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Asymmetric [3 + *n*]-Cycloaddition Reactions of Donor-Acceptor Cyclopropanes

Ming Bao[a] and Michael P. Doyle*[a]

[3 + *n*]-Cycloaddition reactions that employ donor-acceptor cyclopropanes using either chiral catalysts and racemic cyclopropanes or achiral catalysts and chiral, non-racemic, cyclopropanes have become useful transformations for the construction of carbocyclic and heterocyclic compounds, with both processes offering mechanistic and structural advantages in ring formation. Although the vast majority of asymmetric cycloaddition reactions of donor-acceptor cyclopropanes have been performed with racemic cyclopropane compounds catalyzed by Lewis acids with chiral ligands, optically active cyclopropane compounds can serve the same role using Lewis acids without chiral ligands. This review covers the use of chiral catalysts with racemic donor-acceptor cyclopropanes and the use of chiral non-racemic donor-acceptor cyclopropanes with achiral Lewis acid catalysts.

1. Introduction

Donor-acceptor cyclopropanes are useful synthons for the incorporation of three carbon units to form more complex structures, especially through [3 + *n*]-cycloaddition reactions. Arising from the recognition of strain energy within the cyclopropane ring, initial investigations focused on nucleophilic substitution with accompanying stabilization of the carbanion product[1,2] or by electrophilic ring opening and accompanying reactions with nucleophiles[3,4] (Scheme 1a). Realization that acceptor and donor functional groups on adjacent carbon atoms lowered the energy for bond cleavage increased the potential of this synthetic methodology for chemical syntheses (Scheme 1b).[5–7] The donor and acceptor units activate the connected carbon-carbon bond for ring cleavage, but even with these activating groups further enhancement is required to effect nucleophilic attack at the electrophilic center. Lewis acid catalysts provide that further enhancement which allows these annulation reactions to occur effectively and efficiently under moderate conditions.

From the beginning of cycloaddition reactions using cyclopropanes, their 1,1-carboxylate esters have played a key role.[8] The stabilization afforded the malonate anion has been advantageous in nucleophilic substitution reactions, and aryl/vinyl or heteratom, especially oxygen, stabilization of carbocations have provided enhancement in electrophilic reactions. Together, they have made possible extensive uses of donor-acceptor cyclopropanes as three carbon surrogates in organic syntheses, as indicated by the extent of recent authoritative reviews of their applications.[9–17]

To mention but a few examples, cycloaddition reactions of donor-acceptor cyclopropanes have been reported with nitrones (Scheme 2a),[8,18] nitrile amines (Scheme 2b),[19] nitriles (Scheme 2c),[20,21] aldehydes (Scheme 2d),[22] and with vinyl azides (Scheme 2e).[23] Each of these reactions are catalyzed by a Lewis acid on 1,1-dicarboxylate esters, and association with the ester carbonyl oxygens can be monodentate or bidentate, generally unspecified, with bidendate coordination offering the highest degree of stabilization for ring opening. The reaction temperature depends on the degree of activation of the donor-acceptor cyclopropane for ring opening by the Lewis acid catalyst. Polar solvents that can stabilize charged intermediates were initially favored for cycloaddition reactions, but some of these solvents lower the rate of reaction because of their coordination with the Lewis acid catalyst. Dichloromethane is most used currently.

Cycloaddition reactions of donor-acceptor cyclopropanes occur via two possible mechanistic pathways: stepwise and concerted.[8,10,24,25] In the stepwise reaction, the nucleophile reacts with the electrophilic center in the ring opened species (Scheme 3a) or undergoes S_N2 substitution on the activated cyclopropane to effect ring opening (Scheme 3b) with subsequent attachment to the dipolar adduct. In the concerted reaction, bond-making and bond-breaking occur simultaneously but not necessarily to the same degree (Scheme 3c). The high degree of diastereoselectivity observed in early studies could be interpreted as due to either stepwise or concerted reactions, but low diastereocontrol could only be due to the stepwise pathway. In the stepwise process enantiocontrol is the measure of whether reaction occurred with the ring opened species (racemic product from chiral non-racemic cyclopropane) or by S_N2 substitution on the activated cyclopropane, but high diastereocontrol could result from either a stepwise pathway (bond rotation is slow relative to ring closure) or a concerted reaction. In this review we focus on stereocontrol in cycloaddition transformations that occur with donor-acceptor cyclopropanes. Two approaches have been undertaken: the use of chiral catalysts with racemic donor-acceptor cyclopropanes and the use of chiral non-racemic donor-acceptor cyclopropanes with non-chiral Lewis acid catalysts.

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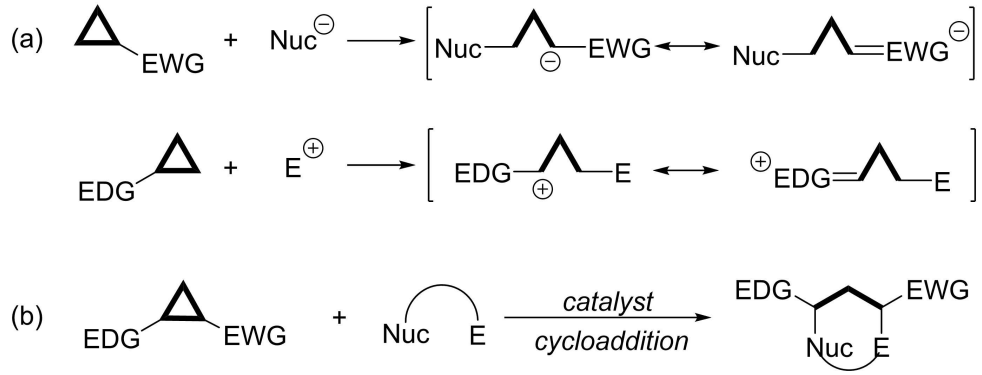

Scheme 1. Strategies for ring-opening of substituted cyclopropanes.

2. Cycloaddition reactions of racemic donor-acceptor cyclopropanes using chiral catalysts

2.1. [3+2]-Cycloaddition reactions

In the past decade, reports of enantioselective cycloadditions of donor-acceptor cyclopropanes have sharply increased due to catalysis by an increasing array of metal-complexes with chiral ligands (Figure 1). Among them, [3+2]-cycloadditions of donor-acceptor cyclopropanes with dipolarophiles provide rapid access to highly functionalized five-membered-ring systems. In 2010, Johnson's group developed an enantioselective synthesis of 2,5-cis-disubstituted pyrrolidines **3** through a dynamic kinetic asymmetric [3+2] annulation of racemic cyclopropanes **1** and (*E*)-aldimines **2** with catalysis by MgI_2 and Pybox ligand **L1** (Scheme 4).[26] Dynamic kinetic resolution occurs if racemization can occur concurrently with kinetic resolution, so that theoretically 100% of the racemic mixture can be converted to one enantiomer, and this laboratory provided the first evidence of this process. Careful selection of the substituted *N*-benzyl protecting group of the aldimine allowed for an increase in enantioselectivity as well as selective deprotection of the pyrrolidine cycloadduct in the presence of other electron-rich benzyl substituents. Mechanistic studies and stereochemical observations suggested that the aldimine dipolarophiles react through the *E* geometry *via* the unusual diaxial transition state **4**.

In 2016, You's group reported a highly enantioselective dearomative [3+2]-cycloaddition reaction of benzothiazoles **5** with cyclopropane-1,1-dicarboxylates **1**. In the presence of a Pybox(**L2**)-MgI_2 catalyst, the cycloaddition reaction afforded a series of hydropyrrolo[2,1-*b*]thiazole compounds **6** with excellent enantiocontrol (up to 97%*ee*) and yields (up to 97%) (Scheme 5).[27] The reaction is general for both cyclopropanes and benzothiazoles. In addition, a highly efficient kinetic resolution of 2-substituted cyclopropane-1,1-dicarboxylates was realized, thus providing a facile way to access both enantiomers of hydropyrrolo[2,1-*b*]thiazole compounds. Recently, the same group developed an enantioselective dearomative [3+2]-cycloaddition reactions of benzazoles with aminocyclopropanes via kinetic resolution. In the presence of a copper complex, derived from $Cu(OTf)_2$ and bisoxazoline, a series of hydropyrrolo-benzazole derivatives containing quaternary stereogenic centers were obtained in high yields (up to 99%) with excellent enantioselectivity (up to 99%*ee*).[28]

Different from the chiral Lewis acid catalysis, in 2022 Lu and coworkers disclosed a phosphine-catalyzed (**P**, Figure 1) highly enantioselective and diastereoselective [3+2] annulation between vinylcyclopropanes **7** and *N*-tosylaldimines **8** under mild reaction conditions, which allows for facile access to a range of highly functionalized chiral pyrrolidines **9** (Scheme 6).[29] The reaction is initiated with nucleophilic attack of the phosphine on the electron-poor double bond to generate a stabilized anion, which subsequently opened the cyclopropane ring to form zwitterionic intermediate **10**, followed by annulation with *N*-tosylaldimines for the synthesis of the pyrrolidine derivatives. Notably, this method makes use of the vinylcyclopropane as a synthon for phosphine-mediated asymmetric annulation reaction, which offers new

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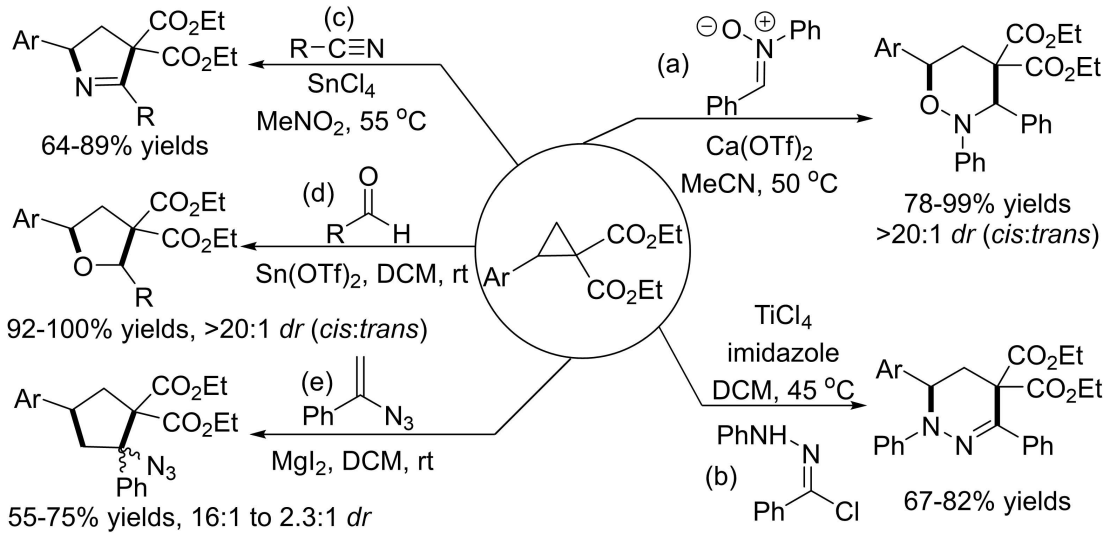
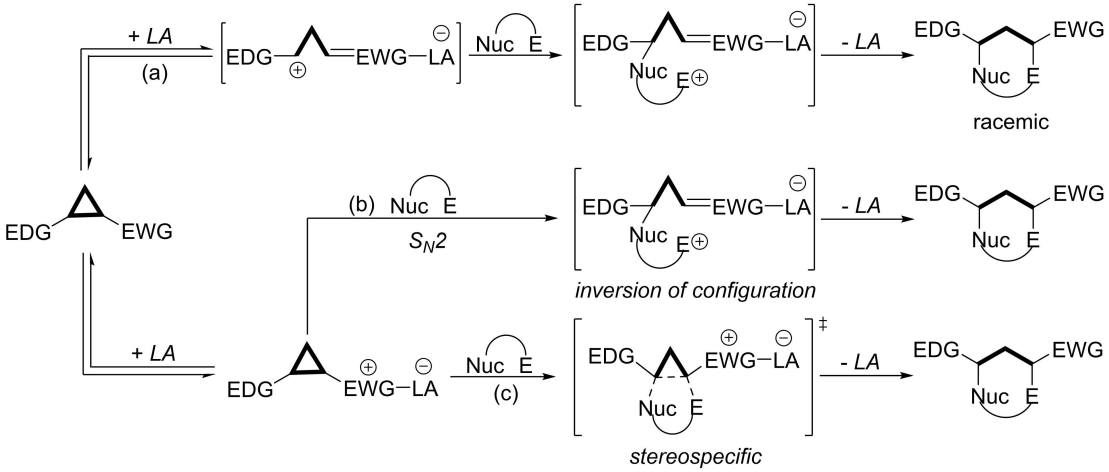
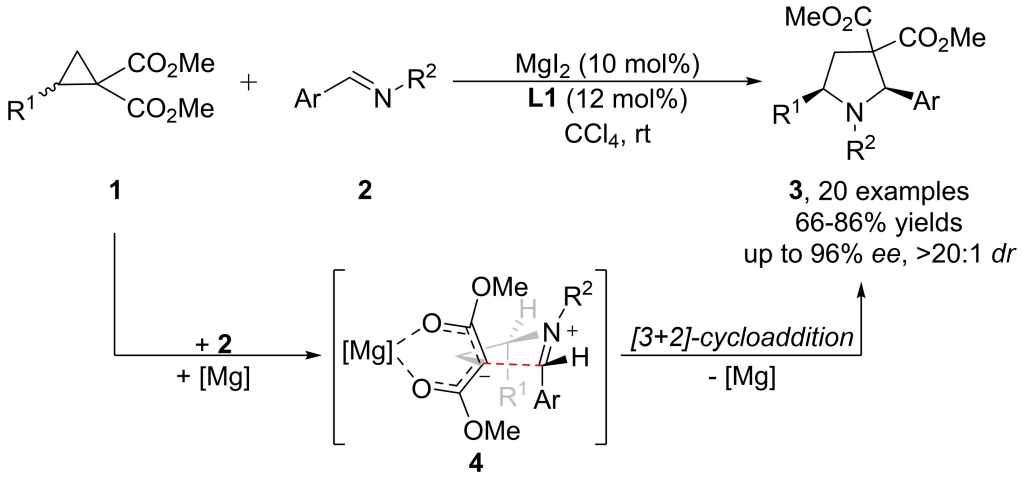


Scheme 2. Cycloaddition reactions of donor-acceptor cyclopropanes.



Scheme 3. Mechanistic pathways of cycloaddition reactions of donor-acceptor cyclopropanes.



Scheme 4. Mg(II)/trisoxazoline catalysis for the synthesis of chiral substituted pyrrolidines.

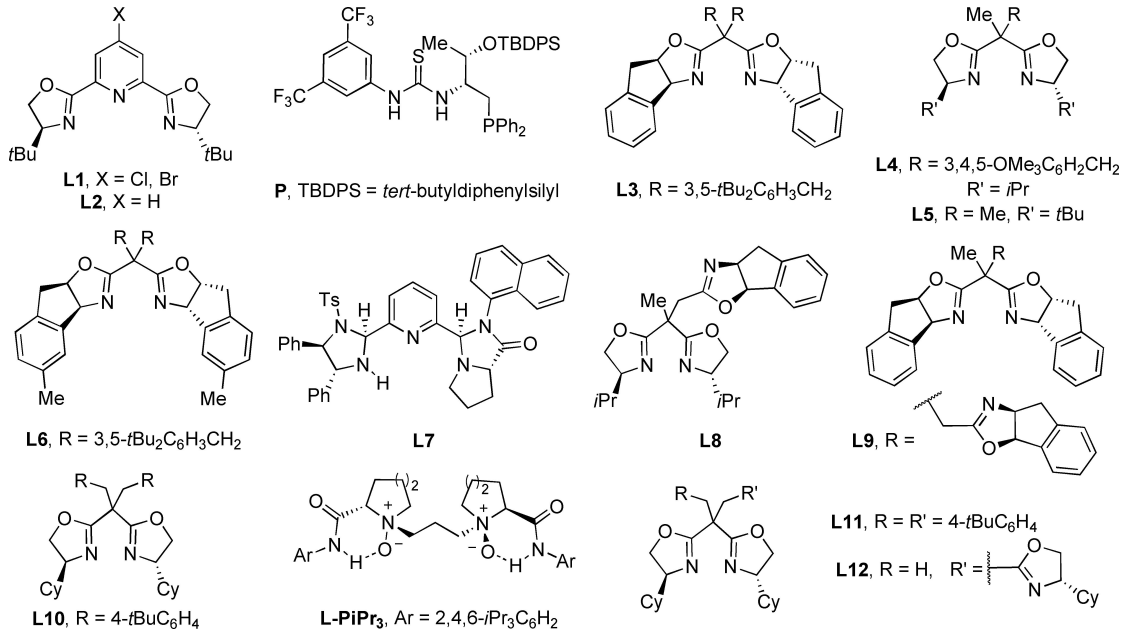
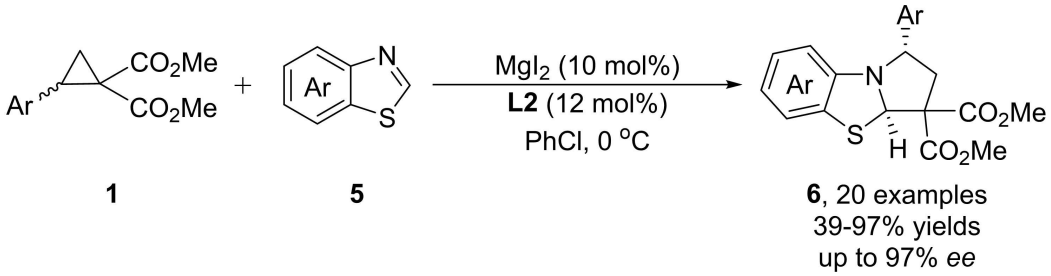
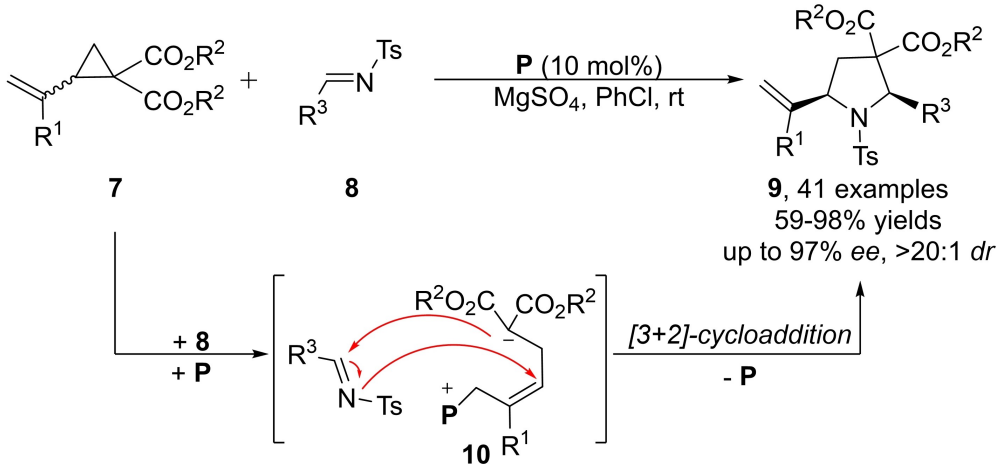


Figure 1. Structures of generally used chiral ligands and catalysts.



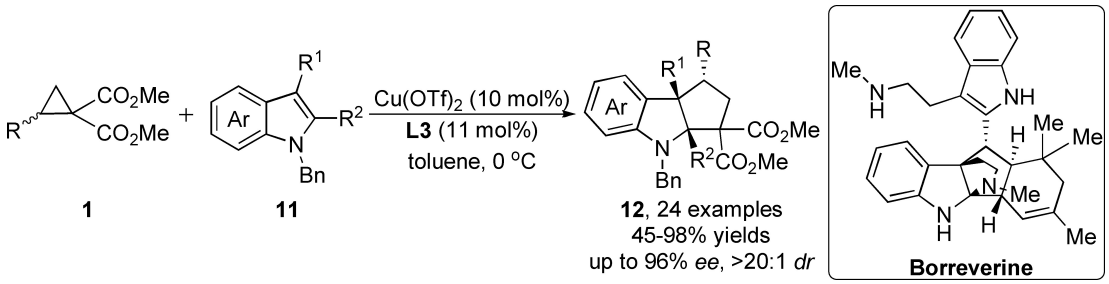
Scheme 5. Mg(II)/trisoxazoline catalysis for the synthesis of chiral hydropyrrolo[2,1-*b*]thiazoles.



Scheme 6. Phosphine catalysis for the synthesis of chiral pyrrolidines.

opportunities for potential applications of cyclopropane substrates in phosphine-catalyzed organic transformations.

In 2013 Tang's group developed for the first time a highly diastereo- and enantioselective bisoxazoline **L3**/Cu(II)-catalyzed C2,C3-cyclopentannulation of indoles **11** with donor-acceptor cyclopropanes **1** representing an asymmetric formal [3+2]-cycloaddition of indoles with racemic cyclopropanes (Scheme 7).[30] This reaction provides rapid and facile access to a series of enantioenriched



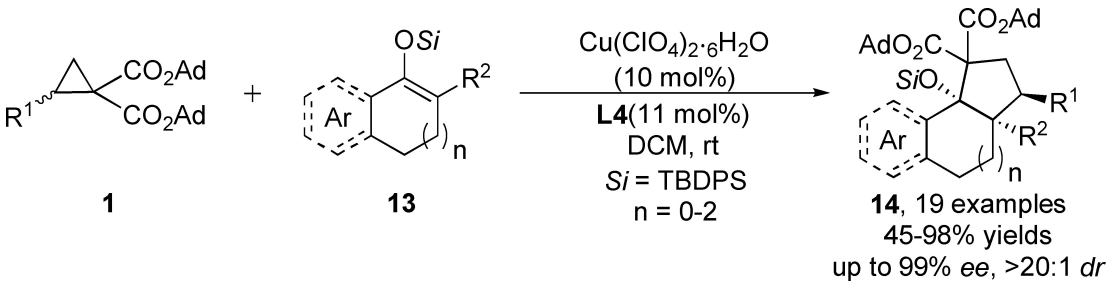
Scheme 7. Cu(II)/bisoxazoline catalysis for the synthesis of chiral cyclopenta-fused indolines.

cyclopenta-fused indoline products **12** and was be further extended to the construction of tetracyclic pyrroloindoline compounds, which is the core structure of Borreverine. Very recently, Guo and co-workers reported a catalytic asymmetric dearomative [3+2] annulation of indoles with donor-acceptor aminocyclopropanes using the rational design of C_1-symmetric bifunctional tridentate imidazoline-pyrroloimidazolone pyridine ligand with $Ni(OTf)_2$ complex, delivering tricyclic indolines containing cyclopentamine moieties in good chemoselectivities, high diastereoselectivities, and excellent enantioselectivities.[31]

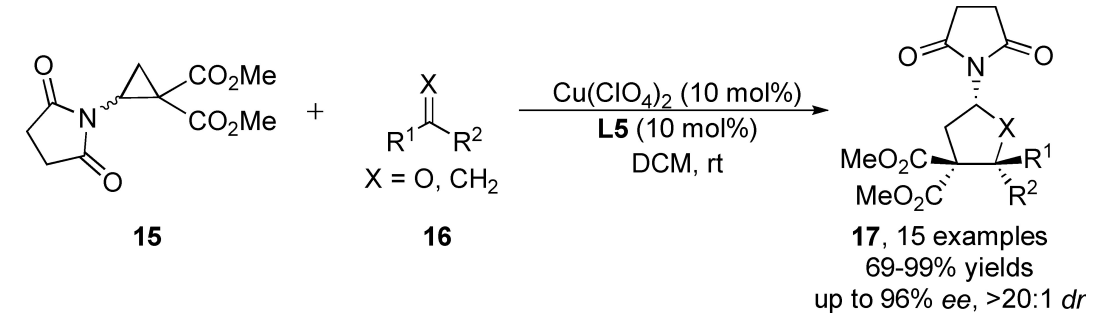
At the same time, Tang and co-workers realized the first examples of formal [3+2]-cycloaddition of cyclic enol silyl ethers **13** with donor-acceptor cyclopropanes **1** providing high diastereo- and enantioselectivity using modified copper(II)/bisoxazoline **L4** catalysts. This methodology offers efficient, new, and facile access to a range of 3*a*-hydroxy [*n*.3.0]carbobicycles **14** (Scheme 8).[32] Moreover, this reaction works well with five- to seven-membered cyclicketone-derived enol silyl ethers, and can be further extended to α,β-unsaturated- and benzocyclicketone-derived substrates.

In 2014, the Waser group reported the first example of a dynamic kinetic asymmetric [3+2] annulation reaction of amidocyclopropanes **15** with both enol ethers and aldehydes **16** (Scheme 9).[33] Using catalysis by a Cu-complex with commercially available bisoxazoline ligand **L5**, cyclopentyl- and tetrahydrofurylamines **17** were obtained in 69–99% yield and up to a 96% *ee* using the same reaction conditions. The method gives access to important enantio-enriched nitrogen building blocks for the synthesis of bioactive compounds.

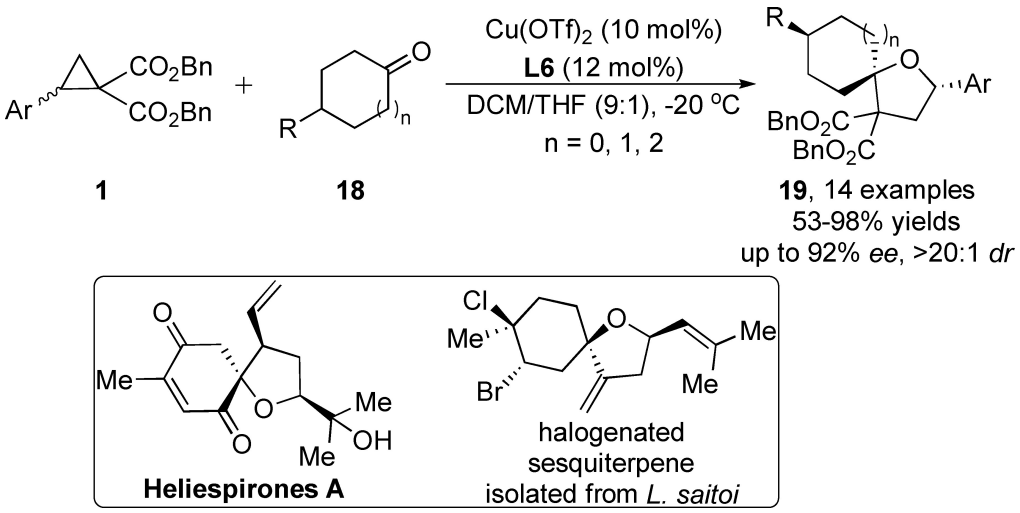
Recently, a copper catalyzed enantioselective [3+2] annulation of donor-acceptor cyclopropanes **1** with cyclic ketones **18** has been developed by Tang's group, providing a concise protocol to enantioenriched 1-oxaspiro[4.5]decanes **19** in up to 98% yield with up to >20:1 *dr* and up to 92% *ee* (Scheme 10).[34] In addition, this method also offers facile access to the enantioselective desymmetrization of various 4-substituted cyclohexanones. Furthermore, the resulting products were easily converted to the core structures of two natural



Scheme 8. Cu(II)/bisoxazoline catalysis for the synthesis of chiral 3*a*-hydroxy [*n*.3.0]carbobicycles.



Scheme 9. Cu(II)/bisoxazoline catalysis for the synthesis of chiral cyclopentylamines and tetrahydrofurylamines.



Scheme 10. Cu(II)/bisoxazoline catalysis for the synthesis of chiral 1-oxaspiro[4.5]decanes.

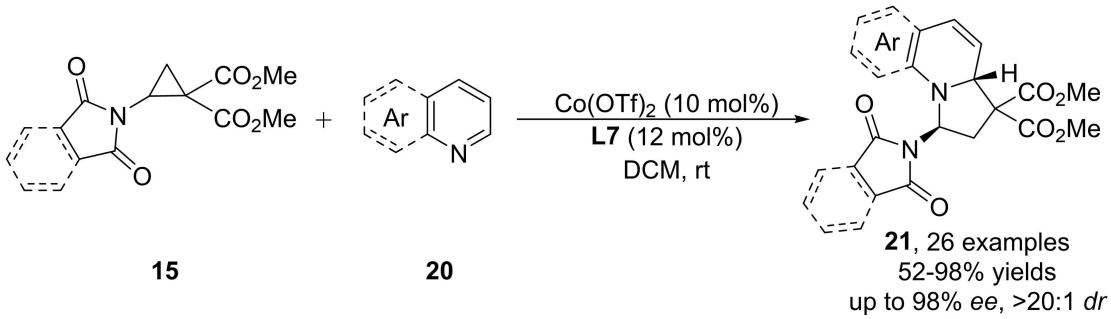
products Heliespirones A and halogenated sesquiterpene isolated from *L. saitoi*.

Very recently, a highly enantioselective dearomative [3+2] annulation of quinolines, isoquinolines, and pyridines **20** with donor-acceptor aminocyclopropanes was achieved by Guo's group. With C_1-symmetric imidazoline-pyrroloimidazolone pyridine **L7** as the tridentate ligand which acted as a bifunctional chiral ligand and $Co(OTf)_2$ as the Lewis acid, diverse chiral indolizidine and benzo-fused indolizidine derivatives **21** were obtained in good yields (up to 98% yield), excellent diastereoselectivities (>20:1 *dr*), and excellent enantioselectivities (up to 98% *ee*) (Scheme 11).[35]

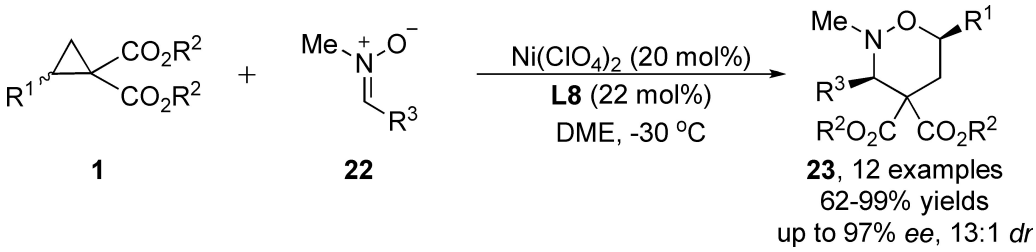
2.2. [3+3]-Cycloaddition reactions

Tetrahydro-1,2-oxazines[36] have potential as therapeutic agents[37] and as chiral building blocks,[38] and their substructure is part of bioactive natural products.[39] Young and Kerr reported the $Yb(OTf)_3$-mediated addition of nitrones, resulting in the formation of racemic tetrahydro-1,2-oxazine products.[40] In 2005, Sibi and co-workers described the first examples of Lewis acid catalysis with a chiral bisoxazoline ligand in the formation of tetrahydro-1,2-oxazines with very high enantioselectivity.[41]

To improve the efficiency and selectivity of the bisoxazoline ligands in specific reactions, Tang's group recently introduced a sidearm strategy for chiral bis-oxazolines which allows modification of the chiral ligands in a three-dimensional manner. This strategy has been successfully applied to several types of reactions. In 2007, they reported that the trisoxazoline (TOX) **L8** with nickel(II) perchlorate catalyzed the [3+3]-cycloaddition of racemic 2-substituted cyclopropane-1,1-dicarboxylates **1** with nitrones **22** to provide easy access to optically active tetrahydro-1,2-oxazine derivatives **23** with high diastereo- and enantioselectivity (Scheme 12).[42] Furthermore, this reaction can be employed for the kinetic resolution of 2-substituted cyclopropane-1,1-dicarboxylates **1** to furnish cyclopropane enantiomers with excellent *ee* values. Later in 2013, the same group developed a highly enantioselective asymmetric [3+3]-cycloaddition of donor-acceptor-substituted cyclopropane diesters **1** with aromatic azomethine imines **24** catalyzed by the same chiral ligated catalysts, which provided a variety of 6,6,6-tricyclic dihydroisoquinoline derivatives **25** in up to 99% yields with excellent diastereo- and enantioselectivities (up to 98% *ee* and >20:1 *dr*) (Scheme 13).[43]



Scheme 11. Co(II)/bisoxazoline catalysis for the synthesis of chiral indolizidine and benzo-fused indolizidines.



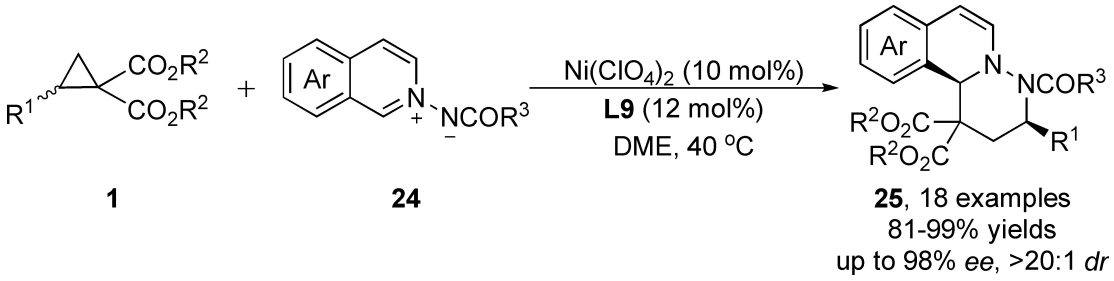
Scheme 12. Ni(II)/trisoxazoline catalysis for the synthesis of chiral tetrahydro-1,2-oxazines.

Two years later, a one-pot catalytic system for the asymmetric synthesis of 1,2,3,4-tetrahydrocarbazoles *via* an enantioselective [3+3] annulation of 2-alkynyl indoles **26** with donor-acceptor cyclopropanes **1** was developed by the Tang's group. In the presence of Lewis acids with chiral bisoxazoline ligand **L10** as catalysts, a series of chiral tetrahydrocarbazoles **27** were furnished in high yields (up to 87%) with good to excellent levels of enantioselectivity (up to 99%*ee*). The reaction proceeds through a nucleophilic addition/ring-opening process to obtain the chiral intermediate **28**, followed by the catalytic Conia-ene cyclization *via* the alkynyl group to form the tetrahydrocarbazole derivatives (Scheme 14).[44]

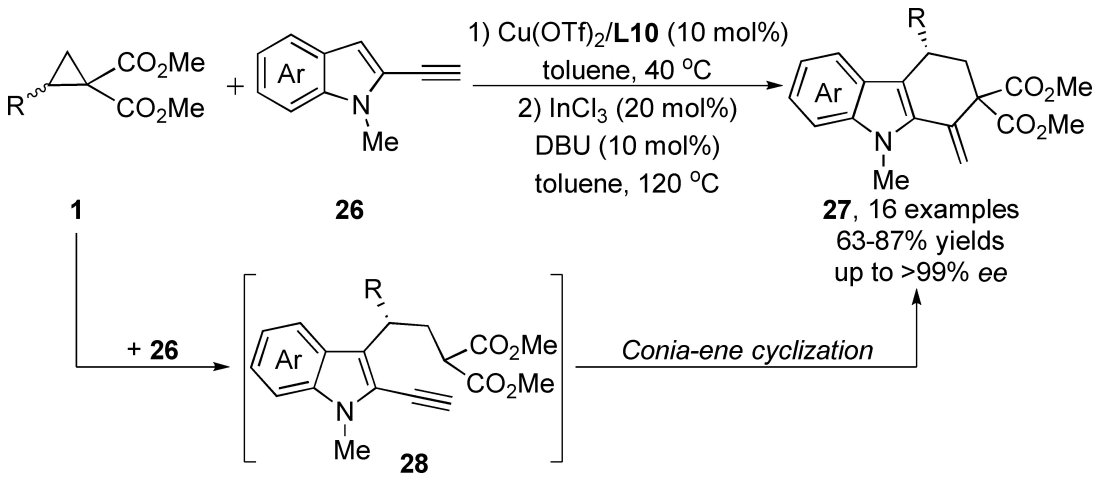
In addition to catalysis by Lewis acids with chiral bisoxazolines, Feng and co-workers reported in 2016 a highly diastereo- and enantioselective [3+3] annulation of donor-acceptor cyclopropanes **1** with mercaptoacetaldehyde **29** by developing a *N*,*N*′-dioxide **L-PiPr$_3$**-Sc(OTf)$_3$ complex system. The corresponding chiral tetrahydrothiopyranols **30** were obtained in moderate yields with excellent diastereoselectivities (up to >20:1 *dr*) and enantioselectivities (up to 99%*ee*) (Scheme 15).[45]

2.3. [3+4]-Cycloaddition reactions

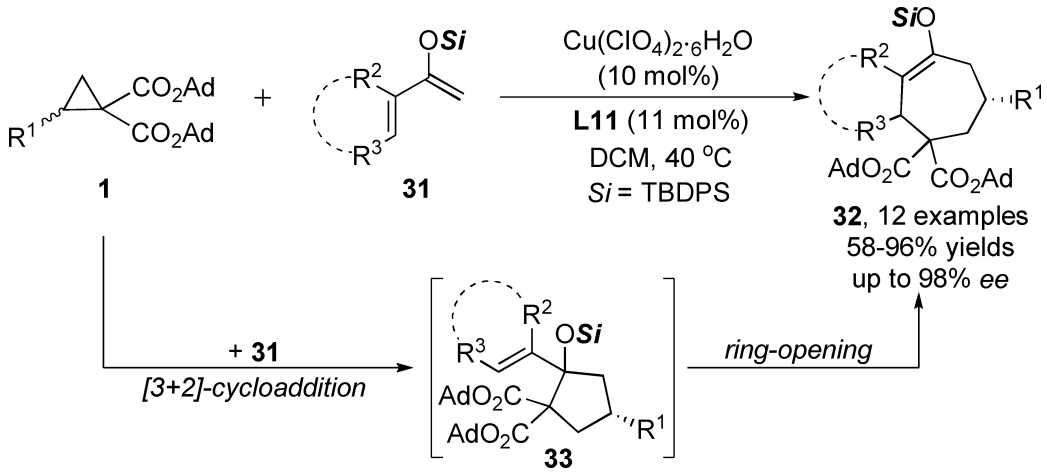
In 2015 Tang's group successfully developed an efficient [3+4] cycloaddition reaction of donor-acceptor cyclopropanes **1** with dienes **31**. The reaction proceeds well with various dienolsilyl ethers in the presence of a Lewis acid, delivering a variety of cycloheptenes and [*n*,5,0]carbobicycles with excellent stereoselectivity. The asymmetric version of this reaction was also



Scheme 13. Ni(II)/trisoxazoline catalysis for the synthesis of chiral 6,6,6-tricyclic dihydroisoquinolines.



Scheme 14. Ni(II)/bisoxazoline catalysis for the synthesis of chiral tetrahydrocarbazoles.



Scheme 16. Cu(II)/trisoxazoline catalysis for the synthesis of chiral [*n*,5,0]carbobicycles.

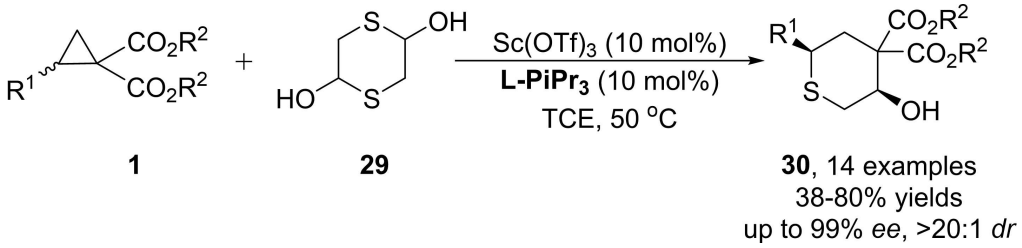
realized using a newly designed chiral CyTOX ligand **L11**, providing a new approach to access optically active cycloheptenes and [*n*,5,0]carbobicycles **32** (Scheme 16).[46] Mechanistic studies revealed that the reaction occurs by a stepwise pathway with an unusual ring opening of the five-membered [3+2] intermediate **33** and sequential intramolecular cyclization to afford the thermodynamically stable [3+4] annulation product.

In 2022, the Waser group reported the Lewis acid catalyzed [3+4] annulative addition of aryl and amino donor-acceptor cyclopropanes **1** with 2-aza-1,3-dienes **34**. Densely substituted azepane derivatives **35** were obtained in good to excellent yields with high diastereoselectivities and enantioselectivities (Scheme 17).[47] The reaction occurred under mild conditions with copper triflate with a trisoxazoline (CyTOX) ligand **L12**.

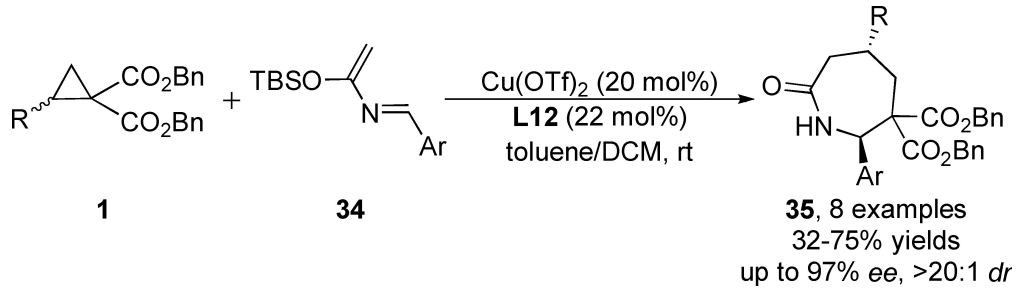
3. Cycloaddition reactions of chiral non-racemic donor-acceptor cyclopropanes using achiral Lewis acid catalysts

3.1. [3+2]-Cycloaddition reactions

Cycloaddition using enantiomerically enriched donor-acceptor cyclopropanes with non-chiral Lewis acid catalysts is another general protocol for the direct construction of chiral cyclic architectures with structural diversity. In 2005, Johnson and coworkers reported a highly diastereoselective synthesis of 2,5-disubstituted tetrahydrofurans *via* the formal $Sn(OTf)_2$-catalyzed cycloaddition of aldehydes with donor-acceptor cyclopropanes bearing a malonyl diester acceptor group and carbon-based resonance donor substituent.[22] As an extension of this work,



Scheme 15. Sc(III)/*N*,*N*′-dioxide **L-PiPr$_3$** catalysis for the synthesis of chiral tetrahydrothiopyranols.



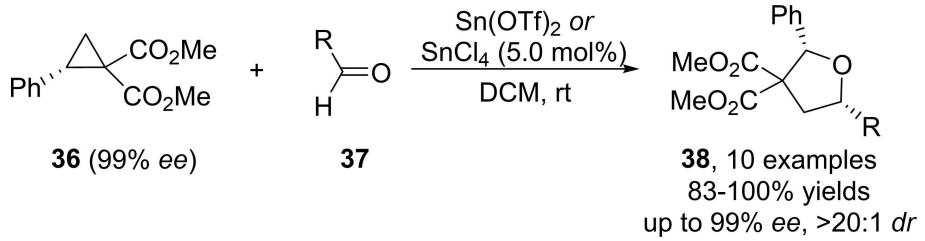
Scheme 17. Cu(II)/trisoxazoline catalysis for the synthesis of chiral substituted azepanes.

they developed an asymmetric version of this new [3+2]-cycloaddition with chiral non-racemic donor-acceptor cyclopropane **36** and aldehydes **37** for the synthesis of 2,5-disubstituted tetrahydrofurans **38** in excellent yields, diastereoselectivities, and a very high degree of absolute stereochemical control. The tetrahydrofuran products were further manipulated to allow for the preparation of more complex optically active heterocycles. This reaction is believed to proceed through an initial S_N2 attack on the activated cyclopropane, and through this process, absolute stereochemical information is transferred to the product (Scheme 18).[48] Three years later, further study by the same group revealed that this reaction carried all the hallmarks of areaction process proceeding *via* an ionic electrophile: substitution at the more highly substituted carbon atom and faster reaction rates with electron releasing groups on both the nucleophile and electrophile.[25]

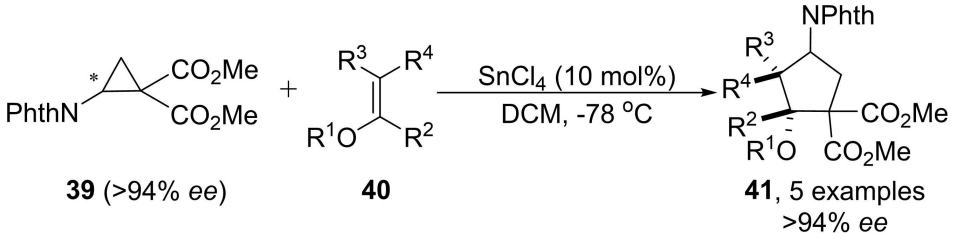
In 2011, the Waser group reported the first catalytic [3+2] annulation of enantiopure amidocyclopropanes **39** with enol ethers **40** for the synthesis of substituted cyclopentylamides **41** in quantitative yields with broad substrate scope. The introduction of a phthalimide group on a cyclopropane diester was key to enabling high yield and selectivity in the reaction (Scheme 19).[49]

A novel synthetic protocol for the synthesis of highly functionalized five-membered carbocyclic β-enaminoesters was developed by Ghorai and co-workers in 2018 *via* domino ring-opening cyclization (DROC)/decarboxylative tautomerization of activated enantiopure cyclopropanes **36** with various malononitrile pro-nucleophiles **42**. The proposed reaction mechanism involves Lewis acid promoted intermolecular S_N2-type ring-opening and concomitant ring-closure in a 5-*exo-dig* fashion of donor-acceptor cyclopropanes with malononitrile to generate the five-membered carbocyclic intermediate **44**, followed by decarboxylation in the presence of Lewis acid *via* forming iminium salt **45**, that afforded chiral β-enaminoesters **43** in good to high yields with generally excellent enantioselectivity (Scheme 20).[50]

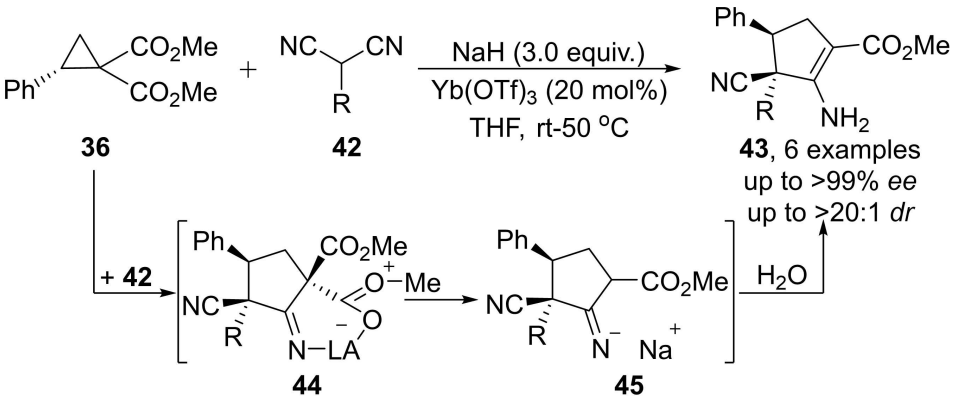
In 2019, Kerrigan's group described a new asymmetric synthesis of highly substituted tetrahydrofurans **48** through a Pd-$(PPh_3)_4$-catalyzed formal [3+2]-cycloaddition of diester substituted vinylcyclopropanes **46** and disubstituted ketenes **47**. This cascade reaction was proposed to be two sequential steps involving



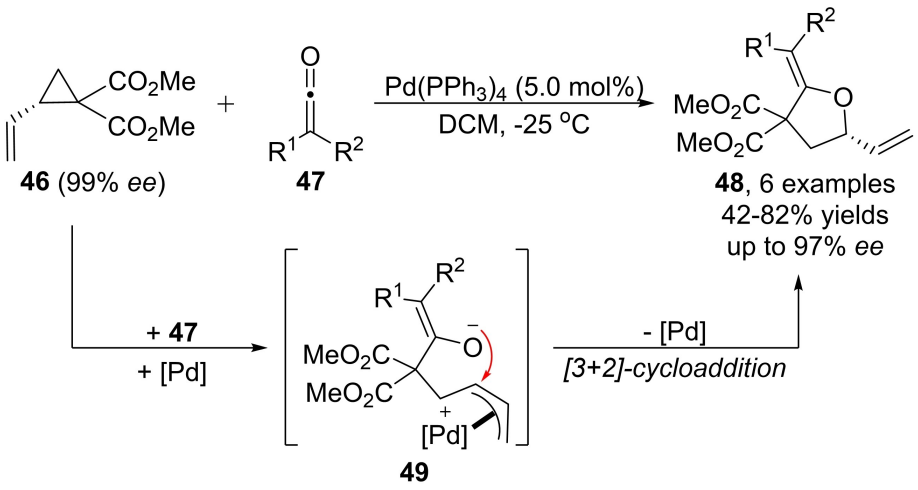
Scheme 18. Non-racemic donor-acceptor cyclopropanes for the synthesis of chiral tetrahydrofurans.



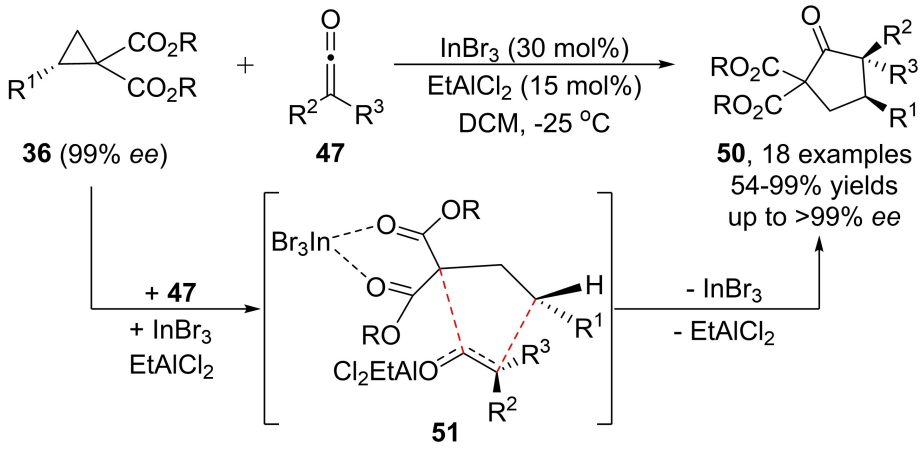
Scheme 19. Non-racemic amidocyclopropanes for the synthesis of chiral cyclopentylamines.



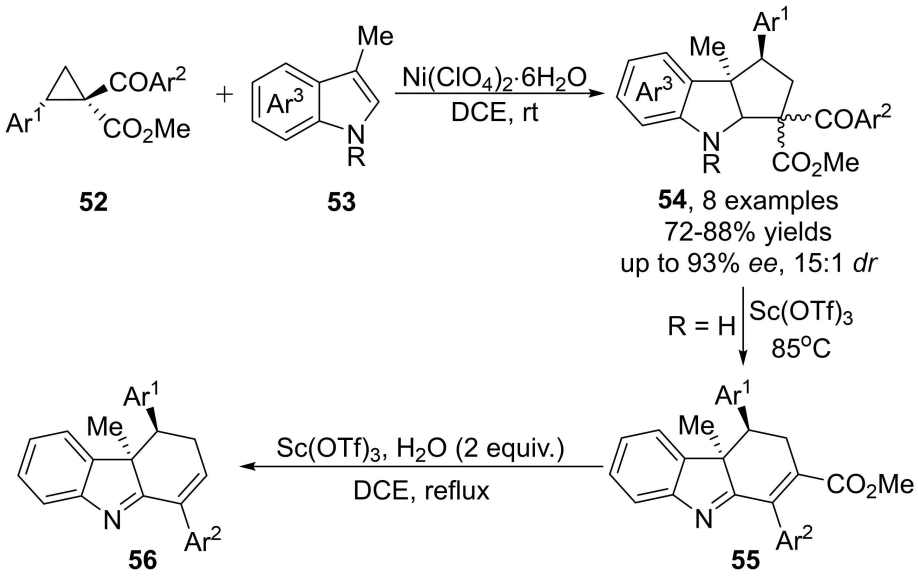
Scheme 20. Non-racemic donor-acceptor cyclopropanes for the synthesis of chiral cyclopentylamines.



Scheme 21. Non-racemic donor-acceptor cyclopropanes for the synthesis of chiral tetrahydrofurans.



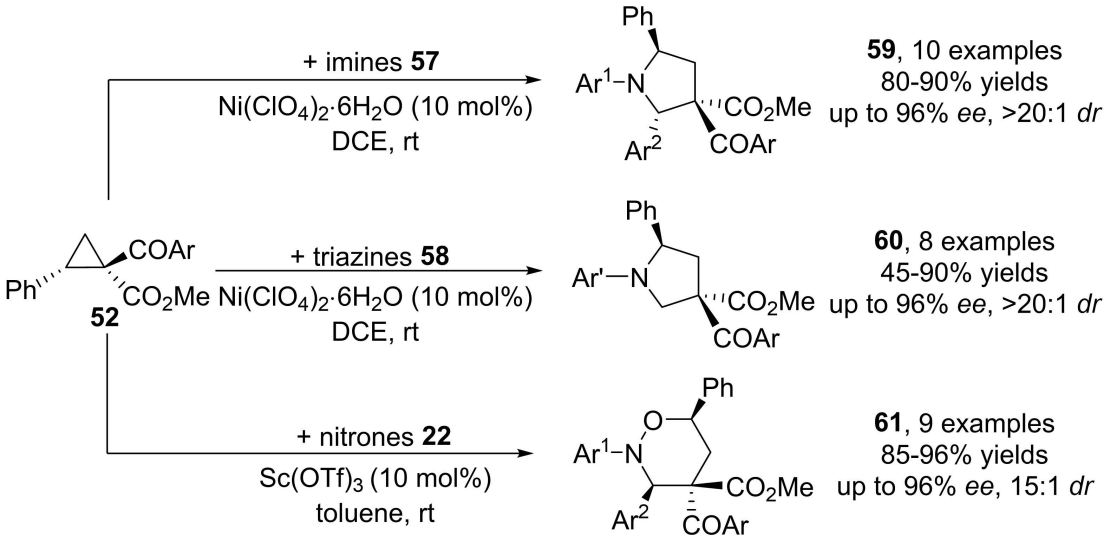
Scheme 22. Non-racemic donor-acceptor cyclopropanes for the synthesis of chiral cyclopentanones.



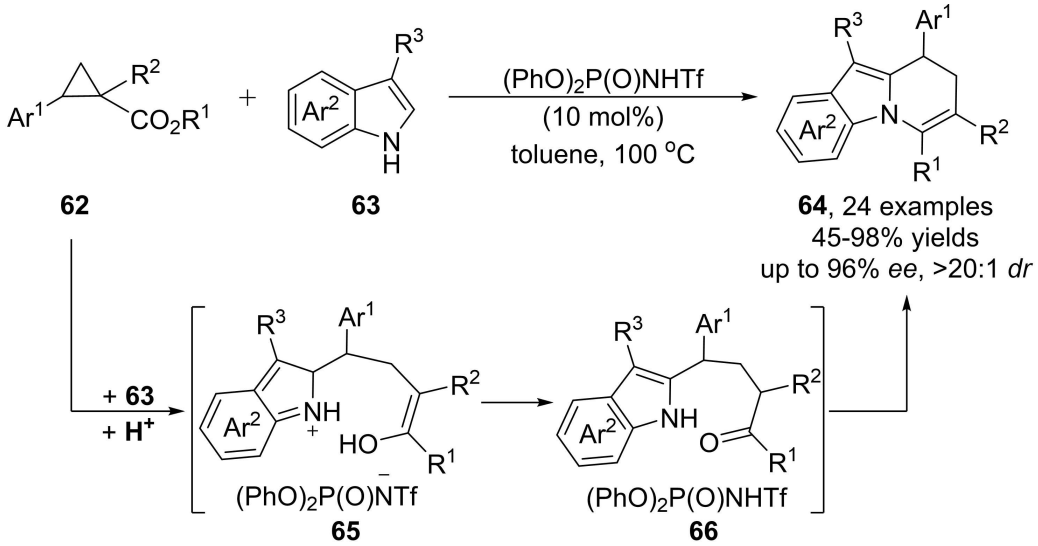
Scheme 23. Non-racemic donor-acceptor cyclopropanes for the synthesis of chiral carbazoles.

inversion of configuration which has been previously postulated for other palladium-catalyzed allylic alkylations:[51–53] initiated byPd-catalyzed ring-opening and inversion of configuration at the chiral center on the donor-acceptor cyclopropane to form intermediate **49**, which undergoes intramolecular *O*-enolate attack on the Pd(II)-π-allyl moiety to give chiral vinyl-substituted tetrahydrofurans with good to excellent enantioselectivities. It should be pointed out that intramolecular *C*-enolate attack on the pendant Pd(II)-π-allyl moiety is disfavored due to steric interactions with the highly substituted *C*-end of the enolate (Scheme 21).[54] In the same year, they developed a dual Lewis acidic In(III)-Al(III) catalytic system that provides access to enantioenriched cyclopentanones **50** with excellent transfer of chirality for the first time from enantiopure donor-acceptor cyclopropanes **36** and disubstituted ketenes **47** through a concerted process involving intermediate **51** (Scheme 22).[55]

Very recently, our group reported a highly enantioselective synthesis of chiral dihydro-3H-carbazole-2-carboxylate derivatives **55** *via* a "one-pot" cyclopentannulation-rearrangement cascade reaction that is sequentially catalyzed by nickel(II) perchlorate hexahydrate and scandium(III) trifluoromethanesulfonate with 3-methylindole **53** and non-racemic donor-acceptor cyclopropanes **52** in high yields and enantioretention under mild reaction conditions. In the stepwise transformation cycloaddition occurs with dominant chirality retention by inversion of configuration on the reactant donor-acceptor cyclopropane. The second step in the cycloaddition process that forms the product diastereoisomers is generally reversible. In addition, a further transformation of these dihydro-3*H*-carbazole-2-carboxylates *via* hydrolysis and decarboxylation under unexpectedly mild reaction conditions provides straightforward access to the decarboxylated dihydro-3*H*-carbazoles **56** in moderate yields with high retention of enantiomeric purity (Scheme 23).[56]



Scheme 24. Non-racemic donor-acceptor cyclopropanes for the synthesis of chiral pyrrolidines and 1,2-oxazinanes.



Scheme 25. Donor-acceptor cyclopropanes for the synthesis of 8,9-dihydropyrido[1,2-*a*]indoles.

At the same time a highly enantioselective preparation of substituted pyrrolidines **59** and **60** and oxazinanes **61** was achieved by our group *via* stereoretentive [3+2]/[3+3]-cycloaddition of non-racemic donor-acceptor cyclopropanes **52** with imines **57**, triazines **58** and nitrones **22** in good to high yields with broad scope under mild reaction conditions (Scheme 24).[57] The initial step in the cycloaddition reaction occurs by inversion of configuration. Coordination of the achiral Lewis acid catalyst with the non-racemic cyclopropyl-β-keto ester forms an activated donor-acceptor cyclopropane complex that can undergo S_N2 substitution by the nucleophile or, if the nucleophile is weakly reactive, undergo racemization that decreases optical purity.

3.2. [4+2]-Cycloaddition reactions

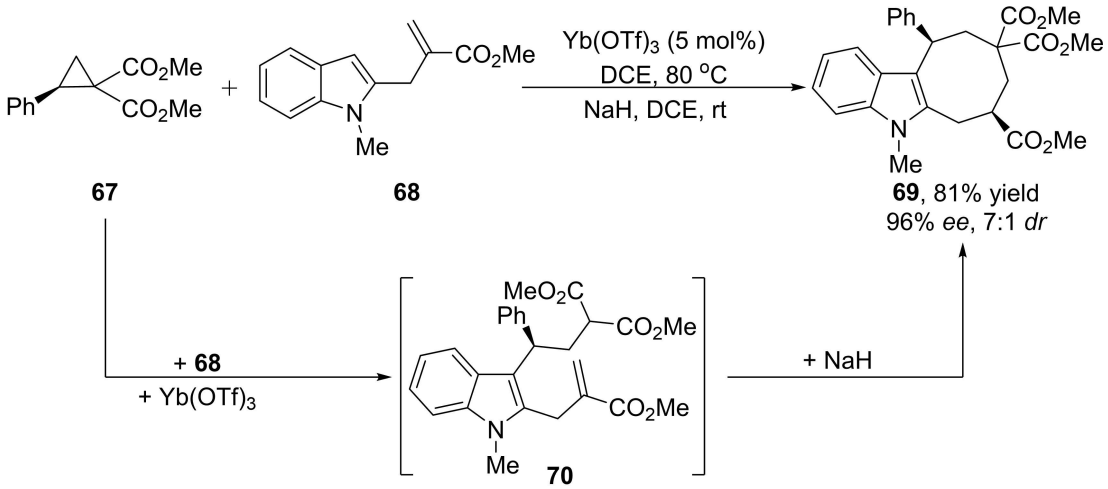
In 2021, Vicario developed a Brønsted acid catalyzed procedure for performing an unexplored [4+2]-cyclocondensation between donor-acceptor cyclopropanes **62** and C3-substituted indoles **63**. This methodology presented a broad scope regarding both counterparts of the reaction, providing the corresponding 8,9-dihydropyrido[1,2-*a*]indoles **64** in good yields and with an excellent level of selectivity (Scheme 25).[58] This reactivity pattern is particularly attractive, as it shows the alternative behavior of *N*-unprotected C3-substituted indoles, in which N and C-2 positions are simultaneously alkylated due to their double nucleophilic character and also forced by the presence of the C3-substituent of the indole that directs the initial alkylation step to the C2-position. The reaction mechanism involves nucleophilic C-2 carbon attack on the acid-activated cyclopropane species to form intermediate **65**, followed by H-transfer to recover indole aromaticity **66**. Subsequent cyclization of **66** and dehydration leads to the final product. Moreover, mechanistic investigations based on computational studies were in concordance with the observed experimental results.

3.3. [3+5]-Annulation reactions

In 2019, a new approach to cycloocta[*b*]indole **69** through formal [3+5] cycloaddition was developed by Nishida. This methodology was realized by using an indole derivative **68** as a C5 unit and a cyclopropane derivative as a C3 unit. These two units have both donor and acceptor properties. Two carbon-carbon bonds were formed stepwise by the successive addition of a Lewis acidic catalyst and a Brønsted base *via* the intermediate **70**. The reaction could be performed as a one-pot process. Optically active cycloocta[*b*]indole was also synthesized by using this methodology with a chiral cyclopropane **67** as a C3 substrate (Scheme 26).[59]

4. Summary and Outlook

Donor-acceptor cyclopropanes are useful building blocks for the incorporation of three carbon units to form the carbocyclic and heterocyclic compounds through [3+*n*]-cycloaddition reactions. As a consequence, substantial effort has been directed towards the development of catalytic asymmetric reactions of donor-acceptor cyclopropanes. Two general protocols in this field have been developed: the use of chiral catalysts with racemic donor-acceptor cyclopropanes and the use of chiral non-racemic donor-acceptor cyclopropanes with achiral Lewis acid catalysts. Numerous chiral ligands have been employed with their viability depended on the Lewis acid that is used for reactions with racemic cyclopropanes, and nickel(II) perchlorate is often effective for reactions with chiral non-racemic cyclopropanes. Applications of enantioselective reactions for donor-acceptor cyclopropanes have been successfully realized for the preparation biologically active products, and chiral non-racemic donor-acceptor cyclopropanes have been used for stereospecific ionic ring-opening polymerization.[60] Despite this significant progress, however, there are still many challenges that need to be addressed for further advances: (1) The racemic donor-acceptor cyclopropanes used in these known enantioselective processes are often limited to



Scheme 26. Donor-acceptor cyclopropane for the synthesis of a chiral cycloocta[*b*]indole.

cyclopropanes with aryl/vinyl donors and geminal dicarbonyl-substituted acceptors; less reactive donor-acceptor cyclopropanes bearing an alkyl donor, or containing only one acceptor group, have been much less explored. (2) Enantioselective reactions of chiral non-racemic donor-acceptor cyclopropanes with achiral Lewis acid catalysts have received much less attention; only few examples of asymmetric [3+*n*] cycloadditions have been reported, and they have limited scope. (3) Access to chiral non-racemic donor-acceptor cyclopropanes is a limitation to the use of achiral catalysts, but there have been significant improvements to their synthesis in recent years. Therefore, further exploration of readily accessible donor-acceptor cyclopropanes and practical catalytic conditions, novel methodology and synthetic applications are foreseeable in due course.

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Conflict of Interests

The authors declare no conflict of interest.

Keywords: Asymmetric catalysis · [3+*n*]-Cycloaddition · Donor-acceptor cyclopropane · Lewis acids · Chiral ligand

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