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REVIEW

Allenes as building blocks in heterocyclic chemistry

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Abstract Allenes have a unique structural feature characterized by having two cumulated double bonds. The inherent instability associated with these 1,2-dienes has been widely exploited for various synthetic purposes. Allenes have thus become important and versatile building blocks in organic chemistry. In this paper some illustrative examples of the chemistry of these building blocks in the synthesis of heterocyclic compounds are presented.

Keywords Allenes · Heterocyclic compounds · Wittig reaction · Aza-Baylis–Hillman reaction · [3 + 2] Cycloaddition

Introduction

For a long time allenes were regarded as chemical curiosities because the presence of two cumulated double bonds was predicted to lead to very unstable systems [1]. Nevertheless, in 1874–1875 Van't Hoff [2] proposed the correct structure of allenes and in 1887 Burton and von Pechmann reported the first synthesis of an allene [3]. However, only when IR and Raman spectroscopy became available as a structural assignment tool was it possible to prove the structure of allenic molecules by their characteristic allenic C–C vibration at about 1,950 cm^{-1} [4].

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The discovery of a significant number of natural compounds that incorporate allenic structures raised the interest in this class of molecules. Illustrative examples are the insect pheromone **1** isolated from male dried bean beetles which represents an interesting allenic target molecule for crop protection [5], the allenic alkaloids **2** and **3** isolated from the skin of the poison-dart frog [6], and panacene (**4**), a metabolite of the sea hare *Aplysia brasiliana* which acts as a fish antifeedent [7] (Fig. 1).

Several of these natural products show interesting biological activities. Nowadays, an approach to "tune" the biological and pharmacological properties of biologically active compounds is to introduce an allenic moiety into the existing backbone of the molecule. Therefore, the development of synthetic methodologies to obtain allenes is in itself an interesting research goal.

There are two interesting aspects of the reactivity of allenes which make them very versatile building blocks in organic chemistry. One is the inherent instability associated with the cumulated double bonds, which makes addition to allenes very favorable, because it involves the relief of strain. The second aspect is the possibility of exploring the selective transfer of the axial chirality of an optically active allene to central chirality as a route to chiral compounds.

The chemistry of these interesting molecules has been one of our topics of research. We developed an asymmetric Wittig reaction that allows the synthesis of allenic esters with axial chirality [8]. This drove us to explore the reactivity of 2,3-butadienoates and in this paper some illustrative examples of the chemistry of these building blocks in the synthesis of heterocyclic compounds will be presented as well as some aspects of the background of the project, which included the synthesis of 2-halo-2*H*-azirines and 4-halo-1,3-oxazoles via a non-classical Wittig reaction.

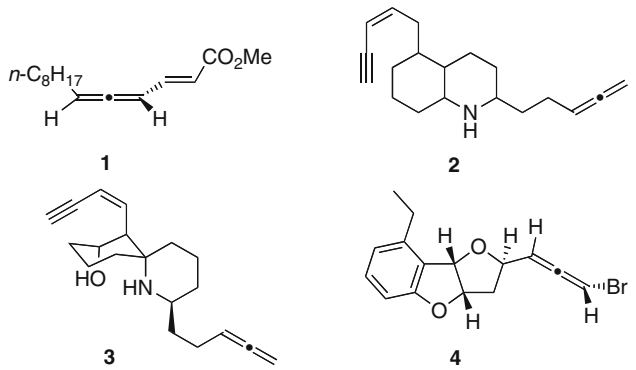


Fig. 1 Examples of natural compounds incorporating allenic structures

A non-classical Wittig reaction in the synthesis of 2-halo-2*H*-azirines and 4-halo-1,3-oxazoles

Synthesis of tetrasubstituted alkenes via a non-classical Wittig reaction

We have been interested in exploring the reactivity of phosphorus ylides, namely their use in a non-classical Wittig reaction which offers a route to tetrasubstituted alkenes. We observed that α-oxophosphorus ylides **5** react with chlorine, bromine, and electrophilic halogen-donor reagents in the presence of a range of nucleophiles to give tetrasubstituted alkenes with elimination of triphenylphosphine oxide. Several of these reactions are highly stereoselective, whereas others give both (*E*)- and (*Z*)-isomers. It was postulated that isomeric halonium ions were intermediates in the formation of the observed products. These halonium ions can interconvert via an acyclic cation **6**. The opening of the two halonium ions by a nucleophile leads to the isomeric alkenes after the elimination of triphenylphosphine oxide (Scheme 1) [9].

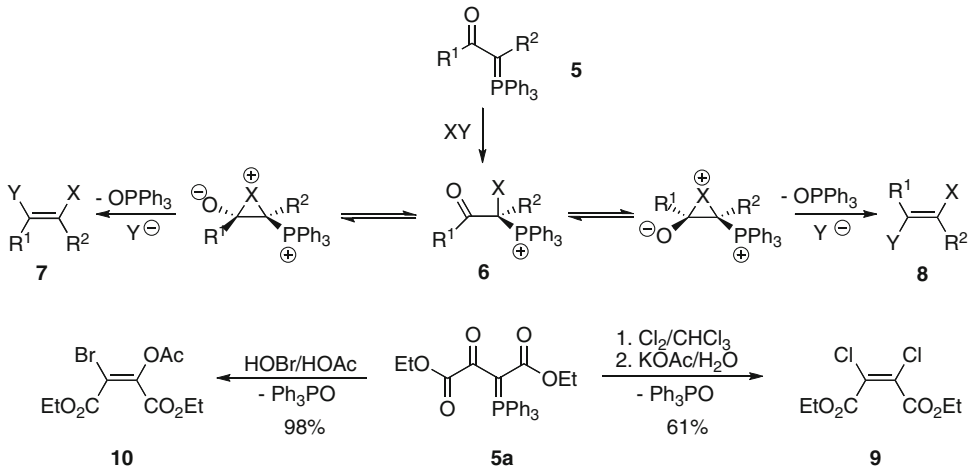
Two selected examples in which the alkenes are obtained stereoselectively are presented in Scheme 1. Ylide **5a** reacts with chlorine in the presence of potassium acetate to give, after 5 min, the diester **9** in 61% yield. Reaction of ylide **5a** with hypobromous acid and acetic acid gives, after 24 h, a single crystalline product in high yield (98%). This was identified as the vinyl acetate **10** and its stereochemistry was established as (*Z*) by an X-ray crystal structure determination [9].

The formation of a halophosphonium salt as an intermediate is in agreement with the known halogenation of α-oxophosphorus ylides, which gives the corresponding halophosphonium salt **11** (Scheme 2) [10]. On the other hand, one example is known of an intramolecular non-classical Wittig reaction of the type described above. The reaction of α-oxophosphorus ylides bearing a terminal carboxylic acid group acting as the nucleophile with halogenating agents leads to the formation of (*E*)- and (*Z*)-halo enol lactones [11, 12]. The cyclization is also thought to proceed via a halophosphonium salt followed by loss of triphenylphosphine oxide. Scheme 2 illustrates one case in which it is possible to isolate the bromophosphonium salt **13** in the reaction of ylide **12** with bromine at 0 °C. Treatment of **13** with triethylamine gives the corresponding bromo enol lactone **14** [12].

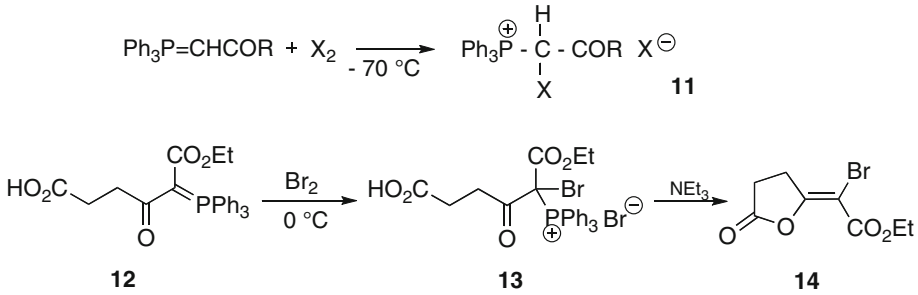
Synthesis of 2-halo-2H-azirines from phosphorus ylides

Of particular interest in this methodology for the synthesis of tetrasubstituted alkenes is the possibility of preparing haloazidoalkenes from the reaction of phosphorus ylides with *N*-halosuccinimide in the presence of azidotrimethylsilane because these compounds are potential precursors of 2-halo-2*H*-azirines. Haloazidoalkenes **15** prepared from phosphorus ylides **5** can be easily converted into the corresponding 2-halo-2*H*-azirines **16** [13, 14] (Scheme 3). The

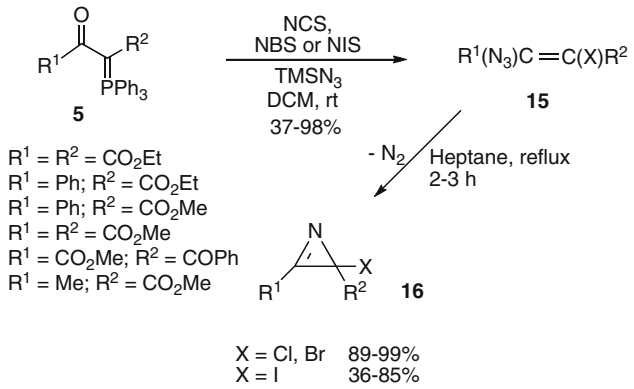
Scheme 1

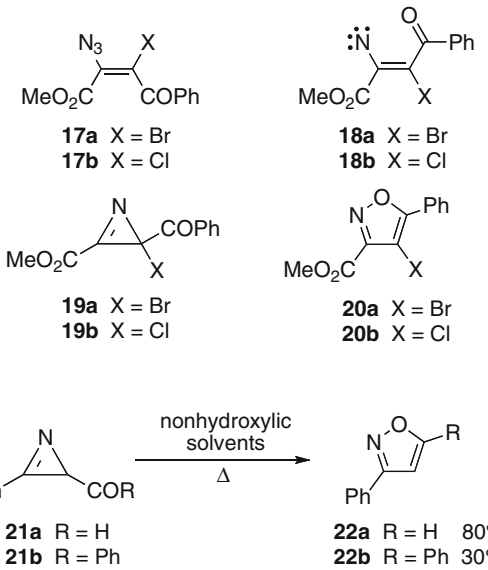


Scheme 2



Scheme 3





Scheme 4

reaction of these ylides with *N*-chlorosuccinimide (NCS) or *N*-bromosuccinimide (NBS) is complete after 5 min. However, the reaction with *N*-iodosuccinimide (NIS) requires the use of excess halogenating agent and is only complete after 4.5 h. The majority of these reactions show high stereoselectivity, leading to the synthesis of alkenes as single isomers. The alkenes are converted into the corresponding 2-halo-2*H*-azirines upon heating in heptane for 2–3 h. 2-Chloro- and 2-bromo-2*H*-azirines are obtained in high yield (89–99%), whereas the yields obtained for the 2-iodo-2*H*-azirine derivatives range from 36 to 85%. 2-Chloro- and 2-bromo-2*H*-azirines with electron-withdrawing groups at C-3 decompose in the condensed phase within 2–3 days at room temperature (rt), whereas azirines with a phenyl or methyl group at C-3 showed higher stability. The 2-iodo-2*H*-azirines show lower stability than the corresponding chloro and bromo derivatives. The study of the reactivity and chemical behavior of these three-membered ring heterocycles has shown their usefulness as building blocks in organic synthesis [15–23].

Synthesis of 4-halo-1,3-oxazoles from phosphorus ylides

In this context, we reported the thermolysis of 2-halo-2-benzoyl-2*H*-azirines [22]. 2-Benzoyl-2-halo-2*H*-azirine-3-carboxylates **19** underwent ring expansion to give products in high yield which were identified as 4-haloisoxazoles **20**. The same products were also obtained in high yield from the thermolysis of haloazidoalkenes **17** via intermediate 2-benzoyl-2-halo-2*H*-azirines **19**.

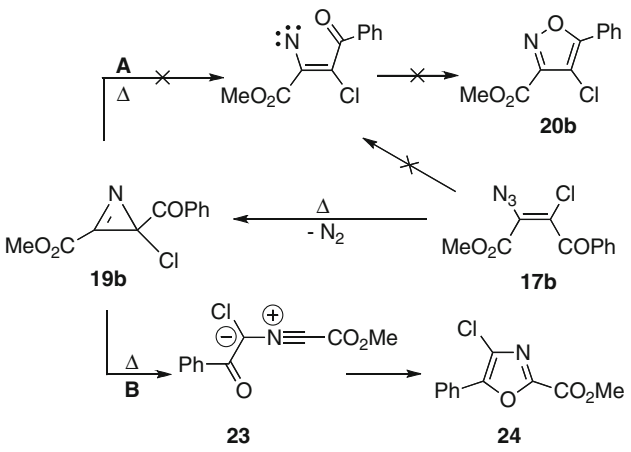
The thermolysis of 2*H*-azirines usually results in cleavage of the N–C2 single bond to give a transient vinylnitrene, the reverse of the cyclization of vinylnitrenes used to prepare 2*H*-azirines. Evidence for the existence of this intermediate comes from the thermal ring opening of 2,3-diaryl-2-cyano-2*H*-azirine in which the vinylnitrene was trapped with phosphanes [24]. On the other hand, it was known that heating a solution of 3-phenyl-2*H*-azirine-2-carboxaldehyde (**21a**) at 200 °C leads to 3-phenylisoxazole (**22a**) in high yield [25]. The same isoxazole can also be obtained in 90% yield by treatment of 3-phenyl-2*H*-azirine-2-carboxaldehyde at 25 °C with Grubbs' catalyst [26]. Furthermore, 2-benzoyl-3-phenyl-2*H*-azirine (**21b**) affords the corresponding isoxazole **22b** upon heating in nonhydroxylic solvents (Scheme 4) [27]. These observations led us to rationalize the thermal

reaction of 2-benzoyl-2-halo-2*H*-azirine-3-carboxylates **19** as being the conversion into isoxazoles **20** via vinyl nitrenes **18**.

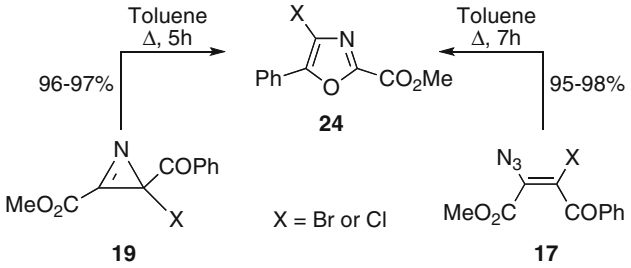
Matrix isolation infrared spectroscopy was used to carry out the structural and vibrational characterization of the chloro compound obtained from the thermolysis of 2*H*-azirine **17b** [23]. This study was supported by theoretical calculations undertaken at the DFT(B3LYP)/6-311 ++G(d,p) level of theory. However, the theoretically predicted spectrum for isoxazole **20b** did not match the experimental IR spectrum. Indeed, it was demonstrated that the studied compound could not be isoxazole **20b** but instead the compound was the isomeric methyl 4-chloro-5-phenyl-1,3-oxazole-2-carboxylate (**24**).

The formation of oxazole **24** from 2*H*-azirine **19b** can be explained by considering the thermal cleavage of the C2–C3 bond to give nitrile ylide **23** followed by recyclization to give the final product. Because the oxazole is obtained in high yield (98%) we can conclude that only the reaction pathway **B** is observed (Scheme 5).

4-Chloro-5-phenylisoxazole-3-carboxylate **20b** was also synthesized by an unambiguous route [28] and studied by matrix-isolation FTIR. It was clear from the analysis of the matrix-isolated FTIR spectra of 4-chloro-5-phenyl-1,3-oxazole-2-carboxylate **24** and methyl 4-chloro-5-phenylisoxazole-3-carboxylate **20b** that this technique allows one to distinguish these isomeric heterocycles easily. Therefore, it was demonstrated that methyl 2-benzoyl-2-halo-2*H*-azirine-3-carboxylates **19** undergo thermal ring expansion to give 4-halo-5-phenyl-1,3-oxazole-2-carboxylates **24** in high yield, products which can also be obtained in high yield from haloazidoalkenes **17** (Scheme 6).



Scheme 5



Scheme 6

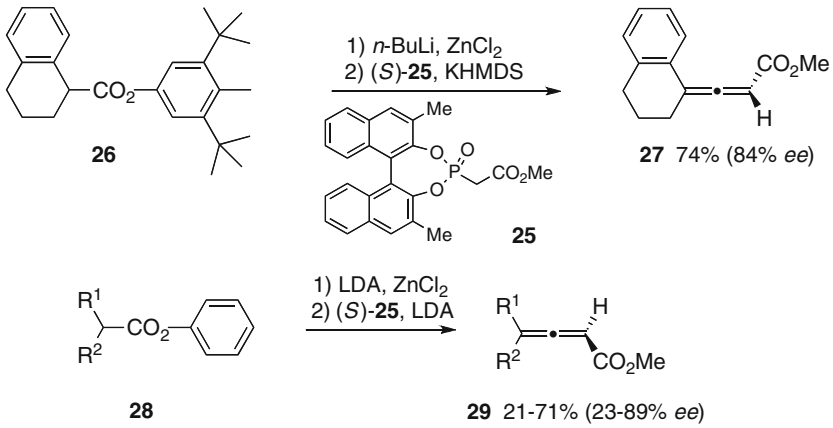
Synthesis of chiral allenic esters via Wittig or Horner–Wadsworth–Emmons reactions

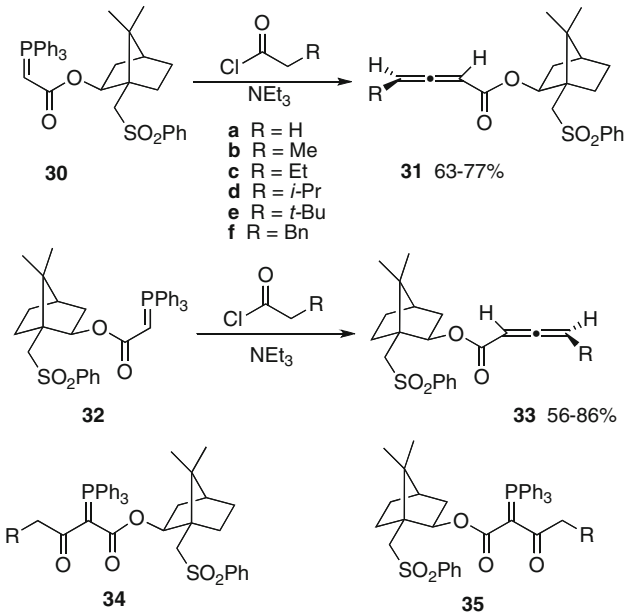
Allenes can be obtained by various synthetic methods, but the use of the Wittig reaction or the Horner–Wadsworth–Emmons (HWE) reaction is of particular interest because they allow regio- and stereocontrol of the carbon–carbon double bond formation. Most of the known methods for optically active allenic compounds are based on the isomerization of propargylic derivatives bearing a stereogenic center. Little attention has been paid to the synthesis of chiral allenes through asymmetric Wittig-type reactions [29]. However, Tömösközi and Bestmann have reported reactions between phosphorus ylides containing chiral alcohol units and acid chlorides in the presence of NEt_3 to afford chiral allenes, although neither the absolute configurations of the products nor the levels of asymmetric induction were determined [30].

Optically active 4,4-disubstituted allenecarboxylates have been prepared by treatment of ketenes generated in situ from phenyl acetates with chiral HWE reagents (Scheme 7) [31, 32]. Enantiomeric excesses up to 84% were obtained by Fuji et al. using HWE reagents of the type shown in Scheme 7. In this study 2,6-di-*tert*-butyl-4-methylphenyl esters (e.g., **26**) were used as precursors of the ketenes. This methodology involves difficulties such as low yields in the preparation of the starting materials probably as a result of the bulkiness of the butylated hydroxytoluene group. However, a procedure for the synthesis of chiral allenecarboxylates from simpler phenyl esters has also been reported [32].

Our interest in exploring the Wittig reaction for different purposes led us to study the reactivity of phosphorus ylide **30** bearing a chiral auxiliary to promote the synthesis of allenes in a selective fashion [8] (Scheme 8). Thus, ketenes have been generated in situ from the corresponding acid chloride in the presence of triethylamine and reacted with phosphorus ylide **30** to give allenes **31** in good yields. In some cases ylides **34**, the result of the acylation of **30**, were also formed as minor products. Only one stereoisomer was obtained in each case and even in the Wittig reaction with ketenes having a bulky substituent such as the *t*-butyl group

Scheme 7





Scheme 8

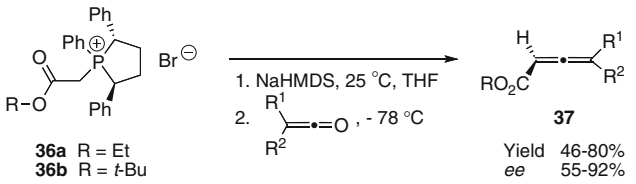
the selective synthesis of the corresponding allene was observed. The stereochemical outcome of this asymmetric Wittig-type reaction can be explained by the assumption that the presence of the chiral 10-(phenylsulfonyl)isoborneol unit in the starting phosphorus ylide determines the geometry of approach of the ketene, thus allowing for asymmetric induction. The (*S*)-configuration was assigned to allenes **31** based on X-ray crystallographic studies. It was also established that the use of a phosphorus ylide **32** bearing a chiral auxiliary enantiomeric to the isoborneol unit of phosphorus ylide **30** allows the selective synthesis of allenes with (*R*)-configuration. Chiro-optical studies of the allenic esters were carried out, confirming that two sets of enantiomeric derivatives were obtained [8].

More recently, Tang et al. reported a chiral ylide-mediated synthesis of optically active allenes [33, 34]. Pseudo-C_2-symmetric chiral ylides were used for the enantioselective preparation of allenic esters via a Wittig reaction with ketenes generated in situ. The absolute configuration of the major product was assigned as (*S*). On the basis of the dipole–dipole interaction model developed by Aggarwal et al. to account for the selectivity of the reaction of stabilized phosphorus ylides with aldehydes [35, 36], the authors were able to explain the observed stereoselectivity. They proposed that the reaction proceeds via $[2\pi + 2\pi]$ cycloaddition to afford an oxaphosphetane, which is converted into the corresponding phosphine oxide and chiral allene. The ketene approaches the *Re* face of the ylide preferentially as a result of the steric hindrance between the substituents of the ketene and the ylide (Scheme 9).

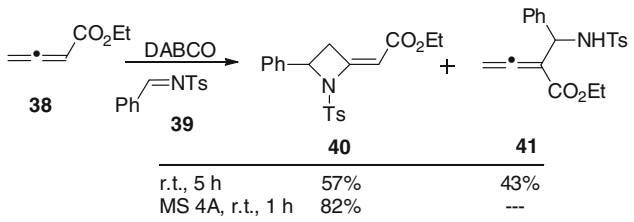
Reactivity of allenic esters

Diastereoselective aza-Baylis–Hillman reactions: synthesis of chiral α-allenylamines and 2-azetines from allenic esters

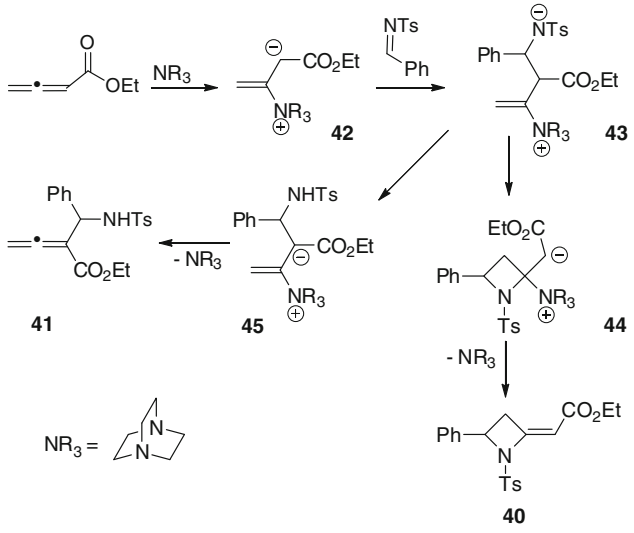
It has been demonstrated that allenes **31** and **33** are interesting building blocks for carrying out stereoselective synthetic procedures. These chiral allenoates have been used in the synthesis of chiral functionalized *β*-amino esters via hydride reductive amination [37, 38]. On the other hand, inverse conjugate addition of carbonucleophiles to allenic esters allows the stereoselective formation of tertiary and quaternary carbon centers [39]. Allenes **31**



Scheme 9



Scheme 10



Scheme 11

and **33** also participate in diastereoselective aza-Baylis–Hillman-type reactions leading to chiral α-allenylamines and 2-azetines [40].

It is known that allenoates act as the Michael acceptor in aza-Baylis–Hillman-type reactions to give functionalized allenes, but they can also lead to 2-methyleneazetidines. The 1,4-diazabicyclo[2.2.2]octane (DABCO)-catalyzed reaction of allenoate **38** with imine **39** in the presence of molecular sieves affords the corresponding azetidine **40** as the only product, whereas in the absence of molecular sieves the azetidine **40** and α-allenylamine **41** were obtained (Scheme 10) [41, 42].

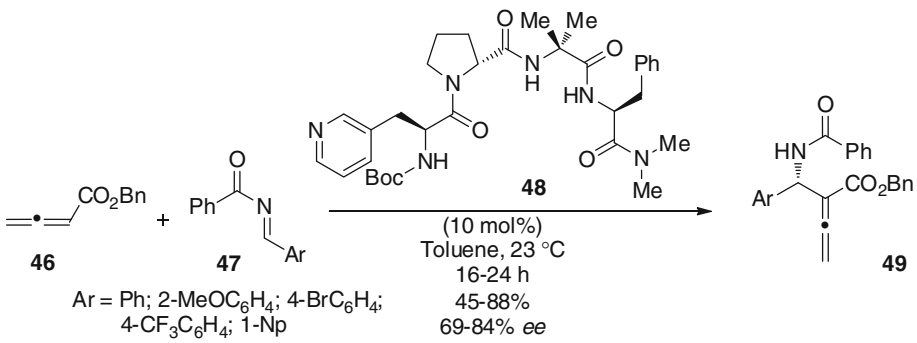
The formation of these products can be explained as outlined in Scheme 11 [41, 42]. Nucleophilic addition of DABCO to the 2,3-allenoate produces **42**, which adds to the imine to give **43**. This intermediate undergoes intramolecular nucleophilic attack to give a cyclic zwitterionic intermediate **44** followed by the elimination of DABCO to afford the 2-methyleneazitidine **40**. Alternatively, zwitterionic intermediate **43** can undergo proton transfer and subsequent elimination of the base to afford the α-allenylamine **41**.

One report on the asymmetric version of the aza-Baylis–Hillman reaction of allenes with imines is known [43]. The authors demonstrated that Boc-L-3-Pal-D-Pro-Aib-L-Phe-NMe_2 (**48**) acts as a chiral catalyst in the reaction of benzyl allenoate (**46**) with *N*-benzoylimines **47** to afford α-allenylamines **49** in high yield and enantiomeric excess (*ee*) (Scheme 12).

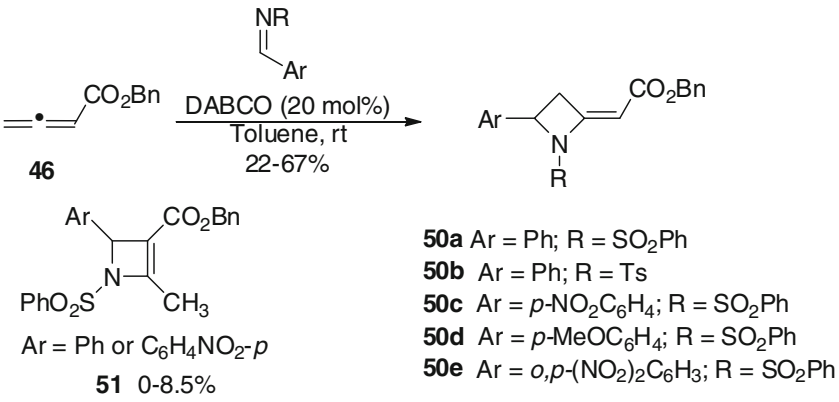
Studies aiming to develop asymmetric versions of the DABCO-catalyzed reaction of allenes with imines as a route to new optically active nitrogen four-membered heterocycles have also been reported [40]. The reaction of benzyl buta-2,3-dienoate (**46**) with a range of *N*-arylidenebenzenesulfonamides allowed one to confirm that the main pathway for these condensations is the formal [2 + 2] cycloaddition leading to 2-methyleneazetidines **50** (Scheme 13). The reaction can also be carried out under microwave irradiation with a very short reaction time (100 °C, 5 min). In two cases a simultaneous formation of 2-azetine derivatives **51** was detected and these four-membered ring heterocycles isolated.

Optically active allenes **31a** and **33a** react with imine **52** to afford chiral 2-azetine derivatives and chiral α-allenylamines (Scheme 14). The DABCO-catalyzed reaction of allene **31a** at room temperature for 1 h gave azetine **54** as the major product (45%), together with the formation of chiral α-allenylamine **53** (8%). Interestingly, by lowering the temperature to −20 °C, the chiral α-allenylamine **53** was isolated as the major product in 52% yield. The structure of this allene was determined by X-ray crystallography, allowing the assignment of the stereochemistry of the new chiral center. The reaction carried out with the

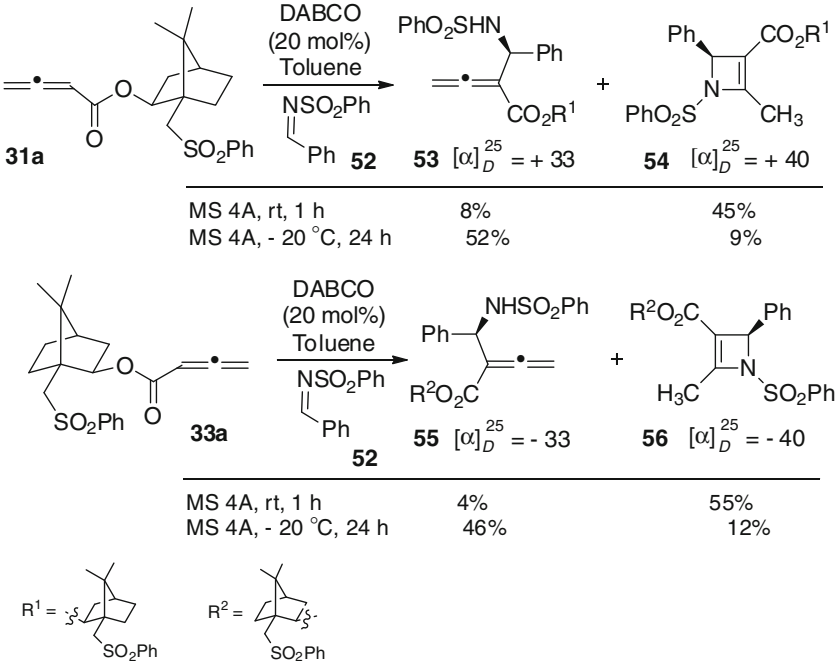
Scheme 12



Scheme 13



Scheme 14



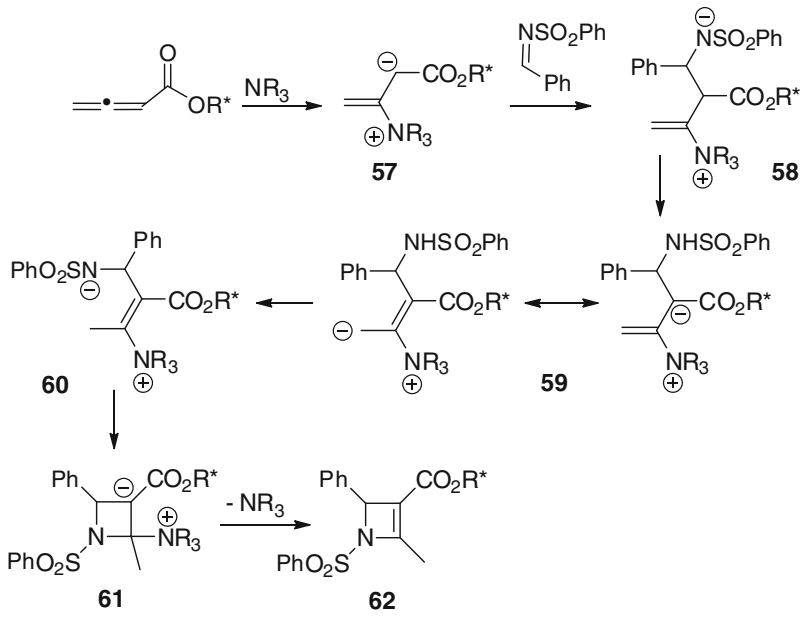
enantiomeric allene **33a** led to similar results. Notice that 2-azetines **54** and **56** show identical NMR spectra and values for the optical rotation with opposite sign indicating that they are enantiomers. The same can be said about the two α-allenylamines. Thus, starting from (−)-(1*R*)-10-phenylsulfonylisobornyl buta-2,3-dienoate products with (*S*)-configuration are obtained, whereas the reaction with (+)-(1*S*)-10-phenylsulfonylisobornyl buta-2,3-dienoate leads to products with (*R*)-configuration.

The formation of the 2-azetines can be explained as outlined in Scheme 15. Nucleophilic addition of DABCO to the 2,3-allenoate produces zwitterionic intermediates **57**, which react with the imine to give **58**, followed by proton transfer. Intermediate **59** undergoes a proton transfer process to afford the nitrogen anion **60**. Cyclization of **60** via an intramolecular conjugate addition leads to another zwitterionic intermediate **61**. Elimination of DABCO produces the final product **62**. The synthesis of these 2-azetines as single stereoisomers is explained by the selective addition of the imine to **57** leading to intermediate **58**.

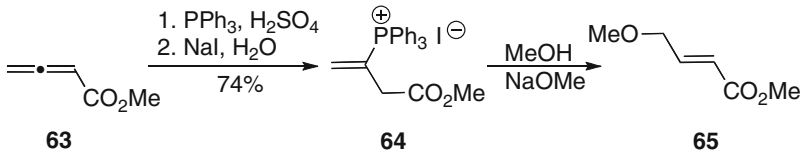
[3 + 2] Annulations and allenoate-Claisen rearrangement

The addition of nucleophiles to electron-deficient allenes occurs at the electrophilic α,β-carbon–carbon double bond to give Michael-type adducts [44–46]. However, reactivity inversion (umpolung) can be achieved. Cristau et al. observed that in the presence of phosphines the addition takes place at the β,γ-carbon–carbon double bond [47]. They found that the reaction of methyl 2,3-butadienoate (**63**) with triphenylphosphine followed by the addition of NaI afforded a phosphonium iodide **64**, which allows the

Scheme 15



Scheme 16



nucleophilic attack at the γ-carbon leading to the synthesis of 4-substituted-but-2-enoate **65** (Scheme 16).

Lu et al. explored the reactivity of the intermediates generated from butadienoates and phosphines as the three-carbon synthon in [3 + 2] annulation reactions. They reported that the reaction with electron-deficient alkenes [48] and *N*-tosylimines [49, 50] leads to the formation of five-membered formal [3 + 2] cycloadducts.

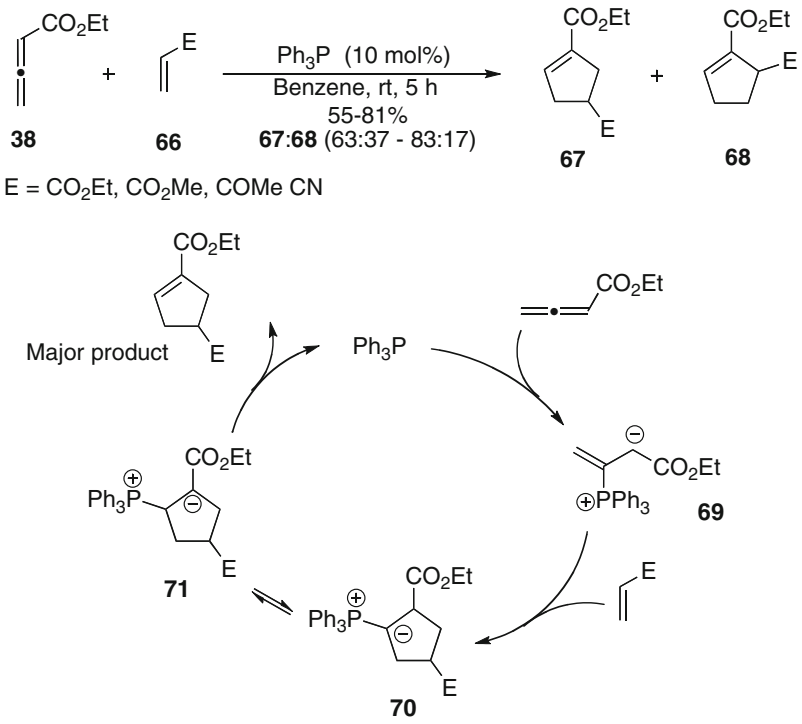
In the presence of a catalytic amount of phosphine ethyl butadienoate (**38**) reacts with electron-deficient alkenes to afford a regioisomeric mixture of cyclopentenes [48]. Thus, the 1,3-dipole **69** generated from the allenic ester and phosphine reacts with the alkene to form a cyclic intermediate **70**, which is in equilibrium with **71** via hydrogen shift. Elimination of phosphine affords the corresponding cycloadduct (Scheme 17). The reaction of diethyl fumarate and diethyl maleate with ethyl butadienoate led to *trans*-**74** and *cis*-**74** as single products (Scheme 18).

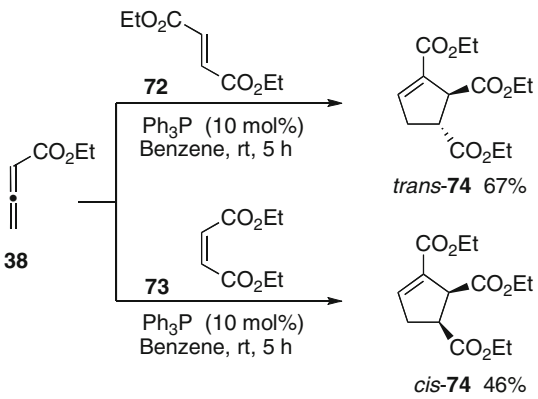
On the other hand, Lu et al. reported that 3-pyrrolines are obtained regioselectively and in high yield from the reaction of methyl butadienoate with aromatic *N*-tosylimines in the presence of triphenylphosphine [49, 50]. The reaction is also triggered by the triphenylphosphine attack to the β-carbon of the allene to give dipolar intermediate **77**, which reacts with the imine to form an open-chain intermediate **78**. Intramolecular nucleophilic addition gives **79** followed by hydrogen shift to generate **80**. Elimination of triphenylphosphine releases the cycloadduct (Scheme 19). The reaction of *N*-tosylimines with ethyl 2,3-butadienoate and ethyl penta-2,3-dienoate has been systematically studied in the presence of various nitrogen and phosphine Lewis base promoters [51, 52].

More nucleophilic phosphines, such as tributylphosphine, instead of triphenylphosphine are required to carry out the reaction of *N*-sulfonylimines with sterically demanding γ-substituted allenoates [53]. In the case of ethyl γ-(*t*-butyl)-allenoate (**81**) attempts to promote the annulation reaction with triphenylphosphine did not lead to any product. However, quantitative yields of the 2,5-disubstituted-3-pyrroline-3-carboxylates (e.g., **82**) and high diastereoselectivity was obtained using tributylphosphine as catalyst (Scheme 20).

Solid-phase synthesis of 3-pyrrolines using resin-bounded allenoates has been reported [54]. The allenoic acids **83** were coupled to the benzyl alcohol unit of the Syn-Phase-PS lanterns grafted with Wang resin. The allenoates **84** were treated with *N*-tosyltolualdimine and 50 mol% triphenylphosphine (for **84a**) or tributylphosphine (for **84b**) to afford the polymer-bond 3-pyrrolines **85**. These heterocycles were cleaved from the resin using 2.5% trifluoroacetic acid (TFA) in dichloromethane (DCM) to

Scheme 17





Scheme 18

give the corresponding acids **86** in 91–93% yield with high diastereoselectivity (*dr* = 99:1 for **86b**) (Scheme 21).

The use of chiral phosphines as catalysts for the formal enantioselective [3 + 2] cycloaddition of electron-deficient allenes with electron-deficient alkenes and imines has also been reported [54–64].

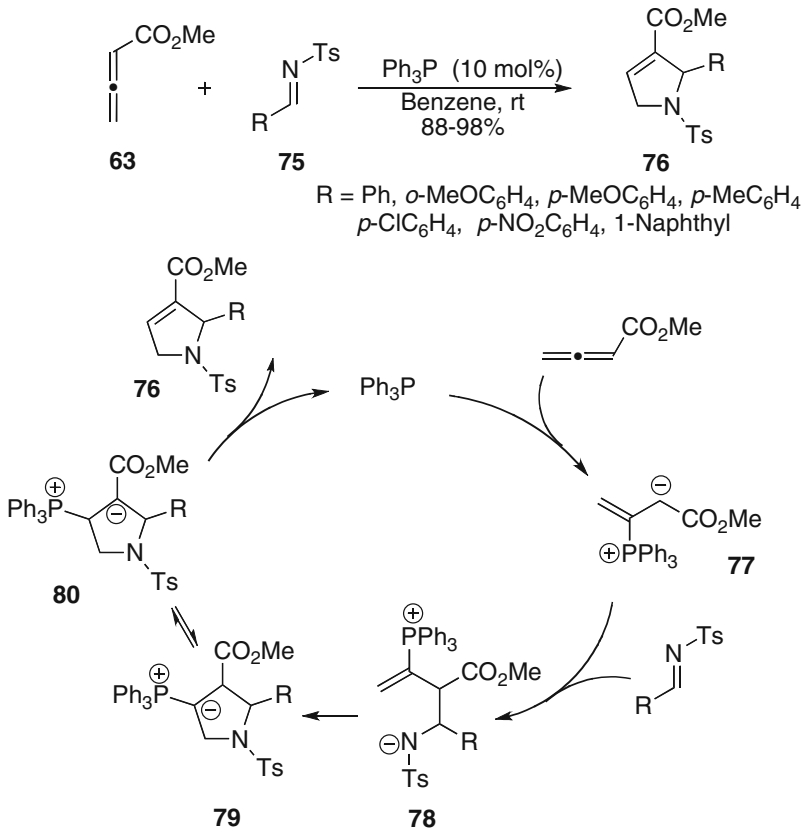
The formal [3 + 2] cycloaddition reactions of butadienoates with *N*-benzylidenebenzenesulfonamide and electron-deficient alkenes can be carried out under microwave irradiation (MW) [65]. The methodology was shown to be efficient for the one-step synthesis of 3-pyrrolines and cyclopentenes in a regio- and diastereoselective manner (e.g., **88** and **89**). This formal [3 + 2] cycloaddition is complete within 5 min (Scheme 22).

Synthesis of functionalized N-vinyl nitrogen-containing heterocycles

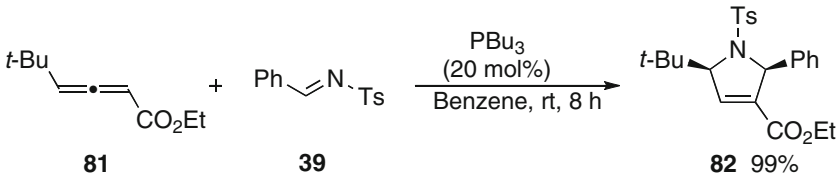
The majority of biologically relevant molecules, namely drugs and natural products, contain nitrogen, thus justifying the continuous efforts by the scientific community to develop synthetic strategies for structures incorporating this heteroatom. Enamines are particularly interesting building blocks for introducing nitrogen-containing moieties in a synthetic sequence [66–69], and aziridines [70, 71] are valuable strained small heterocycles of interest in preparative organic synthesis. In this context, the synthesis of *N*-vinyl nitrogen-containing heterocyclic compounds via microwave-assisted 1,3-dipolar cycloaddition of the azomethine ylide generated by ring opening of a *N*-vinylaziridine has been reported [72].

Michael addition of an aziridine derivative to benzyl 2,3-butadienoate afforded the corresponding *N*-vinyl aziridine **91**. Under microwave irradiation at 150 °C for 10 min the reaction of *N*-vinylaziridine **91** with dimethyl acetylenedicarboxylate (DMAD) led to 3-pyrroline **93** in 75% yield and in a selective way. The microwave methodology for the conrotatory ring opening of aziridine **91** leading to 1,3-dipole **92** and the subsequent cycloaddition proved to be more efficient than the conventional reaction conditions. When the reaction was carried out in refluxing toluene for 6 h, 3-pyrroline **93** was obtained in 40% yield. The microwave-assisted 1,3-dipolar cycloaddition of the in situ generated azomethine ylide **92** in the presence of methyl vinyl ketone (MVK) led to the regio- and

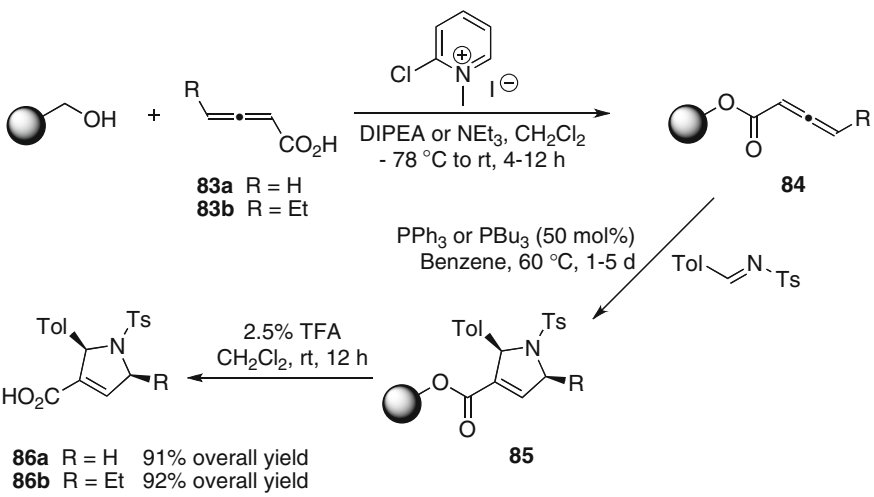
Scheme 19



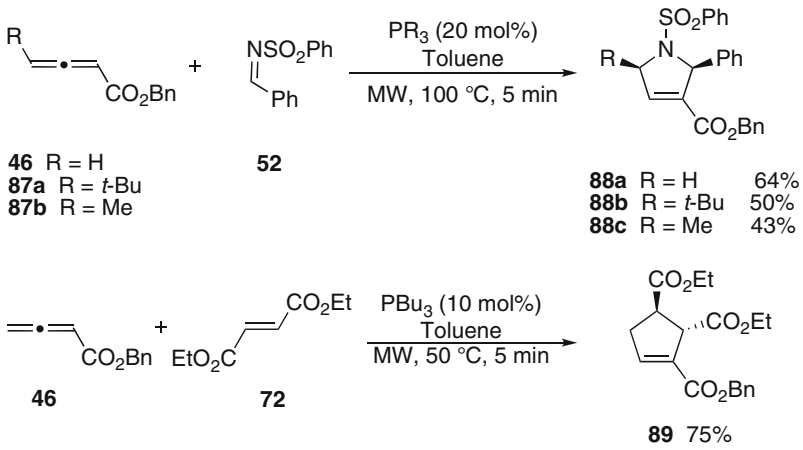
Scheme 20



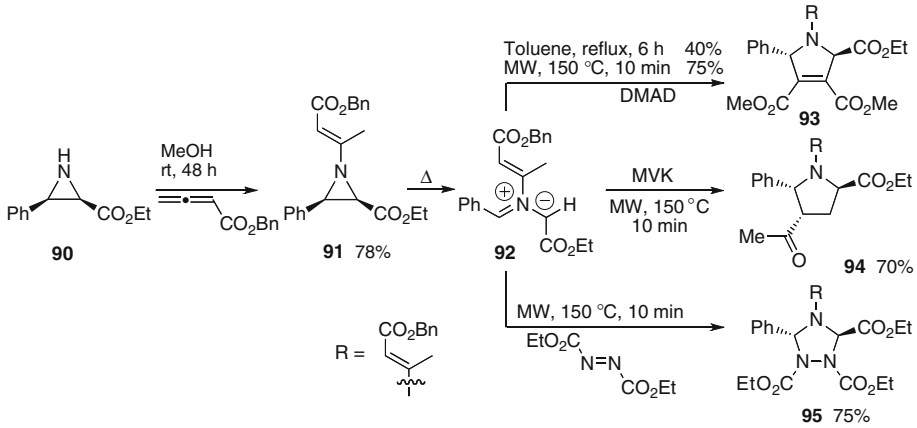
Scheme 21



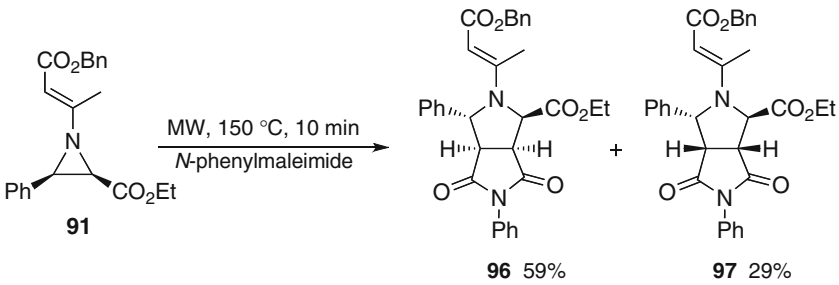
Scheme 22



Scheme 23



Scheme 24



diastereoselective synthesis of pyrrolidine **94** in 70% yield. Dipole **92** can also be trapped by 1,3-dipolar cycloaddition with diethyl diazene-1,2-dicarboxylate to afford pentasubstituted-1,2,4-triazolidine **95** in 75% yield (Scheme 23).

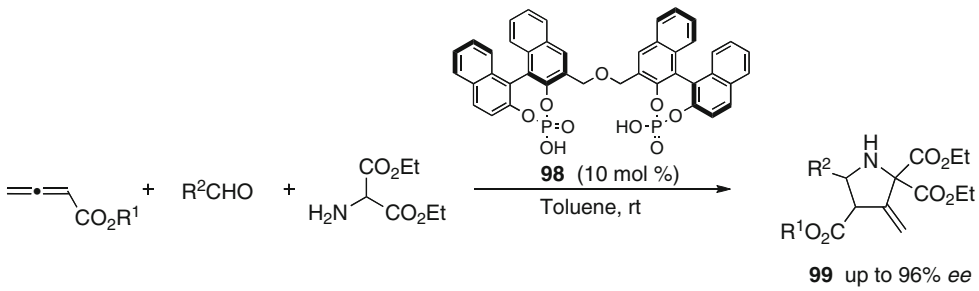
Microwave irradiation of a solution of aziridine **91** and *N*-phenylmaleimide led to the synthesis of two octahydropyrrolo[3,4-*c*]pyrrole derivatives **96** (59%) and **97** (29%) resulting from the *exo* and *endo* approach of the dipole and dipolarophile (Scheme 24).

Reactivity of allenoates toward aziridines: synthesis of functionalized methylenepyrrolidines and pyrroles

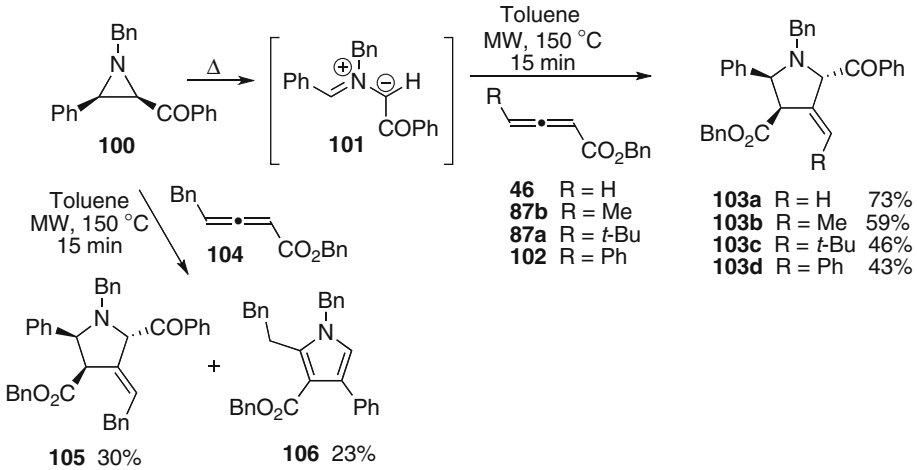
Allenes can participate in cycloadditions as dipolarophiles with a variety of 1,3-dipoles namely nitrile oxides, nitrones, carbonyl ylides, nitrile imines, azides, and diazomethanes, but their 1,3-dipolar cycloaddition with azomethine ylides is an almost unexplored research topic [3, 73–76]. Nevertheless, the enantioselective synthesis of methylenepyrrolidines via bisphosphoric acid catalyzed 1,3-dipolar cycloaddition of allenoates and azomethine ylides generated in situ from aldehydes and amino esters has been reported [77] (Scheme 25).

The cycloaddition of azomethine ylides generated from aziridines via conrotatory electrocyclic ring opening with buta-2,3-dienoates is known [78, 79] (Scheme 26). The microwave-assisted 1,3-dipolar cycloaddition of azomethine ylide **101** generated in situ from *cis*-1-benzyl-2-benzoyl-3-phenylaziridine (**100**) with benzyl buta-2,3-dienoates **46**, **87**, and **102** carried out at 150 °C for 15 min

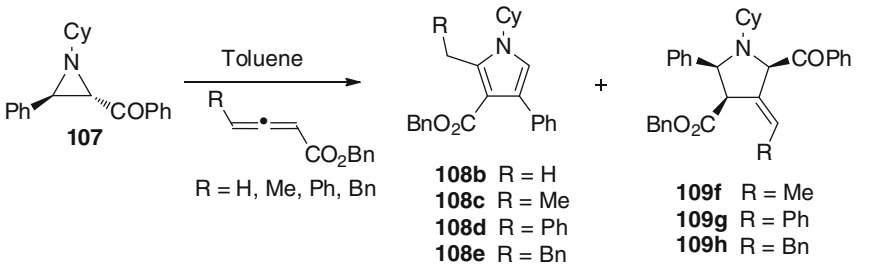
Scheme 25



Scheme 26



Scheme 27

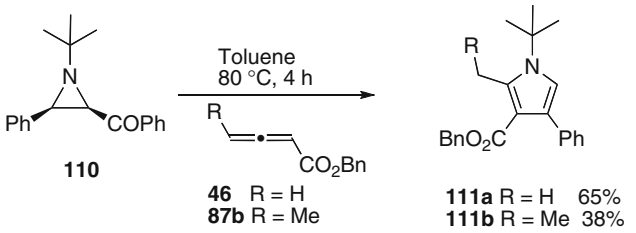


Reaction Conditions	Product (Yield %)	
Reflux, 1.5 h	**108b** (55.5%)	---
Reflux, 1.5 h	**108c** (62%)	**109f** (19%)
MW, 150 °C, 15 min	**108d** (64%)	**109g** (10%)
Reflux, 1.5 h	**108e** (26%)	**109h** (23%)
MW, 150 °C, 15 min	**108e** (65%)	---

afforded the corresponding 4-methylenepyrrolidine **103** in a site-, regio-, and stereoselective fashion. A different outcome was observed from the reaction of aziridine **100** with benzyl 5-phenylpenta-2,3-dienoate (**104**). The expected 4-methylenepyrrolidine **105** was obtained in 30% yield together with the formation of pyrrole **106** in 23% yield resulting from a formal [3 + 2] cycloaddition.

trans-2-Benzoyl-1-cyclohexyl-3-phenylaziridine **107** also reacts with benzyl buta-2,3-dienoates to give the corresponding pyrroles **108** exclusively or as the major product together with the formation of 4-methylenepyrrolidine derivatives **109** (Scheme 27). The reaction of allenoates with *cis*-2-benzoyl-1-cyclohexyl-3-phenylaziridine was characterized by the same reactivity pattern shown by *trans*-2-benzoyl-1-cyclohexyl-3-phenylaziridine **107**, indicating that the outcome of the reaction is not determined by the stereochemistry of the starting aziridine.

cis-2-Benzoyl-3-phenylaziridine **110** bearing a bulky *N*-*t*-butyl substituent leads to the formation of pyrroles upon reaction with allenes **46** and **87b** (Scheme 28). No reaction was observed between allene **102** and *cis*-2-benzoyl-1-*t*-butyl 3-phenylaziridine (**110**).

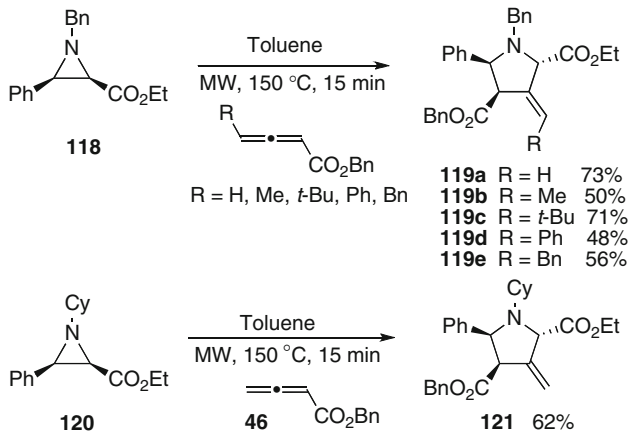


Scheme 28

These results indicate that the nature of the *N*-substituent of the 2-benzoyl-3-phenylaziridines determines the chemical behavior of these three-membered heterocycles in the presence of allenoates. The bulkier cyclohexyl or *t*-butyl *N*-substituent seems to hinder the 1,3-dipolar cycloaddition in favor of the formal [3 + 2] cycloaddition. However, this reaction pathway becomes less favorable with allenoates with a bulkier C-4 substituent.

The formation of the pyrrole derivatives can be explained as outlined in Scheme 29. Nucleophilic addition of the aziridine to the activated allene double bond gives intermediate **112** followed by the intramolecular attack of the carbanion center on the aziridine ring to afford the five-membered heterocycles **113** via C–N bond cleavage. Tautomerizations and the subsequent aromatization lead to pyrrole **114** bearing a hydroxybenzyl side chain, which is converted into the final product and benzaldehyde via retro-aldol type fragmentation.

N-Benzyl- and *N*-cyclohexyl-*cis*-3-phenylaziridine-2-carboxylates react with allenoates to give the corresponding 1,3-cycloadducts (Scheme 30). The microwave-induced conrotatory electrocyclic ring opening of aziridine **118** is followed by 1,3-dipolar cycloaddition of the in situ



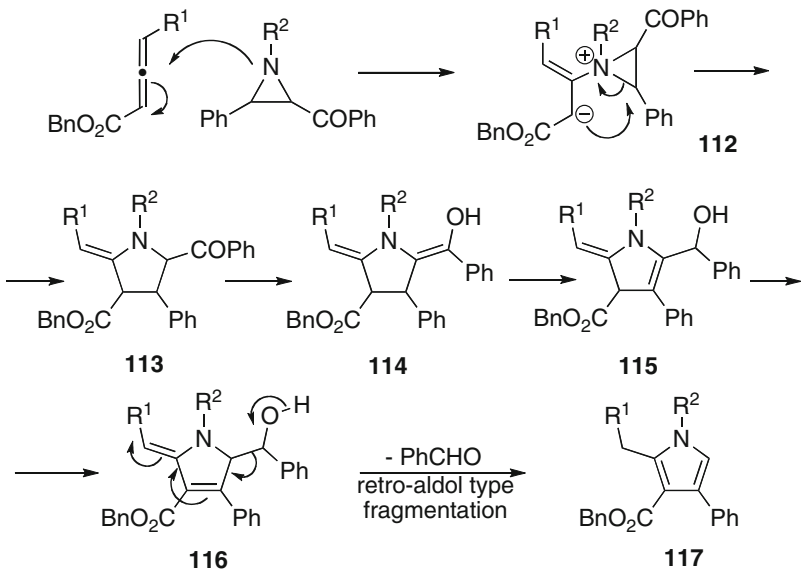
Scheme 30

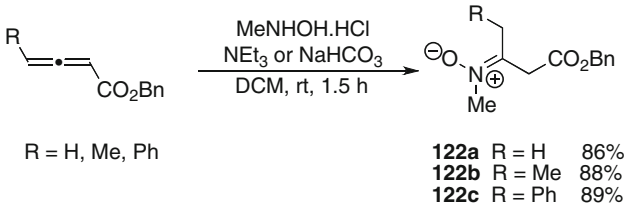
generated azomethine ylide with allenoates to afford methylenepyrrolidines **119** in good yields. A similar chemical behavior was observed between ethyl *N*-cyclohexyl-*cis*-3-phenylaziridine-2-carboxylate (**120**) and benzyl buta-2,3-dienoate (**46**).

4-Isoxazolines and pyrroles from allenoates

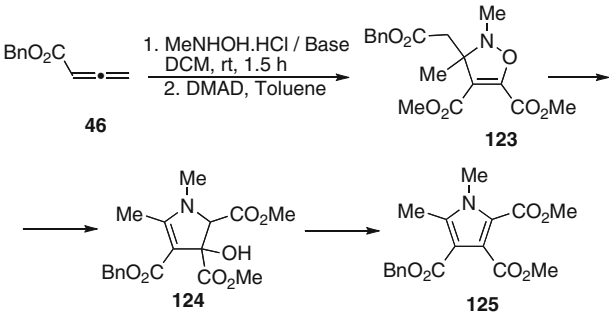
Allenes have been used to generate cyclic and acyclic nitrones through the reaction with hydroxylamines [3]. On the other hand, the main strategy to obtain 4-isoxazolines (2,3-dihydroisoxazoles) has been the 1,3-dipolar cycloaddition between nitrones and alkynes or allenes [3, 80, 81]. These heterocycles are also particularly interesting synthons for cyclic and acyclic compounds owing to their readiness to undergo rearrangement reactions, the driving force being the relatively low thermochemical stability of the N–O bond [81, 82].

Scheme 29





Scheme 31



Entry	Reaction conditions (Second step)	Products (overall yield %)
1	rt, 15 min	**123** (66%)
2	120 °C, 3 h	**124** (45%)
3	MW, 50 °C, 1 min	**123** (60%)
4	MW, 200 °C, 15 min[a]	**125** (46%)
5	MW, 250 °C, 5 min[a]	**125** (43%)

[a]Carried out in trichlorobenzene.

Scheme 32

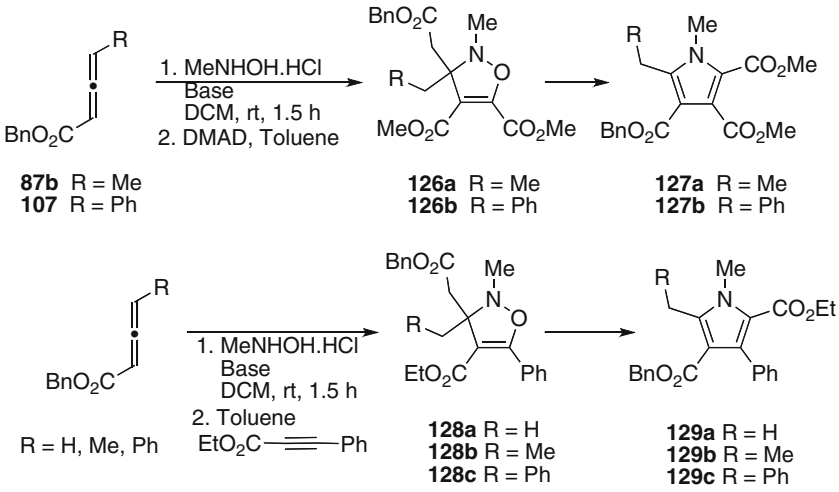
The synthesis of 4-isoxazolines via 1,3-dipolar cycloaddition of nitrones generated from allenoates and the subsequent thermal rearrangement to pyrrole derivatives was further explored [83]. Buta-2,3-dienoates are efficiently converted into the corresponding nitrones **122** upon reaction with *N*-methylhydroxylamine at room temperature in the presence of triethylamine or sodium hydrogencarbonate (Scheme 31).

Nitrone **122a** reacts with DMAD at room temperature for 15 min to give the corresponding 1,3-dipolar cycloadduct **123** in 66% overall yield. Interestingly, at 120 °C 3-hydroxy-2,3-dihydro-1*H*-pyrrole **124** is obtained as the only product. Under microwave irradiation and with the selection of appropriated temperature and reaction time the cycloaddition of nitrone **122a** and DMAD affords 4-isoxazoline **123** or pyrrole **125** selectively [83] (Scheme 32).

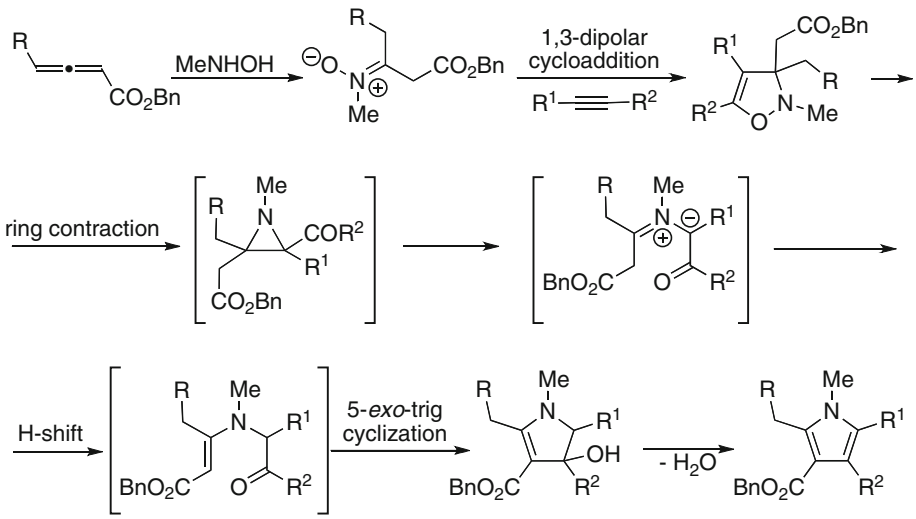
Reaction conditions can also be selected for the synthesis of 4-isoxazolines **126** or pyrroles **127** from the cycloaddition of nitrones **122b** and **122c** with DMAD. On the other hand, nitrones **122** react with ethyl phenylpropiolate under mild reaction conditions to afford 4-isoxazolines **128** in a regioselective fashion, whereas under forcing reaction conditions the corresponding pyrroles **129** were isolated as single products. The synthetic methodology was successful using either conventional reaction conditions or under microwave irradiation [83] (Scheme 33).

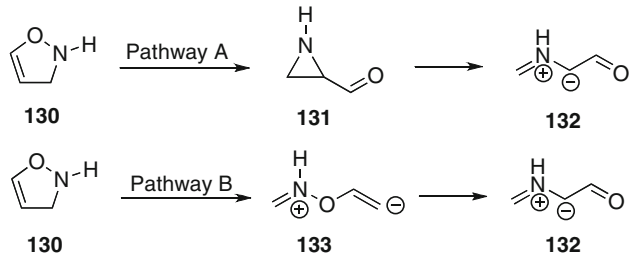
The formation of 4-isoxazolines and pyrroles from allenoates can be explained as outlined in Scheme 34. The initial 1,3-dipolar cycloaddition of the nitrones generated from allenoates affords the target 4-isoxazolines. These heterocycles undergo thermal rearrangement to 2-acylaziridines via N–O bond cleavage. The corresponding azomethine ylides generated via conrotatory aziridine ring opening undergo a proton shift followed by 5-*exo*-trig

Scheme 33



Scheme 34





Scheme 35

cyclization leading to 2,3-dihydro-1*H*-pyrroles, which are converted into 1*H*-pyrroles via dehydration.

This is the most general reactivity pattern of 4-isoxazolines bearing a methyl or methylene group at C-3. However, thermally induced conversion of 4-isoxazolines into azomethine ylides via an alternative mechanism has been proposed. The formation of stable azomethine ylides from isoxazolo[3,2-*a*]isoquinolines has been rationalized by considering a mechanism involving consecutive C3–C4 bond heterolysis and 1,3-sigmatropic shift rather than the accepted mechanism pathway involving acylaziridines as intermediates [84]. Therefore, quantum chemical calculations have been carried out to study the isomerization of the parent system **130** (Scheme 35). However, transition states could only be found for the pathway involving the generation of 2-acylaziridine **131** (Pathway A).

The potential energy profile for thermal isomerization of 4-isoxazoline (**130**) to azomethine ylide **132** is shown in Fig. 2. As can be seen, the ring contraction of 4-isoxazoline to 2-acylaziridine is a very favorable process. On the other hand, the aziridine and the 1,3-dipole resulting from the aziridine ring opening have similar potential energy. The generation of the azomethine ylide is always followed by a stabilizing process, either a ring closure to an oxazoline or a proton shift followed by cyclization leading to pyrroles

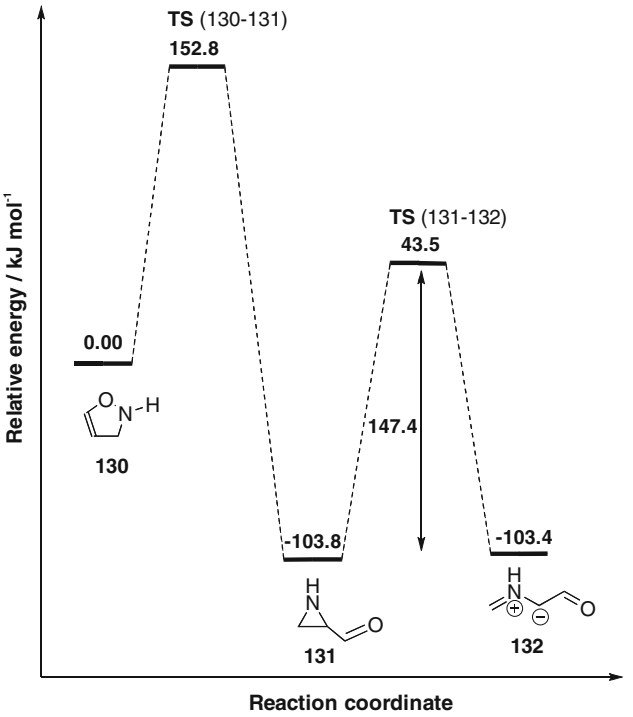


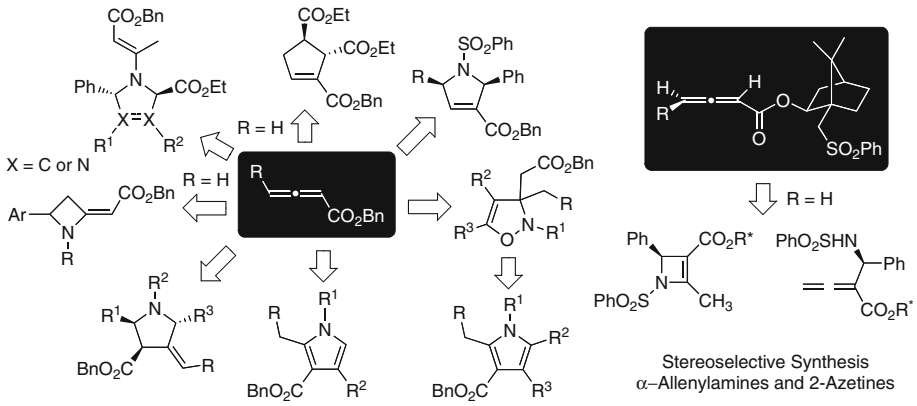
Fig. 2 Potential energy profile for thermal isomerization of 4-isoxazoline **130** to azomethine ylide **131** calculated at B3LYP/6-31G* level of theory

(for derivatives having a methyl or methylene group at C-4). Thus, the quantum chemical calculations corroborate the favorability of the 4-isoxazoline rearrangement to five-membered heterocyles via 2-acylaziridine intermediates.

Conclusion

This review deals with the chemistry of allenes as building blocks in heterocyclic chemistry (Scheme 36). Allenoates

Scheme 36



can be used as dipolarophiles or dipole precursors for the construction of cyclic compounds. Allenoates react with aziridines as 2π components to afford 4-methylenepyrrolidines or pyrroles via [3 + 2] or formal [3 + 2] cycloadditions. Dipolar species obtained from the reaction of allenes with phosphines participate in microwave-induced [3 + 2] annulations with *N*-benzylidenebenzenesulfonamide and electron-deficient alkenes to afford 3-pyrrolines and cyclopentenes. Conrotatory ring opening of *N*-vinyl aziridines resulting from the Michael addition of allenoates to aziridines in the presence of dipolarophiles allow the synthesis of five-membered heterocycles. Allenoates have also been used in the synthesis of functionalized *N*-vinyl nitrogen-containing heterocycles. On the other hand, formal [2 + 2] cycloaddition of buta-2,3-dienoates with *N*-arylidenebenzenesulfonamides in the presence of DABCO yields mainly 2-methyleneazetidines, whereas the DABCO-catalyzed reaction of 2,3-allenoates bearing a chiral auxiliary in the ester moiety with *N*-arylidenebenzenesulfonamides allows the synthesis of optically active α-allenylamines and 2-azetines.

Acknowledgments Thanks are due to FCT (Project PTDC/QUI/64470/2006) COMPETE, QREN, and FEDER for financial support.

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