Review

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Asymmetric Ring-Opening Reactions of Donor-Acceptor Cyclopropanes and Cyclobutanes

Lijia Wang*[a] and Yong Tang*[a, b]

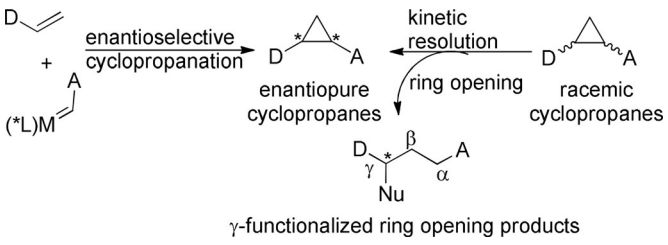
Abstract: Donor-acceptor (DA) cyclopropanes are particularly useful synthetic building blocks, which have been widely applied in the total synthesis of natural products and important chiral molecules in organic synthesis. The asymmetric ring-opening reactions of racemic DA cyclopropanes and cyclobutanes, for example, aryl-substituted 1,1-cyclopropane diesters and aryl-substituted 1,1-cyclobutane diesters, with nucleophiles provides versatile access to optically active γ- and δ-functionalized carbon skeletons, as well as the kinetic resolution of racemic DA cyclopropanes, which are useful chiral skeletons in organic synthesis. Recently, we have developed a series of highly enantioselective ring-opening and annulation reactions of DA cyclopropanes and cyclobutanes with various nucleophiles, such as amines, alcohols, nitrones, azomethine imines, enol silyl ethers, and indoles, by employing nickel and copper catalysts with TOX and SaBOX as ligands. The reactions worked smoothly with excellent diastereoselectivities and enantioselectivities (up to >99/1 *dr* and up to 99% *ee*) over broad substrate scopes.

Keywords: Annulation · cyclobutanes · cyclopropanes · enantioselectivity · ring opening

1. Introduction

Donor-acceptor (DA) cyclopropanes are considered useful building blocks in organic synthesis, and have received remarkable attention from chemists for a long time. Direct enantioselective cyclopropanations,[1] as well as kinetic resolution of racemic DA cyclopropanes, are common approaches to obtain chiral cyclopropanes with high enantioselectivity. In an asymmetric transformation of racemic DA cyclopropanes, the enantiopure cyclopropane can be harvested in company with the γ-functionalized ring-opening product formed by the other enantiomer of cyclopropane (Scheme 1).

Accordingly, racemic DA cyclopropanes, for example, aryl-substituted 1,1-cyclopropane diesters, undergoing kinetic resolution and dynamic kinetic resolution, could serve as versatile synthons in organic transformations. By asymmetric ring-opening and [3+*n*] annulation reactions with nucleophiles, the reactions provide facile access to optically active γ-functionalized carbon skeletons **A** and cyclic molecules **B**.[2] The ring-opening and annulation strategies are successfully applied as key steps in the total synthesis of a number of natural products and pharmaceuticals.[3] In addition, as the small ring analog of DA cyclopropanes, the reactive behavior of DA cyclobutanes have some similarity to the cyclopropanes. The [4+*n*] annulation of DA cyclobutanes have emerged and are attracting increasing attention because of their flexibility and accessibility in the synthesis of structurally interesting molecules (Scheme 2).[3c]



Scheme 1. Enantioselective protocols to obtain enantiopure cyclopropanes.

In recent years, effective strategies, as well as efficient catalyst systems, have been developed.[4] For example, Kerr *et al.* reported the first high pressure reaction of DA cyclopropanes with indoles catalyzed by ytterbium triflate;[4a] Sibi *et al.* developed the first enantioselective addition of nitrones to activated cyclopropanes;[4b] Johnson

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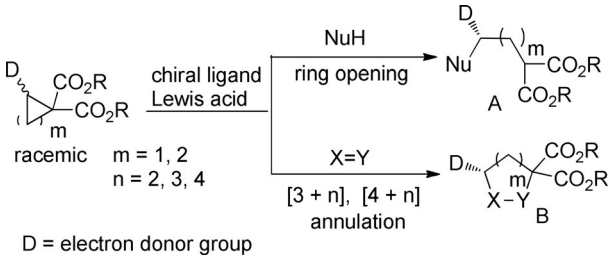


Scheme 2. Ring-opening and annulation reactions of DA cyclopropanes and DA cyclobutanes.

et al. reported the dynamic kinetic asymmetric [3+2] cycloaddition of racemic cyclopropanes with aldehydes and aldimines;[4c,d] Trost *et al.* demonstrated the palladium-catalyzed dynamic kinetic asymmetric [3+2] cycloaddition of vinyl cyclopropanes and alkylidene azlactones;[4e] Waser *et al.* developed dynamic kinetic asymmetric [3+2] annulation reactions of aminocyclopropanes;[4f,g] Maruoka *et al.* realized the reaction of vinyl cyclopropanes and vinyl ethers by an organic thiyl radical catalyst;[4h] and Feng *et al.* reported the enantioselective ring opening/cyclization of cyclopropyl ketones with primary amines.[4i] In this account, we summarize our studies on the ring-opening process of DA cyclopropanes and cyclobutanes, as well as the kinetic resolution of racemic DA cyclopropanes, by employing complexes generated *in situ* from copper or nickel salts with chiral TOX and SaBOX ligands.[5]

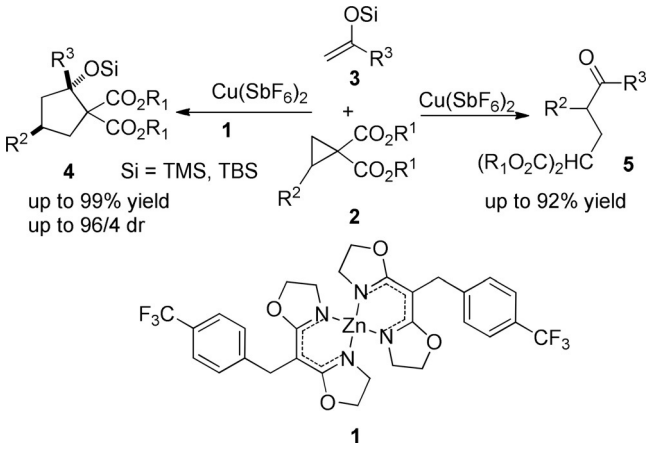
Lijia Wang was born in Fuxin, Liaoning, China. She received her BSc in 2004 and PhD in 2009 from Sichuan University under the supervision of Professor Xiao-Ming Feng. She was a postdoctoral fellow with Professor Keiji Maruoka at Kyoto University from 2009 to 2011. Then she joined Shanghai Institute of Organic Chemistry in 2011, where she was appointed as an associate professor in Professor Yong Tang's group. Her research interest is in the area of developing new methodologies in asymmetric catalysis.

Yong Tang received his BSc from Sichuan Normal University and PhD degrees from Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences. He was a postdoctoral fellow with Professor Yian Shi at Colorado State University, Fort Collins, and with Professor A. Kozikowskiat at Georgetown University. He joined Shanghai Institute of Organic Chemistry in 1999, where he was appointed as an associate professor, and was promoted to research professor in 2000. His research interests include organometallic chemistry centering on olefin polymerization, ylide chemistry in organic synthesis, asymmetric catalysis.

2. [3+*n*] Annulations of DA Cyclopropanes

2.1 The Annulation Reactions of DA Cyclopropanes with Enol Silyl Ethers

The ring-opening reaction of 2-substituted cyclopropane-1,1-dicarboxylates with enol silyl ethers has been reported by Wang *et al.*[6] In 2009, we developed a protocol to control the reaction pathways between [3+2] annulation and ring opening by the choice of the ligand/Lewis acid system. In the presence of a mixture of catalytic $Cu(SbF_6)_2$ and zinc complex **1**, the [3+2] annulations between DA cyclopropanes **2** with enol silyl ethers **3** gave the multi-substituted cyclopentanes **4** in up to 99% yields with excellent diastereoselectivities (up to 96/4 *dr*), while the acyclic ring-opening products, 1,6-dicarbonyl compounds **5**, were afforded in the absence of a ligand (Scheme 3). Interestingly, in the absence of $Cu(SbF_6)_2$, complex **1** could not catalyze both the [3+2] annulation and the ring-opening reaction.[7a]



Scheme 3. Reactions of DA cyclopropanes with enol silyl ethers.

[*n*.3.0]-Bicyclic compounds bearing a tertiary hydroxyl group at the ring junction are present as a key structure in a vast array of biologically active natural products. The [3+2] annulation of DA cyclopropanes with cyclic enol silyl ethers provides a highly efficient method to construct the functionalized fused cyclopentane derivatives. By using an inexpensive copper catalyst (Scheme 4), a series of desired [*n*.3.0]-bicyclic compounds **7**, with multiple contiguous stereocenters, were obtained in high yields with excellent diastereoselectivity. Notably, it was found that the steric bulk of the ester group R^2 is important in controlling the diastereoselectivity. By using the rigid and bulky 2-adamantyl as the R^2 group, the best result was obtained.[7b]

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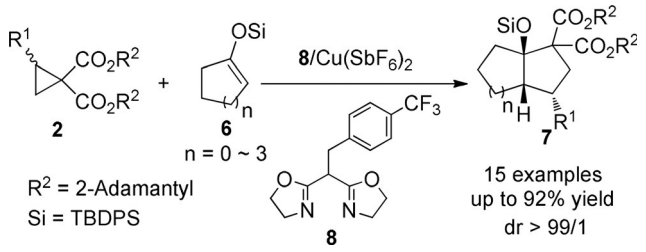
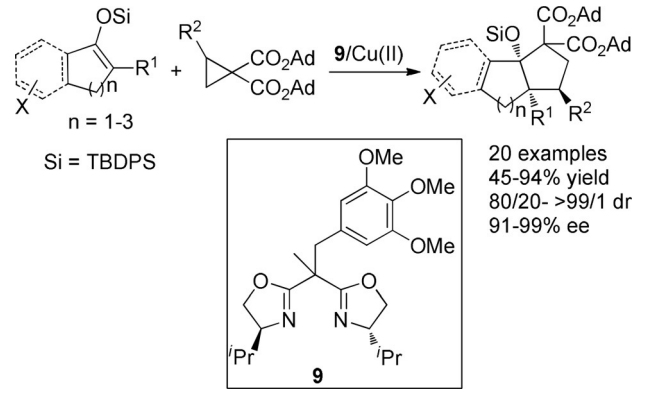


Scheme 4. [3+2] Annulations of DA cyclopropanes with cyclic enol silyl ethers.

A mechanistic study of DFT calculations indicates that the [3+2] annulation is stepwise.[7b] According to the calculations, in the first step (nucleophilic ring opening), the stereoselectivity is poor, and the origin of the high diastereoselectivity is determined by the intramolecular cyclization step (the rate-limiting step).

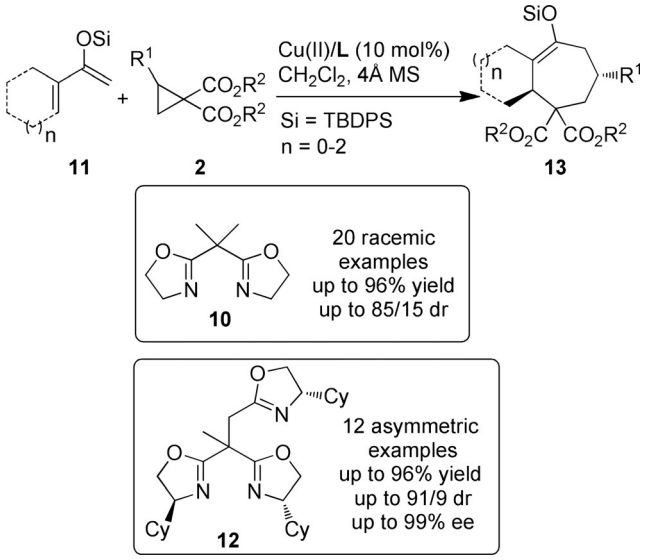
The enantioselective version of the above-mentioned reaction was next explored. A range of 3α-hydroxy [*n*.3.0]carbobicycles were furnished in high optical purity by using copper(II)/**9** catalysts (Scheme 5). Five- to



Scheme 5. Enantioselective [3+2] annulations of DA cyclopropanes with cyclic enol silyl ethers.

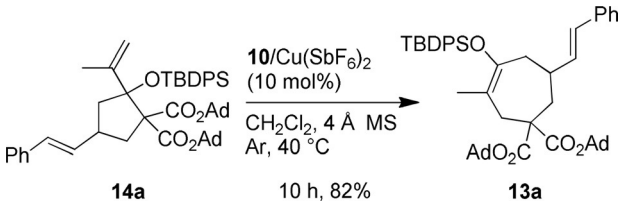
seven-membered enol silyl ethers derived from cyclic ketones were suitable substrates to give the desired products in high yields with up to >99/1 *dr* and up to 99% *ee*. Furthermore, enol silyl ethers derived from benzocyclic ketones also reacted smoothly, leading to the benzene-fused cyclic products in 80–98% yields with >99/1 *dr* and 91–94% *ee*. These reactions represent the first examples of catalytic enantioselective [3+2] annulation reactions of DA cyclopropanes with enol silyl ethers.[7c]

Reactions of DA cyclopropanes with dienol silyl ethers usually resulted in ring-opening products or [3+2] cycloaddition products. We developed a Cu(II)/BOX (**10**) catalyzed [4+3] annulation protocol of DA cyclopropanes with dienol silyl ethers **11**, which served as a new approach for the synthesis of cycloheptenes and [*n*.5.0]carbobicycles. Importantly, the catalytic asymmetric version of this transformation is also realized with high enantioselectivity by employing a newly designed chiral trisoxazoline ligand (Cy-TOX **12**). To the best of our knowledge, these reactions represent the first examples of catalytic asymmetric [4+3] annulation reactions of enol silyl ethers with DA cyclopropanes (Scheme 6). The obtained optically active [*n*.5.0]carbobicycles **13** are present as core structures in plenty of biologically active and natural products.[7d]



Scheme 6. [3+4] Annulations of DA cyclopropanes with dienes.

Monitoring the reaction by ^{1}H NMR reveals that this transformation involves an unusual rearrangement of the five-membered [3+2] intermediate to the thermodynamically stable [4+3] annulation product. According to the mechanistic study, a control experiment was carried out. When **14a** was subjected to the current catalyst system, the corresponding cycloheptene **13a** was obtained in 82% yield after 10 h (Scheme 7).[7d]



Scheme 7. Conversion of [3+2] product to [3+4] product.

2.2 The Annulation Reactions of DA Cyclopropanes with Indoles

Indoles and their analogs are one of the most common subunits existing in a large number of alkaloids. As a robust participant in Friedel-Crafts reactions, the nucleophilic 3-positon of indole could attack the DA cyclopro-

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pane to afford the ring-opening products in the presence of Lewis acids.[8] Recently, we found that a highly diastereo- and enantioselective cyclopentannulation reaction of indoles with cyclopropanes could be realized by using a copper(II)/SaBOX (**18**) catalyst. The reaction worked smoothly with a broad range of indoles and DA cyclopropanes under mild conditions, giving the corresponding [3+2] products with excellent diastereoselectivities (up to >50/1 *dr*) and up to 96% *ee* (Scheme 8).[9a]

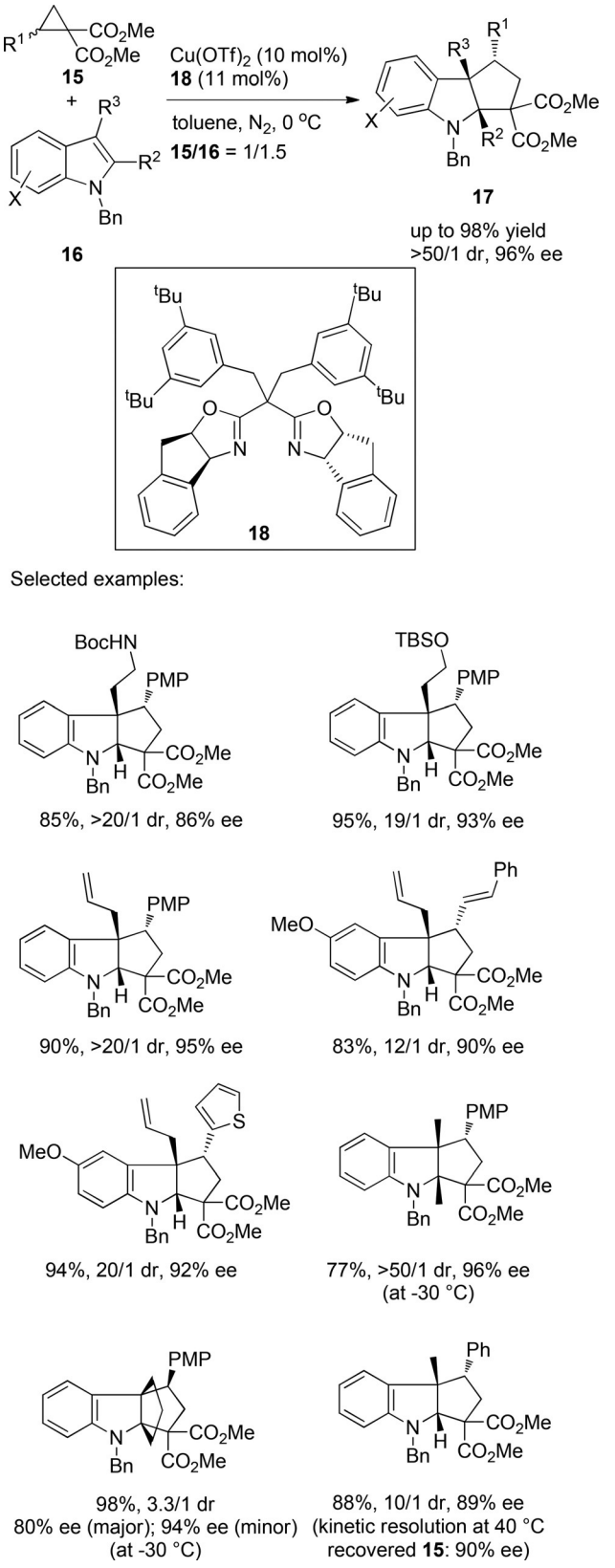
The application of this reaction to a pyrroloindole **19** succeeded with a 2-indole-substituted DA cyclopropane **20** (96% yield, >99/1 *dr*, and 95% *ee*), which established facile access to the tetracyclic core of borreverine (Scheme 9).[9a]

Interestingly, with 2-methyl-substituted indole **22**, only ring-opening product **23** was obtained; 80% yield and 92% *ee* were achieved, and no annulation product was detected (Scheme 10).[9a]

Stereoselective intramolecular [3+2] annulation reactions of DA cyclopropanes with indoles have also been investigated.[9b] With Cu(II)/**24** as the catalyst, a class of tetracyclic cyclopenta-fused spiroindoline skeletons were constructed through the aforementioned strategy. It was found that the remote ester groups of the DA cyclopropanes played an important role in the stereocontrol of this reaction (Table 1). By choosing different ester groups, both *cis*- and *trans*-diastereomers of tetracyclic spiroindolines were obtained with high selectivities. The isopropyl ester is the best for the *trans* diastereomer (entry 4), while the 2-adamantyl ester is highly favorable for the *cis* compound (entry 13). DFT calculations revealed the origin of this remote stereocontrol. The *cis* isomer is predominantly due to the steric repulsions. On the other hand, the *trans* isomer is favored because of the attractive interactions between the alkoxycarbonyl group and the arene.

This method was applied to the synthesis of optically active tetracyclic spiroindolines. By employing the optically pure isopropyl or 2-adamantyl substrate, the intramolecular [3+2] products were furnished with complete retention of the enantiomeric purity (Scheme 11).[9b]

Kerr and coworkers have reported an elegant strategy for the synthesis of tetrahydrocarbazoles that involves a tandem ring opening of DA cyclopropanes with indoles and a Conia-ene cyclization process.[10] Recently, we have developed the enantioselective [3+3] annulation of DA cyclopropanes **15** with 2-alkynyl indoles **28**, leading to one-pot access to the optically active 1,2,3,4-tetrahydrocarbazoles **29**.[9c] In the presence of **30**/Cu(OTf)$_2$ as the catalyst, the indole nucleophilic ring-opening reaction worked smoothly, followed by the Conia-ene cyclization, promoted by an $InCl_3$ catalyst at an elevated temperature. The reaction proceeded well to give high yields (63–87%) and high levels of enantioselectivity (up to 94% *ee*) over a broad substrate scope (Scheme 12).



Scheme 8. [3+2] Annulation reactions of DA cyclopropanes with indoles.

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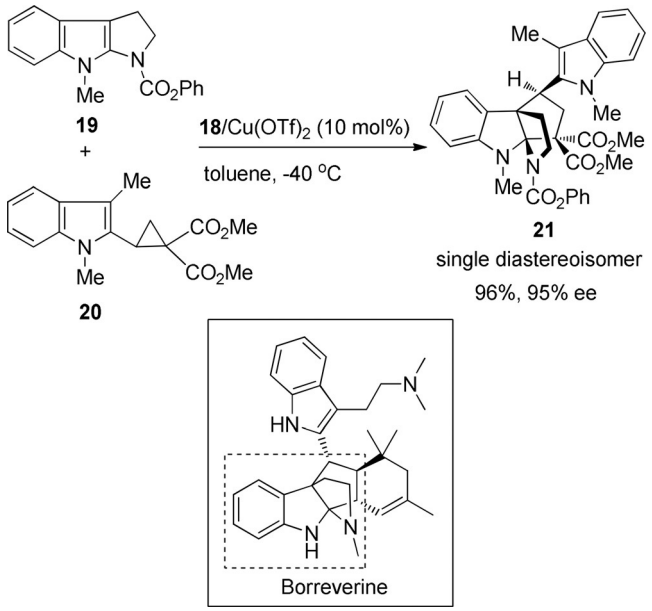
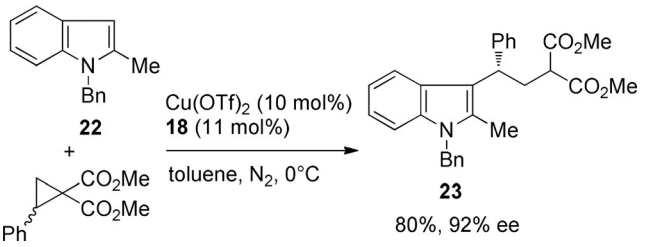


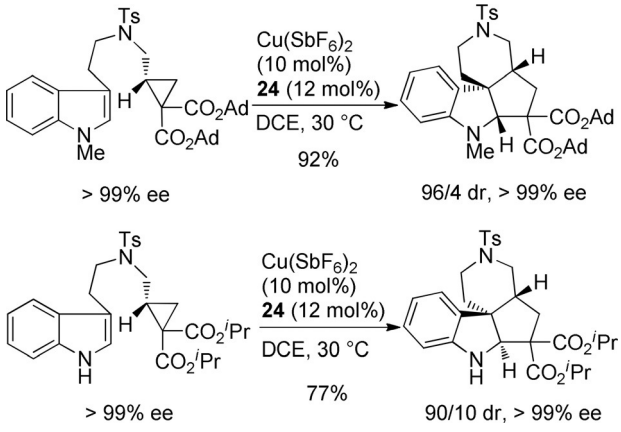
Scheme 9. Synthesis of the core of borreverine.

2.3 The Asymmetric [3+3] Cycloadditions of DA Cyclopropanes with 1,3-Dipoles

1,3-Dipoles, such as nitrones and azomethine imines, readily react with DA cyclopropanes in a cycloaddition

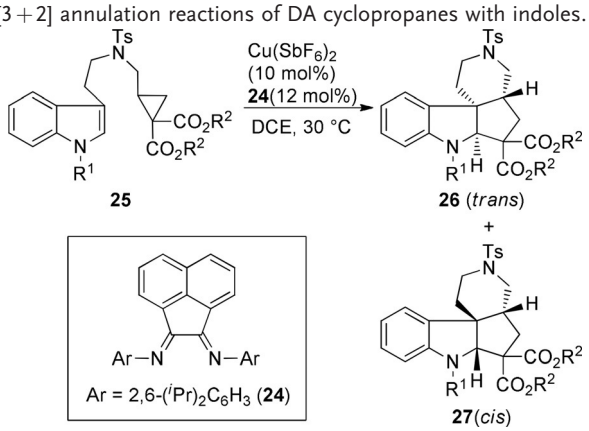


Scheme 10. Ring-opening reaction of a DA cyclopropane with 2-methyl indole.



Scheme 11. Synthesis of chiral tetracyclic spiroindolines from optically pure substrates.

Table 1. Stereoselective intramolecular [3+2] annulation reactions of DA cyclopropanes with indoles.



entry	R^1	R^2	yield (%)	*dr* (**26**/**27**)
1	H	Et	83	83/17
2	H	Me	87	74/26
3	H	*n*Hex	77	78/22
4	H	^{i}Pr	77	90/10
5	H	*c*Hex	83	88/12
6	H	3-Pent	45	89/11
7	H	^{t}Bu	trace	–
8	H	1-Ad	trace	–
9	H	$CH_2{}^t$Bu	64	15/85
10	H	CH_2-1-Ad	52	9/91
11	H	2-Ad	61	6/94
12	CH_3	^{i}Pr	85	84/16
13	CH_3	2-Ad	79	5/95

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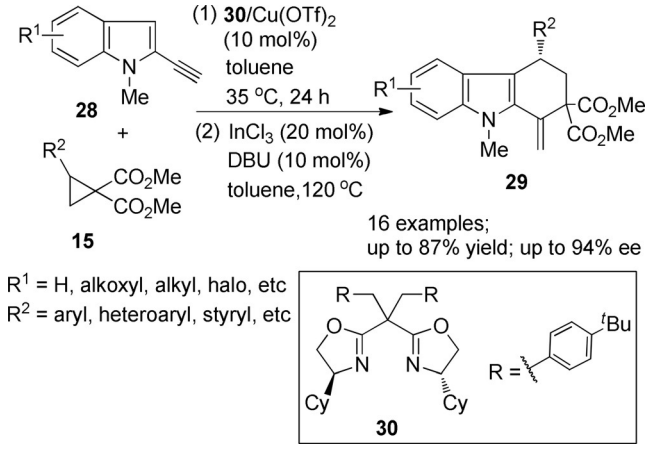
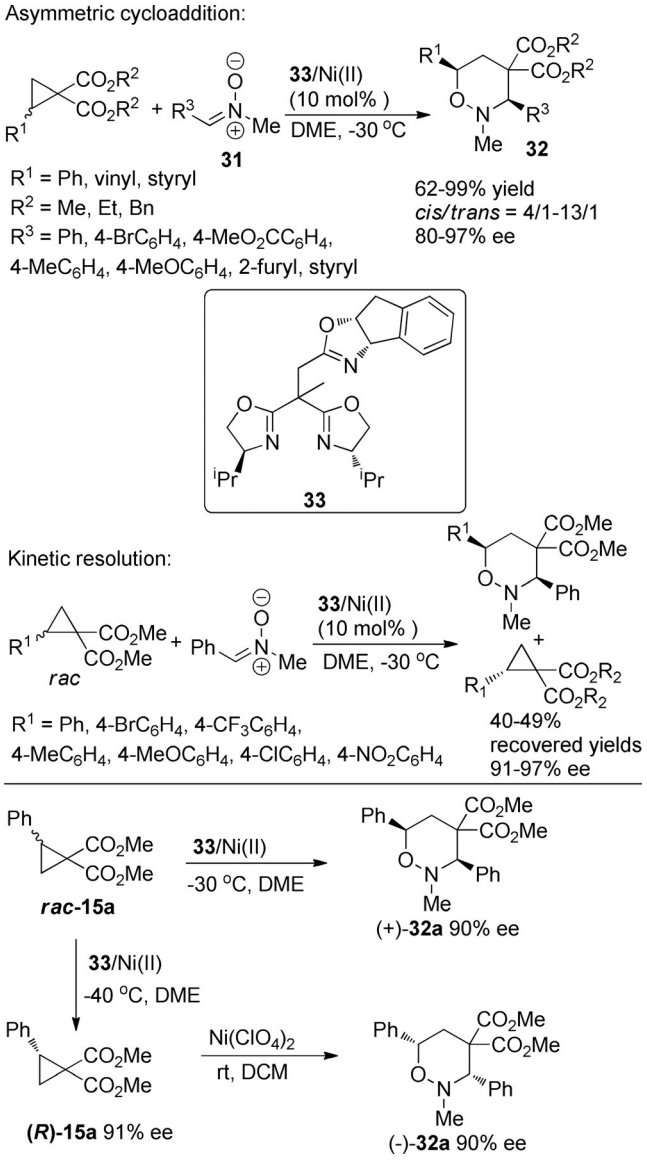


Scheme 12. Enantioselective [3+3] annulations of DA cyclopropanes with 2-alkynyl indoles.



Scheme 13. Asymmetric [3+3] cycloadditions of DA cyclopropanes with nitrones.

fashion. We have devoted great effort in this area to develop effective asymmetric protocols in the construction of synthetically useful heterocyclic molecules. During our investigation, Sibi *et al.* reported, in 2005, an elegant enantioselective [3+3] cycloaddition of cyclopropanes with nitrones catalyzed by a chiral nickel(II) complex.[4a] In their studies, both excellent reactivity and enantioselectivity were obtained for acceptor-activated cyclopropanes (up to 99% yield, up to 95% *ee*), while for DA cyclopropanes, high levels of both yields and *ee* values were achieved, but with poor diastereoselectivity (up to 99% yield, up to 96% *ee*, 0.8/1–1.4/1 *dr*). In 2007, we developed a chiral trisoxazoline (**33**)/Ni(II) catalytic system in the cycloaddition of 2-substituted cyclopropane-1,1-dicarboxylates with nitrones **31** (Scheme 13).[11a] Up to 93/7 *dr* and 80–97% *ee* were achieved. The same catalyst could also be used in the kinetic resolution of DA cyclopropanes, affording the recovered chiral cyclopropanes in excellent *ee* values. Through asymmetric [3+3] cycloaddition or a kinetic resolution/cycloaddition cascade, this protocol provided convenient access to both enantiomers of tetrahydro-1,2-oxazines.

Dihydroisoquinoline, tetrahydroisoquinoline, and their analogs are important synthetic intermediates in organic synthesis. Plenty of alkaloids and other bioactive molecules contain the aforementioned subunits. Using chiral In-TOX (**34**)/Ni(II) as the catalyst, the first enantioselective [3+3] cycloaddition of 1,1- cyclopropane diesters with azomethine imines **35** was developed, furnishing the novel tricyclic dihydroisoquinoline derivatives **36** in up to 99% yields with excellent diastereo- and enantioselectivities (up to >95/5 *dr* and 98% *ee*).[11b] In this reaction, the steric bulk of the two ester groups of the cyclopropane was found to influence the stereochemical control. When the ester groups were enlarged from methyl to neopentyl, the enantioselectivity of the reaction gradually improved in the order: methyl < ethyl < isobutyl < neopentyl. In addition, the product could be easily reduced to the corresponding tetrahydroisoquinolines (Scheme 14).

Under the optimal reaction conditions, as shown in Scheme 14, the scope of aromatic azomethine imines for the In-TOX(**34**)/Ni(II)-catalyzed asymmetric [3+3] cycloadditions with 2-*p*-methoxyphenyl-substituted cyclopropane diester was investigated. As outlined later in Table 4 (Section 5.1), the position of the methyl group on the isoquinoline ring slightly influences the stereoselectivity. Both high *dr* and excellent enantioselectivity could be obtained (85–94% yield, up to >20/1 *dr*, and 86–96% *ee*; Table 2, entries 2–3). In addition, the current system is also suitable for quinoline substrates **35e–f**, affording the corresponding products in good yield, but with a decrease of the stereocontrol (entries 5 and 6).[11b]

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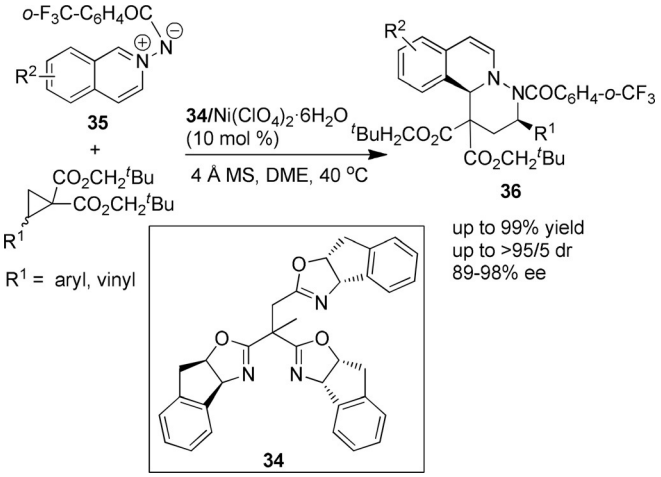
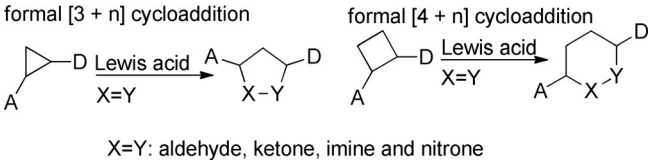


Scheme 14. Asymmetric [3+3] cycloadditions of DA cyclopropanes with azomethine imines.

In this reaction, the chiral indanyl oxazoline sidearm of the In-TOX ligand was proven to be crucial in achieving high enantioselectivity. Meanwhile, it was found that by introducing a trifluoromethyl group to the azomethine imine substrates, the reaction could be speeded up and the enantioselectivity was improved dramatically. Furthermore, for the phenyl-substituted DA cyclopropane and those bearing electron-poor aryl substituents, the [3+3] cycloadditions provide an effective method for the kinetic resolution of DA cyclopropanes. DFT calculations explained the origins of the high enantioselectivity and the role of the sidearm of the chiral ligand.[11b]

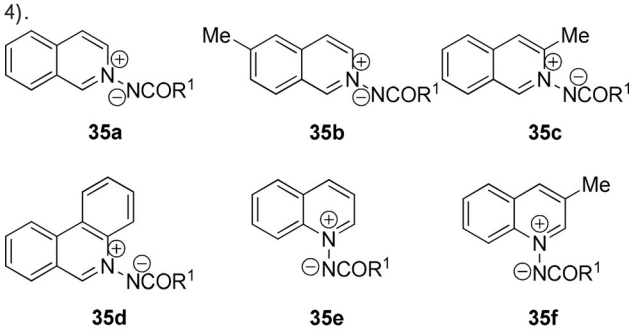
3. Enantioselective [4+3] Annulations of DA Cyclobutanes with Nitrones

The [4+*n*] cycloadditions of D-A cyclobutanes with different dipolarophiles, such as aldehydes, ketones, imines, and nitrones, have emerged and are attracting increasing attention because of their flexibility and accessibility in the synthesis of structurally interesting molecules.[12] Compared with DA cyclopropanes, DA cyclobutanes show lower reactivity than their three-membered ring analogs, probably due to their puckered structures and a slightly lower strain energy compared with that of cyclopropane (27.5 kcal mol^{-1} vs. 26.3 kcal mol^{-1}).



We have developed the first asymmetric [4+3] cycloaddition of 1,1-cyclobutane diester with nitrone catalyzed by the SaBOX (**37**)/Cu(II) complex, producing a broad range of multifunctionalized optically active 1,2-oxazepanes in up to 96% yields with excellent stereocontrol (up to >99/1 *dr* and 97% *ee*).[13] Various DA cyclobutanes, bearing different functional groups, such as phenyl, 2-thienyl, benzo[b]thiophenyl, and alkoxy motifs, are readily accommodated (Scheme 15). For alkoxy-substituted cyclobutanes, although the diastereoselectivity is not high, both the *cis*- and *trans*- isomer could be readily isolated by column chromatography in high yield with excel-

Table 2. Scope of the aromatic azomethine imines in In-TOX (**34**)/Ni(II)-catalyzed asymmetric [3+3] cycloadditions with activated cyclopropane diesters (according to Scheme 14).



entry	35	time (h)	Yield (%)	*dr* (*cis*/*trans*)	*Ee* (%)
1	35a	7	91	>95/5	94
2	35b	9	94	>95/5	96
3	35c	9	85	92/8	86
4	35d	9	81	75/25	88/86
5	35e	5.5	92	42/58	90/95
6	35f	14	99	58/42	88/91

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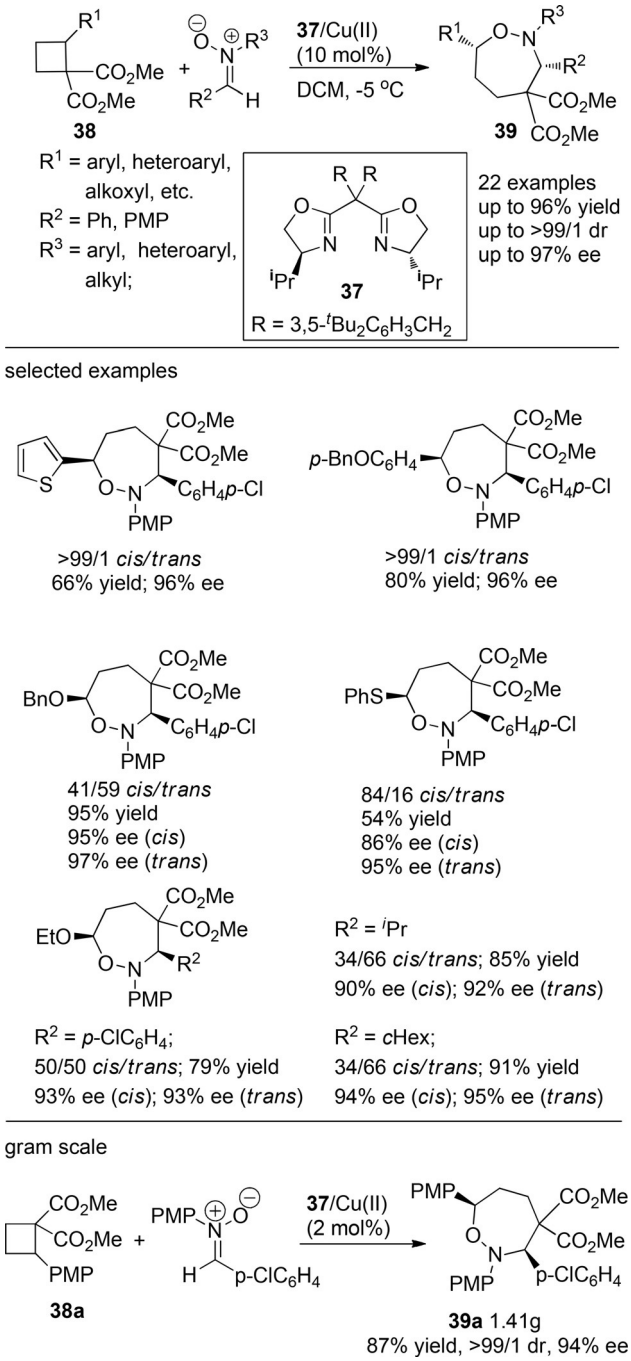


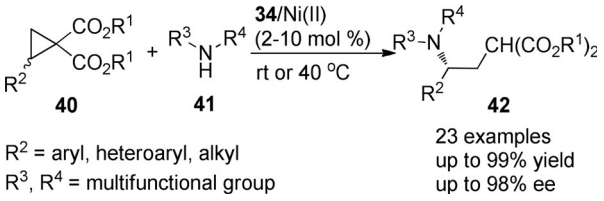
Scheme 15. Enantioselective [4+3] annulations of DA cyclobutanes with nitrones.

lent enantioselectivity. In addition, a test on the application potential of the current catalyst system showed that this process could be scaled up, even with lower catalyst loading. By using 2 mol% of **37**/$Cu(ClO_4)_2 \cdot 6H_2O$, 1.41g of product **39a** was obtained in 87% yield, >99/1 *dr*, and 94% *ee*. The mild reaction conditions, high enantioselectivity, high yield, readily accessible catalyst, easily scaling up, and the broad substrate scope make this method synthetically useful.[13]

4. Enantioselective Ring-opening Reactions of DA Cyclopropanes with Nucleophiles

4.1 The Asymmetric Ring-opening Reaction with Amines

An Ni-catalyzed enantioselective ring-opening reaction of 2-substituted cyclopropane-1,1-dicarboxylates with aliphatic amines has been accomplished. Under mild reaction conditions, a variety of DA cyclopropanes **40** and secondary amines **41** worked well in the presence of **34**/Ni(II) (Scheme 16), affording the corresponding ring-opening products **42** in excellent yield (up to 99%) with excellent enantioselectivity (up to 98% *ee*). This highly enantioselective reaction provides facile access to the optically active γ-substituted γ-amino acid derivatives, which are readily converted into multifunctionalized piperidines and γ-lactams.[14]



Scheme 16. Asymmetric ring-opening reactions with secondary amines.

In this reaction, it was found that the present catalyst system was highly efficient for both the asymmetric ring-opening reaction and the kinetic resolution of dineopentyl cyclopropane carboxylates **40**. The ring-opening products were obtained in good yields with 90–97% *ee*; meanwhile, the optically active DA cyclopropanes in *R* configuration were recovered in good yields with 88–95% *ee* (Table 3).[14]

4.2 The Asymmetric Ring-opening Reaction with Alcohols and Water

Based on our studies of the asymmetric ring openings of DA cyclopropanes with amines, we envisioned that, if successful, this protocol could be applied to oxygen nucleophiles, for example, alcohol and water, as part of a new strategy for the preparation of enantio-enriched γ-hydroxybutyric acid (GHB) derivatives. GHB is a well-known substance, naturally produced in the cells of the human body's central nervous system. γ-Hydroxybutyric carboxylate analogues have aroused intense interest in recent years due to their unique pharmaceutical properties.

However, employing alcohol or water as a nucleophile is quite a challenging task for the following reasons: a) compared with nitrogen or carbon nucleophiles, the nucleophilicity of oxygen is relatively weak; b) the coordination competition with the Lewis acid between oxygen nu-

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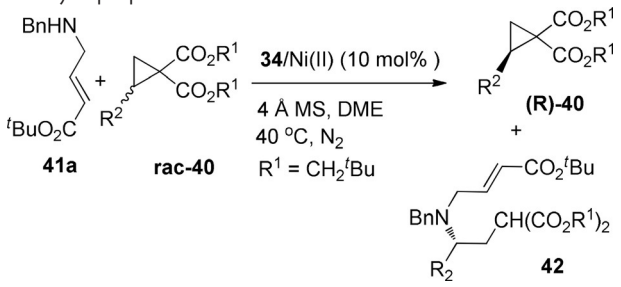
Table 3. Kinetic resolution of 2-substituted cyclopropane diesters.

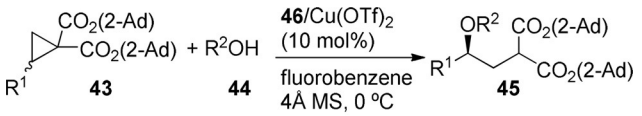


entry	R^2	conv.	(*R*)-**40**		**42**	
			yield (%)	*ee* (%)	yield (%)	*ee* (%)
1	Ph	57	42	93	39	90
2	*p*-ClC_6H_4	55	43	95	40	94
3	*p*-BrC_6H_4	55	46	93	40	97
4	*p*-MeC_6H_4	50	49	88	46	92
5	*m*-MeC_6H_4	57	41	93	42	96

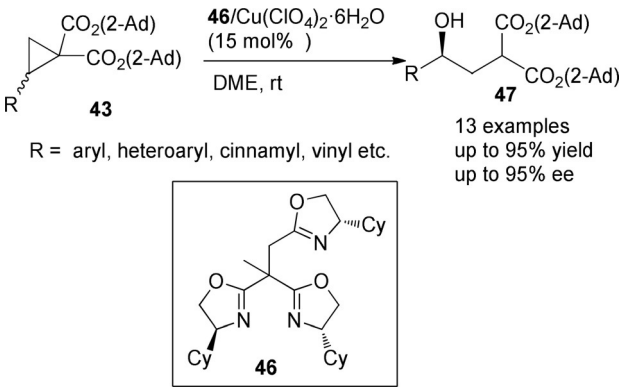
cleophiles and the chiral ligands may cause negative effects on both the activation and enantiotopic differentiation of the cyclopropane; and c) in contrast to our previous studies, which used secondary amines as nucleophiles in the ring-opening reactions of DA cyclopropanes, alcohols are sterically less-hindered nucleophiles. That may cause more difficulties for the chiral induction. Furthermore, since the molecular size of water is small, it is especially hard to control the stereoselectivity. Thus, successful examples, using water as a nucleophile in catalytic asymmetric reactions, are still limited.

We have developed the catalytic enantioselective ring-opening reaction of DA cyclopropanes **43** with a variety of alcohols **44**, including benzyl alcohol, unsaturated alcohols, fatty alcohols, secondary alcohols, and so on. With **46**/Cu(II) as the catalyst, the reaction also performed well over a broad range of DA cyclopropane substrates, leading to the ring-opening products in 56–93 % yields with 85–96 % *ee* under mild conditions. Since the benzyl group could be readily removed, this method provided synthetically useful access to a variety of enantio-enriched substituted GHB diesters (Scheme 17).[15]

We next investigated water as the nucleophile in an effort to obtain the corresponding GHB diesters **47** directly. The reaction proceeded smoothly over a broad range of DA cyclopropane substrates **43** bearing bulky ester groups, including aryl-, heteroaryl-, cinnamyl-, and



Scheme 17. Asymmetric ring-opening reactions with alcohols.



Scheme 18. Asymmetric ring-opening reactions with water.

vinyl-substituted cyclopropanes, leading to the ring-opening products in 70–95 % yields with 82–95 % *ee* at room temperature (Scheme 18). In this study, $Cu(ClO_4)_2 \cdot 6H_2O$ serves as both a Lewis acid and a buffer of the water source, which provides a fine system in the delivery of water to cyclopropanes in the asymmetric catalysis. This process provides a new strategy for the synthesis of versatile chiral γ-substituted GHB derivatives.[15]

5. Enantioselective Cyclopropanation of Olefins with Metal Carbenes

Optically active cyclopropanes are important subunits, widely present in natural products, and drug and pesticide molecules. In some cases, for DA cyclopropanes bearing aryl- and alkyl-donating substituents, the chiral information of the cyclopropanes can be preserved after the ring-opening reactions. Accordingly, considerable effort has been made to develop enantioselective cyclopropanations,

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which can provide direct access to the optically active cyclopropanes. Among the documented strategies, the enantioselective cyclopropanation of olefins with metal carbenes is one of the most efficient and practical methods for affording optically active DA cyclopropanes.[1] Effective methods were well established over a broad range of terminal olefins.

5.1 The Asymmetric Cyclopropanation of 1,2-Disubstituted Alkenes with Diazoacetate

Since Nozaki *et al.*[16] reported the first example of an asymmetric cyclopropanation of alkenes with diazo compounds, a number of elegant methods have been developed in this field on terminal alkenes. In the case of 1,2-disubstituted alkenes, probably due to the high sensitivity of metal carbenes to the steric hindrance and geometry of the alkenes, very few examples have succeeded in achieving high yields, with both high levels of diastereoselectivity and enantioselectivity in the cyclopropanation. In 2012, we developed an efficient catalytic asymmetric cyclopropanation of 1,2-substituted olefins using SaBOX/Cu(I) catalysts (Figure 1). Under mild conditions, both *cis*- and *trans*-1,2-substituted alkenes were transformed into the corresponding 1,2,3-trisubstituted DA cyclopropanes, with both excellent diastereo- and enantioselectivities.[17]

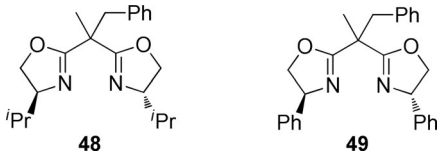
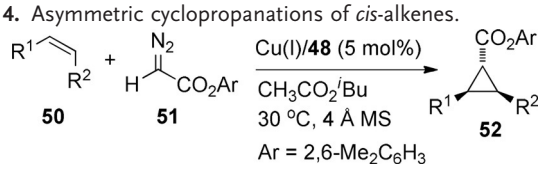


Figure 1. SaBOX Ligands used in asymmetric cyclopropanations of 1,2-substituted olefins.

As shown in Table 4, a series of *cis* β-methyl styrenes, bearing electron-donating and -withdrawing substituents on the phenyl ring, reacted smoothly in the enantioselective cyclopropanation (72–84% yield, 95/5–96/4 *dr*, and 92–94% *ee*; entries 1–4). Both dihydronaphthalene and indole-derived alkenes were tolerated in this reaction system (entries 6–7). The sterically more demanding *cis* β-ethyl styrene also worked well, leading to the corresponding DA cyclopropane in 93/7 *dr* with 86% *ee* (entry 8).[17]

On the other hand, under the catalysis of **49**/CuOTf, the optically active 1,2,3-trisubstituted DA cyclopropanes were produced from a variety of *trans*-1,2-substituted olefins (Table 5). Single diastereomers, with excellent levels of enantioselectivity (94–97% *ee*), were obtained over a broad scope of *trans* β-methyl styrene derivatives, regardless of their electronic nature. More-hindered *trans* alkenes and trisubstituted olefins were also suitable substrates, affording the desired products in high yields with >99/1 *dr* and 96–98% *ee* (entries 8–10). Remarkably, the cyclopropanation of *trans* β-methyl styrene was performed on a 50 mmol scale with only 0.05 mol% catalyst loading, giving 6.16 g of the DA cyclopropane in 44% yield with 98% *ee*, which represents one of the lowest catalyst loadings in copper-catalyzed cyclopropanation reactions so far.[17]

Table 4. Asymmetric cyclopropanations of *cis*-alkenes.



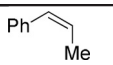
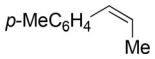
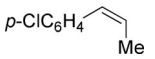
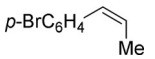
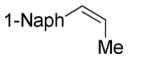
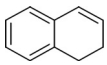
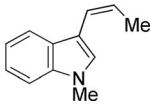
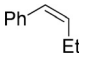
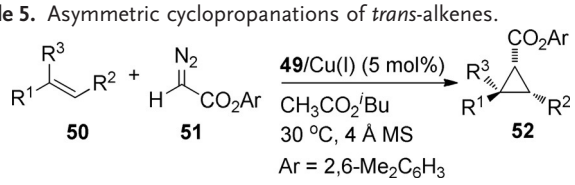
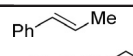
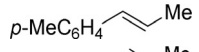
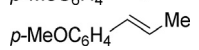
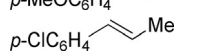
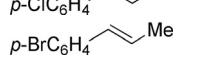
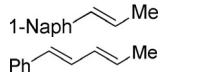
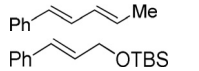
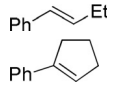
entry	alkene	yield (%)	*dr*	*ee* (%)
1		84	96/4	92
2		78	96/4	93
3		72	95/5	94
4		72	95/5	93
5		60	97/3	89
6		95	97/3	89
7		60	97/3	86
8		66	93/7	86

Table 5. Asymmetric cyclopropanations of *trans*-alkenes.



entry	alkene	yield (%)	*dr*	*ee* (%)
1		89	>99/1	96
2		99	>99/1	96
3		96	>99/1	94
4		96	>99/1	97
5		73	>99/1	96
6		60	>99/1	96
7		97	93/7	96
8		64	>99/1	98
9		84	>99/1	97
10		82	>99/1	96

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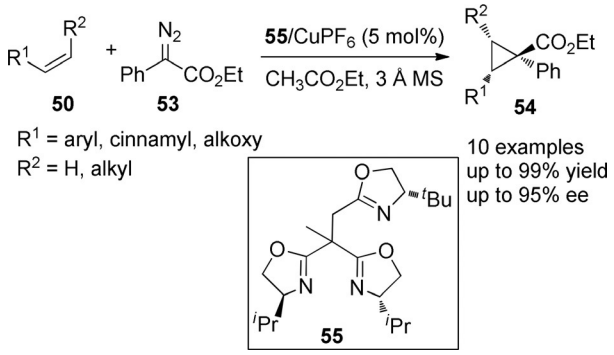
5.2 The Asymmetric Cyclopropanations of Alkenes with Phenyldiazoacetate

Compared with the most employed diazoacetates, for example, ethyl diazoacetate, diazo compounds bearing both donor and acceptor substituents, such as phenyldiazoacetate **53**, lead to more functionalized 1,1-disubstituted DA cyclopropanes. The enantioselective cyclopropanation of alkenes with phenyldiazoacetate was developed by using **55**/Cu(I)-catalysis, providing an efficient method for the synthesis of tri- or tetra-substituted cyclopropane derivatives with high diastereoselectivities and enantioselectivities in high yields (Scheme 19).[18]



Scheme 19. Asymmetric cyclopropanations of alkenes with phenyldiazoacetate.

5.3 The Asymmetric Cyclopropanations of Alkenes with Phenyliodonium Ylide

Catalytic asymmetric cyclopropanation of olefins with metallocarbenes of malonate is one of the most direct methods to produce the optically active 1,1-cyclopropane dicarboxylates. However, only a very few examples of cyclopropanation of terminal olefins with malonate-derived metal carbenes are demonstrated, by employing rhodium catalysts with high levels of diastereoselectivity and enantioselectivity.[19] We have developed the enantioselective cyclopropanation of olefins with phenyliodonium malonate ylide in the presence of **56**/Cu(I) catalyst (Figure 2).[20]

Terminal alkenes with a variety of different substituents were suitable substrates. As shown in Table 6, regardless of the electron nature, alkenes bearing substituents at the

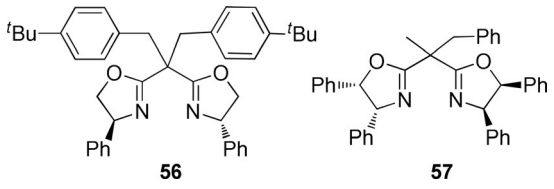
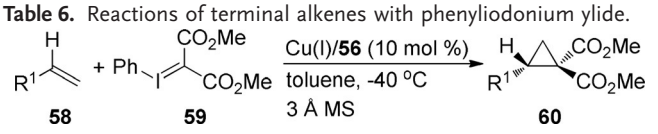


Figure 2. SaBOX Ligands used in asymmetric cyclopropanations.

Table 6. Reactions of terminal alkenes with phenyliodonium ylide.

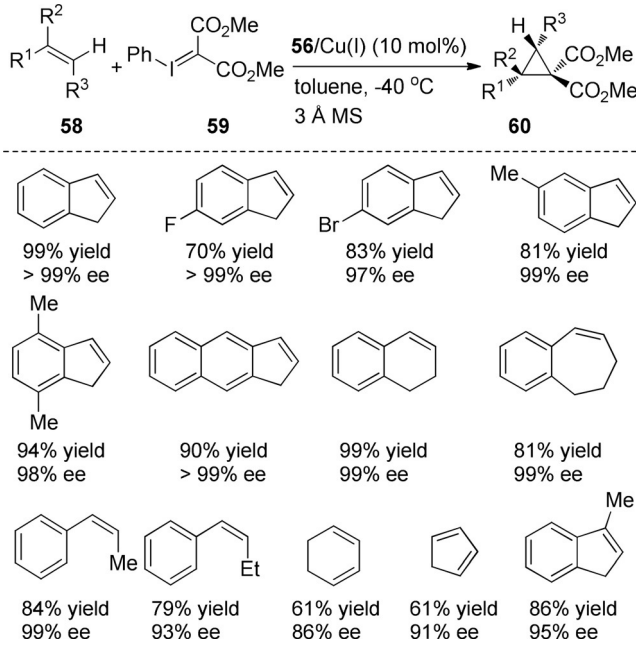


entry	R^1	yield (%)	*ee* (%)
1	*p*-BrC_6H_4	99	95
2	Ph	85	91
3	*p*-ClC_6H_4	93	95
4	*p*-$CF_3C_6H_4$	99	96
5	*p*-$ClCH_2C_6H_4$	79	94
6	*p*-MeC_6H_4	99	92
7	*o*-MeC_6H_4	99	92
8	*m*-MeC_6H_4	97	93
9	*p*-PhC_6H_4	95	92

para-, *ortho*-, and *meta*-positions of the phenyl ring were all tolerated, leading to the desired DA cyclopropanes in high yields with good to excellent enantioselectivities (87–96 % *ee*).[20]

The reaction also performed well with various disubstituted and trisubstituted olefins, affording the corresponding 1,1-cyclopropane diesters in excellent yields (up to 99 %) and as single diastereomers with excellent enantioselectivities (up to > 99 % *ee*) (Scheme 20).[20]

The present method was found potentially useful in organic synthesis, because of the readily accessible starting materials, cheap catalysts, as well as the excellent levels of diastereo- and enantioselectivity.



Scheme 20. Cyclopropanations of alkenes with internal double bonds.

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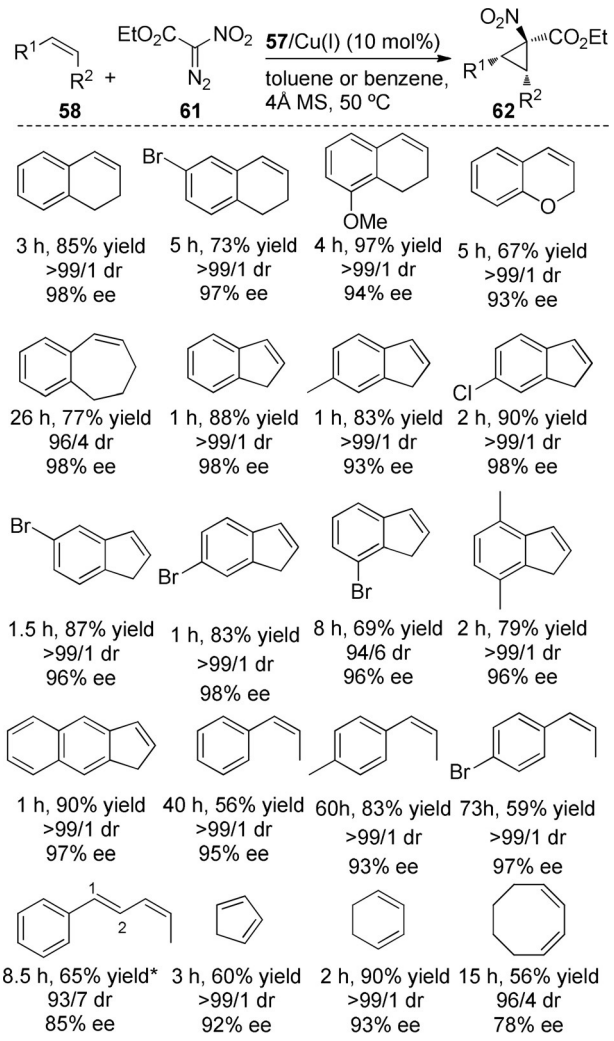
5.4 Cyclopropanations of 1,2-Disubstituted Olefins with α-Nitrodiazoacetates

Nitrocyclopropane carboxylates are an important class of compounds that are suitable precursors of biologically important cyclopropane α-amino acids. One of the most effective methods to prepare these compounds is the asymmetric cyclopropanation of olefins with nitro metal carbene complexes. Like other diazo compounds with two electron-accepting substituents, nitrodiazoacetate is inherently less reactive to forming metal carbene complexes. Usually, when a copper catalyst is used, harsh conditions are required, leading to unsatisfying results on both the reactivity and stereoselectivity. We have developed the asymmetric cyclopropanation of 1,2-disubstituted olefins with α-nitrodiazoacetates using **57**/copper(I) (Figure 2) as the catalyst (Scheme 21). With this cheap and readily available sidearm-modified bisoxazoline-copper(I) complex, the cyclopropanation performed well over a wide scope of *cis*-disubstituted olefins, giving the desired products in 56–97 % yields with 94/6–99/1 *dr* and 92–98 % *ee*. This method provides efficient access to the synthesis of optically active cyclopropane α-amino acids, as well as various chiral unnatural α-amino acid derivatives.[21]



Scheme 21. Asymmetric cyclopropanations of 1,2-disubstituted olefins with α-nitrodiazoacetates.

6. Summary

During the past decade, we have developed a series of catalytic asymmetric reactions with regard to the ring-opening process of donor-acceptor cyclopropanes and cyclobutanes. By employing copper and nickel complexes as the chiral catalysts, a range of highly enantioselective ring-opening and annulation reactions of DA cyclopropanes and cyclobutanes with various nucleophiles, such as amines, alcohols, and water or π-systems, such as nitrones, azomethine imines, enol silyl ethers, and indoles, have been demonstrated in this account. These methods provide versatile access to a number of useful chiral building blocks, for instance, optically active γ- and δ-functionalized carbon skeletons, as well as multifunctionalized heterocycles bearing multiple chiral centers. However, there are still challenges in the field of asymmetric ring-openings and annulations of DA cyclopropanes. For example, enantioselective reactions with DA cyclopropanes containing an alkyl substituent as a donor, or bearing only one acceptor group, have not been solved yet. Meanwhile, asymmetric reactions undergoing a dynamic kinetic resolution pathway are still limited to DA cyclopropanes containing electron rich donors, such as *para*-methylphenyl and alkoxy substituents. Therefore, the development of new catalyst systems and new strategies are still in demand. Furthermore, wider application of the reactions described in this account can be expected in the total synthesis of natural products and important chiral molecules in organic synthesis.

Acknowledgements

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