Cycloaddition Chemistry of Allenamides

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Abstract

Allenamides are electron deficient allenamine equivalents that can participate in a range of cycloaddition events giving rise to novel heterocycles and diverse molecular architectures contained within natural products. This review summarizes some of the recent research in this area, with particular reference to predicting the stereochemical outcomes of such transformations and highlighting recent applications of allenamides in cycloaddition transformations which showcase the utility of this under-utilized synthon.

Keywords

Abbreviations

PPTS p-toluenesulfonic acid, **CSA** camphor sulfonic acid, **DMDO** dimethyl dioxirane, **PKR** Pauson Khand reaction, **RCM** ring closing metathesis, **THF** tetrahydrofuran, *dr* diastereomeric ratio, *de* diastereomeric excess

Introduction

Allenamides represent a fascinating and versatile functional group whose chemical utility has been exploited by a number of groups [1]. The chemistry in which the allenamide subunit has participated is varied and includes amongst other things radical cyclizations [2], acid catalyzed cyclizations [3,4], palladium mediated transformations [5-7], base catalyzed CO_2 capture [8], base catalyzed heterocyclizations [9], gold mediated transformations [10-14] and ruthenium-catalysed aminoallylations [15,16]. This review will cover recent advances in the use and applications of allenamides in cycloaddition transformations. Many of the transformations in this review give rise to structurally diverse heterocycles as well as complex molecular architectures reminiscent of natural products and biologically relevant substrates, all from relatively simple precursors. Since there now exists numerous robust methods for the synthesis of achiral and significantly chiral allenamides[17-22] many of these cycloaddition reactions can now be rendered stereoselective. Cycloadditions involving allenamides can be divided into two areas; cycloadditions directly involving the allenamide olefin, and cycloadditions using the allenamide olefin as a precursor to a nitrogen stabilised allylcation. Consequently, this review will be divided into the following sections; Thermal intramolecular [4+2] cycloadditions; Torque selective ring closures of allenamides; Inverse electron-demand Diels Alder reactions; Cycloisomerization of yne-allenamides including the Pauson Khand reaction; Cyclopropanation; and finally, [4+3] Cycloadditions using nitrogen substituted oxyallyl cations.

Thermal Intramolecular [4+2] cycloadditions

Hsung has reported that allenamides can participate in thermal [4+2] cycloadditions (**Scheme 1**) [23]. While this transformation has been achieved with allenylsulfinimides and *in situ* prepared allenamides this work was the first to demonstrate that such a process could be achieved under purely thermal conditions [24,25]. The transformation of **1** into **2** was initially attempted using a variety of metal catalysts with only AuCl and AgBF₄ showing any appreciable product conversion. Switching to Brønsted acid catalyst such as PPTS and CSA increased the yield of **2**; however, excellent conversion to the [4+2] cycloaddition product was then observed when thermal conditions were employed. The transformation was tolerant of a number of *N*-substitutents and significantly substitution at the allenic γ-position. Allenamide **3** gave a 4:1 mixture of products, namely **4** and **5**, resulting from participation of the α,β- or β,γ-allenic double bond; however, **4** was found to equilbrate to **5** upon prolonged heating at 110ºC in toluene *via* a retro-[4+2], [4+2] cycloaddition. The allenamide diene **6**

also participated in the [4+2] cycloaddition reaction to give the cyclised product **7** in a 78% yield. The connectivity and relative stereochemistry of the products was fully assigned and consequently a mechanistic rationale was proposed as shown below in **Scheme 1**. Significantly, when R ≠ H the cycloaddition occurs with approach of the furan to the more hindered side of the allenic functional group though Hsung and co-workers do not supply a rationale for this contra-steric approach.
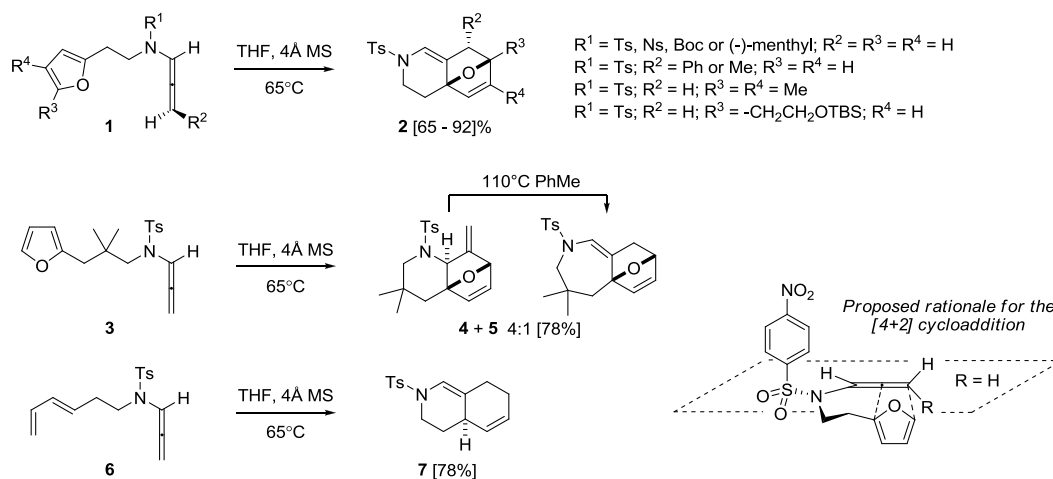
Scheme 1. [4+2] Cycloaddition of allenamides

MS molecular sieves, **Boc** *tert*-butyloxycarbonyl, **PhMe** toluene, **THF** tetrahydrofuran

Notably a tandem propargyl amide isomerisation cycloaddition sequence could be employed and **Scheme 2** shows this procedure for the rapid construction of tricycle **12**. Treatment of **9**, obtained commercially or by treatment with base and oxirane, with propargyl sulfonamide **10** under Mitsunobu conditions gave the propargyl amide **11** and when this was subsequently exposed to ^{t}BuOK in THF at 65ºC it gave the cycloaddition product **12** in 86% over 2-steps. This procedure was also shown to be amenable to substituted propargyl amides and furan derivatives giving their cyclised products **14** and **16**, respectively.
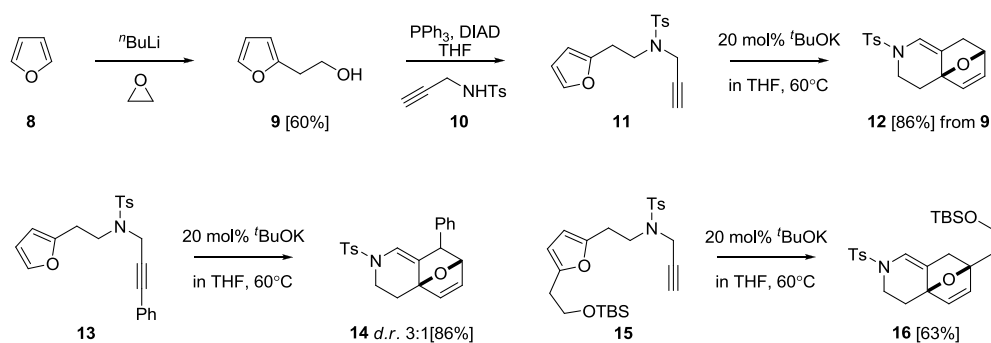

Scheme 2. Tandem propargyl isomerization/[4+2] cycloaddition sequence.

THF tetrahydrofuran, **DIAD** diisopropyl azodicarboxylate

Torque Selective Ring Closures

A tandem isomerization-pericyclic ring-closure sequence on allenamide substrates has been reported. This work was reported by Hsung and co-workers and was built upon a previous disclosure of a regio- and stereo-selective isomerization of allenamides to access amidodiene substrates [26,27]. The regio- and stereo-selective isomerization of a variety of allenamides was shown to be possible *via* either thermal rearrangement or Brønsted acid catalysis as shown below in **Scheme 3**. Both α- and γ-substituted allenamides were rearranged to the amido-dienes with *E*-selectivites of ≥ 20:1. Notably, γ-substituted allenamides such **25** required higher temperatures and longer reaction times than the corresponding α-substituted allenamides **17**. Therefore, allenamide **21** was subjected to thermal isomerization conditions leading to regioselective formation of amidodiene **22**.
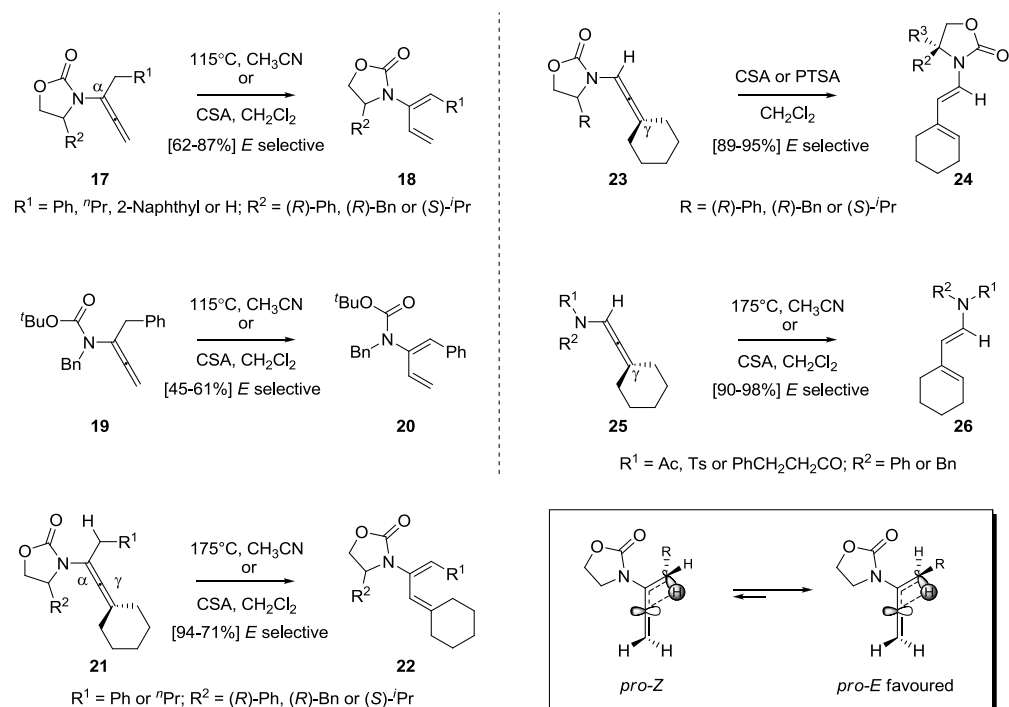

Scheme 3. Regio- and stereoselective isomerization sequence.

PTSA *p*-toluenesulfonic acid, **CSA** camphor sulfonic acid, **Ts** *p*-toluene sulfonate, **Ac** acetyl

<mark>Hsung and co-workers</mark> suggest that energy barrier required for the 1,3-H-shift in the isomerization of allenamides is lowered relative to the corresponding allenic systems *via* either a biradical stabilization by nitrogen or increased *N*-acyl iminium character. Additionally the rationale for the E-selectivity of the α-

subsituted allenamide isomerization is that the *pro-Z* transition state experiences greater allylic strain than the corresponding *pro-E* transition state during the 1,3-H-shift; however, <mark>Hsung</mark> does not rule out a *Z-* to *E-* enamide isomerization subsequent to the 1,3-H-shift.   A tandem α-isomerisation–pericyclic ring-closure sequence was also accomplished leading to cyclic amido-dienes such as **29** from **27** (**Scheme 4**).

R = (*R*)-Bn, (*S*)-*i*Pr or H

Yields [43-57%]
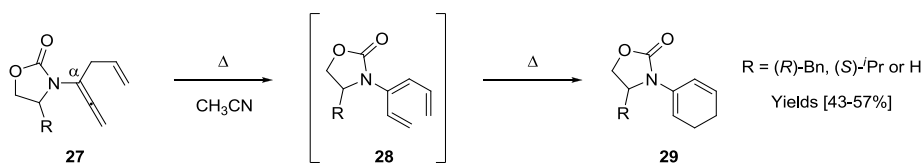
Scheme 4. Tandem isomerization-pericyclic ring-closure of allenamides

This final result lead to <mark>Hsung and co-workers</mark> disclosing a touque selective ring closure of trienes derived from allenamides (**Scheme 5**). These trienes could be derived from either a 1,3-H-shift or a 1,3-H-1,7-H-shift which was dependant upon the starting geometry of the pendant olefin on the allenamide. For example <mark>Hsung</mark> demonstrated that *Z*-allenamide **30** would lead to amidodiene **32** *via* a 1,3-H-1,7-H-isomerization-electrocyclisation event, while *E*-allenamide **33** would lead to amidodiene **35** *via* a 1,3-H isomerization-electrocyclisation pathway. Interestingly, modest asymmetric 1,6-induction from the remote chiral centre on the oxazolidonone was observed for the electrocyclisation of **33** to **35**. <mark>Hsung and co-workers</mark> also reported that such a process could be achieved without the isolation of the intermediate triene. Finally, <mark>Hsung</mark> showcased this allenamide isomerization protocol by incorporating an internal alkene suitable for a tandem [4+2] cycloaddition. When *Z*-allenamide **36** was heated in xylenes the resultant tricyclic **38** was isolated in modest to good yields and significantly as single diastereomers. This process showcased a very rapid and stereoselective synthesis of structurally complex tricycles from relatively simple allenamide precursors.
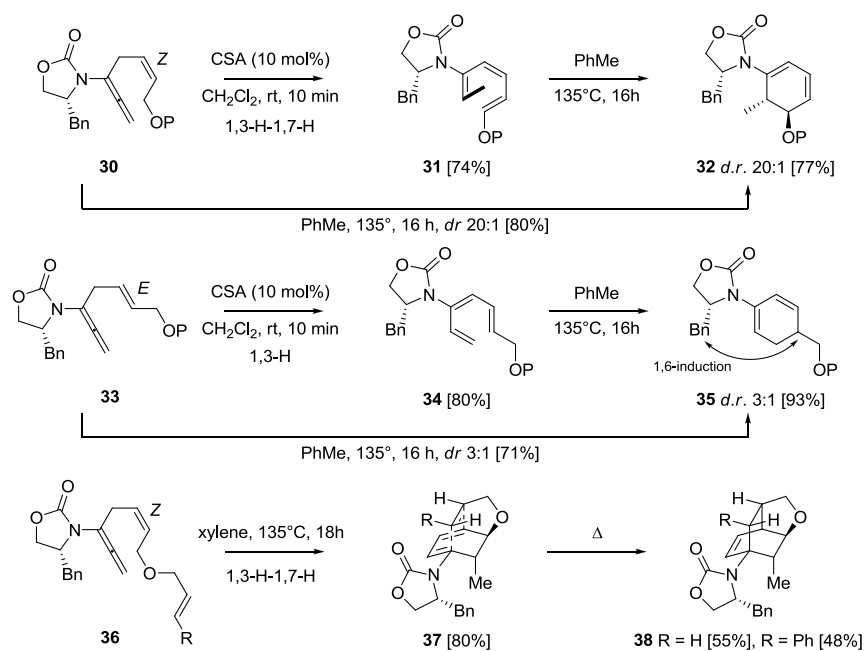
Scheme 5. Tandem torque selective ring-closure/[4+2] cycloaddition

PTSA *p*-toluenesulfonic acid**, CSA** camphor sulfonic acid**, PhMe** toluene

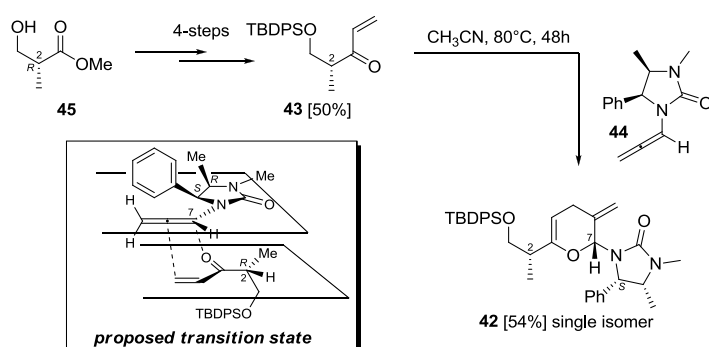## Inverse electron demand Diels-Alder reactions

The use of allenamides in the construction of heterocycles using the inverse electron-demand cycloaddition reaction is well established [28-30]. Therefore this section of the review will highlight first application of this approach for the construction of a natural product subunit [31,32].   Hsung and co-workers have previously developed protocols for the stereoselective inverse electron-demand hetero [4+2] cycloaddition using chiral allenamides (see **Scheme 6**).   However, Hsung has now successfully applied this approach to stereoselective heterocycle synthesis by completing a formal synthesis of (+)-zincophorin **39**. (+)-Zincophorin, M144255 or griseochellin is an ionophoric antibiotic isolated from *Streptomyces griseus* and has been shown to posess strong *in vivo* activity against Gram-positive bacteria and *Clostridium coelchii* [33]. Additionally, its methyl ester has been shown to exhibit strong inhibitory activity against influenza WSN/virus. Due to this biological activity synthetic efforts towards **39** have resulted in total syntheses by the groups of Danishefsky, Cossy and Miyashita[34-36]. Hsung and co-workers envisaged that the tetrahydropyran subunit embedded within **39** could be constructed from chiral enone **43** and the chiral allenamide **44** derived from the Close auxillary. A inverse electron-demand cycloaddition between **43** and **44** would deliver **42** which could then be transformed into Miyashita's intermediate **40** and therefore result in a formal total synthesis of **39**.
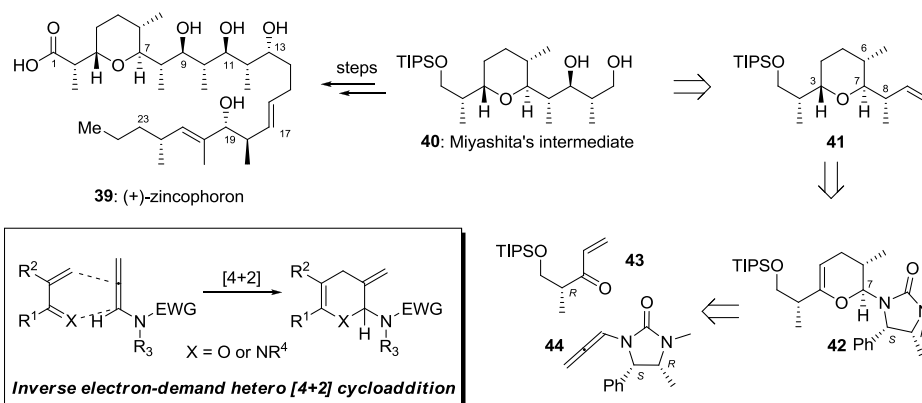
Scheme 6. Hsung's approach to (+)-zincophorin

TIPS triisopropyl

The chiral enone **43** was synthesised from **45** in 4-steps in an overall yield of 50%, while the chiral allenamide **44** was synthesised under standard conditions from the Close auxillary (**Scheme 7**). The key cycloaddition between **43** and **44** was achieved at 80ºC in CH₃CN and gave the desired pyran **42** in 54% yield and as a single isomer. The stereochemistry at C7 was assigned using previous work by the group in the area. Specificall, the stereochemistry was assigned by envoking the trasition state shown in **Scheme 7** where the *S-cis* conformation of the heterodiene approaches the less hindered internal olefin of the allenamide. Hsung also suggests that the high level of diastereoselectivity were a result of a matched transition state between **43** and **44**. With **42** in hand the completion of the formal total synthesis of **39** was achieved in a further nine-steps utilizing a key urea directed Stork-Crabtree hydrogenation of the *exo* double bond contained in **42** and a SnBr₄ mediated crotylation at C7. The formal total synthesis of **39** by Hsung and co-workers represents the first application of a chiral allenamide in natural product synthesis and should hopefully illustrate the usefulness of the allenamide synthon.
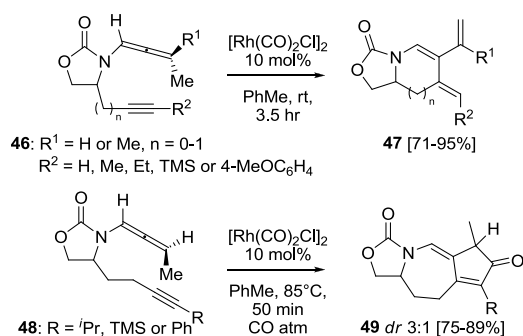

Scheme 7. Inverse electron-demand [4+2] cycloaddition (+)-zincophorin.

TBDPS *tert*-butyldiphenylsilyl

Cycloisomerization of Yne-Allenamides and Pauson-Khand [2+2+1] cycloaddition reaction

Brummond and co-workers succcessfully demonstrated that a Rh(I) catalysed Alder-Ene reaction of functionalised allenamides with alkynes tethered at the C5 of the oxazolidinone ring could be accomplished (**Scheme 8**) [37,38]. The length of the tethered carbon chain was shown to be important; with allenamide **46**, where n = 0 or 1, the allenic Alder-Ene reaction readily gave the cyclopentenyl- or cyclohexenyl-trienes **47** in high yield. However, the attempted cyclisation of allenamide **46** containing a longer tethered alkyne (n = 2) only gave trace amounts of the desired Alder-Ene products. This was remedied by subjecting **48** to the Alder-Ene cyclisation condition at increased temperatures and under an atmosphere of carbon monoxide to afford the cyclocarbonylated products **49** in good to high yields. Additionally, <mark>Brummond</mark> showed that the triene products readily underwent a subsequent Diels-Alder reaction with *N*-phenylmaleimide to give the [4+2] addition product in high yield.


46: R^1 = H or Me, n = 0-1
R^2 = H, Me, Et, TMS or 4-MeOC$_6$H$_4$

47 [71-95%]

48: R = ^{i}Pr, TMS or Ph

49 *dr* 3:1 [75-89%]

Scheme 8. Cycloisomerization of yne-allenamides.

PhMe toluene, **TMS** trimethylsilyl

The PKR is a power method for the construction of cyclopenetenones common to many natural products and biologically relevent substrates. It represents a [2+2+1] cycloaddition reaction between an alkyne and alkene in the presence of Co$_2$(CO)$_8$ or a relevent catalysts with carbon monoxide. In 2004 and 2008 Perez-Castells and co-workers reported a new regio- and stereoselective method for the intermolecular PKR of allenamides (**Scheme 9**) [39,40]. Exposure of allenamides **50** with mono- and di-substituted alkynes **51** gave the cyclopentenones **52** in good to excellent yields. Two procedures were reported for the transformation which differed in catalyst loading and exposure to CO. Additionally, <mark>Perez-Castells and co-workers</mark> reported an intramolecular example where the alkyne was directly attached to the arene. Treatment of **54** with Conditions A gave the product derived from intermolecular cyclisation **53** while intramolecular cyclisation could be achieved with Mo(CH$_3$CN)$_3$(CO)$_3$ giving rise to the quinoline **55**, albeit in modest yield. <mark>Perez-Castells and co-</mark>

comment that this approach does provide an entry in structurally diverse cyclopentenones and access to polycyclic aromatics.
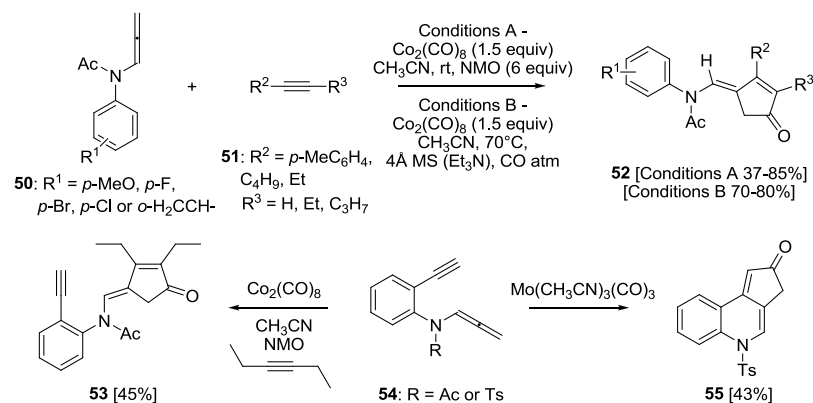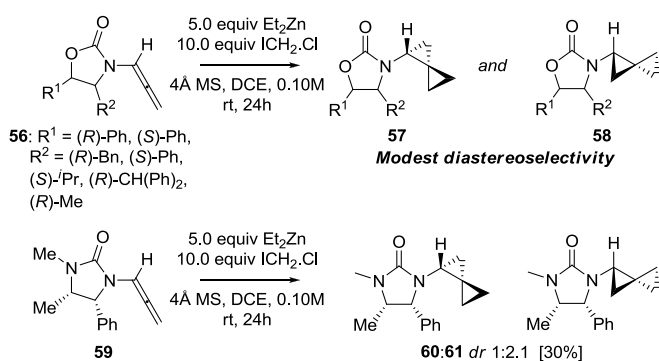

Scheme 9. PKR of allenamides.

Ac Acetyl**, Ts** *p*-toluenesulfonate, **NMO** *N*-methylmorpholine-*N*-Oxide

[2+1] Cycloaddition – Cyclopropanation

Cyclopropanation represents a formal [2+1] cycloaddition event and therefore warrants comment in the context of this review. Hsung has reported the bis-cyclopropanation of allenamides giving amido-spiro[2.2]pentanes, *via* a Simmons-Smith cyclopropanation protocol [41]. This work was based on previous work by the group on the stereoselective cyclopropanation of enamides [42]. The biological context of spiro[2.2]pentanes is worth comment since such structural motifs have been shown to mimic α-{methylenecycloproplyl) acetic acid, a well known inhibitor against acyl-CoA dehydrogenase that is critical in the fatty acid oxidiation pathway.

While the bis-cyclopropanation of achiral allenamides was shown to be possible, the application of this protocol to chiral allenamides (**56**) gave rise to a mixture of amido-spiro[2.2]pentanes (**57** and **58**, **Scheme 10**) with modest diastereoselectivity. Allenamide **59** derived from Close's auxillary exhibited the greatest diastereoselectivity in this study giving amido-spiro[2.2]pentanes **60** and **61** in a 30% overall yield and a *dr* of 1:2.1.

56: R^1 = (R)-Ph, (S)-Ph,
R^2 = (R)-Bn, (S)-Ph,
(S)-^{i}Pr, (R)-CH(Ph)$_2$,
(R)-Me

57

58

Modest diastereoselectivity

59

60:61 *dr* 1:2.1 [30%]

Scheme 10. Hsung's diasteroeselective bis-cyclopropanation of allenamides.

DCE 1,2-dichloroethane, **MS** molecular sieves

Computational calculations suggested that α-substituted allenamides may improve the diastereoselectivity for the bis-cyclopropanation and as such a range of α-substituted allenamides were exposed to the Simmons-Smith conditions (**Scheme 11**). The example below shows allenamide **62** giving the monocyclopropane **63** in 36% and in a *dr* of 5.0:1 and the biscyclopropane **64** in 23% and a *dr*≥20:1. While this result gave a mixtures of mono- and bis-cyclopropanes the dramatic increase in *d.r.* indicates that the inclusion of a α-substitutent on the allenamides increased the diastereoselectivity of the bis-cyclopropanation, and that this protocol potentially provides a straightforward method for the synthesis of biologically relevant amido-spiro[2.2]pentanes.


62: R = CH$_2$C$_6$H$_4$(o-Ph)

63 *dr* 5.0:1 [36%]

64 *dr* ≥20:1 [23%]
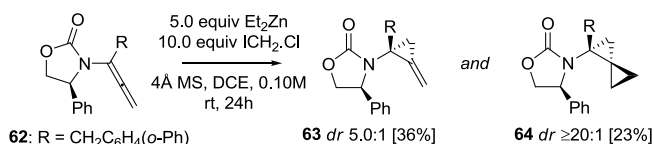
Scheme 11. α-Substituted allenamides in the cyclopropanation reaction.

DCE 1,2-dichloroethane, **MS** molecular sieves

[4+3] Cycloadditions with allenamide derived nitrogen substituted oxyallyl cations

So far this review has concentrated solely on the allenamide olefin taking part in the cycloaddition event; however, the allenamide unit can act as a precursor to reactive allylcations when activated by suitable electrophiles. Such electrophilic activation of allenamides include; Brønsted acid activation of allenamides by Nararro-Vaszquez and co-workers to give rapid access to the protoberberine skeleton [4]; Au(I) and NIS activation by Hegedus and co-workers for accessing dihydrofurans [10]; Fujii and co-workers for accessing dihydroquinolines [11]; Manzo and co-workers for for synthesising vinylimidazolinones [12]; and finally, Kimber and co-workers for enamide synthesis [13,14]. Hsung and co-workers however have utililized a regioselective epoxidation of allenamides **65** to generate nitrogen substituted oxyallyl cations **67** which are

known to participate in reactions with dienes *via* a [4+3] cycloaddition event to providing access to bicycles such as **68** (**Scheme 12**) [43].
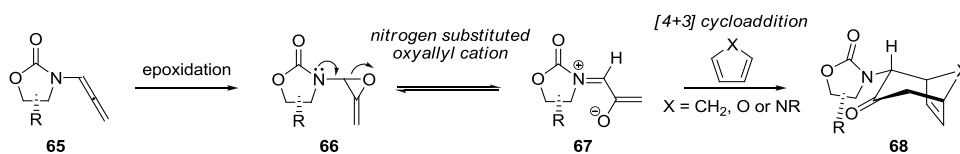
Scheme 12. [4+3] cycloaddition of oxyallyl cations derived from allenamides.

Reports discussing the mechanistic aspects and stereoselectivity of this [4+3]-cycloaddition reaction utilizing nitrogen substituted oxyallyl cations have been published,[44,45] so this section of this review will concentrate on recent synthetic aspects, particularly in the construction of natural product like scaffolds using this approach.

Hsung and co-workers have reported several methods for the intramolecular [4+3] cycloaddition of oxyallyl cations derived from allenamides with a tethered furan (**Scheme 13**). The first report centred on the tethered furan being attached through the nitrogen of the allenamide [46]. For example, treament of **69** with DMDO at -45ºC in CH$_2$Cl$_2$ in the presence of 2.0 equivalents of ZnCl$_2$ gave the tricyclic product **70** in 47% yield and in a *dr* of 60:40. The addition of ZnCl$_2$ was required since in its absence the yield for this transformation was only 20%. The diastereoselectivity for the transformation arose from an intra-[4+3] *exo* approach of the diene to the oxoallyl cation. A shift of the tether to the C5 of the oxazolidinone ring was also investigated as well as the length of the tether (defined by n=0-3, **71**) [46]. When n=0 or 1 the [4+3] cycloaddition reaction of allenemide **71** gave the tricycle **72** in good to excellent yields, where as an increase in the tether length (n = 2 or 3) saw reduced yields. The diastereoselectivity for this transformation was excellent for shorter tethers (n = 0 or 1 *dr*≥96:4) but was significantly eroded for longer tethers (n =3 *dr* 52:48). An explanation for the high diastereoselectivity of this transformation also implied an *exo*-approach of the diene, and the drop in diastereoselectivity for longer tethers suggested that the corresponding oxyallyl cation species possessed less rigidity in its transition state.
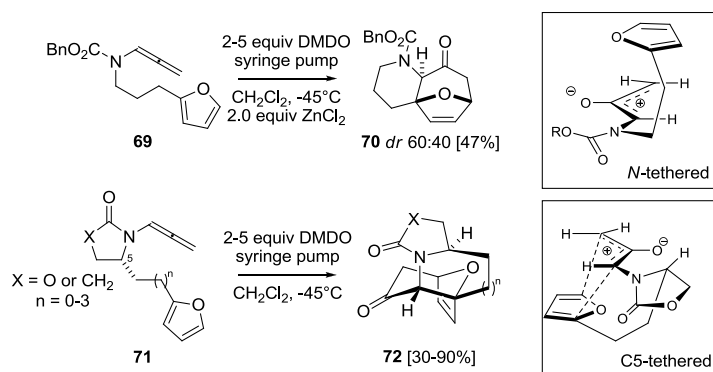
Scheme 13. *N*- and C5-Substituted intramolecular [4+3] cycloadditions.
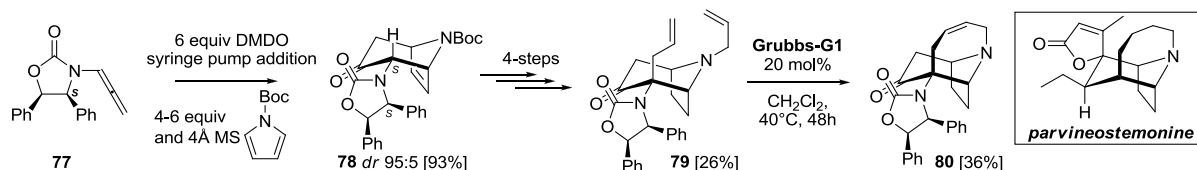
DMSO dimethyldioxirane

A study on α- and γ- tethered furan allenamides has also been undertaken by Hsung and co-workers (**Scheme 14**) [47]. Treatment of α-tethered allenamide **73** where n=2 with DMDO gave the desired tricycle **74a** in 45% yield and in an excellent *dr* of 95:5; however when the chain was extended to n=3 no product was observed. Additionally, when (*S*)-*i*propyl oxazolidinone was used in place of the (*R*)-phenyl oxazolidinone the yield of the tricycle product was was increased to 65%. A transition state was proposed for this transformation where the approach of the diene was *endo* with respect to the oxyallyl cation. Treatment of γ-tethered furan allenamide **75**, as a 1:1 mixture of *P/M* isomers, with DMDO gave the tricycle **76** in a yield of 61% in a *dr* of 9:1. Subsequently, a range of γ-tethered furan allenamides were cyclised in this fashion revealing a general route into this class of tricycle. Additionally, a transition state was proposed which inferred that the diene approaches *exo* to the *in situ* derived oxyallyl cation.
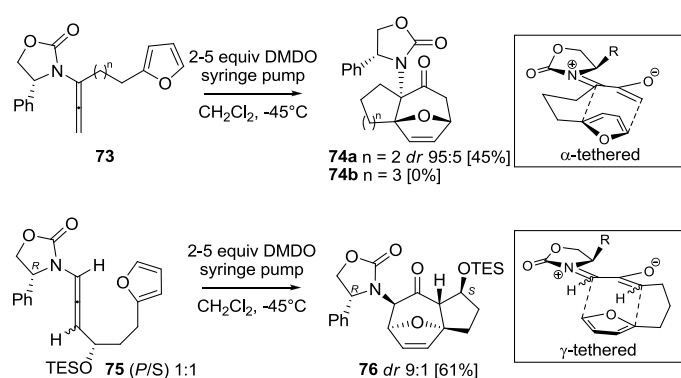
Scheme 14. α- and β-Substituted intramolecular [4+3] cycloadditions.

DMDO dimethyldioxirane, **TES** triethylsilyl

In 2007 Hsung and co-workers revealed a study into the use of this [4+3] cycloaddition reaction of oxyallyl cations with *N*-substituted pyrroles and as a consequence disclosed a novel synthetic route to the alkaloid parvineostemonine (**Scheme 15**) [48]. A stereoselective [4+3] cycloaddition between the oxyallyl cation, derived from the DMDO oxidation of **77**, and *N*-Boc-pyrrole gave the bicycle **78** in 93% yield and in a *de* of 90%. Functional group manipulation of **78** and subsequent alkylation then gave the RCM precursor **79** which when treated with Grubbs 1st generation catalysts gave modest yields of the desired tricycle **80**, representing the core of the alkaloid parvineostemonine.

Scheme 15. Hsung's approach to the core of parvineostemonine.

DMDO dimethyldioxirane, **MS** molecular sieves

Conclusions

The cycloaddition reaction represents one of the most powerful methods for the stereoselective synthesis carbocycles and heterocycles since the outcomes of the reaction can be confidently predicted using defined transition states. The understanding which has been gained over the past decade in the use of chiral allenamides in cycloaddition reactions has allowed researchers to predict with confidence the outcomes of such transformation. Consequently, within the period of this review this has led to the use of allenamides in stereoselective construction of complex natural product and drug-like like scaffolds, and significantly has led to the first use of a chiral allenamide in the synthesis of a complex natural product. Hopefully, this will result in an increased use of allenamides as building blocks in the stereoselective construction of heterocycles for drug design and natural product synthesis. While cyclopropanation of allenamides has the ability to access novel amido-spiro[2.2]pentanes for use methylene cyclopropane mimics, the poor diastereoselectivity seen for some substrates may limit its use. The application of allenamides in the PKR reaction has only been recently touched upon, however such an approach does have the potential to access hitherto unaccessed heterocyclic substrates. With a plethora of methods now existing for the synthesis of structurally diverse allenamides, the cycloaddition chemistry presented in this short review should help to illustrate the synthetic value of allenamides in the construction of heterocycles and structurally diverse substrates.

Acknowledgements

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