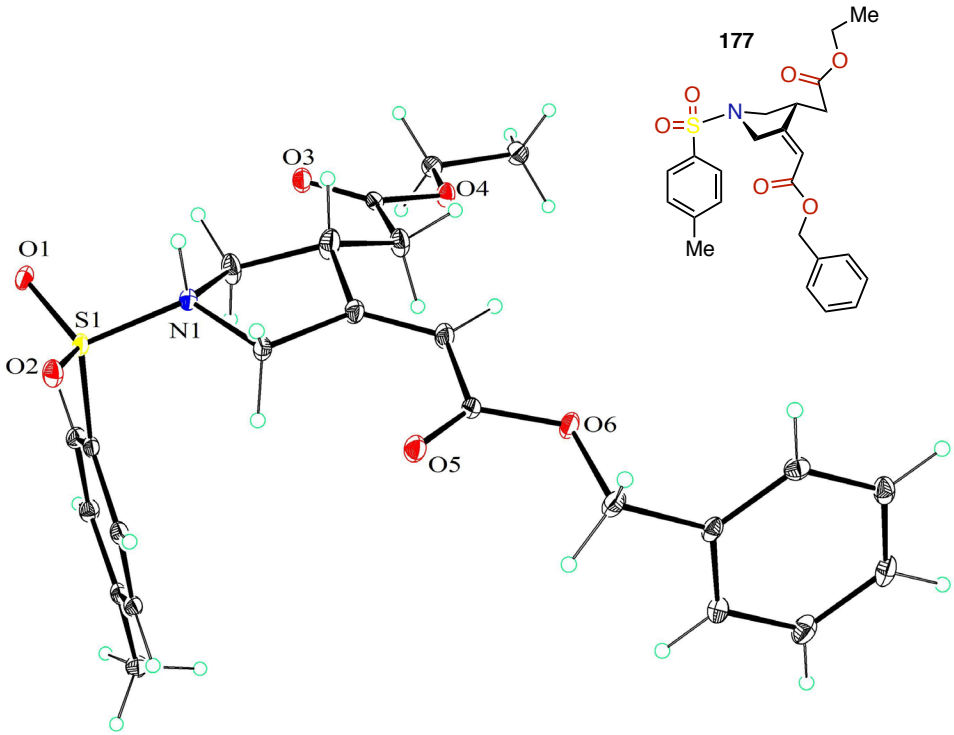


Figure 3.2: X-ray crystal structure of pyrrolidine **177**.

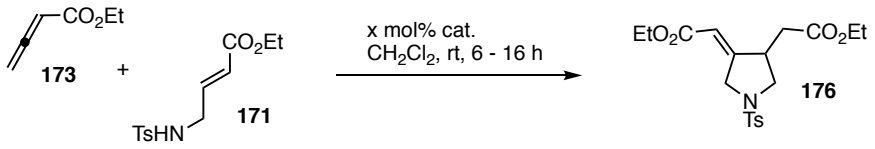
3.2 Optimisation of the phosphine catalysed (3 + 2) annulation

3.2.1 Initial optimisation

In order to improve our understanding of the discovered reaction cascade prior to undertaking a homochiral catalyst screen, a brief optimisation was undertaken (Table 3.2). The conditions originally trialled are provided for reference (Table 3.2, entry 1). When the catalyst loading was reduced a decrease in conversion was observed (Table 3.2,

entry 2). When the more electron rich Me_2PPh catalyst was utilised the reaction yield increased markedly, though this also resulted in decreased diastereoselectivity (Table 3.2, entry 3). Finally, the reaction was trialled with $MePPh_2$, which also improved the yield and but resulted in decreased diastereoselectivity in contrast to triphenylphosphine (Table 3.2, entry 4).

Table 3.2: Initial reaction optimisation.



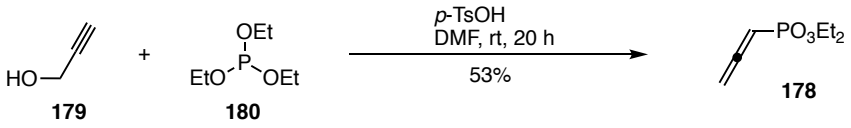
Entry	x mol% cat.	Yield[a]	dr[b]
1	40 mol% PPh_3	34%	5:1
2	20 mol% PPh_3	23%	5:1
3	20 mol% Me_2PPh	86%	3:1
4	20 mol% $MePPh_2$	49%	4:1

[a]Yields represent isolated yields following chromatography. [b]dr determined by ^{1}H NMR spectroscopy.

3.2.2 (3 + 2) annulation with various activated allenes

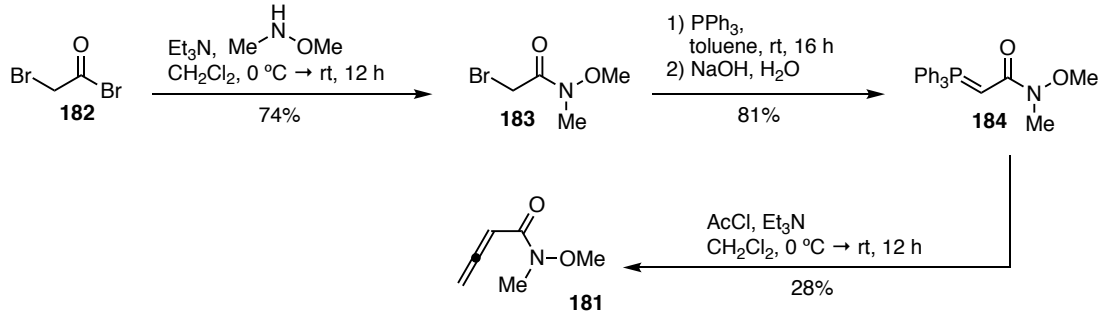
Activated allenes bearing alternative electron withdrawing groups such as Weinreb-amides, phosphonates and ketones have previously been reported to undergo γ-additions under phosphine catalysis,[12] consequently, it was necessary to synthesise these in order to assess which was most suited to the annulation.

Thus, allenyl phosphonate **178** was synthesised in one step via acid-catalysed elimination of propargyl alcohol **179** in the presence of triethylphosphite **180** in accordance with the literature procedure (Scheme 3.8).[13]



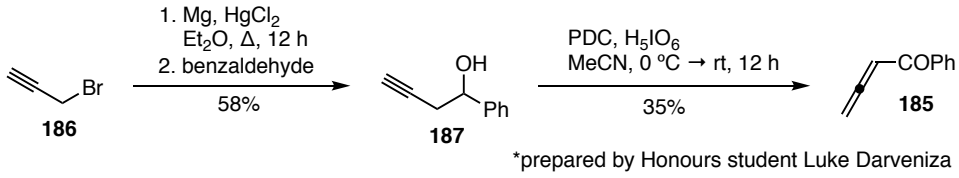
Scheme 3.8: Synthesis of allene **178**.

Weinreb allene **181** was prepared according to the literature in three steps from bromoacetyl bromide **182**.[12] Substitution of bromoacetyl bromide **182** was achieved via treatment with *N,O*-dimethylhydroxylamine under basic conditions to yield bromoacetamide **183**. Bromoacetamide **183** was reacted with triphenylphosphine to afford the corresponding phosphonium salt which was immediately converted to stabilised ylide **184**. Wittig olefination with in situ generated ketene derived from acetyl chloride afforded the desired Weinreb allene **181** (Scheme 3.9).



Scheme 3.9: Preparation of Weinreb allene **181**.

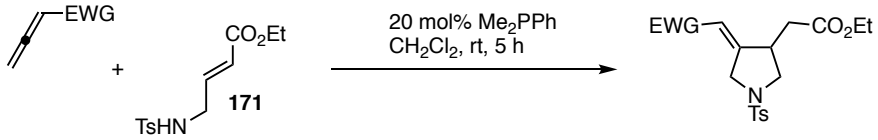
Allenone **185** was prepared by another student in two steps according to a reported synthesis.[14] Treatment of propargyl bromide **186** with magnesium powder in the presence of catalytic mercury(II) chloride afforded the desired Grignard reagent which was reacted with benzaldehyde to give alcohol **187**. Oxidation with PDC facilitates conversion to the corresponding ketone which then undergoes acid-mediated isomerisation to the target allenone **185** (Scheme 3.10).

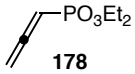
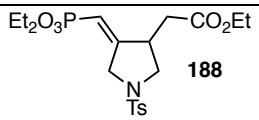
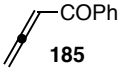
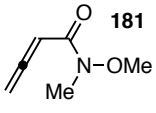
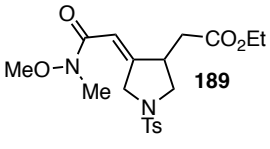


Scheme 3.10: Synthesis of allenone **185**.

The various electron-poor allenes were then reacted with allyl amine **171** utilising 20 mol% Me_2PPh catalyst in accordance with the best conditions determined thus far (Table 3.3). When allenyl phosphonate **178** was reacted under these conditions, the desired pyrrolidine **188** was produced, albeit in poor yield (Table 3.3, entry 1). Reaction of allenone **185** resulted in decomposition of the starting material (Table 3.3, entry 2), while the Weinreb allene **181** allowed the annulation, affording the desired pyrrolidine **189**, although the yields were modest and no diastereoselectivity was observed (Table 3.3, entry 3). Armed with these early insights regarding the optimal reaction conditions, the development of an enantioselective reaction variant which commenced with screening of a range of homochiral phosphine catalysts, was undertaken. These reactions were performed in conjunction with Honours student Luke Darveniza.

Table 3.3: Annulation of various activated allenes.



Entry	Allene	Product
1	 **178**	 **188** 9%, dr 2:1
2	 **185**	decomp.
3	 **181**	 **189** 35%, dr 1:1

3.2.3 Preparation of homochiral phosphine catalysts

An array of homochiral phosphines that had been employed previously in enantioselective organocatalysis with success were deemed to be suitable catalysts for our optimisation studies (Figure 3.3).[4a]

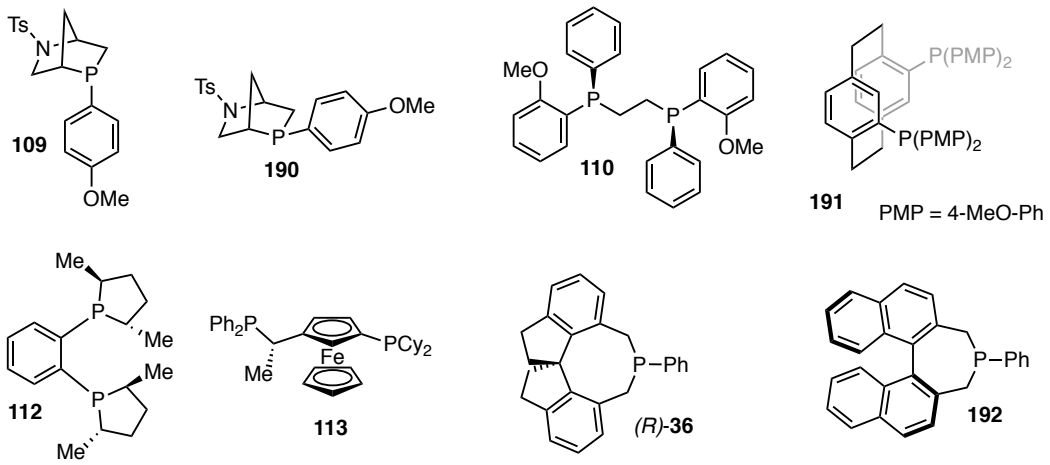
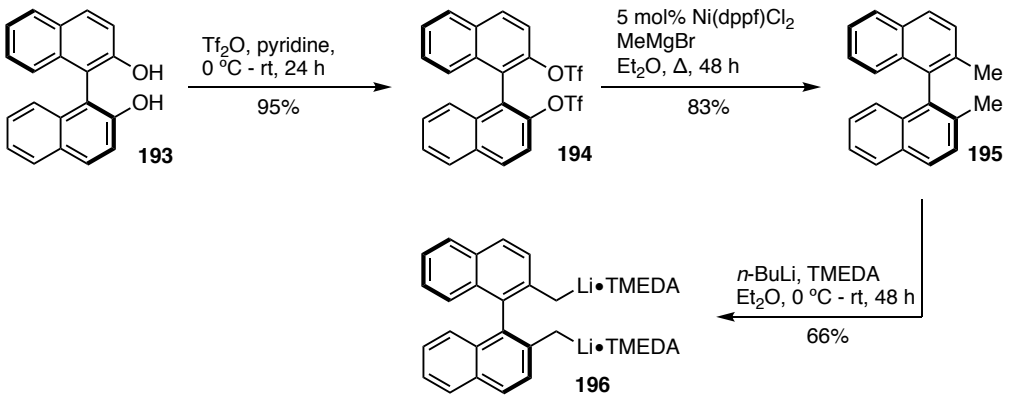


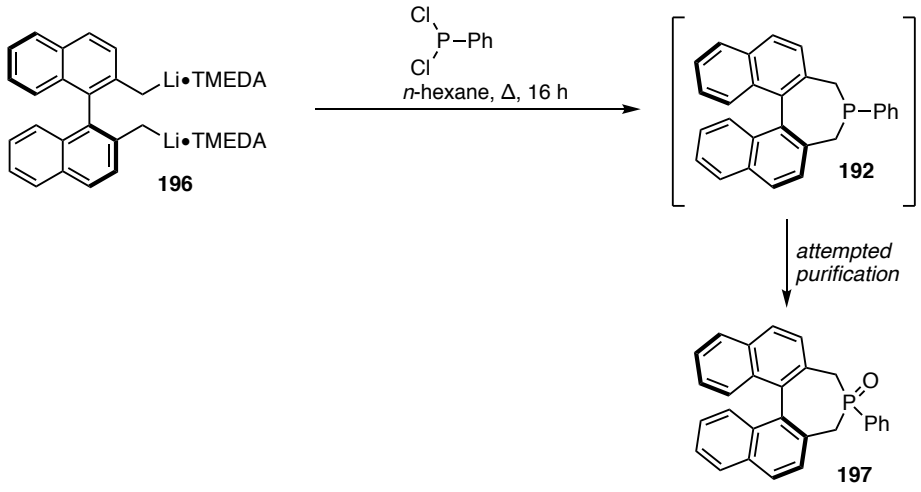
Figure 3.3: Selected phosphines for catalyst screening.

Homochiral phosphines *(R)*-**36**, **109**, **110**, **112**, **113**, **190**, and **191** were purchased, while phosphepine **192** was prepared from *(R)*-BINOL over six steps as it was not commercially available.[15] The synthesis commenced with the sulfonylation of *(R)*-BINOL **193** with triflic anhydride to give triflate **194** in good yields that was then converted to binaphthalene **195** via a nickel-catalysed Kumada cross-coupling reaction with methyl magnesium bromide. Lithiation of binaphthalene **195** with *n*-butyllithium in the presence of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) provided the lithium-TMEDA complex **196**.



Scheme 3.11: Preparation of the lithium-TMEDA complex **196**.

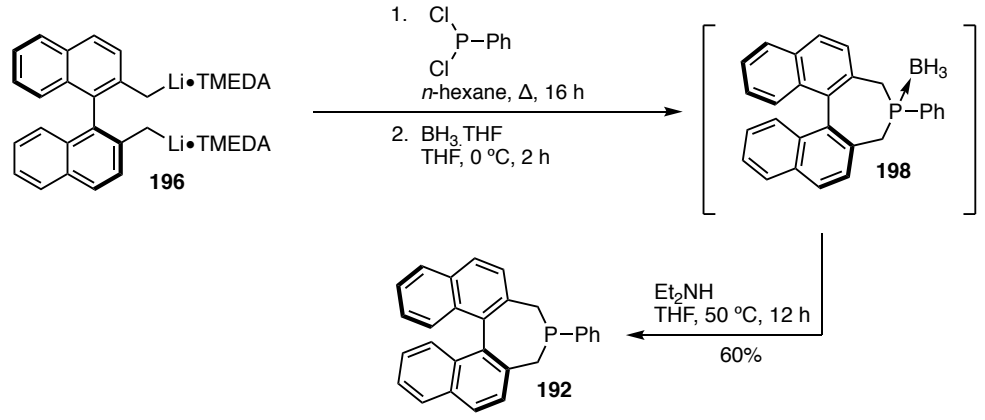
Direct preparation of the desired phosphepine **192** was attempted by treatment with dichlorophenylphosphine in refluxing *n*-hexane, however, this led to an impure product which was difficult to crystallise, and attempted purification via column chromatography on silica led to significant conversion to the phosphine oxide **197** (Scheme 3.12).



Scheme 3.12: Attempted synthesis of phosphepine **192**.

To overcome this, the phosphine was prepared under the same conditions without isolation, and immediately treated with BH_3•THF complex to afford the BH_3 adduct **198**, which had previously been reported to be air and moisture stable.[16] This adduct was stable to column chromatography on silica gel which facilitated removal of undesired

phosphine oxide. Deborylation of adduct **198** was then realised by treatment with diethylamine in methanol to afford the desired phosphepine **192** in high purity (Scheme 3.13).[16b]



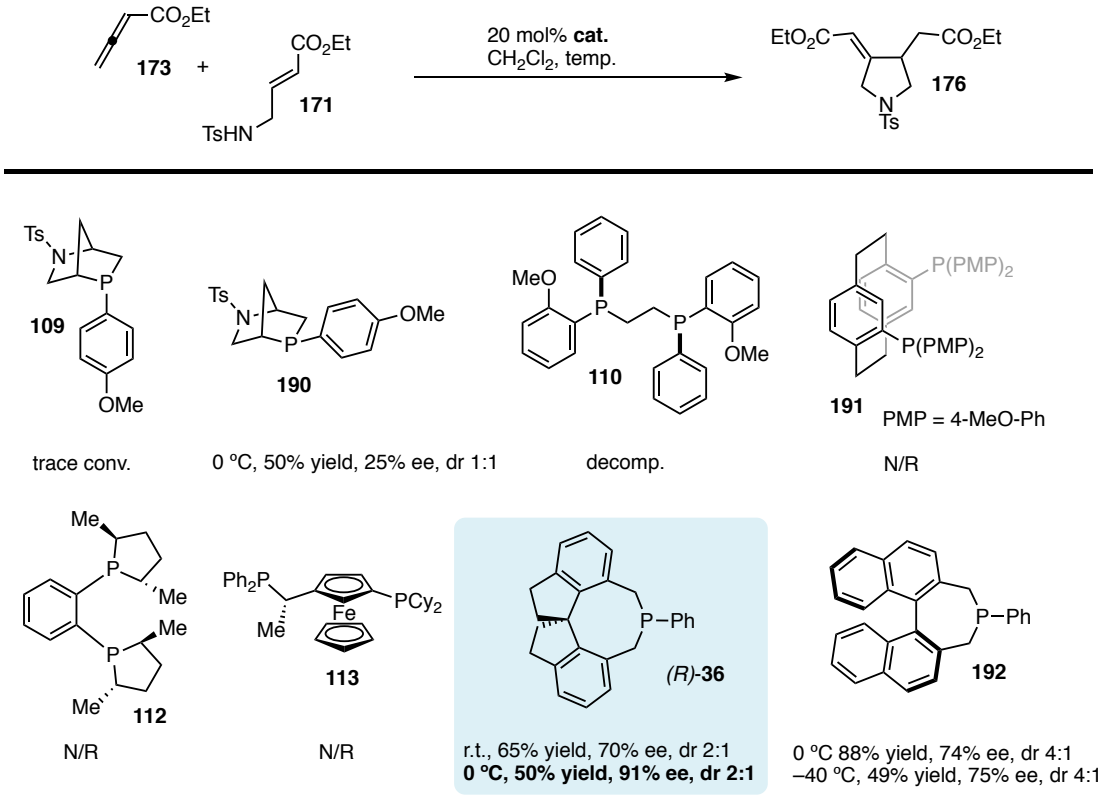
Scheme 3.13: Revised synthesis of phosphepine **192**.

3.2.4 Homochiral catalyst screen

With the desired catalysts in hand, the annulation reaction was performed in CH_2Cl_2 with allenoate **173** and allyl amine **171** using 20 mol% of the phosphine catalyst (Table 3.4). When phosphine **109** developed by Kwon[17] was trialled, little conversion to the product was observed. *Exo*-derivative **190** produced pyrrolidine **176** in 50% yield but with low enantioselectivity and no diastereoselectivity. DIPAMP **110** led to decomposition of the starting material, while Phanephos **191**, DUPHOS **112** and Josiphos **113** all proved unreactive towards the substrates. *(R)*-SITCP **36** was able to afford the pyrrolidine product **176** in good yield and good enantioselectivity, however diastereoselectivity was low. Repeating the reaction at a lower temperature, the yield decreased, diastereoselectivity was unchanged but a significant increase in enantioselectivity was observed. Phosphepine **192** was also trialled and led to excellent conversion at 0 °C, moderate enantioselectivity, and moderate diastereoselectivity. The experiment was

repeated at –40 °C in an attempt to improve enantioselectivity, however, this only decreased the yield, with both enantioselectivity and diastereoselectivity unchanged.

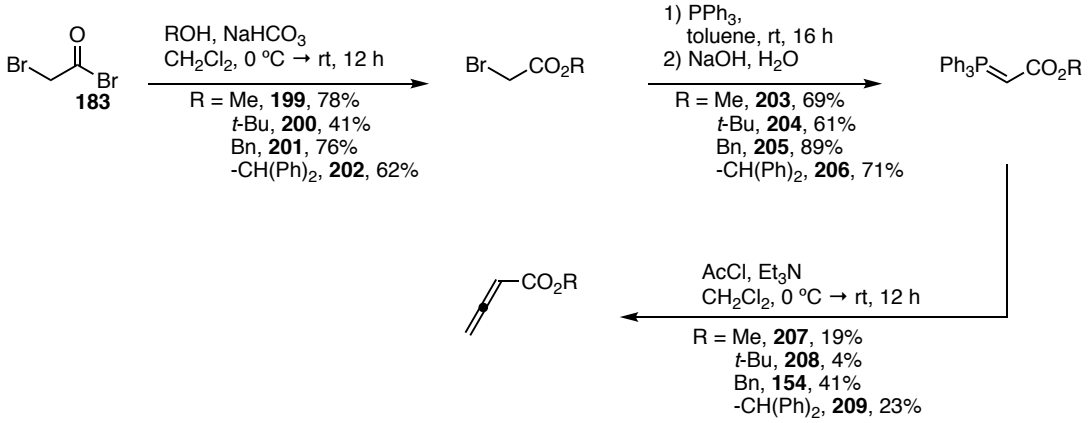
Table 3.4: Homochiral catalyst screen.



3.2.5 Preparation of allenoate substrates

Having established a viable enantioselective, although moderately diastereoselective reaction, our attention turned to alternate allenoates in order to assess the ideal substrate for further optimisation. Initially, a number of ester derivatives were prepared in three steps from bromoacetyl bromide **182** (Scheme 3.14). Substitution of bromoacetyl bromide **182** with the various alcohols afforded the corresponding bromoacetate derivatives **199–202**. Reaction of the bromoacetate derivatives **199–202** with triphenylphosphine and immediate deprotonation of the resultant phosphonium salt led

to the formation of phosphonium ylides **203–206**.[18] Wittig olefination of the *in situ* generated ketene with phosphonium ylides **203–206** then produced the desired allenoates **154** and **207–209** in serviceable yields (Scheme 3.14).

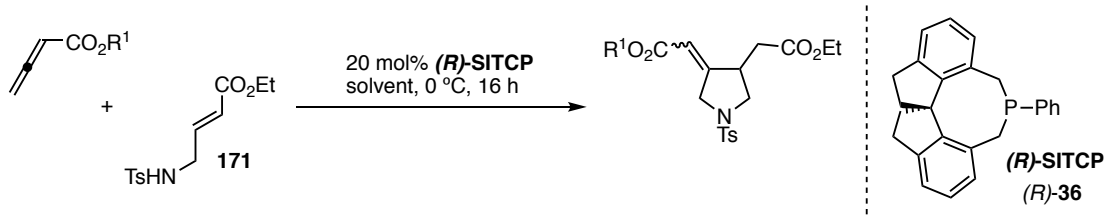


Scheme 3.14: Preparation of allenoate substrates.

3.2.6 Enantioselective reaction optimisation

Based on initial studies, *(R)*-SITCP **36** was selected as the lead catalyst for further optimisation. Previously discussed reaction conditions are listed for reference (Table 3.5, entry 1). Initial optimisations commenced with screening solvents typically used in phosphine organocatalysis. When conducted in toluene, pyrrolidine **176** was afforded with increased enantioselectivity, however reaction yield was reduced, and no diastereoselectivity was observed (Table 3.5, entry 2). The reaction was trialled in THF which resulted in reduced conversion and enantioselectivity, with no improvement in diastereoselectivity (Table 3.5, entry 3). Little conversion was observed when acetonitrile was utilised as the solvent (Table 3.5, entry 4). Next the various allenoates were trialled to assess the effect of steric bulk on the reaction outcome. In this case, larger substituents generally led to products with similar enantioselectivity though yield and diastereoselectivity were slightly decreased (Table 3.5, entries 5–7).

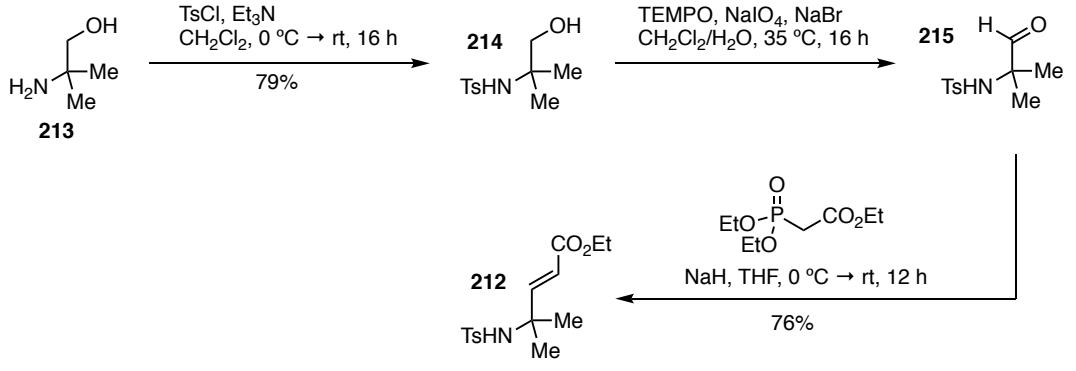
Table 3.5: (3 + 2) annulation of allenoates with allylic amines.



Entry	R^1	Solvent	Yield[a]	er[b]	dr[c]
1	Et	CH_2Cl_2	**176**, 61%	96:4	2:1
2	Et	toluene	**176**, 50%	98:2	1:1
3	Et	THF	**176**, 38%	92:8	1:1
4	Et	MeCN	**176**, 6%	-	-
5	Bn	CH_2Cl_2	**177**, 65%	96:4	1:1
6	*t*-Bu	CH_2Cl_2	**210**, 40%	95:5	1:1
7	-$CHPh_2$	CH_2Cl_2	**211**, 9%	-	1:1

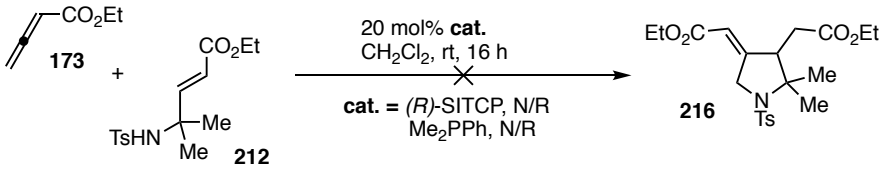
[a]Isolated yield following flash chromatography. [b]er determined by HPLC on a chiral stationary phase. [c]dr determined by ^{1}H NMR spectroscopy.

We hoped that the reaction would still proceed with substituted allyl amines (i.e. **212**), perhaps with greater selectivity due to enhanced rates of cyclisation due to the Thorpe-Ingold effect.[29] To investigate this, allyl amine **212** was synthesised in three steps from β-aminoisobutyl alcohol **213** (Scheme 3.15). Sulfonylation of **213** was achieved via treatment with *p*-toluenesulfonyl chloride in the presence of triethylamine to afford alcohol **214**. Oxidation with TEMPO/periodate provided the corresponding aldehyde **215** which was converted to the desired allyl amine **212** by Horner-Wadsworth-Emmons olefination.



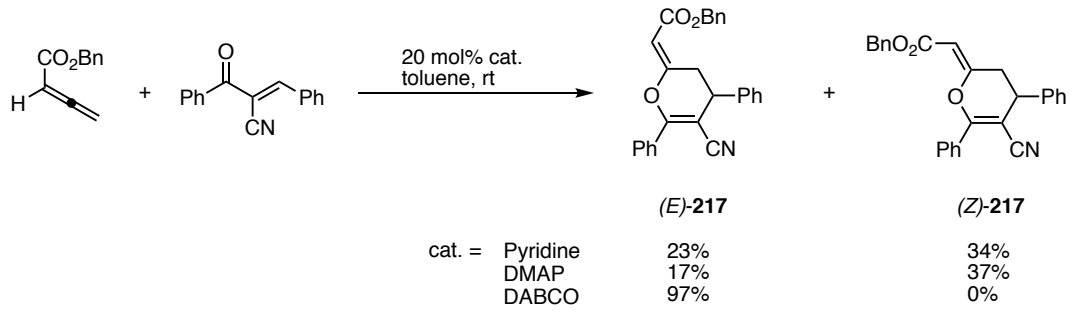
Scheme 3.15: Preparation of allyl amine **212**.

Allyl amine **212** was reacted with allenoate **173** in the presence of 20 mol% *(R)*-SITCP and after 12 hours the crude mixture was analysed by ^{1}H NMR spectroscopy, which indicated that the annulation had not occurred. The reaction was repeated with 20 mol% Me_2PPh but this also failed to give any product of the desired product **216**. In both cases the allenoate was completely consumed, presumably by oligomerisation. Conversely, the allyl amine **212** was fully recovered, suggesting that it was too sterically demanding to behave as a pronucleophile (Scheme 3.16).



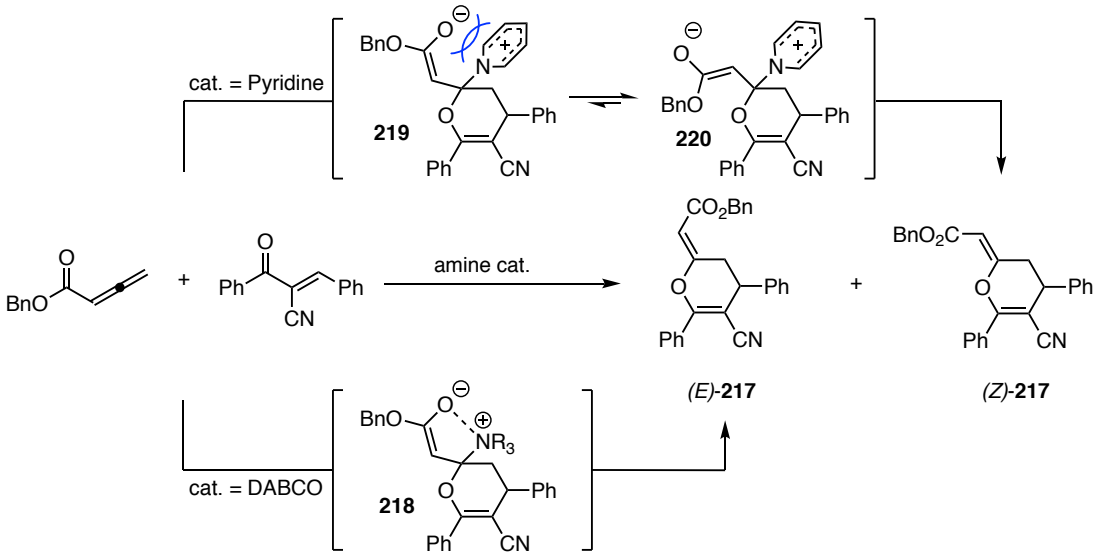
Scheme 3.16: Attempted (3 + 2) annulation of allyl amine **212**.

While our studies had delivered an enantioselective reaction, diastereoselectivity remained challenging. In 2011, Tong et al. reported similar difficulties controlling diastereoselectivity in a related (4 + 2) annulation under ammonium catalysis when pyridyl derived catalysts were utilised (Scheme 3.17).[19] Interestingly, when tertiary amine catalysts were utilised (i.e. DABCO), this allowed *(E)*-**217** to be formed exclusively.



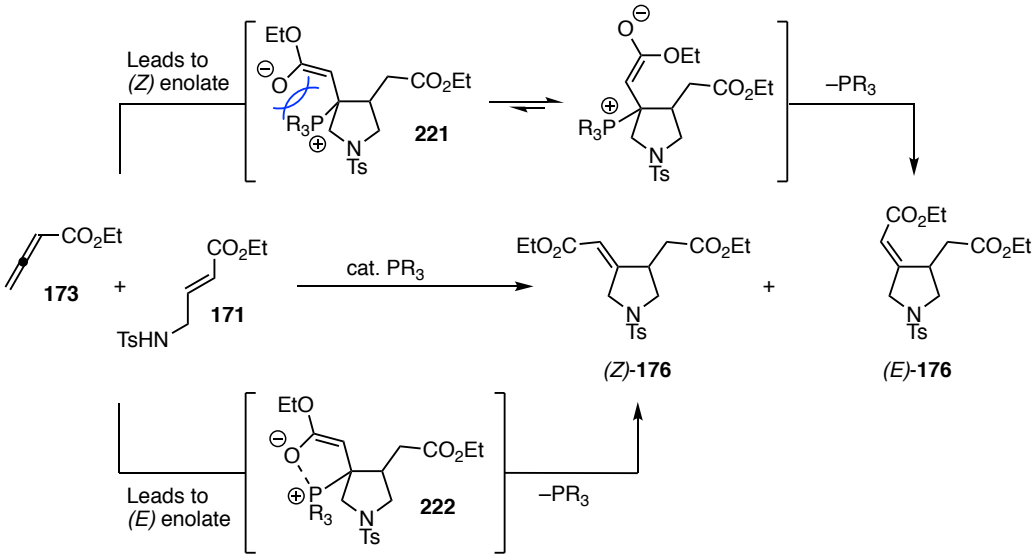
Scheme 3.17: Ammonium catalysed (4 + 2) annulation reported by Tong et al.

This enhanced selectivity was proposed to be due to electrostatic interactions between nitrogen and oxygen in zwitterion **218**, leading to a conformation that can only form *(E)*-**217** upon elimination of the catalyst. In contrast, pyridyl derived amine catalysts such as DMAP and quinoline led to mixtures in which *(Z)*-**217** was the major product. In these cases they reasoned that delocalisation of the positive charge in intermediate **219** leads to weakened nitrogen–oxygen interactions allowing steric effects to bring about the preferential formation of conformer **220**, which leads to *(Z)*-**217** upon elimination of the catalyst (Scheme 3.18).



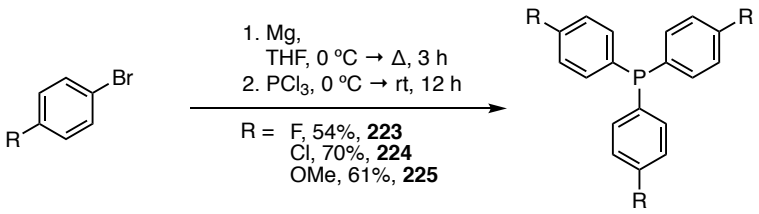
Scheme 3.18: Proposed formation of olefin isomers as reported by Tong et al.

Similarly, phosphorus–oxygen interactions in phosphonium enolate zwitterions[20] (i.e. **221** and **222**) could conceivably affect diastereoselectivity in the (3 + 2) annulation. Perhaps enhanced electrostatic interactions between phosphorus and oxygen such as those present in enolate **222** might lead to the preferential production of *(Z)*–**176**, while steric interactions such as those present in phosphonium enolate **221**, could lead to *(E)*–**176** upon elimination of the phosphine (Scheme 3.19).



Scheme 3.19: Pathways leading to the formation of *(Z)*-**176** and *(E)*-**176**.

Since the diastereoselectivity was very modest, perhaps enhancing either attractive electrostatic interactions of repulsive steric interactions might improve control over diastereoselectivity. Thus, three electronically differentiated triarylphosphines were synthesised to assess whether they impact the diastereoselectivity of the annulation (Scheme 3.20). It was thought that electron deficient triarylphosphines might strengthen phosphorus–oxygen interactions, therefore stabilising the enolate conformer that leads to *(Z)*-**176**.

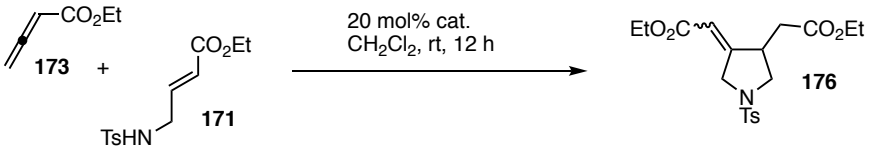


Scheme 3.20: Preparation of triarylphosphines.

When the annulation was conducted with 20 mol% triphenylphosphine, the diastereoselectivity was 5:1 (Table 3.6, entry 1). Using electron deficient triarylphosphines such as **223** and **224**, this was increased to 7.2:1 and 6.4:1 respectively (Table 3.6, entries

2 and 3). Interestingly, use of the electron rich tris(4-methoxyphenyl)phosphine also led to an increase in diastereoselectivity (Table 3.6, entry 4).

Table 3.6: (3 + 2) annulation with electronically differentiated triarylphosphines.

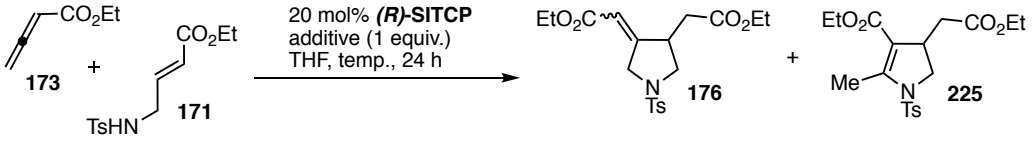


Entry	cat.	dr[a]
1	PPh_3	5:1
2	$P(4\text{-}F\text{-}C_6H_4)_3$	7.2:1
3	$P(4\text{-}Cl\text{-}C_6H_4)_3$	6.4:1
4	$P(4\text{-}MeO\text{-}C_6H_4)_3$	6.2:1

[a]dr determined by ^1H NMR spectroscopy.

Alternatively, it was envisaged that alkali metal salt additives might affect phosphorus–oxygen interactions through coordination to the enolate, thus introducing another route to improved diastereoselectivity. Therefore, a screen of alkali metal salts was undertaken (Table 3.7). The screen was performed in THF to increase the solubility of the salt additives. When the reaction was undertaken in the presence of LiCl, the desired pyrrolidine **176** was isolated in good yields, and improved enantioselectivity and diastereoselectivity with respect to the best result obtained in prior optimisations (Table 3.7, entry 1). When repeated with LiBr at both 0 °C and room temperature, pyrrolidine **176** was isolated in reduced yields, alongside dihydropyrrole **225** (Table 3.7, entries 2 and 3). Addition of LiI resulted in exclusive formation of dihydropyrrole **225** (Table 3.7, entry 4). A range of other alkali metal salts were trialled however conversion to the desired pyrrolidine was poor (Table 3.7, entries 5–9).

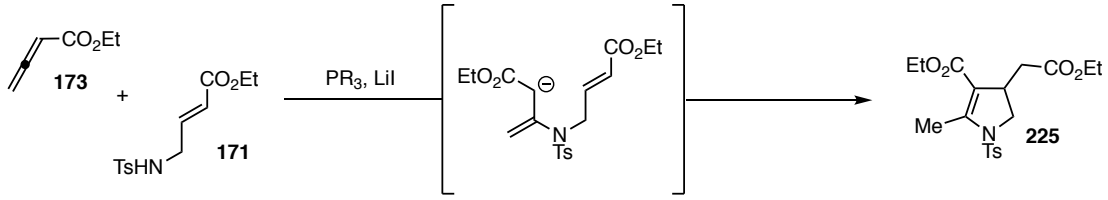
Table 3.7: Screening of alkali metal salt additives.



Entry	Additive (1 equiv.)	Temp.	Yield[a]	er[b] **176**	dr[c] **176**
1	LiCl	0 °C	60% **176**	97:3	3:1
2	LiBr	0 °C	35% **176**, 15% **225**	97:3	3:1
3	LiBr	rt	38% **176**, 13% **225**	97:3	3:1
4	LiI	0 °C	38% **225**	-	-
5	$LiClO_4$	0 °C	trace **176**	-	1:1
6	NaCl	0 °C	trace **176**	-	1:1
7	NaI	0 °C	trace **176**	-	3:1
8	$NaBF_4$	0 °C	trace **176**	-	2:1
9	KI	0 °C	trace **176**	-	1:1

[a]Isolated yield following flash chromatography. [b]er determined by HPLC on a chiral stationary phase. [c]dr determined by ^{1}H NMR spectroscopy. Experiments performed in conjunction with visiting PhD student Sandeep Pimparkar.

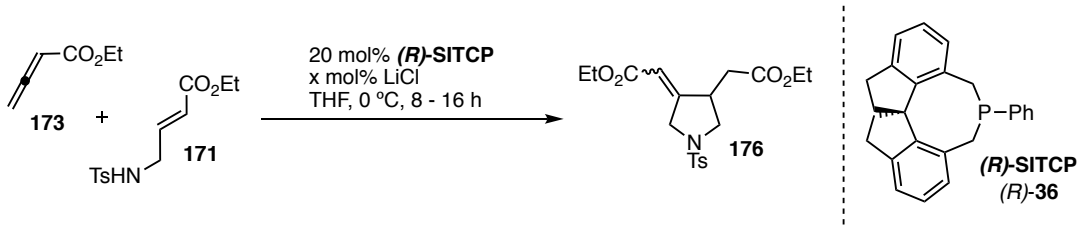
The isolation of dihydropyrrole **225** from experiments where LiBr and LiI were used was unexpected but not unprecedented. It is likely that allenoate **173** is activated by Lewis acidic lithium halides and this results in direct Michael addition of amine **171** to allenoate **173** which then cyclises to dihydropyrrole **225** (Scheme 3.21). This effect was more pronounced for LiI and not present when LiCl was utilised, suggesting that the smaller and harder counterions negated the ability of lithium to activate the allenoate. Supporting the likelihood of a non-phosphine catalysed annulation was analysis of dihydropyrrole **225** by HPLC on a chiral stationary phase which indicated that the product was racemic. As this process was not novel and due to time constraints, it was not investigated further.



Scheme 3.21: Proposed mechanism for the formation of dihydropyrrole **225.**

Results from the additive screen revealed that addition of LiCl improved the outcome of the reaction in terms of yield, diastereoselectivity and enantioselectivity. As a consequence, further optimisation studies were undertaken (Table 3.8). When 40 mol% LiCl was trialled as an additive, pyrrolidine **176** was isolated in good yield, excellent enantiopurity and pleasingly, diastereoselectivity was noticeably increased (Table 3.8, entry 1). To further increase the selectivity, the reaction was repeated at –60 °C, however, no reaction occurred and only starting materials were isolated (Table 3.8, entry 2). Reducing the amount of LiCl to 20 mol% resulted in decreased diastereoselectivity (Table 3.8, entries 3 and 4). Pleasingly, when three equivalents of LiCl were added to the reaction mixture, pyrrolidine **176** was isolated in good yield and excellent enantiopurity with diastereoselectivity significantly improved (Table 3.8, entry 5).

Table 3.8: Reaction optimisation with lithium chloride.

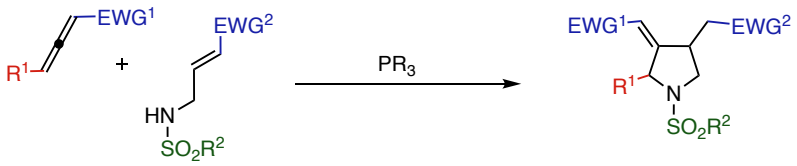


Entry	x mol% LiCl	Temp.	Yield[a]	er[b]	dr[c]
1	40 mol%	0 °C	40%	97:3	3:1
2	40 mol%	–60 °C	N/R	-	-
3	20 mol%	0 °C	trace	-	2:1
4	80 mol%	0 °C	50%	97:3	3:1
5	300 mol%	0 °C	82%	97:3	6:1

[a]Isolated yield following flash chromatography. [b]er determined by HPLC on a chiral stationary phase. [c]dr determined by ^{1}H NMR spectroscopy.

3.3 Scope of the phosphine catalysed (3 + 2) annulation

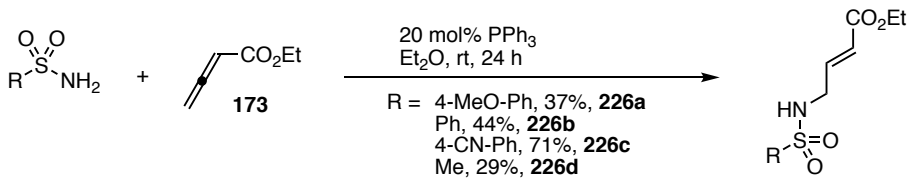
Substrates were prepared concurrent to reaction optimisation for eventual scope studies. Substrates with varied electron withdrawing groups (EWG^1 and EWG^2) and substitution at the terminal position of the allene (R^1), in addition to substitution of the sulfonamide moiety of the allyl amine (R^2) were targeted (Scheme 3.22).



Scheme 3.22: Scope studies.

3.3.1 (3 + 2) annulation of ethyl 2,3-butadienoate with allyl amines

An array of electronically differentiated sulfonyl-protected allyl amines was prepared via direct γ-addition of sulfonamides to allenoate **173** under triphenylphosphine catalysis as reported by Kwon et al. (Scheme 3.23).[9]

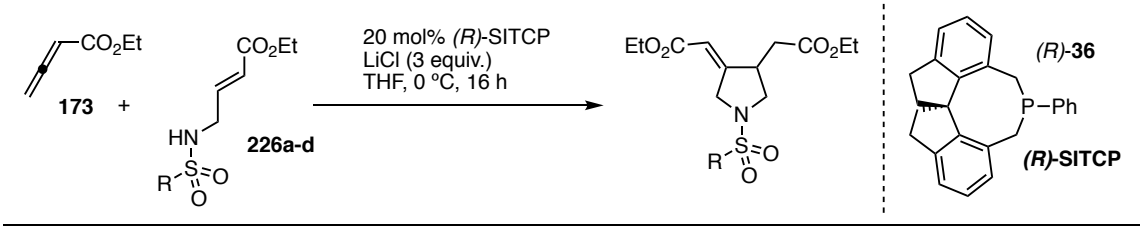


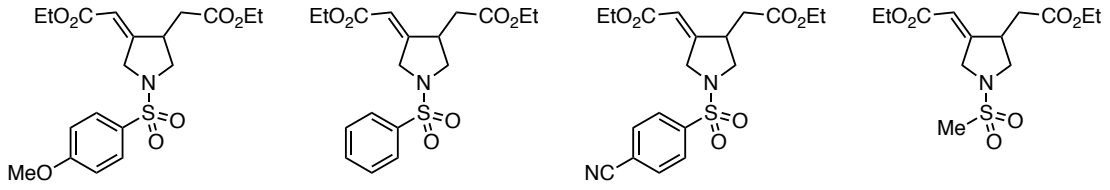
Scheme 3.23: Preparation of sulfonyl-protected allyl amines.

These substrates (i.e. **226a–d**) were then reacted under the optimised conditions using 20 mol% *(R)*-SITCP and three equivalents of LiCl in THF (Table 3.8). When compared with *p*-toluenesulfonyl substituted amines, it was observed that the diastereoselectivity

and yields were generally higher for electron rich sulfonamides. However, all arylsulfonyl substituted allyl amines **226a-c** produced the respective pyrrolidines **227a–c** in good yields (71%, 66% and 60% respectively) and with excellent enantioselectivity (98:2 er, 98:2 er, and 95:5 er respectively). Methanesulfonyl protected allyl amine **226d** did not react under the optimised conditions, this is likely a result of its weakened acidity. This would be consistent with the findings of Virieux et al. who surmised that pronucleophiles with pK_a values greater than ~17.5 were unable to be deprotonated by basic phosphonium species that are generated under phosphine catalysis using allenoates.[21]

Table 3.8: (3 + 2) annulation with substituted allyl amines



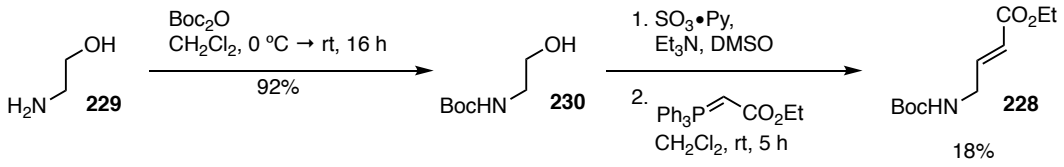


227a, 71%, 98:2 er, 5:1 dr | **227b**, 66%, 98:2 er, 4:1 dr | **227c**, 60%, 95:5 er, 3:1 dr | 0%

Isolated yield following flash chromatography. er determined by HPLC on a chiral stationary phase. dr determined by ^{1}H NMR spectroscopy.

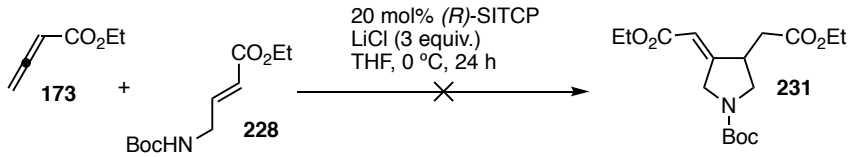
Although sulfonamides readily participate in phosphine catalysed γ- and α-addition reactions, Boc-protected amines are yet to be utilised which is striking due to their similar reactivity and synthetic utility, due to ease of removal. Thus, Boc-protected allyl amine **228** was synthesised in two steps from ethanolamine **229** (Scheme 3.24) starting with Boc protection of ethanolamine **229** to afford alcohol **230** in excellent yield. A Parikh-Doering oxidation of alcohol **230** with the sulfur trioxide pyridine complex

yielded the corresponding aldehyde, which was immediately converted to allyl amine **228** via Wittig olefination in the same pot.[22]



Scheme 3.24: Preparation of Boc-protected amine **228**.

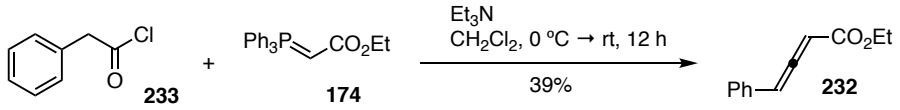
Unfortunately, when trialled under the optimised reaction conditions, no reaction was observed and only starting material was isolated from the reaction mixture. Presumably, this could be due to the lower acidity of carbamates in comparison to sulfonamides, thereby inhibiting their ability to act as pronucleophiles (Scheme 3.25).



Scheme 3.25: Attempted synthesis of Boc-protected pyrrolidine **231**.

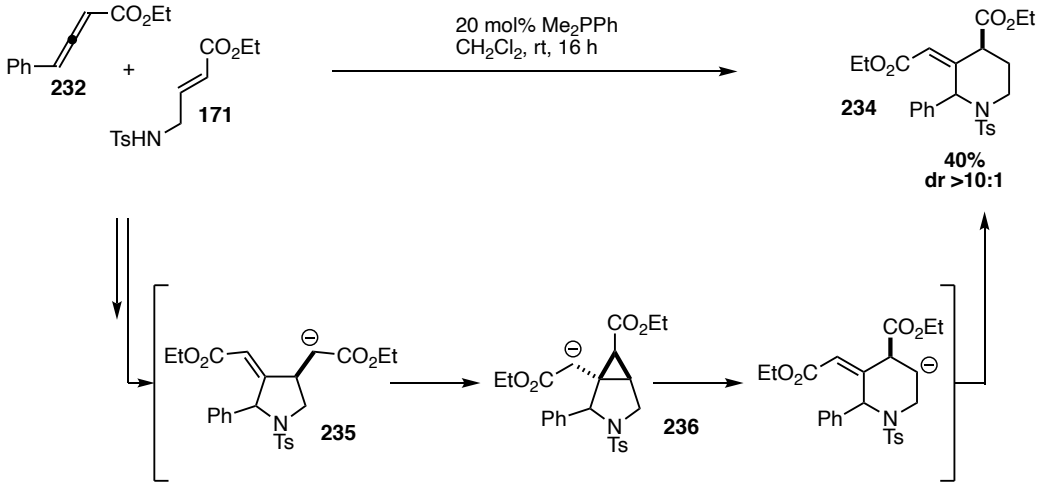
3.3.2 Formal (4 + 2) annulation of allenes and allyl amines

To examine the effect of substituents at the terminal position of the allene, phenyl-substituted allene **232** was prepared according to a reported procedure via Wittig olefination of phenylketene, itself generated *in situ* from phenylacetyl chloride **233** (Scheme 3.26).[23]



Scheme 3.26: Preparation of substituted allene **232**.

When phenyl substituted allene **232** was reacted with allyl amine **174** in the presence of 20 mol% of Me_2PPh, the expected pyrrolidine product was not observed. Instead, piperidine **234** was isolated in 40% yield as with dr >10:1 (Scheme 3.27). Mechanistically, we propose that this product could be formed through 3-*enol-exo-exo-trig* cyclisation of enolate **235** to form cyclopropane **236**, which could undergo ring opening to give piperidine **234**.

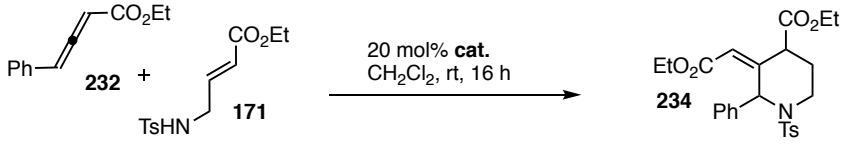


Scheme 3.27: Possible mechanism for the formation of piperidine **234**.

To determine whether this transformation could be developed into an enantioselective method, a screen of homochiral phosphines was undertaken. For reference, the initial achiral reaction conditions are listed (Table 3.9, entry 1). When the reaction was repeated with 20 mol% *(R)*-SITCP, piperidine **234** was not observed in the ^{1}H NMR spectrum of the crude reaction mixture (Table 3.9, entry 2). When *endo*-Kwon phosphine **109** and DIPAMP **110** were employed as the catalyst a similar outcome was observed (Table 3.9,

entries 3 and 4). Pleasingly, when the reaction was attempted with phosphepine **192** the desired piperidine **234** was isolated in 78% yield and with moderate enantiopurity (Table 3.9, entry 5).

Table 3.9: Screening of chiral phosphines.



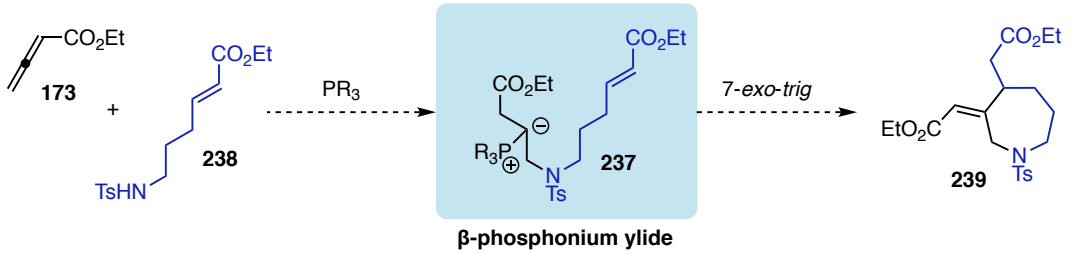
Entry	cat.	Yield **234**[a]	er[b]	dr[c]
1	Me_2PPh	40%	-	>10:1
2	*(R)*-SITCP **36**	0%	-	-
3	*Endo*-Kwon **109**	0%	-	-
4	DIPAMP **110**	0%	-	-
5	**192**	78%	73:27	>10:1

[a]Isolated yield following flash chromatography. [b]er determined by HPLC on a chiral stationary phase. [c]dr determined by ^{1}H NMR spectroscopy.

3.4 Azepane synthesis via phosphine catalysed (5 + 2) annulation

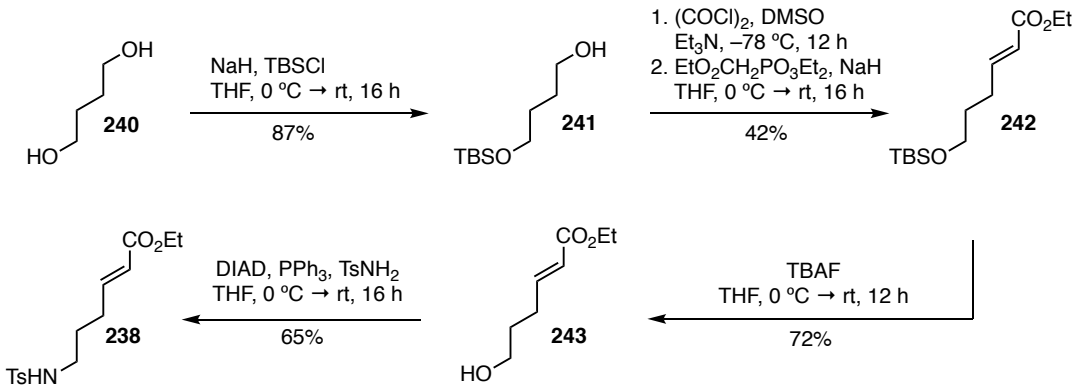
3.4.1 Attempted (5 + 2) annulation via 7-*exo*-*trig* cyclisation

As part of ongoing studies to examine the generality of the reaction, substrates with longer tethers between the amine and Michael-acceptor were explored in an effort to develop an enantioselective synthesis of azepanes (Scheme 3.28). We proposed that if β-phosphonium ylide **237** could be generated through γ-addition of amine **238** to allenoate **173** under phosphine catalysis, then interception of this intermediate via a 7-*exo*-*trig* cyclisation would yield azepane **239**.



Scheme 3.28: Proposed (5 + 2) annulation.

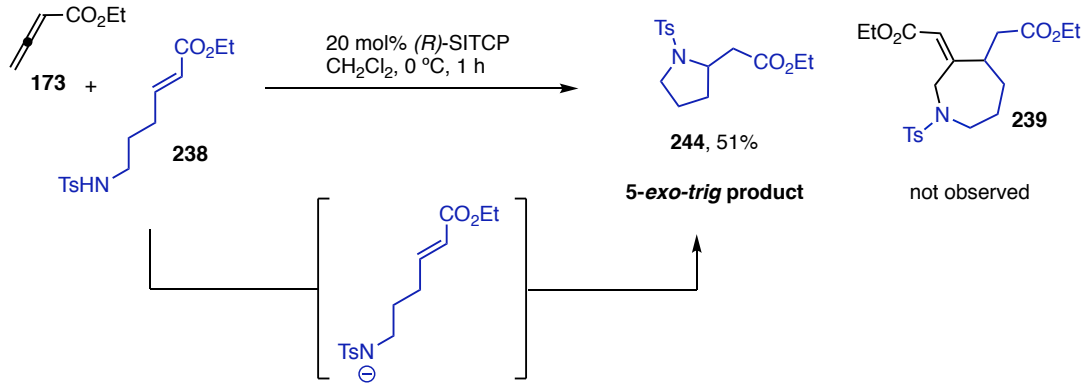
Beginning with commercially available 1,4-butanediol **240**, amine **238** was synthesised in five-steps (Scheme 3.29). Specifically, TBS-protection of diol **240** afforded alcohol **241**, which was oxidised under Swern conditions to afford the corresponding aldehyde, which was converted directly to acrylate **242** via Horner-Wadsworth-Emmons olefination. Deprotection of acrylate **242** was achieved using tetra-*n*-butylammonium fluoride to provide alcohol **243**, with Mitsunobu conditions employed to furnish the desired *p*-toluenesulfonyl protected amine **238**.[24]



Scheme 3.29: Preparation of amine **238**.

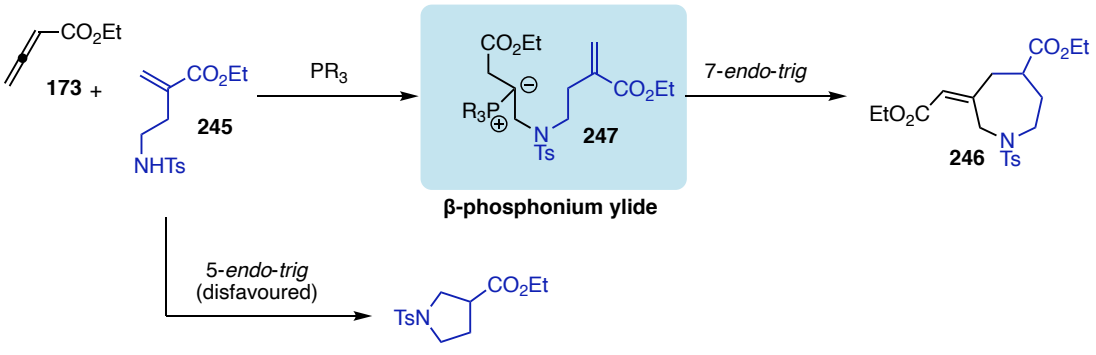
With amine **238** in hand, the proposed (5 + 2) was investigated. Thus, amine **238** was reacted with 20 mol% *(R)*-SITCP at 0 °C in CH_2Cl_2, and after 30 minutes TLC analysis of the reaction mixture indicated that the amine starting material had been fully consumed and that a new compound was present (Scheme 3.30). Upon purification of the

crude reaction mixture it was established that this new product was pyrrolidine **244**, which is likely formed via base-mediated 5-*exo-trig* cyclisation of amine **238**.



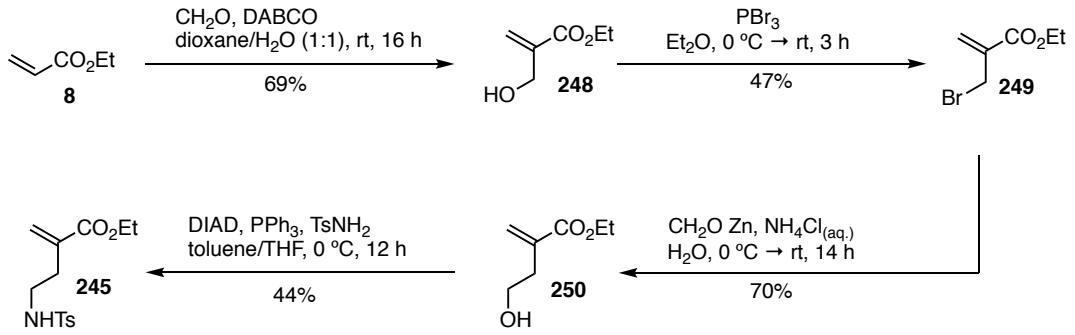
Scheme 3.30: Attempted (5 + 2) via 7-*exo-trig* cyclisation.

An alternative strategy was devised which reduced the possibility of cyclisation of the amine substrate (Scheme 3.31). If a substrate such as amine **245** could be prepared and reacted with an allenoate under phosphine catalysis, then azepane **246** might be accessible via 7-*endo-trig* cyclisation of β-phosphonium ylide **247**. The γ-addition of amine **245** to allenoate **173** should now be the predominant mode of reactivity, since intramolecular cyclisation of amine **245** can only proceed through a disfavoured 5-*endo-trig* ring closure.



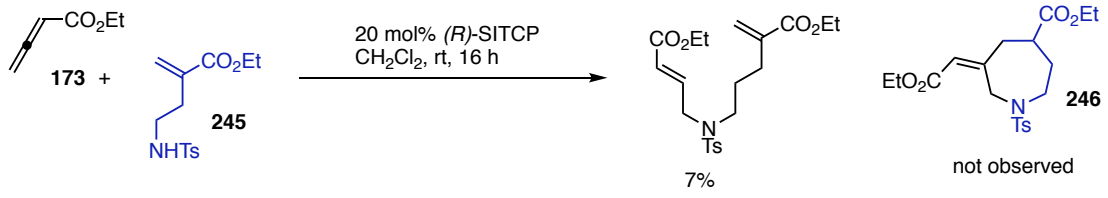
Scheme 3.31: Revised (5 + 2) annulation reaction design.

To assess this idea, amine **245** was prepared from ethyl acrylate **8** in four steps (Scheme 3.32). Firstly, DABCO mediated Morita-Baylis-Hillman reaction of acrylate **8** with formaldehyde provided alcohol **248**.[25] Treatment of alcohol **248** with phosphorus tribromide then gave the corresponding alkyl bromide **249**.[26] with zinc-promoted Barbier-type reaction providing alcohol **250** in 70% yield.[27] A Mitsunobu reaction was then used to provide amine **245** in moderate yield.[24]



Scheme 3.32: Preparation of amine **245**.

Amine **245** was reacted with allenoate **173** in the presence of 20 mol% *(R)*-SITCP at room temperature overnight, unfortunately the desired azepane **246** was not observed in the reaction mixture. The γ-addition product was formed and could be isolated in low yield, however cyclisation was not observed (Scheme 3.33).



Scheme 3.33: Attempted (5 + 2) annulation via 7-*endo-trig* cyclisation.

3.5 Synthetic transformations of pyrrolidine products

Derivatisation studies were undertaken in order to investigate the utility of the pyrrolidine products, additionally, we saw this as a potential solution to issues with the diastereoselectivity of the (3 + 2) annulation. Specifically, we hoped that the stereogenic centre could allow directed functionalisation of the olefin.

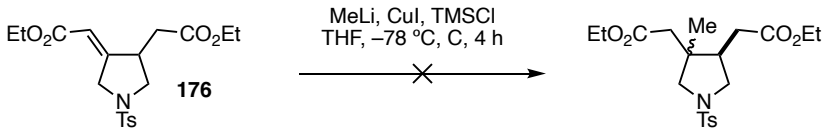
3.5.1 Attempted conjugate addition of Gilman reagents

Initially, we attempted conjugate addition of nucleophiles to pyrrolidine **176** as a simple approach to increase molecular complexity (Scheme 3.34). When pyrrolidine **176** was treated with lithium dimethylcuprate at –78 °C, analysis of the reaction mixture indicated that no reaction had occurred. The reaction temperature was increased to 0 °C, however none of the desired product was isolated.

Scheme 3.34: Attempted conjugate addition of Gilman reagents.

As pyrrolidine **176** contains a β,β-disubstituted double bond, we considered that the reaction conditions might be too mild to effect the desired conjugate addition. Corey and Boaz reported that organocuprate additions conducted in the presence of chlorotrimethylsilane can be suited to β,β-disubstituted alkenes.[28] Consequently, pyrrolidine **176** was subjected to the reported conditions, however, only trace conversion

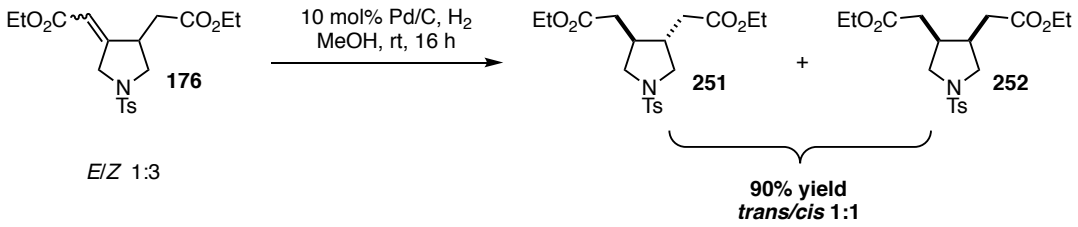
to other materials was observed by ^{1}H NMR analysis of the crude reaction mixture, and the starting material was effectively recovered (Scheme 3.35).



Scheme 3.35: Attempted conjugate addition of organocuprates with TMSCl.

3.5.2 Reduction of the olefin via hydrogenation

Through reduction of the olefin it was hoped that the adjacent stereogenic centre might direct reduction to occur preferentially on the *anti*-face. Thus, racemic pyrrolidine **176** (*E*/*Z* 1:3) was stirred overnight under an atmosphere of hydrogen in the presence of palladium on charcoal (Scheme 3.36). Pleasingly, ^{1}H NMR analysis of the reaction mixture indicated complete conversion of the starting material, however, it was revealed that this resulted in a 1:1 mixture of **251** and **252**.



Scheme 3.36: Hydrogenation of pyrrolidine **176**.

3.6 Conclusion

Enantioselective catalytic reactions proceeding via phosphonium ylides are underrepresented in the literature. In this chapter our discovery and development of a novel (3 + 2) annulation of allenoates and allylic amines occurring via this intermediate is discussed. When conducted with homochiral phosphines it provides access to pyrrolidines with excellent enantioselectivity and moderate diastereoselectivity. Studies have revealed that *(R)*-SITCP is the optimal catalyst, and that utilisation of LiCl improves diastereoselectivity.

In addition to this, our investigation of this process led to the discovery of a (4 + 2) annulation of γ-substituted allenoates and allylic amines for the synthesis of chiral piperidines. Although yet to be optimised, initial studies indicate that this reaction is enantioselective when a homochiral phosphine is used. Investigations into this process are currently ongoing.

3.7 Future outlook

Further studies are currently underway to fully investigate both reactions reported in this chapter.

In particular, for the (3 + 2) annulation, further reaction optimisation with the goal of increasing diastereoselectivity is required. As reported in this chapter, the effect of catalyst electronics for several sterically analogous triarylphosphines was shown to affect reaction diastereoselectivity, and therefore tuning of *(R)*-SITCP type phosphines could be undertaken by altering its electronics.

To fully understand the generality of the reaction significant work is still required. Preliminary scope studies suggest that the reaction is tolerant of various arylsulfonamides,

however, other electron deficient amines should be tested. In particular, trifluoroacetamides are potential candidates for this as they are known pronucleophiles in phosphine catalysis and can be deprotected under much milder conditions than sulfonamides. At the time of writing this thesis we are yet to examine the effect of substituents at the α- or β-position of the allylic amine, both of which might result in diastereoselective reaction variants.

As the (4 + 2) annulation has only been recently discovered, optimisation and scope studies remain to be undertaken. Investigation of the reaction mechanism is of particular importance as this could provide a foundation for further reaction discovery.

3.8 References

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Chapter 4 Experimental

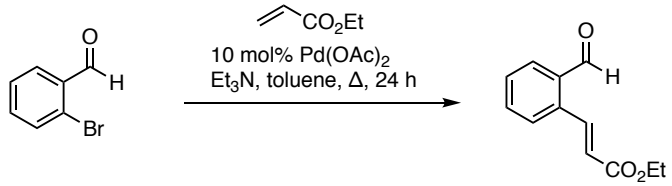
4.1 General Experimental

Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on a Bruker DRX600 spectrometer operating at 150 MHz for carbon nuclei, a Bruker DRX400 spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei, and a Bruker DRX300 spectrometer operating at 300 MHz for proton nuclei. 2D correlation spectra were recorded on a Bruker DRX400 spectrometer. Infrared spectra (ν_{max}) were recorded on an Agilent Cary 630 FTIR Spectrometer. High resolution mass spectra (HRMS) (ESI) were recorded on a Bruker BioApex 47e FTMS fitted with an Analytical electrospray source using NaI for accurate mass calibration. Analytical chiral HPLC was performed with a Perkin Elmer Series 200 HPLC using a RegisCell™ 5μm (4.6 mm x 25 cm) obtained from Regis Technologies, Inc. with visualisation at 238 or 230 nm. Flash column chromatography was performed on silica gel (Davisil LC60A, 40-63 μm silica media) using compressed air. Thin layer chromatography (TLC) was performed using aluminum-backed plates coated with 0.2 mm silica (Merck, DC-Platten, Kieselgel; 60 F254 plates). Eluted plates were visualised using a 254 nm UV lamp and/or by treatment with potassium permanganate stain or vanillin stain followed by heating. Starting materials and reagents were purchased from Sigma-Aldrich or Oakwood and were used as supplied. Tetrahydrofuran (THF) and dichloromethane (CH_2Cl_2) were dried by passing over activated alumina. DMF was dried by stirring with calcium hydride overnight then was filtered and distilled under reduced pressure, and stored over 3 Å molecular sieves. Unless otherwise stated, all reactions were conducted in flame-dried glassware under an atmosphere of nitrogen.

4.2 Experimental procedures for Chapter 2

4.2.1 Synthesis of ynone/cinnamates

Ethyl (*E*)-3-(2-formylphenyl)acrylate (92)

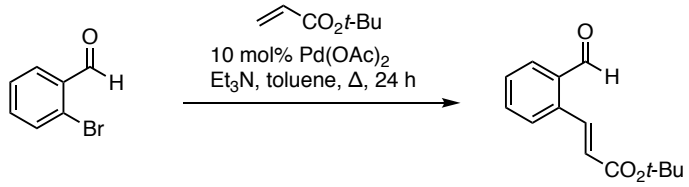


The compound was prepared according to the literature procedure as follows.[1] To a flame dried RBF under N_2 was added 2-bromobenaldehyde (3.0 g, 16 mmol, 1 equiv.), $Pd(OAc)_2$ (360 mg, 1.6 mmol, 0.1 equiv.), PPh_3 (0.85 g, 3 mmol, 0.2 equiv.), Et_3N (4.92 g, 49 mmol, 3 equiv.), and dry toluene (50 mL). This was followed by the addition of ethyl acrylate (4.87 g, 49 mmol, 3 equiv.). The solution was heated to reflux for 24 h. The reaction was quenched by the addition of satd. NH_4Cl solution, the layers separated and the aqueous layer was extracted with EtOAc (3 × 40 mL). The combined organic extracts were washed with brine, dried with Na_2SO_4, filtered and then concentrated under reduced pressure. The resulting crude residue was purified via column chromatography on silica gel to provide the product as a yellow oil (3.28 g, 99%).

R_f 0.31 (3:1, v/v hexanes : EtOAc)

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.33 (s, 1H), 8.49 (d, *J* = 15.9 Hz, 1H), 7.83 – 7.53 (m, 4H), 6.44 (d, *J* = 15.9 Hz, 1H), 4.25 (q, *J* = 7 Hz, 2H), 1.33 (t, *J* = 7 Hz, 3H) ppm

tert-Butyl (_E_)-3-(2-formylphenyl)acrylate

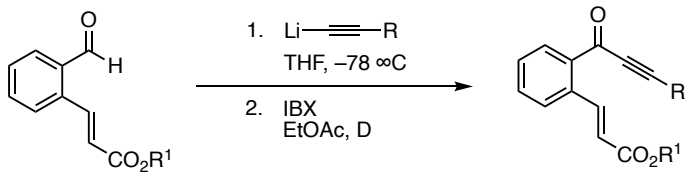


The compound was prepared according to the previously described literature procedure to provide the product as a yellow oil (331 mg, 92%).

R$_f$ 0.39 (3:1, v/v hexanes : EtOAc)

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.32 (s, 1H), 8.47 (d, *J* = 15.9 Hz, 1H), 7.89 – 7.78 (m, 1H), 7.63 – 7.51 (m, 3H), 6.44 (d, *J* = 15.9 Hz, 1H), 1.49 (s, 9H) ppm

General procedure for the synthesis of ynone/cinnamates from (2-formylphenyl)acrylates

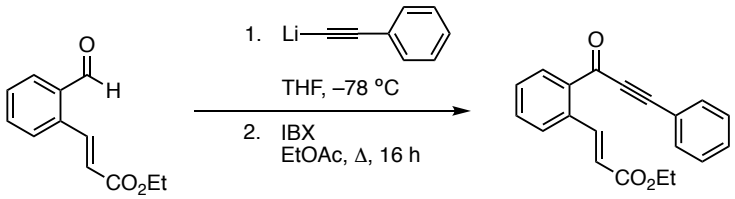


To a solution of aryl substituted acetylene (10 mmol) in THF (20 mL) at –78 °C was added dropwisely, *n*-butyllithium solution (1.6M in hexane, 10.5 mmol). After stirring for a further 1 h at -78 °C, a solution of the alkyl (2-formylphenyl)acrylate (10 mmol) in THF (10 mL) was added dropwisely. Stirring of the reaction at –78 °C was continued until TLC analysis of the reaction mixture indicated complete consumption of the starting material. The reaction was then quenched via slow addition of saturated NH_4Cl solution (10 mL) and then allowed to warm to room temperature. The organic phase was separated and the aqueous phase was extracted with EtOAc (3 × 10 mL), the combined

organics were washed with brine, dried with Na_2SO_4, filtered and the concentrated under reduced pressure to afford the corresponding alkynol as a crude oil which was used in the next step without further purification.

2-Iodoxybenzoic acid (15 mmol) was added to a solution of the crude alkynol in EtOAc (30 mL) and the resulting suspension was heated at reflux until TLC analysis of the reaction mixture indicated complete consumption of the starting material. The reaction mixture was filtered and concentrated to afford the ynone cinnamate as a crude oil which was purified via column chromatography on silica gel (EtOAc/Hexanes).

Ethyl (*E*)-3-(2-(3-phenylpropioloyl)phenyl)acrylate (98)



Following the general procedure the title compound was prepared in 58% yield as a yellow oil which solidified upon standing.

R_f 0.29 (4:1, v/v hexanes : EtOAc)

mp 52 – 55 °C

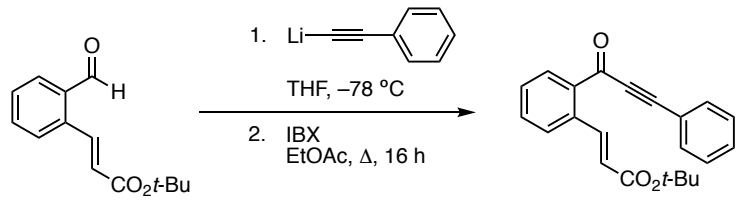
IR ν_{max} 2197, 1707, 1629, 1561, 1445, 1305, 1262, 1187, 974, 758, 678 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, *J* = 16.0 Hz, 1H), 8.28 (*J* = 8 Hz, 1H), 7.65 – 6.30 (m, 8H), 6.32 (d, *J* = 16.0 Hz, 1H), 4.24 (q, 2H), 1.31 (t, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 178.8, 166.4, 136.3, 136.2, 133.3, 133.1, 132.5, 130.9, 129.4, 128.7, 128.4, 121.7, 120.0, 93.5, 88.2, 60.6, 14.3 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{20}H_{17}O_3$, 305.1169, requires 305.1172.

tert-Butyl (_E_)-3-(2-(3-phenylpropioloyl)phenyl)acrylate (122)



Following the general procedure the title compound was prepared in 55% yield as a pale yellow solid.

R$_f$ 0.43 (4:1, v/v hexanes : EtOAc)

mp 123.5 – 126.0 ˚C

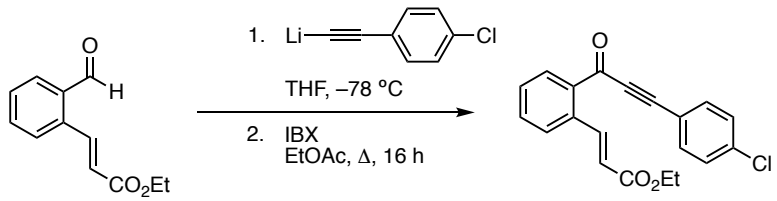
IR ν_{max} 2195, 1691, 1626, 1592, 1369, 1286, 1252, 1209, 1154, 1027, 1011, 966, 841, 757, 690 cm^{-1}

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.38 (d, *J* = 15.8 Hz, 1H), 8.25 (d, *J* = 7.7 Hz, 1H), 7.69 – 7.64 (m, 2H), 7.62 – 7.56 (m, 2H), 7.52 (td, *J* = 7.4 Hz, 1.7 Hz, 1H), 7.49 – 7.47 (m, 1H), 7.42 – 7.39 (m, 1H), 6.26 (d, *J* = 15.8 Hz, 1H), 1.51 (s, 9H) ppm

^{13}C NMR (150 MHz, $CDCl_3$) δ 179.0, 165.9, 142.5, 136.6, 136.3, 133.3, 133.2, 132.5, 131.0, 129.4, 128.8, 128.5, 123.7, 120.2, 93.7, 88.5, 80.8, 28.3 ppm

HRMS (ESI) *m/z* Found: $(M\text{-}O^tBu+H_2O)^+$, $C_{18}H_{13}O_3$, 277.0858, requires 277.0859.

Ethyl (_E_)-3-(2-(3-(4-chlorophenyl)propioloyl)phenyl)acrylate (121d)



Following the general procedure the title compound was prepared in 61% yield as a yellow solid.

R_f 0.36 (4:1, v/v hexanes : EtOAc)

mp 73.1 – 76.4 °C

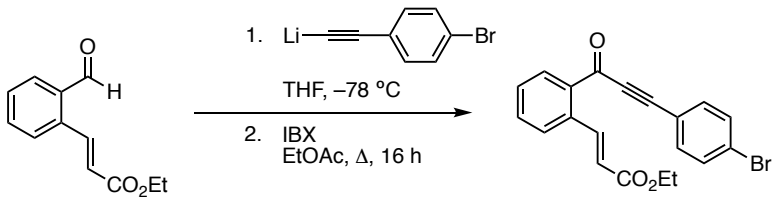
IR ν_{max} 2195, 1710, 1632, 1589, 1561, 1475, 1305, 1267, 1161, 1088, 1004, 971, 829, 761, 713, 678 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, *J* = 15.8 Hz, 1H), 8.28 (d, *J* = 8 Hz, 1H), 7.59 – 7.51 (m, 5H), 7.38 – 7.35 (m, 2H), 6.30 (d, *J* = 15.8 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 1.30 (t, *J* = 7.1 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 166.4, 143.4, 137.3, 136.3, 135.9, 134.2, 133.4, 132.4, 129.4, 129.1, 128.4, 121.7, 118.4, 92.0, 88.9, 60.6, 14.3 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{20}H_{15}O_3Cl$, 339.0773, requires 339.0782.

Ethyl (*E*)-3-(2-(3-(4-bromophenyl)propioloyl)phenyl)acrylate (121e)



Following the general procedure the title compound was prepared in 43% yield as a colourless solid.

R_f 0.32 (4:1, v/v hexanes : EtOAc)

mp 70.7 – 72.1 °C

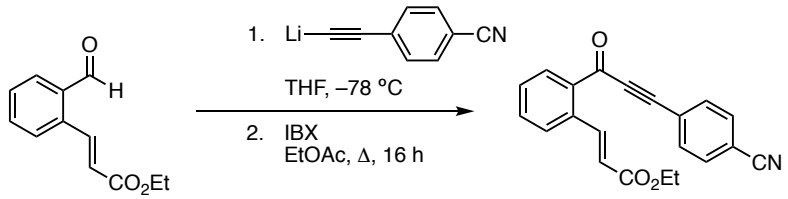
IR ν_{max} 2199, 1711, 1634, 1560, 1476, 1391, 1366, 1306, 1264, 1190, 1162, 1002, 966, 821 cm^{-1}

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.45 (d, *J* = 15.9 Hz, 1H), 8.25 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.62 – 7.60 (m, 2H), 7.56 (d, *J* = 8.3 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 6.33 (dd, *J* = 15.8, 0.7 Hz, 1H), 4.26 (q, *J* = 7.2, 2H), 1.32 (t, *J* = 7.2, 3H) ppm

^{13}C NMR (150 MHz, $CDCl_3$) δ 178.5, 166.4, 143.5, 136.4, 136.0, 134.3, 133.4, 132.4, 132.1, 129.4, 128.5, 125.8, 121.8, 118.9, 92.1, 88.9, 60.7, 14.3 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{20}H_{15}O_3Br$, 382.0274, requires 383.0277.

Ethyl (*E*)-3-(2-(3-(4-cyanophenyl)propioloyl)phenyl)acrylate (121f)



Following the general procedure the title compound was prepared in 62% yield as a viscous yellow oil.

R_f 0.11 (4:1, v/v hexanes : EtOAc)

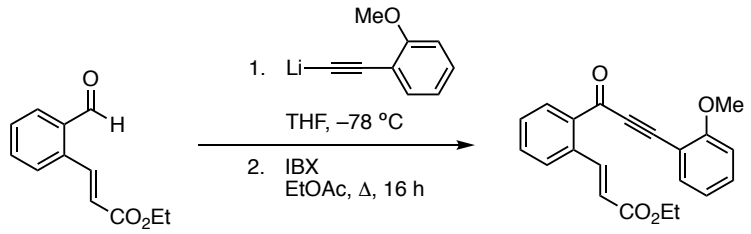
IR ν_{max} 2227, 2202, 1695, 1637, 1562, 1474, 1368, 1274, 1248, 1198, 1095, 1040, 999, 980, 940, 838, 763, 711, 674, 655 cm^{-1}

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.43 (d, *J* = 15.6 Hz, 1H), 8.23 (m, 1H), 7.75 – 7.69 (m, 4H), 7.63 – 7.60 (m, 2H), 7.57 – 7.53 (m, 1H), 6.32 (d, *J* = 15.6 Hz, 1H), 4.25 (q, *J* = 7.2 Hz, 2H), 1.32 (t, *J* = 7.2 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 178.3, 166.5, 143.4, 136.7, 135.7, 133.9, 133.5, 132.7, 132.5, 129.7, 128.8, 125.0, 122.2, 118.0, 114.3, 90.7, 90.2, 60.9, 14.5 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{21}H_{15}NO_3$, 330.1112, requires 330.1125.

Ethyl (*E*)-3-(2-(3-(2-methoxyphenyl)propioloyl)phenyl)acrylate (121a)



Following the general procedure the title compound was prepared in 60% yield as a yellow solid.

R$_f$ 0.17 (4:1, v/v hexanes : EtOAc)

mp 77.6 – 81.6 °C

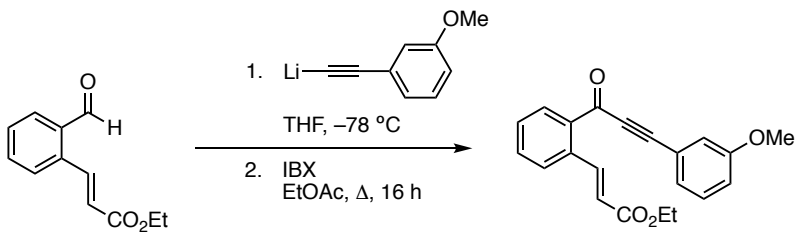
IR ν_{max} 2185, 1709, 1628, 1594, 1562, 1492, 1460, 1435, 1248, 1164, 1002, 969, 752, 672 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51-8.44 (m, 2H), 7.59-7.42 (m, 5H), 7.00-6.92 (m, 2H), 6.30 (d, *J* = 15.9 Hz, 1H), 4.25 (q, *J* = 7.2 Hz, 2H), 3.94 (s, 3H), 1.32 (t, *J* = 7.2 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 178.7, 166.3, 161.8, 143.8, 136.1, 136.0, 134.8, 133.1, 133.1, 132.8, 129.4, 128.2, 121.2, 120.6, 110.8, 109.0, 92.3, 90.7, 60.4, 55.8, 14.2 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{21}H_{18}O_4$, 335.1275, requires 335.1278.

Ethyl (*E*)-3-(2-(3-(3-methoxyphenyl)propioloyl)phenyl)acrylate (121b)



Following the general procedure the title compound was prepared in 71% yield as a viscous yellow oil.

R_f 0.21 (4:1, v/v hexanes : EtOAc)

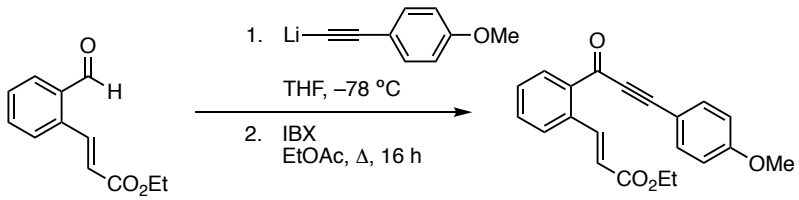
IR ν_{max} 2189, 1709, 1631, 1593, 1573, 1478, 1422, 1366, 1306, 1274, 1229, 1160, 1036, 1013, 973, 897, 784, 754, 682 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, *J* = 15.9 Hz, 1H), 8.29 – 8.22 (m, 1H), 7.62 – 7.48 (m, 3H), 7.30 (t, *J* = 7.9 Hz, 1H), 7.23 (dt, *J* = 7.6, 1.3 Hz, 1H), 7.15 (m, 1H), 7.02 (ddd, *J* = 8.2, 2.7, 1.1 Hz, 1H), 6.32 (d, *J* = 15.9 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 178.9, 166.6, 159.6, 143.7, 136.4, 136.3, 133.4, 132.6, 129.9, 129.6, 128.6, 125.7, 121.8, 121.0, 117.9, 117.7, 93.6, 88.0, 60.7, 55.6, 14.4 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{21}H_{18}O_4$, 335.1273, requires 335.1278.

Ethyl (*E*)-3-(2-(3-(4-methoxyphenyl)propioloyl)phenyl)acrylate (121c)



Following the general procedure the title compound was prepared in 77% yield as a yellow solid.

R_f 0.23 (4:1, v/v hexanes : EtOAc)

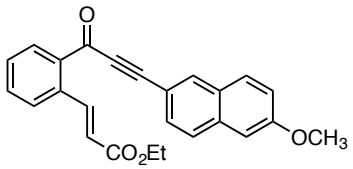
mp 86.1 – 88.7 °C

IR ν_{max} 2189, 1715, 1632, 1599, 1563, 1509, 1477, 1440, 1309, 1274, 1252, 1211, 1165, 1109, 1020, 1004, 827, 747, 680 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 15.9 Hz, 1H), 8.15 (dd, *J* = 7.2, 1.3 Hz, 1H), 7.54 – 7.37 (m, 5H), 6.80 (d, *J* = 8.9 Hz, 2H), 6.22 (d, *J* = 15.9 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.73 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 178.9, 166.5, 162.0, 143.7, 136.5, 136.1, 135.2, 133.1, 132.4, 129.5, 128.4, 121.5, 114.5, 111.7, 95.0, 88.4, 60.6, 55.6, 14.4 ppm **HRMS** (ESI) *m/z* Found: $(M+H)^+$, $C_{21}H_{18}O_4$, 335.1278, requires 335.1272.

Ethyl (*E*)-3-(2-(3-(6-methoxynaphthalen-2-yl)propioloyl)phenyl)acrylate (121g)



Following the general procedure the title compound was prepared in 39% yield as an orange solid.

R_f 0.21 (4:1, v/v hexanes : EtOAc)

mp 99.6 – 101.2 °C

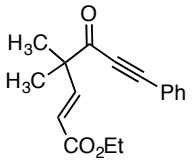
IR ν_{max} 2182, 1717, 1619, 1480, 1390, 1255, 1175, 1123, 1009, 852 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 15.9 Hz, 1H), 8.28 – 8.22 (m, 1H), 8.07 (s, 1H), 7.75 – 7.62 (m, 3H), 7.57 – 7.46 (m, 6H), 7.36 – 7.22 (m, 2H), 7.13 (dd, *J* = 9.0, 2.5 Hz, 2H), 7.06 (d, *J* = 2.5 Hz, 2H), 6.27 (d, *J* = 15.9 Hz, 1H), 4.23 – 4.13 (q, *J* = 7.1 Hz 2H), 3.87 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 4H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 178.8, 166.5, 159.5, 143.7, 136.5, 136.3, 135.7, 134.4, 133.1, 132.4, 129.9, 129.4, 129.1, 128.4, 128.2, 127.3, 121.6, 120.0, 114.6, 106.0, 95.0, 88.5, 60.6, 55.5, 14.3 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{25}H_{20}O_4$, 385.1437, requires 385.1434.

Ethyl (*E*)-4,4-dimethyl-5-oxo-7-phenylhept-2-en-6-ynoate (131)



Following the procedure above the title compound was prepared in 53% yield as a clear oil.

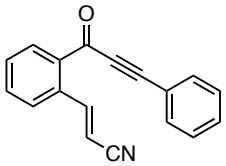
R$_f$ 0.35 (1:4, v/v hexanes : EtOAc)

IR ν_{max} 2196, 1716, 1664, 1648, 1489, 1444, 1366, 1271, 1180, 1058, 1033, 757 cm^{-1} **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.48 – 7.45 (m, 1H), 7.39 (t, *J* = 7.9 Hz, 2H), 7.20 (dd, *J* = 16.0, 0.6 Hz, 1H), 5.99 – 5.91 (m, 1H), 4.25 – 4.18 (q, *J* = 7.1 Hz, 2H), 1.44 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H) ppm

^{13}C NMR (150 MHz, $CDCl_3$) δ 189.13, 166.26, 150.30, 133.18, 130.98, 128.67, 121.20, 119.75, 94.26, 85.98, 60.59, 50.90, 23.54, 14.25 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{17}H_{18}O_3$, 271.1327, requires 271.1329.

(*E*)-3-(2-(3-phenylpropioloyl)phenyl)acrylonitrile (121q)



Following the procedure above the title compound was prepared in 53% yield as a white solid.

R$_f$ 0.29 (4:1, v/v hexanes : EtOAc)

mp 191.8 °C (dec.)

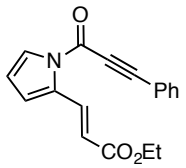
IR ν_{max} 2193, 1737, 1624, 1565, 1490, 1444, 1308, 1207, 1113, 1010, 995, 955 cm^{-1} **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.40 – 8.34 (m, 1H), 8.29 (d, *J* = 16.5 Hz, 1H), 7.68 (dd, *J*

= 8.3, 1.4 Hz, 2H), 7.66 – 7.60 (m, 2H), 7.55 – 7.49 (m, 2H), 7.46 – 7.41 (m, 2H), 5.79 (d, *J* = 16.5 Hz, 1H) ppm

^{13}C NMR (150 MHz, $CDCl_3$) δ 178.5, 150.2, 135.3, 135.2, 133.6, 133.2, 133.1, 131.1, 130.4, 128.8, 127.9, 119.7, 117.8, 99.5, 93.9, 87.7 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{18}H_{11}NO$, 258.0913, requires 258.0913.

Ethyl (*E*)-3-(1-(3-phenylpropioloyl)-1*H*-pyrrol-2-yl)acrylate (137)



Following the procedure above the title compound was prepared in 28% yield as a yellow oil.

R_f 0.28 (1:4, v/v hexanes : EtOAc)

IR ν_{max} 2206, 1703, 1686, 1622, 1405, 1339, 1268, 1175, 1108, 1034, 986, 759 cm^{-1} **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.42 (d, *J* = 15.9 Hz, 1H), 7.72 – 7.62 (m, 3H), 7.55 – 7.48 (m, 1H), 7.48 – 7.39 (m, 2H), 6.79 (ddd, *J* = 3.5, 1.6, 0.8 Hz, 1H), 6.34 (td, *J* = 3.4, 0.6 Hz, 1H), 6.27 (d, *J* = 15.9 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H) ppm

^{13}C NMR (150 MHz, $CDCl_3$) δ 166.8, 151.2, 134.2, 133.1, 131.9, 131.4, 128.8, 125.5, 119.0, 118.0, 116.6, 113.1, 93.1, 81.7, 60.4, 14.3 ppm

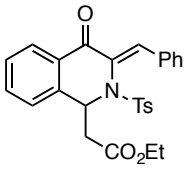
HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{18}H_{15}NO_3$, 294.1122, requires 294.1125.

4.2.2 Phosphine catalysed (5 + 1) annulations

SI-2

To a solution of ynone (0.13 mmol) and sulfonamide (0.13 mmol) in dry toluene (2.6 mL) under N_2 was added, methyldiphenylphosphine (0.1M solution in toluene, 260µL, 0.026 mmol). The reaction was stirred at room temperature until TLC analysis indicated complete consumption of the starting material. The reaction mixture was then concentrated under vacuum and the product purified via column chromatography on silica gel (hexanes/EtOAc or toluene/EtOAc) to afford the isoquinoline product. As these compounds were observed to isomerise more rapidly in $CDCl_3$, NMR experiments were usually conducted in C_6D_6, as such the residual benzene signal results in some carbon signals being obscured, this has been noted wherever it is the case, and structures are assigned unambiguously based on all of the collective spectroscopic data.

Ethyl (*Z*)-2-(3-benzylidene-4-oxo-2-tosyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (100)



Following the general procedure the title compound was prepared in 84% yield.

R_f 0.29 (1:19, v/v toluene : EtOAc)

mp 118.2 – 120.0 °C

IR ν_{max} 1735, 1675, 1598, 1493, 1359, 1292, 1166, 1089, 972 cm^{-1}

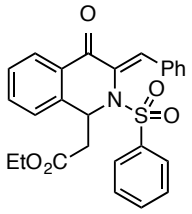
^{1}H-NMR (300 MHz, C_6D_6) δ 8.25 (s, 1H), 8.15 – 8.04 (m, 2H), 7.64 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.35 (d, *J* = 8.2 Hz, 2H), 7.15 – 7.00 (m, 3H), 6.86 (td, *J* = 7.4, 1.4 Hz, 1H), 6.77 (dd, *J* = 7.8, 1.2 Hz, 1H), 6.68 (td, *J* = 7.6, 1.3 Hz, 1H), 6.33 (d, *J* = 8.0 Hz, 2H), 6.08 (dd, *J* = 8.5, 5.9 Hz, 1H), 4.06 – 3.79 (m, 3H), 2.81 (dd, *J* = 16.1, 8.5 Hz, 1H), 2.40 (dd, *J* = 16.1, 5.9 Hz, 1H), 1.68 (s, 3H), 0.84 (t, *J* = 7.1 Hz, 3H) ppm

^{13}C-NMR (100 MHz, C_6D_6) δ 182.1, 169.3, 143.4, 141.2, 140.3, 133.3, 133.2, 131.2, 130.4, 130.1, 129.3, 128.6, 128.2, 127.7, 127.6, 126.6, 61.0, 56.6, 42.3, 21.0, 14.0 ppm (2 peaks missing or overlapped)

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{27}H_{25}NO_5S$, 476.1528, requires 476.1526.

Following the general procedure at 0 °C, and using (*R*)-SITCP catalyst **C** the title compound **2a** was prepared in 85% yield. HPLC RegisCell™, hexane : *i*PrOH 85:15, 1 ml/min, l = 238 nm, fraction t_r = 9.64 (major enantiomer) and 12.38 (minor enantiomer); ee = 14%

Ethyl (*Z*)-2-(3-benzylidene-4-oxo-2-(phenylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (129d)



Following the general procedure the title compound was prepared in 63% yield.

R_f 0.15 (4:1, v/v hexanes : EtOAc)

IR ν_{max} 1733, 1674, 1596, 1447, 1359, 1292, 1272, 1206, 1167, 1088, 1049, 1023, 956, 840 cm^{-1}

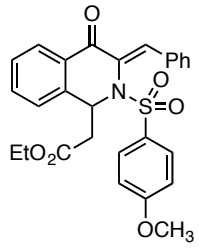
^{1}H-NMR (400 MHz, C_6D_6) δ 8.26 (s, 1H), 8.14 – 8.02 (m, 2H), 7.66 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.45 – 7.35 (m, 2H), 7.13 – 6.97 (m, 3H), 6.78 (dd, *J* = 7.4, 1.3 Hz, 1H), 6.74

– 6.53 (m, 3H), 6.47 (t, *J* = 7.8 Hz, 2H), 6.07 (dd, *J* = 8.3, 6.1 Hz, 1H), 3.99 – 3.77 (m, 2H), 2.80 (dd, *J* = 16.2, 8.3 Hz, 1H), 2.36 (dd, *J* = 16.2, 6.1 Hz, 1H), 0.83 (t, *J* = 7.1 Hz, 3H) ppm

^{13}C-NMR (100 MHz, C_6D_6) δ 181.5, 168.9, 140.9, 139.7, 138.0, 133.2, 132.8, 132.8, 132.1, 130.9, 130.0, 129.5, 128.3, 128.2, 126.1, 60.6, 56.3, 41.9, 13.6 ppm (2 peaks missing or overlapped)

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{26}H_{23}NO_5S$, 462.1367, requires 462.1370.

Ethyl (*Z*)-2-(3-benzylidene-2-((4-methoxyphenyl)sulfonyl)-4-oxo-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (129c)



Following the general procedure the title compound was prepared in 67% yield.

R_f 0.09 (4:1, v/v hexanes : EtOAc)

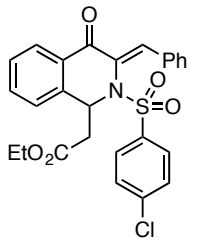
IR ν_{max} 1735, 1674, 1594, 1496, 1358, 1293, 1261, 1159, 1089, 1023, 835, 760, 676, 590 cm^{-1}

^{1}H-NMR (400 MHz, C_6D_6) δ 8.29 (s, 1H), 8.17 – 8.06 (m, 2H), 7.73 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.41 – 7.36 (m, 2H), 7.13 – 7.01 (m, 3H), 6.81 (td, *J* = 7.5, 1.4 Hz, 1H), 6.77 – 6.71 (m, 1H), 6.67 (td, *J* = 7.5, 1.4 Hz, 1H), 6.12 – 6.03 (m, 3H), 3.90 (ddq, *J* = 39.0, 10.8, 7.1 Hz, 2H), 2.93 (s, 3H), 2.82 (dd, *J* = 16.1, 8.3 Hz, 1H), 2.38 (dd, *J* = 16.1, 6.1 Hz, 1H), 0.83 (t, *J* = 7.1 Hz, 3H) ppm

^{13}C-NMR (100 MHz, C_6D_6) δ 181.9, 169.0, 162.7, 140.9, 140.0, 133.3, 132.9, 132.9, 130.9, 130.2, 130.0, 129.9, 129.8, 128.3, 127.3, 126.2, 113.6, 60.6, 56.3, 54.5, 42.0, 13.6 ppm (1 peak missing or overlapping)

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{27}H_{25}NO_5S$, 492.1471, requires 492.1475.

Ethyl (*Z*)-2-(3-benzylidene-2-((4-chlorophenyl)sulfonyl)-4-oxo-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (129b)



Following the general procedure the title compound was prepared in 65% yield.

R$_f$ 0.13 (4:1, v/v hexanes : EtOAc)

mp 157.5 – 160.8 °C

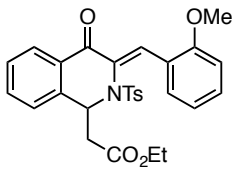
IR ν_{max} 1733, 1670, 1593, 1474, 1425, 1362, 1292, 1206, 1168, 1086, 1050, 947 cm^{-1}

^{1}H-NMR (600 MHz, C_6D_6) δ 8.23 (s, 1H), 8.06 – 8.01 (m, 2H), 7.65 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.14 – 6.99 (m, 4H), 6.75 (td, *J* = 7.5, 1.4 Hz, 1H), 6.67 (td, *J* = 7.6, 1.2 Hz, 1H), 6.62 (dd, *J* = 7.7, 1.1 Hz, 1H), 6.44 – 6.39 (m, 2H), 5.96 (dd, *J* = 8.4, 6.0 Hz, 1H), 3.88 (ddq, *J* = 55.9, 10.8, 7.2 Hz, 2H), 2.75 (dd, *J* = 16.3, 8.4 Hz, 1H), 2.31 (dd, *J* = 16.3, 6.1 Hz, 1H), 0.81 (t, *J* = 7.2 Hz, 3H) ppm

^{13}C-NMR (100 MHz, C_6D_6) δ 181.4, 168.8, 141.1, 139.6, 138.8, 136.26, 133.0, 132.9, 132.8, 131.0, 130.0, 129.2, 129.2, 128.4, 128.3, 128.0, 126.1, 60.6, 56.3, 41.7, 13.6 ppm

HRMS (ESI) *m/z* Found: $(M+K)^+$, $C_{26}H_{22}ClNO_5S$, 534.0539, requires 534.0539.

Ethyl (*Z*)-2-(3-(2-methoxybenzylidene)-4-oxo-2-tosyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (126a)



Following the general procedure the title compound was prepared in 68% yield as a bright yellow crystalline solid.

R_f 0.21 (4:1, v/v hexanes : EtOAc)

mp 109.3 – 114.1 °C

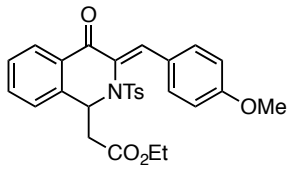
IR ν_{max} 1710, 1672, 1594, 1488, 1462, 1359, 1291, 1241, 1145, 1085, 1022, 974 cm^{-1}

^{1}H-NMR (300 MHz, C_6D_6) δ 9.26 (s, 1H), 9.12 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.67 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.38 (d, *J* = 8.3 Hz, 2H), 7.09 (ddd, *J* = 8.3, 7.3, 1.7 Hz, 1H), 6.97 – 6.91 (m, 1H), 6.83 (td, *J* = 7.4, 1.4 Hz, 1H), 6.76 (dd, *J* = 7.7, 1.3 Hz, 1H), 6.67 (td, *J* = 7.5, 1.4 Hz, 1H), 6.44 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.34 – 6.29 (m, 2H), 6.14 (dd, *J* = 8.3, 6.0 Hz, 1H), 4.09 – 3.86 (m, 2H), 3.22 (s, 3H), 2.90 (dd, *J* = 16.1, 8.3 Hz, 1H), 2.42 (dd, *J* = 16.1, 6.1 Hz, 1H), 1.68 (s, 3H), 0.92 (t, *J* = 7.1 Hz, 3H) ppm

^{13}C-NMR (100 MHz, C_6D_6) δ 181.8, 169.1, 159.7, 142.7, 139.9, 135.2, 134.1, 132.5, 132.4, 131.9, 130.4, 129.3, 129.1, 128.8, 127.1, 126.4, 126.1, 122.5, 120.4, 110.5, 60.6, 56.3, 54.8, 41.9, 20.5, 13.7 ppm

HRMS (ESI) *m/z* Found: $(M+Na)^+$, $C_{28}H_{27}NO_6S$, 528.1452, requires 528.1451.

Ethyl (*Z*)-2-(3-(4-methoxybenzylidene)-4-oxo-2-tosyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (126b)



Following the general procedure the title compound was prepared in 87% yield as a yellow crystalline solid.

R_f 0.24 (4:1, v/v hexanes : EtOAc)

mp 110.5 – 112.0 °C

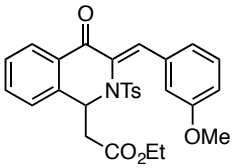
IR ν_{max} 1735, 1671, 1593, 1551, 1510, 1356, 1300, 1257, 1164, 1085, 1025, 956 cm^{-1}

^{1}H-NMR (300 MHz, C_6D_6) δ 8.33 (s, 1H), 8.11 (d, *J* = 8.9 Hz, 2H), 7.69 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.39 (d, *J* = 8.3 Hz, 2H), 6.85 – 6.60 (m, 5H), 6.31 (d, *J* = 8.0 Hz, 2H), 6.19 – 6.07 (m, 1H), 4.05 – 3.79 (m, 2H), 3.20 (s, 3H), 2.87 (dd, *J* = 16.1, 8.3 Hz, 1H), 2.40 (dd, *J* = 16.1, 6.1 Hz, 1H), 1.66 (s, 3H), 0.84 (t, *J* = 7.1 Hz, 3H) ppm

^{13}C-NMR (75 MHz, C_6D_6) δ 181.9, 169.2, 162.3, 142.8, 141.1, 139.9, 135.2, 132.6, 130.6, 129.0, 128.0, 127.2, 126.2, 126.2, 114.0, 60.6, 56.5, 41.9, 20.7, 13.7 ppm (3 peaks missing or overlapping)

HRMS (ESI) *m/z* Found: $(M+Na)^+$, $C_{28}H_{27}NO_6S$, 528.1449, requires 528.1451.

Ethyl (*Z*)-2-(3-(3-methoxybenzylidene)-4-oxo-2-tosyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (126c)



Following the general procedure the title compound was prepared in 84% yield as a yellow crystalline solid.

R_f 0.21 (4:1, v/v hexanes : EtOAc)

mp 118.3 – 120.3 °C

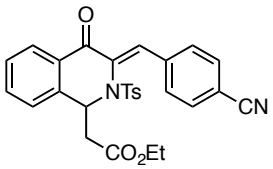
IR ν_{max} 1729, 1673, 1598, 1469, 1433, 1295, 1280, 1255, 1232, 1164, 1086, 1032, 977 cm^{-1}

^{1}H-NMR (300 MHz, C_6D_6) δ 8.42 (s, 1H), 8.26 (d, *J* = 2.2 Hz, 1H), 7.77 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.57 (d, *J* = 7.5 Hz, 1H), 7.47 (d, *J* = 8.3 Hz, 2H), 7.12 (t, *J* = 7.9 Hz, 1H), 7.01 – 6.83 (m, 2H), 6.75 (td, *J* = 7.8, 6.4 Hz, 3H), 6.41 (d, *J* = 8.0 Hz, 3H), 6.17 (dd, *J* = 8.9, 5.5 Hz, 1H), 4.11 – 3.90 (m, 2H), 3.76 (s, 2H), 2.91 (dd, *J* = 16.3, 8.9 Hz, 1H), 2.44 (dd, *J* = 16.3, 5.6 Hz, 1H), 1.77 (s, 4H), 0.91 (t, *J* = 7.1 Hz, 2H) ppm

^{13}C-NMR (100 MHz, C_6D_6) δ 181.8, 169.0, 159.8, 142.9, 141.1, 140.0, 135.3, 134.4, 132.8, 130.34, 129.9, 129.2, 129.0, 127.2, 126.3, 126.1, 118.8, 116.3, 60.6, 56.4, 55.0, 41.8, 20.6, 13.6 ppm (2 peaks missing of overlapping)

HRMS (ESI) *m/z* Found: $(M+Na)^+$, $C_{28}H_{27}NO_6S$, 528.1447, requires 528.1451.

Ethyl (*Z*)-2-(3-(4-cyanobenzylidene)-4-oxo-2-tosyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (126f)



Following the general procedure the title compound was prepared in 60% yield.

R_f 0.26 (4:1, v/v hexanes : EtOAc)

mp 177.7 – 181.5 °C

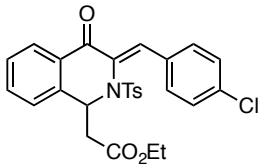
IR ν_{max} 2229, 1737, 1673, 1595, 1457, 1347, 1293, 1164, 1086, 1042, 964 cm^{-1}

^{1}H-NMR (300 MHz, C_6D_6) δ 7.99 (s, 1H), 7.77 – 7.70 (m, 2H), 7.65 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.29 (d, *J* = 8.3 Hz, 2H), 6.98 (d, *J* = 8.5 Hz, 2H), 6.82 – 6.74 (m, 1H), 6.64 (td, *J* = 7.4, 1.0 Hz, 2H), 6.31 – 6.25 (m, 2H), 5.97 (dd, *J* = 8.6, 5.6 Hz, 1H), 4.15 – 3.56 (m, 2H), 2.65 (dd, *J* = 16.1, 8.6 Hz, 1H), 2.29 (dd, *J* = 16.1, 5.7 Hz, 1H), 1.65 (s, 3H), 0.84 (t, *J* = 7.1 Hz, 3H) ppm

^{13}C-NMR (75 MHz, C_6D_6) δ 181.9, 169.4, 144.0, 140.6, 138.6, 137.5, 135.6, 134.0, 133.8, 133.0, 132.6, 132.2, 131.9, 131.7, 130.3, 129.7, 126.9, 118.9, 114.5, 61.5, 56.9, 42.87, 21.2, 14.3 ppm

HRMS (ESI) *m/z* Found: $(M+Na)^+$, $C_{28}H_{24}N_2O_5S$, 523.1292, requires 523.1298.

Ethyl (*Z*)-2-(3-(4-chlorobenzylidene)-4-oxo-2-tosyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (126d)



Following the general procedure the title compound was prepared in 72% yield.

R$_f$ 0.27 (4:1, v/v hexanes : EtOAc)

mp 169.8 – 171.8 °C

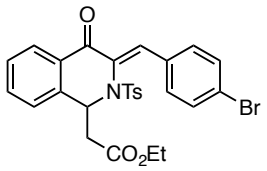
IR ν_{max} 1729, 1672, 1596, 1489, 1456, 1358, 1292, 1209, 1164, 1086, 1012, 959, 669 cm^{-1}

^{1}H-NMR (400 MHz, C_6D_6) δ 8.13 (s, 1H), 7.86 (d, *J* = 8.6 Hz, 2H), 7.68 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.36 (d, *J* = 8.3 Hz, 2H), 7.05 (d, *J* = 8.6 Hz, 2H), 6.82 (td, *J* = 7.5, 1.5 Hz, 1H), 6.72 – 6.64 (m, 2H), 6.36 – 6.27 (m, 2H), 6.05 (dd, *J* = 8.6, 5.8 Hz, 1H), 4.03 – 3.79 (m, 2H), 2.74 (dd, *J* = 16.1, 8.7 Hz, 1H), 2.34 (dd, *J* = 16.2, 5.8 Hz, 1H), 1.68 (s, 3H), 0.86 (t, *J* = 7.1 Hz, 3H) ppm

^{13}C-NMR (100 MHz, C_6D_6) δ 181.5, 168.8, 143.1, 139.9, 139.2, 136.8, 135.0, 133.9, 132.9, 131.7, 130.0, 130.0, 128.9, 128.5, 127.8, 127.3, 126.2, 60.7, 56.3, 42.0, 20.6, 13.6 ppm

HRMS (ESI) *m/z* Found: $(M+Na)^+$, $C_{27}H_{24}ClNO_5S$, 532.0951, requires 532.0956.

Ethyl (*Z*)-2-(3-(4-bromobenzylidene)-4-oxo-2-tosyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (126e)



Following the general procedure the title compound was prepared in 70% yield.

R_f 0.28 (4:1, v/v hexanes : EtOAc)

mp 167.1 – 175.5 °C

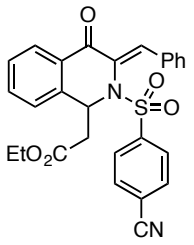
IR ν_{max} 1735, 1677, 1598, 1584, 1487, 1402, 1359, 1294, 1166, 1074, 1010, 957, 675 cm^{-1}

^{1}H-NMR (400 MHz, C_6D_6) δ 8.12 (s, 1H), 7.78 (d, *J* = 8.6 Hz, 2H), 7.69 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.37 (d, *J* = 8.3 Hz, 2H), 7.22 (d, *J* = 8.6 Hz, 2H), 6.85 – 6.78 (m, 1H), 6.71 – 6.65 (m, 2H), 6.35 – 6.30 (m, 2H), 6.06 (dd, *J* = 8.6, 5.8 Hz, 1H), 3.91 (ddq, *J* = 38.8, 10.8, 7.1 Hz, 2H), 2.74 (dd, *J* = 16.1, 8.7 Hz, 1H), 2.34 (dd, *J* = 16.1, 5.8 Hz, 1H), 1.68 (s, 3H), 0.86 (t, *J* = 7.1 Hz, 3H) ppm

^{13}C-NMR (100 MHz, C_6D_6) δ 181.5, 168.8, 143.0, 139.9, 139.3, 135.0, 134.0, 132.9, 132.0, 131.5, 130.2, 130.0, 128.9, 126.1, 125.5, 60.7, 56.2, 41.95, 20.6, 13.6 ppm (3 peaks missing or overlapping)

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{27}H_{24}BrNO_5S$, 554.0632, requires 554.0631.

Ethyl (*Z*)-2-(3-benzylidene-2-((4-cyanophenyl)sulfonyl)-4-oxo-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (129a)



Following the general procedure the title compound was prepared in 60% yield and purified via trituration from THF/hexanes.

R*f* 0.14 (4:1, v/v hexanes : EtOAc)

mp 237.3 – 238.3 °C

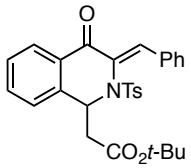
IR ν_{max} 2233, 1740, 1671, 1446, 1361, 1295, 1272, 1162, 1082, 1052, 970, 838 cm^{-1}

^{1}H-NMR (600 MHz, C_6D_6) 8.08 – 8.05 (m, 2H), 8.05 (s, 1H), 7.56 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.54 (d, *J* = 8.7 Hz, 1H), 7.49 – 7.42 (m, 4H), 7.36 – 7.33 (m, 2H), 7.24 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.22 – 7.20 (m, 1H), 5.90 (dd, *J* = 8.4, 6.0 Hz, 1H), 4.11 (ddq, *J* = 57.7, 10.8, 7.2 Hz, 2H), 2.99 (dd, *J* = 16.5, 8.5 Hz, 1H), 2.68 (dd, *J* = 16.5, 6.1 Hz, 1H), 1.13 (t, *J* = 7.2 Hz, 3H) ppm

^{13}C-NMR (150 MHz, C_6D_6) δ 181.8, 169.3, 142.2, 141.5, 139.3, 134.1, 132.9, 132.5, 132.4, 132.0, 129.7, 128.8, 128.8, 128.4, 128.2, 128.0, 126.4, 117.1, 116.5, 61.5, 56.5, 41.88, 14.1 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{27}H_{22}N_2O_5S$, 487.1323, requires 487.1322.

tert-Butyl (_Z_)-2-(3-benzylidene-4-oxo-2-tosyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (127b)



Following the general procedure the title compound was prepared in 73% yield.

R$_f$ 0.32 (4:1, v/v hexanes : EtOAc)

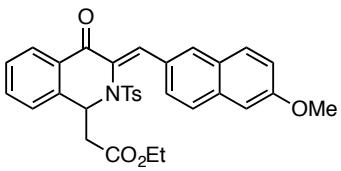
IR ν_{max} 1727, 1675, 1596, 1449, 1360, 1293, 1207, 1165, 1088, 956 cm^{-1}

^{1}H-NMR (600 MHz, C_6D_6) δ 8.29 (s, 1H), 8.17 – 8.07 (m, 2H), 7.67 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.35 (d, *J* = 8.2 Hz, 2H), 7.13 (d, *J* = 7.9 Hz, 2H), 7.08 – 7.03 (m, 1H), 6.81 (td, *J* = 7.4, 1.4 Hz, 1H), 6.77 (dd, *J* = 7.7, 1.3 Hz, 1H), 6.66 (td, *J* = 7.5, 1.3 Hz, 1H), 6.32 – 6.27 (m, 2H), 6.12 – 6.07 (m, 1H), 2.88 (dd, *J* = 16.2, 7.7 Hz, 1H), 2.42 (dd, *J* = 16.1, 6.3 Hz, 1H), 1.66 (s, 3H), 1.36 (s, 9H) ppm

^{13}C-NMR (150 MHz, C_6D_6) δ 181.7, 168.3, 142.8, 140.7, 140.2, 135.2, 133.4, 132.8, 132.7, 130.8, 130.1, 129.7, 128.9, 128.3, 127.3, 127.1, 126.3, 80.8, 56.3, 43.2, 27.7, 20.5 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{29}H_{29}NO_5S$, 504.1847, requires 504.1839.

Ethyl (_Z_)-2-(3-((6-methoxynaphthalen-2-yl)methylene)-4-oxo-2-tosyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (126g)



Following the general procedure the title compound was prepared in 60% yield as a bright orange waxy solid.

R$_f$ 0.12 (19:1, v/v toluene : EtOAc)

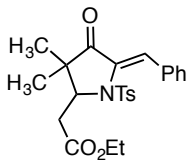
IR ν_{max} 1734, 1671, 1588, 1481, 1392, 1356, 1263, 1196, 1135, 1087, 1026, 813 cm^{-1}

^{1}H-NMR (600 MHz, C_6D_6) δ 8.64 (dd, *J* = 8.7, 1.8 Hz, 1H), 8.49 (s, 1H), 8.17 – 8.14 (m, 1H), 7.73 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.54 (dd, *J* = 17.4, 8.8 Hz, 2H), 7.42 (d, *J* = 8.2 Hz, 2H), 7.10 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.85 – 6.79 (m, 2H), 6.75 – 6.67 (m, 2H), 6.34 – 6.31 (m, 2H), 6.17 (dd, *J* = 8.6, 5.9 Hz, 1H), 3.92 (ddq, *J* = 75.0, 10.6, 7.1 Hz, 2H), 3.33 (s, 3H), 2.92 (dd, *J* = 16.3, 8.6 Hz, 1H), 2.43 (dd, *J* = 16.3, 5.9 Hz, 1H), 1.66 (s, 3H), 0.78 (t, *J* = 7.2 Hz, 3H) ppm

^{13}C-NMR (150 MHz, C_6D_6) δ 181.8, 169.1, 159.6, 142.8, 141.4, 140.0, 136.4, 135.3, 132.6, 130.9, 130.4, 129.1, 128.9, 128.7, 128.6, 127.4, 127.2, 126.7, 126.1, 119.1, 105.8, 60.6, 56.3, 54.5, 41.9, 20.6, 13.5 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{32}H_{29}NO_6S$, 556.1783, requires 556.1788.

Ethyl (*Z*)-2-(5-benzylidene-3,3-dimethyl-4-oxo-1-tosylpyrrolidin-2-yl)acetate (136)



Following the general procedure the title compound was prepared in 34% yield as a pale yellow oil.

R_f 0.14 (3:1, v/v hexanes : EtOAc)

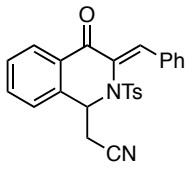
IR ν_{max} 1729, 1597, 1447, 1347, 1163, 1135, 1028, 811 cm^{-1}

^{1}H-NMR (400 MHz, C_6D_6) δ 7.79 (s, 1H), 7.75 (dd, *J* = 8.2, 2.0 Hz, 4H), 7.12 (dd, *J* = 8.3, 6.9 Hz, 2H), 7.08 – 7.01 (m, 1H), 6.61 (d, *J* = 8.2 Hz, 2H), 4.47 (dd, *J* = 8.3, 3.8 Hz, 1H), 3.90 (qd, *J* = 7.1, 4.8 Hz, 2H), 2.80 (dd, *J* = 16.7, 3.8 Hz, 1H), 2.64 (dd, *J* = 16.7, 8.3 Hz, 1H), 1.76 (s, 3H), 0.92 (t, *J* = 7.2 Hz, 3H), 0.89 (s, 3H), 0.46 (s, 3H) ppm

^{13}C-NMR (100 MHz, C_6D_6) δ 200.5, 170.2, 144.0, 135.5, 133.8, 130.7, 130.6, 129.5, 128.7, 124.2, 64.4, 60.4, 46.7, 38.6, 25.3, 20.7, 17.8, 13.7 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{24}H_{27}NO_5S$, 442.1681, requires 442.1683.

(*Z*)-2-(3-Benzylidene-4-oxo-2-tosyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetonitrile (127a)



Following the general procedure the title compound was prepared in 46% yield as a pale yellow oil.

R$_f$ 0.22 (19:1, v/v toluene : EtOAc)

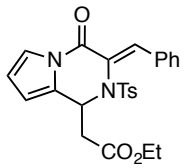
IR ν_{max} 1676, 1597, 1493, 1449, 1361, 1292, 1186, 1167, 1087, 969 cm^{-1}

^{1}H-NMR (600 MHz, C_6D_6) δ 8.23 (s, 1H), 8.15 – 8.10 (m, 1H), 7.63 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.26 (d, *J* = 8.3 Hz, 2H), 7.19 (d, *J* = 7.7 Hz, 2H), 7.09 – 7.05 (m, 1H), 6.76 (td, *J* = 7.5, 1.4 Hz, 1H), 6.63 (td, *J* = 7.6, 1.2 Hz, 1H), 6.50 (dd, *J* = 7.7, 1.0 Hz, 1H), 6.27 (d, *J* = 8.0 Hz, 2H), 5.41 (t, *J* = 7.6 Hz, 1H), 2.12 (dd, *J* = 16.9, 7.3 Hz, 1H), 1.74 (dd, *J* = 16.8, 7.7 Hz, 1H), 1.62 (s, 3H) ppm

^{13}C-NMR (150 MHz, C_6D_6) δ 180.1, 142.5, 141.0, 136.2, 133.6, 132.0, 130.6, 129.0, 128.1, 127.7, 127.5, 126.6, 126.5, 125.8, 115.1, 54.9, 23.9, 19.7 ppm (3 peaks missing or overlapping)

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{25}H_{20}N_2O_3S$, 429.1271, requires 429.1267.

Ethyl (*Z*)-2-(3-benzylidene-4-oxo-2-tosyl-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazin-1-yl)acetate (143)



Following the general procedure the title compound was prepared in 73% yield as a white crystalline solid.

R$_f$ 0.28 (1:19, v/v toluene : EtOAc)

mp 162.9 – 164.3 °C

IR ν_{max} 1713, 1699, 1617, 1407, 1360, 1302, 1259, 1165, 1086, 1016, 948, 863 cm^{-1}

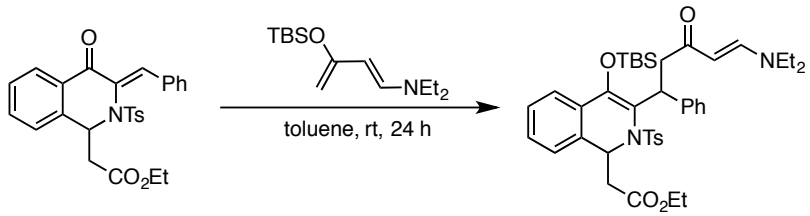
^{1}H-NMR (600 MHz, C_6D_6) δ 8.00 (s, 1H), 7.85 – 7.77 (m, 1H), 7.31 (d, *J* = 8.3 Hz, 2H), 6.92 – 6.87 (m, 2H), 6.86 – 6.83 (m, 1H), 6.70 (dd, *J* = 3.3, 1.5 Hz, 1H), 6.33 – 6.28 (m, 2H), 5.94 (ddd, *J* = 7.8, 7.0, 0.8 Hz, 1H), 5.53 (ddd, *J* = 3.3, 1.6, 0.8 Hz, 1H), 5.47 (t, *J* = 3.2 Hz, 1H), 3.77 – 3.60 (m, 2H), 2.49 (dd, *J* = 16.1, 7.0 Hz, 1H), 2.17 (dd, *J* = 16.1, 7.9 Hz, 1H), 1.55 (s, 3H), 0.65 (t, *J* = 7.1 Hz, 3H) ppm

^{13}C-NMR (150 MHz, C_6D_6) δ 167.8, 157.1, 142.9, 142.5, 133.4, 131.9, 131.8, 130.4, 128.4, 127.5, 122.7, 115.7, 111.5, 108.9, 59.6, 50.7, 40.1, 19.9, 12.8 ppm (2 peaks missing or overlapping)

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_xH_xNO_xS$, 465.1472, requires 465.1479.

4.2.3 Derivatisation studies

Ethyl (*E*)-2-(4-((*tert*-butyldimethylsilyl)oxy)-3-(5-(diethylamino)-3-oxo-1-phenylpent-4-en-1-yl)-2-tosyl-1,2-dihydroisoquinolin-1-yl)acetate (150)



To a solution of ethyl (*Z*)-2-(3-benzylidene-4-oxo-2-tosyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate **100** (60 mg, 13 mmol) in toluene (5 mL) under N_2 was added diene **149** (160 mg, 0.63 mmol) at rt. The reaction mixture was stirred for 24 h, at which point TLC analysis of the reaction mixture indicated complete consumption of the starting material. The reaction mixture was concentrated under reduced pressure and the crude residue was purified via column chromatography on silica gel to provide the product as a light brown oil (47 mg, 51% yield).

R_f 0.54 (4:1, v/v hexanes : EtOAc)

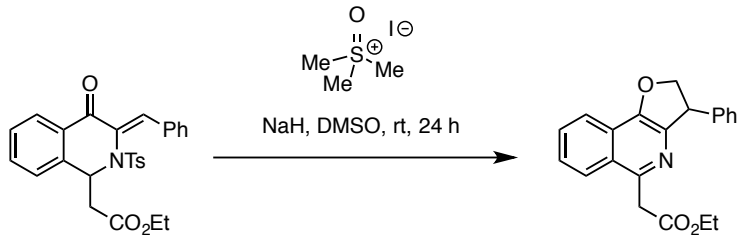
IR ν_{max} 2931, 1735, 1600, 1560, 1466, 1358, 1250, 1196, 1097, 960 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.58 (m, 2H), 7.50 (d, *J* = 12.9 Hz, 1H), 7.38 – 7.32 (m, 2H), 7.30 – 7.26 (m, 2H), 7.25 – 7.20 (m, 1H), 7.05 – 6.83 (m, 6H), 5.28 (dd, *J* = 9.8, 5.0 Hz, 1H), 5.17 (dd, *J* = 12.3, 8.3 Hz, 2H), 4.12 (dd, *J* = 15.6, 11.9 Hz, 1H), 4.00 (qd, *J* = 7.2, 5.0 Hz, 2H), 3.21 (d, *J* = 7.7 Hz, 4H), 3.00 (dd, *J* = 15.6, 3.2 Hz, 1H), 2.40 – 2.24 (m, 4H), 1.98 (dd, *J* = 15.5, 5.0 Hz, 1H), 1.24 – 1.03 (m, 9H), 0.47 (s, 3H), 0.00 (s, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8, 172.1, 152.2, 148.5, 144.9, 142.5, 137.2, 136.1, 132.5, 131.7, 130.5, 130.2, 129.9, 129.8, 128.6, 128.4, 128.2, 126.0, 124.7, 62.8, 57.4, 43.5, 40.4, 28.5, 23.6, 20.7, 16.3, 0.0, -0.3 ppm (3 peaks missing or overlapping)

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{41}H_{54}N_2O_6SSi$, 731.3545, requires 731.3545.

Ethyl 2-(3-phenyl-2,3-dihydrofuro[3,2-*c*]isoquinolin-5-yl)acetate (151)



To a dry Schlenk flask containing NaH (60% dispersion in mineral oil) (4 mg, 0.17 mmol) and trimethylsulfoxonium iodide (37 mg, 0.17 mmol) was added dry DMSO (1 mL). The resulting suspension was stirred for 30 minutes at which point a solution of ethyl (*Z*)-2-(3-benzylidene-4-oxo-2-tosyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (40 mg, 0.08 mmol) in dry DMSO (1 mL) was added dropwisely. The reaction mixture was allowed to stir overnight until TLC analysis of the reaction mixture indicated complete consumption of the starting material. The reaction was cooled and quenched with water (4 mL), extracted with Et_2O (2 x 5 mL). The organic extract was washed with water (2 x 5 mL), brine, dried with $MgSO_4$, filtered and then concentrated under reduced pressure. The crude residue was purified via column chromatography on silica gel to afford the product as a white solid (27 mg, 96% yield)

R_f 0.35 (4:1, v/v hexanes : EtOAc)

mp 118.3 – 121.8 °C

IR ν_{max} 1731, 1632, 1587, 1509, 1495, 1444, 1384, 1320, 1259, 1161, 1088, 1030, 1009, 916, 762 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.91 (m, 2H), 7.62 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1H), 7.52 (ddd, *J* = 8.5, 6.9, 1.3 Hz, 1H), 7.27 – 7.21 (m, 2H), 7.17 – 7.13 (m, 2H), 5.12 (dd, *J* = 9.9, 9.0 Hz, 1H), 4.85 (dd, *J* = 9.9, 6.1 Hz, 1H), 4.66 (dd, *J* = 9.0, 6.1 Hz, 1H), 4.24 – 4.10 (m, 2H), 4.04 (qd, *J* = 7.1, 1.7 Hz, 2H), 1.08 (t, *J* = 7.1 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 147.3, 142.4, 129.5, 128.8, 127.9, 127.4, 127.3, 127.0, 125.1, 123.8, 121.4, 79.7, 61.0, 49.2, 41.9, 14.1 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{21}H_{20}NO_3$, 334.1442, requires 334.1438.

Ethyl 2-(3-((dodecylthio)(phenyl)methyl)-4-hydroxyisoquinolin-1-yl)acetate (152)

Adapted from the literature procedure[2]: N_2 was bubbled through a solution of ethyl (*Z*)-2-(3-benzylidene-2-((4-cyanophenyl)sulfonyl)-4-oxo-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (60 mg, 0.13 mmol) and 1-dodecanethiol (160 µL, 0.66 mmol) in dimethylformamide (2 mL) for 10 minutes and then DBU (95 µL, 0.63 mmol) was added dropwisely. The solution became yellow and was stirred for 30 mins under N_2 at which point TLC analysis indicated complete consumption of the starting material. This was followed by the addition of water (2 mL), the layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 5 mL). The combined organic extracts were

dried with Na_2SO_4, filtered and then purified via column chromatography on silica gel to provide the product as a pale yellow oil (57 mg, 84% yield).

R_f 0.61 (4:1, v/v hexanes : EtOAc)

IR ν_{max} 2923, 2853, 1735, 1582, 1450, 1390, 1252, 1155, 1030, 765 cm^{-1}

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.74 (s, 1H), 8.34 (d, *J* = 8.4 Hz, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.70 (t, *J* = 7.7 Hz, 1H), 7.62 (t, *J* = 7.8 Hz, 1H), 7.39 (d, *J* = 7.6 Hz, 2H), 7.28 (d, *J* = 7.2 Hz, 1H), 7.24 – 7.20 (m, 1H), 5.71 (s, 1H), 4.27 – 4.15 (m, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 2.62 (dt, *J* = 13.6, 7.1 Hz, 1H), 2.49 (dt, *J* = 12.6, 7.6 Hz, 1H), 1.69 – 1.55 (m, 3H), 1.37 – 1.18 (m, 18H), 1.16 (t, *J* = 7.1 Hz, 3H), 0.88 (t, *J* = 7.1 Hz, 3H) ppm

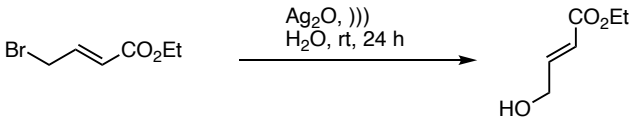
^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 145.4, 138.5, 129.1, 128.6, 128.1, 127.8, 127.6, 124.8, 122.2, 60.9, 54.5, 41.7, 32.4, 31.9, 29.6, 29.6, 29.4, 29.3, 29.1, 29.0, 23.0, 14.1, 14.1 ppm

HRMS (ESI) *m/z* Found: $(M-H)^-$, $C_{32}H_{43}NO_3S$, 520.2896, requires 520.2891.

4.3 Experimental procedures for Chapter 3

4.3.1 Synthesis of bifunctional donor-acceptors

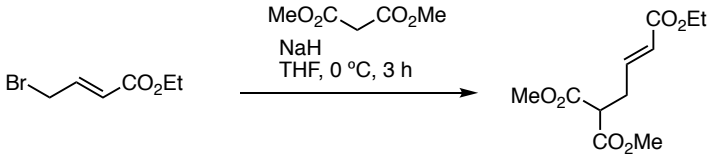
Ethyl (*E*)-4-hydroxybut-2-enoate (168)



Ethyl 4-bromocrotonate (2.78 mL, 15 mmol, 1 equiv.), Ag_2O (3.51 g, 15 mmol, 1 equiv.) and H_2O (20 mL) were added to an RBF. The suspension was sonicated at room temperature for 24 hours. The reaction was then diluted with EtOAc (40 mL) and filtered. The phases were separated and the aqueous phase was extracted with EtOAc (3 x 10 mL), the combined extracts were washed with brine (20 mL) and then concentrated under reduced pressure to yield the crude residue which was purified via column chromatography on silica gel (1:1 Et_2O/hexanes) to yield the pure product as a yellow oil (0.94 g, 48%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (d, *J* = 15.2 Hz, 1H), 6.07 (d, *J* = 15.2 Hz, 1H), 4.32 (m, 2H), 4.19 (d, *J* = 7.1 Hz, 2H), 2.22 (br s, 1H), 1.27 (t, *J* = 7.1 Hz, 3H) ppm

4-Ethyl 1,1-dimethyl (*E*)-but-3-ene-1,1,4-tricarboxylate (170)

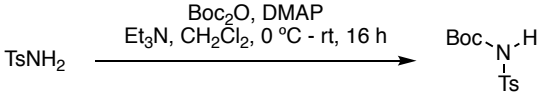


Sodium hydride (60% wt. in mineral oil) (207 mg, 5.2 mmol, 1 equiv.) was added to a flame dried RBF under N_2 followed by THF (20 mL). The solution was cooled to 0 °C and then dimethyl malonate (0.82 g, 6.2 mmol, 1.2 equiv.) was added dropwisely over 10 minutes. The reaction was stirred for a further 30 minutes followed by dropwise addition

of ethyl 4-bromoacetate (1.0 g, 5.2 mmol, 1 equiv.). The solution was maintained at 0 °C for 3 hours at which point TLC analysis indicated consumption of the starting material. The reaction was quenched with satd. NH_4Cl solution (20 mL) the phases separated. The aqueous phase was extracted with EtOAc (3 x 20 mL) and the combined organics were then washed with satd. $NaHCO_3$ solution (20 mL), brine (25 mL) and then concentrated under reduced pressure to yield a crude oil which was purified via column chromatography on silica gel and afforded as a yellow oil (0.49 g, 39%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.14 (dtd, *J* = 15.8, 7.1, 1.9 Hz, 1H), 6.07 (dd, *J* = 15.6, 1.8 Hz, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.43 – 3.45 (m, 2H), 3.43 (s, 3H), 3.42 (s, 3H), 2.80 – 2.72 (m, 1H), 1.14 (t, *J* = 7.2 Hz, 3H).

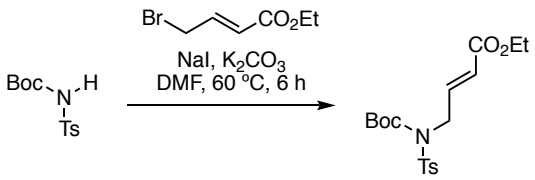
***tert*-Butyl tosylcarbamate (172)**



p-Toluenesulfonamide (5.00 g, 29 mmol, 1 equiv.) and DMAP (0.71 g, 6 mmol, 0.2 equiv.) were added to an RBF followed by CH_2Cl_2 (100 mL) and Et_3N (4.1 mL, 29 mmol, 1 equiv.). The solution was cooled to 0 °C and then Boc_2O (7.65 g, 35 mmol, 1.2 equiv.) was added as a solid in three portions over 10 minutes. The reaction was then stirred overnight and allowed to warm to room temperature. 0.1 M HCl (40 mL) was added and the phases separated. The aqueous phase was extracted with EtOAc (3 x 50 mL) and the combined organics were then washed with satd. $NaHCO_3$ solution (50 mL), brine (50 mL) and then concentrated under reduced pressure to yield a crude solid which was used without further purification (7.51 g, 95%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.4 Hz, 2H), 7.25 (dd, *J* = 8.7, 0.8 Hz, 2H), 2.38 (s, 3H), 1.32 (s, 9H) ppm

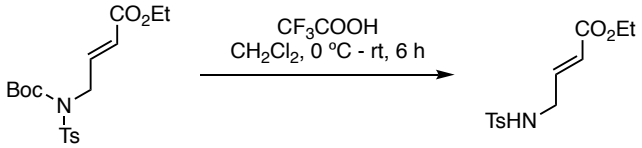
Ethyl (*E*)-4-((*N*-(*tert*-butoxycarbonyl)-4-methylphenyl)sulfonamido)but-2-enoate[3]



tert-Butyl tosylcarbamate (2.7 g, 9.9 mmol, 1.0 equiv.), sodium iodide (0.3 g, 2.0 mmol, 0.2 equiv.) and potassium carbonate (2.7 g, 19.8 mmol, 2.0 equiv.) were added to a solution of ethyl 4-bromocrotonate (1.4 mL, 9.9 mmol, 1.0 equiv.) in DMF (20 mL) under nitrogen. The suspension was then heated to 60 °C and stirred for six hours at which point TLC analysis indicated that the starting material had been consumed. Ether (30 mL) was then added and the layers separated, the organic phase was washed with H_2O (3 x 30 mL) and then concentrated under reduced pressure. The crude residue was purified via column chromatography on silica gel (30% EtOAc/Hexane) to yield the product as a white solid (2.3 g, 60%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.4 Hz, 2H), 7.31 (dd, *J* = 8.7, 0.8 Hz, 2H), 6.94 (dt, *J* = 15.7, 5.4 Hz, 1H), 6.00 (dt, *J* = 15.7, 1.7 Hz, 1H), 4.58 (dd, *J* = 5.4, 1.7 Hz, 2H), 4.21 (q, *J* = 7.1 Hz, 2H), 2.44 (s, 3H), 1.35 (s, 9H), 1.30 (t, *J* = 7.1 Hz, 3H) ppm

Ethyl (*E*)-4-((4-methylphenyl)sulfonamido)but-2-enoate (171)[3]



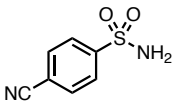
Ethyl (*E*)-4-((*N*-(*tert*-butoxycarbonyl)-4-methylphenyl)sulfonamido)but-2-enoate (2.3 g, 6.0 mmol, 1.0 equiv.) and CH_2Cl_2 (50 mL) were added to an RBF and the solution was cooled to 0 °C. Trifluoroacetic acid (2.8 mL, 36.0 mmol, 6.0 equiv.) was then added dropwisely, and the solution was stirred overnight and allowed to warm to room temperature. The reaction mixture was concentrated under reduced pressure and purified

via column chromatography on silica gel (30% EtOAc/Hexane) to yield the product as a light brown crystalline solid (1.2 g, 70%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.3 Hz, 2H), 7.25 (d, 2H), 6.69 (dt, *J* = 15.7, 5.3 Hz, 1H), 5.95 – 5.71 (m, 1H), 4.42 (t, *J* = 6.3 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.69 (ddd, *J* = 6.5, 5.3, 1.9 Hz, 2H), 2.36 (s, 3H), 1.20 (t, *J* = 7.1 Hz, 3H) ppm

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.8, 143.9, 142.4, 136.8, 130.0, 127.3, 123.0, 60.7, 43.9, 21.6, 14.3 ppm

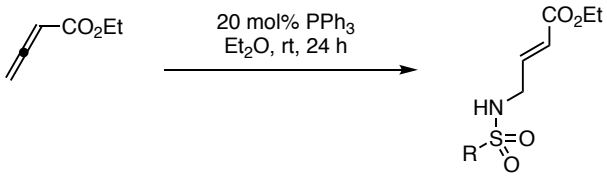
4-Cyanobenzenesulfonamide[4]



15 M Aqueous ammonia (20 mL) was added to a solution of 4-cyanobenzenesulfonyl chloride (3.0 g, 15.0 mmol) in $CHCl_3$ (40 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and then heated to reflux overnight. A precipitate formed which was filtered, dried and then recrystallised twice from refluxing EtOH, the yield the product as a white solid (2.4 g, 88%).

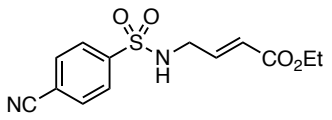
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.7 Hz, 2H), 7.77 (d, *J* = 8.7 Hz, 2H), 4.83 (s, 2H) ppm

General procedure for the synthesis of allylic amines from sulfonamides and allenoates



To a solution of arylsulfonamide (1 equiv.) and ethyl 2,3-butadienoate (1.5 equiv.) in diethyl ether under nitrogen was added PPh_3 (0.2 equiv.). The reaction mixture was stirred overnight and monitored via TLC until consumption of the starting material. The reaction was then concentrated under reduced pressure to yield the crude residue, which was purified via column chromatography on silica gel (EtOAc/Hexanes).

Ethyl (*E*)-4-((4-cyanophenyl)sulfonamido)but-2-enoate (77)[5]

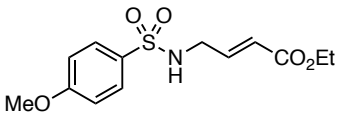


4-Cyanobenzenesulfonamide was prepared according the general procedure as white solid (315 mg, 71%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 – 7.84 (m, 2H), 7.77 (dd, *J* = 8.2, 1.4 Hz, 2H), 6.67 (dt, *J* = 15.7, 5.3 Hz, 1H), 5.84 (dd, *J* = 15.7, 1.7 Hz, 1H), 5.25 (t, *J* = 6.4 Hz, 1H), 4.23 – 3.99 (m, 2H), 3.79 – 3.64 (m, 2H), 1.31 – 1.09 (m, 3H) ppm

^{13}C NMR (151 MHz, $CDCl_3$) δ 164.6, 143.3, 140.7, 132.1, 126.7, 122.3, 116.2, 115.6, 59.8, 42.8, 13.2 ppm

Ethyl (*E*)-4-((4-methoxyphenyl)sulfonamido)but-2-enoate (75)[5]

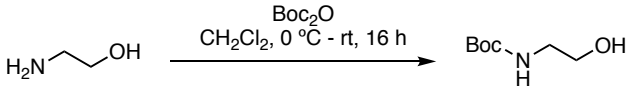


4-Methoxybenzenesulfonamide was prepared according to the general procedure as a tan solid (190 mg, 37%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.9 Hz, 2H), 7.00 (d, *J* = 8.9 Hz, 2H), 6.77 (dt, *J* = 15.7, 5.3 Hz, 1H), 5.93 (dt, *J* = 15.7, 1.9 Hz, 1H), 4.46 (t, *J* = 6.5 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.89 (s, 3H), 3.76 (ddd, *J* = 6.9, 5.4, 1.8 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H) ppm

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.6, 162.1, 141.1, 130.2, 128.3, 122.0, 113.4, 59.6, 54.6, 42.8, 13.2 ppm

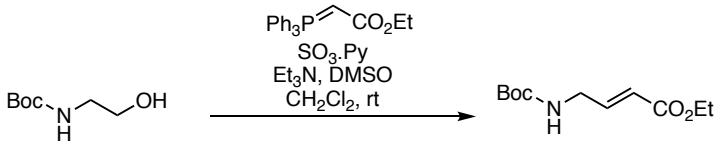
tert-Butyl (2-hydroxyethyl)carbamate (230)[6]



Ethanolamine (1.8 mL, 30.0 mmol, 1.0 equiv.) was added slowly to a solution of Boc_2O (6.5 g, 30.0 mmol, 1.0 equiv.) in CH_2Cl_2 at 0 °C. The solution was allowed to warm to room temperature and stirred for 16 hours. The reaction mixture was then diluted with H_2O (20 mL) and EtOAc (20 mL) and the phases separated. The aqueous phase was extracted with EtOAc (3 x 20 mL), and the combined organic layers were washed with brine (20 mL), dried with Na_2SO_4, filtered and concentrated under reduced pressure to yield the product as a colourless liquid which was used without further purification (4.7 g, 92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.70 (t, *J* = 5.0 Hz, 2H), 3.29 (t, *J* = 5.1 Hz, 2H), 1.45 (s, 9H) ppm

Ethyl (*E*)-4-((*tert*-butoxycarbonyl)amino)but-2-enoate (228)[6]



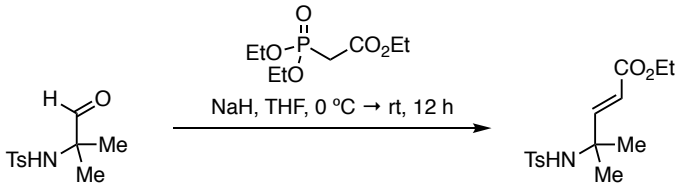
DMSO (23.5 mL, 33.1 mmol, 1.15 equiv.) and triethylamine (24.2 mL, 173.4 mmol, 6.0 equiv.) were added to solution of *tert*-butyl (2-hydroxyethyl)carbamate (4.7 g, 28.9 mmol, 1.0 equiv.) in CH_2Cl_2 (200 mL). Ethyl 2-(triphenylphosphaneylidene)acetate (20.1 g, 57.8 mmol, 2.0 equiv.) was then added and the mixture was stirred until a clear solution formed. SO_3.Py complex (13.8 g, 86.7 mmol, 3.0 equiv.) was added directly to the reaction which was stirred for a further five hours at room temperature. The pH was

adjusted to ~3 with 1 M HCl, the layers were separated and then the aqueous was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried with Na_2SO_4, filtered and concentrated under reduced pressure to yield a pink oil. The crude residue was purified via column chromatography on silica gel (30% EtOAc/Hexane) to yield the product as a white crystalline solid (1.2 g, 18%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (dt, *J* = 15.7, 4.9 Hz, 1H), 5.95 (dt, *J* = 15.7, 1.9 Hz, 1H), 4.66 (s, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.93 (s, 2H), 1.45 (s, 9H), 1.30 (t, *J* = 7.1 Hz, 3H) ppm

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.2, 156.8, 144.7, 121.4, 81.4, 76.7, 60.5, 40.1, 28.4, 14.2 ppm

Ethyl (*E*)-4-methyl-4-((4-methylphenyl)sulfonamido)pent-2-enoate (212)



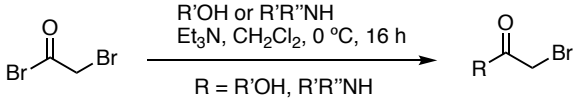
A flame dried RBF was charged with NaH (60% wt. in mineral oil) (0.18 g, 4.56 mmol, 1.1 equiv.) and then dry THF (20 mL) was added and the reaction was cooled to 0 °C. Triethylphosphonoacetate (0.90 mL, 4.56 mmol, 1.1 equiv) was added dropwisely and the reaction was stirred for a further 30 minutes. A solution of 4-methyl-*N*-(2-methyl-1-oxopropan-2-yl)benzenesulfonamide (1.00 g, 4.14 mmol, 1 equiv.) in dry THF (20 mL) was then added dropwisely over 20 minutes and the reaction was allowed to warm to room temperature and stirred overnight. The reaction was quenched with satd. NH_4Cl solution (20 mL), separated, the aqueous extracted with EtOAc (3 x 25 mL), the organics were washed with brine, dried Na_2SO_4, filtered and then concentrated under reduced pressure to yield the crude residue. The residue was purified via column chromatography

on silica gel (30% EtOAc/hexanes) to yield the pure product as a white crystalline solid (0.98 g, 76%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.27 – 7.23 (m, 2H), 6.73 (d, *J* = 15.9 Hz, 1H), 5.80 (d, *J* = 15.9 Hz, 1H), 4.14 (p, *J* = 6.9 Hz, 2H), 2.39 (s, 3H), 1.34 (s, 6H), 1.25 (t, *J* = 7.2 Hz, 3H).

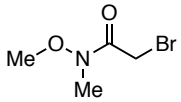
4.3.2 Synthesis of allenoates

General procedure for the synthesis of bromoacetates from bromoacetyl bromide



Triethylamine (100 mmol, 1.0 equiv.) was added to a solution of the alcohol or amine (100 mmol, 1.0 equiv.) in CH_2Cl_2, and the resultant solution was cooled to 0 °C. Bromoacetyl bromide (100 mmol, 1.0 equiv.) was then added dropwisely and the reaction was stirred at room temperature overnight. H_2O (200 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 x 100 mL), the combined organic layers were washed with 1 M HCl (100 mL), sat. $NaHCO_3$ solution (100 mL) and brine (100 mL). The organics were dried with Na_2SO_4, filtered and then concentrated under reduced pressure. The crude residues were purified via vacuum distillation to yield the pure products.

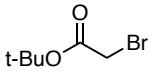
2-Bromo-*N*-methoxy-*N*-methylacetamide (183)[7]



The compound was prepared following the general procedure to yield the product as a clear colourless oil (13.5 g, 74%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.08 (s, 3H), 3.83 (s, 2H), 3.71 (s, 3H) ppm

tert-Butyl 2-bromoacetate (200)[8]

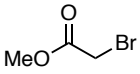


The compound was prepared following the general procedure to yield the product as a clear colourless oil (11.2 g, 41%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 2H), 1.49 (s, 9H) ppm

^{13}C NMR (151 MHz, $CDCl_3$) δ 166.3, 82.9, 27.8, 27.7 ppm

Methyl 2-bromoacetate (199)[9]

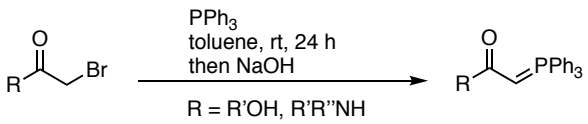


The compound was prepared following the general procedure to yield the product as a clear colourless oil (3.3 g, 21.7 mmol, 22%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 2H), 3.72 (s, 3H) ppm

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7, 53.2, 25.5 ppm

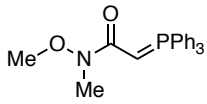
General procedure for the synthesis of Wittig reagents from bromoacetates



These compounds were prepared according to a modified literature procedure.[10] Triphenylphosphine (19.4 g, 74.0 mmol, 1.0 equiv.) was added to a solution of the corresponding bromoacetate or bromoacetamide (74.0 mmol, 1.0 equiv.) in toluene (150 mL) and allowed to stir overnight at room temperature. A precipitate formed, which was filtered and washed with hexanes. The solid was then suspended in toluene (250 mL), 2.5 M NaOH solution (280 mL) was added, and the mixture was stirred until both

phases became clear. The phases were then separated and the organic layer was dried with Na_2SO_4, filtered and concentrated under reduced pressure to yield the products.

_N_-Methoxy-_N_-methyl-2-(triphenylphosphaneylidene)acetamide (184)[10]

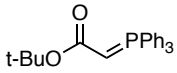


This compound was prepared following the general procedure to yield the product as a white solid (10.6 g, 40%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.23 (m, 15H), 3.65 (s, 3H), 3.00 (s, 3H) ppm

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.0, 138.3, 137.4, 134.1, 133.1, 65.4, 61.5, 37.7 ppm

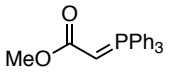
***tert*-Butyl 2-(triphenylphosphaneylidene)acetate (208)**[10]



This compound was prepared following the general procedure to yield the product as a white solid (13.3 g, 35.3 mmol, 61%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60 (s, 1H), 0.98 (s, 9H) ppm

Methyl 2-(triphenylphosphaneylidene)acetate (203)[10]

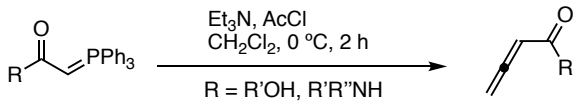


This compound was prepared following the general procedure to yield the product as a white solid (5.0 g, 15.0 mmol, 69%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 – 7.36 (m, 15H), 3.57 (s, 3H) ppm (C-H broad)

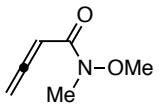
^{13}C NMR (101 MHz, $CDCl_3$) δ 165.7, 132.2, 131.9, 128.6, 128.4, 60.6, 50.3 ppm

General procedure for the synthesis of allenes from Wittig reagents



These compounds were prepared according to a modified literature procedure.[11] Triethylamine (1.1 equiv.) was added to a stirred solution of the corresponding Wittig reagent (1.0 equiv.) in CH_2Cl_2 at 0 ˚C. Acetyl chloride (1.1 equiv.) was then added dropwisely, and the reaction was stirred until TLC indicated consumption of the Wittig reagent. The solution was then concentrated carefully under reduced pressure at in a cold rotovap bath. Pentane (100 mL) was then added to the gummy residue in addition to 25 g of silica gel, and the mixture was stirred for two hours with periodic grinding of large chunks of material to ensure a fine suspension was formed. The mixture was filtered, concentrated under reduced pressure in a cold rotovap bath, and then purified via filtration through a plug of silica gel (5% EtOAc/hexanes) to yield the pure products.

***N*-Methoxy-*N*-methylbuta-2,3-dienamide (181)[11]**

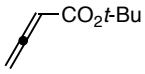


This reagent was prepared using the general procedure to provide the product as a yellow oil (204.4 mg, 8%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.15 (t, *J* = 6.6 Hz, 1H), 5.17 (d, *J* = 6.6 Hz, 2H), 3.65 (s, 3H), 3.18 (s, 3H) ppm

^{13}C NMR (101 MHz, $CDCl_3$) δ 201.4, 147.2, 95.7, 86.1, 61.7, 40.5 ppm

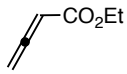
tert-Butyl buta-2,3-dienoate (208)[11]



This reagent was prepared by Honours student Luke Darveniza using the general procedure to provide the product as a yellow liquid (85.4 mg, 0.6 mmol, 4%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.48 (t, *J* = 6.5 Hz, 1H), 5.09 (d, *J* = 6.5 Hz, 2H), 1.47 (s, 9H) ppm

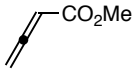
Ethyl buta-2,3-dienoate (173)



This reagent was prepared using the general procedure from commercially available Ethyl 2-(triphenylphosphaneylidene)acetate to provide the product as a yellow volatile liquid (1.98 g, 35%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.63 (t, *J* = 6.5 Hz, 1H), 5.21 (d, *J* = 6.5 Hz, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 3H).

Methyl buta-2,3-dienoate (207)

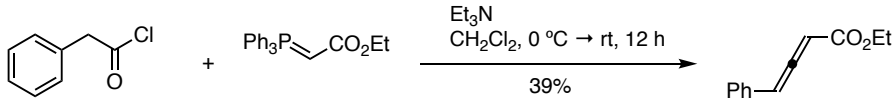


This reagent was prepared using the general procedure to provide the product as a colourless volatile liquid 279.8 mg, 2.9 mmol, 19%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.58 (t, *J* = 6.4 Hz, 1H), 5.16 (d, *J* = 6.6 Hz, 2H), 3.69 (s, 3H) ppm

^{13}C NMR (101 MHz, $CDCl_3$) δ 215.8, 166.2, 87.7, 79.3, 52.2 ppm

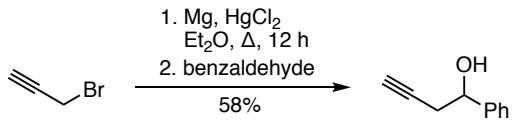
Ethyl 4-phenyl-3λ^5-buta-2,3-dienoate (232)



Triethylamine (0.9 mL, 6.47 mmol, 1.1 equiv.) was added to a stirred solution of the corresponding Wittig reagent (2.05 g, 5.88 mmol, 1.0 equiv.) in CH_2Cl_2 (50 mL) at 0 °C. Phenylacetyl chloride (0.85 mL, 6.47 mmol, 1.1 equiv.) was then added dropwisely, and the reaction was stirred until TLC indicated consumption of the Wittig reagent. The solution was then concentrated under reduced pressure and *n*-pentane (100 mL) was then added to the residue in addition to ~15 g of silica gel, and the mixture was stirred for two hours with periodic grinding of large chunks of material to ensure a fine suspension was formed. The mixture was filtered, concentrated under reduced pressure in a cold rotovap bath, and then purified via filtration through a plug of silica gel (5% EtOAc/hexanes) to yield the pure products.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29 – 7.19 (m, 5H), 6.55 (d, *J* = 6.4 Hz, 1H), 5.94 (dd, *J* = 6.4, 0.6 Hz, 1H), 4.21 – 4.10 (m, 2H), 1.26 – 1.19 (m, 3H).

1-Phenylbut-3-yn-1-ol (187)[12]



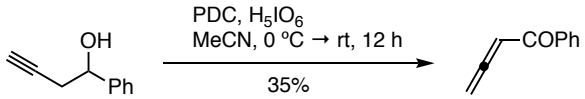
*prepared by Honours student Luke Darveniza

This compound was prepared by another student according to the literature procedure and was purified by column chromatography (30% EtOAc/Hexane) to yield the product as a yellow oil (2.6 g, 58%). Data was consistent with the literature.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 6.96 (m, 5H), 4.80 (dd, *J* = 6.9, 6.0 Hz, 1H), 3.52 (s, 1H), 2.60 (ddd, *J* = 6.0, 3.8, 2.7 Hz, 2H), 1.98 (s, 1H) ppm

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.4, 128.5, 128.0, 125.7, 80.7, 77.3, 72.4, 71.0, 29.5 ppm

1-Phenylbuta-2,3-dien-1-one (185)[12]



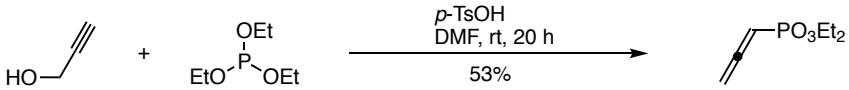
*prepared by Honours student Luke Darveniza

This compound was prepared by another student according to the following procedure. A solution of 1-phenylbut-3-yn-1-ol (1.3 g, 9.0 mmol, 1.0 equiv) in MeCN (40 mL) was added via a dropping funnel to a solution of periodic acid (2.2 g, 9.5 mmol, 1.1 equiv.) in MeCN (40 mL) at 0 ˚C. PDC (39.0 mg, 0.2 mmol, 0.02 equiv.) was then added in three portions and the reaction was stirred at 0 ˚C. When TLC indicated that the starting material had been consumed, the reaction mixture was diluted with 100 mL EtOAc, washed with 50:50 brine/H_2O (50 mL), satd. $Na_2S_2O_3$ (50 mL), brine (50 mL), dried with Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified via column chromatography on silica gel (10% EtOAc/Hexane) to yield the pure product as a dark red oil (453.1 mg, 35%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.75 (m, 2H), 7.51 – 7.46 (m, 1H), 7.38 (dd, *J* = 8.4, 7.0 Hz, 2H), 6.37 (t, *J* = 6.5 Hz, 1H), 5.19 (d, *J* = 6.5 Hz, 2H) ppm

^{13}C NMR (101 MHz, $CDCl_3$) δ 213.9, 207.3, 128.7, 128.4, 128.2, 105.0, 79.3 ppm

Diethyl propa-1,2-dien-1-ylphosphonate (178)[13]



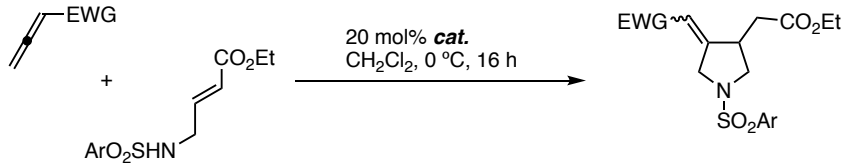
A solution of propargyl alcohol (3.0 mL, 50 mmol, 2.0 equiv.), triethylphosphite (4.3 mL, 25.0 mmol, 1.0 equiv.) and *p*-toluenesulfonic acid (215.0 mg, 1.25 mmol, 0.05 equiv.) in dry DMF (10 mL) was stirred at room temperature for 18 h and followed via TLC analysis which indicated complete consumption of the starting material. The reaction was then concentrated under reduced pressure and the crude residue was purified via column chromatography on silica gel (5% MeOH/CH_2Cl_2) to yield the product as a colourless oil (462 mg, 11%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.27 (t, *J* = 6.9 Hz, 1H), 4.96 (dd, *J* = 13.6, 6.9 Hz, 2H), 4.06 (p, *J* = 7.3 Hz, 4H), 1.28 (t, *J* = 7.1 Hz, 6H) ppm

^{13}C NMR (101 MHz, $CDCl_3$) δ 214.7, 78.6, 76.0, 62.4, 16.2 ppm

4.3.3 Annulation of activated allenes with bifunctional donor-acceptors

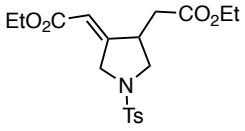
General procedure for the annulation of allenes with allylic amines



To a 5 mL flame dried RBF under nitrogen was added the allylic amine (0.15 mmol, 1.0 equiv.), CH_2Cl_2 (1.5 mL) and then the allenoate (0.22 mmol, 1.5 equiv.). Me_2PPh (0.030 mmol, 0.2 equiv.) was then added, and the reaction was left to stir at room temperature until TLC analysis indicated complete consumption of the starting material. Upon

completion, the reaction mixture was concentrated under reduced pressure and then the crude residue was purified via column chromatography on silica gel (EtOAc/hexanes).

Ethyl 2-(4-(2-ethoxy-2-oxoethyl)-1-tosylpyrrolidin-3-ylidene)acetate (176)



Following the general procedure the product was afforded as a colourless oil (30.5 mg, 86%, *dr* 3:1).

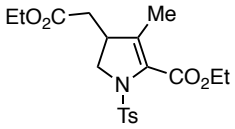
IR υ_{max} = 1705, 1515, 1450, 1339, 1213, 1057, 909, 738 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 5.70 (q, *J* = 2.5 Hz, 1H), 4.26 (dd, *J* = 2.7, 1.4 Hz, 2H), 4.13 (q, 4H), 3.50 (dd, *J* = 9.6, 7.1 Hz, 1H), 3.19 (dtdd, *J* = 8.7, 7.0, 5.6, 1.7 Hz, 1H), 3.02 (dd, *J* = 9.6, 6.3 Hz, 1H), 2.57 – 2.44 (m, 2H), 2.42 (s, 3H), 1.25 (td, *J* = 7.1, 3.8 Hz, 6H) ppm

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.6, 143.7, 141.3, 127.8, 127.1, 125.1, 120.0, 105.0, 67.4, 52.5, 47.1, 30.9, 25.4, 22.7 (1 peak missing or overlapping) ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{19}H_{25}NO_6S$, 396.1474, requires 396.1475.

Ethyl 2-(4-(2-ethoxy-2-oxoethyl)-1-tosylpyrrolidin-3-ylidene)acetate (225)



This product was formed via when the general procedure was followed with the addition of LiBr or LiI additives (Table 3.7, *vide infra*).

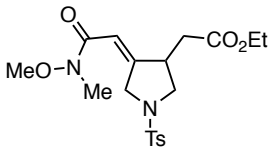
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.71 (d, *J* = 7.9 Hz, 2H), 7.34 (d, *J* = 7.9 Hz, 2H), 4.19 – 4.07 (m, 4H), 3.90 (t, *J* = 10.5 Hz, 1H), 3.75 (dd, *J* = 11.1, 3.4 Hz, 1H), 3.30 (t, *J* =

10.1 Hz, 1H), 2.68 (dd, *J* = 16.4, 2.4 Hz, 1H), 2.50 (s, 3H), 2.44 (s, 3H), 1.99 (dd, *J* = 16.4, 10.9 Hz, 1H), 1.29 – 1.20 (m, 6H) ppm

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 165.6, 153.1, 144.9, 135.7, 130.4, 127.6, 113.3, 60.9, 60.3, 55.3, 38.5, 36.4, 21.9, 14.7, 14.6, 14.2 ppm

HRMS (ESI) *m/z* Found $(M+H)^+$, $C_{19}H_{26}NO_6S$, 396.1472, requires 396.1475.

Ethyl 2-(4-(2-(methoxy(methyl)amino)-2-oxoethylidene)-1-tosylpyrrolidin-3-yl)acetate (189)



Following the general procedure the product was afforded as a colourless oil (31.2 mg, 35%, *dr*: 1:1). the

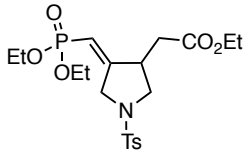
IR υ_{max} = 2960, 1732, 1669, 1637, 1349, 1161, 1093, 1034, 662 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.68 (m, 2H), 7.38 – 7.29 (m, 2H), 6.26 (s, 1H), 4.35 – 4.27 (m, 1H), 4.18 – 4.07 (m, 3H), 3.94 (d, *J* = 8.3 Hz, 1H), 3.65 (d, *J* = 1.7 Hz, 3H), 3.55 – 3.39 (m, 1H), 3.18 (d, *J* = 3.6 Hz, 3H), 3.14 – 2.98 (m, 1H), 2.80 – 2.70 (m, 1H), 2.58 – 2.49 (m, 1H), 2.44 (s, 3H), 1.28 – 1.21 (m, 3H) ppm

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6, 156.9, 143.7, 142.2, 128.7, 127.0, 109.1, 60.7, 59.6, 52.3, 42.7, 28.7, 13.2 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{19}H_{26}N_2O_6S$, 411.1592, requires 411.1584.

Ethyl 2-(4-((diethoxyphosphoryl)methylene)-1-tosylpyrrolidin-3-yl)acetate (188)



Following the general procedure the product was afforded as a colourless oil (9.0 mg, 9%, *dr* 2:1).

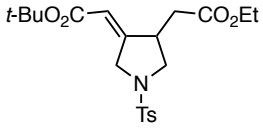
IR υ_{max} = 2982, 1730, 1346, 1244, 1161, 1018, 960, 814, 664 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.58 (m, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 5.41 (d, *J* = 14.2 Hz, 1H), 4.21 – 3.83 (m, 6H), 3.51 – 3.36 (m, 1H), 3.08 (s, 1H), 3.01 – 2.87 (m, 1H), 2.47 (dd, *J* = 16.3, 5.2 Hz, 1H), 2.37 (s, 3H), 1.21 (dt, *J* = 21.6, 7.6 Hz, 10H) ppm

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9, 161.8, 144.0, 132.1, 129.8, 128.0, 77.4, 76.7, 61.9, 61.0, 52.1, 51.6, 41.5, 37.0, 21.6, 16.3, 14.1 ppm

HRMS (ESI) m/z Found: $(M+H)^+$, $C_{20}H_{31}NO_7PS$, 460.1554, requires 460.1553.

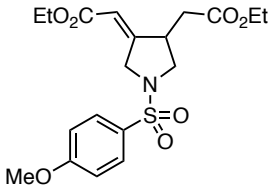
***tert*-Butyl 2-(4-(2-ethoxy-2-oxoethyl)-1-tosylpyrrolidin-3-ylidene)acetate (210)**



This product was synthesized by Luke Darveniza following the general procedure to afford the product as a colourless oil (37.3 mg, 40%, *dr* 1:1). Characterisation was incomplete for this compound.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.70 (m, 2H), 7.36 – 7.31 (m, 2H), 5.62 (dq, *J* = 11.1, 2.3 Hz, 1H), 4.22 (dd, *J* = 2.6, 1.4 Hz, 1H), 4.14 (t, *J* = 7.1 Hz, 2H), 3.73 (dd, *J* = 5.3, 1.9 Hz, 1H), 3.61 – 3.42 (m, 2H), 3.20 – 3.12 (m, 1H), 3.09 – 2.94 (m, 2H), 2.43 (s, 3H), 1.45 (s, 9H), 1.28 – 1.22 (m, 3H) ppm

Ethyl 2-(4-(2-ethoxy-2-oxoethyl)-1-((4-methoxyphenyl)sulfonyl)pyrrolidin-3-ylidene)acetate (227a)



Following the general procedure the product was afforded as a colourless oil (37.5 mg, 71%).

R$_f$ = 0.35 (30% EtOAc/hexanes)

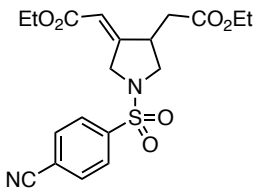
IR υ_{max} = 2980, 1731, 1596, 1498, 1348, 1261, 1160, 1094, 1028, 837, 669 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.63 (m, 2H), 6.94 (dd, *J* = 8.9, 2.0 Hz, 2H), 5.70 – 5.59 (m, 1H), 4.23 – 4.15 (m, 2H), 4.13 – 3.98 (m, 4H), 3.80 (s, 3H), 3.47 – 3.37 (m, 1H), 3.13 (dtd, *J* = 10.6, 5.3, 2.8 Hz, 1H), 2.94 (dd, *J* = 9.6, 6.3 Hz, 1H), 2.49 – 2.33 (m, 2H), 1.19 (td, *J* = 7.1, 3.1 Hz, 6H) ppm

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 164.5, 162.2, 158.7, 129.0, 125.6, 113.3, 112.8, 76.3, 60.0, 59.4, 54.6, 51.4, 51.0, 39.6, 36.1, 13.2, 13.1 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{19}H_{26}NO_7S$, 412.1423, requires 412.1424.

Ethyl 2-(1-((4-cyanophenyl)sulfonyl)-4-(2-ethoxy-2-oxoethyl)pyrrolidin-3-ylidene)acetate (227c)



Following the general procedure the product was afforded as a colourless oil (55.8 mg, 60%).

R$_f$ = 0.33 (30% EtOAc/hexanes)

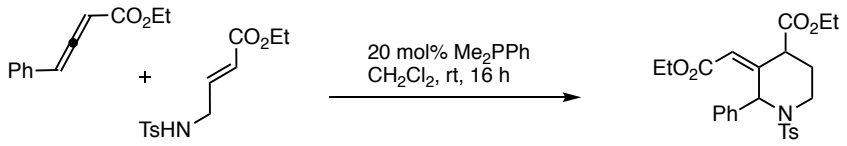
IR υ_{max} = 2926, 2233, 1712, 1353, 1165, 1092, 1033, 804 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 – 7.90 (m, 2H), 7.88 – 7.79 (m, 2H), 5.81 – 5.63 (m, 1H), 4.39 – 4.26 (m, 2H), 4.26 – 3.88 (m, 4H), 3.58 (dd, *J* = 9.6, 7.3 Hz, 1H), 3.26 – 3.17 (m, 1H), 3.06 (dd, *J* = 9.7, 6.5 Hz, 1H), 2.68 – 2.29 (m, 2H), 1.25 (td, *J* = 7.1, 2.6 Hz, 6H) ppm

^{13}C NMR (151 MHz, $CDCl_3$) δ 169.7, 164.4, 157.6, 138.8, 132.0, 127.4, 116.2, 115.8, 113.2, 60.1, 59.5, 51.2, 51.0, 39.5, 35.8, 13.2 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{19}H_{22}N_2O_6S$, 407.1267, requires 407.1271.

Ethyl (*Z*)-3-(2-ethoxy-2-oxoethylidene)-2-phenyl-1-tosylpiperidine-4-carboxylate (234)



Ethyl (*E*)-4-((4-methylphenyl)sulfonamido)but-2-enoate (30 mg, 0.11 mmol, 1 equiv.) was added to a flame dried RBF followed by dry CH_2Cl_2 (2 mL). Ethyl 4-phenylbuta-2,3-dienoate (30 mg, 0.16 mmol, 1.5 equiv.) was then added followed by Me_2PPh (3 mg, 0.02 mmol, 0.2 equiv) and the reaction was stirred at room temperature for 16 hours at which point TLC analysis indicated consumption of the starting material. The reaction was concentrated under reduced pressure and then purified by column chromatography on silica gel (20% EtOAc/hexanes) to yield the product as a clear oil (21 mg, 40%).

R_f 0.21 (20% EtOAc/hexanes)

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.3 Hz, 2H), 7.35 – 7.31 (m, 2H), 7.31 – 7.27 (m, 2H), 7.25 – 7.22 (m, 1H), 7.20 – 7.16 (m, *J* = 7.9 Hz, 1H), 6.56 (dd, *J* = 2.7, 1.5 Hz, 1H), 5.50 (dd, *J* = 2.7, 1.6 Hz, 1H), 4.84 – 4.79 (m, 1H), 4.11 (qd, *J* = 7.1, 1.6 Hz, 2H), 4.04 (q, *J* = 7.1 Hz, 2H), 2.51 (ddd, *J* = 16.3, 9.5, 6.7 Hz, 1H), 2.46 – 2.35 (m, 1H),

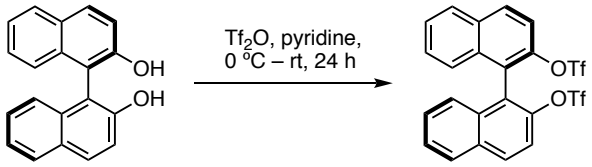
2.34 (s, 3H), 2.25 (dddd, *J* = 14.2, 9.5, 6.7, 3.9 Hz, 1H), 1.87 (dddd, *J* = 14.3, 9.4, 7.4, 5.5 Hz, 1H), 1.18 (t, *J* = 7.1 Hz, 3H) 1.16 (t, *J* = 7.1 Hz, 3H) ppm

^{13}C NMR (151 MHz, $CDCl_3$) δ 174.6, 163.0, 144.0, 139.1, 138.7, 134.9, 134.3, 129.8, 128.7, 128.2, 127.8, 127.2, 69.6, 65.9, 61.1, 60.3, 30.4, 30.3, 21.6, 14.2, 14.1 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{25}H_{30}NO_6S$, 472.1787, requires 472.1788.

4.3.4 Synthesis of phosphepine catalyst 197

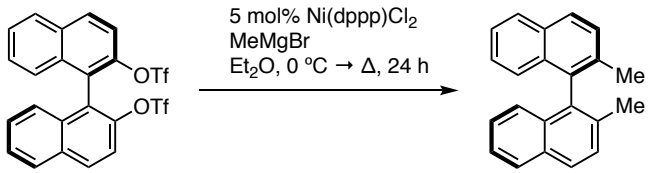
[1,1'-binaphthalene]-2,2'-diyl bis(trifluoromethanesulfonate) (194)



(R)-BINOL (4.04 g, 14.1 mmol, 1.00 equiv) was dissolved in pyridine (4 mL) and the solution was cooled to 0 °C. Triflic anhydride (5.09 mL, 30.3 mmol, 2.15 equiv.) was then added dropwisely over 10 minutes and the solution was allowed to warm to room temperature and stirred overnight. 1 M HCl (30 mL) was added and the solution was then extracted with CH_2Cl_2 (3 x 30 mL). The organic extracts were washed with 1M HCl (3 x 20 mL), then satd. $NaHCO_3$ (2 x 30 mL), brine and then dried with Na_2SO_4, filtered and concentrated under reduced pressure to afford the product as a viscous liquid which solidified upon standing (7.35 g, 95%). The material was deemed to be pure enough and used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 9.1 Hz, 2H), 8.01 (d, *J* = 8.3 Hz, 2H), 7.65 – 7.55 (m, 4H), 7.41 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 2H), 7.29 – 7.22 (m, 2H) ppm

2,2'-dimethyl-1,1'-binaphthalene (195)

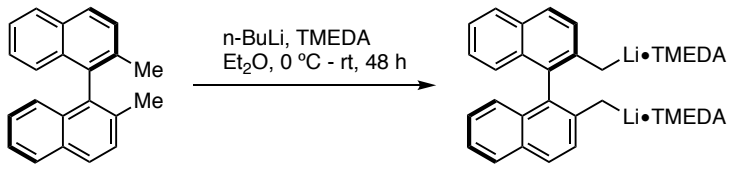


This compound was prepared according to a literature procedure.[14] A solution of [1,1'-binaphthalene]-2,2'-diyl bis(trifluoromethanesulfonate) (6.00 g, 10.9 mmol, 1 equiv.) and $Ni(dppp)Cl_2$ (295 mg, 0.54 mmol, 0.05 equiv.) in dry Et_2O (35 mL) under N_2 was cooled to 0 °C and then MeMgBr solution (7.99 mL, 3 M in Et_2O, 2.2 equiv.) was added dropwisely. The reaction was allowed to warm to room temperature and then heated to reflux and stirred for a further 24 h. The reaction was quenched by the addition of H_2O (20 mL), extracted with Et_2O (2 x 20 mL), washed with brine (20 mL), dried with $MgSO_4$, filtered, concentrated and then purified via column chromatography on silica gel (hexanes) to afford the product as a white crystalline solid (2.56 g, 83%).

$\mathbf{R_f}$ = 0.70 (hexanes)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 9.0 Hz, 2H). 8.02 (d, *J* = 9.0 Hz, 2H), 7.64 – 7.56 (m, 4H), 7.40 (t, *J* = 9.0 Hz, 2H), 7.24 (d, *J* = 9.0 Hz, 2H), 1.53 (s, 6H) ppm

Lithium-TMEDA complex (196)

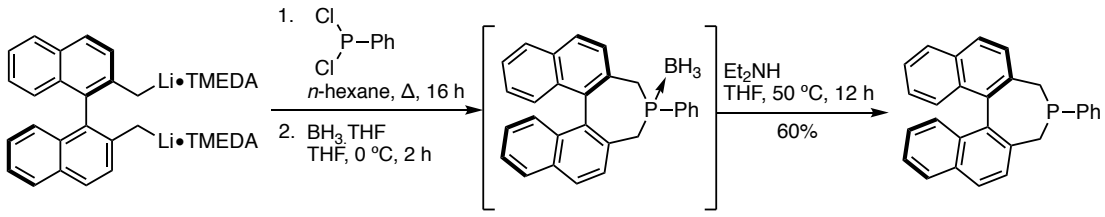


This compound was prepared according to the literature procedure.[14] *n*-BuLi solution (30 mL, 49.1 mol, 1.6 M in hexanes) was added to a flame dried Schlenk flask under N_2 and the solvent was removed using a vacuum pump. The remaining residue was dissolved in dry Et_2O (20 mL) and cooled to 0 °C. A solution of *(R)*-2,2′-dimethyl-1,1′-binaphthyl (5.34 g, 18.9 mmol) in dry Et_2O (40 mL) was added dropwisely over 45 minutes at which

point the reaction became red colour. Once the addition was complete, TMEDA (7.36 mL, 49.1 mmol) was added slowly and the reaction was then stirred for 48 h and allowed to warm to room temperature to yield a fine deep red suspension. The solid was allowed to settle and the supernatant was decanted using a syringe, and then washed twice with dry *n*-hexane (2 x 5 mL). The solid was then dried under vacuum and stored in a glovebox under argon (6.32 g, 66%). The complex was observed to be very sensitive to air and moisture, and even momentary exposure to air resulted in a change to a white solid. As a result of this, all manipulations and reactions of this complex must be performed under a dry and inert atmosphere. The complex was observed to be stable when stored in a glovebox over a period of six months.

^{1}H NMR (600 MHz, C_6D_6) δ 7.54 (dd, *J* = 7.7, 1.4 Hz, 2H), 7.36 (d, *J* = 8.8 Hz, 2H), 7.14 (d, *J* = 8.8 Hz, 2H), 7.10 – 7.06 (m, 2H), 6.94 (ddd, *J* = 8.3, 6.6, 1.5 Hz, 2H), 6.71 (ddd, *J* = 7.8, 6.7, 1.2 Hz, 2H), 2.27 – 1.08 (alkyl protons, multiplet too broad) ppm

4-Phenyl-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]phosphepine (192)



This was prepared according to a literature procedure.[15] A flame dried Schlenk flask was charged with dilithium complex **196** (1.03 g, 1.96 mmol, 1 equiv.) in a glovebox under argon. The flask was then connected to a Schlenk line and all further manipulations were conducted with a Schlenk line using air-free technique. Dry *n*-hexane was added (30 mL) followed by a solution of dichlorophenylphosphine (0.32 mL, 2.35 mmol, 1.2 equiv.) in dry *n*-hexane (30 mL). The solution was brought to reflux and stirred for a further 16 hours. A mixture of toluene/degassed H_2O (20 mL) was added, the layers were separated

and the organic phase was dried with Na_2SO_4 and filtered via filter-cannula. The solvent was removed via a high vacuum pump and the residue was dissolved in THF (25 mL), cooled to 0 °C, and then Borane-THF complex was added (2.35 mL, 1.0 M in THF, 1.2 equiv.). The reaction was stirred for a further 2 hours and quenched via the addition of H_2O and then extracted with toluene (3 x 20 mL). The organic extracts were washed with brine (20 mL), dried with Na_2SO_4 and then concentrated to afford the adduct as a white solid which was purified via column chromatography on silica gel (CH_2Cl_2/hexanes) and then used directly in the next step.

Phosphine-BH_3 adduct **198** was added to a flame dried Schlenk flask under N_2 and then dissolved in dry and degassed THF (25 mL). Freshly distilled and degassed Et_2NH (25 mL) was then added dropwisely and the reaction was heated to 50 °C and stirred at this temperature for 12 h. The reaction was allowed to cool to room temperature and the solvent was removed under reduced pressure. Degassed and dried MeOH (20 mL) was then added and the suspension was sonicated for 10 minutes, filtered and the residue was then recrystallised from dry and degassed toluene/pentane to afford the product as a white solid (448 mg, 60% over 2 steps).

^{1}H NMR (600 MHz, C_6D_6) δ 7.96 – 7.84 (m, 2H), 7.68 (ddd, *J* = 24.1, 8.4, 1.0 Hz, 2H), 7.42 (d, *J* = 27.8 Hz, 2H), 7.31 – 7.21 (m, 10H), 6.90 (d, *J* = 8.4 Hz, 1H), 3.00 (dd, *J* = 16.7, 11.7 Hz, 1H), 2.94 – 2.81 (m, 2H), 2.74 (dd, *J* = 14.4, 4.6 Hz, 1H) ppm

^{31}P NMR (202 MHz, C_6D_6) δ 6.42 ppm

4.4 References

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Appendix 1

X-ray crystal structure of isoquinolinone 100

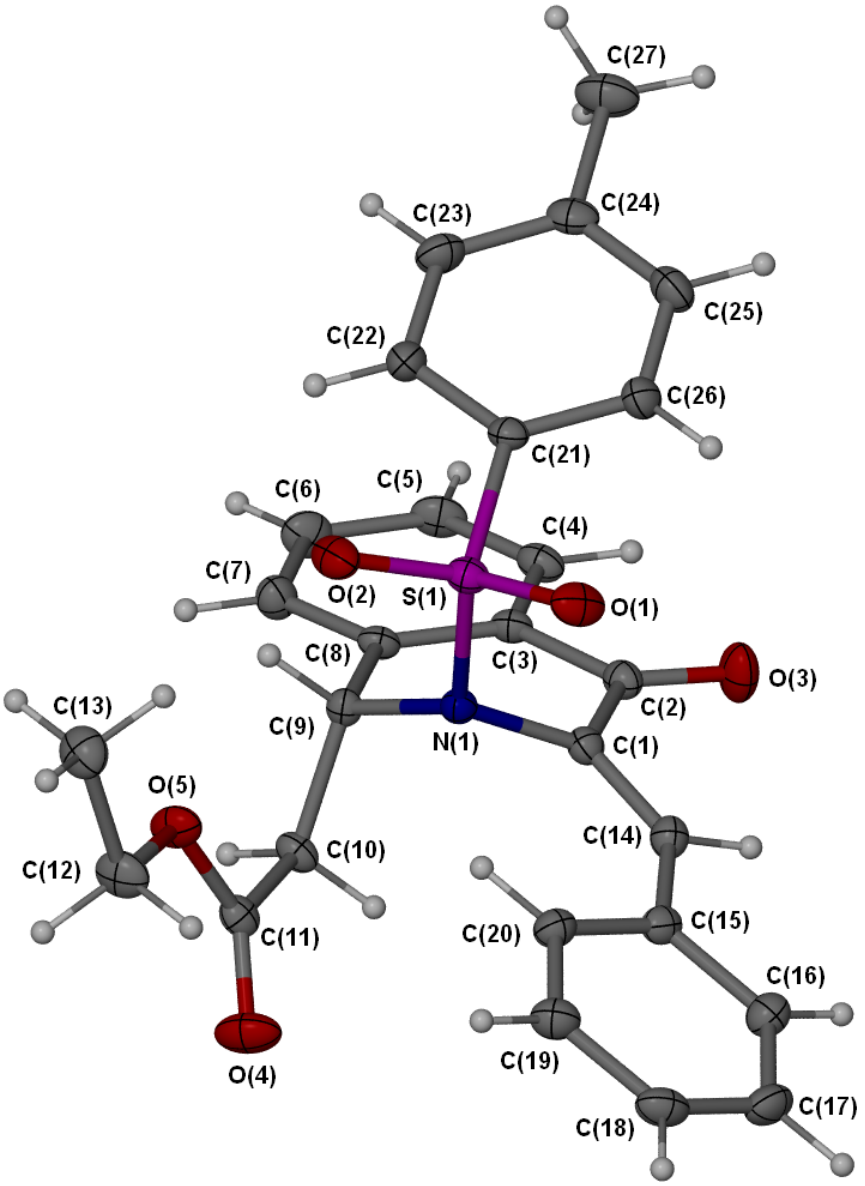

Figure 1. Molecular diagram of $C_{27}H_{25}NO_5S$ with non-hydrogen atoms represented by 50% thermal ellipsoids and hydrogen atoms as spheres of arbitrary size.

Table 1. Crystal data and structure refinement for mx10_16.

Identification code	shelx
Empirical formula	C27 H25 N O5 S
Formula weight	475.54
Temperature	123(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P2(1)/n
Unit cell dimensions	a = 10.6859(10) A alpha = 90 deg. b = 13.7251(15) A beta = 93.143(6) deg. c = 15.4139(13) A gamma = 90 deg.
Volume	2257.3(4) A^3
Z, Calculated density	4, 1.399 Mg/m^3
Absorption coefficient	0.184 mm^-1
F(000)	1000
Crystal size	0.25 x 0.25 x 0.25 mm
Theta range for data collection	2.382 to 27.999 deg.
Limiting indices	-14<=h<=14, -15<=k<=18, -20<=l<=17
Reflections collected / unique	14049 / 5396 [R(int) = 0.0456]
Completeness to theta = 25.242	99.2 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7461 and 0.6988
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5396 / 0 / 308
Goodness-of-fit on F^2	1.040
Final R indices [I>2sigma(I)]	R1 = 0.0428, wR2 = 0.0995
R indices (all data)	R1 = 0.0622, wR2 = 0.1116

Extinction coefficient	n/a
Largest diff. peak and hole	0.326 and -0.416 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for mx10_16. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
S(1)	3171(1)	1432(1)	846(1)	19(1)
O(1)	2562(1)	1409(1)	4(1)	27(1)
O(2)	2720(1)	858(1)	1532(1)	26(1)
O(3)	5228(1)	3917(1)	-91(1)	32(1)
O(4)	510(1)	3813(1)	2488(1)	34(1)
O(5)	1318(1)	2337(1)	2747(1)	25(1)
N(1)	3077(1)	2592(1)	1165(1)	16(1)
C(1)	3413(2)	3294(1)	524(1)	17(1)
C(2)	4760(2)	3579(1)	544(1)	19(1)
C(3)	5485(2)	3445(1)	1377(1)	18(1)
C(4)	6752(2)	3694(1)	1432(1)	22(1)
C(5)	7440(2)	3613(1)	2208(1)	26(1)
C(6)	6869(2)	3295(2)	2940(1)	27(1)
C(7)	5613(2)	3049(1)	2897(1)	23(1)
C(8)	4916(2)	3114(1)	2110(1)	17(1)
C(9)	3553(1)	2811(1)	2064(1)	16(1)
C(10)	2722(2)	3593(1)	2443(1)	20(1)
C(11)	1390(2)	3275(1)	2553(1)	19(1)
C(12)	76(2)	1928(1)	2822(1)	27(1)
C(13)	218(2)	843(1)	2846(1)	29(1)
C(14)	2613(2)	3710(1)	-66(1)	20(1)

	C(15)	1258(2)	3648(1)	-233(1) 19(1)
	C(16)	731(2)	4242(1)	-892(1) 24(1)
	C(17)	-552(2)	4252(2)	-1087(1) 28(1)
	C(18)	-1329(2)	3674(1)	-624(1) 27(1)
	C(19)	-821(2)	3082(1)	35(1) 25(1)
	C(20)	458(2)	3062(1)	227(1) 21(1)
	C(21)	4764(2)	1168(1)	750(1) 18(1)
	C(22)	5484(2)	863(1)	1478(1) 24(1)
	C(23)	6751(2)	701(1)	1402(1) 27(1)
	C(24)	7304(2)	822(1)	619(1) 24(1)
	C(25)	6559(2)	1117(1)	-97(1) 27(1)
	C(26)	5292(2)	1294(1)	-39(1) 23(1)
	C(27)	8676(2)	600(2)	543(2) 34(1)

Table 3. Bond lengths [A] and angles [deg] for mx10_16.

S(1)-O(1)	1.4204(13)
S(1)-O(2)	1.4235(13)
S(1)-N(1)	1.6710(14)
S(1)-C(21)	1.7541(17)
O(3)-C(2)	1.215(2)
O(4)-C(11)	1.195(2)
O(5)-C(11)	1.326(2)
O(5)-C(12)	1.451(2)
N(1)-C(1)	1.440(2)
N(1)-C(9)	1.480(2)
C(1)-C(14)	1.341(2)
C(1)-C(2)	1.490(2)
C(2)-C(3)	1.475(2)
C(3)-C(8)	1.389(2)
C(3)-C(4)	1.395(2)
C(4)-C(5)	1.374(3)
C(5)-C(6)	1.383(3)
C(6)-C(7)	1.381(2)
C(7)-C(8)	1.390(2)
C(8)-C(9)	1.512(2)
C(9)-C(10)	1.529(2)
C(10)-C(11)	1.508(2)
C(12)-C(13)	1.497(3)
C(14)-C(15)	1.460(2)
C(15)-C(20)	1.395(2)
C(15)-C(16)	1.397(2)
C(16)-C(17)	1.388(2)
C(17)-C(18)	1.375(3)
C(18)-C(19)	1.388(3)
C(19)-C(20)	1.382(2)
C(21)-C(26)	1.379(2)
C(21)-C(22)	1.390(2)
C(22)-C(23)	1.383(2)
C(23)-C(24)	1.382(3)
C(24)-C(25)	1.386(3)
C(24)-C(27)	1.509(2)
C(25)-C(26)	1.382(3)

O(1)-S(1)-O(2)	120.61(8)
O(1)-S(1)-N(1)	104.98(7)
O(2)-S(1)-N(1)	106.35(7)
O(1)-S(1)-C(21)	108.40(8)
O(2)-S(1)-C(21)	108.54(8)
N(1)-S(1)-C(21)	107.22(7)
C(11)-O(5)-C(12)	117.26(13)
C(1)-N(1)-C(9)	114.95(13)
C(1)-N(1)-S(1)	114.45(11)
C(9)-N(1)-S(1)	116.45(11)
C(14)-C(1)-N(1)	125.22(15)
C(14)-C(1)-C(2)	118.78(15)
N(1)-C(1)-C(2)	116.00(14)
O(3)-C(2)-C(3)	121.94(15)

O(3)-C(2)-C(1)	121.56(16)
C(3)-C(2)-C(1)	116.50(14)
C(8)-C(3)-C(4)	119.91(16)
C(8)-C(3)-C(2)	121.12(14)
C(4)-C(3)-C(2)	118.93(16)
C(5)-C(4)-C(3)	120.24(17)
C(4)-C(5)-C(6)	119.81(16)
C(7)-C(6)-C(5)	120.55(17)
C(6)-C(7)-C(8)	120.00(17)
C(3)-C(8)-C(7)	119.47(15)
C(3)-C(8)-C(9)	121.02(14)
C(7)-C(8)-C(9)	119.51(15)
N(1)-C(9)-C(8)	112.32(13)
N(1)-C(9)-C(10)	108.89(13)
C(8)-C(9)-C(10)	111.51(13)
C(11)-C(10)-C(9)	114.29(14)
O(4)-C(11)-O(5)	124.37(16)
O(4)-C(11)-C(10)	123.72(17)
O(5)-C(11)-C(10)	111.90(14)
O(5)-C(12)-C(13)	107.15(15)
C(1)-C(14)-C(15)	133.21(17)
C(20)-C(15)-C(16)	118.17(16)
C(20)-C(15)-C(14)	125.01(16)
C(16)-C(15)-C(14)	116.80(16)
C(17)-C(16)-C(15)	121.14(17)
C(18)-C(17)-C(16)	119.94(17)
C(17)-C(18)-C(19)	119.66(17)
C(20)-C(19)-C(18)	120.66(18)
C(19)-C(20)-C(15)	120.42(16)
C(26)-C(21)-C(22)	120.90(16)
C(26)-C(21)-S(1)	119.71(13)
C(22)-C(21)-S(1)	119.36(13)
C(23)-C(22)-C(21)	118.78(17)
C(24)-C(23)-C(22)	121.46(17)
C(23)-C(24)-C(25)	118.40(17)
C(23)-C(24)-C(27)	120.53(17)
C(25)-C(24)-C(27)	121.03(18)
C(26)-C(25)-C(24)	121.43(18)
C(21)-C(26)-C(25)	119.03(17)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for mx10_16.
The anisotropic displacement factor exponent takes the form:
-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
S(1)	18(1)	16(1)	22(1)	-2(1)	2(1)	0(1)
O(1)	25(1)	26(1)	28(1)	-10(1)	-5(1)	1(1)
O(2)	28(1)	18(1)	34(1)	1(1)	10(1)	-2(1)
O(3)	26(1)	45(1)	25(1)	9(1)	6(1)	-7(1)
O(4)	18(1)	25(1)	58(1)	0(1)	4(1)	2(1)
O(5)	15(1)	24(1)	37(1)	3(1)	6(1)	-2(1)
N(1)	16(1)	14(1)	17(1)	0(1)	1(1)	0(1)
C(1)	18(1)	17(1)	17(1)	-1(1)	2(1)	-1(1)
C(2)	19(1)	18(1)	22(1)	0(1)	5(1)	-1(1)
C(3)	14(1)	16(1)	22(1)	-1(1)	2(1)	1(1)
C(4)	17(1)	20(1)	29(1)	-3(1)	6(1)	-1(1)
C(5)	12(1)	28(1)	37(1)	-5(1)	-1(1)	-1(1)
C(6)	19(1)	35(1)	28(1)	-4(1)	-6(1)	1(1)
C(7)	20(1)	28(1)	21(1)	0(1)	0(1)	1(1)
C(8)	13(1)	17(1)	21(1)	-3(1)	1(1)	1(1)
C(9)	14(1)	18(1)	16(1)	1(1)	0(1)	-2(1)
C(10)	16(1)	22(1)	22(1)	-4(1)	5(1)	-2(1)
C(11)	18(1)	22(1)	18(1)	-4(1)	1(1)	-2(1)
C(12)	17(1)	27(1)	39(1)	-1(1)	8(1)	-5(1)
C(13)	30(1)	25(1)	32(1)	1(1)	7(1)	-7(1)
C(14)	22(1)	20(1)	19(1)	1(1)	2(1)	-2(1)

```
    C(15)    21(1)      20(1)      18(1)      -2(1)      -2(1)
2(1)
    C(16)    26(1)      22(1)      25(1)       2(1)       0(1)
0(1)
    C(17)    29(1)      28(1)      26(1)       2(1)      -5(1)
9(1)
    C(18)    20(1)      29(1)      31(1)      -6(1)      -2(1)
6(1)
    C(19)    21(1)      24(1)      30(1)      -1(1)       2(1)
2(1)
    C(20)    21(1)      21(1)      23(1)       1(1)      -1(1)
3(1)
    C(21)    18(1)      15(1)      21(1)      -1(1)       3(1)
2(1)
    C(22)    27(1)      24(1)      21(1)       2(1)       3(1)
6(1)
    C(23)    24(1)      27(1)      29(1)       2(1)      -3(1)
6(1)
    C(24)    22(1)      16(1)      34(1)      -4(1)       3(1)
1(1)
    C(25)    26(1)      29(1)      25(1)      -2(1)       9(1)
1(1)
    C(26)    24(1)      26(1)      18(1)      -1(1)       2(1)
3(1)
    C(27)    21(1)      30(1)      52(1)      -4(1)       6(1)
2(1)
```

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for mx10_16.

	x	y	z	U(eq)
H(4)	7141	3920	930	26
H(5)	8306	3775	2242	31
H(6)	7344	3245	3478	33
H(7)	5227	2837	3404	28
H(9)	3477	2206	2418	19
H(10A)	3099	3793	3017	24
H(10B)	2713	4171	2059	24
H(12A)	-482	2125	2319	33
H(12B)	-290	2162	3360	33
H(13A)	-606	540	2896	43
H(13B)	580	620	2310	43
H(13C)	772	657	3346	43
H(14)	3010	4133	-454	24
H(16)	1260	4646	-1213	29
H(17)	-894	4658	-1540	33
H(18)	-2208	3680	-755	32
H(19)	-1358	2686	358	30
H(20)	793	2647	675	26
H(22)	5113	768	2018	29
H(23)	7252	502	1899	32
H(25)	6926	1200	-639	32
H(26)	4794	1498	-535	27
H(27A)	9181	1071	889	51

	H(27B)	8883	646	-67
51				
	H(27C)	8856	-60	758
51				

X-ray crystal structure of pyrrolidine 177

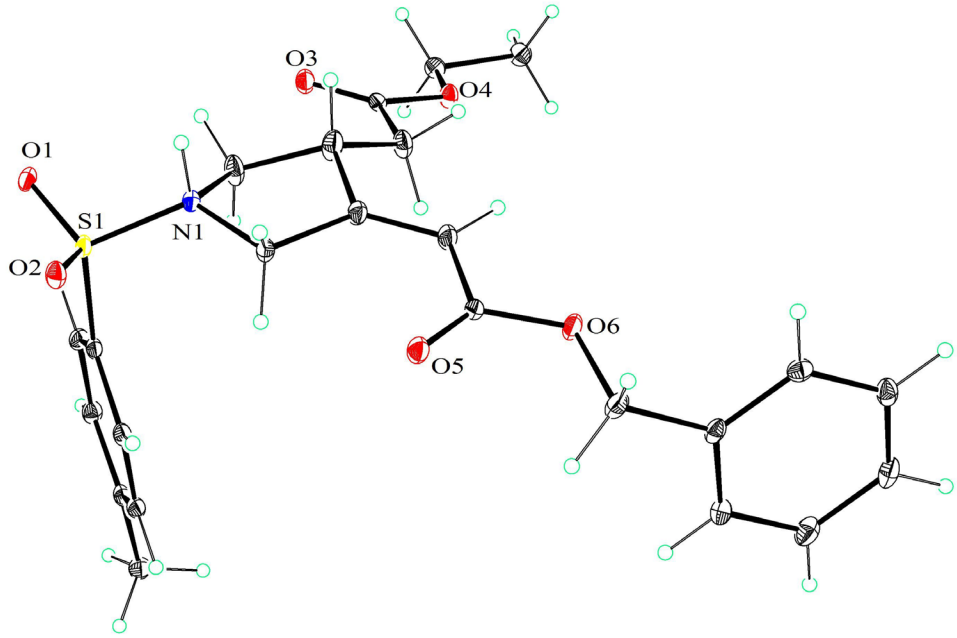

Table 1 Crystal data and structure refinement for CDJH1.

Identification code	CDJH1
Empirical formula	$C_{24}H_{28}NO_6S$
Formula weight	458.53
Temperature/K	123
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	12.1392(8)
b/Å	8.5856(6)

c/Å	20.8757(15)
α/°	90.00
β/°	95.013(3)
γ/°	90.00
Volume/$Å^3$	2167.4(3)
Z	4
$\rho_{calc}g/cm^3$	1.405
μ/mm^{-1}	0.192
F(000)	972.0
Crystal size/mm^3	0.1 × 0.1 × 0.03
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.94 to 51.7
Index ranges	-14 ≤ h ≤ 14, -10 ≤ k ≤ 10, -25 ≤ l ≤ 25
Reflections collected	27511
Independent reflections	4184 [R_{int} = 0.0317, R_{sigma} = 0.0225]
Data/restraints/parameters	4184/0/291
Goodness-of-fit on F^2	1.047
Final R indexes [I>=2σ (I)]	R_1 = 0.0429, wR_2 = 0.1065
Final R indexes [all data]	R_1 = 0.0506, wR_2 = 0.1121
Largest diff. peak/hole / e $Å^{-3}$	1.05/-0.73

Table 2 Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for CDJH1. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	**U(eq)**
S1	1736.9(4)	6724.8(6)	3834.4(2)	21.09(14)
O1	1541.1(11)	6389.7(18)	3164.8(7)	26.6(3)
O2	1155.2(11)	7963.7(17)	4109.2(7)	26.7(3)
O4	7152.4(11)	3985.0(17)	3676.2(7)	26.0(3)
O3	5514.7(12)	4270.8(19)	3107.3(7)	29.3(4)
O5	4238.4(12)	9019.7(19)	5835.3(7)	28.9(3)
O6	6028.9(12)	8551.2(19)	6139.9(7)	29.6(4)
N1	3045.1(13)	7161(2)	3963.4(8)	21.6(4)
C18	1534.2(15)	5010(2)	4267.0(9)	21.2(4)
C19	1375.4(15)	5086(2)	4916.8(9)	22.3(4)
C12	6901.5(17)	8548(2)	7196.2(9)	22.9(4)
C4	3451.7(16)	7777(2)	4598.6(9)	22.0(4)
C21	1365.3(15)	2280(3)	4965(1)	22.9(4)
C20	1297.0(16)	3721(3)	5258.5(10)	23.9(4)
C6	6148.8(16)	4602(2)	3558.4(9)	22.0(4)
C10	5127.5(16)	8533(2)	5721.4(9)	22.0(4)
C22	1494.2(17)	2237(3)	4309.7(10)	25.4(4)
C23	1586.3(16)	3586(3)	3960.8(10)	24.3(4)

C17	7908.6(17)	9299(3)	7187.9(10)	25.8(4)
C9	5405.9(17)	7829(3)	5116.8(10)	27.6(5)
C7	7465.9(17)	2770(3)	3246.6(10)	25.5(4)
C16	8836.8(17)	8743(3)	7549.6(10)	28.6(5)
C24	1333.3(18)	802(3)	5344.1(10)	28.2(5)
C13	6828.4(18)	7239(3)	7573.7(10)	27.8(5)
C3	4667.5(16)	7488(3)	4627.9(10)	25.4(4)
C8	8668.8(18)	2455(3)	3420.6(11)	31.3(5)
C1	3859.3(17)	6058(3)	3740.9(12)	34.3(5)
C11	5906.6(18)	9116(3)	6786.5(9)	28.2(5)
C5	5936.4(17)	5704(3)	4088.9(11)	31.4(5)
C15	8759.6(18)	7430(3)	7922.0(11)	31.7(5)
C14	7757(2)	6686(3)	7936.5(11)	33.6(5)
C2	4940.6(19)	6721(3)	4007.6(11)	36.2(6)

Table 3 Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for CDJH1. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	**U_{11}**	**U_{22}**	**U_{33}**	**U_{23}**	**U_{13}**	**U_{12}**
S1	14.2(2)	27.9(3)	20.4(3)	-0.58(19)	-2.90(17)	2.85(19)
O1	21.4(7)	37.8(9)	19.3(7)	1.2(6)	-5.3(6)	2.3(6)
O2	19.0(7)	30.4(8)	30.1(8)	-1.4(6)	-1.6(6)	5.7(6)
O4	19.4(7)	30.5(8)	27.5(8)	-3.3(6)	-1.1(6)	5.5(6)

O3	20.4(7)	40.1(9)	26.8(8)	-3.6(7)	-1.3(6)	0.8(6)
O5	21.4(7)	39.8(9)	24.9(8)	-0.5(7)	-1.3(6)	4.7(6)
O6	19.7(7)	50.4(10)	17.8(7)	-4.1(7)	-3.3(6)	4.8(7)
N1	16.1(8)	28.7(9)	19.6(8)	1.1(7)	-1.1(6)	0.8(7)
C18	12.7(9)	29.1(11)	21.4(10)	-0.9(8)	-1.1(7)	0.9(8)
C19	15.5(9)	28.8(11)	22.6(10)	-6.0(8)	1.0(7)	0.6(8)
C12	23.4(10)	28.6(11)	16.1(9)	-6.1(8)	-1.4(8)	4.6(8)
C4	17.6(9)	26.5(10)	21.4(10)	-1.8(8)	-2.6(7)	0.2(8)
C21	13.4(9)	32.0(11)	23(1)	-1.5(8)	-0.2(7)	0.9(8)
C20	16.6(9)	34.8(12)	20.3(10)	-3.4(8)	1.8(8)	-0.2(8)
C6	15.5(9)	26.8(11)	23.7(10)	4.9(8)	2.2(8)	-1.5(8)
C10	18.4(10)	26.4(11)	20.5(10)	5.5(8)	-1.8(8)	-3.0(8)
C22	22.9(10)	29.0(11)	24(1)	-6.2(9)	0.3(8)	0.9(8)
C23	21.7(10)	32.9(12)	17.9(10)	-4.8(8)	0.5(8)	0.3(8)
C17	29.7(11)	28.4(11)	19.8(10)	-3.7(8)	5.0(8)	0.9(9)
C9	16.6(9)	41.3(13)	24.6(11)	-1.1(9)	-0.9(8)	2.8(9)
C7	24(1)	26.3(11)	26.5(11)	-1.0(9)	4.1(8)	2.3(8)
C16	21.5(10)	37.4(12)	26.9(11)	-13.1(9)	1.2(8)	-1.1(9)
C24	27.4(11)	31.1(12)	26.1(11)	-1.2(9)	2.8(8)	0.7(9)
C13	27.0(11)	31.0(12)	24.4(11)	-3.5(9)	-3.1(8)	-3.5(9)
C3	18.5(10)	33.5(12)	23.6(10)	1.3(9)	-1.1(8)	4.2(8)
C8	26.0(11)	36.2(13)	31.9(12)	-0.8(10)	4.2(9)	6.8(9)

C1	17.9(10)	49.5(14)	35.0(12)	-15.5(11)	0.0(9)	4.9(10)
C11	27.2(11)	39.2(13)	17.5(10)	-3.7(9)	-1.8(8)	8.2(9)
C5	18.8(10)	40.1(13)	34.6(12)	-7.7(10)	-1.2(9)	3.6(9)
C15	27.6(11)	38.6(13)	26.9(11)	-7.8(10)	-9.4(9)	7.4(10)
C14	40.9(13)	29.2(12)	28.5(12)	3.1(9)	-8.5(10)	0.7(10)
C2	24.9(11)	52.4(15)	30.2(12)	-9.0(11)	-4.0(9)	9(1)

Table 4 Bond Lengths for CDJH1.

Atom	**Atom**	**Length/Å**	**Atom**	**Atom**	**Length/Å**
S1	O1	1.4267(15)	C12	C11	1.499(3)
S1	O2	1.4248(15)	C4	C3	1.492(3)
S1	N1	1.6309(16)	C21	C20	1.386(3)
S1	C18	1.756(2)	C21	C22	1.391(3)
O4	C6	1.332(2)	C21	C24	1.498(3)
O4	C7	1.448(2)	C6	C5	1.496(3)
O3	C6	1.197(2)	C10	C9	1.466(3)
O5	C10	1.200(2)	C22	C23	1.378(3)
O6	C10	1.339(2)	C17	C16	1.385(3)
O6	C11	1.454(2)	C9	C3	1.331(3)
N1	C4	1.472(2)	C7	C8	1.498(3)
N1	C1	1.473(3)	C16	C15	1.377(3)

C18	C19	1.388(3)	C13	C14	1.386(3)
C18	C23	1.384(3)	C3	C2	1.515(3)
C19	C20	1.380(3)	C1	C2	1.493(3)
C12	C17	1.383(3)	C5	C2	1.489(3)
C12	C13	1.380(3)	C15	C14	1.377(3)

Table 5 Bond Angles for CDJH1.

Atom	**Atom**	**Atom**	**Angle/°**	**Atom**	**Atom**	**Atom**	**Angle/°**
O1	S1	N1	106.54(9)	O3	C6	O4	124.45(19)
O1	S1	C18	108.43(9)	O3	C6	C5	126.30(18)
O2	S1	O1	119.94(9)	O5	C10	O6	124.35(19)
O2	S1	N1	105.76(9)	O5	C10	C9	126.39(18)
O2	S1	C18	108.80(9)	O6	C10	C9	109.26(17)
N1	S1	C18	106.61(9)	C23	C22	C21	121.3(2)
C6	O4	C7	117.25(16)	C22	C23	C18	119.29(19)
C10	O6	C11	117.74(16)	C12	C17	C16	120.7(2)
C4	N1	S1	118.44(13)	C3	C9	C10	124.10(19)
C4	N1	C1	109.48(15)	O4	C7	C8	106.45(17)
C1	N1	S1	118.08(14)	C15	C16	C17	119.8(2)
C19	C18	S1	120.05(16)	C12	C13	C14	120.1(2)
C23	C18	S1	119.30(15)	C4	C3	C2	109.06(17)

C23	C18	C19	120.58(19)	C9	C3	C4	126.34(19)
C20	C19	C18	119.13(19)	C9	C3	C2	124.60(19)
C17	C12	C11	120.7(2)	N1	C1	C2	103.30(18)
C13	C12	C17	119.17(19)	O6	C11	C12	106.18(16)
C13	C12	C11	120.13(19)	C2	C5	C6	118.50(18)
N1	C4	C3	103.30(16)	C14	C15	C16	119.7(2)
C20	C21	C22	118.3(2)	C15	C14	C13	120.5(2)
C20	C21	C24	121.15(18)	C1	C2	C3	103.50(18)
C22	C21	C24	120.49(19)	C5	C2	C3	113.19(19)
C19	C20	C21	121.34(19)	C5	C2	C1	119.9(2)
O4	C6	C5	109.20(17)				

Table 6 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for CDJH1.

Atom	*x*	*y*	*z*	**U(eq)**
H1	3114	8015	3695	26
H19	1321	6066	5124	27
H4A	3115	7216	4947	26
H4B	3290	8903	4631	26
H20	1194	3769	5704	29
H22	1519	1259	4099	30
H23	1685	3538	3515	29

H17	7964	10204	6931	31
H9	6161	7601	5071	33
H7A	7342	3116	2794	31
H7B	7024	1818	3301	31
H16	9525	9267	7541	34
H24A	2062	611	5571	42
H24B	1137	-68	5052	42
H24C	780	895	5657	42
H13	6141	6716	7585	33
H8A	8924	1648	3136	47
H8B	8777	2099	3868	47
H8C	9093	3412	3371	47
H1A	3813	6014	3265	41
H1B	3747	4999	3911	41
H11A	5221	8702	6946	34
H11B	5874	10268	6791	34
H5A	5887	5082	4485	38
H5B	6592	6387	4164	38
H15	9395	7039	8168	38
H14	7702	5787	8197	40
H2	5121	7581	3711	43

Appendix 2

Publication from thesis

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Phosphine catalysed (5 + 1) annulation of ynone/cinnamates with primary amines†

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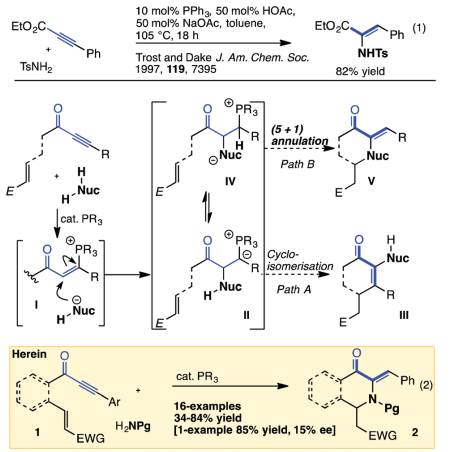
The (5 + 1) annulation of ynone/cinnamates and related substrates with protected primary amines gives rise to isoquinolones, pyrrolidinones and pyrrolopiperazines in good to excellent yields under phosphine catalysis. The reaction is viable with chiral phosphines, although the selectivity is poor.

Phosphine addition to ynoates and allenoates enables a host of cycloisomerisation, cycloaddition, and coupling reactions.[1–5] Substrates bearing γ-protons typically react with enhanced γ-nucleophilicity and α-electrophilicity,[6,7] while Trost observed that substrates lacking γ-protons undergo α-amination *via* a formal α-umpolung reaction (eqn (1)).[8] While the latter chemistry represents an early contribution to the field of phosphine organocatalysis, its use in more complex reaction designs has received modest attention.[2g] Mechanistically, the α-amination reaction likely occurs by phosphine 1,4-addition and pro-nucleophile deprotonation to yield β-phosphonium **I**. Nucleophilic attack on phosphonium **I** then provides a β-phosphonium ylide **II** (Scheme 1). As part of our interest in reaction discovery *via* umpolung events β to the carbonyl,[9] we saw in this sequence an opportunity for the development of new reaction cascades. Specifically, could cyclisation of ylide **II** to a tethered Michael acceptor be developed to yield, after elimination of the catalyst, cycloalkanone **III**, or would proton transfer generate intermediate **IV**, which could cyclise in a (5 + 1) annulation to eventually provide **V**? Either scenario would involve reaction development *via* underdeveloped reactive intermediates and deliver complex materials, potentially with enantioselectivity. During the course of studies on this concept the viability of the former scenario (*i.e.* Path A **II** → **III**) was supported by studies from Sasai who found that phosphonium ylides analogous to **II** (although formed by γ-functionalisation) could engage in Michael additions to give (3 + 2) annulated materials.[10]



Scheme 1 Background and reaction design.

Herein, we report our studies on this topic that have led to the discovery of a (5 + 1) annulation of ynone/Michael acceptors (*i.e.* **1**) with primary amines (eqn (2)). In addition to providing access to a range of dihydroisoquinolones (**2**), privileged heterocycles in medicinal chemistry,[11] related pyrrolidinones and pyrrolopiperazines can be prepared (*vide infra*). The enantioselective variant is viable although the selectivity is poor.

Reaction discovery commenced with a survey of pro-nucleophiles suited to the α-amination of ynoates in the presence of 20 mol% phenyldimethyl phosphine.[8] Although phthalimide, Boc-amine and (phenylsulfonyl)acetonitrile provided the Michael adducts **3** (Table 1, entries 1–3), $TsNH_2$ gave materials consistent with our design, specifically dihydroisoquinolone **2a** in 72% yield (Table 1, entry 4).

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