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REVIEW ARTICLE

The conversion of allenes to strained three-membered heterocycles

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This article reviews methods for converting allenes to strained, three-membered methylene heterocycles, and also covers the reactivity of these products. Specifically, the synthesis and reactivity of methylene aziridines, allene oxides/spirodiepoxides, methylene silacyclopropanes, methylene phosphiranes, and methylene thiiranes are described, including applications to the synthesis of complex molecules. Due to the primary focus on heterocyclic motifs, the all-carbon analogue of these species (methylene cyclopropane) is only briefly discussed.

1. Introduction

The chemistry of methylene cyclopropanes (MCP) and their heteroatom analogues[1] (Figure 1) has been an area of considerable interest for over fifty years. The appeal of these compounds as building blocks for synthesis stems from their considerable ring strain (generally 12-13 kcal/mol greater than the parent three-membered ring[2]), which confers a significant thermodynamic driving force to otherwise unfavourable processes. In addition, the ability to exploit further reactivity at either the three-membered ring or at the exocyclic double bond make these compounds versatile intermediates, including as trimethylenemethane-type precursors in an array of cyclization chemistries.[3] Their general stability at ambient conditions also contributes to the continued interest in exploring both the syntheses and reactivities of these unique motifs.

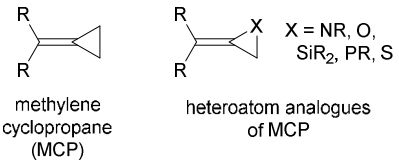
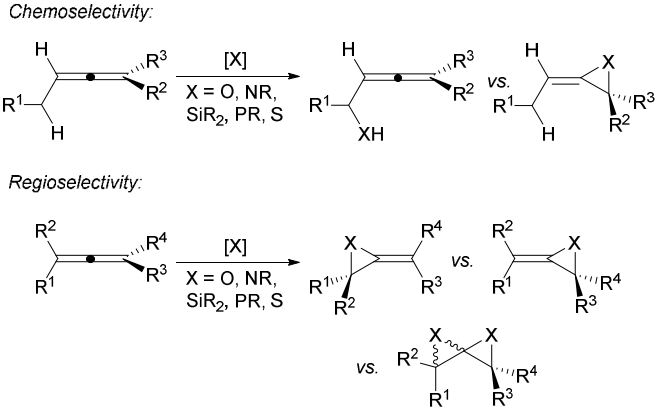


Figure 1 Structures of methylene cyclopropane and heteroatom analogues covered in this review.

Methylene cyclopropanes have been studied to a far greater extent than their heteroatom analogues, as they present fewer challenges in terms of their synthesis and reactivity. In contrast, heteroatom analogues of MCPs can often undergo unproductive side reactions and *in situ* decomposition; the installation of bulky groups on the ring and the exocyclic olefin has been the typical way of circumventing these issues. More recently, however, inventive approaches to harness the synthetic potential of these more reactive heterocyclic versions of MCPs have been developed that provide powerful tools for the stereocontrolled construction of diverse heteroatom-containing products.

Allene cyclopropanation is the most common method to access MCPs.[4] Surprisingly, the corresponding reactions of allenes to derive heteroatom analogues have been under-utilized, even though several benefits to employing them as substrates can be envisaged. Allenes containing a variety of substitution patterns are easily synthesized from readily available propargylic alcohols, and the number of enantioselective methods has been rapidly increasing in the past few years.[5] Since the axial chirality of allenes can typically be transferred with good fidelity to central or point chirality in the products, allene functionalization offers an opportunity to generate enantioenriched motifs.[6]

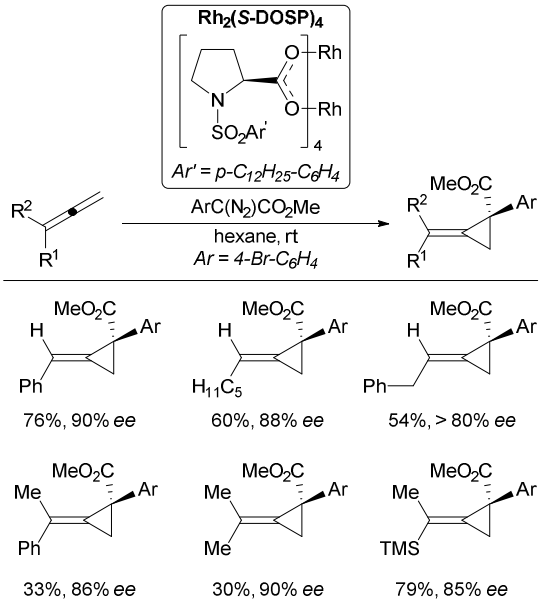
Several issues need to be considered to achieve general and useful additions of heteroatom groups to allenes (Scheme 1). First, chemoselectivity issues can be challenging, as both the allene and the allenic C-H bond may undergo functionalization, particularly in the synthesis of bicyclic methylene aziridines *via* nitrene transfer. Regioselective reaction of one double bond of the allene over the other is another potential problem, as well as the ability to control the *E* or *Z* geometry in the resulting products.



Scheme 1 Issues of chemo- and regioselectivity in allene functionalization.

This review article will encompass methods of converting allenes to the heteroatom analogues of MCPs; specifically, nitrogen, oxygen, silicon, phosphorous, and sulphur analogues. Their subsequent reactivities to generate complex heteroatom-containing motifs will also be discussed. These compounds will be covered in ascending atomic number, starting with nitrogen and ending with sulphur. When allenic C-H insertion represents a competing process to functionalization of the C=C bond, these reactions will also be discussed. Examples where both double bonds of the allene are functionalized, such as the spiro[2.2]pentane products resulting from double epoxidation of an allene, will also be addressed. [3]Radialene formation from the corresponding use of cumulenes will be briefly mentioned where relevant. As our focus is primarily on the heteroatom analogues of methylene cyclopropane, and as carbene addition to allenes has been extensively reviewed, only the most recent work pertaining to MCP formation will be discussed.

Finally, to clarify an issue of terminology, we point out that the terms "methylene" and "alkylidene" are often used interchangeably throughout the text. In the past, the term "methylene" referred only to species containing a terminal exocyclic double bond, with "alkylidene" being employed for substituted products. However, many groups have begun to use "methylene" to describe all members of these classes of compounds and we have adopted this convention.



Scheme 2 Asymmetric cyclopropanation of terminal allenes.

2. Methylene cyclopropanes (MCPs)

2.1 Introduction

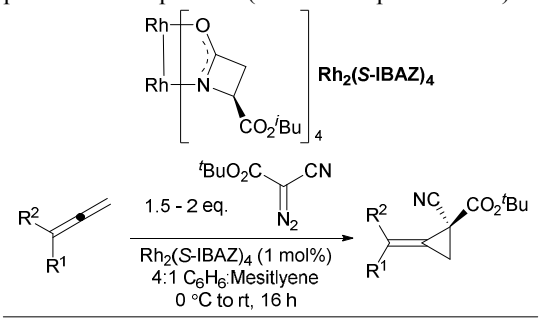
As previously mentioned, the focus of this review is the synthesis and reactions of heteroatom analogues of methylene cyclopropanes employing allenes as starting materials. For an in-depth discussion of allene cyclopropanation, the reader is referred to a number of recent review articles that have been published in this area.[4] Herein, we present a brief summary of the literature published in this field since 2009.

2.2 Work since 2009

Gregg and co-workers addressed the challenge of enantioselective MCP synthesis by employing a chiral rhodium (II) catalyst to promote carbene addition to monosubstituted allenes.[7] Rh_2(*S*-DOSP)$_4$ was found to be the best catalyst for the enantioselective transfer of donor-acceptor carbenoids to allenes, in analogy to its successful use in asymmetric styrene cyclopropanation.[8] Enantioselectivities between 80% and 90% were observed for both monosubstituted and disubstituted allenes (Scheme 2); however, disubstituted allenes suffered from low yields (30-33%) owing to decreased reactivity. The exception was the electron-rich 1-methyl-1-(trimethylsilyl)allene (Scheme 2, bottom right). Competition experiments and electronic effect studies outlined in a later publication[9] confirmed that the rates of allene cyclopropanation were highly dependent on the steric and electronic properties of the allene.

The Charette group recently disclosed an asymmetric cyclopropanation reaction of allenes employing diacceptor diazo carbene precursors.[10] The use of a nitrile as one of the 'acceptor' groups was critical for obtaining high yields with terminal allenes. The reaction could be carried out in a racemic fashion with $Rh_2(OPiv)_4$, but employing the chiral azetidinate ligand (*S*-IBAZ) provided MCP products in high *ee* with good to excellent diastereoselectivities (Table 1). However, allenes bearing electron-withdrawing groups (entry 5) and 1,1-disubstituted allenes (entry 6) gave considerably lower yields. Aryl, aliphatic, and heteroatom substituents were tolerated under the reaction conditions.

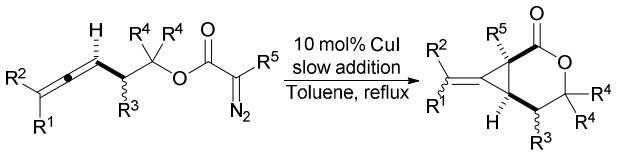
Table 1 Asymmetric cyclopropanation of allenes with diacceptor diazo compounds. (NPhth = N-phthalimido)



entry	R^1	R^2	Yield	*dr*	*ee*
1	Ph	H	92	> 97:3	95
2	CH_2Ph	H	86	93:7	>90
3	CH_2-NPhth	H	80	> 97:3	82
4	NPhth	H	48	93:7	90
5	CO_2Et	H	29	80:20	n.d.
6	Ph	Me	43	> 97:3	96
7	$SiMe_3$	Me	83	> 97:3	90

The Schomaker group has recently explored the intramolecular cyclopropanation of axially chiral allenes, with the goal of utilizing these MCPs as intermediates for the construction of stereotriad or tetrad building blocks for complex molecule synthesis.[11] Cu(I) and Cu(II) salts were found to give exclusive cyclopropanation in allenes containing a tethered diacceptor diazo group, with CuI giving the highest yields (Table 2).[12] While yields were generally good for 1,3-disubstituted allenes (entries 1,2), a trisubstituted allene gave low yields of the MCP (entry 3) due to steric effects. The *E*:*Z* selectivities were generally above 5:1. Single acceptor diazo compounds also behaved well under the reaction conditions (Entry 4). The synthetic utility of these bicyclic MCPs is currently under investigation.

Table 2 Cu-catalysed intramolecular cyclopropanation of allenes.

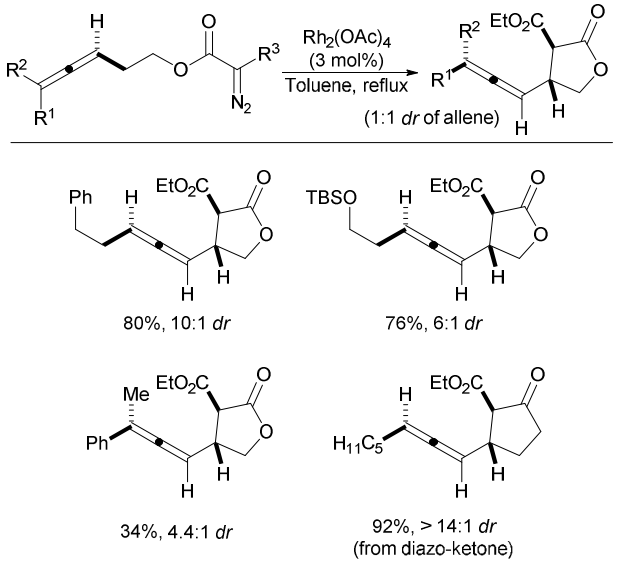


entry	R^1	R^2	R^3	R^4	R^5	yield	*E*:*Z*
1	$Ph(CH_2)_2$	H	H	H	CO_2Et	77%	7.9:1
2	C_5H_{11}	H	H	H	CO_2Et	67%	6.7:1
3	C_3H_7	C_3H_7	H	H	CO_2Et	23%	NA
4	C_5H_{11}	H	Me	H	H	68%[a]	> 20:1
5	C_5H_{11}	H	H	Me	CO_2Et	18%	19:1
6	C_5H_{11}	H	H	H	H	68%	2.3:1
7	C_5H_{11}	H	H	H	CO_2Me	30%	9.3:1

[a] diastereomeric ratio not able to be determined by NMR

Interestingly, the use of rhodium catalysts for the intramolecular cyclopropanation of allenes favoured allenic C-H insertion instead of cyclopropanation. Prior to this report, only a single instance of allenic C-H insertion with carbenes had been reported.[13] The use of $Rh_2(OAc)_4$ typically gave good to excellent yields of the allenyl lactone products, with excellent selectivity for a *syn* insertion product (Scheme 3). However, due to the use of racemic allene substrates, the major

Scheme 3 Intramolecular allenic C-H insertion.



diastereomer still possessed a 1:1 *dr* with respect to the allene stereochemistry. Yields were good across a range of di- and trisubstituted allenes. This work is informative as an example of the profound impact the choice of metal catalyst exercises on the chemoselectivity of carbene addition to allenes.

3. Methylene aziridines (MAs)

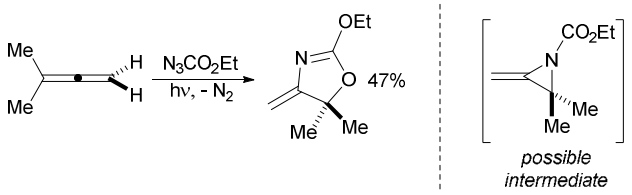
3.1 Introduction

In contrast to allene cyclopropanation, the corresponding aziridination of allenes has not been extensively explored. This is due in part to the greater lability of methylene aziridines, particularly when the nitrogen bears an electron-withdrawing group. The development of mild and chemoselective protocols for allene aziridination has been key to the recent progress in the use of methylene aziridines as useful synthetic intermediates.[14] Rhodium catalysts for nitrene transfer are the most common; however, new transition metal catalysts, such as silver, have been recently identified to promote this process in a highly chemoselective fashion (*vide infra*).

In keeping with the theme of this review, only synthetic approaches that access methylene aziridines directly from allenes will be covered. This excludes the impressive body of work reported by the Shipman group, where a host of methylene aziridines were generated from N-(2-bromoallyl)-alkylamines; the reader is directed to previous reviews for an in-depth discussion of their contributions.[15] In addition, the related work of the Feldman group on thermal rearrangements of allenyl azides will not be covered, as their substrates give less-strained five-membered heterocyclic products.[16] However, reports in which direct nitrene additions to an allene were unsuccessful in yielding MA products will be covered, as the nature of the side products often provides insight into how the overall process can be improved. In addition, allenic C-H amination will be discussed when it is relevant as a competing process to allene aziridination.

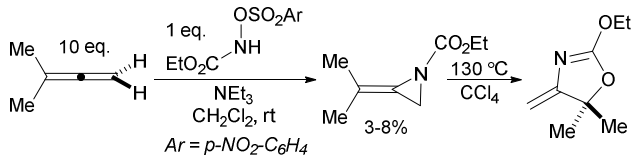
3.2 Work prior to 2000: intermolecular nitrene transfer to allenes

The first formal nitrogen atom transfer to an allene was described by Bleiholder and Shechter in the reaction of ethyl azidoformate and dimethylallene (Scheme 4).[16] Instead of the expected aziridination product, a methylene oxazoline was obtained in 47% yield as the sole product. The authors speculated that the oxazoline arose from a transient methylene aziridine, but could not rule out a direct [3+2] cycloaddition of the allene with carbethoxynitrene. A [3+2] cycloaddition of the azide and allene, followed by N_2 extrusion and rearrangement, had been observed with sulfonyl azides in the same work and would also account for the observed product.



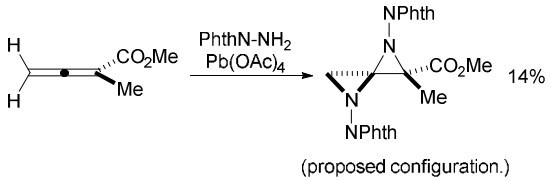
Scheme 4 Photolysis of ethyl azidoformate in the presence of dimethylallene.

Gilbert and co-workers reinvestigated this work in the reaction of a nosyloxycarbamate with various allenes.[17] Intriguingly, trace amounts of methylene aziridines could be isolated using this reagent, as confirmed by MS and NMR analysis (Scheme 5). Thermolysis of the MA products gave Shechter's oxazoline product (Scheme 4, above), demonstrating the competency of methylene aziridines as intermediates in the formation of the oxazoline. Based on the known mechanism of nosyloxycarbamate decomposition,[18] a triplet nitrene was invoked as the aziridinating agent.



Scheme 5 The first isolation of methylene aziridines.

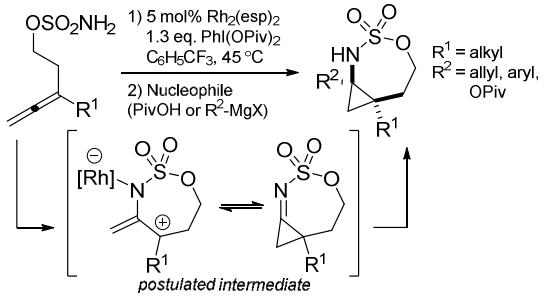
Concurrently with these reports, Atkinson and Malpass described the bis-aziridination of methyl 2-methylbuta-2,3-dienonate to form a diazaspiro[2.2]pentane (DASP) product.[19] The addition of the phthalimidonitrene, generated from N-amino phthalimide and $Pb(OAc)_4$, to an allenoate gave no observable methylene aziridine products, but yielded the DASP product in greater than 9:1 *dr* (Scheme 6). At room temperature, this compound existed as a mixture of N-invertomers, but a single major diastereomer could be observed by ^{1}H NMR at temperatures below -5 ºC. The reactivity of this spiro compound was not investigated, and no further syntheses of DASPs were reported until the work of Schomaker *et al.* in 2012 (*vide infra*).[20]



Scheme 6 Intermolecular DASP formation from an allenoate.

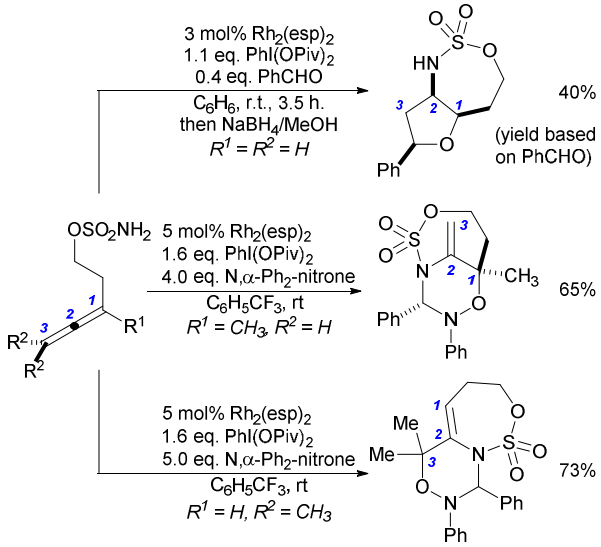
3.3 Intramolecular nitrene transfer reactions of homoallenic sulfamates

Allene aziridination has seen a resurgence of activity since the popularization of sulfamate-based nitrene precursors by the Du Bois group in the early 2000's.[21] The first application of intramolecular Rh-catalyzed allene aziridination was reported by the Blakey group in 2009.[22] In the presence of $Rh_2(esp)_2$ and $PhI(OPiv)_2$, 1,1-disubstituted allene sulfamates yielded iminocyclopropanes that were isolated as the pivalate aminals (Scheme 7). It was demonstrated that Grignard reagents were capable of adding cleanly to these intermediates to give densely substituted aminocyclopropanes. Blakey proposed that the iminocyclopropane was formed by rearrangement of an initial amidoallyl cation and support for this intermediate was seen in the partial racemization of an enantioenriched allene substrate under the reaction conditions. The group did not report the observation of bicyclic methylene aziridine formation during the course of their reactions; however, the observance of the iminocyclopropane valence tautomer suggests it could have formed as a transient intermediate.



Scheme 7 Aminocyclopropane formation from allenes.

The 2-amidoallylcationic character of the intermediate cyclopropylimine was demonstrated through the [3+2] cycloaddition of these intermediates with benzaldehyde, as well as a [3+3] cycloaddition using N,α-diphenyl nitrone as a coupling partner (Scheme 8, top and middle). Both reactions were highly selective, providing the cycloadducts with excellent regio- and diastereoselectivity. The scope of the [3+3] reaction was further explored,[23] and it was found that the regioselectivity of the process could be controlled by the allene substitution pattern. As seen in Figure X, a trisubstituted allene favoured C-O bond formation at C3 of the allene to give a different regioisomer, compared to disubstituted allenes (Scheme 8, bottom).

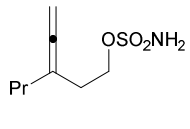
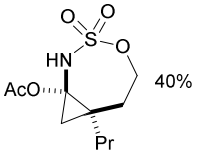
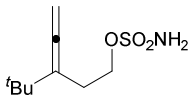
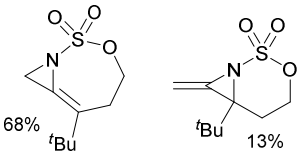
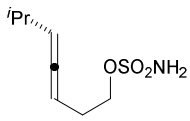
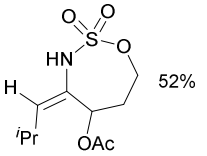
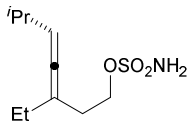
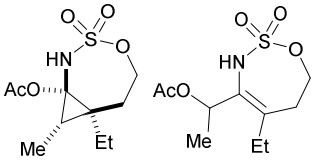


Scheme 8 Cyclizations of 2-amidoallyl cations generated from sulfamoyl allenes.

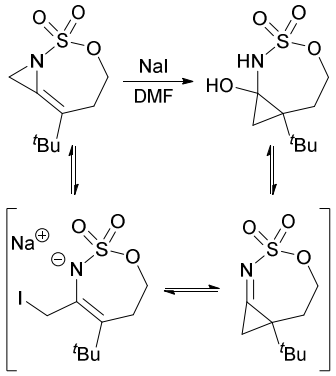
Soon after the initial publication by Blakey, the Robertson group reported similar findings in their experiments with homoallenic sulfamates.[24] They also noted that the nature of the allene substitution pattern had a profound effect on the regioselectivity of nitrene transfer. While several 1,1-disubstituted allenes gave the same aminocyclopropane products observed by Blakey (Table 3, entry 1), a more hindered -^{t}Bu substrate gave the novel bicyclic methylene aziridine products as a 5:1 mixture of regioisomers (entry 2). Aziridination of the distal olefin was preferred, primarily giving a 7-membered ring. A 1,3-disubstituted allene (entry 3) gave an enesulfamate product, likely formed by acetate ring-opening of a bicyclic MA similar to the result described in entry 2. Finally, a trisubstituted allene reacted with poor regioselectivity, giving a 1:1 mixture of aminocyclopropane and enesulfamate products (entry 4). While moderate yields were observed for a number of these reactions, the authors note that their reaction conditions are unoptimized.

Interestingly, Robertson noted that rearrangement of a methylene aziridine to the corresponding aminocyclopropane could be achieved by treatment with NaI in DMF (Scheme 9). This pathway offers a potential explanation for why bicyclic methylene aziridines had thus far been difficult to isolate in these reactions.

Table 3 Cyclizations of homoallenic sulfamates.

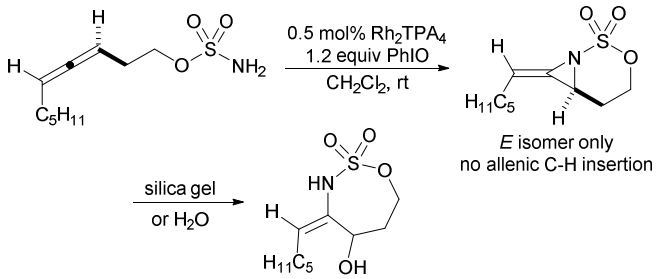
Entry	Substrate	Product(s)
1		 40%
2		 68% 13%
3		 52%
4		 26% 28%

Conditions: $Rh_2(OAc)_4$ (5 mol%), $PhI(OAc)_2$ (1.3 eq.), MgO (2.3 eq.), CH_2Cl_2, 20 °C, 18 h.



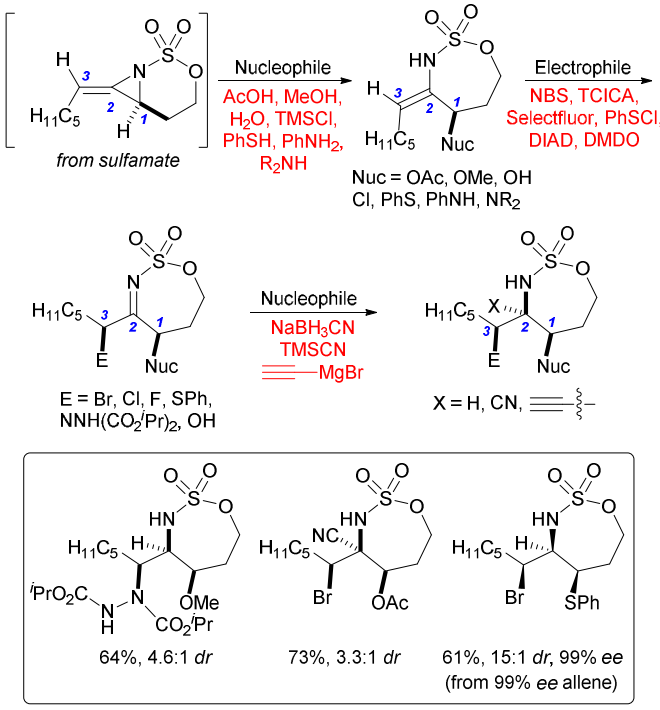
Scheme 9 Conversion of a methylene aziridine to an iminocyclopropane hemiaminal.

The Schomaker group investigated the reactivity of homoallenic sulfamates in further detail, with an eye towards isolating bicyclic MAs and exploring their utility as reactive scaffolds for the construction of complex amine-containing stereotriads.[25] In contrast to Robertson, who was unable to observe a bicyclic MA from the aziridination of 1,3-disubstituted allenes, Schomaker and co-workers found that the MA could be observed if acetic acid was precluded from the reaction mixture to prevent a facile ring-opening reaction. This was accomplished by replacing the $PhI(OAc)_2$ oxidant with iodosylbenzene (PhIO). The water generated from PhIO could be readily scavenged by adding 4 Å molecular sieves to the reaction. Under these conditions, a pentyl-substituted homoallenic sulfamate reacted with excellent chemo-, regio-, and stereoselectivity in generating only the *E* bicyclic MA (Scheme 10). None of the iminocyclopropane tautomer was observed. This unstable intermediate underwent ring-opening with water on silica gel, so these products were generally used without further purification.



Scheme 10 Selective synthesis of a bicyclic sulfamoyl methylene aziridine.

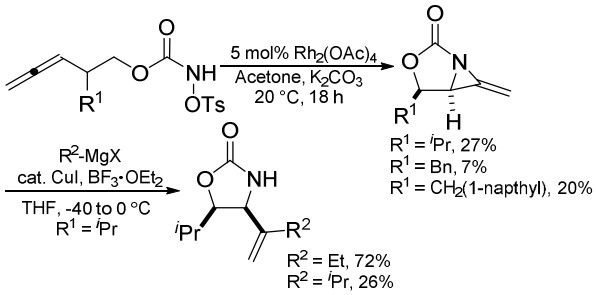
The Schomaker group utilized these reactive bicyclic methylene aziridines to form "all-heteroatom stereotriads"-motifs of three contiguous carbon atoms containing stereodefined heteroatom substituents. This was accomplished by a four-step, one-pot process involving aziridination of the allene, ring-opening, electrophilic substitution of the resulting enesulfamate, and nucleophilic trapping of the imine intermediate. In the first step (Scheme 11), mild nucleophiles including alcohols, carboxylic acids, amines, thiols, halides, and even water proved capable of ring-opening the bicyclic MA at room temperature without the need for exogenous Lewis acid additives. Similar to their enamide and enecarbamate[26] counterparts, the resulting enesulfamates reacted with a variety of heteroatom-based electrophiles to introduce halogen, oxygen, sulphur, and nitrogen groups at each of the three original allene carbons. Finally, the resulting imines could be trapped with hydride, cyanide, or Grignard nucleophiles to give stereotriads as shown in Scheme 11. The diastereoselectivity for this overall process was noteworthy, with the majority of the stereotriad products being obtained in > 10:1 *dr* favouring a 1,2-*syn*:2,3-*syn* stereochemistry. While the enesulfamate intermediate could be isolated if desired, it was demonstrated that the homoallenic sulfamate could be converted to a stereotriad in one-pot, with no intermediate purifications. Importantly, the stereochemistry of an enantioenriched allene could be transferred to the stereotriad with complete fidelity, yielding enantioenriched amine stereotriads. In an extension of this chemistry, the Schomaker group is currently investigating methods to selectively obtain any one of four possible diastereomeric amine stereotriads from a single enantioenriched allene using allene aziridination as a key step.



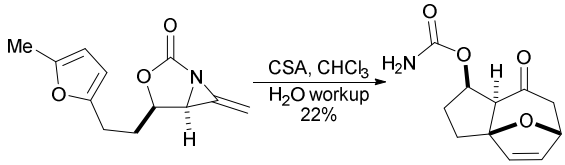
Scheme 11 Conversion of bicyclic MAs to "all-heteroatom stereotriads".

3.4 Intramolecular nitrene transfer reactions of homoallenic carbamates

Concurrent with the work being carried out on the amination of homoallenic sulfamates, the corresponding homoallenic carbamates and tosyloxycarbamates were investigated as substrates for allene aziridination, with the first report coming from the Robertson group.[27] Under the conditions of Rh catalysis, tosyloxycarbamates gave bicyclic MA products in low but reproducible yields (Scheme 12). The reactivity of the resulting [5.3]-bicyclic aziridines was investigated in the ring-opening with organocuprates, with the Csp^2-N bond cleaved in preference to the expected Csp^3-N bond (Scheme 12, bottom). Intramolecular [4+3] cycloaddition was demonstrated using a tethered furan (Scheme 13), analogous to work reported by Shipman on the reactivity of monocyclic methylene aziridines.[28] Although yields were modest, this work represented the first synthesis of carbamoyl methylene aziridines since the work of Gilbert and co-workers in 1975 (Scheme 5, *vide supra*).



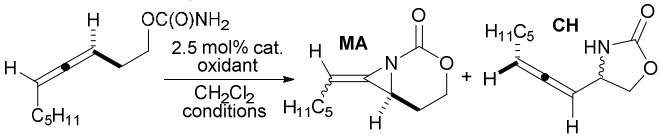
Scheme 12 Synthesis and ring-opening of carbamoyl bicyclic MAs.



Scheme 13 Intramolecular [4+3] cycloaddition of a bicyclic MA.

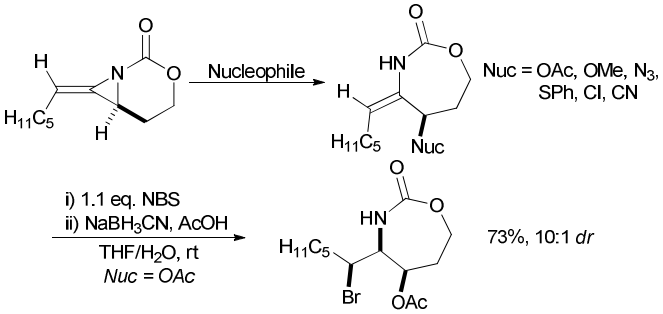
The Schomaker group has also explored the intramolecular aziridination of homoallenic tosyloxycarbamates, noting similarly low yields for formation of the bicyclic MAs.[29] They found that yields could be significantly improved by using homoallenic carbamates in the presence of an exogenous iodine (III) oxidant. Compared to the corresponding sulfamoyl-derived MAs, these substrates were less sensitive to ring-opening by acid and commercially available $PhI(OAc)_2$ could be employed as an oxidant. Both the *E* and *Z* isomers of the bicyclic MA were formed in these reactions, in addition to the allenic C-H insertion product (Table 4). Rhodium (II) triphenylacetate (Rh_2TPA_4) in conjunction with PhIO was found to give the highest selectivity for the (*E*)-methylene aziridine (entry 4).

Table 4 Reactivity of homoallenic carbamates.



entry	catalyst	oxidant	additive	temp (°C)	%MA (*E*:*Z*)	%CH
1	$Rh_2(esp)_2$	$PhI(OAc)_2$	2.6 eq. MgO	35	46% (1.5:1)	44%
2	$Rh_2(esp)_2$	$PhI(OPiv)_2$	2.6 eq. MgO	35	42% (4.1:1)	45%
3	$Rh_2(esp)_2$	PhIO	4 A MS	rt	66% (3.0:1)	16%
4	$Rh_2(TPA)_4$	PhIO	4 A MS	rt	80% (4.0:1)	15%

The Schomaker group then investigated the reactivity of the [6.3]-bicyclic MAs. In contrast to Robertson's substrates, the MAs reacted with nucleophiles to give the desired Csp^3-N bond-cleavage products. The resulting enecarbamates were capable of reacting further to generate stereotriad products in an analogous manner to the sulfamoyl substrates (Scheme 14).



Scheme 14 Reactivity of carbamoyl bicyclic MAs.

To gain a better understanding of the factors controlling the chemo- and stereoselectivity of carbamoyl allene aziridination, the effect of tether length and substitution was probed (Table 5).[30] In all cases, the installation of a methyl group on the tether between the allene and carbamate increased the rate of allenic C-H insertion (Table 5, entries 2-5). The use of a trisubstituted allene gave poor yields of both products (entry 6). In the cases of a three-carbon tether (entries 7-8), C-H insertion was the exclusive product.

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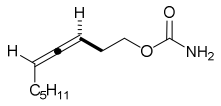
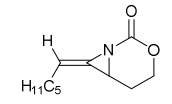
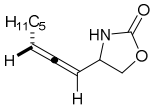
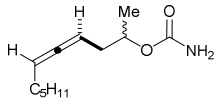
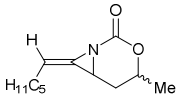
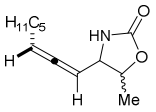
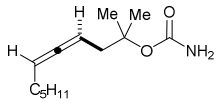
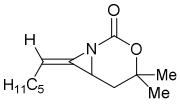
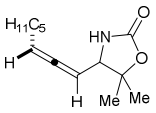
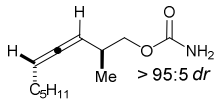
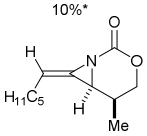
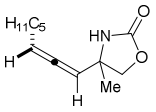
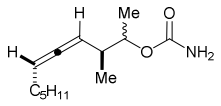
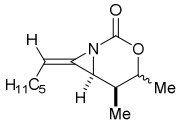
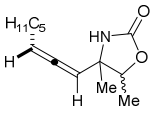
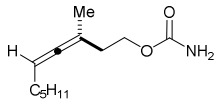
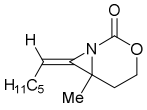
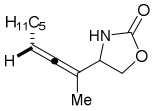
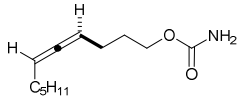
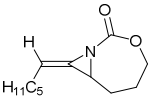
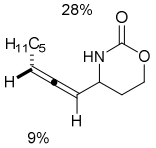
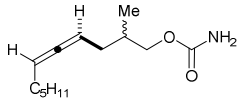
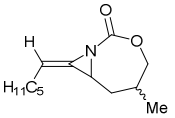
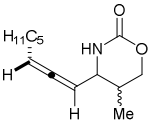
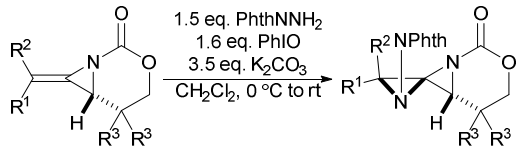
Table 5 Chemoselectivity in carbamoyl allene aziridination.

entry	substrate	conditions	products	
1		$Rh_2(esp)_2$, $PhI(OPiv)_2$, MgO	 42%, (1.5:1 *E*/*Z*)	 45%
2		$Rh_2(esp)_2$ $PhI(OPiv)_2$ MgO	 39%, (2.2:1 *E*/*Z*)	 29% (2:1 *dr*)
3		$Rh_2(esp)_2$ $PhI(OPiv)_2$ MgO	 10%*	 72%
4	 > 95:5 *dr*	$Rh_2(esp)_2$ $PhI(OPiv)_2$ MgO	 21% (3:1 *E*/*Z*)	 57%
5		$Rh_2(esp)_2$ PhIO 4A MS	 12%*	 61% (1.3:1 *dr*)
6		$Rh_2(esp)_2$ PhIO 4A MS	 18%	 28%
7		$Rh_2(esp)_2$ $PhI(OPiv)_2$ MgO	 0%	 9%
8		$Rh_2(esp)_2$ PhIO 4A MS	 0%	 70% (2:1 *dr*)

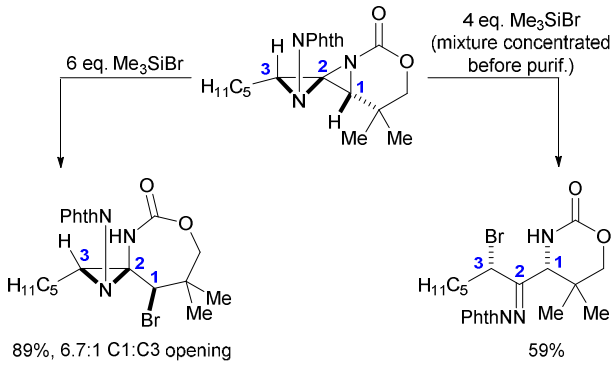
Direct functionalization of the exocyclic olefin of the MA was also explored as a route to stereotriad products, with the unique bicyclic nature of the ring yielding highly diastereoselective transformations. N-aminophthalimide in the presence of a hypervalent iodine oxidant added to the bicyclic methylene aziridines with complete facial selectivity to give tricyclic DASP products,[20] in analogy to the work of Atkinson and Malpass (see Scheme 6). Both the *E* and *Z* isomers of the MA could be used in this reaction, giving diastereomeric DASP products (Table 6, entries 1, 2). The addition of nucleophiles to the DASP typically favored ring-opening at C1 to give N,N-aminal products (Scheme 15, left). In certain cases, however, manipulation of the reaction conditions could induce C3 ring-opening to yield α,α'-disubstituted hydrazones (Scheme 15, right). As with previous work, the entire transformation of the allene to the stereotriad could be carried out in one pot, and the stereochemical information contained in an enantioenriched allene was transferred to the products with excellent fidelity.

The attempted hydrolysis of a ring-opened DASP led to an unusual cascade reaction.[31] As illustrated in Scheme 16, ring opening of the DASP with acetic acid followed by treatment with $Bi(OTf)_3$ delivered an unexpected diaminoketone product. Although the acetate was not conserved in the final product, its presence was crucial to the success of the rearrangement. Diastereoselective reduction to the 1,3-diamino-2-ol was achieved using excess $NaBH(OAc)_3$, although a *gem*-dimethyl

Table 6 Bicyclic MA aziridination to give DASP products.

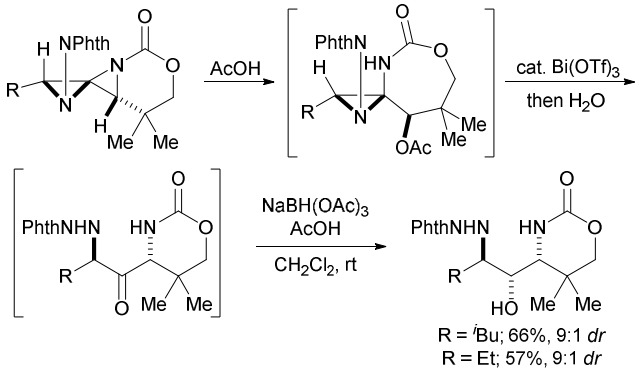


Entry	R^1	R^2	R^3	Yield
1	C_5H_{11}	H	Me	72%
2	H	C_5H_{11}	Me	33%
3	C_5H_{11}	H	H	65%
4	*t*Bu	H	H	79%
5	$Ph(CH_2)_2$	H	H	75%



Scheme 15 Opening at C1 and C3 of a DASP using Me_3SiBr.

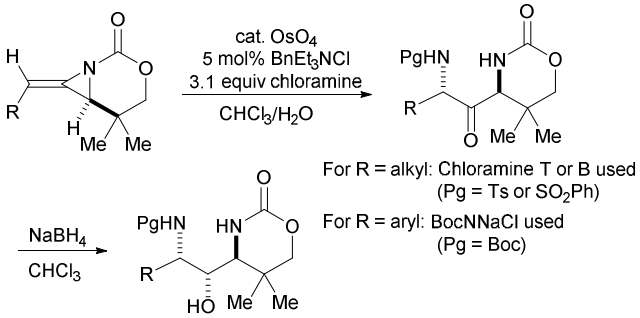
motif was required to achieve high diastereoselectivities. This entire sequence could be carried out starting from the allene in one pot with comparable overall yields to the two-pot process.



Scheme 16 $Bi(OTf)_3$-catalysed ring-opening/rearrangement of DASP's, followed by diastereoselective reduction.

Due to difficulties in cleaving the N-aminophthalimide group, an alternative route to these products was desirable. Gratifyingly, the Sharpless Os-catalysed aminohydroxylation of the MA gave direct access to the 1,3-diaminoketone products, with the exocyclic nitrogen protected with a readily cleavable sulfonyl or Boc group (Scheme 17).[32] In these reactions, selective reduction was achieved by the use of $NaBH_4$ in halogenated solvents. The process was general for a variety of alkyl and aryl-substituted MAs, with the identity of the chloramine crucial to obtaining good yields (Scheme 17).

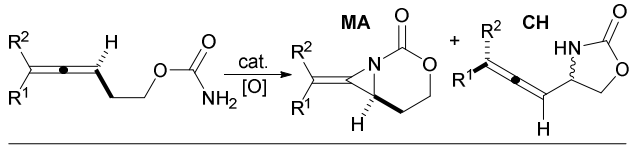
Despite its reactivity in nitrene transfer reactions, the high substrate contained gem-dimethyl group in the tether between the allene and the carbamate (Table 7, entry 2), in contrast to $Rh_2(esp)_2$, which favoured C-H insertion by a factor of 17:1. cost of rhodium remains a drawback to its use. In addition, the

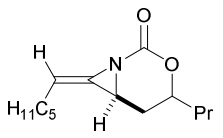
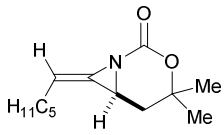
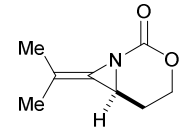
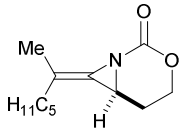
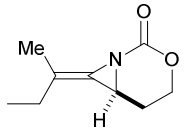


Scheme 17 Aminohydroxylation/reduction of bicyclic MAs.

chemoselectivity of the allene amination event is often substrate-controlled under the conditions of Rh catalysis, leading to mixtures of aziridination and C-H amination products. To address this concern, the Schomaker group investigated other transition metal catalysts for the aziridination of homoallenic carbamates. Catalysts formed *in situ* from silver triflate and bipyridyl-type ligands were found to be well-suited to this reaction, giving both increased yields and chemoselectivity compared to conventional Rh catalysts.[33] Whereas the aziridination:insertion ratio for rhodium catalysts was largely substrate-controlled (recall Table 5), a 1:1.25 mixture of AgOTf and phenanthroline gave uniformly high preference for aziridination, even in cases where Rh catalysts gave only allenic C-H insertion (Table 7). For example, aziridination was favoured with Ag by a factor of 6:1 when the

Table 7 Silver *vs.* rhodium catalysis in the amination of homoallenic carbamates.

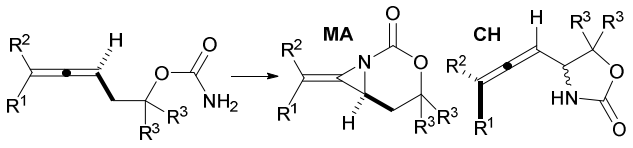


entry	desired product	catalyst	MA:CH	*E*:*Z*	yield
1		$Rh_2(esp)_2$	1:1	---	34%
		AgOTf/phen	9:1	4.8:1	80%
2		$Rh_2(esp)_2$	1:17	2:1	5%
		AgOTf/phen	5.9:1	1.9:1	70%
3		$Rh_2(esp)_2$	2:1	---	35%
		AgOTf/phen	>20:1	---	79%
4		$Rh_2(esp)_2$	1:1.3	2.3:1	34%
		AgOTf/phen	11.5:1	2.6:1	87%
5		$Rh_2(esp)_2$	1.1:1	---	32%
		AgOTf/phen	19:1	2.3:1	70%

substrate contained a *gem*-dimethyl group in the tether between the allene and the carbamate (Table 7, entry 2), in contrast to $Rh_2(esp)_2$, which favoured C-H insertion by a factor of 17:1.

In the course of these investigations, it was discovered that the chemoselectivity of C-N bond formation could be reversed to favour allenic C-H insertion by simply changing the AgOTf: phenanthroline ratio to 1:3.[34] This selectivity was reagent-controlled across a broad range of homoallenic carbamates (Table 8). NMR spectroscopy of catalyst solutions suggested that the major species in solution at low ligand loadings contained a 1:1 ratio of Ag:phen, while the major species at higher ligand loadings consisted of a complex have two ligands bound to the metal center. The group has termed their ability to favour different catalytically active species using a single metal and ligand "dynamic catalysis," and is currently investigating its application to other carbon-carbon and carbon-heteroatom bond-forming reactions involving allenes.

Table 8 Selective and tunable amination of allenes.



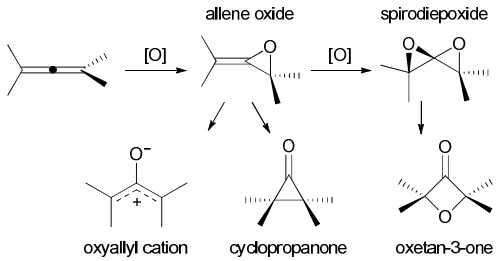
entry	R^1	R^2	R^3	AgOTf:phen[a,b]	MA:CH	MA	C-H
1	Me	Me	H	1:1.25	1:20	<4%	79%
				1:3	100:0	81%	0%
2	C_5H_{11}	H	Me	1:1.25	1:5.9	13%	79%
				1:3	76:1	76%	1%
3	C_5H_{11}	H	H	1:1.25	1:4	18%	72%
				1:3	13:1	65%	5%
				1:3[d]	100:1	71%	<1%
4	^{t}Bu	H	H	1:1.25[c]	1:3.7	18%	67%
				1:3	100:0	83%	0%
5	C_5H_{11}	Me	H	1:1.25	1:11.5	7%	87%
				1:3	100:0	88%	0%
6	Et	Me	H	1:1.25	1:19	4%	70%
				1:3	100:0	78%	0%
7	^{i}Bu	H	H	1:1.25	1:4.8	12%	57%
				1:3	19:1	74%	4%
				1:3[d]	100:1	68%	<1%
8	$(CH_2)_2Ph$	H	H	1:1.25	0:100	0%	61%
				1:3	24:1	74%	3%
				1:3[d]	100:1	71%	<1%

[a]Aziridination: 20% AgOTf, 25% phen, 2 equiv PhIO, 4 Å MS, CH_2Cl_2.
[b]C-H insertion: 10% AgOTf, 30% phen, 3.5 equiv PhIO, 4 Å MS, CH_2Cl_2.
[c]2,2'-bipyridine ligand. [d]10 mol% BHT used

4. Allene oxides and spirodiepoxides (SDEs)

4.1 Introduction

Of all the heteroatom analogues of methylene cyclopropane, allene oxides and the related spirodiepoxides (SDE) have been the most extensively studied. A wide variety of oxidants have been used to generate these motifs from allenes, including peracids, dioxiranes, oxaziridines, and hydrogen peroxide with a transition metal catalyst (such as W or V). The choice of oxidant, specific reaction conditions and the allene substitution pattern all have a profound impact on the intermediates that are favoured in these epoxidation reactions (Scheme 18).

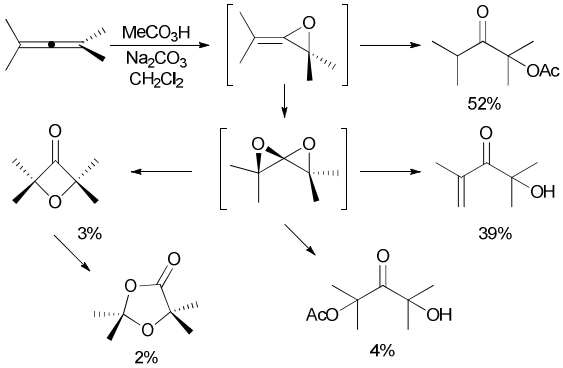


Scheme 18 Reactive intermediates and products accessible from allene epoxidation.

This section on allene epoxidation is divided into four sub-sections based on the types of transformations performed on these intermediates. The first two sections deal with nucleophilic ring-opening of allene oxides and SDEs to generate α-substituted ketones. Work prior to 1993 in allene epoxidation is covered in the first sub-section, with a few modern examples that are thematically related. Work since 1993 is detailed in the second sub-section. The final two sub-sections deal with transformations of oxyallyl cations generated from allene oxides, including oxidative [4π] electrocyclizations of vinylallenes and oxidative [4+3] cycloadditions of allenamides.

4.2 Peracid/DMDO oxidation of allenes followed by nucleophilic ring-opening: work prior to 1993

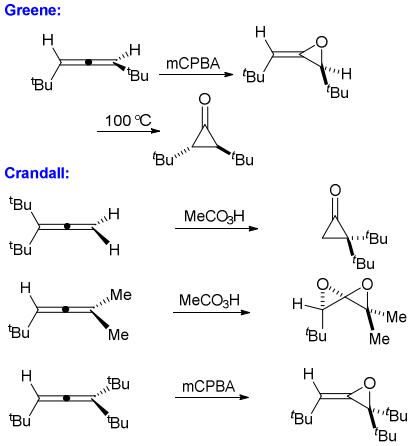
Initial attempts at allene oxidation were first carried out by the Crandall group in 1966 using peracid reagents.[35] The $MeCO_3H$ oxidation of tetramethylallene was investigated, with the goal of isolating an allene oxide or its valence tautomer, cyclopropanone. However, neither of the expected products were observed; rather, a number of α-oxygenated ketones were isolated, including an oxetan-3-one and its Baeyer-Villiger oxidation product (Scheme 19). Crandall proposed that these products arose from either allene oxide or spirodiepoxide intermediates, but no spectroscopic evidence of their existence was obtained.



Scheme 19 Fates of allene oxides and spirodiepoxides.

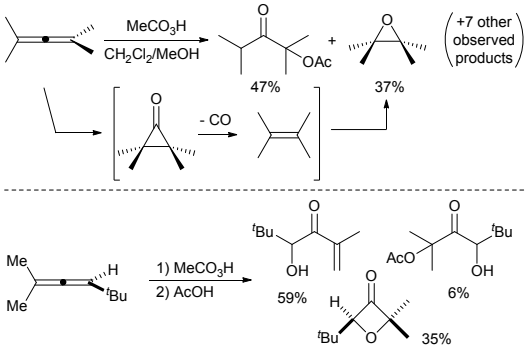
Two years later, the groups of Crandall and Greene simultaneously reported the isolation of an allene oxide, its cyclopropanone tautomer, and an SDE. The use of bulky, *tert*-

butyl-substituted allenes provided intermediates stable enough to be isolated by distillation. Greene reported the allene oxide resulting from oxidation of 1,3-di-*tert*-butylallene and confirmed its thermal isomerization to a cyclopropanone (Scheme 20).[36] Concurrently with Greene, Crandall reported the isolation of a cyclopropanone formed from 1,1-di-*tert*-butylallene, but the allene oxide was not observed.[37] He also reported the first stable spirodiepoxide derived from 1,1-dimethyl-3-*tert*-butylallene.[38] Another stable allene oxide was later reported from mCPBA oxidation of 1,1,3-tri-*tert*-butylallene (Scheme 20).[39] The products were verified by NMR and MS, and showed reactivity similar to that observed in Scheme 19.



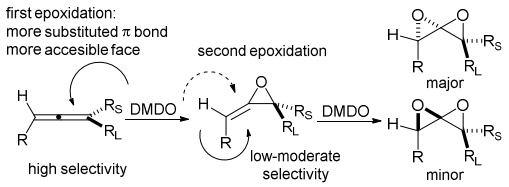
Scheme 20 Early isolation of allene oxidation products.

One drawback to the use of peracid reagents for allene epoxidation was the propensity of the allene oxide and SDE to give multiple products under the acidic reaction conditions. As seen in Scheme 21, the oxidation of tetramethylallene in methanol with no basic additive gave two major products resulting from reaction of the allene oxide, as well as minor amounts of seven other products.[40] The surprising observance of tetramethylethylene oxide was rationalized by "oxidative decarbonylation" of a cyclopropanone intermediate. When more sterically hindered allenes were employed, the spirodiepoxides could be isolated, but upon treatment with acid decomposed to mixtures of oxetan-3-one and α–hydroxyketone products (Scheme 21, bottom).[41] It should be noted that the addition of base sometimes improved the regioselectivity (recall Scheme 19), but multiple products were often observed.



Scheme 21 Reactivity of allene oxides and SDEs under acidic conditions.

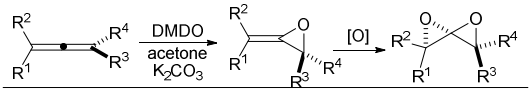
The development of dimethyldioxirane (DMDO) as a mild alternative to peracetic acids provided access to SDEs in higher yields. In 1988, fourteen years after their last report, Crandall and co-workers described the DMDO oxidation of alkyl-substituted allenes to spirodiepoxides in high yields and diastereoselectivities.[42] Simple steric and electronic arguments were used to rationalize the stereochemical outcome of the reaction (Scheme 22). If the substituent effects on the rate of epoxidation are assumed to be comparable to those of alkenes, the first epoxidation should occur at the more substituted (i.e., more electron-rich) olefin of the allene, with the oxidant approaching from the π-face opposite the bulkier substituent on the adjacent olefin. The second epoxidation also occurs at the π-face opposite the bulkiest group of the newly formed epoxide. Good to excellent diastereoselectivities were observed for two trisubstituted allenes (Table 9, entries 1 and 2) and a monosubstituted allene (entry 5). Two symmetrical allenes (entries 3 and 4) also gave moderate to good yields. Ring-opening of an SDE was achieved with a number of different nucleophiles (Table 10), with generally good yields and good to excellent regioselectivity. As expected, nucleophiles preferred to attack at the less substituted position of the SDE.



Scheme 22 General model for stereoselectivity in the bisepoxidation of allenes.

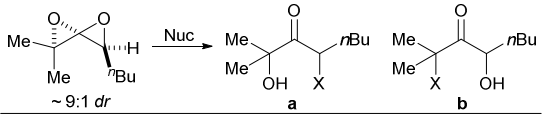
While the diastereoselectivities of epoxidation were generally high for the substrates in Table 9, a number of 1,3-disubstituted allenes gave mixtures of several diastereomers. The relative diastereoselectivities observed for these substrates (Scheme 23) could be rationalized by steric preferences. As the steric bulk of the R group increases, oxidation is increasingly favoured at the π-faces *anti* to these groups; thus, increasing the size of R from ^{n}Pr to ^{i}Pr to ^{t}Bu leads to an increase in the diastereoselectivity.

Table 9 Formation of SDEs *via* DMDO oxidation.



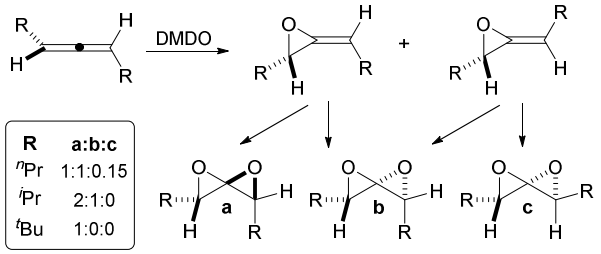
entry	R^1	R^2	R^3	R^4	yield	*dr*
1	Me	Me	^{t}Bu	H	84%	> 10:1
2	Me	Me	^{n}Bu	H	95%	9:1
3	Me	Me	Me	Me	44%	NA
4	^{n}Bu	^{n}Bu	H	H	80%	NA
5	*n*-oct	H	H	H	50%	5:1

Table 10 Nucleophilic ring-opening of an SDE.



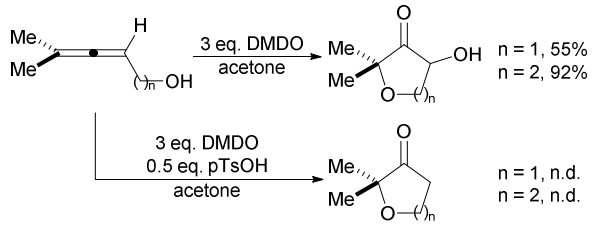
~ 9:1 *dr*

Nuc	X	Yield	a:b	Nuc	X	Yield	a:b
			a				**b**
H_2O/THF	OH	80%	NA	NH_3	NH_2	nd	10:1
Bu_4NOAc/AcOH	OAc	quant.	100:0	$^{n}PrNH_2$	$^{n}PrNH$	83%	10:1
$^{n}PrOH/K_2CO_3$	OPr	95%	83:17	1-imidazolyl	imid.	48%	100:0
$^{n}PrOH$/NaH	OPr	78%	97:3	PhSH	SPh	55%	100:0
$BnNH_2$	BnNH	61%	100:0	Bu_4NF	F	35%	100:0



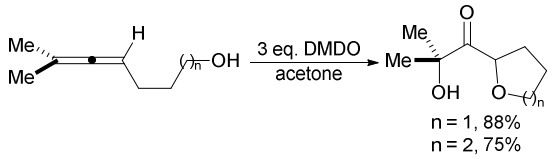
Scheme 23 DMDO oxidation of 1,3-disubstituted allenes.

The Crandall group next turned their attention to tandem epoxidation/ring-opening reactions utilizing allenes with tethered nucleophiles. The oxidative rearrangement of trisubstituted allenyl alcohols under neutral conditions (DMDO/acetone) resulted in SDE formation and subsequent ring-opening to give hydroxytetrahydrofuranone and pyranone products (Scheme 24, top).[43] Under acidic conditions, the allene oxides were intercepted to give the corresponding deoxy analogues (Scheme 24, bottom), but yields were not reported. In cases where diastereomeric products could be formed, the *dr* was usually lower than 3:1, indicating unselective oxidation. The Bertrand group observed analogous products from the treatment of allenyl alcohols with H_2O_2 in benzonitrile.[43]



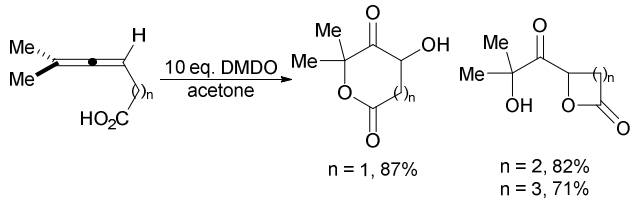
Scheme 24 Oxidation of allenic and homoallenic alcohols.

Crandall reported that increasing the tether length between the allene and alcohol gave ring-opening at the proximal position of the allene, resulting in good yields when five or six-membered ring formation was possible (Scheme 25).



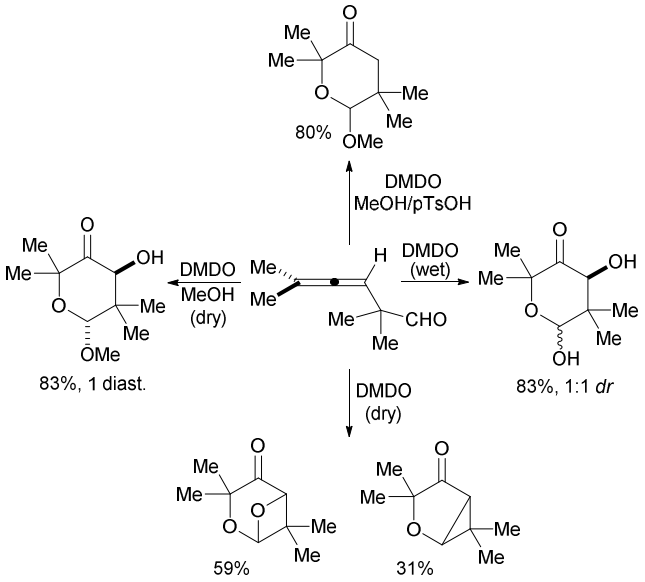
Scheme 25 Oxidation of γ- and δ-allenyl alcohols.

Analogous results were obtained for allenyl acids.[44] The tether length dictated whether distal or proximal ring-opening occurred to give hydroxy-lactone products (Scheme 26). Products containing an α-hydroxy ketone motif (n = 0, 1) were sensitive to ketol transposition. Oxidation of the allene oxide to the SDE generally outcompeted intramolecular ring-opening under neutral conditions.



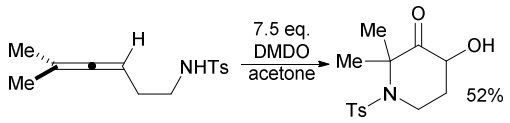
Scheme 26 Oxidation of allenyl carboxylic acids.

Crandall further demonstrated that pendant aldehydes could ring-open allene oxidation products, generating oxocarbenium ions that could be trapped by a number of nucleophiles (Scheme 27).[45] Although competing aldehyde oxidation to the carboxylic acid was a concern, this only occurred for less reactive monosubstituted allenes.

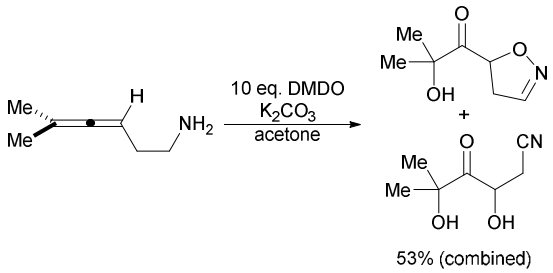


Scheme 27 Oxidation of allenyl aldehydes.

Similar to the reactivity observed in Schemes 24-27, a β-allenyl tosylamide resulted in the formation of a hydroxypiperidone in moderate yield (Scheme 28),[46] although these reactions also suffered from ketol transposition. Although an unprotected allenyl amine gave N-oxidation under the reaction conditions, the resulting oxime trapped the spirodiepoxide to form an isoxazoline (Scheme 29). Under basic conditions, the isoxazoline rearranged to an α-hydroxy-β-cyano ketone.



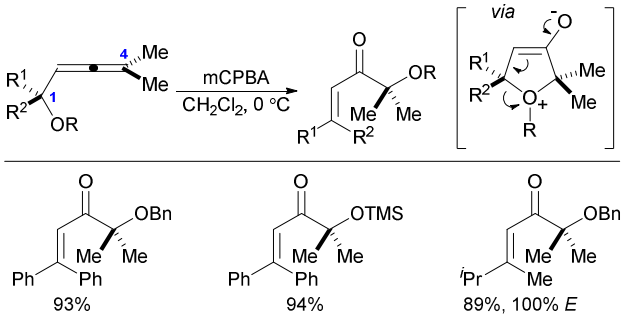
Scheme 28 Oxidation of allenyl tosylamides.



Scheme 29 Oxidation of allenyl amines

In 2010, Malacria and co-workers reported the epoxidation of allenic ethers with *m*CPBA to give α-alkoxy enones.[47] The products were thought to arise from ring-openings of allene oxides to give modified enolates capable of retro-Michael

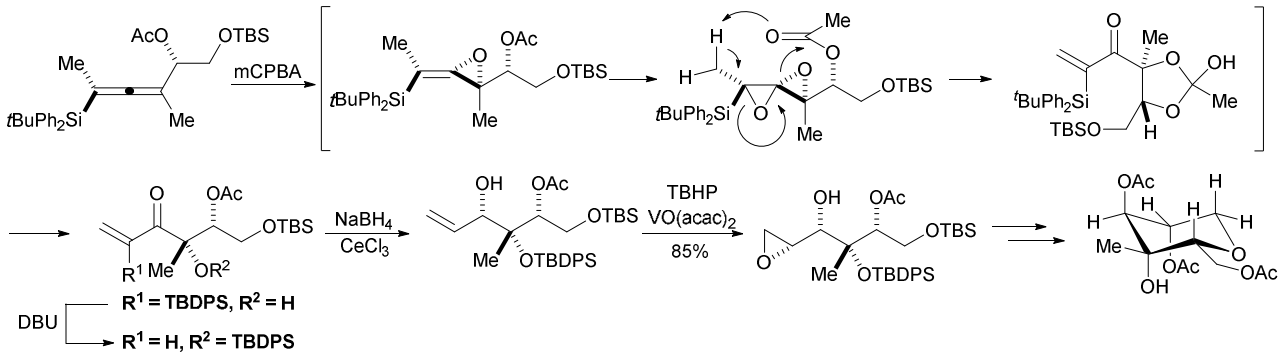
addition (Scheme 30). The reaction was tolerant of a variety of ether substituents and proceeded in high yield for trisubstituted allenes. Allenes that were less substituted at C4 gave little to no product, presumably due to the low nucleophilicity of the remote olefin. Use of excess *m*CPBA gave rise to epoxy ketones in a single pot.



Scheme 30 Oxidation of allenic ethers.

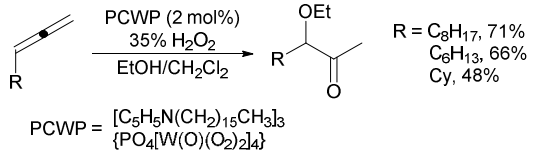
4.3 Peracid/DMDO oxidation of allenes followed by nucleophilic ring-opening: work after 1993

In 1993, Marshall and Tang disclosed a method for the synthesis of carbohydrates *via* allene bisepoxidation.[48] Treatment of a silyl-substituted allene with *m*CPBA yielded a silyl enone as a single diastereomer. Formation of the enone occurred *via* acetate-assisted elimination as depicted in Scheme 31. Treatment with DBU facilitated C-to-O silyl migration to protect the newly formed alcohol. Reduction of the enone under Luche conditions, followed by $VO(acac)_2$-catalyzed epoxidation, provided an advanced intermediate in 85% yield as a single diastereomer. A series of deprotections and cyclization led to an analogue of deoxypyranose. This impressive work highlights the usefulness of allene oxidation for generating complex, stereodefined frameworks that can be utilized in later steps for highly diastereoselective transformations.



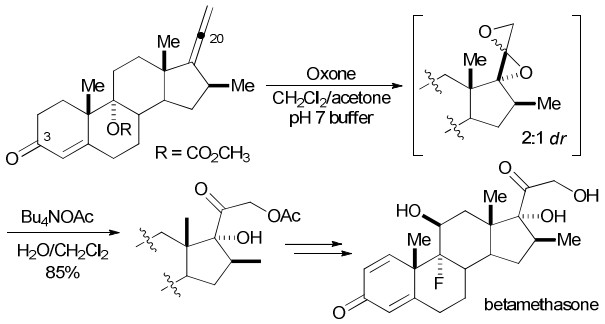
Scheme 31 Deoxypryanose synthesis *via* a spirodiepoxide intermediate.

The one-pot conversion of allenes to α-alkoxy ketones using H_2O_2, peroxotungstophosphate, and alcohols was reported by Ishii and co-workers in 1994 (Scheme 32).[49] Ethanol in CH_2Cl_2 gave the highest yields and selectivities. While the reaction proceeded in good yield and selectivity for monosubstituted allenes, 1,1- and 1,3-disubstituted allenes were not efficient substrates. Allene oxides were suggested as intermediates for this process, but were not directly observed.



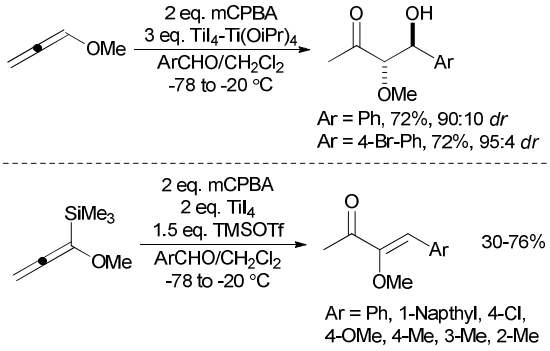
Scheme 32 Peroxotungstophosphate-mediated oxidation of allenes.

In 1996, chemists at Schering-Plough reported an alternative approach to the corticoid betamethasone that proceeded through an SDE intermediate (Scheme 33).[50] Treatment of the steroidal allene with *in situ*-generated DMDO provided the requisite SDE in 2:1 *dr*; however, ring-opening with Bu_4NOAc provided a single ketone product, indicating that the source of diastereoselectivity was at C20. The disubstituted ketone was obtained in 85% over two steps, and was readily carried on to a known betamethasone precursor.



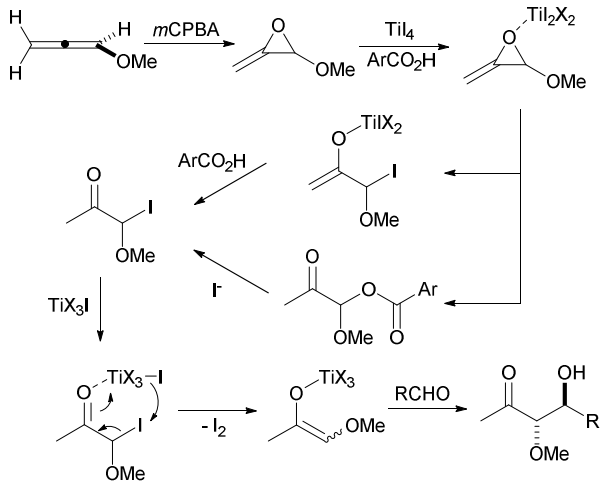
Scheme 33 Formal synthesis of betamethasone.

In 2000, Shimizu and co-workers demonstrated the use of methoxyallenes as enolate equivalents for the stereoselective formation of 2,3-dialkoxy and 3-hydroxy-2-methoxyketones.[51] Initial investigations into these transformations involved the mono-epoxidation of methoxyallene with *m*CPBA, followed by addition of TiI_4 to generate an α-OMe titanium enolate, with aryl acetals used as electrophiles. The stereoselectivity of the transformation was greatly improved by switching to aldehyde electrophiles and adding stoichiometric $Ti(O^iPr)_4$ to the reaction (Scheme 34, top). Similarly, Shimizu has incorporated a TMS group into the allene to carry out *in situ* Petersen olefinations to generate enone products (Scheme 34, bottom).[52]



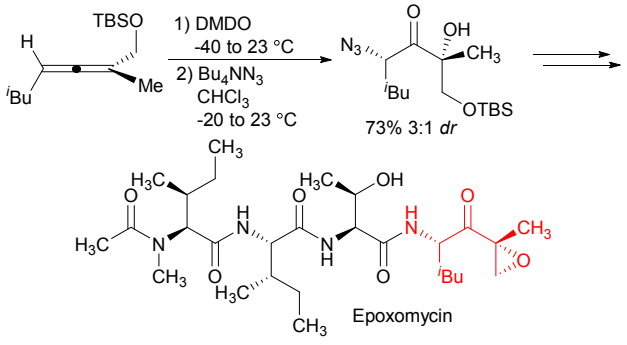
Scheme 34 Methoxyallene as an enolate equivalent.

The relationship between the methyoxyallene and the purported titanium enolate is not obvious. Shimizu proposed a mechanism wherein the allene oxide first binds to the Ti(IV) species (Scheme 35). Ring-opening and tautomerization forms an α-iodo ketone, which undergoes reductive enolization to form a titanium enolate capable of engaging in aldol chemistry.



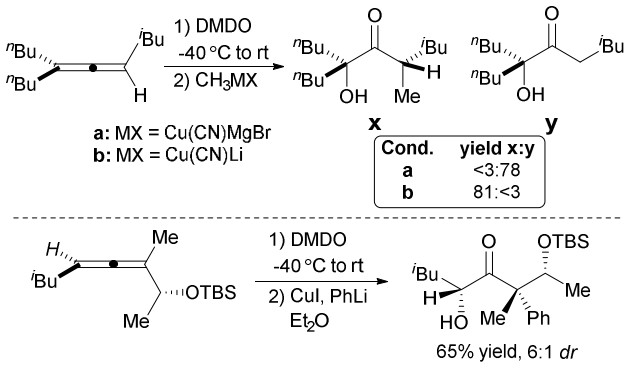
Scheme 35 Proposed mechanism of Ti-enolate formation.

The Williams group initiated their investigations into allene epoxidation in 2004 with the total synthesis of epoxomycin.[53] Bisepoxidation of a trisubstituted allene, followed by azide ring-opening, provided rapid access to the α,β-epoxy-α'-amino fragment of epoxomycin (Scheme 36). Although the *dr* was moderate for this reaction, it assembled the sensitive bis-substituted ketone in a single step while avoiding epimerization at both of the stereocenters. This strategy was later employed to access several unnatural stereoisomers of epoxomycin.[54]



Scheme 36 Total synthesis of epoxomycin.

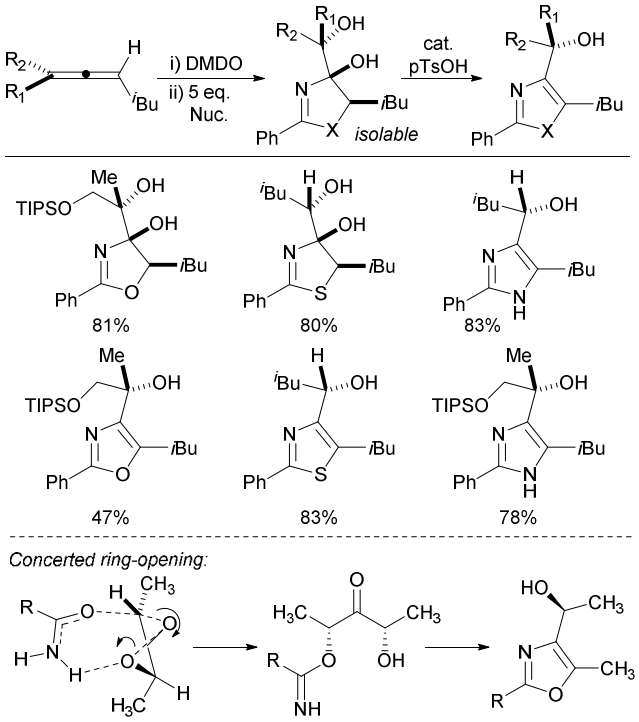
In 2007, Williams and co-workers described the copper-mediated ring-opening of SDEs with carbon nucleophiles to form densely functionalized α-hydroxy ketones (Scheme 37).[55] Initial experiments with higher order cuprates gave poor regioselectivity in the desired ring-opening cascade; however, cyanocuprates improved the selectivity. Lewis-acidic Grignard-derived cyanocuprates led to an unexpected reduced product (Scheme 37, top), but lithium-derived cyanocuprates provided the desired products in good yield. For aryl nucleophiles, more reactive Gilman reagents were necessary to provide the desired products in good yield (Scheme 37, bottom). The diasteromeric ratios of the ketone products were identical compared to the spirodiepoxide intermediates, with the cuprate addition occurring with inversion of stereochemistry.



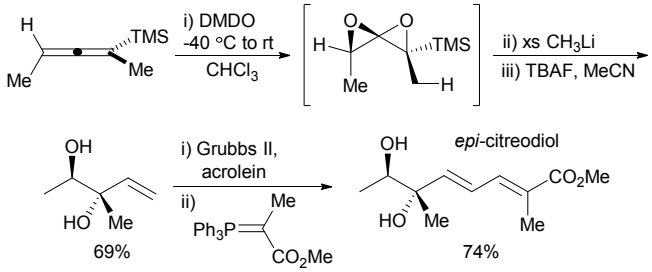
Scheme 37 Organocuprate opening of SDEs.

Subsequent investigations by the Williams group employed amide and thioamide nucleophiles to demonstrate that spirodiepoxides could serve as direct precursors to complex heteroaromatics.[56] The additions of benzamide, thiobenzamide, and benzamidine to spirodiepoxides furnished oxazoles, thiazoles, and imidazoles, respectively, in good yields (Scheme 38). Williams rationalized the unusually high reactivity of these neutral nucleophiles by suggesting that hydrogen bonding between the nucleophile and SDE occurs to activate the substrate for a concerted, asynchronous ring-opening of both epoxides. Computational work provided support for a concerted ring-opening mechanism over a stepwise process.

An important consideration in using spirodiepoxides for the synthesis of complex molecules is the lack of site selectivity in the first epoxidation of 1,3-disubstituted allenes, and the generally modest stereoselectivity of the second epoxidation (recall Scheme 23). In one report, Williams and co-workers overcame this challenge by the use of electronically and sterically biased silylallene substrates, similar to the work of Marshall (see Scheme 31, above).[57] Thus, epoxidation of a silylallene gave the spirodiepoxide as a single diastereomer, owing to the ability of the TMS group to direct the first oxidation to the proximal olefin, as well as control the facial selectivity of the second oxidation (Scheme 39). Treatment with excess CH_3Li led to eliminative ring-opening, followed by diastereoselective reduction of the resulting ketone.[58] After silyl deprotection, the resulting diol was rapidly carried on to *epi*-citreodiol.



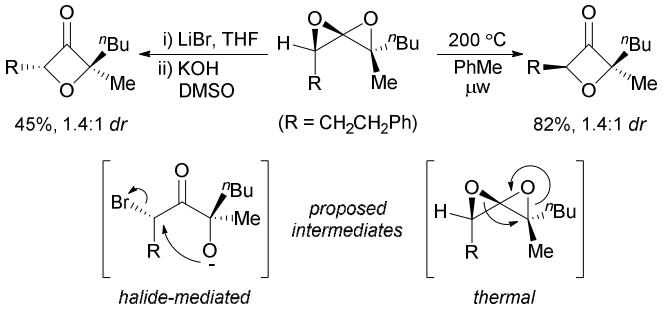
Scheme 38 Formation of complex heterocycles by SDE ring-opening.



Scheme 39 Generation of complex heterocycles by epoxidation of silyl allenes.

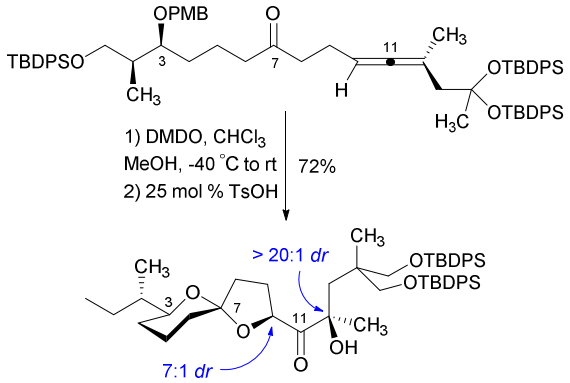
More recently, the Williams group optimized the transformation of spirodiepoxides to oxetan-3-ones, which were originally isolated as minor products of allene oxidations (see Scheme 19).[59] Two diastereodivergent methods for their synthesis were developed; the first involved halide ring-opening followed by base-mediated ring closure, while the second approach utilized a thermal rearrangement (Scheme 40). The differential stereochemical outcome was rationalized by a double displacement in the bromide/base-mediated reaction, and a concerted rearrangement in the case of the thermal reaction. The *dr* of the products matched the *dr*'s of the SDEs in all cases, which were generally modest for unsymmetrical allenes.

To conclude this discussion, efforts by the Williams group to apply allene epoxidation to complex molecule synthesis will be described. In a 2007 synthesis towards pectenotoxin 4, Williams and co-workers employed allene bis-epoxidation to form both a spiroketal and α-hydroxy ketone moiety (Scheme



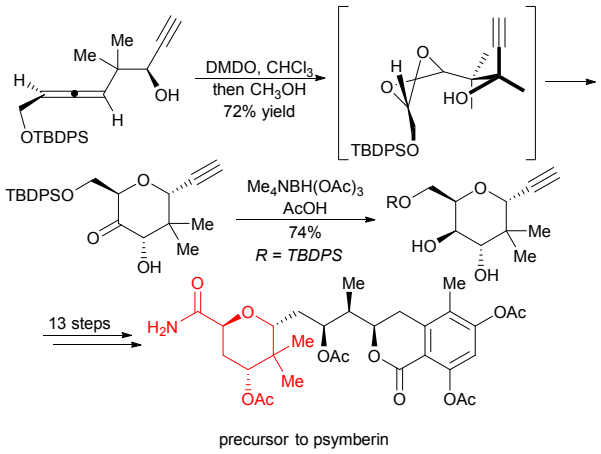
Scheme 40 Conversion of SDE's to oxetan-3-ones.

41).[60] The SDE intermediate (not shown) was formed in high *dr*, due to masking of a ketone group as a bis-TBDPS protected acetal. While the exact sequence of events could not be proven for this transformation, spiroketal formation likely occurs by ring-opening of the SDE by the C7 ketone, followed by *in situ* deprotection of the C3 PMB-alcohol to trap the oxocarbenium ion intermediate.



Scheme 41 Synthesis of the A-B ring system of Pectenotoxin 4.

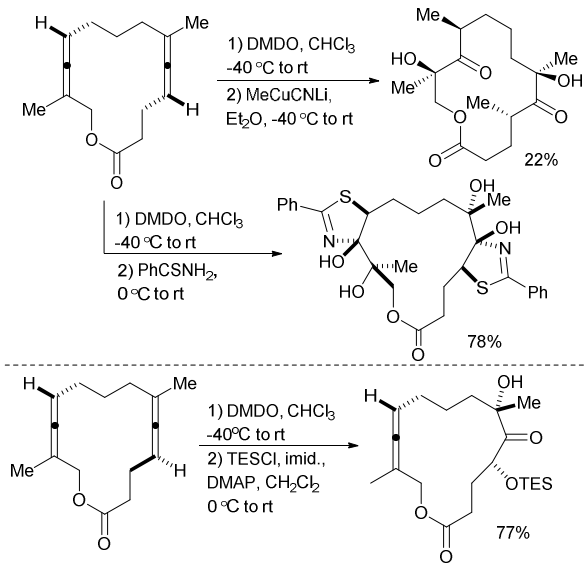
Intramolecular ring-opening of a spirodiepoxide was also utilized in a formal total synthesis of the antitumor agent psymberin by the Williams group.[61] The highly substituted pyran core was assembled *via* DMDO bisepoxidation of the allene shown in Scheme 42. The SDE underwent intramolecular ring-opening and rearrangement to yield a single diastereomer of the pyranone. Stereoselective reduction of the ketone provided the triol in 74% yield and 20:1 *dr*. Subsequent



Scheme 42 Formal total synthesis of psymberin.

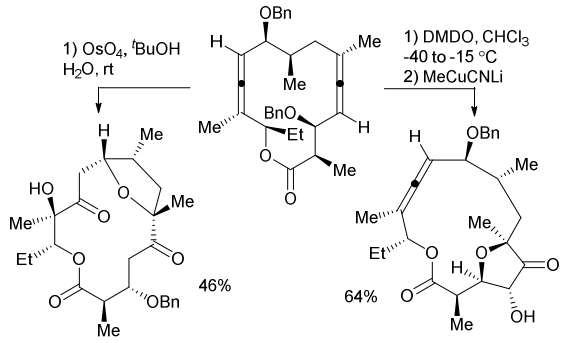
transformations removed an undesired alcohol and the fragment was successfully converted to a known precursor of psymberin, demonstrating the utility of SDE openings to generate complex heterocycles.

Perhaps the most impressive demonstration of the potential of spirodiepoxides in total synthesis is the use of macrocyclic bis[allenes] to prepare analogues of the important antibiotic macrolide erythromycin. Initial studies were carried out on a model substrate containing chirality only at the two allenes (Scheme 43).[62] Epoxidation of both allenes, followed by addition of methyl cuprate, gave the ring-opened product in modest yield; however, ring-opening with thiobenzamide resulted in higher yields. If fewer equivalents of oxidant were used, one allene was preferentially reacted over the other, allowing for multiple nucleophiles to be incorporated into the macrocyclic framework.



Scheme 43 Model studies on bis[allene] epoxidation.

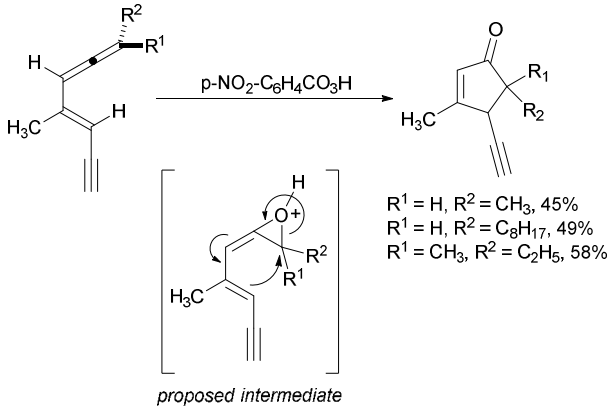
Further studies on a more complex substrate demonstrated the versatility of bisallenes for the synthesis of the erythronolides.[63] Allene osmylation was an effective strategy for accessing hydroxylated macrolides, while DMDO epoxidation was useful for the selective oxidation of a single allene. When lithium methylcyanocuprate was added to the resulting epoxide, a pyranone was attained in 64% yield (Scheme 44, right). The improved selectivities for this more complex substrate demonstrate both the challenge and promise of achieving predictable transformations with spirodiepoxides.



Scheme 44 Further transformations toward erythronolides.

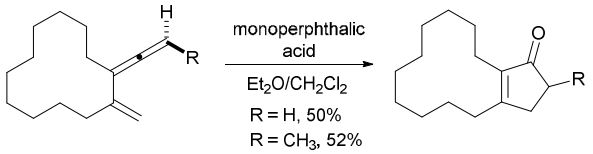
4.4 Epoxidation of vinylallenes followed by [4π] electrocyclization

Several groups have demonstrated the utility of vinylallenes as precursors for the formation of oxypentadienyl cations, which undergo Nazarov-type cyclizations to give substituted cyclopentenones. In 1977, Gore and co-workers described the treatment of vinylallenes with peracids to yield cyclopentenones in moderate yield (Scheme 45).[64] Side products consistent with carboxylate ring-opening of allene oxides were observed. Rather than invoking an oxypentadienyl cation capable of undergoing 4π electrocyclization, Gore proposed a concerted rearrangement of the allene oxide to account for the observed products. Such a mechanism implies suprafacial ring closure; however, stereochemical confirmation of the mechanism was not reported.



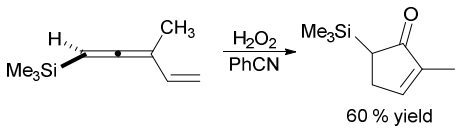
Scheme 45 Early work in oxidative [4π] rearrangement of vinylallenes.

Subsequent to this initial work, Bertrand and co-workers reported the similar transformation of a macrocyclic vinylallene to form bicyclic cyclopentenones (Scheme 46).[65] The products were described as potential intermediates towards exaltone and muscone.



Scheme 46 Oxidative rearrangement of macrocyclic vinylallenes.

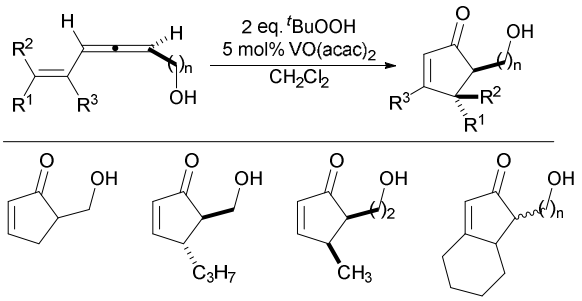
The scope of these transformations was further expanded by Santelli and co-workers (Scheme 47), who described a single example of the cyclization of a silyl-substituted vinyl allene in 60% yield, utilizing H_2O_2 in benzonitrile.[66]



Scheme 47 Oxidative vinylallene rearrangement by Santelli.

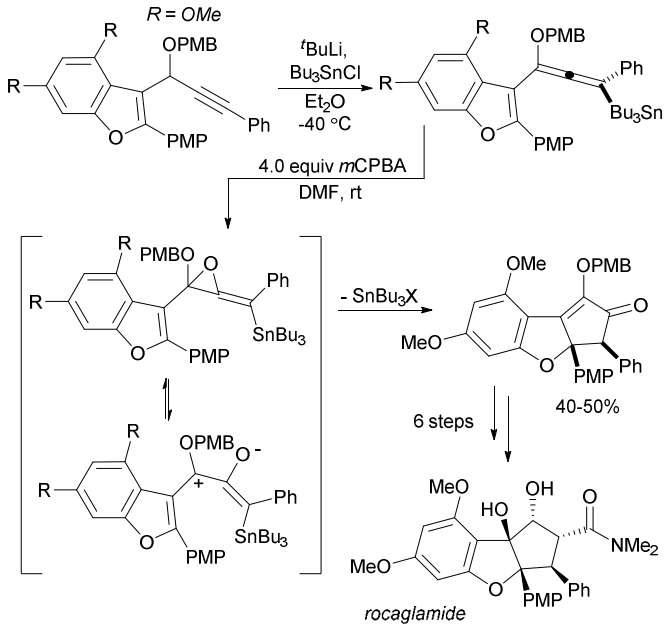
In 1988, Kim and Cha described the epoxidation of vinylallenes with free β-hydroxy groups using $VO(acac)_2$/^{t}BuOOH to yield cyclopentenones after rearrangement (Scheme 48).[67] They hypothesized that these

products arose from antarafacial cyclization of an oxypentadienyl cation intermediate, a proposal consistent with the observed stereochemistry.



Scheme 48 Cyclizations of vinyl allene alcohols by Cha (yields reported as a range of 40-70%).

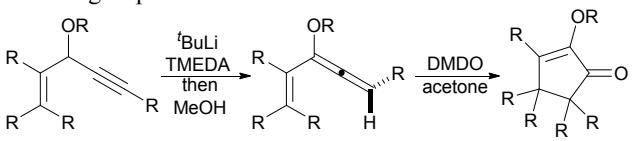
Frontier and co-workers employed the Nazarov cyclization of oxyallyl cations derived from allenes in the total synthesis of the anticancer agent rocaglamide.[68] The stannyl alkoxyallene shown in Scheme 49 was derived by deprotonation and trapping of a propargyl PMB ester by $SnBu_3Cl$. Addition of mCPBA triggered the oxidation/rearrangement process to give the fused cyclopentenone core of rocaglamide. The use of the alkoxyallene to generate the oxyallyl cation was critical, as previous work with more traditional divinyl ketones was not successful.[69]

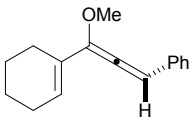
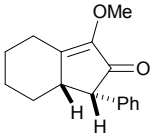
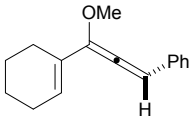
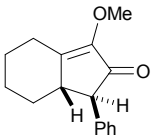
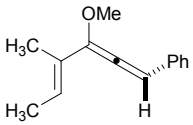
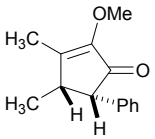
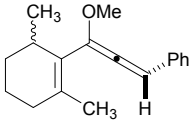
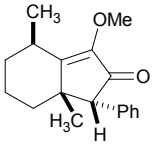
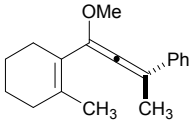
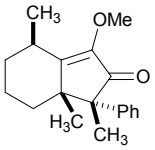


Scheme 49 Allene oxidation/Nazarov cyclization in the total synthesis of rocaglamide.

Frontier later optimized the allene oxidation/cyclization protocol.[70] With simpler substrates, the allenyl lithium intermediate could be trapped with methanol rather than a stannyl chloride, and the substitution of DMDO for *m*CPBA to give higher yields of the rearranged product. Table 11 shows selected substrates employed in this transformation. A *cis* configuration between the newly formed stereocenters was generally favoured; however, epimerization to the more stable *trans* isomer was possible (entries 1 and 2). Impressively, an adjacent stereocenter completely controlled the torquoselectivity of the electrocyclization, resulting in a single diastereomer (Entry 4). Finally, two contiguous quaternary centres could be formed by this method (Entry 5), demonstrating the usefulness of allenes as alternative precursors to Nazarov-type intermediates.

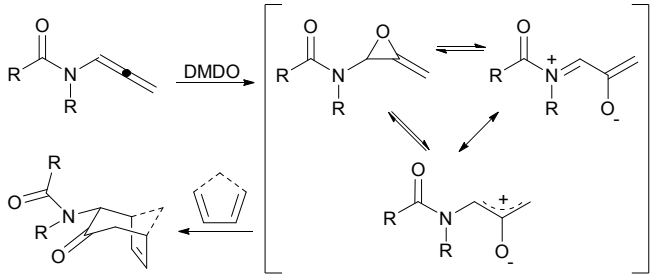
Table 11 Scope of allene oxidation/Nazarov cyclization by Frontier group.



entry	alkoxyallene	product	%yield (over 2 steps)
1			57
2			57 (epimerized by silica gel chromatography)
3			41
4			56
5			44

4.5 DMDO epoxidation of allenamides followed by [4+3] cycloaddition

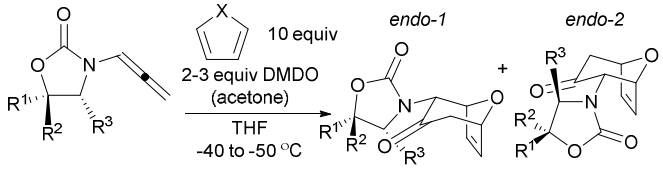
The use of oxyallyl cations in [4+3] cycloadditions is a well-precedented method for generating 7-membered carbocycles;[71] however, these intermediates are most commonly generated from α-halo ketones. In 2001, Hsung and co-workers demonstrated that monoepoxidation of allenamides generates nitrogen-stabilized oxyallyl cations that readily undergo [4+3] cycloadditions with dienes. In addition to activating the allene for epoxidation and stabilizing the electrophilic oxyallyl cation, the nitrogen atom provides a framework for incorporating chiral auxiliaries to control the absolute stereochemistry of the reaction products (Scheme 50).



Scheme 50 Generation of N-stabilized oxyallyl cations *via* allenamide oxidation.

In their first report (Table 12), the Hsung group utilized an Evans auxiliary to control the facial selectivity of intermolecular [4+3] reactions of allenamides with furan.[72] The cyclization was found to be exclusively selective for the *endo* product, with several chiral oxazolidinones providing a single stereoisomer in high *dr*. Cyclopentadiene was tolerated, albeit in lower yields (entry 2). Of the Lewis acids screened, only $ZnCl_2$ was found to offer substantial improvement in *dr*, although it was not required in every case. Epoxidation of the product was not reported as a side reaction.

Table 12 Intermolecular [4+3] of allenamides using the Evans auxiliary.



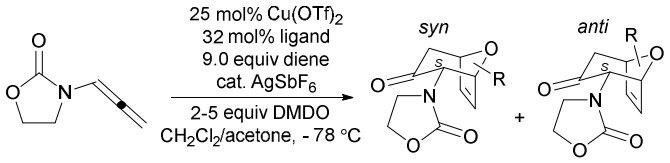
entry	R^1	R^2	R^3	X	yield	*endo-1:endo-2*
1	H	H	Ph	O	77[a]	94:6
2	H	H	Ph	CH_2	40[a]	> 95:5
3	H	H	Bn	O	67	77:23
4	H	H	$CHPh_2$	O	74	> 95:5
5	Ph	Ph	^{i}Pr	O	72	94:6

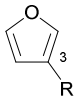
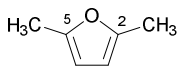
[a] 2.0 eq. of $ZnCl_2$ was used.

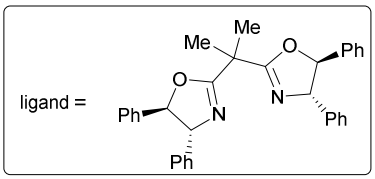
A catalytic asymmetric variant of this process was reported in 2004.[73] Using a chiral Cu(II) bisoxazoline complex, *ee*'s of up to 99% could be achieved, offering an alternative to chiral auxiliaries for gaining access to enantioenriched products (Table 13). Although $ZnCl_2$ had previously been beneficial in these reactions (see Table 12), the use of chiral zinc complexes did not provide useful levels of enantioinduction. However, the addition of $AgSbF_6$ improved both yields and *ee*'s. The system tolerated substituted furans, with the *syn/anti* ratios depending on the placement of the substituents. While 2-substituted furans favoured the *syn* product shown in Table 13 (where the furan substituent is positioned proximal to the oxazolidinone group), 3-substituted substrates favoured the *anti* product. This trend in diastereoselectivity held true when reactions of this type were investigated in later work.[74]

In addition to intermolecular examples, two different intramolecular [4+3] reactions were reported. By tethering both the allene and the diene to nitrogen, (Scheme 51, top), tricyclic systems could be generated.[75] Diastereoselectivities were poor unless an oxazolidinone or lactam linker was incorporated into the tether. Incorporating the furan through a 1,3-disubstituted allene (Scheme 51, bottom) gave similar motifs with generally good *dr*.[76] The allene stereochemistry had no impact on the

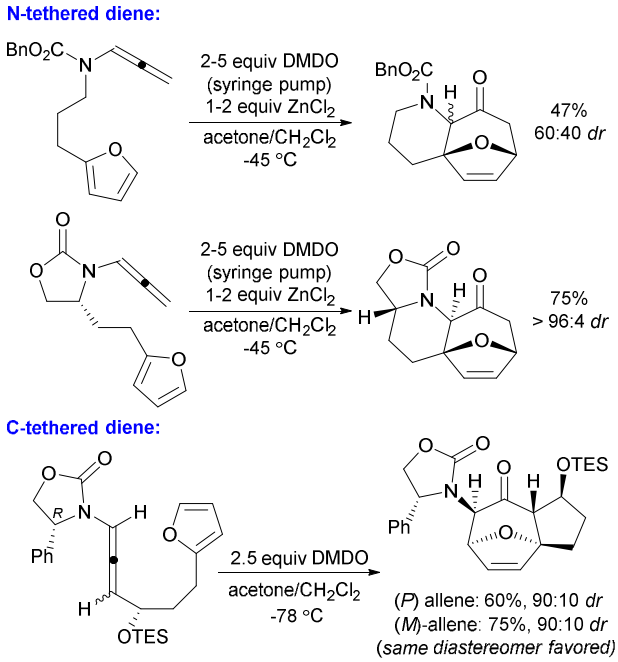
Table 13 Catalytic asymmetric [4+3] using a Cu(II)-BOX catalyst.



entry	diene	R	yield	*syn:anti*	%*ee*
1		H	91	NA	99
2		Me	88	20:1	71
3		Me	91	*anti* only	99
4		Br	58	1:14	84
5		-	81	NA	36



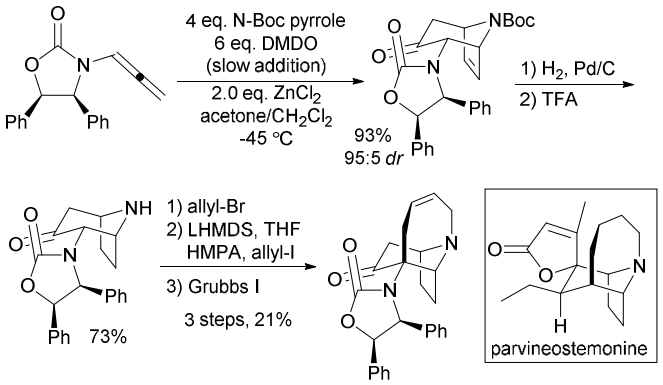
stereochemical outcome of the reaction, indicating the likely intermediacy of a cationic intermediate. Often these systems required a slow addition of DMDO; fast addition led to low yields that were attributed to competing furan oxidation.



Scheme 51 Top: intramolecular [4+3] cycloaddition *via* an N-tethered diene. Bottom: intramolecular [4+3] cycloaddition *via* a C-tethered 1,3-disubstituted allene.

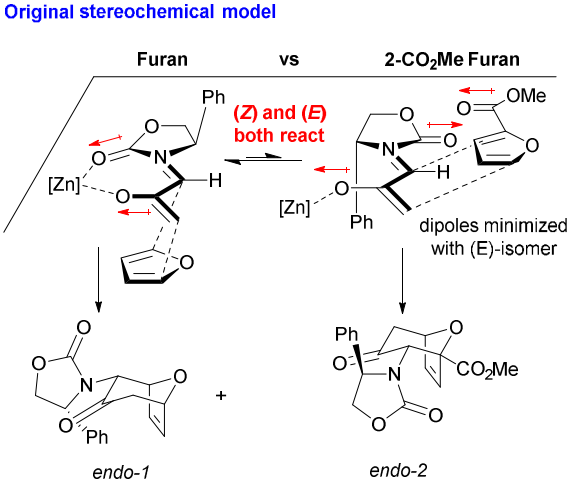
Intermolecular [4+3] reactions with pyrrole were also demonstrated.[77] These reactions typically proceeded with good diastereoselectivity, provided the pyrroles contained an electron-withdrawing group to prevent oxidation by DMDO.

The utility of these products was demonstrated in the synthesis of the tricyclic core of parvineostemonine (Scheme 52).



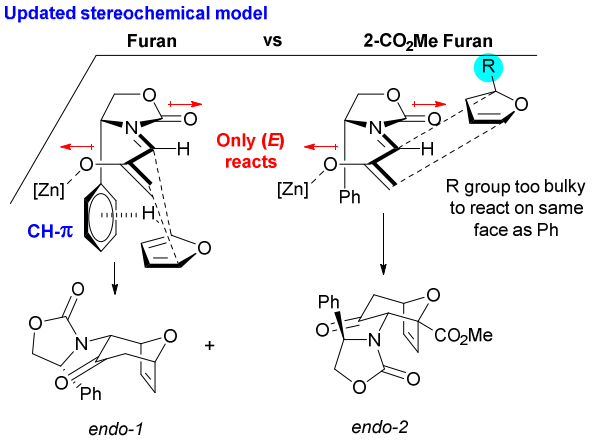
Scheme 52 Synthesis of the core of parvineostemonine *via* [4+3] reactions with N-Boc pyrroles.

Initial explanations of the stereochemical outcome of the intermolecular [4+3] reactions of furans were based on the presumed steric influence of the chiral oxazolidinone. Of the (*E*) and (*Z*)-oxyallyl cations that can be generated by oxidation of the allenamide, Hsung argued that the (Z)-isomer was likely to lead to the major product due to its ability to chelate metal additives such as $ZnCl_2$ (this additive improves the *dr*, but does not change the selectivity). In this conformation, the major diastereomer is obtained by approach of furan from opposite the bulky phenyl ring (Scheme 53, left). However, Hsung and co-workers were surprised to find that methyl 2-furanoate gave the opposite diastereomer of product (as verified by X-ray analysis).[78] At first, this outcome was rationalized by favourable dipole-dipole interactions of the (*E*)-oxyallyl cation with this substrate (Scheme 53, right).



Scheme 53 Original stereochemical model for intermolecular [4+3] reactions of oxyallyl cation and furan.

Later computational work by Hsung cast doubt on their initial hypothesis, as energy calculations showed that the (*E*)-oxyallyl cation was significantly more stable than the (*Z*)-isomer, even in the presence of zinc.[79] In order for furan to result in the production of the major diastereomer from this conformation, it would have to approach the cation from the same face as the phenyl ring. Indeed, transition state modeling showed that a CH-π interaction between furan and the phenyl group stabilized this approach. In the case of methyl-2-furanoate, a diastereomeric product was obtained due to its greater steric bulk, as it was found to prefer approach from opposite the phenyl ring (Scheme 54). Later work with other substituted furans corroborated the validity of this model.[80]



Scheme 54 Updated stereochemical model based on computational data.

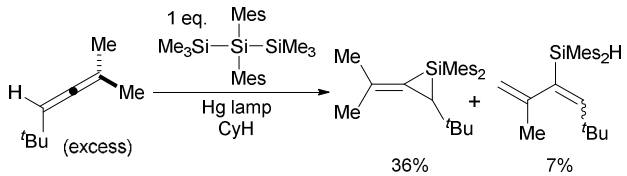
5. Methylene silacyclopropanes (MSPs)

5.1 Introduction

The synthesis and reactivity of methylene silacyclopropanes (MSPs) has been primarily investigated by the groups of Ando and Woerpel. Both groups explored the intermolecular addition of silylene units to allenes, with the Ando group generating silylenes by photolysis of trisilanes, and the Woerpel group using Ag(I) salts to mediate silylene transfer from more readily available silacyclopropanes.

5.2 Photo-induced silylene transfer

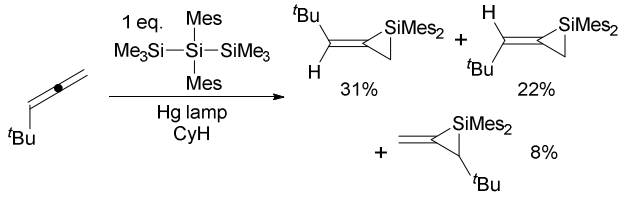
The first observation of silylene addition to allenes was reported by Ando and co-workers in 1986.[81] Dimesitylsilylene was generated by mercury lamp photolysis of a trisilane precursor in the presence of excess *tert*-butyldimethylallene, and a single cycloadduct was isolated in 36% yield (Scheme 55). A diene by-product arising from methylene silacyclopropane decomposition was also observed. In contrast to the regioselectivity seen for allene epoxidation (Section 4), the MSP arising from reaction of the more substituted double bond was not detected.



Scheme 55 Methylene silacyclopropane formation *via* trisilane irradiation.

A monosubstituted allene gave all three possible regio- and stereoisomeric outcomes, favouring the (*Z*)-methylene silacyclopropane formed from reaction of the terminal olefin (Scheme 56). The authors hypothesized that the preponderance

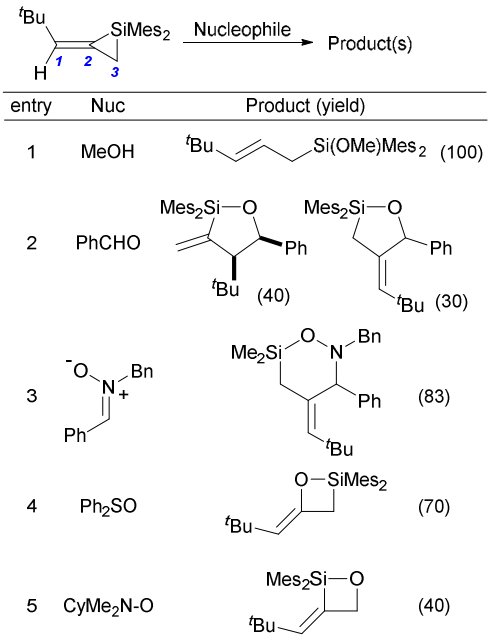
of this product, easily purified by recrystallization from hexane, was likely due to its photolytic stability, rather than any thermodynamic or kinetic preference. Allenes lacking the bulky -^{t}Bu group did not give isolable methylene siliranes.



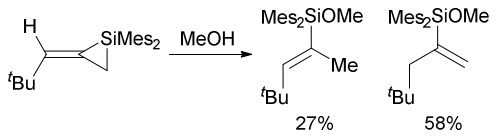
Scheme 56 Silacyclopropanation of *tert*-butylallene.

The reactivity of the (*Z*)-MSP was investigated with a variety of oxygen nucleophiles, and its reactivity was found to be distinct from that of its aza or oxo-analogues (Table 14).[82] Addition of methanol gave Csp^2-Si bond cleavage, with methoxide preferentially bonding to silicon (entry 1). A formal [3+2] reaction with benzaldehyde gave near-equal amounts of Csp^2-Si and Csp^3-Si bond cleavage (entry 2). A nitrone [3+3] cycloaddition gave good regioselectivity, again favouring Si-O bond formation. Finally, divergent oxidation was achieved by the use of either diphenyl sulphoxide or an amine oxide (entries 4 and 5). The authors believe that the striking lability of the Csp^2-Si bond is likely due to steric repulsion between the *tert*-butyl group and the mesitylene groups on silicon, as well as the increased polarity of the vinylsilane moiety.

Table 14 Reactions of a (*Z*)-methylene silacyclopropane.



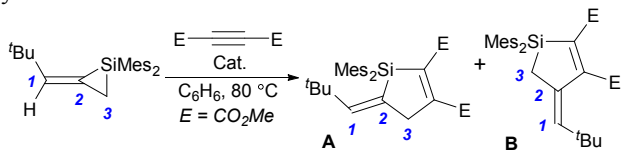
The proposed explanation for the lability of the Csp^2-Si bond was tested in the reaction of the (*E*)-MSP. When the (*E*)-isomer was reacted with methanol, the regioselectivity switched to give Csp^3-Si bond-cleavage (Scheme 57). This agrees with the hypothesis that Csp^2-Si bond cleavage is driven by the relief of ^{t}Bu-Mes strain.



Scheme 57 Reaction of an (*E*)-methylene silacyclopropane.

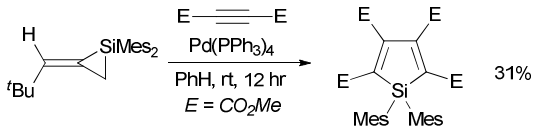
The Ando group also explored transition metal-mediated [3+2] cyclizations of MSPs with olefins.[83] Again, the regioselectivity varied widely based on catalyst identity and substrate geometry. In the Pd-mediated cyclization of the ^{t}Bu-substituted (*Z*)-MSP and dimethyl acetylenedicarboxylate, the relative rates of Csp^2-Si vs. Csp^3-Si bond cleavage could be completely controlled by variation of the Pd source (Table 15). The authors do not offer a conclusive explanation for this outcome, but do speculate that the high coordination affinity of the alkyne towards Pd(0) may have some effect on the regioselectivity in the case of $Pd(PPh_3)_4$ (entry 1).

Table 15 Effect of catalyst on the regioselectivity of the [3+2] cycloaddition.



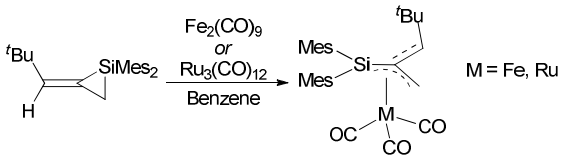
entry	catalyst	X	Y	entry	catalyst	A	B
1	$Pd(PPh_3)_4$	86%	trace	3	$PdCl_2(PEt_3)_2$	35%	55%
2	$PdCl_2(PPh_3)_2$	60%	25%	4	$PdCl_2(PhCN)_2$	trace	87%

Employing the (*E*)-isomer gave a completely different product, forming a silole in low yield (Scheme 58). This product likely arises from decomposition of the MSP to reform the parent allene and dimesitylsilylene, which undergoes a [2+2+1] reaction with excess alkyne. Other unreactive alkenes were observed to give similar decomposition products resulting from regeneration of the silylene.



Scheme 58 Silole formation from (*E*)-methylene silacyclopropane.

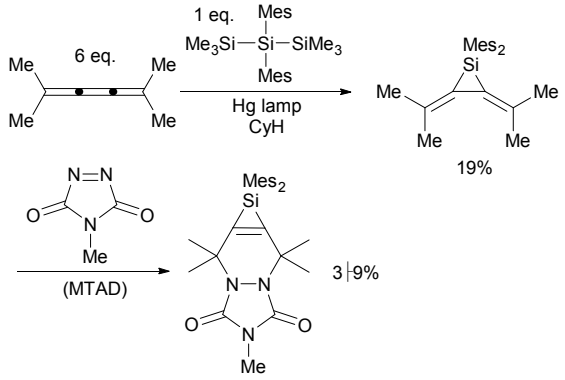
In later work, the Ando group provided direct evidence for the existence of silatrimethylenemethane (SiTMM) intermediates by heating the (Z)-MSP with $Fe_2(CO)_9$ or $Ru_3(CO)_{12}$.[84] Air-stable, crystalline complexes were obtained from these reactions that could be purified by preparative TLC. X-ray analysis confirmed the presence of the SiTMM motif (Scheme 59).



Scheme 59 Formation of silatrimethylenemethane.

The Ando group also reported the first observation of a sila[3]radialene by addition of demesitylsilylene to tetramethylbutatriene (Scheme 60).[85] The complex underwent

a [3+2] cycloaddition with 4-methyl-1,2,4-triazoline-3,5-dione (MTAD), but its further reactivity was not explored.

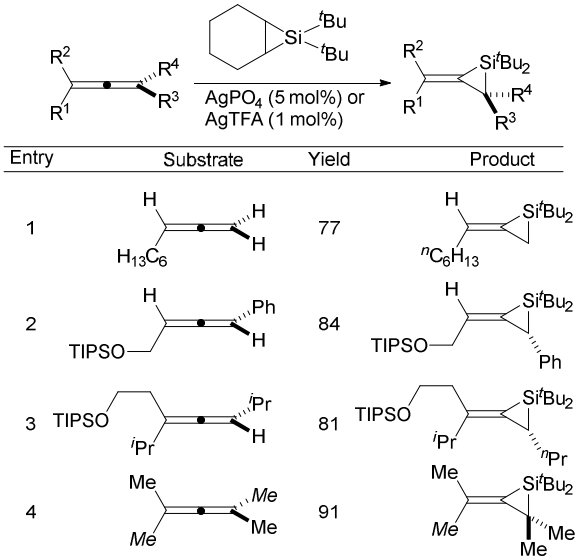


Scheme 60 Synthesis and reactivity of sila[3]radialenes.

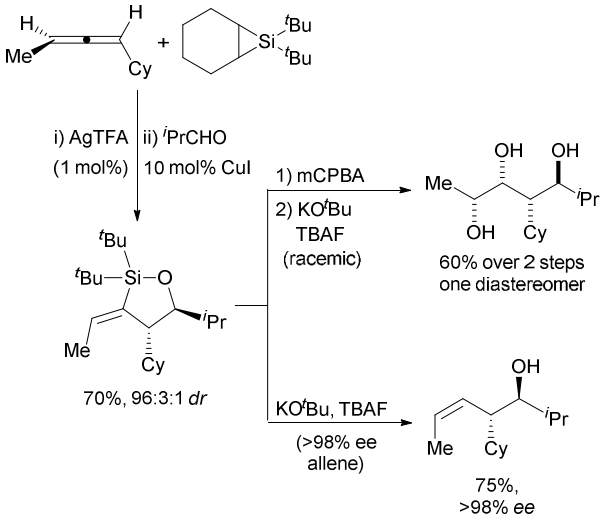
5.3 Ag-mediated silylene transfer

Woerpel and co-workers reinvestigated allene silacyclopropanation in 2009[86] by utilizing Ag-mediated silylene transfer methodology previously developed in their group.[87] Di-*tert*-butylsilylene was generated under mild conditions by silver-mediated decomposition of the silabicyclo[4.1.0]heptane shown in Table 16. In addition to achieving high yields, nearly complete regio- and stereoselectivity was observed for intermolecular silylene transfer, provided the groups at the 1 and 3 positions of the allene were sterically differentiated (Table 16). Efficient silylene transfer was observed for mono-, di-, tri-, and even tetra-substituted allenes, with no bis-silacyclopropanation products observed. Again, unlike the regioselectivity observed for allene epoxidation (see Section 4), silylene addition was generally favoured at the less-substituted double bond of the allene (entries 1 and 3). In the case of a 1,3-disubstituted allene, reaction of the styrenyl olefin was favoured (entry 2).

Table 16 Intermolecular Ag-mediated silylene addition to allenes.

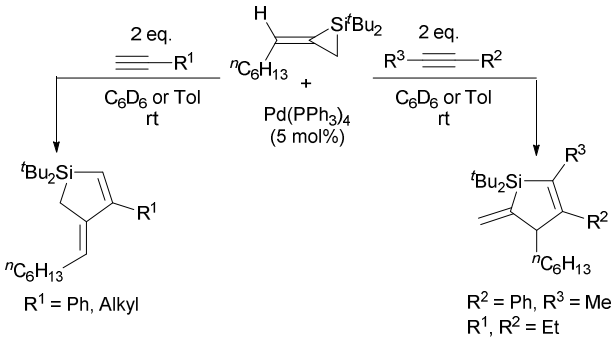


A Lewis acid-mediated cycloaddition of the MS products with aldehydes was demonstrated (Scheme 61). The reactions were highly regioselective for Csp^3-Si bond cleavage to give stereodefined oxasilacyclopentanes, which could be carried on in stereospecific transformations to yield single diastereomers of 1,2,4-triols and homoallylic alcohols. Efficient chirality transfer was demonstrated for an enantioenriched substrate.



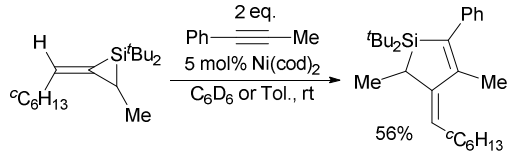
Scheme 61 Transformation of oxasilacyclopentanes.

Similar to the work carried out by the Ando group (see Table 15 and Scheme 58), Woerpel and co-workers investigated the transition metal-catalysed insertion of olefins into monosubstituted methylene silacyclopropanes (Scheme 62).[88] Csp^2-Si bond insertion was observed for terminal alkynes, while allylic transposition products were formed in the case of internal alkynes and alkenes. Interestingly, substitution of the *n*-hexyl group for a methoxy group on the silacyclopropane led to the same observed reactivity.



Scheme 62 Cycloadditions of MS with alkynes.

The use of methylene silacyclopropanes derived from 1,3-disubstituted allenes gave competitive silole formation (recall Figure 58). The use of $Ni(cod)_2$ as the catalyst restored the desired reactivity (Scheme 63), but in moderate yields and limited generality.



Scheme 63 Ni-catalysed insertion of alkynes into MSPs derived from disubstituted allenes.

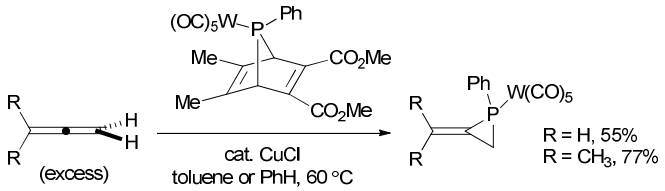
6. Methylene phosphiranes (MPs)

6.1 Introduction

The synthesis and reactivity of methylene phosphiranes has been reported by the Lammertsma and Mathey groups. Thus far, allenes have been the exclusive starting material for their synthesis, with tungsten or iron-stabilized phosphinidenes[89] providing the MP products in generally good yield. Most commonly, a phosphanorbornadiene is used as the phosphinidene precursor, with mild thermolysis (~55 °C) occurring under Cu-catalysed conditions to generate the phosphinidene. While this field remains relatively unexplored, the general stability of the MP products suggests there is room for further investigation of these species.

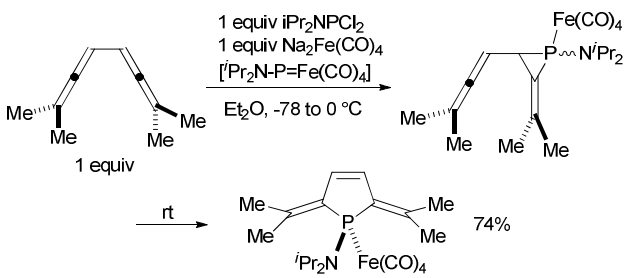
6.2 Metal-stabilized phosphinidene transfer from phosphanorbornadienes

In 1997, Lammertsma and co-workers reported the addition of tungsten-stabilized phosphinidenes to allenes to generate methylene phosphirane products.[90] Using the 7-phosphanorbornadiene reagent developed by Mathey,[91] clean phosphinidene transfer to allene and dimethylallene was observed to generate isolable methylene phosphinidene products (Scheme 64). The tungsten-bound methylene phosphiranes were unusually stable, as the MPs were able to withstand heating at 80 °C for several days, as well as silica gel chromatography. Cleavage of $W(CO)_5$ could be achieved by treatment with iodine followed by N-methylimidazole, although the demetalated products were slightly unstable at room temperature. The reactivity of the methylene phosphirane products was not investigated in this initial publication.



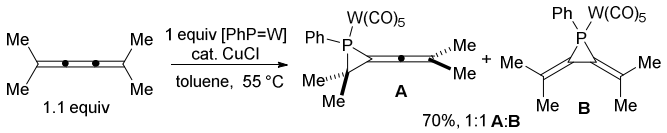
Scheme 64 Synthesis of methylene phosphiranes *via* phosphinidene transfer.

Lammertsma later demonstrated that an iron-bound phosphinidene also reacted with allene to give an MP product.[92] In an additional reaction involving a conjugated bisallene (Scheme 65), a single cyclization product was identified at low temperature that cyclized upon warming to give a phosphole.



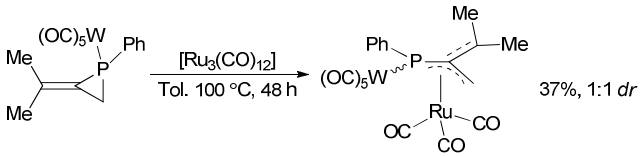
Scheme 65 Addition of Fe-bound phosphinidene to a bisallene.

The addition of phosphinidenes to cumulenes was also investigated (Scheme 66).[93] Addition of $PhP=W(CO)_5$ to tetramethylcumulene gave an alkenylidene phosphirane and a phospha[3]radialene in a 1:1 ratio. The alkenylidene product could be converted to the phospha[3]radialene by heating in toluene. Similarly to its silicon analogue (see Scheme 60), the phospha[3]radialene was shown to undergo a hetero-Diels Alder reaction with MTAD (not shown).

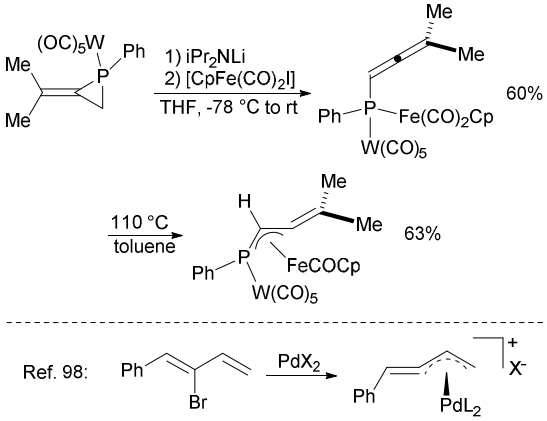


Scheme 66 Phosphinidene addition to cumulenes.

Mathey and co-workers investigated the reactivity of methylene phosphiranes with a series of metal complexes. In efforts to observe the formation of a stable phosphatrimethylenemethane (PTMM) intermediate, the MP of dimethylallene was heated in toluene with $Ru_3(CO)_{12}$ (Scheme 67).[94] Gratifyingly, the Ru-PTMM adduct was obtained as a crystalline solid, with X-ray analysis showing the η^4-bound ruthenium centre. In an additional report, lithiation of the same MP followed by treatment with $[CpFe(CO)_2I]$ gave a (1,2,3-η)-1-phosphabutadienyl complex, as observed by NMR and X-ray analysis (Scheme 68, top).[95] This demonstrated its analogy to the well-known all-carbon analogue, which is a presumed intermediate in certain Pd-catalysed allene syntheses (Scheme 68, bottom).[96]



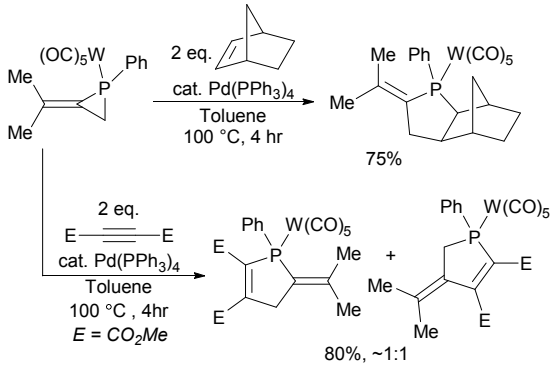
Scheme 67 Synthesis of a PTMM complex.



Scheme 68 Synthesis of (1,2,3-η)-1-phosphabutadienyl complex, and analogy to Pd π-allyl intermediates.

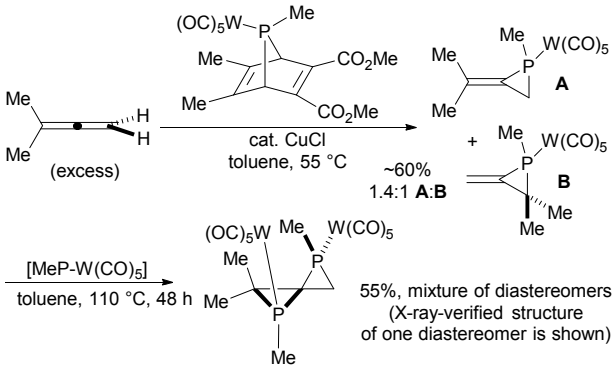
The Mathey group also demonstrated the ability of methylene phosphiranes to undergo cycloadditions with olefins,[97] in analogy to the work of Ando and Woerpel described above (Sections 5.2 and 5.3). In the presence of catalytic $Pd(PPh_3)_4$, a dimethyl-substituted phosphirane gave a single [3+2] cycloadduct with norbornene (Scheme 69). Exclusive cleavage of the Csp^3-P bond occurred. Reaction with dimethyl

acetylenedicarboxylate, however, gave both Csp^2-P and Csp^3-P cleavage products in a near-1:1 ratio. Prolonged heating at elevated temperatures (100 ºC) was required to facilitate these reactions.



Scheme 69 [3+2] cycloadditions of MPs with olefins.

Mathey and co-workers also described the generation of a 1,4-diphosphaspiropentane by the use of the more reactive MeP-$W(CO)_5$ phosphinidene.[98] Cu-catalysed thermolysis of the corresponding phosphanorbornadiene in dimethylallene gave two MP regioisomers in a 1.4:1 ratio (Scheme 70). This contrasts with the P-Ph reagent, which gives a single regioisomer. The mixture was resubjected to treatment with MeP-$W(CO)_5$ under forcing conditions to generate the phosphaspiropentane as two diastereomers that were separable by chromatography. X-Ray analysis verified the stereochemistry of one of the diastereomers. The further reactivity of these species has not been reported.



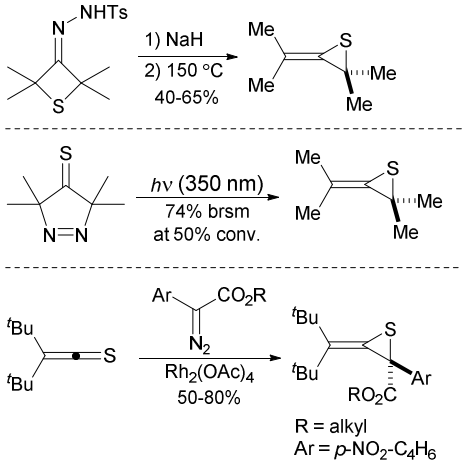
Scheme 70 Synthesis of 1,4-diphosphaspiropentanes.

7. Methylene thiiranes (MTs) / allene episulphides

7.1 Introduction

Of the strained heterocycles presented in this article, methylene thiiranes (MTs) are less frequently obtained from allenes.[99] More commonly, MTs are obtained by the decomposition of hydrazones[100] or diazolines[101] (Scheme 71). The addition of diazo compounds to thioketenes has also been explored.[102] However, recent progress has been made in their synthesis from allenes, and these advances (as well as historical examples) are addressed below.

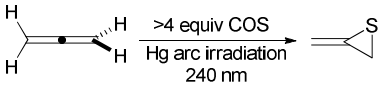
The Ando group has investigated the chemistry of MTs and thiiranoradialenes in significant detail, in analogy to their work on methylene silacyclopropanes (see Section 5). However, to the best of our knowledge, none of their MT substrates are derived from allenes. Thus, their work will not be covered in this review. The reader is referred to their publications for further information on this subject.[103]



Scheme 71 Alternative methods of MT synthesis

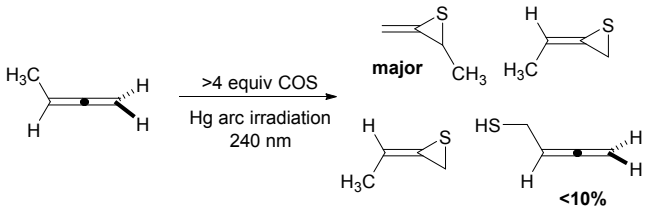
7.2 Synthesis and reactivity of methylene thiiranes generated from allenes

The first example of allene episulphidation was reported by Green and co-workers in 1984 (Scheme 72).[104] UV photolysis of carbonyl sulphide in the presence of allene led to methylene thiirane as the major product, as verified by MS, NMR, and IR. Although the product persisted for several hours in the gas phase at room temperature, it polymerized during storage at temperatures as low as -196 °C.



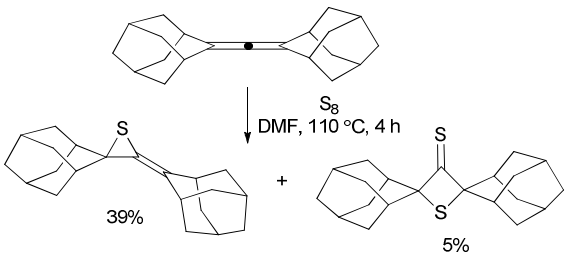
Scheme 72 Episulfidation of allene.

The corresponding episulphidation of methylallene generated all three possible methylene thiiranes, favouring reaction of the more substituted olefin (Scheme 73). The products also decomposed in less than a day at room temperature. A small degree (< 10%) of allenic C-H insertion at the methyl group was also observed. While these studies demonstrated that allene episulphidation was possible, the results were not synthetically applicable.



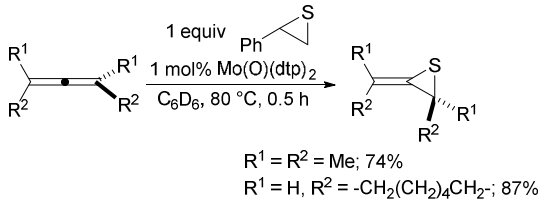
Scheme 73 Episulphidation of methylallene.

In a single example by Ando, the episulphidation of bisadamantylideneallene was accomplished by heating in DMF with elemental sulphur.[105] A thietanethione by-product was also observed (Scheme 74). Although this procedure worked moderately well for this substrate, it is not a common method for the preparation of MTs.



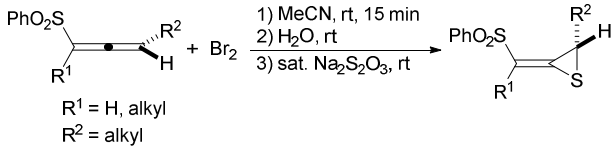
Scheme 74 Formation of methylene thiiranes from elemental sulphur.

A more general method for the direct episulphidation of allenes was reported by Adam and co-workers (Scheme 75).[106] Using phenyl thiirane as the sulphur source, a dithiophosphate molybdenum (IV) oxo catalyst gave high yields of sulphur transfer to both cyclic and linear allenes. Lower yields were obtained when phenyl thiirane was substituted for elemental sulphur or sodium tetrasulphide. No dithiospiropentane by-products were reported. As expected, this system was applicable to alkene substrates, and promoted efficient sulphur transfer in substrates that had previously shown poor reactivity.



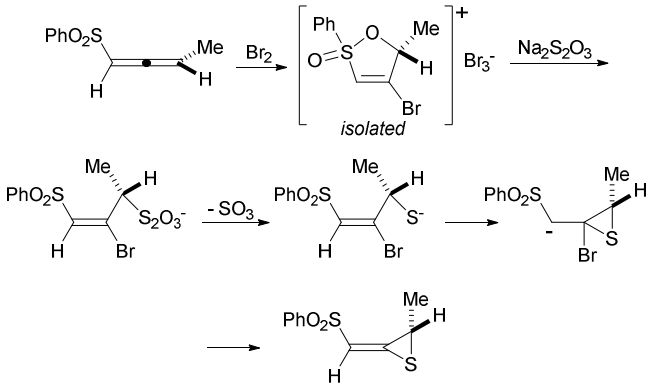
Scheme 75 Facile intermolecular episulphidation of allenes catalysed by a Mo complex.

Shengming Ma and co-workers later reported the serendipitous formation of methylene thiiranes from allenyl sulphones.[107] This outcome occurred when the allene was treated with bromine under aqueous conditions, followed by an aqueous NaS_2O_3 workup (Scheme 76). The reaction was general for a number of 1,3-disubstituted and 1,1,3-trisubstituted allenes, and gave efficient chirality transfer for enantioenriched substrates. The methylene thiirane products were stable to column chromatography.



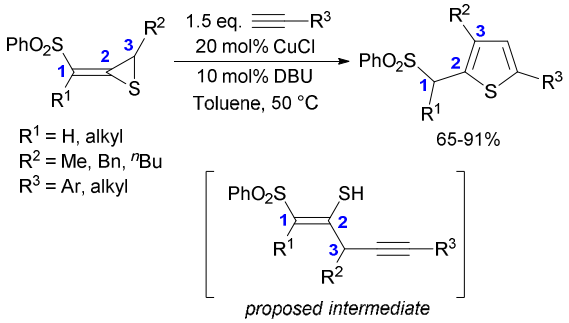
Scheme 76 Br_2-mediated synthesis of methylene thiiranes from allene sulfones.

Isolation of a possible reaction intermediate shed light on the putative reaction mechanism (Scheme 77). Ring-opening of the observed intermediate by thiosulfate generates the first C-S of the product; extrusion of SO_3, followed by conjugate addition of sulphide to the α,β-unsaturated sulphone forms the second. Elimination of Br^- generates the exocyclic olefin.



Scheme 77 Proposed mechanism of MT formation.

The Cheng Ma group demonstrated the utility of these products in a copper-catalysed alkyne addition to generate functionalized thiophenes (Scheme 78).[108] The authors suggest the products arise from cycloisomerization of an enyne intermediate, generated by alkyne addition to C3 of the methylene thiirane.



Scheme 78 Addition of alkynes to MTs.

Conclusions

While three-membered heterocycles derived from allenes were originally synthesized as structural curiosities, they have recently emerged as attractive scaffolds for the synthesis of complex organic motifs. Challenges in chemoselectivity (insertion vs. cyclization), regioselectivity, and (in select cases) enantioselectivity, have been met using a variety of solutions.

In the past decade, interest in these strained moieties has led to the development of a diverse array of allene-derived heterocycles. Of these methods, synthesis and transformation of allene oxides and spirodiepoxides are best developed, with methods available for ring-opening cascades to form α,α'-disubstituted ketones, the generation of oxyallyl cations for electrocyclizations and cycloadditions, and the formation of enolate equivalents. These methods have been utilized in a number of natural product total syntheses including steroids, polyketides and polypeptides. While methods for the synthesis of methylene aziridines are not as well-developed, several groups have described their synthesis and utility as templates for the synthesis of all-heteroatom stereotriads. Methods for the synthesis of silicon, phosphorous and sulphur-containing motifs have also been reported, although their reactivity has not been thoroughly explored.

Future work will likely include the development of directed methods for site-selective allene functionalization, new transformations for the manipulation of these heterocycles, and

the further application of these products in the synthesis of biologically active molecules.

Notes and references

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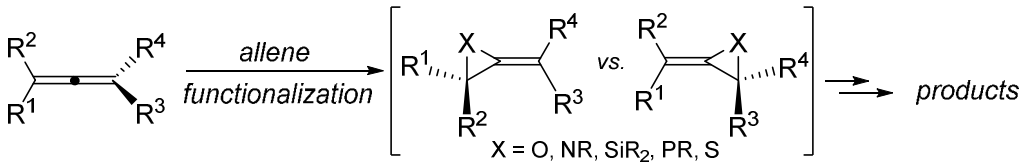

The addition of heteroatoms to an allenic double bond yields strained heterocycles that serve as scaffolds for further useful transformations.

Christopher Adams received his Bachelor's Degree at the University of California, Irvine, while working in the group of Dr. David Van Vranken. He also spent a summer as an intern in the Small Molecule Medicinal Chemistry division of Amgen in Thousand Oaks, California. He is currently an organic chemistry PhD student at the University of Wisconsin, Madison in the Schomaker group. His research focus is on the generation and manipulation of methylene aziridines to obtain diverse aminated products.

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51x51mm (300 x 300 DPI)

Jennifer began her research career at Dow Chemical in Organic Chemicals and Polymers, later moving to Ag Chemicals, where she participated in the route selection and scale-up campaigns for two new herbicides. She obtained her Ph.D. with Professor Babak Borhan at Michigan State University in 2006, then moved to Berkeley as an NIH postdoctoral fellow in the labs of Professor Robert G. Bergman and F. Dean Toste. She joined the faculty at UW-Madison in 2009, where her research focuses on catalyst-controlled chemoselectivity, new reactivity for first-row transition metals and the application of allene aziridination to the synthesis of complex molecules.

60x79mm (300 x 300 DPI)

Eileen Burke graduated from Montana State University-Bozeman in 2012 with a BS in chemistry. In 2011, she was an intern in the NSF-REU/Lando program at the University of Minnesota under Dr. William Tolman. While there, she studied indium catalysts for the polymerization of lactide. She is now a graduate student at the University of Wisconsin-Madison studying synthetic organic chemistry under Dr. Jennifer Schomaker.