Exploiting [2 + 2] cycloaddition chemistry: achievements with allenes

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The allene moiety represents an excellent partner for the [2 + 2] cycloaddition with alkenes and alkynes, affording the cyclobutane and cyclobutene skeletons in a single step. This strategy has been widely studied under thermal, photochemical and microwave induced conditions. More recently, the use of transition metal catalysis has been introduced as an alternative relying on the activation of the allenic component. On the other hand, the intramolecular version has attracted much attention as a strategy for the synthesis of polycyclic compounds in a regio- and stereoselective fashion. This *critical review* focuses on the most recently developed [2 + 2] cycloadditions on allenes along with remarkable early works accounting for the mechanism, the regio- and diastereoselectivity of the cycloadducts formed (103 references).

1. Introduction

During the last few years, the chemistry of allenes has been extensively studied and many reviews on their preparation and reactivities have been published.¹ They have shown an interesting reactivity and selectivity affording complex structures in a limited number of steps.² In fact, the chemistry of allenes has been applied for the preparation of natural and non-natural products of interest. In particular, the [2 + 2]

cycloaddition of allenes represents an important strategy for the preparation of cyclobutane derivatives with high atom economy. The importance of the cyclobutane containing compounds both as target molecules as well as useful building blocks for the construction of more complex structures has been widely demonstrated.³ In particular, due to the inherent ring strain, cyclobutanes can undergo fragmentation and ring-expansion reactions for the synthesis of both acyclic and cyclic systems.⁴ A high number of strategies has been published, showing the reactivity of these substrates.⁵

Although the thermal process is forbidden by the Woodward–Hoffmann rules,⁶ and the Fukui's frontier orbital theory,⁷ the [2 + 2] cycloaddition of allenes has been studied photochemically, under thermal conditions involving diradical intermediates, and more recently by the use of transition metal catalysts. It is of special interest when the [2 + 2] cycloaddition is carried out in an intramolecular fashion for the construction

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Benito Alcaide

Benito Alcaide was born in Aldea del Rey, Ciudad Real, Spain, in 1950. He received his BS degree (1972) and PhD degree (1978) from the Universidad Complutense de Madrid (UCM) under the supervision of Professor Franco Fernández. After a 4 year postdoctoral period working on the chemistry of α -iminoketones and related compounds, he began working on β -lactam chemistry. In 1984 he assumed a position of Associate Professor of Organic Chemistry and in 1990 was promoted to Full Professor at the UCM. His current recent interests include β -lactam chemistry, asymmetric synthesis of compounds of biological interest, allenes, metal-promoted cyclizations, and organocatalysis.

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of polycyclic structures in one step, thus bringing many benefits.

In this contribution, we wish to review the most recent advances on the [2+2] cycloaddition chemistry of allenes, but also take into account early works, concerning mechanistic studies, as a base for a better understanding. Most of the examples are thermal [2+2] cycloadditions, however, recently an increased interest in the study of the [2+2] cycloaddition promoted by metal catalysts has been observed.

2. Thermal [2+2] cycloadditions

Thermal [2+2] cycloaddition of allenes has been studied in depth in a wide variety of allenic systems, and many examples have been reported in literature. In general, the [2+2] cycloaddition of allenes requires high temperatures (over 200 °C) and long reaction times, suffering sometimes low regio- and stereoselectivity on the observed compounds. On the other hand, because the thermal process is not allowed by the Woodward–Hoffmann rules⁶ and the Fukui's frontier orbital theory,⁷ the mechanistic details associated with this process have constituted an important topic of study. In fact, although some authors have reported the concertedness of the reaction by a contribution of the cumulated orthogonal π -bond of allene *via* a $[(\pi_{2s} + \pi_{2s})_{\text{allene}} + \pi_{2s} \text{ alkene}]$ process, most of the examples have been explained *via* a stepwise diradical mechanism.

On the other hand, microwave irradiation has been employed as an unconventional energy source for a wide number of organic reactions and has been recognized as a powerful tool for the preparation of complex structures in short reaction times, with a minimization of decomposition and by-products with an improvement of stereo-, regio- or chemoselectivity instead of conventional thermal conditions.⁸

In the following section the mechanistic aspects of the dimerization and intermolecular [2+2] cycloaddition of allenes have been discussed. Literature from 1970 to 1992, approximately, has provided an excellent base to understand the reactivity, regio- and stereoselectivity and the reversibility of the intermediates involved in the process. In addition, more

recent examples of the intermolecular version followed by intramolecular examples in allenenes and allenynes have been presented.

2.1 Dimerization and intermolecular [2+2] cycloadditions of allenes under thermal conditions

Allene dimerization which results in the formation of substituted dimethylenecyclobutanes has been studied intensely.⁹ When the allene is symmetrically substituted, two possible regioisomers are obtained (Scheme 1).

However, when the allene moiety is not symmetrically substituted, a mixture of several dienes can be formed: head-to-head adduct **1**, head-to-tail adduct **2** and tail-to-tail adducts **3** and **4**, along with the corresponding *cis*-, *trans*-, *Z*- and *E*-isomers (Scheme 2).¹⁰

The high stereoselectivity observed of some [2+2] cycloadditions of allenic systems pointed toward the possibility that these reactions were concerted reactions,¹¹ with allene acting in an antarafacial manner to the way that ketene has been demonstrated to behave.¹² For example, it has been described that chloroallene and 1,1-dimethylallene dimerize predominantly in a head-to-head manner (Scheme 3).¹¹

By contrast, 1,1-difluoroallene¹³ and 3,3-dimethyl-1-cyanoallene¹⁴ dimerize in a head-to-tail manner. This results cannot be rationalized on the basis of a $[\pi_{2s} + \pi_{2s}]$ concerted process (Scheme 4). These experiments have shown the importance of the nature of the substituents in the allene moiety along with steric and electronic factors in the transition states.

Early studies on the secondary deuterium isotope effects of allene cycloadditions have indicated that [2+2] dimerization

Scheme 1 Possible regioisomers observed in the dimerization of symmetrically substituted allenes through intermolecular [2+2] cycloaddition reaction.

Cristina Aragoncillo

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at the UCM in the research group of Prof. Alcaide. Her research is focused on β -lactam chemistry, asymmetric synthesis, allene chemistry, and metal-catalyzed coupling reactions.

Scheme 2 Possible regioisomers observed in the dimerization of non-symmetrically substituted allenes.

Scheme 3 [2+2] Dimerization of chloroallene and 1,1-dimethylallene. Reagents and conditions: (a) Et₂O, 60 °C, 3–4 days.

Scheme 4 [2+2] Dimerization of difluoroallene and 3,3-dimethyl-1-cyanoallene. Reagents and conditions: (a) 250–295 °C. (b) 100 °C, 45 min, N₂.

of allenes is not a synchronous process.¹⁵ In this context, the intermediacy of a perpendicular or freely rotating diradical **5** has been proposed in the thermal dimerization of **6** (Scheme 5). However, further proof of the stereospecificity of allene cycloaddition,¹⁶ which together with a striking preference for the more sterically crowded products (dimers having the exocyclic substituents in the hindered inward positions, tail-to-tail dimer **3** in Scheme 2) observed in the dimerization of substituted allenes, needed the development of a concerted two-step mechanism for allene dimerization.¹⁷

In this view, a bisallyl diradical intermediate either retains its stereochemical integrity through its existence (presumably *via* a secondary orbital overlap), or it is formed from allene and close products in separate but individually stereospecific steps (presumably under steric and orbital symmetry control). MO calculations on **5** and its interconversion with its various stable valence isomers have demonstrated that **5** appears to

Scheme 5 Formation of a freely rotating diradical **5** in the thermal dimerization of **6**.

have no constraining electronic preference as to either molecular geometry or π orbital symmetry.¹⁸

The question of whether a bisallyl diradical **5** is necessarily an intermediate in allene dimerization and, if it is an orthogonal or freely rotating specie has proven difficult to answer. Kiefer has reported the thermal and photochemical generation of 2,2'-bis(1,1-dimethylallyl) diradical from an azocyclane precursor.¹⁹ From the results obtained, the authors have suggested that intermediate **5** has a small but significant energy minimum at or near the perpendicular (D_{2d}) geometry, rather than a freely rotating 2–2' bond. This is in line with expectations based on Hückel calculations¹⁸ and terminology, which describe **5** as “effectively orthogonal”.²⁰

Thus, the regio- and stereoselectivity observed in thermal dimerization of allenes has been interpreted on the basis of bis-allyl-diradical intermediates type **5**, although a concerted pathway [$(\pi_{2s} + \pi_{2s})_{\text{allene}} + \pi_{2s} \text{ alkene}$] explains the results in many instances.²¹

Approach of two molecules of allene takes place in a crossed configuration, followed by bond formation between the central *sp* carbons. Simultaneous conrotatory twisting generates a perpendicular 2,2'-bisallyl diradical **5**, which after rotation and disrotatory closure leads to the corresponding dimer **7** (Scheme 6).

On the other hand, considerable attention has been devoted to the study of the cycloaddition reactions of allenes with alkenes and alkynes. For example, the [2+2] cycloaddition of 1,1-dimethylallene with dimethylfumarate has afforded two cycloadducts **8** and **9** in a 11.5:1 ratio in which >99% stereoselectivity is claimed (Scheme 7).²² The reaction of optically active 2,3-pentadiene with acrylonitrile is reported to give four stereoisomeric adducts, all of which are optically active.²³ Despite these seemingly stereochemically concordant results, different mechanisms have been proposed: in the former, a concerted [$\pi_{2s} + \pi_{2s}$] process was proposed; in the latter, a two-step, diradical intermediate mechanism.

In order to get a better understanding of the mechanistic details of the [2+2] cycloaddition reaction of allenes with alkenes and alkynes, Pasto has carried out several studies involving the relative reactivity of different substituted allenes with alkenes and alkynes.

Scheme 6 Mechanistic proposal for the dimerization of allenes by [2+2] cycloaddition.

Scheme 7 [2+2] Cycloaddition of 1,1-dimethylallene with dimethylfumarate. Reagents and conditions: (a) 160–180 °C, 18–70 h.

Scheme 8 [2 + 2] Cycloaddition of 1,1-di- and monosubstituted allenes **10a–g** with 1,1-dichloro-2,2-difluoroethene. Reagents and conditions: (a) 160 °C, 1–2 days.

First, this author has studied the cycloaddition of substituted allenes with 1,1-dichloro-2,2-difluoroethene as a model for the two-step diradical-intermediate [2 + 2] cycloaddition of allenes.²⁴ Thus, the stereoselectivities, chemoselectivities, relative reactivities and kinetic isotope effects in the cycloaddition reaction of substituted allenes with 1,1-dichloro-2,2-difluoroethene, have been determined by comparison with the radical-chain addition of benzenethiol to substituted allenes.²⁵

The cycloaddition reaction of 1,1-di- and monosubstituted allenes **10a–f** with 1,1-dichloro-2,2-difluoroethene has been carried out at 160 °C in a sealed tube affording mixtures of the adducts **11–14** (Scheme 8).

The formation of the [2 + 2] cycloaddition products has been rationalized in terms of the mechanism shown in Scheme 9. The formation of the stereoisomeric adducts **11** and **12** requires the formation of the two stereoisomeric diradical intermediates **15** and **16**, the former undergoing ring closure to form only **11** and **14** and the latter to form only **12** and **14**.

A priori, radical formation should be more favored at the most substituted terminal carbon atom of the allene

Scheme 9 Mechanistic proposal to explain the formation of compounds **11**, **12** and **14** via diradical intermediates **15** and **16**.²⁴

Scheme 10 Formation of diradical intermediate by attack of the most highly substituted double bond.

chromophore. This requires attack on the 2p AO on C2 of the most highly substituted double bond with rotation of the developing radical center to form the planar allyl radical portion of the intermediate, as it is illustrated in Scheme 10. In fact, the KIE's measured for the addition to 1,1-dimethylallene has confirmed this prediction.²⁴

The stereoselectivity observed about the exocyclic double bond in the cycloadducts has been interpreted in terms of steric interactions generated in the transition states for formation of **15** and **16**, the rate of formation of the latter decreasing with increasing size of R. Thus, during the formation of **15** and **16**, the rotational and translational motions illustrated in **15** and **16** in Scheme 11 must occur. In **17** the largest group R' attached to C1 rotates away from the approaching reagent X = Y. This mode of rotation generates no adverse steric effects between R' and the approaching reagent X = Y but does result ultimately in the formation of the less thermodynamically *endo* orientation of R' in the allyl radical. Rotation of the R' group toward the approaching reagent X = Y as in **18** generates an adverse steric interaction between R' and X = Y, which will increase as the size of R' increases. This mode of rotation, however results in the formation of the most thermodynamically stable allyl radical. The experimental results have definitely indicated that the steric effects between R (R') and the approaching reagent, generated on rotation of the RCR' portion of the allene, dominate and that the extent of rotation is greater than that of translation in the transition state, suggestive of a rather early transition state.

The decrease in reactivity in the monoalkylallene and 1,1-dialkylallene series as the size of the R group increases has been explained due to a decrease in the rate of formation of diradical intermediate type **16**. The increase in reactivity in the sequence monoalkyl- < 1,1-dialkyl- < 1,1,3-trialkylallenes is due to an incremental raising in the energies of the π

Scheme 11 Transition states proposed for formation of radicals type **15** and **16**.

MO's in the sequence, which result in an increase in the rate of reaction.

The chemoselectivity has also been determined by steric interactions generated in the transition states for ring closure, favoring closure to the least substituted end of the allyl radical as the degree of substitution and size of the alkyl groups increase. Thus, the direction of ring closure of the diradical intermediate is dependent on the degree of substitution at the termini of the allyl radical portion of the diradical intermediate and on the size of the alkyl group(s) attached to the allyl radical. The diradical intermediates derived from the 1,1-dialkylallenes show significantly greater tendency to ring close to the least substituted end of the allyl radical. This is undoubtedly due to the greater steric congestion encountered in the transition state for ring closure to the most highly substituted end. However, the data derived with monoalkylallenes have shown that as the size of the R group increases, ring closure to the most highly substituted end of the allyl radical increases. This steric effect seems to be in opposition to that causing the difference between the relative importance of the two modes of ring closure of the mono- and disubstituted systems.

The above criteria have been applied to the results derived from the cycloaddition reactions of substituted allenes with *N*-phenylmaleimide.²⁶ In these experiments, four expected cycloadducts were obtained along with ene products. The chemoselectivities, stereospecificities, and relative reactivities have been explained *via* two-step diradical-intermediate processes.

Due to the nature of 1,1-dichloro-2,2-difluoroethene and *N*-phenylmaleimide, information on possible cleavage and internal rotation processes of the diradical intermediate was not accessible. In order to gain more detailed information on the competing reactions of diradical intermediates, reactions of substituted allenes with diethyl fumarate and maleate have been investigated.²⁷

The reaction of diethyl fumarate (DEF) with 1,1-dimethylallene has afforded adducts **19–21**, all containing the *trans*-diester stereochemistry (Scheme 12). However, the reaction of dimethylallene with diethyl maleate (DEM) has afforded both *cis*- and *trans*-diester products **19–24**. Interestingly, isomerization of diethyl maleate to diethylfumarate in the presence of 1,1-dimethylallene has been observed.

T (°C)	DEF (a)			DEM (a)					
	19	20	21	19	20	21	22	23	24
160	(8.5%)	(9.2%)	(5.1%)	(8.5%)	(9.2%)	(5.1%)	(18.0%)	(47.0%)	(11.8%)
180	(9.4%)	(29.3%)	(33.5%)	(9.4%)	(29.3%)	(33.5%)	(1.0%)	(21.1%)	(5.7%)
200	(3.2%)	(20.3%)	(59.3%)	(3.2%)	(20.3%)	(59.3%)	(1.2%)	(6.0%)	(6.4%)

Scheme 12 [2 + 2] Cycloaddition of 1,1-dimethylallene with diethyl maleate and diethyl fumarate. Reagents and conditions: (a) 160, 180 or 200° C, toluene, sealed tube.

Scheme 13 Formation of diradicals **25–28** in the [2 + 2] cycloaddition of 1,1-dimethylallene with diethyl maleate and diethyl fumarate.²⁷

The results have been rationalized in terms of a diradical mechanism in which internal rotation and cleavage reactions of the diradical intermediate compete with ring closure reactions. The results have been accounted as shown in Scheme 13 in which the diradical intermediates derived from dimethylallene and diethylmaleate (**25** and **26**) undergo internal rotation to generate the diradical intermediates derived from the reaction of 1,1-dimethylallene and DEF (**27** and **28**). However, the diradical intermediates derived from 1,1-dimethylallene and DEF do not undergo rotation to those derived from 1,1-dimethylallene and DEM (Scheme 13).

In **27** and **28** the large ester functions are antiperiplanar, representing the lowest energy conformations. In **25** and **26** derived from DEM the ester groups must be initially eclipsed. Such conformations represent energy maxima, and must undergo rotational relaxation to form synclinal-type conformations or undergo further rotation to form **27** and **28**. The trend towards identical **19:20** ratios from DEF and DEM at higher temperatures has suggested that a minimum-energy conformation close to the eclipsed conformations must exit, but the barriers to rotation and cleavage must be rather small, and more rotation and cleavage occur at higher temperatures with **25** and **26**. In order to account for the observed product distribution in the reactions, slight modifications in the conformations **25–28** have been required. Slight rotations about the newly formed C–C bond result in lower energy conformations in which either the C–H (**29** and **30**) or the C–ester bond (**31** and **32**) is in the plane of the allyl radical. Of these conformations **29** and **30** should be of lower energy than **31** and **32**, due to smaller 1,3-diaxial-type interactions and should be favored (Scheme 14). An analysis of the steric interactions in the transition states presented for diradical-intermediate formation has suggested that **27** should be favored over **28**. Thus, cycloadduct **20** would be expected to be the dominant cycloadduct formed.

A similar analysis of the rotational processes in the diradical intermediates **25** and **26** formed in the reaction of 1,1-dimethylallene with DEM is shown in Scheme 15. In this Scheme only the more favored rotational relaxations of **25** and **26** to **33** and **34** have been shown, which undergo subsequent ring closure to form the *cis*-diester products **22** and **23**. In **25** and **26** the ester functions are eclipsed or synclinal, which have much higher

Scheme 14 Diradical conformations proposed for the formation of compounds **19** and **20** during the [2+2] cycloaddition of dimethylallene with diethyl fumarate.²⁷

Scheme 15 Diradical conformations proposed for the formation of compounds **19**, **20**, **22** and **23** during the [2+2] cycloaddition of dimethylallene with diethyl maleate.²⁷

energy conformations than those in which the ester functions are antiperiplanar or anticlinal. Thus, the rotation barriers from **33** to **29**, and **34** to **30** must be relatively small, providing for facile conformation isomerization. The substantially lower **19:20** product ratio observed in the reaction of 1,1-dimethylallene with DEM, compared to that observed in the reaction of 1,1-dimethylallene with DEF, have indicated that **34** undergoes rotation to form **30** in a lower extension than **33** does to form **29**.

Scheme 16 [2+2] Cycloaddition reaction of monoalkylallenes with DEF. Reagents and conditions: (a) DEF as solvent, 160 °C, 10–12 days.

Therefore, for the reactions of 1,1-dimethylallene with DEM, higher-energy diradical intermediates are formed compared to those from the reaction of 1,1-dimethylallene with DEF. The product distribution suggests that the energy barriers to ring closure are approximately the same in the two reactions but that the energy barrier to rotation is significantly reduced in the eclipsed or synclinal diradicals allowing internal rotation to compete effectively with ring closure. It also appears that the energy barrier for cleavage is similarly affected.

In contrast, the reaction of monoalkylallenes with DEF has provided a mixture of *trans*-diester adducts **35–38** (Scheme 16).²⁷ It has been indicated that the yield of **36** relative to **35** decreases as the size of the alkyl group increases, suggesting a two-step, diradical mechanism. *Trans*, *cis*-cycloadduct **37** is formed predominantly over *trans*, *trans*-adduct **38** when R is *tert*-butyl.

Models have indicated that the transition states for formation of **35** would involve diradical intermediates **39** and **40** (Scheme 17). Intermediate **39** will undergo predominant rotational relaxation to form **41** which undergoes ring closure to form **35**. The minor rotational pathway from **39** will form **42** which closes to afford the minor *trans*,*trans*-adduct **38**. Intermediate **40** will undergo predominant rotational relaxation

Scheme 17 Diradical conformations proposed for the formation of compounds **35**, **37** and **38** during the [2+2] cycloaddition of monoalkylallene with diethyl fumarate.²⁷

to form **43**. If ring closure occurs faster than any other rotational process in **43**, ring closure from **43** will form only the *trans,cis*-adduct **37**. The minor rotational pathway in **40** will produce **44** and ultimately **35**. Thus, the conformational preferences in the diradical intermediates with antiperiplanar or anticlinal ester functions determine the product distributions.

Another studied feature of the [2 + 2] cycloaddition process has been the reversibility of formation of the diradical intermediates. Initially, the reversibility of the cycloaddition has been indicated by the *cis* to *trans* isomerization of the substituted allene or from the stereochemistry about the exocyclic double bonds in the cycloadducts. Due to the limited number of substituted alkenes in which *cis* to *trans* isomerization of the alkene can be monitored, the use of chiral allenes has solved this problem, thus the reversibility of formation of the diradical intermediates being indicated by the loss of enantiomeric excess (*ee*) of the starting allene and a decrease in the *ee* of the cycloadducts with extent of reaction.²⁸ The results derived from the cycloaddition reaction of chiral allenes have provided stereochemical information on the formation of the diradical intermediates and on their ring closure. First, the stereochemical features of the [2 + 2] cycloaddition reaction of enantioenriched 1,3-dimethylallene and acrylonitrile affording cycloadducts **45–48** have been studied (Scheme 18). Two separate experiments have been carried out starting from 1,3-dimethylallene in 30.3% *ee* and recovering it in 28.3% *ee*; and secondly by using 1,3-dimethylallene in 28.3% *ee* and recovering it in 25% *ee*. The *ee*'s of the starting and recovered 1,3-dimethylallene have suggested that formation of diradical intermediates is irreversible, or if the intermediates are formed reversibly, there is essentially complete chirality transfer of 1,3-dimethylallene to the intermediates.

Molecular mechanics calculations on the possible orientations of approach of the acrylonitrile to (*S*)-(+)-1,3-dimethylallene have indicated that the lower energy orientation is the one in which acrylonitrile is oriented in the upward direction (diastereomers **49** and **50**), being **49** of lower energy than **50** (Scheme 19). Scheme 19 shows the corresponding diradicals **51–54** derived from the approaching of 1,3-dimethylallene to acrylonitrile. Ring closure of diradicals **51–54** at the right or the left end of the allyl radical will produce cyclobutanes **45–48**.

Scheme 18 [2 + 2] Cycloaddition of (*S*)-(+)-1,3-dimethylallene with acrylonitrile. (a) Reagents and conditions: (a) toluene-*d*₈, hydroquinone, 148 °C, 5 days.

Scheme 19 Lower energy possible orientations of approach of (*S*)-(+)-1,3-dimethylallene to acrylonitrile.²⁸

Cycloadducts **45** and **46** can be formed *via* three different channels; for **45**, channels *a*, *c* and *d*, and for **46**, channels *a*, *b* and *c*. In both of these two sets of reaction channels, two ring-closed products possessing the *S* configuration at C2 and one having the *R* configuration at C2 may be formed. The latter channels result in reduction of the *ee* transferred to the cycloadducts **45** and **46**. In addition, the energy barriers for racemization of **51** and **53** appear to be low enough to allow for some competitive racemization, further reducing the *ee*'s retained in **45** and **46**. The observed *ee*'s of **45** and **46** are in all probability derived from ring closure of the diradical intermediates **52** and **54**, which are of higher intrinsic asymmetry and are not capable of undergoing racemization competitive with ring closure.

In contrast, cycloadducts **47** and **48** are formed only *via* single reaction channels (*d* and *b*, respectively), both leading to the *S* configuration at C2 in the cycloadducts. This, along with the expectation that racemization of **52** and **54** will not be competitive with ring closure will result in higher transfers of the *ee* of the 1,3-dimethylallene to these products. The fact that only 37 and 29% of the *ee* of the starting 1,3-dimethylallene has been transferred to the cycloadducts, along with the fact that the recovered unreacted 1,3-dimethylallene has not lose any *ee* during the course of the reaction, has implied that the diradical intermediates **51–54** are formed irreversibly.

On the other hand, [2 + 2] cycloaddition of (*S*)-(+)-1,3-dimethylallene with methyl acrylate has produced the four cycloadducts **55–58** (Scheme 20).²⁸

It has been observed that there is no loss in the *ee* of the 1,3-dimethylallene during the course of the cycloaddition reaction, which, in view of the fact that derived cycloadducts possess lesser *ee*'s than the starting 1,3-dimethylallene, indicates that the formation of the diradical intermediates is irreversible.

Scheme 20 [2 + 2] Cycloaddition of (*S*)-(+)-1,3-dimethylallene with methyl acrylate. (a) Reagents and conditions: (a) toluene- d_8 , hydroquinone, 160 °C, 3 days.

Fig. 1 Approaches of methyl acrylate to 1,3-dimethylallene.

It has been observed that the *ee*'s of the cycloadducts derived from methyl acrylate are significantly higher than those possessed by the cycloadducts with acrylonitrile. Molecular mechanics calculations for the reaction of methyl acrylate with 1,3-dimethylallene have indicated greater preferences for the approaches shown in **59** and **60** compared to the approaches in which the ester groups are oriented in an upward manner (Fig. 1).

This may be expected to result in greater diastereoselectivity in the formation of the activated complexes. In addition, the larger size of the methyl ester function compared to the cyano group will result in an increase in the energy barriers for the rotation about the C1–C5 bond and potentially about the C1–C2 bond, thus resulting in less racemization of the intermediates. The formation of the cycloadducts **55–58** follows a parallel pathway to that illustrated in Scheme 19 for the formation of the diradical intermediates and cycloadducts with acrylonitrile.

The next step has been the study of the cycloaddition reaction of *N*-phenylmaleimide (NPM) and dimethyl fumarate with an excess of enantioenriched 1,3-dimethylallene²⁹ with varying initial enantiomeric excesses of the 1,3-dimethylallene and different concentrations of reactants. These reactions involve the irreversible formation of the diradical intermediates in which a new tetrahedral stereogenic atom is generated. The chirality of these diradical intermediates is “locked in”, as a consequence there is no mechanism for the racemization of these intermediates. Thus, it has been observed that the *ee* of the 1,3-dimethylallene is transferred to the diradical intermediate which appears in the cycloadducts. In addition, the results of molecular modeling calculations have indicated that three separate, minimum energy reaction channels are operative, proceeding through different conformations of the reactants in approaching the activated complexes which result directly in the formation of different minimum-energy conformations of the diradical intermediates. These different conformations of the diradical intermediates undergo ring closure to specific cycloadducts.

Scheme 21 [2 + 2] Cycloaddition of (*S*)-(+)-1,3-dimethylallene with 1,1-dichloro-2,2-difluoroethene. (a) Reagents and conditions: diethyl ether, 160 °C, 48 h.

Later on, the reaction of enantioenriched (*S*)-(+)-1,3-dimethylallene with 1,1-dichloro-2,2-difluoroethene was studied. This reaction affords two cycloadducts (Scheme 21).³⁰ The major cycloadduct **61** retained a higher percentage of the *ee* of the starting 1,3-dimethylallene (>30%) than the minor cycloadduct **62** does (>10%). The results of molecular modeling calculations on the conformations of the two reactants in approaching the activated complexes for diradical intermediate formation, and on models for the *anti,anti* and *anti,syn* diradical intermediates, have provided a most reasonable interpretation of the results involving one major continuous, low energy reaction pathway *via* the *anti,syn* diradical intermediate leading to cycloadduct formation.

Molecular modeling calculations on the conformational preferences for the approach of 1,3-dimethylallene and 1,1-dichloro-2,2-difluoroethene have suggested a perpendicular approach of the two reactants and conformation of the diradical intermediates **63** and **64** as shown in Fig. 2.

Due to the relatively high *ee* observed on cycloadduct **61**, it has been concluded that the formation of the *anti,syn* diradical intermediates must substantially predominate over the formation of the *anti,anti* diradical intermediate.

A surprising result was obtained in the reaction of enantioenriched (*S*)-(+)-1,3-dimethylallene with 1,1-diphenyl-ethene, which does not lead to detectable formation of [2 + 2] cycloadducts,³⁰ but does result in the racemization of 1,3-dimethylallene. These results have been interpreted as it is shown in Scheme 22, which involves the reversible formation of the two diradical intermediates **65** and **66**. Intermediate **65** possesses a plane of symmetry, which is formed reversibly resulting in the loss of the optical activity of 1,3-dimethylallene. Intermediate **66** is chiral, which on cleavage will return to the 1,3-dimethylallene in the same extent of chirality as it inherited from 1,3-dimethylallene. The lack of apparent formation of cycloadducts in the reaction does not mean that they are not formed at all, it only shows that if formed they will be formed in quantities too small to be detected. Cycloadducts **67** and **68**

Fig. 2 Diradical intermediates preferred in the [2 + 2] cycloaddition reaction of 1,3-dimethylallene with 1,1-dichloro-2,2-difluoroethene.

Scheme 22 [2+2] Cycloaddition of (S)-(+)-1,3-dimethylallene with 1,1-diphenylethene.³⁰

are quite sterically congested and could well be formed in very unfavorable equilibria.

On the contrary, the cycloaddition reactions of 1,1-dimethylallene with a number of alkynes have afforded substituted methylenecyclobutenes **69–73**, although in some cases isolation by chromatography of cycloadducts was not possible (Scheme 23).³¹

Ring closure of the diradical intermediate **74** formed occurs exclusively at the less substituted end of the allyl radical, except with ethyl propiolate in which a minor amount of ring closure occurs at the dimethyl-substituted end of the allyl radical. In the cycloaddition reaction with ethyl phenylpropiolate, apparently only the diradical intermediate **75** is formed which is stabilized by the phenyl group, whereas in **76** the radical center is stabilized by the ester group (Fig. 3).

Following the series of Pasto's work, the stereochemical features of the [2+2] cycloaddition reaction of 1,3-dimethylallene with methyl propiolate have been reported.³² The cycloaddition reaction of enantioenriched 1,3-dimethylallene with methyl propiolate was carried out at 130 °C affording two cycloadducts **77** and **78** in a ratio of 41.8:58.2, along with some remaining unreacted 1,3-dimethylallene (Scheme 24).

Scheme 23 [2+2] Cycloaddition of 1,1-dimethylallene with different alkynes. Reagents and conditions: (a) Toluene- d_8 , 160° C, 16 h.

Fig. 3 Proposed diradicals **74–76** for the [2+2] cycloaddition reaction of 1,1-dimethylallene with alkynes.

Scheme 24 [2+2] Cycloaddition of (S)-(+)-1,3-dimethylallene with methylpropiolate. Reagents and conditions: (a) Toluene- d_8 , hydroquinone, 130 °C, 24 h.³²

A mechanistic scheme for the formation of the cycloadducts **77** and **78** has been proposed. The approach **A** of methylpropiolate to (S)-1,3-dimethylallene is favored over the alternative approach **B** (Fig. 4).

Collapse of **A** to the diradical intermediates **80** and **81** will produce the intermediates possessing the absolute configurations shown, with **81** existing in a perpendicular conformation calculated to be the lowest in energy for the parent system, and **80** existing in a slightly nonperpendicular conformation (Scheme 24). Racemization of **80** requires a 180° rotation about the C1–C2 bond, however, this is not expected to occur. Intermediate **81**, however, is achiral and can undergo ring closure to form only racemic **78**. The facts that intermediate **81**

Fig. 4 Approaches proposed for the reaction of enantioenriched (*S*)-1,3-dimethylallene with methylpropiolate.

can give rise to only racemic **78** and that **78** possesses an *ee* comparable to that of **77** indicate that the majority of **78** is produced from chiral **80**. If one assumes that both **77** and **78** are formed from **80** with the same extent of transfer of the *ee* of **80**, it is then possible to apportion the relative extent of ring closure of **80** to the *anti* and *syn* ends of the allyl radical intermediates **80** and **81**. The results have indicated that there is a high preference for the formation of the *anti*,*syn* diradical intermediate **80**, which prefers to undergo ring closure to the *syn*-methyl-substituted end of the allyl radical.

In 2000, Hammond studied the stability of α -fluoroallenylphosphonate **82** under thermal conditions.³³ Heating compound **82** in a sealed tube furnished dimer **83** exclusively in 73% yield (Scheme 25). This result contrasts with the mechanistic scenario accounting for a concerted [2 + 2] process in the allene dimerization. Probably, the bulky phosphorous substituent on the allene moiety allows rotation in the bisallyl diradical intermediate yielding the corresponding tail-to-tail dimer.

Another interesting example showing the dependence of the nature of the substituents attached to the allene moiety in the regiochemistry of the [2 + 2] cycloadducts has been reported by McGlinchey in 2004.³⁴ Thus, during the attempted studies of the Diels–Alder reaction between 9-phenylethynylfluorene **84** and tetracyclone **85**, under thermal conditions, two products resulting from the dimerization of the isomeric allene **86** were obtained. The major product, 8,16-diphenyl-diindeno[1,2,3-*de*:1',2',3'-*mn*]naphthacene **87**, and a minor component, the dihydronaphthacene **88** bearing fluorenyl moieties spiro-bonded at the C5 and C11 positions were identified (Scheme 26).³⁴ Both compounds were not the expected Diels–Alder adducts, but rather are derived from the dimerization of 9-phenylethynylfluorene **84**, presumably *via* its isomeric allene **86**, with which is in equilibrium. Thus, when the allene **86** was heated in refluxing heptane two products were formed, a yellow material (84% yield) that was identified as the head-to-tail [2 + 2] dimer **89**, and an unidentified red dimer (8%). Therefore, compounds

Scheme 26 Thermally induced dimerization reaction of 9-phenylethynylfluorene **84** *via* its isomeric allene counterpart **86**. Reagents and conditions: (a) Heptane, Δ .

87 and **88** should be formed from dimer **89** under heating conditions.

More recently, the same authors have described the syntheses and dimerizations of fluorenylidene-derived allenes **90a** and **90b** to form bis(alkylidene)cyclobutanes **91a** and **91b** (Scheme 27).³⁵ Reaction of 9-ethynyl-9*H*-fluoren-9-ol **92a** with dilute aqueous HBr at 0 °C to room temperature for 5 h gave the corresponding cyclobutane **91a** in 85%. On the other hand, reaction of 9-phenylethynylfluorene **92b** with triethylamine at 0 °C to room temperature overnight provided the [2 + 2] head-to-tail dimer **91b**. In both cases, dimers **91a** and **91b** were obtained without isolation of the precursor allenes **90a** and **90b**.³⁶

A stepwise process involving a diallylic diradical intermediate **93** has been proposed. The orthogonal arrangement of the substituents in allenes **90**, together with the obvious preference of large groups to minimise steric hindrance, suggests that the initial approaching geometry of two molecules of **90** is favored by a C2-type trajectory (Scheme 28).

More recently, Swamy has described the [2 + 2] dimerization of allene **94** during the attempted studies of the Diels–Alder reaction between allene **94** and anthracene under thermal

Scheme 25 Dimerization reaction of α -fluoroallenylphosphonate **82**. Reagents and conditions: (a) THF, sealed tube, 140 °C, 1.5 h.

Scheme 27 Dimerization reaction of fluorenylidene-derived allenes **90a** and **90b**. Reagents and conditions: (a) AcOH, HBr, RT, 5 h. (b) Pentane, Et₃N, 0 °C to RT, overnight.

Scheme 28 Proposed mechanism for the formation of dimers **91a** and **91b**.³⁶

Scheme 29 Dimerization reaction of phosphorous-derived allene **94**. Reagents and conditions: (a) 185 °C, 6 h.

conditions.³⁷ Head-to-head dimer **95** was obtained in 68% yield (Scheme 29). A concerted diradical mechanism similar to that shown in Scheme 6 should be involved in the formation of compound **95**.

In 2005, Jung and co-workers reported that the cycloaddition of silyloxydienes **96a** and **96b** with allenecarboxylate **97** gave cyclobutanes **98a** and **98b** in moderate yields (Scheme 30). Hydrolysis of the silyl ethers **98a** and **98b** in acidic ethanol furnished the corresponding substituted 1-alkenyl-3-alkylenecyclobutanols **99a** and **99b** in good yields. Finally, treatment of cycloadducts **99a** and **99b** with a lithium base at low temperature gave the corresponding cyclohexenones **100a** and **100b**. Apparently, the [2 + 2] cycloadducts thermally rearrange *via* a formal [3,3]-sigmatropic shift, providing the corresponding *endo* adducts **100a** and **100b** diastereoselectively.³⁸ The versatility of the above methodology

Scheme 30 [2 + 2] Cycloaddition reaction of 2-silyloxydienes **96a** and **96b** with allenecarboxylate **97**. Reagents and conditions: (a) Toluene, 80 or 130 °C, pressure tube, 24–48 h. (b) *p*-TsOH, EtOH, THF, RT, 2h. (c) LiHMDS, –78 to 0 °C, 1.5 h.

Scheme 31 Intermolecular [2 + 2] cycloaddition of 4-vinylidenoxazolidin-2-ones **101** with several terminal alkynes and alkenes. Reagents and conditions: (a) Alkyne or alkene as solvent, 80–100 °C, N₂, 4–48 h.

has been applied to the enantioselective synthesis of (–)-dysidiolide,³⁹ (±)-hedychenone⁴⁰ and (±)-hedychilactone **B**⁴¹ *via* stepwise allenolate diene cycloaddition.

In 2003, Tamaru developed the thermal intermolecular [2 + 2] cycloaddition of vinylidenoxazolidin-2-ones **101a–c** with terminal alkynes, alkenes, and 1,3-dienes, regardless of their electronic nature, showing a exclusive preference over the [4 + 2] cycloaddition. Thus, the corresponding 3-substituted (*Z*)-methylene-cyclobutenes **102**, 3-substituted methylene-cyclobutanes **103**, and 3-vinylmethylene-cyclobutanes **104**, have been obtained in good to excellent yields.⁴² Firstly, the [2 + 2] cycloaddition of vinylidenoxazolidin-2-ones **101** with alkynes was investigated. Treatment of compounds **101** with an excess of phenylacetylene or ethyl propiolate at 100 °C afforded the corresponding methylene-cyclobutanes (*Z*)-**102**, as single isomers in good yields. Surprisingly, of the two conceivable stereoisomers, only *Z* isomers were isolated (Scheme 31). Next, the authors examined the reaction of vinylidenoxazolidin-2-ones **101** with alkenes of different structural and electronic substituents. In general, alkenes bearing conjugated π -systems and electron-withdrawing groups showed parallel results, obtaining the corresponding [2 + 2] cycloadducts **103** in good yields. However, alkenes bearing electron-donating substituents displayed a completely different reactivity yielding tetrahydropyridines *via* a formal [4 + 2] cycloaddition reaction.

Analogously, vinylidenoxazolidin-2-ones **101a** and **101c** displayed no dienophilic reactivity toward dienes, but instead, selectively underwent [2 + 2] cycloaddition to provide 3-vinyl-1-methylene-cyclobutanes **104a–j** in good to excellent yields (Scheme 32).

The regioselectivity observed for the [2 + 2] cycloaddition of allenes **101a** and **101c** with dienes, depends on the nature of the substituents attached to the diene moiety. Thus, 1-substituted dienes react at the distal non-substituted 3,4-double bonds (**104c**, **104h** and **104i**), while 2-substituted dienes react selectively at the 1,2-double bonds, irrespectively of the electronic nature of the substituents (**104b**, **104f** and **104g**), and unsymmetrically 2,3-substituted dienes react selectively at the double bonds with higher electron density (**104j**).

The mechanistic details associated with the thermal [2 + 2] cycloaddition of 4-vinylidenoxazolidin-2-ones **101a–c** have pointed to a concerted mechanism, involving a six-electron Hückel [$(\pi_{2s} + \pi_{2s})_{\text{allene}} + \pi_{2s}$] transition state, based on the

Scheme 32 Intermolecular [2+2] cycloaddition between 4-vinylideneoxazolidin-2-ones **101a** and **101c** with 1,3-dienes. Reagents and conditions: (a) Dioxane, 80–100 °C, N_2 , 9–24 h.

frontier orbital theory (Fig. 5). The unique reactivity associated with **101** might be attributed to a strong $\sigma^*(N-SO_2)-\pi^*(C_\alpha=C_\beta)$ interaction of **101a** and **101c** [or $\sigma^*(N-CO)-\pi^*(C_\alpha=C_\beta)$ interaction for **101b**], which produces (1) the lowering of the $\pi^*(C_\alpha=C_\beta)$ energy level (and hence, lowering of the activation energy for the [2+2] addition) and (2) the rehybridization of the $\pi^*(C_\alpha=C_\beta)$ orbitals (sp^3 -like, and hence, better overlap between the p orbitals of alkene C1 and allene C_β in the opposite face to N-Ts). As it is shown in

Fig. 5 Explanation for the thermal, concerted [2+2] cycloaddition on “the orbital interaction in three-systems”: (a) reactions for electron-deficient alkenes and alkynes, (b) reactions for electron-rich and conjugated alkenes and alkynes.⁴²

Fig. 5a for electron-deficient alkynes and alkenes and in Fig. 5b for electron-rich and conjugated alkynes and alkenes, the three-systems interaction, with a coaxial overlap of the p orbitals of C_α and C2 and a perpendicular overlap of the p orbitals of C_β and C1, necessitates a 90° counter-clockwise rotation of the oxazolidinone ring (*i.e.*, a rotation of the N-Ts group toward C2) to furnish compounds (*Z*)-**102–104**.

In 2002 Nair and coworkers studied the [2+2] cycloaddition of allenes with [60]fullerene for the preparation of novel cyclobutane annulated fullerene derivatives. Thus, treatment of allenamides **105** with [60]fullerene in refluxing toluene has afforded the corresponding cyclobutane annulated fullerene derivatives **106** in moderate yields (Scheme 33).⁴³ The mechanism of the reaction has been rationalized as outlined in Scheme 33. The electron deficient fullerene cage can stabilize the negative charge, thereby facilitating the intramolecular attack to the iminium moiety. A possible charge transfer complex formation between the allenamide **105** and [60]fullerene, which will bring the $C1'-C2'$ double bond of the allene in close proximity to the cage, would facilitate the [2+2] cycloaddition.

The [2+2] cycloaddition reaction has also been promoted under high pressure conditions. In particular, in 2003 Scheeren group studied the reaction of enol ethers **107** with the 1,2-propadienyl sulfone **108** at 15 kbar, providing regioselectively the corresponding (3-alkoxycyclobutylidene)methyl 4-methylphenyl sulfones **109** in good yields (62–75%) (Scheme 34).⁴⁴ Interestingly, substitution on the enol ether moiety does not affect the regioselectivity of the reaction, which is determined by the electron-richness of the reacting alkene.

Very recently, in 2009 Ogasawara⁴⁵ described the stereoselective intermolecular [2+2] cycloaddition of allenes **110** with ketenes **111**, affording a mixture of several isomers

Scheme 33 Reaction and proposed mechanism for the [2+2] cycloaddition reaction between allenamides **105** and [60]fullerene. Reagents and conditions: (a) Toluene, 110 °C, 12 h.⁴³

Scheme 34 High pressure-promoted [2+2] cycloaddition of 4-methylphenyl-1,2-propadienyl sulfone **108** with enol ethers **107**. Reagents and conditions: (a) HP (15 kbar), RT or 50 °C, 16 h.

Scheme 35 Intermolecular [2+2] cycloaddition of allenes with ketenes. Reagents and conditions: (a) Ether/DME, 23 °C, 8 h.

depending on the nature of the endocyclic structure of the starting allene (Scheme 35). Thus, the reaction of the cyclic allene **110a** with dichloroketene **111a** produced a mixture of four isomers. However, the smaller-membered cyclic allenes exhibited different stereoselectivity in the [2+2] cycloaddition. As an example, reaction of **110b** with ketene **111a** afforded only two isomers. More remarkably, the reaction between nine-membered **110c** with **111a** and **111b** gave adducts **112** as single isomers in 73 and 65% yield, respectively. The results obtained have indicated that the cyclic structures in the smaller endocyclic allenes direct a reacting ketene from the unencumbered face as expected (see Fig. 6).

In addition, the authors have studied the axial-to-central chirality transfer by the asymmetric synthesis of the scalemic endocyclic allene **116**. Reaction of allene **116** with ketene **111a** afforded the [2+2] cycloaddition product enantiomerically enriched **117** in 64% *ee* and 60% yield.⁴⁵ The chirality transfer of the reaction was estimated to be >98% (Scheme 36).

Fig. 6 Steric properties of endocyclic allenes.

Scheme 36 [2+2] Intermolecular cycloaddition of enriched allene **116** with ketene **111a**. Reagents and conditions: (a) Ether/DME, 23 °C, 8 h.

2.2 Intramolecular [2+2] cycloadditions under thermal conditions

Considering the intramolecular [2+2] cycloaddition of allenenes and allenynes **118**, two regioisomers can be formed, the proximal cycloadduct **119** by reaction with the internal 2π component, and the distal cycloadduct **120** by reaction with the external 2π component of the allene moiety (Scheme 37).

The intramolecular thermal [2+2] cycloaddition of allenenes and allenynes has offered an interesting opportunity to prepare selectively polycyclic compounds. In general, the regioselectivity of the cycloaddition depends on the steric nature of the substituents attached to the allene or alkene/alkyne moieties, providing the corresponding proximal or distal adducts.

Pioneering works by Padwa's group have shown the dependence of the substituents of the allene moiety (α- or γ-tethered allenyl sulfones) into the thermal intramolecular [2+2] cycloaddition.⁴⁶ Thus, the thermal [2+2] cycloaddition of several α-tethered allenyl sulfones **121** took place across the non-activated π-system of the allene, affording the corresponding distal cycloadducts **122** in excellent yields with complete stereospecificity (Scheme 38).

Formation of cycloadducts **122** can be explained as depicted in Scheme 39. The initial rate-determining carbon-carbon bond formation occurs between the central allene carbon and the proximal alkene carbon atom. Although the regioselectivity on the alkene system is due to less clear-cut

Scheme 37 Possible regioisomers observed in the intramolecular [2+2] cycloaddition of allenenes and allenynes.

Scheme 38 [2+2] Cycloaddition of α-tethered allenyl sulfones **121**. Reagents and conditions: (a) Benzene, 80 °C, 45 min–22 h.

Scheme 39 Stereospecificity of the [2+2] cycloaddition of allenyl sulfones **121**.⁴⁶

parameters. Evidently, it is easier for stepwise bonding to occur in a 1,6-*exo* manner (leading to diradical **123**) than in a 1,7-*endo* fashion (through diradical **124**).

An interesting change in the regioselectivity of the [2+2] cycloaddition has been observed with allenes **125**. In fact, heating allenes **125** in xylene produced the proximal cycloadducts **126**, which correspond to a formal [2+2] cycloaddition across the more activated double bond (Scheme 40). Thus, substitution at the 7-position effectively caused a crossover in the allene regioselectivity. These reactions proceeded through a similar mechanism, in which the central allene carbon is involved in the initial carbon–carbon bond formation with the distal alkene carbon, to give an intermediate diradical **127**. The resulting methylenecycloheptyl diradical **127** undergoes subsequent closure to form the bicyclo[3.2.0]heptane ring **126**.

Alkynes can isomerize to the corresponding allenes under selected conditions. This process is favored if the migrating π -bond in conjugation with an alkene, alkyne or aromatic ring and usually this reaction is performed under basic conditions employing KOH, Na₂CO₃ or KOtBu. This isomerization has also proven to be very useful in the [2+2] cycloaddition of allenes. Thus, the [2+2] cycloaddition has been studied in γ -tethered-allenes **128**. Treatment of propargyl sulfones **129** with triethylamine under thermal conditions allowed for equilibrium concentrations of allenes **128** to be formed, which then underwent rapid intramolecular cycloaddition to give the methylenecyclobutanes **130** (Scheme 41).⁴⁷ A diradical intermediate **131** arising from initial attack of the terminal olefinic carbon onto the central allene carbon atom should be involved in the formation of tricycles **130**. It is assumed that the

Scheme 41 Intramolecular [2+2] cycloaddition in γ -tethered-allene systems **128**. Reagents and conditions: (a) Benzene, Et₃N (cat.), reflux, 5–24 h.⁴⁷

resulting diradical intermediate **131** would rapidly close (before bond rotation can occur) to the more stable *cis*-fused 4,5-ring systems **130**.

The regiochemical outcome observed in allenes **125** is in agreement with the results reported by Strenström in 2003. Thus, the intramolecular [2+2] cycloaddition on phenylsulfonyl allene **132** has been studied in order to prepare ($\pm$)- Δ^6 -protoilludene. However, thermal treatment of allene **132** provided the tricyclic structure **133**, with the observed regiochemistry of the [2+2] cycloaddition being opposite to the desired one (Scheme 42).⁴⁸ A seven-membered diradical intermediate analogue to **127** should explain the formation of compound **133**.

In our research group, we have used the thermal [2+2] cycloaddition of 2-azetidinone-tethered enallenols for the synthesis

Scheme 40 Change in the regioselectivity of the [2+2] cycloaddition in α -tethered-allene systems **125**. Reagents and conditions: (a) Xylenes, reflux, 6–12 h.⁴⁶

Scheme 42 Intramolecular [2+2] cycloaddition of phenylsulfonyl allene **132**. Reagents and conditions: (a) Xylenes, Δ , 80 h.

Scheme 43 Synthesis of tricyclic β -lactams **136–138** by formal [2 + 2] cycloaddition reaction of 2-azetidinone-tethered enallenols **134** and **135**. Reagents and conditions: (a) Toluene, 220 °C, sealed tube, for $R^1 = H$: 10 h; for $R^1 = Me, Ph$: 1.5–8 h.

of racemic and enantiopure strained tricyclic β -lactams containing a cyclobutane ring.⁴⁹ It was observed that the regioselectivity of this cycloaddition reaction is determined by the presence or absence of an alkyl substituent at the internal alkene carbon atom. Thus, treatment of allenenes **134** and **135** in toluene at 220 °C in a sealed tube afforded tricyclic β -lactams **136–138**, in reasonable yields and complete regio- and diastereoselectivity, (Scheme 43). The tricyclic ring structures **136–138** arise from the formal [2 + 2] cycloaddition of the alkene with the distal bond of the allene moiety. Interestingly, the regioselectivity of the process is not affected by the substitution at the allene group.

On the other hand, it was observed that the presence of an internal substituent at the alkene moiety switched the regioselectivity. Thus, exposure of allenols **139–141** to the above thermal conditions afforded methylenecyclobutane 2-azetidinones **142–146** as the only products in reasonable yields (Scheme 44).

Scheme 44 Change in the regioselectivity of the intramolecular [2 + 2] cycloaddition reaction of 2-azetidinone-tethered enallenols **139–141**. Reagents and conditions: (a) Toluene, 220 °C, sealed tube, 5–7 h.

Scheme 45 Radical mechanistic proposals for the formation of strained tricycles **136–138**.⁴⁹

Formation of fused strained tricycles **136–138** has been rationalized by a radical mechanism involving an exocyclic diradical intermediate **147** through initial carbon–carbon bond formation between the central allene and proximal alkene carbon atoms (*path A*, Scheme 45). An alternative mechanism may also be proposed (*path B*, Scheme 45). This pathway would involve and endocyclic diradical intermediate **148**, arising from the initial attack of the terminal olefinic carbon onto the distal allene carbon. Both pathways would include a rapid ring closure of the diradical intermediates before bond rotation.

Analogously, formation of tricycles **142–145** has been rationalized by a mechanism which includes an exocyclic diradical intermediate **149** through initial carbon–carbon bond formation involving the proximal allene and internal alkene carbon atoms (*path C*, Scheme 46). An alternative pathway leading to compounds **142–145** has also been proposed in *path D*. This proposal would involve an endocyclic diradical intermediate **150**, arising from the initial attack of the terminal olefinic carbon onto the central allene carbon. The final ring-closing step of the diradical intermediates would account for the cyclobutane formation.

It seems that the regioselectivity in this type of [2 + 2] cycloaddition reaction is determined by the presence or absence of an alkyl substituent at the internal alkene carbon atom, as the allenenes **134** and **135** that are lacking a methyl group exclusively produced addition at the β,γ -double bond, while the allenenes **139** and **141**, which bear a methyl group at the internal olefinic carbon underwent a formal [2 + 2] cycloaddition reaction at the α,β -double bond. *Path A* (Scheme 45) looks valid for the formation of products **136–138**. For this case, the Me group stabilizes the exocyclic

Scheme 46 Radical mechanistic proposals for the formation of strained tricycles **142–145**.⁴⁹

Scheme 47 Thermal intramolecular [2+2] cycloaddition reaction of allenenes **151a–f**. Reagents and conditions: (a) DMF, 150 °C, 1–30 h.

diradical, and the presence of the double bond promotes the allylic radical **147** over the alternative endocyclic vinylic radical **148** in *path B*. However, it could be presumed that for the formation of compounds **142–145**, *path D* (Scheme 45) is more reasonable. The simultaneous stabilization of the endocyclic diradical **150** by the presence of a methyl substituent and allylic stabilization makes this radical favoured over the exocyclic diradical **149**.

In a more recent work, Ohno and Tanaka have presented a stereoselective route to [4.2.0] octane derivatives using thermal [2+2] cycloaddition of unactivated allenenes **151a–j**.⁵⁰ The reactions were carried out using dimethylformamide as the solvent at 150 °C, leading to 3-azabicyclo[4.2.0]oct-5-ene derivatives **152a–j** in good to excellent yields, with complete

Scheme 48 Thermal intramolecular [2+2] cycloaddition reaction of allenenes **151g–j** having substituent(s) on the allenic carbon. Reagents and conditions: (a) DMF, 150 °C, 1–36 h.

Scheme 49 Mechanistic proposal accounting for the stereoselectivity of the thermal intramolecular [2+2] cycloaddition of allenenes **150**.⁵⁰

regioselectivity (Scheme 47 and 48). The [2+2] cycloaddition of allenenes bearing substituents on the allene moiety were also investigated. Monosubstitution at the proximal and distal carbons in allenenes **151g** and **151i** was tolerated and the expected products **152g** and **152i** were, respectively obtained in high yields (90–94%). On the other hand, decreased reactivity toward the cycloaddition was observed with allenenes **151h** and **151j** bearing a geminal dimethyl group at the terminal position, leading to cycloadducts **152h** (46%; 3:1 mixture of diastereomers) and **152j** (63%) in longer reaction time (Scheme 48).

The stereoselective formation of cycloadducts **152** from terminal allenenes **151** is illustrated in Scheme 49. Among the two conformations, **153** and **154** of the first cyclization, **154** would be destabilized by unfavourable steric interaction between the methylene protons of the terminal allenic carbon and the R' group of the terminal olefin. Accordingly, the first cyclization preferentially would occur through **153** to give a diradical intermediate **155**. Since the geometry of the olefin is completely preserved to yield the cycloadduct **152** without formation of **156**, the second cyclization would involve a rapid ring closure before the bond rotation can occur. The fact that diastereomer **157** derived from the relatively unstable conformer **154** was not detected from terminal allenenes would suggest that the energy difference between the two conformers **153** and **154** is significant in the case of terminal allenenes.

On the other hand, the substitution on the terminal alkyne moiety is essential for the [2+2] cycloaddition of allenynes, providing the corresponding distal adducts with complete regioselectivity. Ohno and Tanaka, have investigated the thermal cycloaddition of allenynes **158** and the desired bicyclic compounds **159** were produced in good yields (Scheme 50).⁵⁰ It has been observed that the effect of electron-donating and electron-withdrawing substituents on the aryl group is not dramatic. Likewise as in the reaction of allenenes, the α -substituent of the allene moiety has proven to be significantly

$R^1 = \text{Mts, Ts}$
 $R^2 = \text{Ph, 4-Me-C}_6\text{H}_4, 4\text{-MeOC}_6\text{H}_4, 4\text{-CO}_2\text{Me-C}_6\text{H}_4$

$R^1 = \text{Mts, Ts; } R^2 = \text{H, Me, Bn}$

Scheme 50 Intramolecular [2 + 2] cycloaddition reaction of allenyne **158** and **160**. Reagents and conditions: (a) Dioxane, reflux, for **158**: 2–3 h; for **160**: 8–117 h.

important. For instance, the reaction of allenyne **160** bearing smaller substituents at the α -position required longer reaction times (8–117 h).

Mukai and coworkers have examined the thermal [2 + 2] cycloaddition of allenyne **162** and **163** affording bicyclo[4.2.0] and [5.2.0] distal adducts as the only isomeric products (Scheme 51).⁵¹ Allenynes **162** and **163** were cleanly converted to bicyclo[4.2.0]octa-1,6-dienes **164** and

$R = \text{Me, nPr, nBu, Ph, TMS}$
 $X = \text{O, NTs}$

$R = \text{Me, Ph, TMS}$
 $X = \text{O, NTs}$

$X = \text{O, CH}_2, \text{NTs,}$
 $Y = \text{CH}_2, \text{C(CO}_2\text{Me)}_2$

Scheme 51 Intramolecular [2 + 2] cycloaddition of allenyne **162**, **163** and **167** having a phenylsulfonyl functionality on the allenyl group. Reagents and conditions: (a) Xylenes or mesitylene, reflux, N_2 , 7–30 h.

Scheme 52 Mechanism for the regioselective formation of the [m.2.0] frameworks through intramolecular [2 + 2] cycloaddition of allenyne.⁵¹

bicyclo[5.2.0]nona-1,7-dienes **165**, respectively, in high yields. Furthermore, this method has been shown to be applicable to the construction of bicyclo[6.2.0]deca-1,8-dienes **166** from homologous allenyne **167**.

The mechanism for the regioselective formation of the bicyclo[m.2.0] frameworks has been rationalized by invoking diradical intermediates (Scheme 52). For the thermal reaction of **163**, for instance, there are two possible pathways. *Route A* should involve allyl radical intermediate **168** formed by initial combination between the sp-hybridized carbon center of the allenyl moiety and the internal alkyne carbon. The resulting seven-membered diradical intermediate, having an allyl as well as phenylvinyl radical species, would immediately collapse into compound **165**. An alternative initial connection of the sp-hybridized carbon of the allenyl moiety with the external alkyne carbon might lead to the eight membered intermediate **169** containing allyl and vinyl radicals. The ring-closing reaction of these intermediates would give rise to the production of compound **170** (*route B*, Scheme 52). The fact that compound **163** exclusively gave **165** in a high yield would strongly reflect the preferential formation of radicals **168** over **169** due to easier formation. The latter diradical species are eight-membered ring systems, while the former are seven-membered cycles. Similarly, the exclusive formation of compounds **164** and **166** may be rationalized by considering the ring size of the diradical species (6-membered *versus* 7-membered rings and 8-membered *versus* 9-membered rings).

Very recently Ma has reported an efficient synthesis of 3-oxabicyclo[4.2.0]octa-1(8),5-dien-4-ones **171** via the intramolecular [2 + 2] cycloaddition of propargylic 2,3-allenoates **172** under conventional heating conditions (Scheme 53).⁵² The authors have found that when R^1 is an aryl group and R^3 is a phenyl group, Diels–Alder aromatization adducts **173** were

$R^1 = \text{Ph, naphthyl}$
 $R^2 = \text{Me, Et, nPr, nBu, TMS, Bn}$
 $R^3 = \text{Ph, TMS}$

Scheme 53 [2 + 2] Cycloaddition of propargylic 2,3-allenoates **172**. Reagents and conditions: (a) Toluene, reflux, 8–72 h.

formed as by-products in yields ranging from 5 to 25%. However, when R^3 is TMS, no Diels–Alder aromatization adducts were formed. Furthermore, when R^1 is an alkyl group, the reactions take longer time with lower yields. However, R^2 can be H, alkyl, benzyl, and allyl groups. A dramatic alkynic substituent effect on the selectivity of the reaction has been observed: when R^3 is TMS, the [2 + 2] cycloaddition reaction of propargylic 2,3-allenoates proceeded smoothly, probably due to their stabilization effect for the possible diradical intermediates involved in the reaction. The regioselectivity observed in the [2 + 2] cycloaddition of propargylic 2,3-allenoates **172** could be explained *via* formation of diradical species intermediates, analogously as it has been illustrated in Scheme 52 for allenynes **163**.

In 2005, Brummond and co-workers reported that the microwave irradiation of alkynyl allenes **174** and **175** provides an efficient route to bicyclo[4.2.0]octadienes and bicyclo[5.2.0]-nonadiene **176** and **177**. The reaction takes place with complete regioselectivity for the distal double bond of the allene; thus selectively forming a variety of hetero- and carbocyclic substrates (Scheme 54).⁵³ The authors have found that the optimum conditions for performing this allenic [2 + 2] cycloaddition reaction were a 3 M solution of an ionic liquid, 1-ethyl-3-methylimidazolium hexafluorophosphate, in toluene at 250 °C (MWI) for 15 min. The scope of the reaction has been investigated by subjecting alkynyl allenes possessing a wide range of substituents and functionalities. The substitution on the terminal alkynes appeared to be a controlling factor in the efficiency of these reactions, with the phenyl group giving the highest conversions. Once again, the regioselectivity observed in compounds **174** and **175** is in agreement with previous results in related systems.

Independently, Oh's group has developed an efficient, simple and eco-friendly synthetic method for the preparation of fused bicyclic [m,2,0]alkadienes from 1,5-, 1,6- and 1,7-allenyl carboxylates **178** and **179**.⁵⁴ Thus, compounds **178**

Scheme 54 Microwave-assisted intramolecular [2 + 2] cycloaddition of allenynes **174** and **175**. Reagents and conditions: (a) Toluene, ionic liquid (1-ethyl-3-methylimidazolium hexafluorophosphate), MWI at 250 °C, 15 min.

Scheme 55 Microwave irradiation of allenynes **178** and **179**. Reagents and conditions: (a) Toluene, MWI, 70 °C, 10–45 min.

Scheme 56 Explanation for the synthesis of compounds **180** and **181** under microwave irradiation conditions.⁵⁴

and **179** were cleanly converted into their corresponding distal [2 + 2] cycloadducts **180** and **181** under microwave irradiation (Scheme 55).

Scheme 56 shows a possible explanation for the formation of compounds **180** and **181**. Microwave heating on substrates **178** and **179** might break one unsaturated bond to form a transient diradical such as **182**, which would undergo rapid cyclization to give the adducts **180** and **181**.

The microwave induced intramolecular allenyne [2 + 2] cycloaddition of a variety of 1-allenyl-2-propargyl-substituted derivatives **183**, as a synthetic route to the [5.6.4] ring core of sterpurene, has been reported in 2008 by Ovaska's group. Thus, irradiation of allenynes **183** smoothly afforded polycyclic compounds **184**, in which the π -component was the external double bond of the allene moiety, as single isomers in excellent yields (70–92%) (Scheme 57).⁵⁵ The reaction has been shown to be rather general and independent of the type of substituent on the triple bond with the exception of terminal alkynes, which decomposed under the reaction conditions employed. Furthermore, only allenic systems having the OH and the propargylic moieties in *cis* configuration were found to be reactive under the above conditions.

R = H, Et, Ph, TMS, TBS, *p*-TBSO-C₆H₄

Scheme 57 Intramolecular [2 + 2] cycloaddition of 1-allenyl-2-propargyl-substituted derivatives **183**. Reagents and conditions: (a) Phenetole, MWI, 150–200 °C, 30–45 min.

Scheme 58 Intramolecular [2+2] versus [4+2] cycloadditions of benzoannulated allenyne **186**. Reagents and conditions: (a) Et₂O, SOCl₂, py, 0 °C to RT.

On the other hand, bispropargylic alcohol **185** has shown to be an excellent precursor of allene **186**. In this context, Wang and co-workers have investigated the competence of the [2+2] cycloaddition versus [4+2] cycloaddition of allenes derived from bispropargylic alcohols under basic conditions. Thus, treatment of bisalkyne **185** with thionyl chloride in pyridine smoothly afforded adduct **187** in 74% yield accompanied by a small amount of the 1*H*-cyclobut[*a*]indene **188** (12%), the [2+2] cycloaddition product derived from the reaction of the allenic and the acetylenic moieties in intermediate **186** (Scheme 58).⁵⁶

Surprisingly, treatment of bisalkynol **189** with thionyl chloride produced the [2+2] cycloaddition adduct **190** exclusively in 81% yield (Scheme 59). This dramatic change of the reaction pathway has been attributed to the emergence of a steric strain due to the non bonded interactions with the chloro substituent along the pathway toward the formal Diels–Alder adduct. In fact, the importance of steric interactions in determining the reaction pathway has been supported by the monoprotected phenanthrenequinone examples. Thus, with a sterically more demanding, 5,5-dimethyl-1,3-dioxane protective group in **191**, only the [2+2] cycloaddition adduct

Scheme 59 Intramolecular [2+2] versus [4+2] cycloadditions of benzoannulated allenyne. Reagents and conditions: (a) Et₂O, SOCl₂, py, 0 °C to RT.

Scheme 60 [2+2] Cycloaddition reaction of bis(propargyl alcohols) **196** via transient bis(phosphinylallenes) **198**. Reagents and conditions: (a) Ph₂P(O)Cl, Et₃N, THF, from –78 °C to RT, 4 h.

192 was also obtained. However, with a sterically less demanding ethylene ketal protective group in **193**, a 1 : 1 mixture of the [2+2] and the [4+2] cycloaddition adducts **194** and **195** was isolated.

Later on, Kitagaki and Mukai reported that the reaction of benzene-bridged bis(propargyl alcohols) **196** with chlorodialkylphosphines exclusively afford 3,8-bis(dialkylphosphinyl)naphtho[*b*]cyclobutenes **197**. Firstly, a dual [2,3]-sigmatropic rearrangement of the bisalkynols **196** gave intermediate 1,2-bis(α-phosphinylallenyl)benzenes **198**, which spontaneously undergo intramolecular [2+2] cycloaddition (Scheme 60).⁵⁷ Compounds **197** were obtained in high yields in all cases.

Formation of compounds **197** has been rationalized via the intermediacy of diradical intermediates **199** as shown in Scheme 61. The bis(phosphinylallenes) **198**, derived from the corresponding bis(propargylic phosphinites) by [2,3]-sigmatropic rearrangement, would be converted into the diradical species **199**, which subsequently undergo intramolecular [2+2] cycloaddition to produce tricycles **197**. The aromaticity of the final products is also a remarkable feature in the regiochemistry observed of the [2+2] cycloaddition, and will be the driving force to obtain compounds **197** as sole isomers.

Another example of competitive reaction involving the [2+2] cycloaddition of allenyne was presented by Cook's group in 2003. During the synthesis of a dicyclopenta[*a,e*]pentalene via Pauson–Khand reaction, the monocyclized [5.4] system **200** was obtained upon heating the diyne-diallene **201** in toluene at 100 °C (Scheme 62).⁵⁸

Ketene is also a suitable partner for the [2+2] cycloaddition with allenes, though, only the intermolecular version has been published.⁵⁹ However, Halcomb has reported the intramolecular [2+2] cycloaddition of ketenes with allenes. Thermal intramolecular [2+2] cycloaddition between an *in situ* generated ketene

Scheme 61 Mechanistic explanation for the formation of adducts **197**.⁵⁷

Scheme 62 Formation of the [2+2] adduct **200** when attempting the Pauson–Khand reaction of bis-allenyl **201**. Reagents and conditions: (a) Toluene, 100 °C.

Scheme 63 Intramolecular ketene-allene [2+2] cycloaddition. Reagents and conditions: (a) Oxalyl chloride (3 equiv.), Et₃N (2.5 equiv.), benzene, RT, 4–10 h; then reflux, 12 h.

and a 1,2-diene, in compounds **202**, afforded 7-methylidenebicyclo[3.2.0] heptanones **203** and 7-methylidenebicyclo[3.1.1]heptanones **204** (Scheme 63).⁶⁰ Compounds **203** arose from formation of a bond between the central ketene carbon and the central allene carbon to afford the [3.2.0] fused bicyclic system. However, the [3.1.1] bridged bicyclic systems **204** have resulted from bond formation involving the alkoxy-substituted carbon of the ketene and the internal allene carbon. The [3.2.0] bicyclic adduct has been obtained as the major isomer for **202b** (R = nBu) and **202c** (R = H). By contrast, the selectivity of the cycloaddition was different for **202a** (R = TMS); the [3.1.1] bicycloheptanone **203a** was obtained as the major product. Besides, the *E*-olefin isomer was generally the major geometric isomer observed. Interestingly, no products derived from the cycloaddition of the ketene with the distal allenic carbon were observed.

The preference for *E*-olefin isomer formation has been explained in terms of steric demand; the ketene would prefer to approach the internal π -bond of the allene from the face which is not blocked by the substituent on the distal carbon of the external π -bond.

3. Photochemical [2+2] cycloadditions

The [2+2] photocycloaddition reaction is one of the most frequently employed photochemical transformation allowing

Scheme 64 Formation of the two possible regioisomers in the [2+2] photocycloaddition of 2-cyclopentenone and an allene.

the construction of the cyclobutane ring.⁶¹ In particular, this strategy is very important in the synthesis of natural products.⁶² In fact, it has been demonstrated that the intramolecular photocycloaddition of monosubstituted allenes with chiral enones is a useful strategy for the construction of carbon–carbon bonds in polycyclic structures.⁶³ Wiesner has been the first to demonstrate the utility of the intramolecular diastereoselective allene–enone [2+2] cycloaddition in natural products synthesis.⁶⁴ Later, Pirrung employed the intramolecular allene–enone cycloaddition in an elegant synthesis of pentalenolactone **G**.⁶⁵ In addition, the photochemical additions to enones are believed to proceed through the intermediacy of a 1,4-diradical species which may revert to the starting allene and enone with loss of allene optical activity. In fact, Becker's studies as well as seminal contributions by Corey in related alkene–enone cycloadditions have provided a starting point from which to investigate asymmetric induction with optically active 1,3-disubstituted allenes.

The photochemical cycloaddition of allene to 2-cyclopentenone affording fused cyclobutane adducts with preferential head-to-head regiochemistry has been reported (Scheme 64).⁶⁶ This result is in contrast to the preferential head-to-tail orientation of addition to cyclic enones observed with the majority of mono-substituted alkenes.⁶⁷

The origin of the regioselectivity and the mechanism of the allene photocycloaddition reaction with cyclic enones have been the subject of debate.⁶⁸ In particular, seminal papers of Kice and co-workers have contributed dealing with radical additions to allenes and have been applied to discuss the regiochemical outcome of [2+2] cycloadditions of conjugated enones to allenes.⁶⁹ By analogy to the corresponding reaction with simple alkenes it is assumed that the addition occurs from the enone triplet excited state and proceeds *via* triplet 1,4-diradical intermediates formed by bonding of an allene to either the 2-position or the 3-position of the enone. Scheme 65 shows the diradical intermediates formed. Diradicals **205** and **206** are the possible precursors of the head-to-tail cycloadduct, while diradicals **207** and **208** are the possible precursors of the head-to-head cycloadduct (Scheme 65).

Weedon, postulated that in the addition of allene to cyclopentenone, the relative amounts of the four triplet 1,4-diradicals could be determined by trapping experiments using H₂S.⁷⁰ In these trapping experiments, diradical **205** formed 68% of the intermediates, while diradicals **207**, **208** and **206** arose 29%, 3% and 0%, respectively.⁷¹ This data indicates that addition at the α -position of the enone is overwhelmingly favored. Also in contrast to the exciplex model which depends on the relative amounts of the various diradicals, the product distributions have been interpreted as depending on the competition of the particular diradicals between reversion

Scheme 65 Diradicals **205–208** formed in the intermolecular photocycloaddition of 2-cyclopentenone and an allene.⁶⁹

to reactants and closure products. In particular, since the diradicals have nearly free rotation about the new single bond formed, the conformation of the triplet diradical upon spin inversion should be an important factor in determining whether the molecule will close to products or revert to starting materials.

In this context, theoretical studies of regioselectivity in the photochemical cycloaddition of allene to cyclopentenone, including energetics, conformations, spin–orbit coupling constants and the singlet–triplet energy splittings of the intermediate diradicals, have been reported by Goddard.⁷² This author postulated that the diradical containing the allyl fragment was predicted to be approximately 83 kJ mol^{−1} lower in energy than the other two. Using a model for the reaction mechanism in which the relaxed triplet excited state of allene reacts with ground state cyclopentenone, the reaction barriers to forming these allylic substituted systems are lower by *ca.* 33–42 kJ mol^{−1} in comparison to the other two. The conformation of the diradicals upon spin inversion is in all probability one important factor in determining whether the diradicals close to products or revert to starting materials. The sp³ hybridization at the bond-forming carbon in the vinyl (nonallylic) systems leads to nearly free rotation about that bond, and three shallow minima and the corresponding transition states for internal rotation were located. One minimum has the two carbon centers which carry the excess spin density about 3.8 Å apart while in the other minima the distances are ~3.1 Å. Taking these distances into account, it has been estimated that very few of the intermediates formed from the addition to the carbonyl close to products. In contrast, a high percentage of the systems formed from attack β to the carbonyl are predicted to yield products. In the allylic substituted systems, carbon centers with some radical character are always relatively close

Scheme 66 Diastereoselective [2+2] photocycloaddition of allenic coumarins **209**. Reagents and conditions: (a) $h\nu$, cyclohexane or dichloromethane, 23 °C, 4 h.

to the site of radical character in the cyclopentenone ring. Thus, the relative ratio of cycloadducts can be estimated from the distribution of the diradicals. The transition state energies do not agree with the interpretations of experimental data by Weedon. The theoretical predictions suggest that the two allyl substituted systems should form most, if not all, of the 1,4-diradical intermediates. In fact, it was predicted that the four 1,4-diradicals **205:207:208:206** would form in a ratio of 0:83:0:17. Taking to account that the arbitrarily relative efficiency of ring closure for **205**, **206**, **207** and **208** is, 10%, 80%, 80% and 100%, respectively, formation of head-to-head and head-to-tail adducts have been estimated to be 80:20.

A remarkable example was reported by Carreira in 1994, involving the photocycloaddition of optically active *tert*-butyl-substituted allenes with enones to give photoadducts in excellent yields and up to 99% asymmetric induction (Scheme 66).⁷³ Thus, [2+2] photocycloaddition of allenic coumarins **209** cleanly afforded tetracycles **210** in excellent yields.

The high levels of asymmetric induction were rationalized according to the accepted model proposed by Becker for intramolecular allene photocycloadditions.⁷⁴ The triplet enone C β adds to the less hindered end of the allene C3', opposite to the *tert*-butyl substituent, to give a 1,4-diradical intermediate **211** which undergoes spin inversion and collapses to the *exo*-methylenecyclobutanes **212** (Scheme 67). The observation of high enone face selectivity is accommodated by *exo*-approach of the allene onto the enone such that H3' and not C2' resides over the ring. The high levels of asymmetric induction in the photoadducts are consistent with the observation that the configuration of the newly formed vicinal stereocenters is established kinetically upon formation of the C β –C3' bond and that for **209** reversion does not occur competitively with ring closure ($k_c \gg k_r$). However, subtle conformational effects can effect the relative rates of closure, k_c , and reversion, k_r (Scheme 67). In addition to proceeding with high levels of

Scheme 67 Rationalization of the high levels of asymmetric induction on the intramolecular [2+2] photocycloaddition of allenic coumarins **209**.⁷⁴

211

Fig. 7 Proposed transition-state for the formation of compounds **210** illustrating the optimal geometry of the 1,4-diradical **211** formed.

enantioselectivity, the [2 + 2] cycloaddition of allenic coumarins **209** affords in each case a single olefin diastereomer.

The formation of a single alkene may result from conformational memory effects in the 1,4-diradical intermediate **211** as it undergoes intersystem crossing and ring closure (Fig. 7). It has been proposed that in the coumarin-derived 1,4-diradicals, the orbitals are disposed in an arrangement with an interorbital angle close to 90°. Thus, the formation of a single olefin diastereomer from **209** is a consequence of two rapid, successive processes, intersystem crossing and ring closure, which allow the initial orientation of the *tert*-butyl substituent on the allene to be reflected in the stereochemistry of the products.

Later on, the same authors demonstrated the synthetic utility of the allene-enone [2 + 2] photocycloaddition by incorporation of a removable silane group onto the allenyl moiety.⁷⁵ In analogy to the reported investigation involving *tert*-butyl-substituted allenes, the coumarin-derived adducts **212** were obtained as single alkene diastereomers starting from allenic coumarins **213** (Scheme 68).

More recently, Winkler and co-workers have reported the intramolecular photoaddition of vinylogous allenamide-type compounds **214**, as an approach to the synthesis of pyrroles and furans **215** in moderate to good yields (31–87%) (Scheme 69).⁷⁶ Formation of pyrroles and furans **215** takes place from the corresponding cyclobutane photoadducts **216** which have been obtained *via* the [2 + 2] cycloaddition of the starting allenamides **214**.

The regiochemical outcome of the cycloaddition ring closure depends mainly on the presence or absence of an electron-withdrawing group at the nitrogen. In fact, when the substituent is H or Me, products derived from parallel cycloaddition of the terminal allenic double bond to the olefin *via* **217** were observed. However, irradiation of vinylogous amide or imide (R = Ac), *via* **218** and **219**, has lead to the selective formation of crossed photoadduct **220** (Scheme 70).

Scheme 68 [2 + 2] Photocycloadditions of allenic coumarins **213**. Reagents and conditions: (a) $h\nu$, cyclohexane or dichloromethane, 23 °C, 1.5 h.

Scheme 69 Synthesis of pyrroles and furans *via* intramolecular [2 + 2] photocycloaddition of allenamide-type compounds **214**. Reagents and conditions: (a) $h\nu$, 1.0 mM, MeCN, pyrex photoreactor, 30 min.

Scheme 70 Regiochemical outcome of the photochemical ring closure of allenamides **214**.⁷⁶

The photochemistry of divinylmethanes⁷⁷ in which one vinyl moiety is an α,β -unsaturated ester⁷⁸ or an ylidenemalononitrile⁷⁹ has been found to undergo regioselective di- π -methane rearrangement by multiplicity of the excited state. Interest on the photochemoselectivity by multiplicity control has been demonstrated in the photochemistry of β -allenyl-substituted alkylidenemalonates and α,β -unsaturated esters affording the intramolecular [2 + 2] cycloaddition predominantly under direct and sensitized photolyses.^{80,81}

In this context, Tsuno reported that allenyl(vinyl)methanes **221** and **222** have a triplet excited state of the allene or vinyl moiety and their states produces a cross-conjugated triene from the excited state of the allenyl chromophore and an intramolecular [2 + 2] cycloadduct from the vinyl chromophore.⁸² The direct photolysis of the diester **221a** in hexane gave a cross-conjugated triene **223a**, bicyclo[2.1.0]pentane **224a**, pyran **225a** and cyclopropene **226a** (Scheme 71).⁸³ On the other hand, the direct photolysis of the monoester **223b** afforded adducts **223b**, **224b**, and **226b** (Scheme 71). Irradiation of the isolated [2 + 2] cycloadducts **224** afforded cyclopropenes **226**. Though the acetone-sensitized photolyses of **221** afforded triene **223**, and the [2 + 2] cycloaddition products **224**, polymeric materials were significantly produced. From the results obtained, it has been reported that acetone and acetophenone are good sensitizers for the isomerization to the trienes **223** and to the [2 + 2] cycloadducts **224**.

The direct photolysis of **222a** in acetonitrile gave mainly cross-conjugated triene **227a** and bicyclo[2.1.0]pentane **228a**. In the case of acetone-sensitization of **222a**, the bicyclo[2.1.0]pentane **228a** and indene **229a** were obtained. In addition,

Scheme 71 Direct photolysis reaction of allenenic esters **221**. Reagents and conditions: (a) $h\nu$, hexane, RT, 25–33 h.

acetone, acetophenone, benzophenone and thioxanthen-9-one have shown sensitizing effects for the formation of **227** and **228** (Scheme 72).

The direct photolysis of **222b** in acetonitrile afforded and allenyl cyclopropane **230b**, bicyclo[2.1.0]pentane **228b**, and

Scheme 72 Direct photolysis reaction of allenenic dinitriles **222**. Reagents and conditions: (a) $h\nu$, MeCN, RT, 5–55 h.

1,3-phenyl rearrangement compound **231b** as intramolecular photoproducts and further led to considerably polymeric compounds and small amounts of unidentified intramolecular compounds. On the other hand, the dinitrile **222c** under direct photolysis underwent mainly a di- π -methane rearrangement product **230c** and the intramolecular [2 + 2] cycloadduct **228** was obtained as a by-product. However, the acetone-sensitization of **222b** or **222c** gave the intramolecular [2 + 2] cycloadduct **228b** or **228c** in better yields (53 and 59%, respectively).

The sensitizing effects of esters **221a** and **221b** and nitrile **222a** have suggested that the trienes and [2 + 2] cycloadducts are derived from the triplet excited state of a different chromophore in the substrates. The triplet energy required for the formation of the [2 + 2] cycloadduct from ester **221a** or **221b** is estimated to be *ca.* 300 kJ mol⁻¹, while that from the nitrile **222a** is *ca.* 250 kJ mol⁻¹. These results are in agreement with previous reports of the photochemistry on the γ -allenyl-substituted α,β -unsaturated esters, where the triplet energy required for the formation of the [2 + 2] cycloadduct is estimated to be *ca.* 300 kJ mol⁻¹ and the activated chromophore is the vinyl moiety.⁸⁴ Furthermore, the triplet energy of the ylidene malonitrile has been reported to be *ca.* 250 kJ mol⁻¹. The reported triplet energy corresponds with the estimated values for **222a**. Hence, the intramolecular [2 + 2] cycloaddition of **221** and **222a** under the sensitized photolyses occurs from the triplet of the vinyl chromophore. On the other hand, the triplet energy required for the formation of trienes **223** or **230a** from **221** and **222a** is estimated to be *ca.* 260 kJ mol⁻¹. It has been suggested that the triplet energy of monophenyl-substituted allene lies in the range of 250–270 kJ mol⁻¹. Because this range includes the estimated triplet energy of the phenyl-substituted allenyl chromophore for esters **221a** and **221b**, acetone and acetophenone having higher triplet energy competitively affect both chromophores in **221a** and **221b**, although the sensitizers such as benzophenone, 2-benzoylpyridine and thioxanthen-9-one in the range of 260–290 kJ mol⁻¹ can reach the excited state for the allenyl chromophore. The reaction mechanism of the intramolecular [2 + 2] cycloaddition of the allenyl(vinyl)-methanes by trapping experiments of a diradical intermediate using hydrogen selenide has been proved.⁸¹ Thus, the excited state of the vinyl chromophore in **221** and **222a** initially bonds between C2 and C6 to afford a cyclopenta-1,3-diyl radical **232** or **233** from which ring closure yields the intramolecular [2 + 2] cycloadducts (Scheme 73 and 74). On the other hand, for the formation of the trienes, it has been considered that the excited state of the allenyl chromophore bonds between C3 and C5 to yield **234** and **235**, which undergoes a 1,2-phenyl migration to yield the trienes. This reaction pathway have been supported by PM3 MO calculation, where the optimal structure of diradical **236** corresponds to the structure of **223b**. 2-Methyl-1,3-butadiene under direct photolyses has been recognized to have a quenching effect on the formation of the [2 + 2] cycloadducts. The intramolecular [2 + 2] cycloaddition of the allenyl(vinyl) methanes occurs *via* both the singlet and triplet pathways, in the cases of the photochemistry of **221**. Hence, due to the quenching effects, the trienes are derived *via* the triplet excited state.

The direct photolysis of **221a** gave pyran **225a**, which was not obtained from sensitised photolyses and its formation did

not show the quenching effect by 2-methyl-1,3-butadiene. Therefore, **225a** is derived from the photochemical intramolecular oxa-Diels–Alder reaction *via* singlet-excited state of a *Z*-carbonyl in **221a** (Scheme 73).

The direct photolysis of **222b** and **222c** gave allenyl-cyclopropanes **230b** and **230c**, *i.e.* di- π -methane rearrangement compounds, while the diesters which have the same allenyl chromophore in **222b** and **222c** led mainly to the [2+2] cycloadducts. Such a difference has been explained by the MO coefficients of the vinyl chromophore. The MO coefficient for the α -carbon of the 2,2-dimethylpropyldienemalonate is larger than that of the β -one. Hence, γ -allenylsubstituted α,β -unsaturated esters undergo preferential interaction between the allene center and the α -carbon. However, the PM3 MO calculation for 2,2-dimethylpropyldienemalononitrile as a model of the vinyl moiety in **222** indicates that the MO coefficient (0.68) of the β -carbon is larger than that (0.50) of the α -carbon. In the photochemistry of **222b** and **222c**, therefore, the di- π -methane rearrangement occurred by preferential MO interaction between the C5 and C3 (Scheme 74). On the other hand, it seems that the minor compounds **231** were produced by the MO interaction between C5 and C2 in the nitriles **222b** and **222c** (Scheme 74).

Apparently, cyclopropanes **226** are derived *via* the photochemical pathway of the [2+2] cycloadducts **224** (Scheme 75).

On the basis of the photochemistry of γ -allenyl-substituted α,β -unsaturated esters and nitriles, it has been shown: (a) Due to the HOMO of a 1,2-propadienyl group lies at the C2–C3 moiety and the MO coefficients of C3 is higher value than that of the C2, the 1,2-propadienyl substituted esters undergo more ineffective intramolecular [2+2] cycloaddition than the 3-methyl-1,2-propadienyl-substituted esters; (b) The allenyl-(vinyl)methanes initially bond between the allene center carbon and the α -carbon of the α,β -unsaturated ester or the nitrile moiety to give cyclopentane-1,3-dienyl radicals; (c) The intramolecular [2+2] cycloaddition occurs *via* both singlet and triplet excited states; (d) The triplet intramolecular [2+2] cycloaddition occurs from the excited state of the α,β -unsaturated ester or the nitrile moiety.

Later on, the photolyses of γ -allenyl-substituted alkylidene-cycloalkanones **237** gave [2+2] cycloadducts **238** and **239** in very low yields along with (*Z*)-form **240** and pyran **241**. Analogously, [2+2] cycloaddition of γ -(3-methyl-1,2-butadienyl)-substituted 3-alkylidenepenta-2,4-diones **242** afforded [2+2] cycloadducts **243a** and **243b** in very low yields along with compounds **244** and **245** (Scheme 76 and 77).⁸⁵

Analogous tendency to the photochemistry of γ -allenyl-substituted α,β -unsaturated esters were observed.^{80,84} Thus, it is obvious that the HOMO in the allenyl moiety contributes greatly to the photochemical intramolecular [2+2] cycloaddition

Scheme 76 Photochemical reaction of allenenic ketones **237**. Reagents and conditions: (a) $h\nu$, hexane, RT, 9h.

Scheme 77 Photochemical reaction of allenenic diketones **242**. Reagents and conditions: (a) $h\nu$, hexane, RT, 9 h.

of these enones. The triplet energies of the enones **240a** and **240b** are *ca.* 280 kJ mol^{−1}, and further, those of the diketones **242a** and **242b** are estimated to be in range of 280–260 kJ mol^{−1}. These estimated triplet energies are close to the reported triplet energies of the α,β -unsaturated enones. Therefore, the intramolecular [2+2] cycloaddition by the triplet sensitization occurs from the triplet excited state of the enone moiety. The MO coefficients obtained by PM3 MO calculations seems that the interaction between the α -carbon of the enone and the center carbon of the allene may be possible. However, the intramolecular [2+2] cycloaddition of **237** and **240** is hardly prohibited due to the steric hindrance by the alkyl-substituent at the α -position of the enone moiety. For example, overlapping between the MO's of the center carbon of the allene and of the α -carbon of these *exo*-cycloalkenones is blocked.

In the case of the photochemistry of the 1,2-propadienyl-substituted diketone **242a**, the intramolecular [2+2] cycloadduct **243a** is obtained, because it is considered that some MO interaction between the α -carbon and the center carbon of the allene in **242a** occurs (Scheme 77). On the other hand, in the case of the photochemistry of the diketone **242b**, the intramolecular [2+2] cycloaddition progresses preferentially.

Successful construction of the tricyclic core of solanoelepin A (**Fig. 8**) through intramolecular [2+2] photocycloaddition

Scheme 75 Formation of cyclopropanes **226** from [2+2] cycloadducts **226**.

Fig. 8 Structure of solanoelepin A.

Scheme 78 Examination of the intramolecular [2 + 2] photocycloaddition of allenene **246a**. Reagents and conditions: (a) $h\nu$ (300 nm), MeCN/acetone (9 : 1), 5 h.

of an allene butenolide has been achieved.⁸⁶ A model system, compound **246a**, was chosen in 2006 by Hiemstra and co-workers to examine the allene [2 + 2] photocycloaddition. The key [2 + 2] cycloaddition of allene **246a** which was carried out in a 9 : 1 (acetonitrile/acetone) solution proceeded remarkably well leading to the single product **247a** in good yield (Scheme 78). The exclusive formation of compound **247a** emphasizes the great preference for five-membered ring formation in the intramolecular [2 + 2] cycloaddition. The authors have explained the selectivity by the formation of an allylic radical intermediate **248** instead of the corresponding less stable vinyl radical **249** (Scheme 79). Application of the key photocycloaddition to the appropriate substituted allene butenolides **246b** and **246c** resulted in the desired crossed cycloadducts **247b** and **247c** in good yields, which after further elaboration should give the right-hand substructure of the natural product (Scheme 80).

More recently, a similar approach has been described for the stereoselective synthesis of tricyclo[3.3.0]oxoheptane core of bielschowskysin by a [2 + 2] cycloaddition of an allene butenolide derived of L-malic acid (Scheme 81).⁸⁷ Thus, irradiation of an allene-linked γ -butenolide **250** cleanly underwent a [2 + 2] cycloaddition to the single diastereomeric photoadduct **251** in 70% yield.

Scheme 79 Possible diradical intermediates involved in the intramolecular photocycloaddition of allenenes **246**.⁸⁶

Scheme 80 Synthesis of the tricyclic core structure of solanoelepin A. Reagents and conditions: (a) $h\nu$ (300 nm), MeCN/acetone (9 : 1), 5 h.

Scheme 81 Synthesis of the tricyclo[3.3.0]oxoheptane core of bielschowskysin. Reagents and conditions: (a) $h\nu$, hexane-CH₂Cl₂, RT, 12 h.

4. Metal-catalyzed [2 + 2] cycloadditions

Metal catalysis is a very powerful tool for synthetic transformations. In particular, it has provided novel opportunities for the highly selective [2 + 2] cycloaddition reactions of allenes since complexation of the metal to the allene moiety significantly modifies its reactivity, opening a new route to access to cyclobutane compounds.⁸⁸ In general, this approach has been explained in terms of the reductive elimination of metallacyclopentanes and metallacyclopentenes as the key step in the formation of the four membered rings. In addition to the rate improvements observed in the presence of a metal catalyst, the opportunity to achieve enantioselective transformations by adding chiral ligands is one of the most important characteristics of this strategy.

4.1 Intermolecular metal-catalyzed [2 + 2] cycloadditions

It is noteworthy that metal-catalyzed [2 + 2] dimerization of allenes takes place with complete control of the regioselectivity and it is independent of the steric and electronic nature of the substituents attached to the allene moiety. Therefore the examples reported so far provide better results, in terms of regioselectivity and yields, than under thermal conditions.

In 2000, Saito and Yamamoto described the regioselective nickel-catalyzed [2 + 2] annulation of electron-deficient allenes **252** under mild conditions to give the head-to-head cyclo-dimerization products. The corresponding bismethylene-cyclobutanes **253** were isolated as single isomers in good to fair yields (Scheme 82).⁸⁹ However, it is noteworthy that the reaction of 1-hexylallene (1,2-nonadiene) resulted in the formation of a complex mixture which was composed of oligomeric compounds. Therefore, the presence of an electron-withdrawing group is crucial for the [2 + 2] cycloaddition to proceed efficiently in a highly regioselective manner. In addition, the catalytic reaction did not proceed in the presence of bidentate ligands, assuming that the reaction stopped in the middle of the catalytic cycle of the [2 + 2] reaction.

Scheme 82 Nickel(0)-catalyzed [2 + 2] dimerization of electron-deficient allenes **253**. Reagents and conditions: (a) 10 mol% Ni(PPh₃)₄, toluene, –15 to –10 °C or RT, 0.5–3 h.

Scheme 83 Proposed mechanism for the nickel(0)-catalyzed [2+2] annulation of electron-deficient allenes **252**.⁸⁹

It has been assumed that the reaction proceeds as shown in Scheme 83. The reaction of two molecules of allene **252** under nickel(0) catalysis would produce the nickelacyclopentane **254** by regioselective coordination, followed by C–C bond formation. At this step, intermediate **254** would undergo quick reductive elimination to give cyclobutane **253** as the final product. The observed high regioselectivity of the reaction has been explained in terms of the regioselective formation of metallacycle **254**, which would be controlled by the stereoelectronic effects of the substituent in allenes **252**. The facile reductive elimination of the nickel(0) species from the five-membered metallacycle **254**, which is the most characteristic feature of this [2+2] cyclodimerization, would be promoted by the electron-withdrawing groups attached to the allene functionality.

On the other hand, preparation of 1,3-dimethylenecyclobutanes is not straightforward. The current method involves a six-step synthesis.⁹⁰ The simplest access would result from [2+2] allene thermal cyclodimerization. However, it leads to a 1,2-isomer with small amounts of the 1,3-isomer (85:15).⁹¹ Another interesting synthesis of 1,3-dimethylenecyclobutanes **255** has been described by Dixneuf's group, *via* a sequential Ru-catalyzed [2+2] cyclodimerization of allenyl boronate **256** and palladium-catalyzed Suzuki coupling (Scheme 84).⁹² The reaction of allenyl boronate **256** in the presence of 5 mol % of

Scheme 84 Synthesis of 1,3-dimethylenecyclobutanes **255** *via* sequential ruthenium-catalyzed [2+2] cyclodimerization of allenyl boronate and palladium-catalyzed Suzuki coupling. Reagents and conditions: (a) 5 mol% [Cp*RuCl(COD)], dioxane, 100 °C, 2 h. (b) ArI, 1 mol% Pd(PPh₃)₄, K₂CO₃, H₂O–THF, 80 °C, 2 h. (c) Recrystallization.

[Cp*RuCl(COD)] in refluxing dioxane at 100 °C followed by addition of an aryl iodide in presence of base (K₂CO₃) and catalytic amount of Pd(PPh₃)₄, cleanly afforded the [2+2] cyclodimerization products **255**. Although a mixture of the two phenyl-substituted isomers (*E,E*) and (*Z,Z*) was obtained, fortunately after recrystallization, major isomers (*E,E*) were isolated in moderate yields.

Total regioselectivity has been achieved during the dimerization of phenylallene **257** by using a sterically hindered ruthenium catalyst, [Cp*Ru(PPh₃)(MeCN)₂][PF₆], giving the tail to tail coupling compound **258**, in 44% yield (Scheme 85).⁹²

In 2003, Akiyama and co-workers studied the enantioselective [2+2] cycloaddition reaction of 1-methoxyallenylsilanes **259** with an α -imino ester catalyzed by the system [Cu(MeCN)₄]BF₄/(*R*)-Tol-BINAP, affording 3-methyleneazetidine-2-carboxylates **260** in good yields (60–90%) and with excellent enantiomeric excesses (58–97%).⁹³ Besides, the acid-catalyzed ring opening of the azetidines **260** has opened a new route to access homochiral acylsilanes **261** quantitatively (Scheme 86).

4.2 Intramolecular metal-catalyzed [2+2] cycloadditions

Gold is an effective heterogeneous and homogeneous catalyst in particular in redox reactions and nucleophilic additions to π systems. In fact, although it was considered to be catalytically inactive, gold has shown a rich coordination and organometallic chemistry.⁹⁴ Very recently, Toste and co-workers have developed the first transition-metal catalyzed cycloisomerization of 1,6-allenes **262** and **263** to alkylidene-cyclobutanes **264** and **265**, respectively (Scheme 87). Thus, the reaction of 1,6-allenes **262** and **263** with 5 mol% of Ph₃PAuCl/AgBF₄ in 0.1M CH₂Cl₂ afforded the corresponding [2+2] proximal adducts **264** and **265** in excellent yields. A variety

Scheme 85 Cyclodimerization of phenylallene **257** using a sterically hindered ruthenium catalyst. Reagents and conditions: (a) 10 mol% [Cp*Ru(PPh₃)(MeCN)₂][PF₆], DMF, 110 °C, 6 h.

Scheme 86 Copper(i)-catalyzed enantioselective [2+2] cycloaddition of 1-methoxyallenylsilanes **259** with an α -imino ester. Reagents and conditions: (a) 10 mol% [Cu(MeCN)₄]BF₄, 10 mol% (*R*)-Tol-BINAP, THF, MS 4 Å, –78 °C, 9–24 h. (b) 1N HCl, 0 °C.

Scheme 87 Gold(I)-catalyzed intramolecular [2 + 2] cycloaddition of allenenes **262** and **263**. Reagents and conditions: (a) 5 mol% Ph_3PAuCl , 5 mol% AgBF_4 , CH_2Cl_2 , RT, 2–24 h.

of aryl-substituted alkenes underwent the gold(I)-catalyzed intramolecular [2 + 2] cycloaddition with allenenes.⁹⁵

This methodology has been successfully applied to the enantioselective version by using a chiral dinuclear gold(I)-biarylphosphine complex **266**. The reaction of allenenes **262** with the catalyst generated *in situ* from 3 mol% of (*R*)-DTBM-SEGP $\text{HOS}(\text{AuCl})_2$ and 6 mol% of AgBF_4 afforded the corresponding cyclobutanes **264** in excellent yields and enantioselectivities (Scheme 88).

Scheme 88 Enantioselective gold(I)-catalyzed intramolecular allenene [2 + 2] cycloaddition. Reagents and conditions: (a) 3 mol% **266**, 6 mol% AgBF_4 , DCM (0.1 M), 4 °C or RT.

It has been suggested that the gold(I)-catalyzed cycloaddition proceeds through a stepwise mechanism involving a series of carbocationic intermediates. In accordance with a stepwise mechanism involving a benzylic cation, cyclobutanes **264** would be formed from the gold-catalyzed cycloaddition of *trans*- and *cis*-alkenes **262**. Scheme 89 shows the likely mechanism for the gold(I)-catalyzed reaction. Addition of the nucleophilic alkene to gold(I)-activated allene **267** results in the formation of a carbocationic intermediate **268**. In the presence of methanol, kinetically formed carbocation **268** should be trapped to give *trans*-cyclopentane **269**. The cyclopentane stereochemistry of the methanol adduct would be the opposite to the cyclobutane product, implying that the initial cyclization is reversible. Therefore, in the absence of an

Scheme 89 Proposed mechanism of the gold(I)-catalyzed intramolecular [2 + 2] cycloaddition of allenenes **262**.⁹⁵

Scheme 90 Mo-catalyzed intramolecular [2+2] cycloaddition of *gem*-difluoroallenes **271**. Reagents and conditions: (a) 10 mol% Mo(CO)₆, DMSO/toluene, 100 °C.

exogenous nucleophile, the reaction proceeds through *cis*-disubstituted intermediates **270**. Cyclobutenes **264** are then formed from the reaction of vinyl-gold with benzylic carbocations.

In addition to the excellent yields and *ee*'s, this methodology has turned out to be very elegant because proximal adducts are obtained as the only isomers. However, under thermal conditions, distal adducts are regioselectively obtained for related allenyl systems (see compounds **151**, Scheme 47 and 48).

During studies of the Pauson–Khand reaction of functionalized *gem*-difluoroallenes **271**, Hammond's group has discovered that under molybdenum-catalyzed conditions the intramolecular [2+2+1] cycloaddition did not occur, but novel fused *gem*-difluorocyclobutenes **272** were isolated instead (Scheme 90).⁹⁶ Mechanistically, this reaction has been explained as a formal [2+2] cycloaddition, with the molybdacycle undergoing a reductive elimination, rather than a CO insertion.

In the same context, Cook and co-workers have observed the formation of the hybrid [2+2]/[2+2+1] cycloadducts **273** and **274** during the molybdenum-mediated reaction of the bisallene-bisalkyne **201**.⁹⁷ Thus, when compound **201** was heated in toluene at 100 °C in the presence of a slight excess of Mo(CO)₆ (2.2 equiv.) and 10 equiv. of DMSO, a mixture of diastereomers composed of the [5.5.5.4] tetracycles **273** and **274** in a ratio of 5:4 was obtained (Scheme 91). Interestingly, the Mo-catalyzed reaction of compound **201** promotes the [2+2] cycloaddition of both allenes which was not the case for the thermal conditions described in Scheme 62.

More recently, Mukai has described the same competitive reaction in bisallenes **275** (Scheme 92).⁹⁸ Thus, in the rhodium(I)-catalyzed reaction of bisallenes **275**, bicyclo[5.3.0] compounds **276** have been obtained together with [2+2] cycloadducts **277**.

Oh and co-workers have studied the palladium-catalyzed [2+2] cycloaddition of allenes **178** and **179**, tested previously

Scheme 91 Molybdenum-mediated [2+2]/[2+2+1] cycloaddition of the bisallene-bisalkyne **201**. Reagents and conditions: (a) 2.2 equiv. Mo(CO)₆, 10 equiv. DMSO, toluene, 100 °C.

Scheme 92 Rh(i)-catalyzed intramolecular [2+2] cycloaddition of bisallenes **275**. Reagents and conditions: (a) 5 mol% Rh (i), toluene, 80 °C, CO (1 atm.), 1–18 h.

under microwave conditions, resulting in the formation of the corresponding distal cycloadducts **180** and **181** in good yields (Scheme 93).⁵⁴ The optimal conditions for this reaction were found to be the use of Pd(PPh₃)₂Cl₂ (5 mol%) in refluxing toluene, obtaining the corresponding bicyclic compounds without forming any other side product. However, allenes **179d** and **179e** were inert under the metal-catalyzed conditions, showing the microwave irradiation to be a more efficient technique for this family of allenes (see Scheme 55).

From a mechanistic point of view, it is believed that the palladium(II) first forms a π -complex with both the triple bond and a double bond of substrates **178** and **179**. Such π -complexes are known to undergo migratory C–C coupling to give palladacyclopentenes **278**. Reductive elimination of intermediates **278** would produce compounds **180** and **181** and would regenerate palladium(II) for the next cycle (Scheme 94).

Scheme 93 Pd-catalyzed intramolecular [2+2] cycloaddition of allenes **178** and **181**. Reagents and conditions: (a) 5 mol% PdCl₂(PPh₃)₂, toluene, 110 °C, 12 h.

Scheme 94 Proposed mechanism for the Pd-catalyzed [2+2] cycloaddition of allenes **178** and **179**.⁵⁴

$R^1 = \text{nBu, cyclohexyl, Ph}$
 $R^2 = 1\text{-Np, Ph}$

Scheme 95 Gold-catalyzed [2 + 2] cycloaddition of masked allenyne, alkadiynylic pivaloates **279** and **280**. Reagents and conditions: (a) 10 mol% $\text{AuCl(PPh}_3\text{)}$, 10 mol% AgSbF_6 , DCE, 25–80 °C, 1–15 h.

More recently, the same authors have reported the synthesis of fused cyclobutenes *via* gold-catalyzed [2 + 2] cyclization of 1,8-alkadiynylic pivaloates, masked allenyne.⁹⁹ Substrates **279** and **280** were smoothly transformed to the [3.2.0] and [4.2.0] bicycles **281** and **282** by treatment with a catalytic amount of $\text{AuCl(PPh}_3\text{)}$ (Scheme 95). The corresponding cycloadducts were obtained in good yields in all cases.

A plausible mechanism for the gold-catalyzed cyclization of bisalkynyl pivaloates **279** and **280** has been proposed (Scheme 96). Firstly, coordination of gold(i) to the propargylic ester would induce migration of the pivaloate to give the allene intermediate **283**. The allene **283** underwent [2 + 2] cycloaddition to give the intermediate **284**, which led to the isolated products **281** and **282** upon hydrolysis.

Scheme 96 Proposed mechanism for the gold-catalyzed [2 + 2] cycloaddition of masked allenyne, alkadiynylic pivaloates **279** and **280**.⁹⁹

$R^1 = 3\text{-MeO-C}_6\text{H}_4, 4\text{-MeO-C}_6\text{H}_4,$
 2-Np, Ph, Me
 $R^2 = \text{Me, iPr; } R^3 = \text{H, Me}$

Scheme 97 Cycloisomerization of allenyne **285** catalyzed by PtCl_2 . Reagents and conditions: (a) 10 mol% PtCl_2 , toluene, 80 °C, 12–24 h.

Platinum complexes have also been used in cycloisomerization reactions of enynes, which afford a wide spectrum of products depending on structural variations such as the nature of the substituents on the enyne and the tethers connecting these groups.¹⁰⁰ Murakami and co-workers have reported that the treatment of compounds **285** with a catalytic amount of platinum(II) chloride in toluene at 80 °C cleanly afforded the corresponding bicyclic cyclobutenes **286** in good yields (Scheme 97).¹⁰¹

Scheme 98 illustrates the mechanism for the formation of cyclobutenes **286**. Coordination of the alkyne moiety of **285** to PtCl_2 would form a platinum(II)-alkyne complex **287**, which will undergo *endo*-cyclization with the proximal allenic carbon–carbon double bond to form a seven membered ring. The resulting carbocation **288** is in resonance with **289**, **290** and **291**. The relatively more stable carbocation **289** would abstract a proton from the methyl group, and finally, cyclobutenylplatinum hydride **292** would undergo reductive elimination to provide **286**.

The chemistry of bis-allenes is an emerging area and recently several reports have been published under metal-catalyzed conditions.¹⁰² Thus, in 2006, Ma's group has reported the [2 + 2] cycloaddition in 1,5-bisallenenes **293–295** using palladium(0), as metal promoter, in the presence of $n\text{Bu}_4\text{NI}$ and K_2CO_3 ,

Scheme 98 Mechanism for the cycloisomerization of allenyne **285** catalyzed by PtCl_2 .¹⁰¹

Scheme 99 Pd(0)-catalyzed [2+2] cycloaddition of 1,5-bisallenes **293–295**. Reagents and conditions: (a) 10 mol% [Pd(PPh₃)₄], K₂CO₃, *n*Bu₄NI, 80–85 °C, 4–19 h.

affording bicycle [3.2.0] products **296–298** in moderate to good yields (54–66%) without formation of other regioisomers (Scheme 99).¹⁰³ Interestingly, reaction of compound (*S*)-**295** containing the chiral L-valine ester moiety, afforded bicycle **298** in greater than 99% *ee*, which indicates that the reaction proceeded without racemization of the α -amino acid ester. However, compounds with substituents on the proximal side did not provide the expected [3.2.0] products, probably due to steric reasons. In the course of optimizing the reaction, it was noted that the reaction failed on using *n*Bu₄NI alone. The I[−] species in *n*Bu₄NI may act as a ligand facilitating the reductive elimination process.

A plausible model for the highly diastereoselective Pd(0)-catalyzed [2+2] cycloaddition of 1,5-bisallenyl compound (*S*)-**295** is shown in Scheme 100. Coordination between the Pd atom and the lone pair of electrons of the N atom in the intermediate **299**, along with the requirement of the Pd atom to be distant from the bulkier CO₂Et group, would lead to the exclusive formation of **298**. The inversion of the nitrogen center may be very difficult in this case because of the presence of the bicyclic skeleton.

Although Ma's contribution is an isolated example, this methodology opens a new route to study the intra- and intermolecular [2+2] dimerization of bisallenes in a regio- and stereocontrolled manner under mild conditions.

Scheme 100 Model accounting for the diastereoselective palladium-catalyzed [2+2] cycloaddition of 1,5-bisallene (*S*)-**297**.¹⁰³

5. Concluding remarks

In this review we have presented the most recent advances in [2+2] cycloaddition of allenes, showing this methodology to be an established process to access a large number of polycyclic structures containing the cyclobutane skeleton. The reactions discussed herein demonstrate the high synthetic potential of allenes undergoing [2+2] cycloaddition under several reaction conditions with almost complete regioselectivity, which is controlled by the stereo-electronic nature of the substituents attached to the allene moiety. In addition it has also been demonstrated that metal catalyzed [2+2] cycloaddition proceed in most cases with better yields and controlled regioselectivity, which is not accessible under thermal or photochemical conditions. It is believed that the continued and renewed investigation on [2+2] cycloadditions of allenes will enrich the synthetic applications to access a high diversity of complex structures, including natural products.

6. Abbreviations

Ac	acetyl
AO	atomic orbital
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Bz	benzoyl
Cp	cyclopentenyl
COD	cyclooctadienyl
DCE	1,1-dichloroethane
DEF	diethyl fumarate
DEM	diethyl maleate
DMA	dimethylallene
DME	1,2-dimethoxyethane
DMF	dimethylformamide
dr	diastereomeric ratio
DTBM-SEGPHOS	(4,4'-bi-1,3-benzodioxole)-5,5'-diyl-bis[bis(3,5-di- <i>tert</i> -butyl-4-methoxyphenyl)phosphine]
dppp	1,3-bis(diphenylphosphino)propane
ee	enantiomeric excess
EWG	electron withdrawing group
HP	high pressure
KIE	kinetic isotope effect
LiHMDS	lithium hexamethyldisilazide
MO	molecular orbital theory
MOM	methoxymethyl
MS	molecular sieves
Mts	2,4,6-trimethylphenylsulfonyl
MWI	microwave irradiation
NPM	<i>N</i> -phenylmaleimide
Np	naphthyl
Piv	pivaloyl
PMO	perturbation molecular orbital theory
PMP	<i>p</i> -methoxyphenyl
<i>p</i> -TSOH	<i>p</i> -toluenesulfonic acid
py	pyridine
TIPS	triisopropylsilyl
TMS	trimethylsilyl

Tol tolyl
Ts p-toluenesulfonyl

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References

- 1 *The Chemistry of Allenes*, ed. S. R. Landor, Academic Press, London, 1982, vol. 1, *Modern Allene Chemistry*, ed. N. Krause and A. S. K. Hashmi, Wiley-VCH, Weinheim, 2004, vol. 1 and 2, and references therein; Cumulenes and Allenes, *Science of Synthesis, Houben-Weyl Method of Molecular Transformation*, ed. N. Krause, George Thieme, Stuttgart, 2007, vol. 44.
- 2 D. J. Pasto, *Tetrahedron*, 1984, **40**, 2805–2827; R. Zimmer, C. U. Dinesh, E. Nandan and F. A. Khan, *Chem. Rev.*, 2000, **100**, 3067–3125; H.-U. Reissig, W. Schade, G. M. O. Amombo, R. Pulz and A. Hausherr, *Pure Appl. Chem.*, 2002, **74**, 175–180; A. Hoffmann-Röder and N. Krause, *Angew. Chem., Int. Ed.*, 2004, **43**, 1196–1216; S. Ma, *Chem. Rev.*, 2005, **105**, 2829–2872; S. Ma, in *Topics in Organometallic Chemistry*, ed. J. Tsuji, Springer-Verlag, Heidelberg, 2005, pp. 183–210; M. Brasholz, H.-U. Reissig and R. Zimmer, *Acc. Chem. Res.*, 2009, **42**, 45–56.
- 3 J. E. Baldwin, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon Press, Oxford, 1991, vol. 5, pp. 63–84; M. T. Crimmins, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon Press, Oxford, 1991, vol. 5, pp. 123–150; *The Chemistry of Cyclobutanes*, ed. Z. Rappoport and J. F. Liebman, Wiley, 2005; *Stereoselective Synthesis, Methods of Organic Chemistry (Houben-Weyl)*, ed. G. Helmchen, R. W. Hoffmann, J. Mulzer and E. Schaumann, Thieme: Stuttgart, Germany, 1996, vol. 5, pp. 3061–3125; E. Lee-Ruff and G. Mladenova, *Chem. Rev.*, 2003, **103**, 1449–1483.
- 4 For a recent review, see: J. C. Namyslo and D. Kaufmann, *Chem. Rev.*, 2003, **103**, 1485–1538.
- 5 For selected, recent examples of fragmentation and ring-expansion of substituted cyclobutanes, see: M. Murakami, S. Ashida and T. Matsuda, *J. Am. Chem. Soc.*, 2005, **127**, 6932–6933; P. A. Wender, N. M. Deschamps and R. Sun, *Angew. Chem., Int. Ed.*, 2006, **45**, 3957–3960; N. Maulide and I. E. Markó, *Org. Lett.*, 2007, **9**, 3757–3760; B. M. Trost and J. Xie, *J. Am. Chem. Soc.*, 2008, **130**, 6231–6242; J. M. Um, H. Xu, K. N. Houk and W. Tang, *J. Am. Chem. Soc.*, 2009, **131**, 6664–6665.
- 6 R. Hoffmann and R. B. Woodward, *J. Am. Chem. Soc.*, 1965, **87**, 2046–2048; R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, 1969, **8**, 781–853; in *The Conservation of Orbital Symmetry*, ed. R. B. Woodward and R. Hoffmann, Academic Press, New York, 1970.
- 7 S. Inagaki, H. Fujimoto and K. Fukui, *J. Am. Chem. Soc.*, 1976, **98**, 4693–4701.
- 8 R. S. Varma, *Pure Appl. Chem.*, 2001, **73**, 193–198; P. Lidstrom, J. Tierney, B. Wathey and J. Westman, *Tetrahedron*, 2001, **57**, 9225–9283; C. O. Kappe, *Angew. Chem., Int. Ed.*, 2004, **43**, 6250–6284; M. Nüchter, B. Ondruschka, W. Bonrath and A. Gum, *Green Chem.*, 2004, **6**, 128–141; B. A. Roberts and C. R. Strauss, *Acc. Chem. Res.*, 2005, **38**, 653–661; N. Hoffmann, *Chem. Rev.*, 2008, **108**, 1052–1103.
- 9 A. T. Blomquist and J. A. Verdol, *J. Am. Chem. Soc.*, 1956, **78**, 109–112; H. A. Staab and H.-A. Kurmeier, *Chem. Ber.*, 1968, **101**, 2697–2708; A. Roedig and N. Detzer, *Justus Liebigs Ann. Chem.*, 1971, **749**, 153–158; A. Roedig, N. Detzer and G. Bonse, *Justus Liebigs Ann. Chem.*, 1971, **752**, 60–63; N. Detzer and A. Roedig, *Tetrahedron*, 1971, **27**, 5697–5703; S. R. Byrn, E. Maverick, O. J. Muscio, Jr., K. N. Trueblood and T. L. Jacobs, *J. Am. Chem. Soc.*, 1971, **93**, 6680–6682; P. Binger and U. Schuchardt, *Chem. Ber.*, 1980, **113**, 1063–1071; H. Jendralla and K. Laumen, *Chem. Ber.*, 1983, **116**, 2136–2164; R. W. Saalfrank, W. Paul and P. Schierling, *Chem. Ber.*, 1985, **118**, 2150–2155; A. J. Brattesani, E. Maverick, O. J. Muscio, Jr. and T. L. Jacobs, *J. Org. Chem.*, 1992, **57**, 7346–7349.
- 10 J. J. Gajewski and C. N. Shih, *J. Org. Chem.*, 1972, **37**, 64–68.
- 11 A. Roedig and N. Defzer, *Justus Liebigs Ann. Chem.*, 1967, **710**, 1–6; A. Roedig, *Angew. Chem., Int. Ed. Engl.*, 1969, **8**, 150–151; W. R. Moore, R. D. Bach and T. M. Ozretich, *J. Am. Chem. Soc.*, 1969, **91**, 5918–5919; T. L. Jacobs, J. R. McClenon and O. J. Muscio, Jr., *J. Am. Chem. Soc.*, 1969, **91**, 6038–6041; E. V. Dehmlow, *Tetrahedron Lett.*, 1969, **10**, 4283–4286; J. J. Gajewski and W. A. Black, *Tetrahedron Lett.*, 1970, **11**, 899–902.
- 12 R. Montaigne and L. Ghosez, *Angew. Chem., Int. Ed. Engl.*, 1968, **7**, 221; R. Huisgen and P. Otto, *J. Am. Chem. Soc.*, 1968, **90**, 5342–5343; R. Huisgen, L. A. Feiler and P. Otto, *Tetrahedron Lett.*, 1968, **9**, 4485–4490; W. T. Brady and R. Roe Jr, *J. Am. Chem. Soc.*, 1970, **92**, 4618–4621; H. M. Frey and N. S. Issacs, *J. Chem. Soc. B*, 1970, 830–832; J. E. Baldwin and J. A. Kapecki, *J. Am. Chem. Soc.*, 1970, **92**, 4868–4873.
- 13 W. H. Knoth and D. D. Coffman, *J. Am. Chem. Soc.*, 1960, **82**, 3873–3875.
- 14 C. W. N. Crumper, Z. T. Formum, P. M. Greaves and S. R. Landor, *J. Chem. Soc., Perkin Trans. 2*, 1973, 885–888.
- 15 W. R. Dolbier and S. H. Dai, *J. Am. Chem. Soc.*, 1968, **90**, 5028–5030; W. R. Dolbier, Jr. and S. H. Dai, *J. Am. Chem. Soc.*, 1970, **92**, 1774–1776; S. H. Dai and W. R. Dolbier, Jr., *J. Am. Chem. Soc.*, 1972, **94**, 3946–3952.
- 16 W. R. Moore, R. D. Bach and T. M. Ozretich, *J. Am. Chem. Soc.*, 1969, **91**, 5918–5919; J. E. Baldwin and U. V. Roy, *J. Chem. Soc. D*, 1969, 1225–1226.
- 17 O. J. Muscio, Jr. and T. L. Jacobs, *Tetrahedron Lett.*, 1969, **10**, 2867–2870; T. L. Jacobs, J. R. McClenon and O. J. Muscio, Jr., *J. Am. Chem. Soc.*, 1969, **91**, 6038–6041; J. J. Gajewski and C. N. Shih, *J. Am. Chem. Soc.*, 1969, **91**, 5900–5901; T. L. Jacobs and O. J. Muscio, Jr., *Tetrahedron Lett.*, 1970, **11**, 4829–4832.
- 18 B. G. Odell, R. Hoffmann and A. Imamura, *J. Chem. Soc. B*, 1970, 1675–1682.
- 19 T. J. Levek and E. F. Kiefer, *J. Am. Chem. Soc.*, 1976, **98**, 1875–1879.
- 20 J. J. Gajewski and C. N. Shih, *J. Am. Chem. Soc.*, 1972, **94**, 1675–1678.
- 21 D. J. Pasto, *J. Am. Chem. Soc.*, 1979, **101**, 37–46.
- 22 E. F. Kiefer and M. Y. Okamura, *J. Am. Chem. Soc.*, 1968, **90**, 4187–4189.
- 23 J. E. Baldwin and U. V. Roy, *J. Chem. Soc. D*, 1969, 1225–1226.
- 24 D. J. Pasto and S. E. Warren, *J. Am. Chem. Soc.*, 1982, **104**, 3670–3676.
- 25 D. J. Pasto, S. E. Warren and M. A. Morrison, *J. Org. Chem.*, 1981, **46**, 2837–2841; D. J. Pasto and S. E. Warren, *J. Org. Chem.*, 1981, **46**, 2842–2846; D. J. Pasto and G. L'Hermine, *J. Org. Chem.*, 1990, **55**, 685–694.
- 26 D. J. Pasto, P. F. Heid and S. E. Warren, *J. Am. Chem. Soc.*, 1982, **104**, 3676–3685.
- 27 D. J. Pasto and S.-H. Yang, *J. Am. Chem. Soc.*, 1984, **106**, 152–157.
- 28 D. J. Pasto and K. D. Sugi, *J. Org. Chem.*, 1991, **56**, 3795–3801.
- 29 D. J. Pasto and K. D. Sugi, *J. Org. Chem.*, 1991, **56**, 6216–6224.
- 30 D. J. Pasto and K. D. Sugi, *J. Org. Chem.*, 1992, **57**, 12–17.
- 31 D. J. Pasto and W. Kong, *J. Org. Chem.*, 1988, **53**, 4807–4810.
- 32 D. J. Pasto and K. D. Sugi, *J. Org. Chem.*, 1992, **57**, 1146–1150.
- 33 Y. Gu, T. Hama and G. B. Hammond, *Chem. Commun.*, 2000, 395–396.
- 34 L. E. Harrington, J. F. Britten and M. J. McGlinchey, *Org. Lett.*, 2004, **6**, 787–790.
- 35 E. V. Banide, Y. Ortin, C. M. Seward, L. E. Harrington, H. Müller-Bunz and M. J. McGlinchey, *Chem.-Eur. J.*, 2006, **12**, 3275–3286.
- 36 E. V. Banide, B. C. Molloy, Y. Ortin, H. Müller-Bunz and M. J. McGlinchey, *Eur. J. Org. Chem.*, 2007, 2611–2622.
- 37 N. N. B. Kumar, M. Chakravarty, N. S. Kumar, K. V. Sajna and K. C. K. Swamy, *J. Chem. Sci.*, 2009, **121**, 23–36.
- 38 M. E. Jung and N. Nishimura, *J. Am. Chem. Soc.*, 1999, **121**, 3529–3530; M. E. Jung, N. Nishimura and A. R. Novack,

- J. Am. Chem. Soc.*, 2005, **127**, 11206–11207; M. E. Jung and A. R. Novack, *Tetrahedron Lett.*, 2005, **46**, 8237–8240.
- 39 M. E. Jung and N. Nishimura, *Org. Lett.*, 2001, **3**, 2113–2115.
- 40 M. E. Jung and M. Murakami, *Org. Lett.*, 2006, **8**, 5857–5859.
- 41 M. E. Jung and M. Murakami, *Org. Lett.*, 2007, **9**, 461–463.
- 42 M. Kimura, Y. Horino, Y. Wakamiya, T. Okajima and Y. Tamaru, *J. Am. Chem. Soc.*, 1997, **119**, 10869–10870; Y. Horino, M. Kimura, S. Tanaka, T. Okajima and Y. Tamaru, *Chem.–Eur. J.*, 2003, **9**, 2419–2438.
- 43 V. Nair, D. Sethumadhavan, S. M. Nair, P. Shanmugam, P. M. Treasa and G. K. Eigendorf, *Synthesis*, 2002, 1655–1657.
- 44 R. W. M. Aben, S. Braverman and H. W. Scheeren, *Eur. J. Org. Chem.*, 2003, 894–897.
- 45 M. Ogasawara, A. Okada, K. Nakajima and T. Takahashi, *Org. Lett.*, 2009, **11**, 177–180.
- 46 A. Padwa, M. A. Filipkowski, M. Meske, S. H. Watterson and Z. Ni, *J. Am. Chem. Soc.*, 1993, **115**, 3776–3777; A. Padwa, M. Meske, S. S. Murphree, S. H. Watterson and Z. Ni, *J. Am. Chem. Soc.*, 1995, **117**, 7071–7080.
- 47 A. Padwa, H. Lipka, S. H. Watterson and S. S. Murphree, *J. Org. Chem.*, 2003, **68**, 6238–6250.
- 48 T. V. Hansen, L. Skattebøl and Y. Strenstrøm, *Tetrahedron*, 2003, **59**, 3461–3466.
- 49 B. Alcaide, P. Almendros, C. Aragoncillo, M. C. Redondo and M. R. Torres, *Chem.–Eur. J.*, 2006, **12**, 1539–1546.
- 50 H. Ohno, T. Mizutani, Y. Kadoh, A. Aso, K. Miyamura, N. Fujii and T. Tanaka, *J. Org. Chem.*, 2007, **72**, 4378–4389.
- 51 C. Mukai, Y. Hara, Y. Miyashita and F. Inagaki, *J. Org. Chem.*, 2007, **72**, 4454–4461.
- 52 X. Jiang and S. Ma, *Tetrahedron*, 2007, **63**, 7589–7595.
- 53 K. M. Brummond and D. Chen, *Org. Lett.*, 2005, **7**, 3473–3475.
- 54 C. H. Oh, D. I. Park, S. H. Jung, V. R. Reddy, A. K. Gupta and Y. M. Kim, *Synlett*, 2005, 2092–2094; C. H. Oh, A. K. Gupta, D. I. Park and N. Kim, *Chem. Commun.*, 2005, 5670–5672.
- 55 T. V. Ovaska and R. E. Kyne, *Tetrahedron Lett.*, 2008, **49**, 376–378.
- 56 H. Li, H.-R. Zhang, J. L. Petersen and K. K. Wang, *J. Org. Chem.*, 2001, **66**, 6662–6668; Y. Yang, J. L. Petersen and K. K. Wang, *J. Org. Chem.*, 2003, **68**, 5832–5837; Y. Yang, J. L. Petersen and K. Wang, *J. Org. Chem.*, 2003, **68**, 8545–8549.
- 57 S. Kitagaki, Y. Okumura and C. Mukai, *Tetrahedron*, 2006, **62**, 10311–10320.
- 58 H. Cao, J. Flippen-Anderson and J. M. Cook, *J. Am. Chem. Soc.*, 2003, **125**, 3230–3231.
- 59 J. C. Martin, P. G. Gott, V. W. Goodlett and R. H. Hasek, *J. Org. Chem.*, 1965, **30**, 4175–4180; H. A. Bampfield and P. R. Brook, *J. Chem. Soc., Chem. Commun.*, 1974, 171–172; H. A. Bampfield and P. R. Brook, *J. Chem. Soc., Chem. Commun.*, 1974, 171–172; H. A. Bampfield, P. R. Brook and W. S. McDonald, *J. Chem. Soc.*, 1975, 132–133; W. T. Brady, J. D. Stockton and A. D. Patel, *J. Org. Chem.*, 1974, **39**, 236–238; D. C. England and C. G. Krespan, *J. Org. Chem.*, 1970, **35**, 3322–3327; T. Minami, T. Okauchi, H. Matsuki, M. Nakamura, J. Ichikawa and M. Ishida, *J. Org. Chem.*, 1996, **61**, 8132–8140.
- 60 K. L. McCaleb and R. Halcomb, *Org. Lett.*, 2000, **2**, 2631–2634.
- 61 For general reviews on [2+2]-photocycloaddition reactions, see: S. A. Fleming, in *Molecular and Supramolecular Photochemistry: Synthetic Organic Photochemistry*, ed. A. G. Griesbeck and J. Mattay, Dekker, New York, 2005, vol. 12, pp. 141–160; P. Margaretha, in *Molecular and Supramolecular Photochemistry: Synthetic Organic Photochemistry*, ed. A. G. Griesbeck and J. Mattay, Dekker, New York, 2005, vol. 12, pp. 211–237.
- 62 S. W. Baldwin, in *Organic Photochemistry*, ed. A. Padwa, Dekker, New York, 1981, vol. 5, pp. 123–225; W. Oppolzer, *Acc. Chem. Res.*, 1982, **15**, 135; A. C. Weedon, in *Synthetic Organic Photochemistry*, ed. W. M. Horspool, Plenum, New York, 1984, pp. 61–144; D. I. Schuster, in *Chemistry of enones*, ed. S. Patai and Z. Rappoport, Wiley, New York, 1989, vol. 5, pp. 623–756; D. De Keukeleire and S.-L. He, *Chem. Rev.*, 1993, **93**, 359; *CRC, Handbook of Organic Photochemistry and Photobiology*, ed. W. M. Horspool and P.-S. Song, CRC Press, Boca Raton, FL, 1995, ch. 52 and 53; M. T. Crimmins, *Chem. Rev.*, 1988, **88**, 1453.
- 63 K. Wiesner, *Tetrahedron*, 1975, **31**, 1655; S. L. Schreiber, *Science*, 1985, **227**, 857; M. T. Crimmins, *Chem. Rev.*, 1988, **88**, 1453–1473; M. T. Crimmins and T. L. Reinhold, *Organic Reactions*, Wiley, New York, 1993, vol. 44, p. 297; J. D. Winkler, C. M. Bowen and F. Liotta, *Chem. Rev.*, 1995, **95**, 2003–2020.
- 64 K. Wiesner, V. Musil and K. J. Wiesner, *Tetrahedron Lett.*, 1968, **9**, 5643–5646.
- 65 M. C. Pirrong and S. A. Thomson, *J. Org. Chem.*, 1988, **53**, 227–230.
- 66 P. E. Eaton, *Tetrahedron Lett.*, 1964, **5**, 3695–3698.
- 67 M. Tada and Y. Niedo, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 1416–1418; G. L. Lange, M. G. Organ and M. Lee, *Tetrahedron Lett.*, 1990, **31**, 4689–4692; G. V. T. Swapna, A. B. Lakshmi, J. M. Rao and A. C. Kunwar, *Tetrahedron*, 1989, **45**, 1777–1782; D. Andrew, D. J. Hastings, D. L. Oldroyd, A. Rudolph, A. C. Weedon, D. F. Wong and B. Zhang, *Pure Appl. Chem.*, 1992, **64**, 1327–1334.
- 68 J. F. Blount, *Tetrahedron Lett.*, 1980, **21**, 4413–4416; K. Wiesner, *Tetrahedron*, 1975, **31**, 1655–1658; D. Becker, M. Nagler, Z. Harel and A. Gillon, *J. Org. Chem.*, 1983, **48**, 2584–2590.
- 69 Y.-H. Kang and J. L. Kice, *Tetrahedron Lett.*, 1982, **23**, 5373–5374; J. L. Kice and Y.-H. Kang, *Tetrahedron*, 1985, **41**, 4739–4746.
- 70 D. J. Hastings and A. C. Weedon, *J. Am. Chem. Soc.*, 1991, **113**, 8525–8527; D. J. Hastings and A. C. Weedon, *Tetrahedron Lett.*, 1991, **32**, 4107–4110; D. J. Maradyn and A. C. Weedon, *Tetrahedron Lett.*, 1994, **35**, 8107–8110; D. Andrew, D. J. Hastings and A. C. Weedon, *J. Am. Chem. Soc.*, 1994, **116**, 10870–10882; D. J. Maradyn and A. C. Weedon, *J. Am. Chem. Soc.*, 1995, **117**, 5359–5360; D. Andrew and A. C. Weedon, *J. Am. Chem. Soc.*, 1995, **117**, 5647–5663.
- 71 D. J. Maradyn, L. K. Sydnes and A. C. Weedon, *Tetrahedron Lett.*, 1993, **34**, 2413–2416.
- 72 R. D. J. Froese, G. L. Lange and J. D. Goddard, *J. Org. Chem.*, 1996, **61**, 952–961.
- 73 E. M. Carreria, C. A. Hastings, M. S. Shepard, L. A. Yerkey and D. B. Millward, *J. Am. Chem. Soc.*, 1994, **116**, 6622–6630.
- 74 D. Becker, M. Nagler, Y. Sahali and N. Haddad, *J. Org. Chem.*, 1991, **56**, 4537–4543.
- 75 M. S. Shepard and E. M. Carreira, *J. Am. Chem. Soc.*, 1997, **119**, 2597–2605.
- 76 J. D. Winkler and J. R. Ragains, *Org. Lett.*, 2006, **8**, 4031–4033.
- 77 For reviews on the photochemistry of divinylmethanes, see: H. E. Zimmerman and D. Armesto, *Chem. Rev.*, 1996, **96**, 3065–3112; H. E. Zimmerman, *Org. Photochem.*, 1991, **11**, 1–36; H. E. Zimmerman, *Acc. Chem. Res.*, 1982, **15**, 312–317; S. S. Hixson and H. E. Zimmerman, *Chem. Rev.*, 1973, **73**, 531–551.
- 78 H. E. Zimmerman and R. E. Factor, *Tetrahedron*, 1981, **37**, 125–141; P. Baekström, *Tetrahedron*, 1978, **34**, 3331–3335; P. Baekström, *J. Chem. Soc., Chem. Commun.*, 1976, 476–477; M. J. Bullivant and G. Pattenden, *J. Chem. Soc., Perkin Trans. 1*, 1976, 256–258.
- 79 H. E. Zimmerman, D. Armesto, M. G. Amezuza, T. P. Gannett and R. P. Johnson, *J. Am. Chem. Soc.*, 1979, **101**, 6367–6383; H. E. Zimmerman and J. M. Cassel, *J. Org. Chem.*, 1989, **54**, 3800–3816.
- 80 K. Sugiyama and T. Tsuno, *Chem. Express*, 1992, **7**, 929–932.
- 81 T. Tsuno and K. Sugiyama, *Bull. Chem. Soc. Jpn.*, 1999, **72**, 519–531.
- 82 T. Tsuno, H. Hoshino and K. Sugiyama, *Tetrahedron Lett.*, 1997, **38**, 1581–1584.
- 83 T. Tsuno, H. Hoshino, R. Okuda and K. Sugiyama, *Tetrahedron*, 2001, **57**, 4831–4840.
- 84 T. Tsuno and K. Sugiyama, *Chem. Lett.*, 1991, 503–507; T. Tsuno and K. Sugiyama, *Bull. Chem. Soc. Jpn.*, 1995, **68**, 3175–3188; T. Tsuno, H. Hoshino and K. Sugiyama, *Tetrahedron Lett.*, 1997, **38**, 1581–1726.
- 85 T. Tsuno, M. Yoshida, T. Iwata and K. Sugiyama, *Tetrahedron*, 2002, **58**, 7681–7689.
- 86 B. T. B. Hue, J. Dijkink, S. Kuiper, S. van Schaik, J. H. van Maarseveen and H. Hiemstra, *Eur. J. Org. Chem.*, 2006, 127–137.
- 87 R. Miaou, S. G. Gramani and M. J. Lear, *Tetrahedron Lett.*, 2009, **50**, 1731–1733.
- 88 M. Lautens, W. Klute and W. Tam, *Chem. Rev.*, 1996, **96**, 49–92.
- 89 S. Saito, K. Hirayama, C. Kabuto and Y. Yamamoto, *J. Am. Chem. Soc.*, 2000, **122**, 10776–10780.

- 90 F. F. Caserio, S. H. Parker, R. Piccolini and J. D. Roberts, *J. Am. Chem. Soc.*, 1958, **80**, 5507–5513.
- 91 A. T. Blomquist and J. A. Verdol, *J. Am. Chem. Soc.*, 1956, **78**, 109–112; W. T. Borden, I. L. Reich, L. A. Sharpe and R. B. Weinberg, *J. Org. Chem.*, 1975, **40**, 2438–2442.
- 92 E. Bustelo, C. Guérot, A. Hercouet, B. Carboni, L. Toupet and P. H. Dixneuf, *J. Am. Chem. Soc.*, 2005, **127**, 11582–11583.
- 93 T. Akiyama, K. Daidouji and K. Fuchibe, *Org. Lett.*, 2003, **5**, 3691–3693.
- 94 A. S. K. Hashmi and G. J. Hutchings, *Angew. Chem., Int. Ed.*, 2006, **45**, 7896–7936.
- 95 M. R. Luzung, P. Mauleón and F. D. Toste, *J. Am. Chem. Soc.*, 2007, **129**, 12402–12403.
- 96 Q. Shen and G. B. Hammond, *J. Am. Chem. Soc.*, 2002, **124**, 6534–6535.
- 97 H. Cao, S. G. Van Ornum, J. Deschamps, J. Flippen-Anderson, F. Laib and J. M. Cook, *J. Am. Chem. Soc.*, 2005, **127**, 933–943.
- 98 F. Inagaki, S. Narita, T. Hasegawa, S. Kitagaki and C. Mukai, *Angew. Chem., Int. Ed.*, 2009, **48**, 2007–2011.
- 99 C. H. Oh and A. Kim, *Synlett*, 2008, 777–781.
- 100 C. Bruneau, *Angew. Chem., Int. Ed.*, 2005, **44**, 2328–2334; A. M. Echavarren and C. Nevado, *Chem. Soc. Rev.*, 2004, **33**, 431–436.
- 101 T. Matsuda, S. Kadowaki, T. Goya and M. Murakami, *Synlett*, 2006, 575–578.
- 102 M. D. Clay and A. G. Fullis, *Angew. Chem., Int. Ed.*, 2005, **44**, 4039–4042; S. M. Kim, J. H. Park, Y. K. Kang and Y. K. Chung, *Angew. Chem., Int. Ed.*, 2009, **48**, 4532–4535.
- 103 X. Jiang, X. Cheng and S. Ma, *Angew. Chem., Int. Ed.*, 2006, **45**, 8009–8013.