Small-Ring Systems

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Cyclobutane and Cyclobutene Synthesis: Catalytic Enantioselective [2+2] Cycloadditions

*Yao Xu, Michael L. Conner, and M. Kevin Brown**

alkenes · cycloaddition · enantioselectivity · small-ring systems · synthetic methods

Cyclobutanes and cyclobutenes are important structural motifs found in numerous biologically significant molecules, and they are useful intermediates for chemical synthesis. Consequently, [2+2] cycloadditions to access cyclobutanes and cyclobutenes have been established to be particularly useful transformations. Within the last 10 years, an increase in the frequency of publications for catalytic enantioselective [2+2] cycloadditions has occurred. These reactions provide access to a wide array of enantiomerically enriched chemical diversity that was not previously attainable. Described in this review are the advances made in catalytic enantioselective [2+2] cycloadditions to access cyclobutanes and cyclobutenes.

1. Introduction

Cycloadditions are one of the most important and venerable transformations in organic chemical synthesis.[1] Consequently, development of catalytic enantioselective variants of these reactions has been the subject of much interest. Numerous [4+2], [3+2], and other higher-order cycloaddition reactions have been reported, and their utility demonstrated in the total synthesis of complex molecules.[1] Conversely, catalytic enantioselective [2+2] cycloadditions are significantly less investigated. However, within the last decade there has been a substantial increase in the number of reports in this area.[2] These reactions are significant because they provide an efficient route to access the cyclobutane scaffold, require simple and readily available alkene chemical inputs, and are completely atom-economical (Scheme 1 a).[3,4] Furthermore, the products are important for several reasons: 1) Cyclobutanes and cyclobutenes are extremely useful intermediates for chemical synthesis.[3] A vast array of ring-expansion or ring-cleavage reactions can be carried out to provide a variety of carbocycles, heterocycles, and ring-opened products (Scheme 1 a). 2) Cyclobutanes and cyclobutenes are found in a number of natural products (Scheme 1 b).[5–7] 3) Drug discovery efforts have identified cyclobutane-containing molecules as promising therapeutic agents.[8] Their activities may be attributed to the structural rigidity of the molecules, which in turn allows a defined spatial arrangement of its substituents—a feature that is often favorable in drug design (Scheme 1 c).[9]

This review focuses on catalytic enantioselective [2+2] cycloadditions for accessing cyclobutanes and cyclobutenes. The different sections describe similar but complementary approaches. The first section focuses exclusively on photochemical approaches. The second section will cover polarized [2+2] cycloadditions. The third will discuss transition metal catalyzed processes. Other catalytic enantioselective methods for accessing enantiomerically enriched cyclobutanes and cyclobutenes are known, such as ring expansions[10] and direct functionalization of cyclobutanes,[11] but they will not be discussed herein.

2. Photochemical Reactions

Photochemical [2+2] cycloadditions for accessing cyclobutanes is a well-established method.[12] However, the transfer of these reactions to catalytic enantioselective processes has been met with significant challenges.[13] These challenges are primarily due to nominal catalyst interactions with high-energy excited-state or radical-based intermediates which undergo reaction with minimal activation barriers. Only within the last decade have viable and attractive solutions been disclosed. Outlined below are the three approaches that have been taken to provide solutions to this problem.

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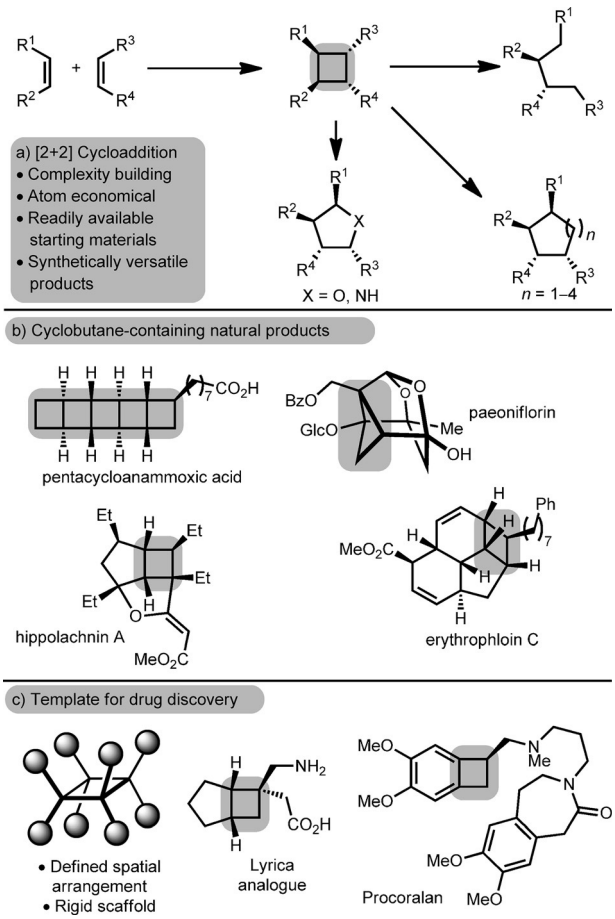
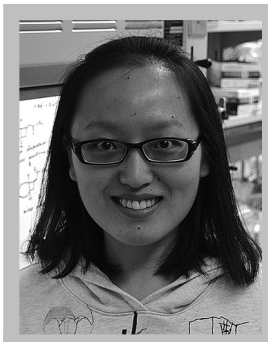
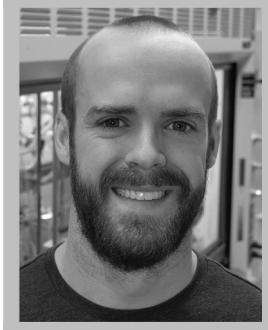


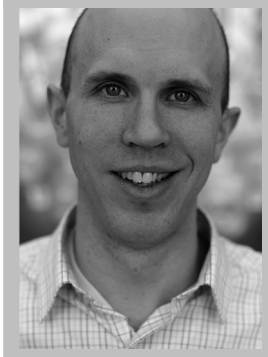
Scheme 1. The significance of cyclobutanes.



Yao Xu was born in Lanzhou, China. She carried out her undergraduate study at Tianjin Normal University and obtained her B.S. degree in 2012. Then she joined Professor Brown's research group at Indiana University and is currently investigating catalytic enantioselective [2+2] cycloadditions and their application to natural product synthesis.



Michael L. Conner obtained his B.S. from Texas Tech University in 2012. Currently, he is carrying out his Ph.D. work in the lab of M. Kevin Brown at Indiana University focusing on the development of novel catalytic enantioselective [2+2] cycloaddition reactions.



M. Kevin Brown received his B.A. from Hamilton college in 2002 and his Ph.D. from Boston College with Professor Amir Hoveyda in 2008. After completion of his graduate studies he began an NIH funded postdoctoral fellowship in the laboratories of E. J. Corey at Harvard University. In 2011, Professor Brown joined the faculty at Indiana University. His research focuses broadly on the development and application of new stereoselective chemical reactions.

2.1. Energy Transfer

Photochemical [2+2] cycloadditions often employ a photosensitizer. Inherent to these processes is the transfer of energy from an excited-state photosensitizer to a cycloaddition substrate. To overcome the problem of selective energy transfer to the substrate/catalyst complex rather than the unbound substrate, Bach and co-workers developed a solution (Scheme 2).[14] In these systems, a photosensitizer is covalently bound to a motif such that, upon excitation, energy transfer will preferentially occur to the proximally bound substrate. It should be noted that contemporaneous efforts by Krische and co-workers describe a catalyst based on the same principles for [2+2] cycloaddition, however, enantioselectivities were low (60:40 e.r.).[15] The catalyst **9** was specifically designed to interact with a quinolone-derived substrate through two-point binding. Highly enantioselective reactions were observed in these systems for several substrate classes (**1**, **4**, and **7**), however, formation of regioisomers was common. A plausible pre-transition-state assembly (**10**) is illustrated in Scheme 2.

Reactions with **9** have also been extended to intermolecular cycloadditions of 2-pyridones (e.g., **12**) with acetylenedicarboxylates (e.g., **11**; Scheme 3).[16] The products of these reactions were generated in good to high enantioselectivities. The absolute stereochemical outcome was easily rationalized with models analogous to that illustrated in Scheme 2.

More recently, Bach and co-workers designed a new catalyst which incorporates a thioxanthone unit that absorbs in the visible-light region ($\lambda \approx 400$–700 nm) and is capable of energy transfer (Scheme 4).[17] Thus, upon exposure of the quinoline **17** to the catalyst **24** and visible-light irradiation, the cyclobutane **18** was formed in good yield and excellent enantioselectivity. A variety of other quinoline substrates which bear different tether substituents and alkene substitution patterns were tolerated (products **19**–**21**, **23**). A closely related pre-transition-state assembly (**25**) to that illustrated in Scheme 2, is likely operative with **24**.

2.2. Direct Absorption

For photochemical [2+2] cycloadditions that do not employ a photosensitizer, the substrate must undergo direct absorption to an excited state. Enantioselective variants of these reactions are challenging, as a chiral catalyst must influence the absorption or emission properties of the substrate. In the absence of such effects, the non-enantioselective background reaction would be difficult to overcome.

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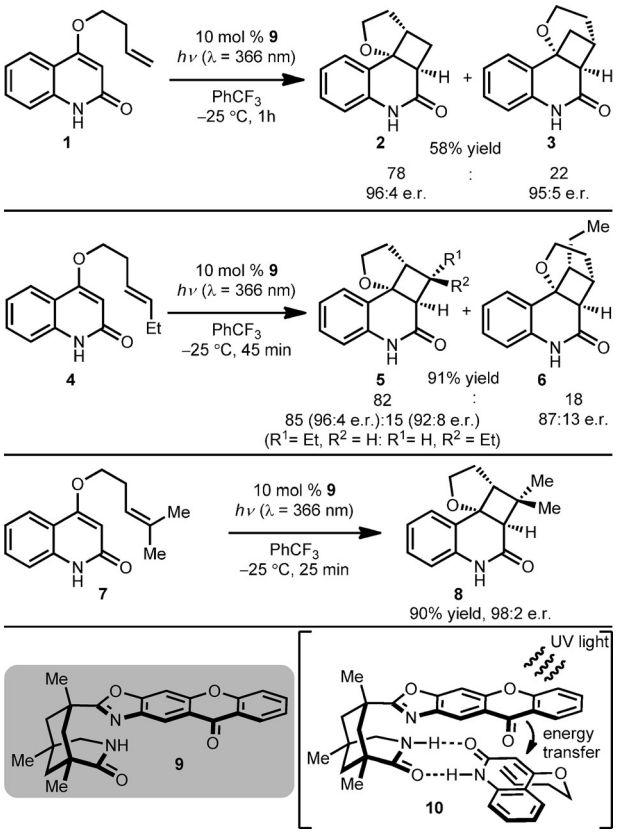
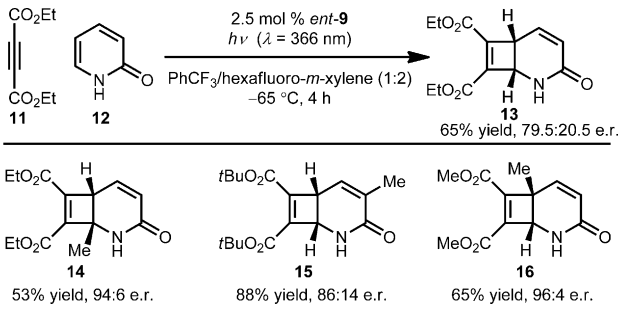
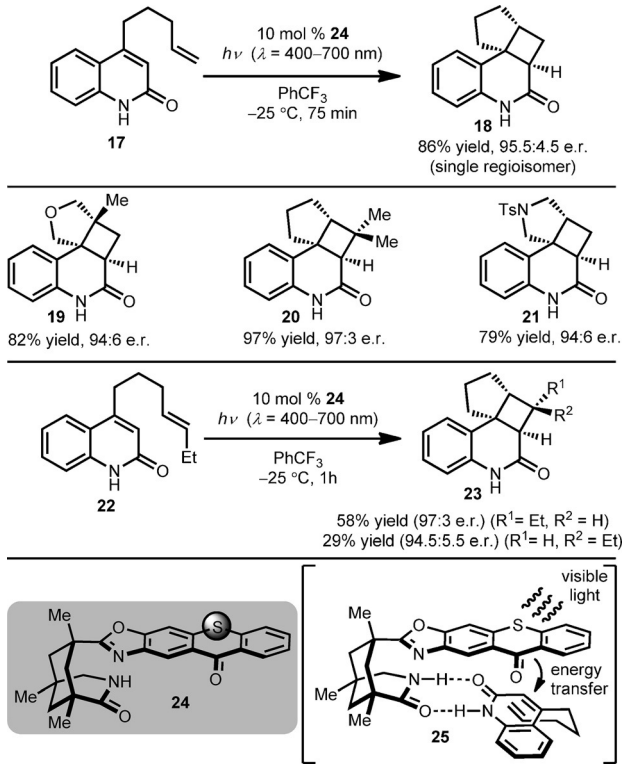


Scheme 2. Photochemical [2+2] (Bach et al.).

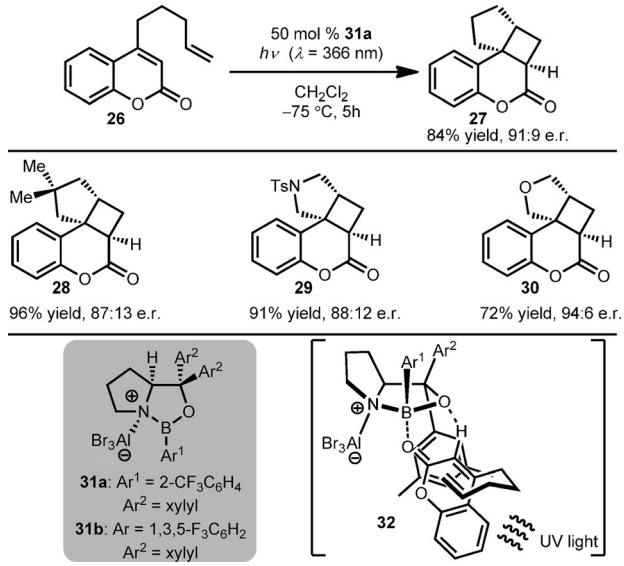


Scheme 3. Intermolecular photochemical [2+2] (Bach et al.).

Lewis and Barancyk reported that the Lewis acid, $BF_3{\cdot}OEt_2$, was crucial to the success of the photochemical [2+2] cycloaddition between coumarin and 2,3-dimethyl-2-butene.[18] Building upon this precedent, Bach and co-workers, identified the chiral oxazaborolidine catalyst **31a** to be effective for promoting the enantioselective [2+2] cycloaddition of the coumarin derivative **26** and thus provide **27** (Scheme 5).[19] The Lewis acid served two roles in this reaction, the first being Lewis acid complexation to the substrate to induce a bathochromatic absorption shift, thus allowing selective excitation, provided the wavelength of light was carefully selected. The second was that the Lewis acid stabilizes the excited state, thus permitting a greater chance of productive cycloaddition relative to nonproductive relaxation. A relatively high catalyst loading (50 mol%) was



Scheme 4. Visible-light photochemical [2+2] (Bach et al.). Ts = 4-toluenesulfonyl.



Scheme 5. Lewis acid promoted photochemical [2+2] (Bach et al.).

necessary to reduce the competing racemic background reaction. A pre-transition state (**32**) rationalizing the stereochemical outcome of these reactions is illustrated in Scheme 5 and is based on [4+2] cycloadditions with closely related catalysts.[20]

Subsequent reports by Bach have demonstrated the application of this method to two other classes of substrates (Scheme 6). In the first example, cycloalkenones (**33**) under-

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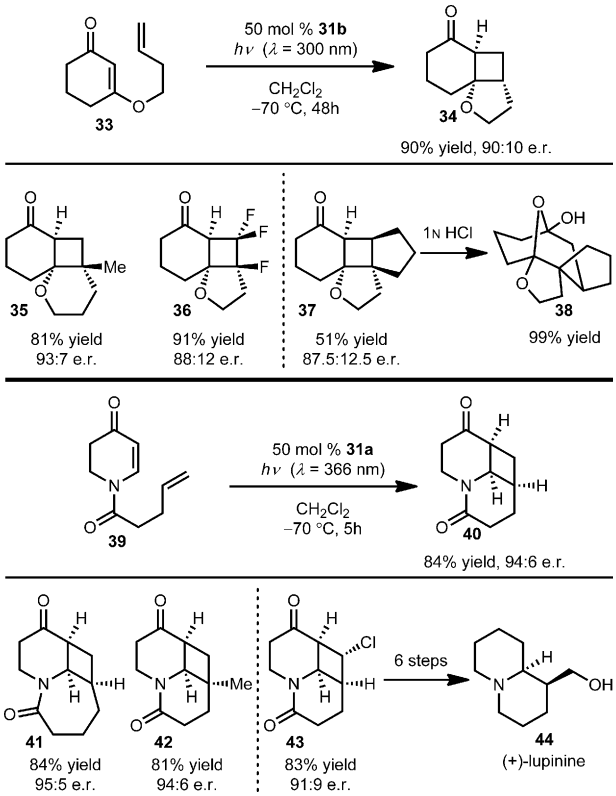
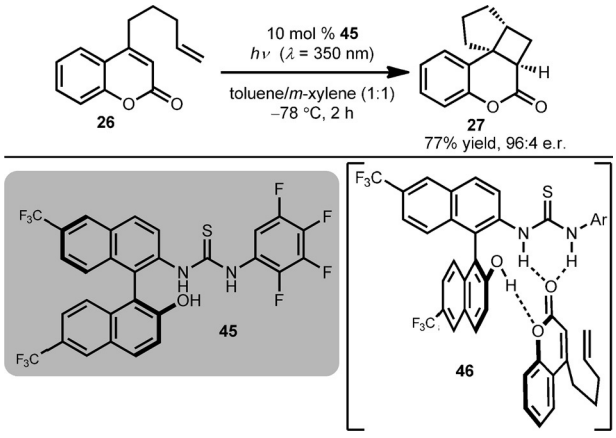


Scheme 6. Lewis acid promoted photochemical [2+2] (Bach et al.).

went cycloadditions with closely related oxazaborolidine **31b** to provide the cyclobutanes **34**–**37** with good levels of enantioselectivity and yield.[21] These intermediates were found to undergo facile acid-catalyzed rearrangement to give interesting polycyclic scaffolds (**38**). In the second example, synthetically useful cyclobutanes (**40**–**43**) were accessed by cycloaddition of 4-pyridones (e.g., **39**).[22] The cyclobutane **43** was used to access the natural product (+)-lupinine (**44**) in only six steps.

Sibi, Sivaguru, and co-workers have recently reported the highly enantioselective cycloaddition of coumarins (e.g., **26**), promoted by the thiourea catalyst **45** (Scheme 7).[23] This catalyst was proposed to operate in a similar manner to that of

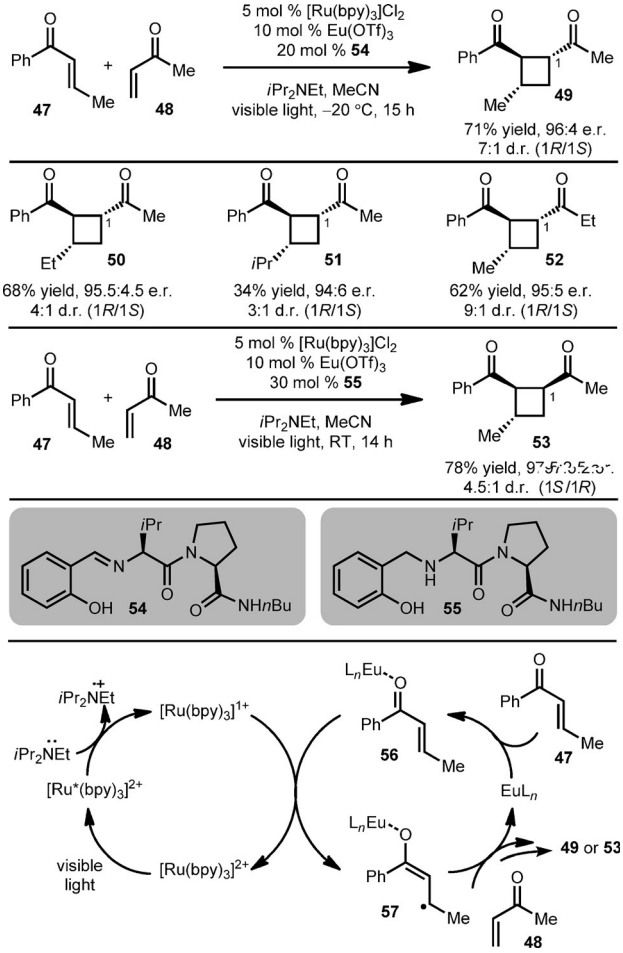


Scheme 7. Photochemical [2+2] (Sibi and Sivaguru et al.).

oxazaborolidine catalysts in that a bathochromatic absorption shift occurs upon substrate binding. It was proposed that the catalyst engages in a dual hydrogen-bonding interaction with the substrate according to the model (**46**) illustrated in Scheme 7.

2.3. Visible-Light Photocatalysis

A new class of photochemical catalytic enantioselective [2+2] cycloadditions was recently reported by Yoon and co-workers (Scheme 8).[24] In early studies, the Yoon group



Scheme 8. Visible-light photocatalysis (Yoon et al.). bpy = 2,2'-bipyridine.

discovered that Lewis acids accelerate visible-light photoinduced, electron-transfer, [2+2] cycloadditions of unsaturated carbonyls.[25] Building upon this precedent, the amino-acid-based chiral ligand **54**, in combination with $Eu(OTf)_3$, was found to impart high enantioselectivities and good diastereoselectivities in the formation of the cyclobutanes **49**–**52**. Notably, with the reduced form of the amino-acid-based catalyst (**55**) a different diastereomer was observed as the major product (**53**) with excellent levels of enantioselectivity. The reactions likely proceeded according to the catalytic cycle illustrated in Scheme 8. Visible-light induced

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excitation of $[Ru(bpy)_3]^{2+}$ likely occurs to generate the photoexcited state $[Ru^*(bpy)_3]^{2+}$. This complex can be reduced with a tertiary amine to form $[Ru(bpy)_3]^{1+}$, which upon subsequent electron transfer with the Lewis acid activated carbonyl (**56**) generates the radical anion **57**. This species then undergoes stepwise [2+2] cycloaddition, with ultimate loss of an electron, to generate the cyclobutane products.

3. Polarized [2+2] Cycloadditions

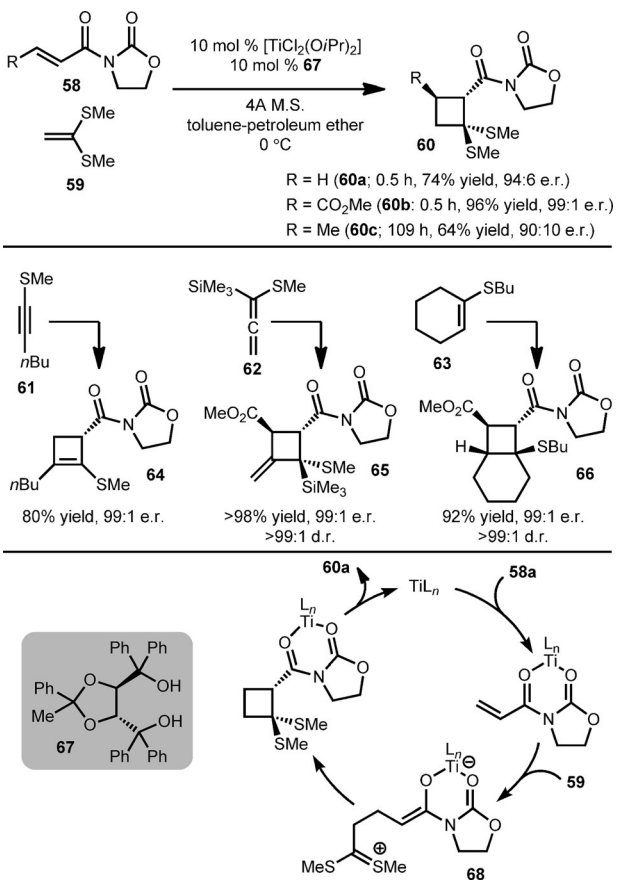
Perhaps the most well investigated approach towards catalytic enantioselective [2+2] cycloadditions involves the use of polarized alkenes. In this approach, a catalyst is employed to either activate the nucleophile towards electrophilic attack or the electrophile towards nucleophilic attack. These systems typically involve stepwise reaction mechanisms which consequently involve the generation of charged intermediates.

3.1. Lewis Acid Catalyzed Reactions

Lewis acid catalyzed enantioselective polarized [2+2] cycloadditions are the most well established examples.[26] Several highly enantioselective variations have been reported and can be further classified by the proposed reaction mechanism, which is closely tied to the identity of Lewis acid and substrate.

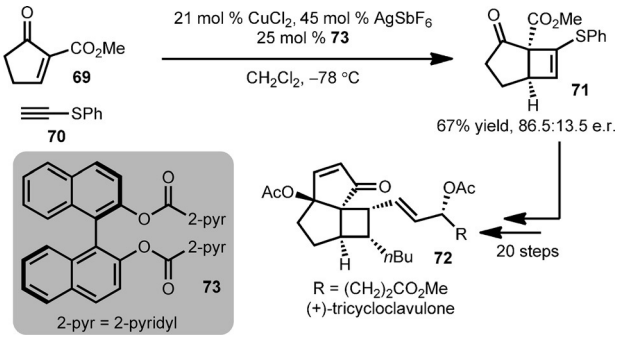
3.1.1. Sigma Lewis Acids: Stepwise Reactions

In 1989, Narasaka and co-workers reported the first method for catalytic enantioselective [2+2] cycloadditions (Scheme 9).[27] The process employed a Ti-TADDOL catalyst [$TiCl_2(OiPr)_2$ + **67**] which allowed reaction of unsaturated oxazolidinones (**58**) and alkenyl (**59**, **63**), allenyl (**62**), and alkynyl sulfides (**61**) with excellent levels of enantioselectivity.[27,28] Either unsubstituted or ester-substituted, unsaturated oxazolidinones were necessary for high levels of reactivity. Reactions with cyclic alkenyl sulfides (**63**) or allenyl sulfides (**62**) are particularly impressive as high levels of diastereoselectivity and enantioselectivity were observed. These reactions were proposed to proceed by a stepwise process with the formation of the dipolar intermediate **68** according to the catalytic cycle illustrated in Scheme 9.[29]



Scheme 9. Lewis acid catalyzed [2+2] cycloadditions (Narasaka et al.). M.S. = molecular sieves.

In efforts towards the total synthesis of (+)-tricycloclavulone (**72**), Iguchi and co-workers developed a catalytic enantioselective [2+2] cycloaddition of the alkynyl sulfide **70** and cyclopentenone derivative **69** (Scheme 10).[30] The chiral ligand **73** in combination of $CuCl_2$ and $AgSbF_6$ was identified to be optimal after more common chiral catalysts (e.g., Ti/TADDOL and Cu/BOX) were found to be ineffective. The substrate scope of this process has not yet been reported. However, subsequent studies utilized this method toward the formal synthesis of (+)-precapnelladiene.[30c]



Scheme 10. Lewis acid catalyzed [2+2] cycloadditions (Iguchi et al.). pyr = pyridine.

The oxazaborolidine catalyst **80** was shown by Corey and co-workers to be effective for the highly enantioselective and diastereoselective [2+2] cycloaddition of a variety of cyclic enol ethers (e.g., **74**) and trifluoroethylacrylate (**75**) (Scheme 11).[31] The product **78** was easily converted into a derivative of the Wieland–Miescher Ketone (**79**). A model that justifies the stereochemical outcome with dihydrofuran is illustrated (**81**).[20]

Ishihara and co-workers disclosed a copper-catalyzed enantioselective cycloaddition of the propiolamide **82** with enol ethers (e.g., **83**; Scheme 12).[32] The products (**84**, **86**) are generated with good levels of enantioselectivity and yield.

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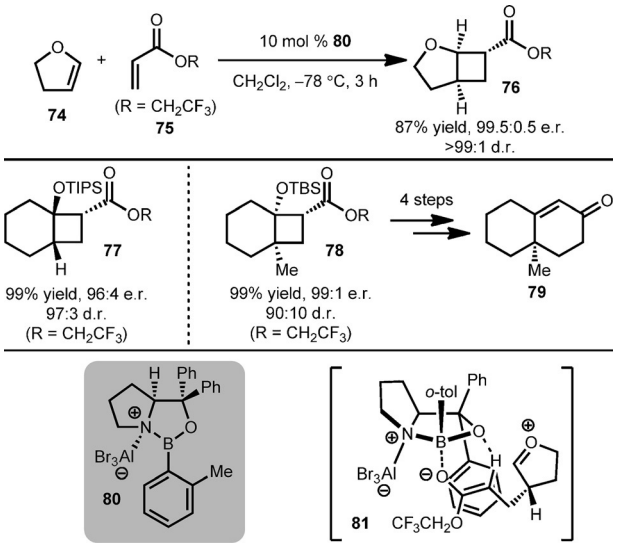
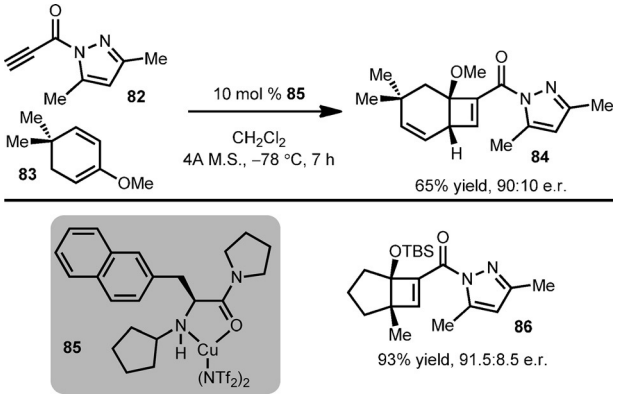
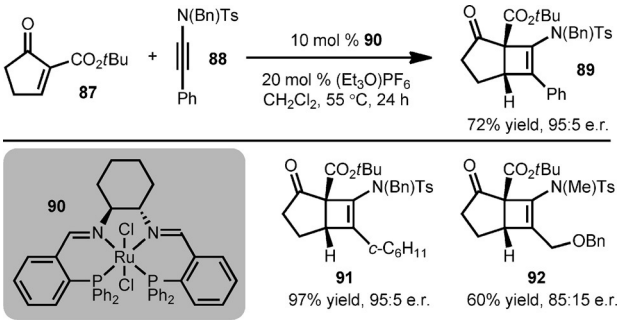


Scheme 11. Lewis acid catalyzed [2+2] cycloadditions (Corey et al.). TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl.



Scheme 12. Lewis acid catalyzed [2+2] cycloadditions (Ishihara et al.). Tf = trifluoromethanesulfonyl.

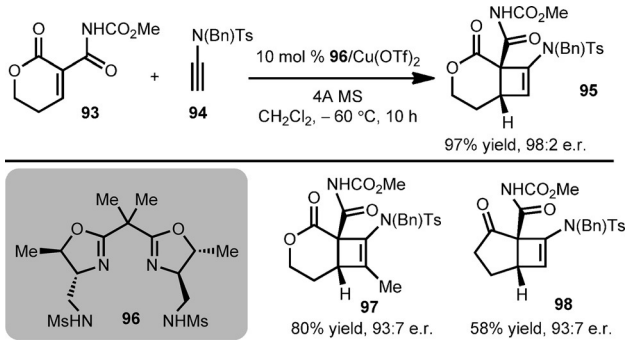


Scheme 13. Lewis acid catalyzed [2+2] cycloadditions (Mezzetti et al.).

Interestingly the reaction with the diene **83** led to exclusive formation of the [2+2] and not the [4+2] cycloadduct.

In 2011, Mezzetti, reported a catalytic enantioselective [2+2] cycloaddition of the cyclopentenone derivative **87** with ynamides (i.e., Ficini Reaction),[33] and it was promoted by the dicationic ruthenium/PNNP complex **90** (Scheme 13).[34] The [3.2.0] products (**89**, **91**, and **92**) were generally formed in good enantioselectivity and yield. Reactions with cyclohexenone derivatives proceeded with much lower levels of enantioselectivity (78.5:21.5 e.r.).

Recently, Nakada reported a related Ficini reaction catalyzed by the ligand **96** in combination with $Cu(OTf)_2$ (Scheme 14).[35,36] A variety of cyclic unsaturated carbonyls

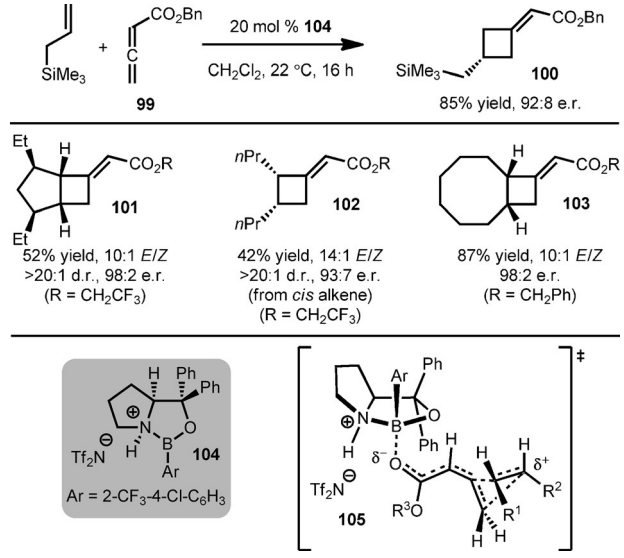


Scheme 14. Lewis acid catalyzed [2+2] cycloadditions (Nakada et al.).

underwent reaction with good levels of enantioselectivity to provide highly substituted cyclobutenes (e.g., **95**, **97**, and **98**). Ynamides substituted with groups other than methyl underwent reaction with reduced levels of enantioselectivity (e.g., cyclohexyl-substituted ynamide, 55:45 e.r.).

3.1.2. Sigma Lewis Acids: Concerted Reactions

The reactions discussed in the preceding section all involve the Lewis acid activation of an unsaturated carbonyl compound and cycloaddition by a stepwise process (Schemes 9–14). The Brown group recently disclosed a catalytic enantioselective [2+2] cycloaddition of allenoates (e.g., **99**) and alkenes that is proposed to proceed by a concerted mechanism (Scheme 15).[37] Since full charges do not likely need to be supported, weakly polarized alkenes (e.g., cyclo-



Scheme 15. Lewis acid catalyzed [2+2] cycloadditions (Brown et al.).

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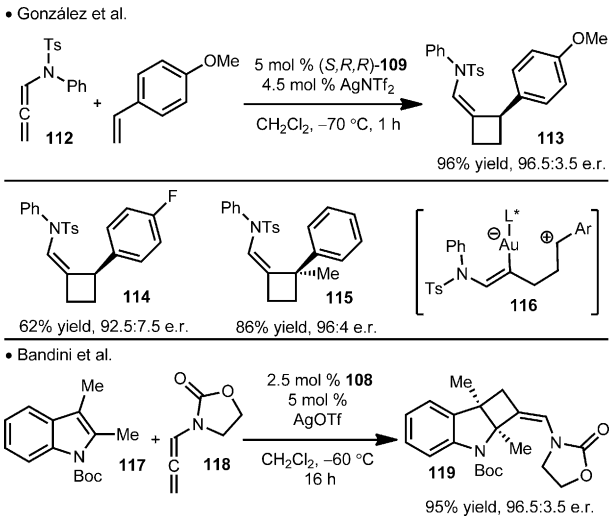
hexene, 1-hexene) can be employed. The oxazaborolidine catalyst **104** was identified to be effective for promoting the cycloaddition of a variety of alkenes. Reactions with substituted allenoates (α or γ) led to formation of the desired product with poor levels of enantioselectivity. The concerted versus stepwise nature of these reactions was probed by the reaction of *cis*- and *trans*-4-octene. In both cases a stereospecific reaction was observed, thus suggesting the reactions are concerted (or involves an ephemeral intermediate). Based on the stereochemical outcome of a reaction a pre-transition-state assembly was proposed (**105**), and is related to the models illustrated in Schemes 5 and 11 for similar catalysts.[20]

3.1.3. π-Philic Lewis Acids

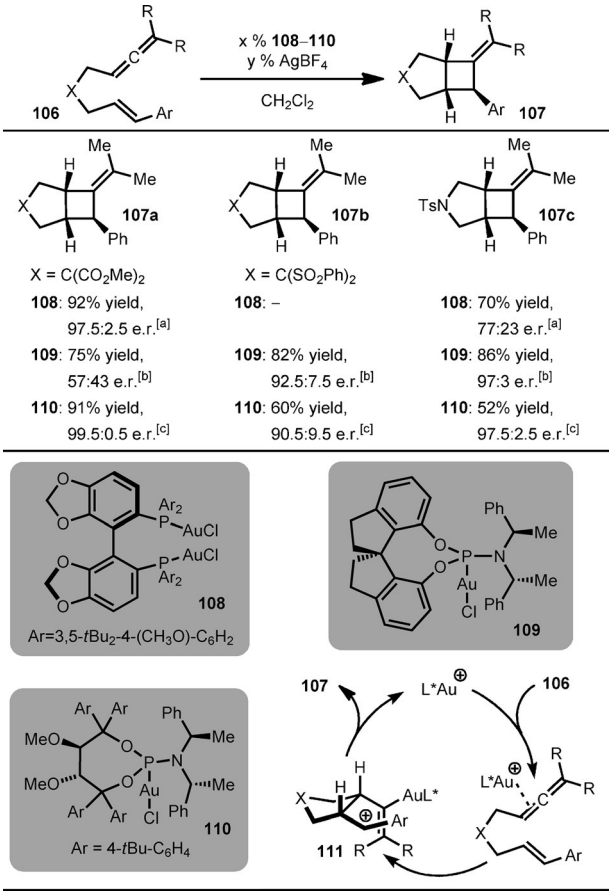
In 2007, Toste and co-workers first reported gold-catalyzed intramolecular [2+2] cycloadditions of allenenes (e.g., **106**; Scheme 16).[38,39b] This method is applicable for the cycloaddition of styrenyl alkenes and trisubstituted allenes. The requirement of styrenyl alkenes is largely due to the stepwise nature of this process, which involves the carbocation intermediate **111**. By using the dinuclear gold-bis(arylphosphine) complex **108**, the cycloadducts are generated in excellent enantioselectivities and yields. Subsequent studies showed the gold-phosphoramidite complexes **109** and **110** to provide superior levels of enantioselectivity. Two series of complexes were identified to be optimal. Toste and co-workers advanced **109**[39a] and efforts by Fürstner and co-workers led to the disclosure of **110**.[40]

In late 2012, González and co-workers reported the gold-catalyzed enantioselective intermolecular [2+2] cycloaddition between the allenamide **112** and a variety of styrenes (Scheme 17).[41] To achieve broad substrate scope with high



Scheme 17. Gold-catalyzed [2+2] cycloadditions (González et al. and Bandini et al.). Boc = *tert*-butoxycarbonyl.

enantioselectivity, a family of phosphoramidite ligands was employed (**109** is representative). The reaction was compatible with electron-rich or moderately deactivated styrene derivatives. Notably, the formation of quaternary carbon centers proceeded with excellent levels of enantioselectivity (**115**). In a related method, Bandini demonstrated that the allenamide **118** and 2,3-disubstituted indoles (e.g., **117**) could undergo a [2+2] cycloaddition promoted by **108** (Scheme 17).[42] Similar to the gold-catalyzed processes described previously (Scheme 16) the reactions with allenamides are proposed to be stepwise and involve the formation of a cationic intermediate (e.g., **116**).



Scheme 16. Gold-catalyzed [2+2] cycloadditions (Toste et al. and Fürstner et al.). Conditions: [a] 3 mol% **108**, 6 mol% $AgBF_4$, RT. [b] 5 mol% **109**, 5 mol% $AgBF_4$, 25 °C. [c] 5.5 mol% **110**, 6 mol% $AgBF_4$, 0 °C.

3.2. Amine-Catalyzed Reactions

Transformations of this type proceed through initial condensation of the chiral amine component with an aldehyde. The resulting activated iminium/enamine can then be trapped with a variety of alkene partners to achieve a range of substituted cyclobutane rings. Hydrolysis of the imine intermediate releases the catalyst to continue the cycle.

3.2.1. Iminium Catalysis

Ishihara, Nakano et al. reported an organocatalytic enantioselective [2+2] cycloaddition of α-acyloxyacroleins (e.g., **121**) and alkenes to obtain cyclobutanes such as **122**

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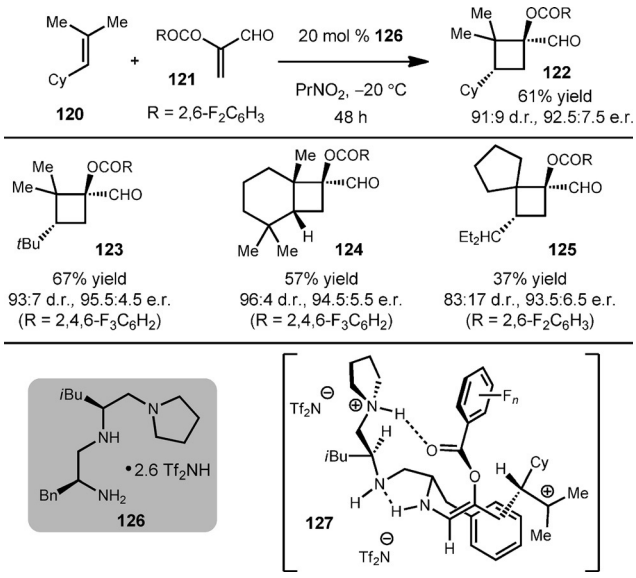
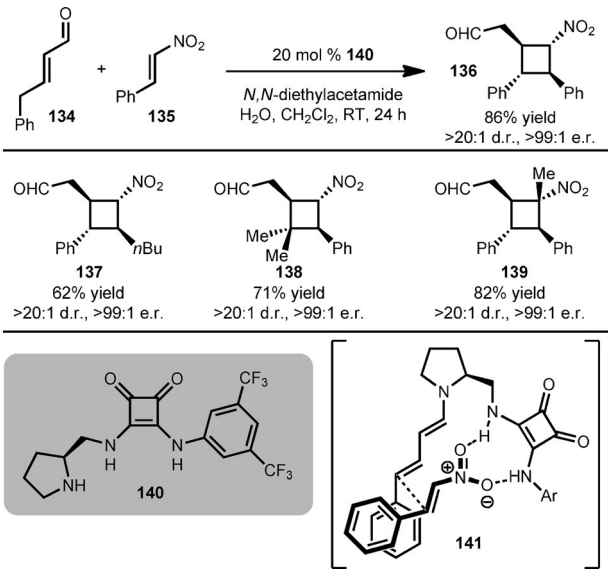


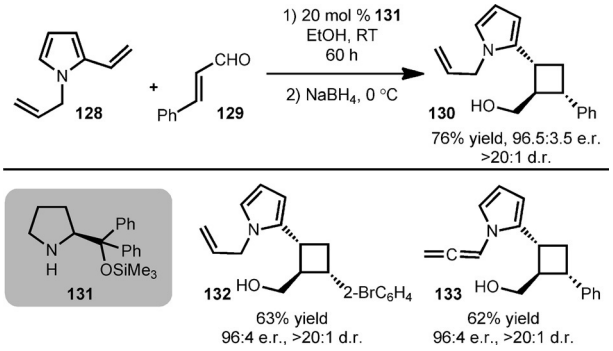
Scheme 18. Amine-catalyzed [2+2] cycloadditions (Ishihara et al.).



Scheme 20. Amine-catalyzed [2+2] cycloadditions (Jørgensen et al.).

(Scheme 18).[43] It is notable that this method allowed for the cycloaddition of relatively unactivated alkenes and that the products contain vicinal quaternary centers. A model (**127**) that rationalizes the stereochemical outcome is illustrated in Scheme 18.

More recently, a versatile synthesis of pyrrole-substituted cyclobutane rings was reported by Xu and co-workers (Scheme 19).[44] The catalyst **131** was found to readily



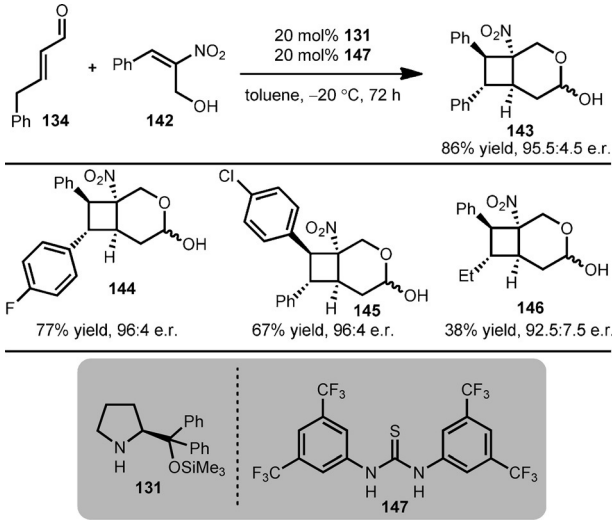
Scheme 19. Amine-catalyzed [2+2] cycloadditions (Xu et al.).

promote the [2+2] cycloaddition of cinnamaldehyde derivatives (e.g., **129**) with a variety of substituted pyrroles (e.g., **128**). It should be noted that the [2+2] cycloaddition proceeded with complete control of diastereoselectivity.

3.2.2. Enamine Catalysis

Jørgensen[45] and Vicario[46] have independently reported the [2+2] cycloaddition of nitroolefins (e.g., **135**) and enolizable α,β-unsaturated aldehydes (e.g., **134**; Scheme 20).[47] Through use of the bifunctional squaramide catalyst **140**, Jørgensen and co-workers were able to generate the fully substituted cyclobutane products **136–139** with excellent diastereo- and enantioselectivity.[45] Computational evaluation of the reaction mechanism supports the proposed bifunctional nature of the catalyst (**141**).

In a complementary approach, Vicario and co-workers employed two catalysts (**131** and **147**) operating synergistically to achieve the cycloaddition (Scheme 21).[46] The gen-



Scheme 21. Amine-catalyzed [2+2] cycloadditions (Vicario et al.).

erated lactols **143–146** were formed as 1:1 mixtures of the α- and β-anomers, with complete control of diastereoselectivity at all other stereogenic centers. These reactions were proposed to operate by addition of a dienamine intermediate to a thiourea-activated nitroalkene.

The synthesis of chiral spiro-cyclobutyl oxindoles has been achieved through the cycloaddition of **148** and **134** catalyzed by the bifunctional α,α-diphenylprolinol catalyst **150** (Scheme 22).[48] The process functions well to yield the

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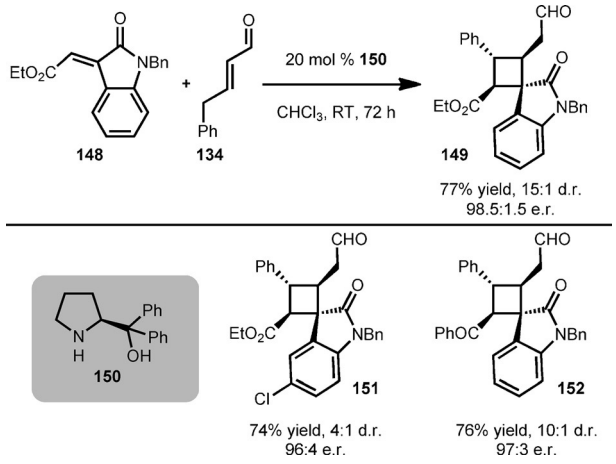
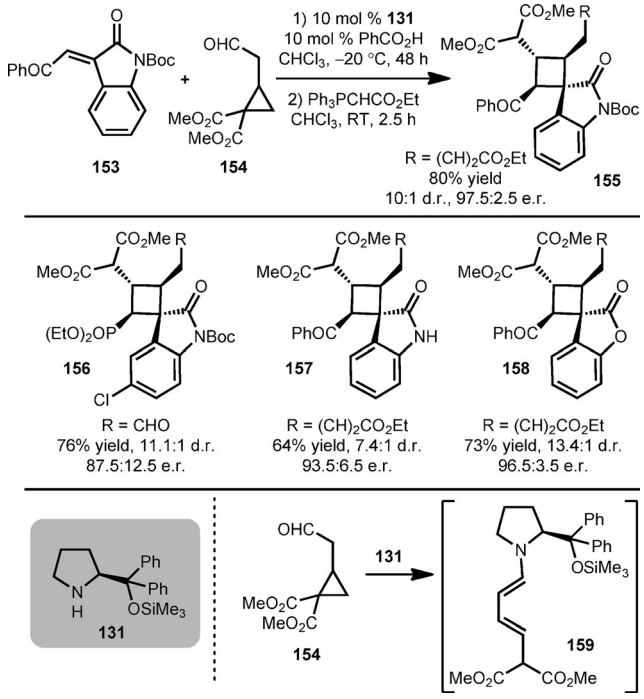


Scheme 22. Amine-catalyzed [2+2] cycloadditions (Wang et al.).



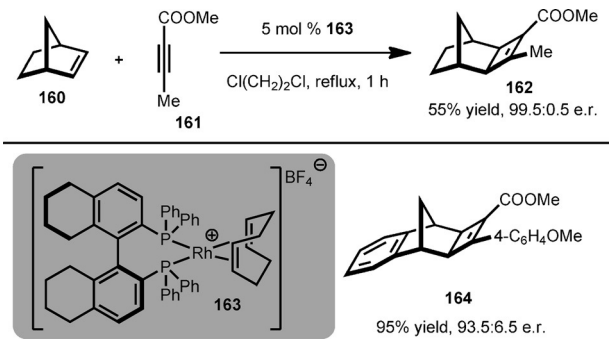
Scheme 23. Amine-catalyzed [2+2] cycloadditions (Jørgensen et al.). TMS = trimethylsilyl.

cyclobutane products **149**, **151**, and **152**, having four contiguous stereocenters (one being quaternary).

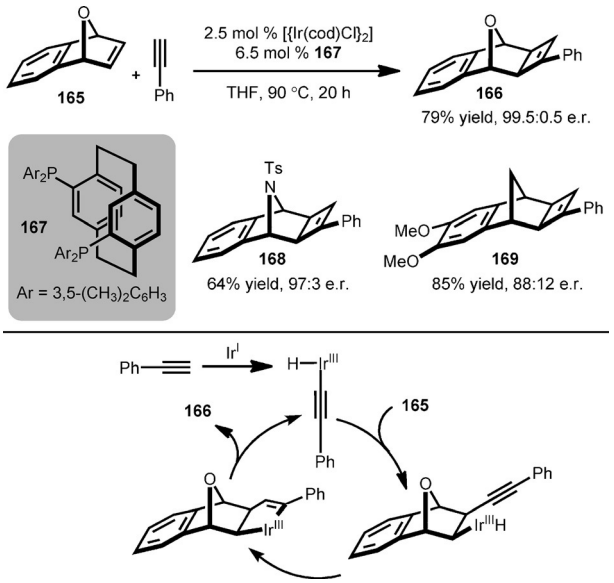
Very recently, Jørgensen and co-workers reported a strategy to access the spiro-cyclobutyl oxindole core (Scheme 23).[49] It was demonstrated that treatment of the β-cyclopropyl aldehyde **154** with **153** in the presence of **131** and $PhCO_2H$ led to formation of the highly substituted cyclobutane **155**. These reactions were proposed to proceed by catalyst-induced fragmentation of **154** to provide the dienamine **159**.

4. Transition Metal Catalyzed Reactions

In 2006, Shibata and co-workers reported the catalytic enantioselective cycloaddition of norbornene derivatives (e.g., **160**) with alkynyl esters (e.g., **161**), a reaction promoted by the rhodium complex **163** (Scheme 24).[50] This method



Scheme 24. Rhodium-catalyzed [2+2] cycloadditions (Shibata et al.).



Scheme 25. Iridium-catalyzed [2+2] cycloadditions (Shao and Fan et al.). cod = 1,5-cyclooctadiene.

generated tri- and tetracyclic cyclobutenes in good enantioselectivity and yield.

Subsequently, Shao and co-workers demonstrated the iridium-catalyzed enantioselective [2+2] cycloaddition of bicyclic alkenes and terminal alkynes with good to excellent levels of enantioselectivity (Scheme 25).[51] Kinetic resolution of racemic bicyclic alkenes has also been demonstrated.[52a] On the basis of mechanism studies, carried out by Fan and co-workers, it was proposed that oxidative addition of iridium occurs to generate a [hydrido(acetylene)iridium(III)] complex.[52b] Migratory insertion followed by reinsertion and reductive elimination provides **166**.

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5. Conclusions and Future Perspectives

As evidenced in the preceding sections, many discrete variants of catalytic enantioselective [2+2] cycloadditions have been established. The development of photochemical catalytic enantioselective [2+2] cycloadditions has broken barriers to what may have been considered unattainable methods resulting from difficulties with controlling high-energy and/or excited-state intermediates. Polarized [2+2] cycloadditions were initially established and demonstrated to be useful with highly electron-rich and/or electron-poor π components. Recently, efforts have been focused on extending the scope of these processes to other interesting classes of substrates, especially with weakly polarized alkenes. In the arena of transition metal catalyzed reactions, exciting reports of [2+2] cycloadditions have emerged. Despite all of these efforts, there are many useful [2+2] cycloadditions which do not have an enantioselective variant; for example, several of the known transition metal catalyzed processes,[53] as well as the venerable ketene–alkene [2+2] cycloaddition.[54,55] In addition, the utility of these methods has only rarely been demonstrated in the synthesis of complex molecules.[22,30] Continued efforts in these areas will undoubtedly lead to fundamentally new methods and an increase in the scope and practicality of existing strategies.

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