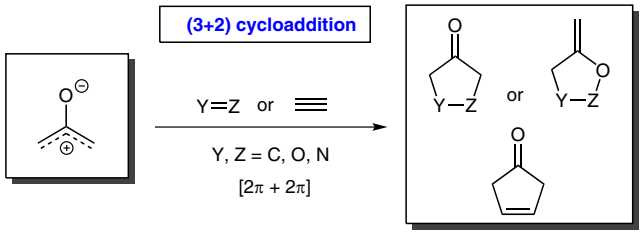
Synthesis H. Li, J. Wu Short Review

(3+2)-Cycloaddition Reactions of Oxyallyl Cations

Hui Li

Jimmy Wu*

Department of Chemistry, Dartmouth College, Hanover, NH 03755, USA
jimmy.wu@dartmouth.edu



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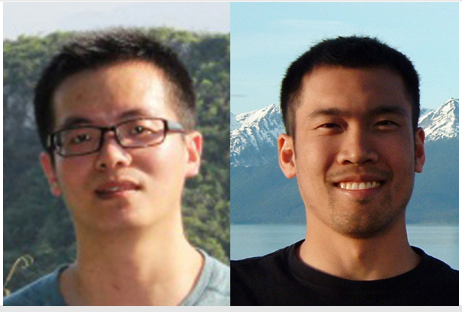
Abstract The (3+2)-cycloaddition reaction involving oxyallyl cations has proven to be a versatile and efficient approach for the construction of five-membered carbo- and heterocycles, which are prevalent frameworks in natural products and pharmaceuticals. The following article will provide a brief summary of recent disclosures on this process featuring chemo-, regio- and diastereoselective oxyallyl cycloadditions with both electron-rich and electron-deficient 2π partners.

Key words cycloaddtion, oxyallyl cation, heterocycles, regioselectivity, diastereoselectivity



Hui Li received his B.Sc. degree in pharmaceutical science from Tianjin University (China) under the supervision of Prof. Kang Zhao in 2010. He then moved to the USA in 2011 and joined Prof. Jimmy Wu's research group at Dartmouth College to continue his interest in organic synthesis.

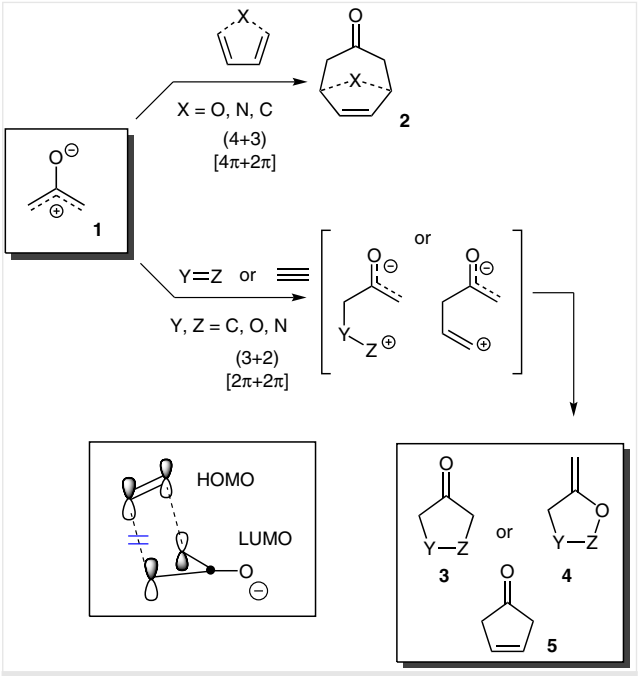
Jimmy Wu received his A.B. degree in chemistry from Princeton University (USA) in 1998. He then spent two years as an associate chemist at Merck Process Research (USA) before moving to Harvard University (USA) in 2001. There, he obtained his Ph.D. in organic chemistry from Prof. David A. Evans in 2005. He continued his studies as a postdoctoral fellow with Prof. Barry M. Trost at Stanford University (USA). He then joined the Department of Chemistry at Dartmouth College (USA) in the summer of 2007 and is now an associate professor. His current interest includes novel annulation of indoles, redox-chain reactions, the chemistry of phosphorothioate esters, and natural product synthesis.

1 Introduction

The chemistry of oxyallyl cations **1** has been a fertile ground for the design and development of powerful reaction processes. Cycloaddition reactions, in particular, are highly valued for their synthetic utility. This one-step process represents a facile approach to construct a variety of ring types and increase molecular complexity.[1] Both (4+3)- and (3+2)-cycloaddition modes of oxyallyl cations are known under thermal conditions and have been investigated for decades.[2] As shown in Scheme 1, the (4+3) cycloadditions with dienes provide access to seven-membered carbocycles **2** and have been incorporated in a number of elegant syntheses of natural products.[3]

The (3+2) cycloaddition of oxyallyl cations **1** with a 2π partner, although less intensively investigated compared to the (4+3) counterpart, remains an attractive research topic. In this [2π+2π] process (Scheme 1), orbital symmetry considerations indicate that a concerted mechanism is not allowed under thermal conditions. Instead, the reaction can proceed via a step-wise pathway, which makes it reasonable to regard this process as a formal cycloaddition. Generally, the reaction would start with electrophilic bond formation of the oxyallyl cation with one atom of the 2π partner to give a zwitterionic intermediate. The cation on the other atom of the 2π partner may then be captured by either the O or C atom on the oxyallyl moiety to furnish five-membered rings **4**–**5** (e.g., cyclopentanones), which are ubiquitous in nature as well as useful building blocks.[4,5]

The (3+2) cycloaddition possesses several different features relative to the (4+3) process. First, the (4+3) cycloaddition typically provides carbocycles with the formation of two C–C bonds. In the case of (3+2) annulations, the oxygen



Scheme 1 Generic (4+3)- and (3+2)-cycloaddition reactions of oxyallyl cations

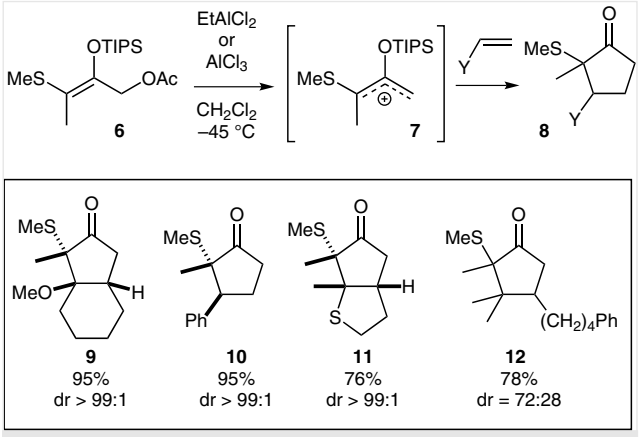
atom of oxyallyl intermediates may also participate in the reaction to afford oxacyclic species **4**. Second, electron-rich 4π partners (i.e., dienes) are generally required in the (4+3) cycloaddition reactions since oxyallyl cations are electrophilic. However, electron-deficient 2π partners such as carbonyls or diethyl azodicarboxylate have been demonstrated by Noyori,[6] Hoffmann,[7] Fry,[8] and Cookson[9] in 1970s to be compatible with the (3+2) mode. This distinct difference enables facile access to a broader range of five-membered heterocycles including furanones, 1,3-dioxolanes, pyrazolidones, etc. Third, an alkyne may also capture the oxyallyl cations in the (3+2) cycloaddition to produce cyclopentenones **5** while a diene is generally used in the (4+3) approach.

Recent advances in the oxyallyl (3+2) cycloadditions featured the emergence of highly chemo-, regio- and diastereoselective processes, which indicated renewed interest in this field. To the best of our knowledge, reviews concerning oxyallyl (3+2) cycloadditions have remained relatively scarce since the 1990s. Thus, in this article we focus on some of these reactions, developed during the past two decades, that involve the cycloaddition of various oxyallyl cations with both electron-rich and -deficient 2π partners. The discussion will be divided into sections based on the types of oxyallyl cations and/or precursors.

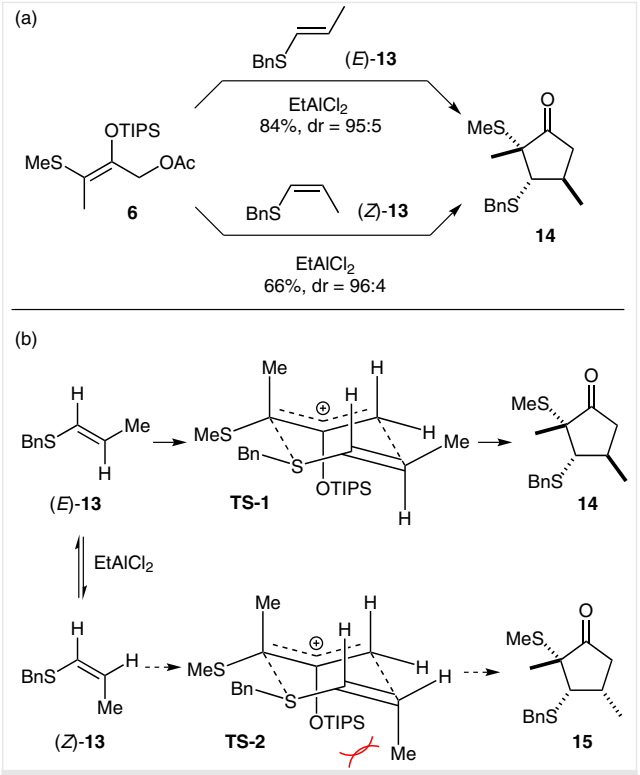
2 Heteroatom-Substituted Oxyallyl Cations

Heteroatom-substituted oxyallyl cations have been extensively studied to participate in dipolar cycloaddtions since the last century.[10] Although they are commonly utilized in (4+3) cycloadditions, Kuwajima demonstrated a highly regio- and stereoselective (3+2) cyclopentannulation by employing sulfur-substituted oxyallyl cations.[11,12]

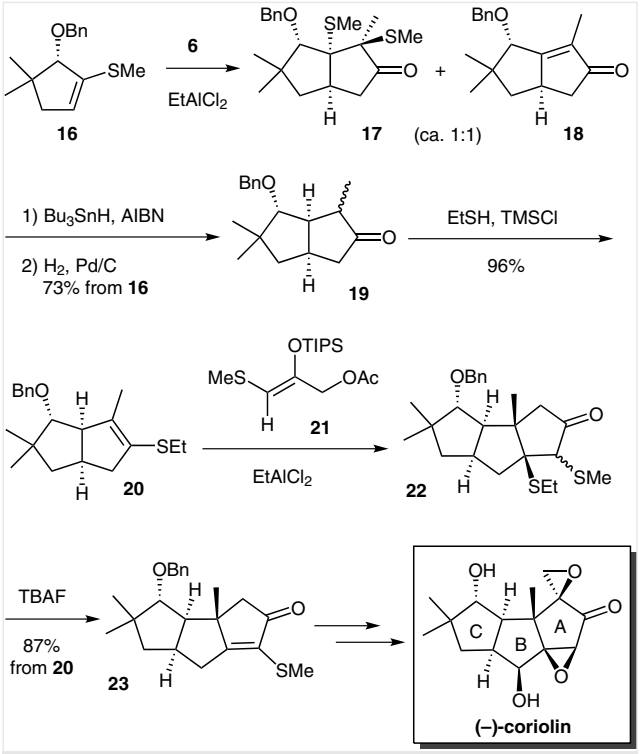
As shown in Scheme 2, the 3-(alkylthio)-2-siloxyallyl cation **7**, which was generated from allyl acetate **6** by the treatment of $EtAlCl_2$ or $AlCl_3$, was able to react with various kinds of olefins including enol ethers, vinyl sulfides, stryrenes, and trialkylolefins to afford the corresponding cyclopentanones in good yields (e.g., **9**–**12**). Notably, these reactions proceeded in almost complete regioselectivity by forming the sterically more hindered isomers as the predominant product in every case. Moreover, surprisingly high stereoselectivity was observed in the reaction of **6** with vinyl sulfides. As shown in Scheme 3 (a), both the *E*- and the *Z*-isomers of 2-(benzylthio)but-2-ene (**13**) afforded the same diastereomer **14** as the major product. This may be due to the rapid geometric isomerization between (*E*)-**13** and (*Z*)-**13** under the influence of $EtAlCl_2$ (Scheme 3, b). To further rationalize the origin of diastereoselectivity, chair-like six-membered transition-state models **TS-1** and **TS-2** were also proposed, which featured the orbital interaction between the sulfur atom of the vinyl sulfide and the α-carbon of the oxyallyl cation (Scheme 3, b). Since **TS-2** contains a 1,3-diaxial steric repulsion between the β-methyl group of (*Z*)-**13** and the siloxy group of the oxyallyl cation, this cycloaddition would be slower than that of (*E*)-**13**. The authors propose that the cycloaddition reactions of both (*E*)-**13** and (*Z*)-**13** proceed through **TS-1** in a step-wise manner to first form the C–C bond distal to both sulfur atoms. This generates an intermediate that proceeds to forge the second C–C bond without further bond rotation to give **14** as the major product.



Scheme 2 (3+2) Cycloadducts derived by using various olefins



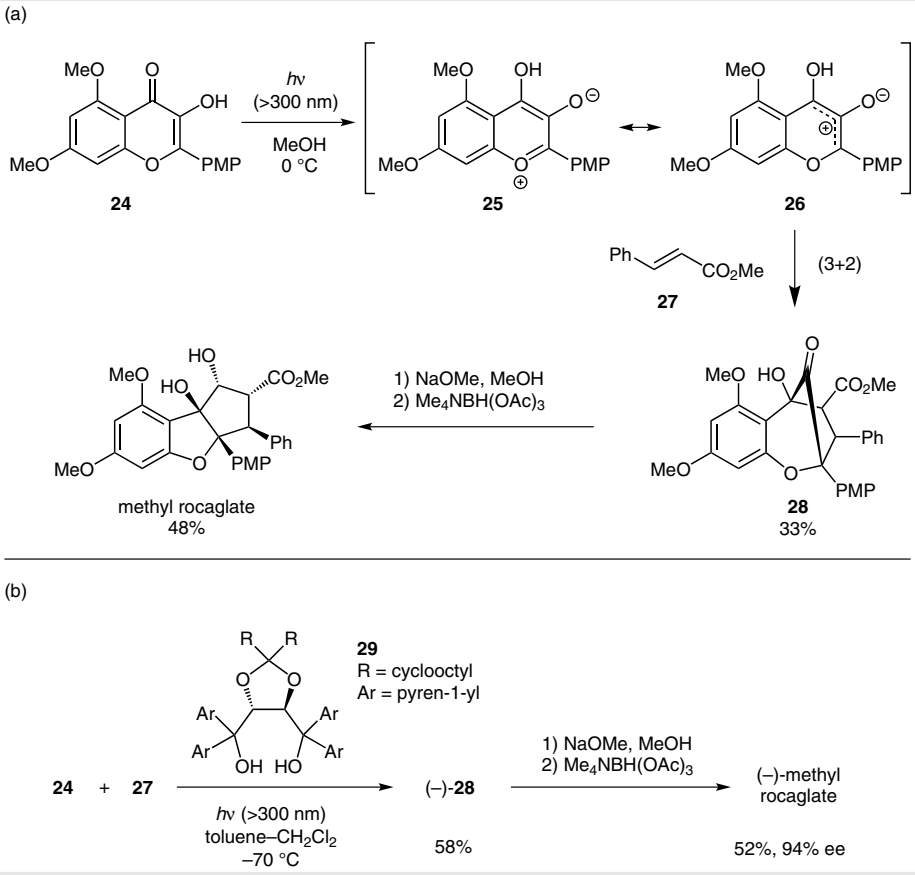
Scheme 3 (a) Stereoselective cycloaddition using vinyl sulfides (*E*)-**13** and (*Z*)-**13**. *Reagents and conditions*: CH_2Cl_2, –45 °C. (b) Proposed transition-state model resulting in high stereoselectivity.



Scheme 4 Construction of the A and B rings of coriolin by (3+2)-cycloaddition reactions

Due to its wide range of applicability, as well as the high selectivity, the above (3+2)-cycloaddition strategy was successfully incorporated in the total synthesis of (–)-coriolin in a following report by the same group.[13,14] As shown in Scheme 4, the ABC triquinane ring system of coriolin was constructed via two successive (3+2)-cycloaddition reactions. Treatment of benzyl ether **16** with vinyl sulfide **6** in the presence of $EtAlCl_2$ provided a 1:1 mixture of annulated products **17** and **18** in diastereomerically pure forms. The crude mixture was then subjected to a desulfurization–hydrogenation sequence to give bicyclic ketone **19** in a yield of 73% for three steps. The use of enthanethiol and chlorotrimethylsilane transformed **19** to vinyl sulfide **20**. Subsequently, **20** underwent a second (3+2) cycloaddition with **21** to install the A-ring unit of (–)-coriolin, which was followed by the TBAF-mediated β-elimination of ethanethiol to give enone **23**, which was eventually taken on to (–)-coriolin.

The heteroaromatic oxidopyrylium species, which are widely used in (5+2) dipolar cycloadditions,[15] may also act as stabilized oxyallyl cations. For example, Porco and coworkers demonstrated that the oxidopyrylium betaine **25** or **26** derived from excited-state intramolecular proton transfer (ESIPT) of 3-hydroxyflavone **24** could undergo (3+2) cycloaddition with electron-deficient methyl cinnamate (**27**) (Scheme 5, a).[16] The resulting (3+2)-cycloadduct **28** could be further transformed into methyl rocaglate with an α-ketol rearrangement/reduction sequence. The (3+2) photocycloaddition of **24** and **27** may also proceed enantioselectively by using functionalized TADDOL derivative **29** as chiral Brønsted acids (Scheme 5, b).[17] As a result, (–)-methyl rocaglate was obtained in 94% ee with a similar strategy as mentioned above. It was proposed that the hydrogen bonding interaction between the phenoxide oxygen of oxidopyrylium **25** or **26** and the free hydroxyl group of TADDOL derivative **29** may play an important role in stabilizing the oxyallyl intermediate, as well as controlling the stereofacial approach of the 2π partner **27**. Notably, the above (3+2) photocycloaddition involving oxidopyrylium ions allowed facile access to several other rocaglate natural products including rocaglaol, rocaglamide, silvestrol, episilvestrol, as well as several derivatives (e.g., **30**–**32**) (Figure 1).[18]



Scheme 5 (a) Synthesis of methyl rocaglate by employing (3+2) photocycloaddition as a key step; PMP = *p*-methoxybenzyl. (b) TADDOL-mediated enantioselective (3+2) photocycloaddition and its application towards (–)-methyl rocaglate.

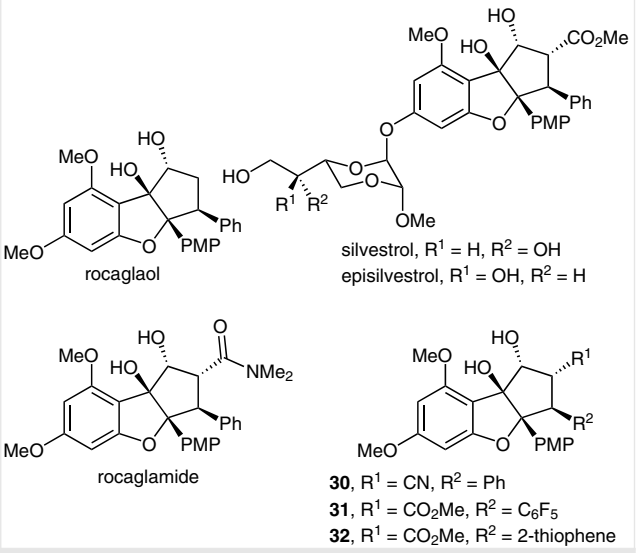
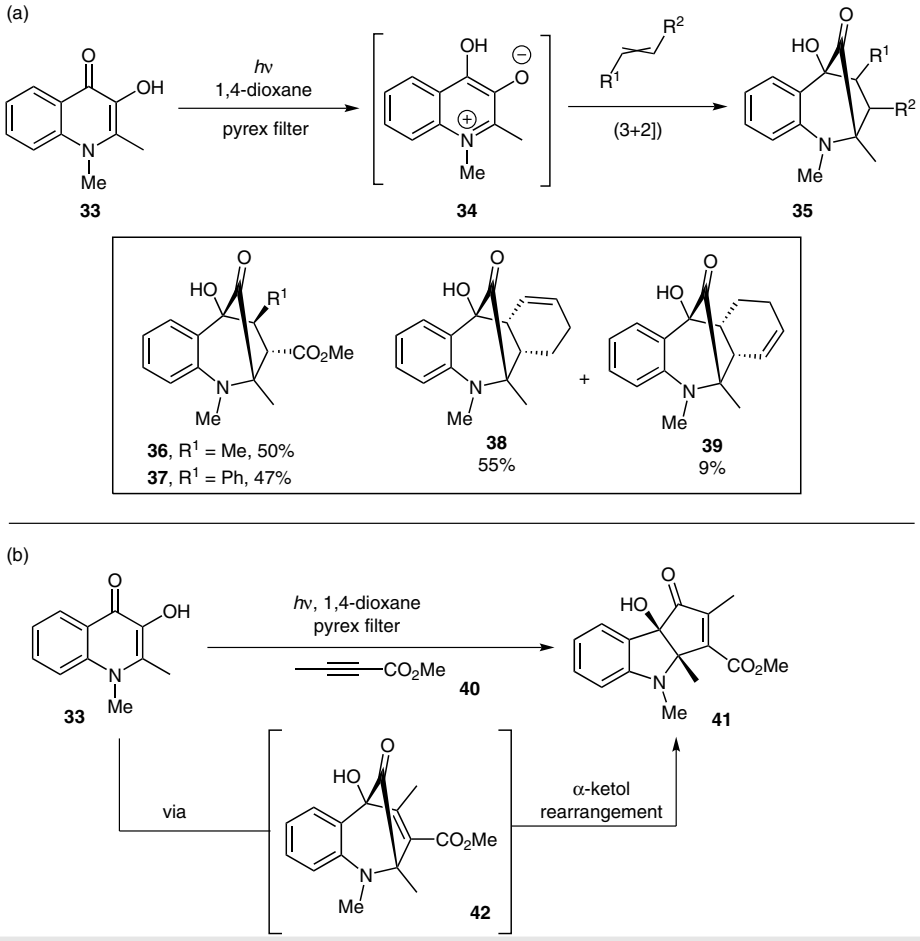


Figure 1 Rocaglate natural products and derivatives synthesized by employing (3+2) photocycloaddition as a key step

Afterwards, an analogous photocycloaddition involving an oxidoquinolinium variant was also disclosed by the same group.[19] As shown in Scheme 6 (a), irradiation of 1,2-dimethyl-3-hydroxylquinolinone (**33**) could promote the generation of 3-oxidoquinolinium species **34**, which may then participate in (3+2) cycloadditions with appropriate 2π partners. While the reaction of **33** with electron-deficient 2π partners afforded only single cycloadducts **36** and **37**, respectively, electron-rich olefins such as cyclohexadiene tend to afford two regioisomers (e.g., **38** and **39**). Notably, attempts to use the electron-deficient methyl butynoate **40** as a 2π partner did not give the presumed (3+2) product **42**, but a rearranged cycloadduct **41**. The doubly conjugated enone of **42** is assumed to provide a strong, thermodynamic driving force for the α-ketol rearrangement.

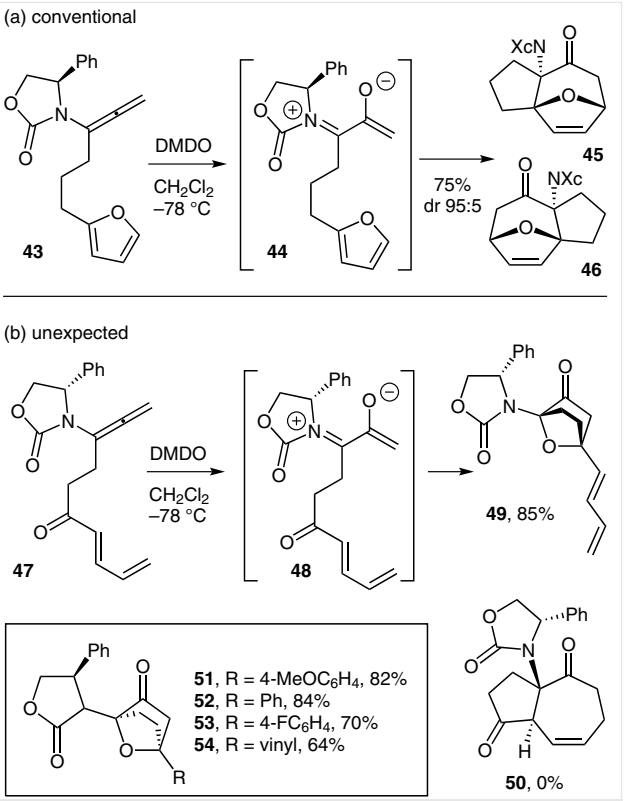


Scheme 6 (a) (3+2) Photocycloaddition of oxidoquinolinium ions with electron-rich and -deficient olefins. (b) (3+2) Photocycloaddition of oxidoquinolinium ions with electron-deficient alkyne.

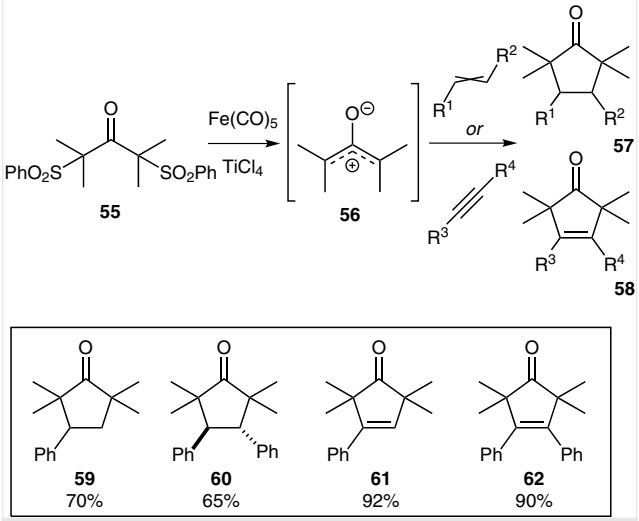
In addition to the above heteroatom-substituted oxyallyl cations, Hsung, Houk, Krenske, and co-workers recently reported an unexpected (3+2) cycloaddition of nitrogen-stabilized oxyallyl cations with the electron-deficient carbonyl groups of a tethered dienone.[20] Despite the fact that other oxyallyls like **44** do undergo intramolecular (4+3) cycloadditions (Scheme 7, a),[21] the treatment of allene amide **47** with dimethyldioxirane (DMDO) proceeds only through the (3+2) pathway to generate oxabicyclic species **49** (Scheme 7, b). The density functional theory calculations (DFT) on current system indicated a transition state that features simultaneous interactions of the oxyallyl LUMO with the carbonyl π and lone-pair orbitals. They termed this process as 'hemipseudopericyclic', which is halfway between purely pericyclic and purely pseudopericyclic reactions. Further investigation on (3+2) cycloadditions was conducted theoretically and experimentally by employing various carbonyl sources including aldehydes, ketones, esters, and amides. Only tethered ketones with electron-rich substituents are amenable in this process (e.g., **51**–**54**).

3 Oxyallyl Cations Derived from Substituted Ketones

As mentioned earlier, the use of α,α-dihalo ketones as oxyallyl sources has been well established since the 1970s upon the treatment with reducing agents such as $Fe_2(CO)_9$, $Fe(CO)_5$, and Zn/Cu couple.[22] Other disubstituted ketones, in principle, may also produce oxyallyl cations under appropriate reductive conditions. For example, Hardinger showed that bis(sulfonyl) ketone **55** could generate oxyallyl intermediate **56** upon treatment with $Fe(CO)_5$ and $TiCl_4$.[23] Subsequent (3+2) trapping of **56** with alkenes would furnish the corresponding cyclopentanones (e.g., **59** and **60**). Moreover, electron-rich alkynes also turned out to be compatible 2π partners (e.g., **61** and **62**) (Scheme 8).

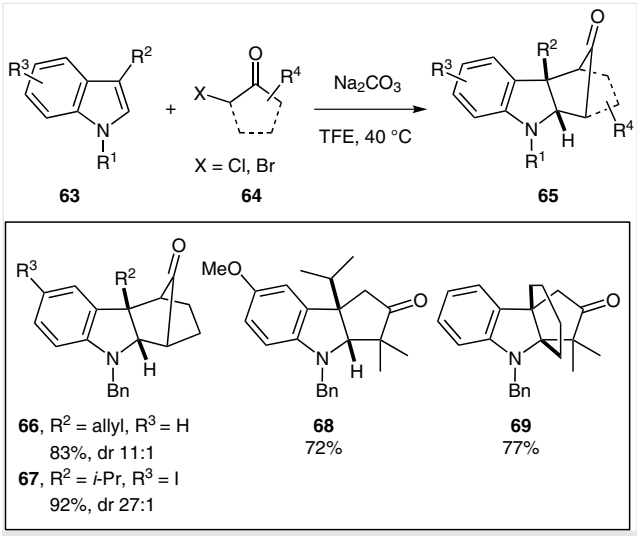


Scheme 7 (a) Intramolecular (4+3) cycloadditions of allene amide-derived oxazolidinone substituted oxyallyls with tethered furan; (b) Intramolecular (3+2) cycloadditions of allene amide-derived oxazolidinone substituted oxyallyls with tethered carbonyls.



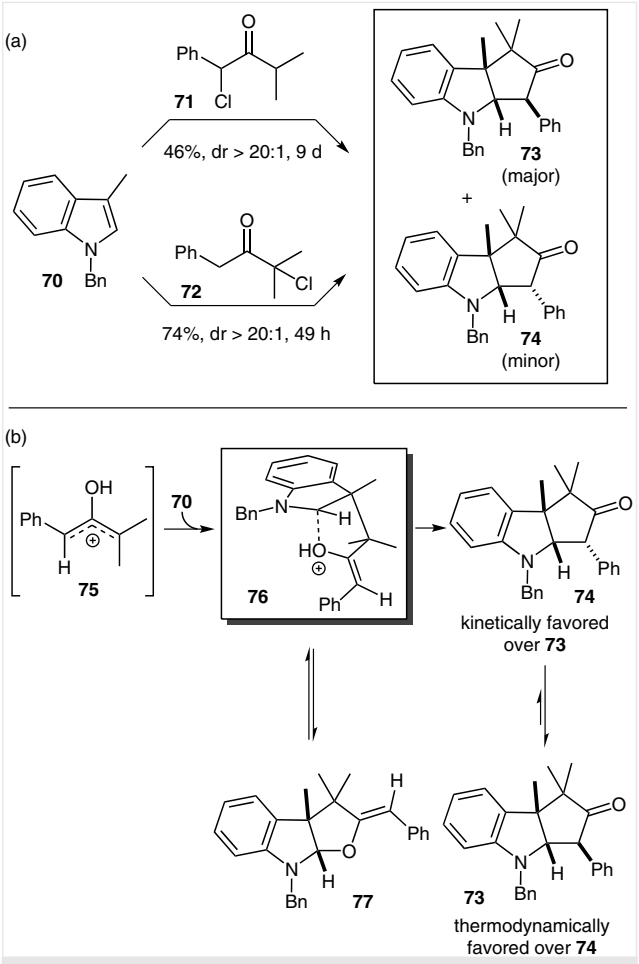
Scheme 8 (3+2) Cycloaddition between bis(sulfonyl) ketone-derived oxyallyls with alkenes and alkynes

In addition to disubstituted ketones, monosubstituted ones may also act as oxyallyl precursors. Recently, Wu and Hughes reported a regio- and diastereoselective (3+2) annulation of electron-rich 3-substituted indoles **63** with α-halo ketones **64** (Scheme 9).[24] This method provides easy access to highly functionalized cyclopenta- or cyclohexa-fused indoline compounds **65**, which are common structures of many natural products. Impressive regiochemical control was observed in the cycloaddition employing acyclic α-halo ketones (e.g., **68**, **69**).



Scheme 9 (3+2) Cycloaddition between 3-substituted indoles and α-halo ketones

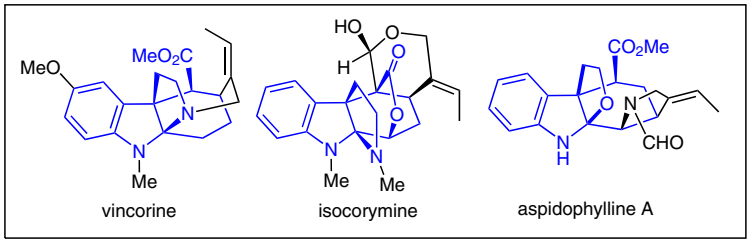
It is also interesting that the regioisomeric, acyclic α-halo ketones **71** and **72** both afforded **73** as the major product with high diastereoselectivity (>20:1) (Scheme 10, a). Notably, a common O-alkylated intermediate **77** was isolated (Scheme 10, b), suggesting that the reactions of α-halo ketones **71** and **72** may proceed via the same hydroxyallyl intermediate **76**. As illustrated in their proposed mechanism (Scheme 10, b), the first C–C bond formation between hydroxyallyl **75** and *N*-benzylskatole (**70**) generates intermediate **76**, which possesses a weak C···OH interaction. Removal of the proton with carbonate base at this point would furnish the observed intermediate **77**. Alternatively, the pronated form **77** could re-dissociate and alkylate at carbon to generate the kinetically favored cycloadduct **74**, which can then isomerize to the thermodynamically favored product **73**. The above rearrangements, as well as the kinetic and thermodynamic properties of **73** and **74** are in accordance with experimental observations and computational studies.

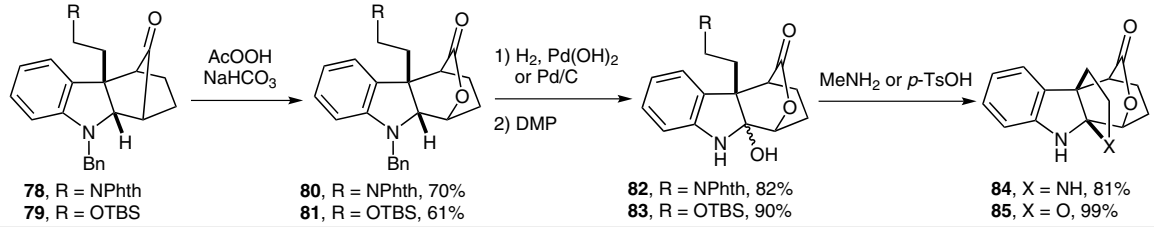


Scheme 10 (a) (3+2) Cycloaddition of *N*-benzylskatole with α-halo ketones. *Reagents and conditions*: Na_2CO_3, TFE, 40 °C. (b) Proposed mechanism.

Furthermore, DFT calculations in the above (3+2) cycloaddition did raise the question of whether hydroxyallyl cation **75** or its zwitterionic form is the real reactive species. While other cycloaddition reactions are thought to proceed through zwitterionic oxyallyl cations,[25] DFT studies on the current system predicted that a pathway for the formation of product **74** via hydroxyallyl **75** is a lower-energy route than that emanating from the corresponding zwitterionic form. Harmata and Schreiner have also observed similar divergent reactivity between oxyallyl and hydroxyallyl cations before.[26]

The synthetic potential of this (3+2)-cycloaddition process was demonstrated by a concise synthesis of the core structures of vincorine, isocorymine, and aspidophylline A. As shown in Scheme 11, Baeyer–Villiger oxidation of the (3+2)-cycloadduct **78** afforded tertracyclic lactone **80** in 70% yield. Compound **80** was then subject to a debenzylation–oxidation sequence to give hemiaminal **82**. Cleavage of the phthalimide group with $MeNH_2$ liberated the amine, which spontaneously closed to furnish the pyrrolidine ring of pentacycle **84**. Compound **84** maps well to the cores of vincorine and isocorymine. By employing a similar strategy, pentacycle **85** was obtained from (3+2)-cycloadduct **79**, which provided a good starting point for the synthesis of aspidophylline A.

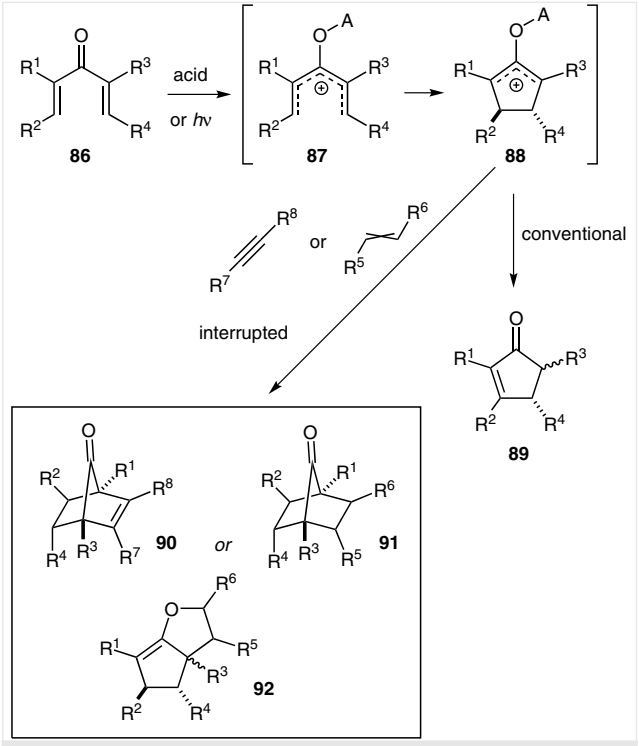




Scheme 11 Synthesis of core structures for vincorine, isocorymine, and aspidophylline A (n.b., drawn as their enantiomers)

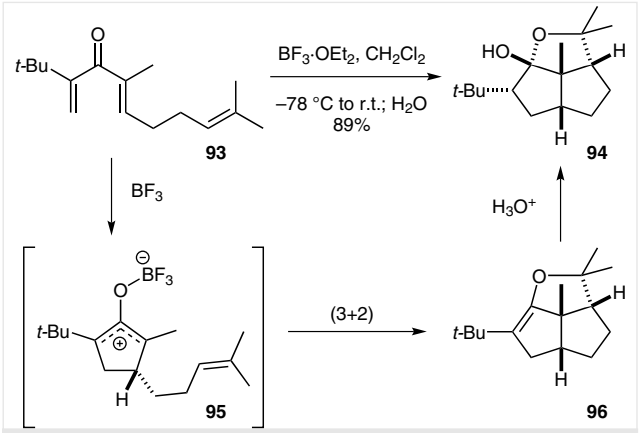
4 Oxyallyl Cations from Interrupted Nazarov Cyclizations

The Nazarov cyclization entails the 4π-electrocyclic ring closure of a conjugated pentadienyl cation **87**, which is derived from dienone **86** upon treatment with acids or irradiation, to form a cyclopentenyl cation **88** (Scheme 12).[27] Conventionally, a β-elimination of the adjacent proton would furnish cyclopentenone **89**. In the interrupted Nazarov reaction;[28] however, the reactive intermediate **88** may be intercepted by a 2π partner (an alkene or alkyne) to undergo a (3+2) cycloaddition at a rate competitive to the normal elimination route.



Scheme 12 Conventional versus interrupted Nazarov reaction

In 1998, West and co-workers reported the first intramolecular (3+2) cycloaddition of olefins and Nazarov-derived oxyallyl cations.[29] As shown in Scheme 13, diquinane **94** was obtained from achiral trienone **93**. It was presumed that activation of trienone **93** generated the reactive cyclopentenyl intermediate **95**, which underwent intramolecular (3+2) trapping by the proximal olefin to afford tricyclic compound **96**. It is noteworthy that the oxygen atom of the oxyallyl moiety preferentially participated in the annulation with the formation of a C–O bond.[24] Upon aqueous workup, the structurally strained enol moiety was hydrolyzed to give hemiketal **94** with selective protonation from the convex face.



Scheme 13 (3+2) Cycloaddition of Nazarov-derived oxyallyl cation with pendant olefin

Afterwards, the same group found allylsilanes and vinyl sulfides to be amenable in the intermolecular mode of (3+2) cycloaddition involving Nazarov-derived oxyallyls (Figure 2).[30,31] Complete regioselectivity was observed in the reactions employing allylsilanes as 2π partners (e.g., **97**), since allylsilane selectively attacks the least substituted end of unsymmetrically substituted oxyallyl cations. This is in accordance with Noyori's earlier observation that regioselectivity is predicated on pathways intercepting the more stabilized enolate.

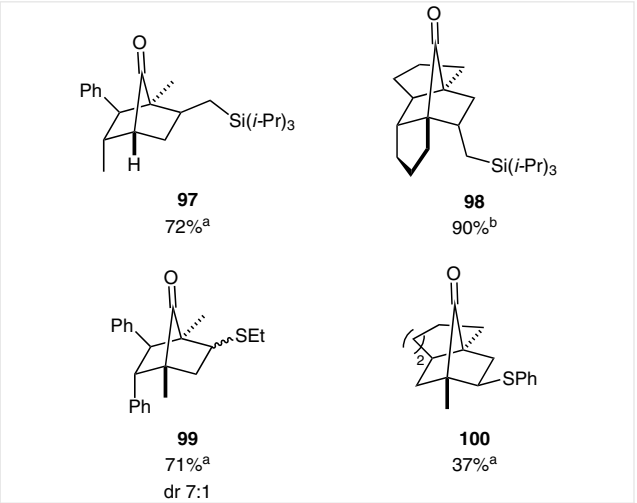
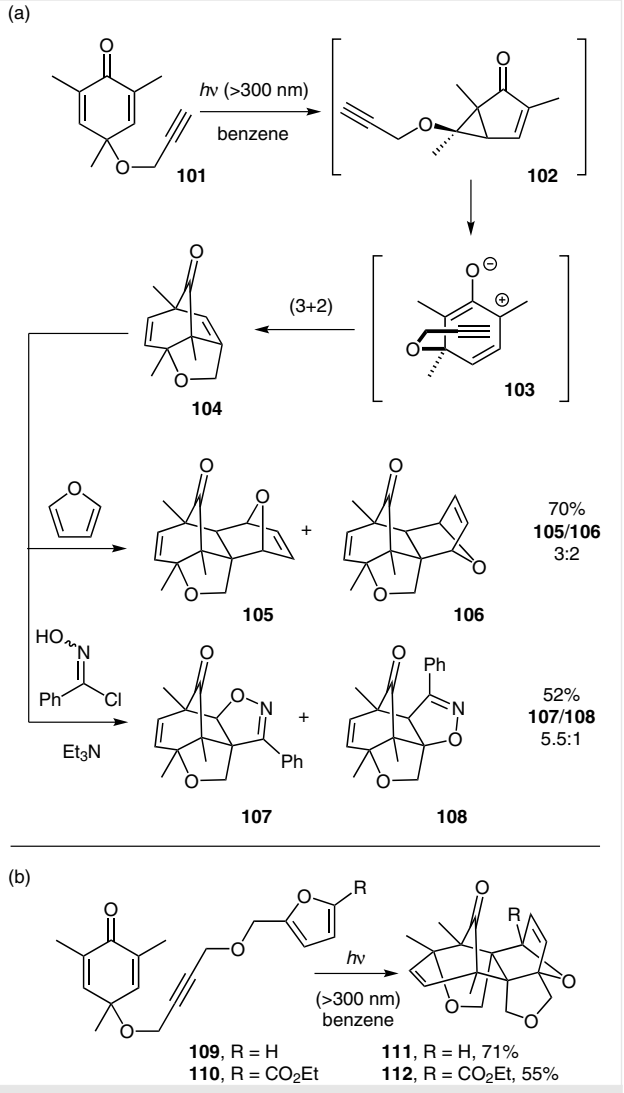


Figure 2 (3+2) Cycloadducts by using allylsilanes and vinyl sulfides as 2π partners. *Reagents and conditions*: (a) $BF_3{\cdot}OEt_2$; (b) $SnCl_4$.

As mentioned earlier, irradiation may also promote the formation of oxyallyl speices. Stephenson and Porco recently demonstrated a tandem dienone photorearrangement-cycloaddition reaction of alkyne-tethered cyclohexadienones (Scheme 14, a) to produce highly complex architectures.[32] It was surmised that photochemical rearrangement of substituted dienone **101** would lead to the formation of

oxyallyl cation **103** via the Nazarov-type cyclopentenone **102**.[33] The reactive 1,3-dipole **103** then underwent intramolecular (3+2) cycloaddition with tethered alkyne to form cycloadduct **104**. The resulting strained cyclic alkene **104**, which turned out to be unstable during purification, could be further elaborated by either inter- (Scheme 14, a) or intramolecular cycloaddition (Scheme 14, b) with furans or a nitrile oxide (via oxime) to generate polycyclic, bridged frameworks. Impressively, in the reaction to yield compound **112** (Scheme 14, b), four rings and six stereogenic centers were generated in this single process.



Scheme 14 Tandem dienone photorearrangement-cyclization to afford polycyclic structures

While the reactive cyclic oxyallyl cations **88** have usually been derived from dienones **86** in traditional Nazarov reactions, they may also be generated from different sources (Scheme 15). For example, Burnell and co-workers reported in 2010 that treatment of allenyl vinyl ketone **113** with $BF_3{\cdot}OEt_2$ could lead to the cyclic oxyallyl cation **114** through Nazarov cyclization.[34] In the presence of appropriate olefins, the reactive intermediate **114** may be captured in the (3+2) cycloadditions. As shown in Scheme 15, electron-rich styrenes reacted smoothly to afford bridged (3+2) cycloadducts **116**, **117**, and **118** as single diastereomers. When aliphatic dienes were employed, the reaction provided a mixture of (3+2) and (4+3) products regioselectively and diastereoselectively (e.g., **119**–**122**). It was indicated that the proportion of (3+2) to (4+3) products is highly dependent on the diene substituents.

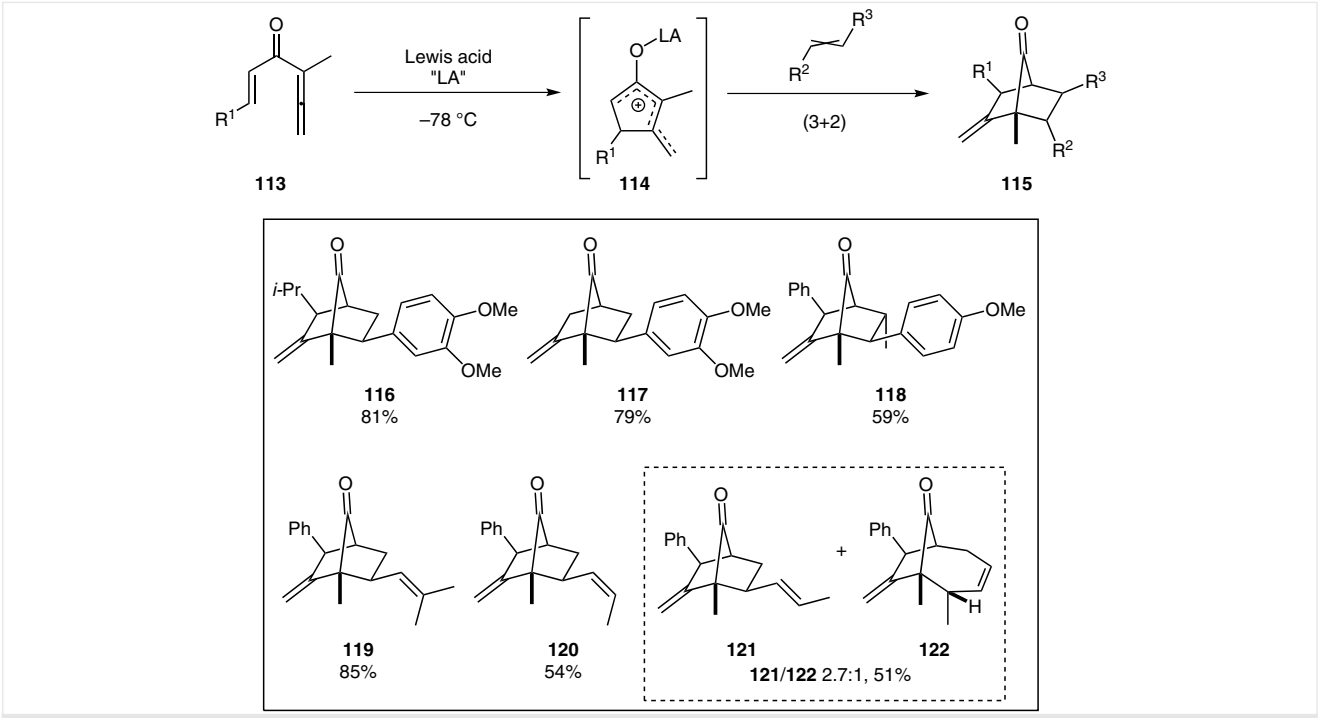
In addition, Yadav and co-workers recently described (3+2) trapping of oxyallyl cations generated from homo-Nazarov cyclization of 2-(*tert*-butyldiphenylsilylmethyl)cyclopropyl vinyl ketones **123** with allylsilanes (Scheme 16).[35] This reaction was proposed to begin with the cleavage of σ_{C-C} bond of the cyclopropyl ring on **123** to generate enolate **124**. The positive charge was proposed to be stabilized by the proximal silyl group. Intermediate **124** then underwent ring-closure to give oxyallyl cations **125**, which was then captured by allylsilanes in a (3+2) manner. Although the reaction proceeded with only moderate regioselectivity (e.g., **128**/**129** = 2:1), exclusive *exo*-cycloaddition was observed.

5 1-Alkylidene-2-oxyallyl Cations

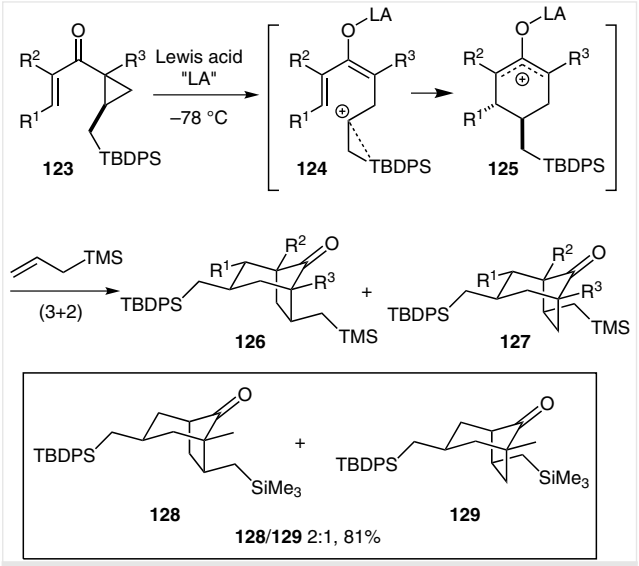
In 2006, Fujita reported that the ring opening of alkylidenecyclopropanone acetal **130** under acidic conditions would produce the 1-alkylidene-2-oxyallyl cation **131** as an intermediate, which then undergoes (3+2) or (4+3) cycloadditions in the presence of olefins or dienes (Scheme 17).[36] While the reaction of **131** with excess furan delivered a mixture of (4+3) cycloadducts and rearranged products from the (3+2) cycloadducts, the reaction with 2,3-benzofuran **132** furnished (3+2) cycloadduct **133** as a single regioisomer in 76% yield.

6 Summary and Outlook

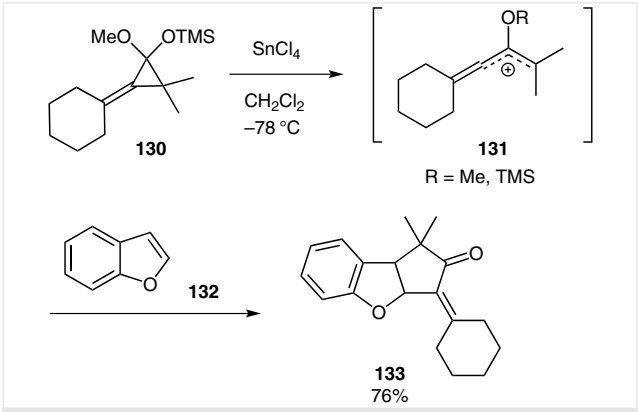
The cycloaddition chemistry of oxyallyl cations represents a versatile process in the rapid generation of molecular diversity and complexity. The (3+2) cycloaddition, in particular, enables efficient construction of five-membered carbo- and heterocycles. As discussed above, a variety of oxyallyl cations are able to participate in this [2π+2π] process including those stabilized by heteroatoms and those



Scheme 15 (3+2) Cycloaddition of allenyl vinyl ketone-derived oxyallyl cation with olefins



Scheme 16 (3+2) Cycloaddition of cyclopropyl vinyl ketone-derived oxyallyl cation with allylsilanes



Scheme 17 (3+2) Cycloaddition of 1-alkylidene-2-oxyallyl cation with 2,3-benzofuran

'unstablized' species. Both classes of oxyallyl cations can either be cyclic or acyclic and may be derived from different sources. Due to the electrophilic nature of oxyallyl cations, electron-rich alkenes or alkynes are generally favorable 2π partners. However, electron-deficient 2π partners including α,β-unsaturated ketones (e.g., methyl cinnamate, methyl butynoate), carbonyl groups, and diethyl azodicarboxylate are also amenable in some cases.

The past twenty years have witnessed the development of many chemo-, regio- and diastereoselective oxyallyl (3+2) cycloadditions. Some of them have also been successfully employed in the elegant syntheses of natural products. Despite the impressive progress that has been made in the oxyallyl (3+2) cycloadditions, there is still plenty of room for improvement and further exploration. For example, the development of catalytic and enantioselective processes

still remains relatively rare. It is our hope that this article will stimulate continued interest in the (3+2) cycloaddition of oxyallyl cations and make it a prolonged and prominent research area for developing novel methods used for natural product syntheses.

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