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Side Arm Strategy for Catalyst Design: Modifying Bisoxazolines for Remote Control of Enantioselection and Related

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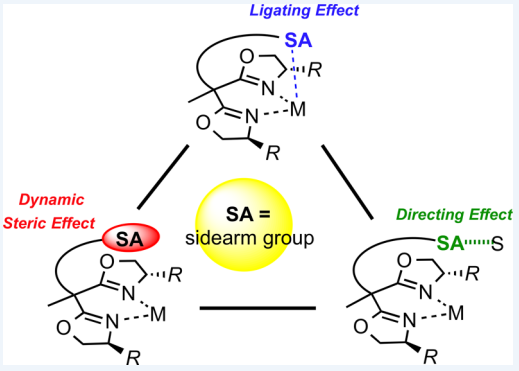
CONSPECTUS: In asymmetric catalysis, the remote control of enantioselection is usually difficult due to the long distance communication between the chiral center of the catalyst and the reactive site of the substrate. The development of efficient and highly enantioselective catalysts for such reactions is of great importance and highly desirable. The stereocontrol over an asymmetric reaction is a delicate process (ca. 3.0 kcal/mol difference in transition states can lead to >99/1 enantiomeric selectivity at room temperature), it therefore requires fine-tuning on the electronic nature of the central metal together with a precisely created cavity to accommodate the substrates and reagents. We envision that a solution is the design of new catalysts by finding an easy and efficient way to tune the electronic properties, the chiral space, and the shape of the catalytic site. Since an extra coordination group in the organometallic complex could not only alter the microenvironment around the metal center in a three-dimensional manner but also tune the electronic properties of the metal center, about 10 years ago, we introduced a side arm strategy for ligand/catalyst design.



This Account describes our efforts toward this goal. Based on this side arm strategy, we have developed two series of ligands based on the bisoxazoline framework; namely, trisoxazoline (TOX) ligands and side armed bisoxazoline (SaBOX). The "side arms" are shown to play multiple roles in different cases, for example, as a ligating group, a steric group, or a directing group, which are dependent on the metal and the functionality at the side arm. Metal catalysts based on these ligands have proven to be highly efficient for a number of asymmetric transformations, including Friedel–Crafts reaction, Kinugasa reaction, Nazarov reaction, 1,2-Stevens rearrangement, Cannizzaro reaction, and cyclopropanation. In comparison with the parent BOX ligands, the metal catalysts based on these TOX and SaBOX ligands usually exhibit higher efficiency and diastereo- and enantioselectivity with better impurity tolerance and stability. Moreover, in several TOX–metal complex catalyzed reactions such as Friedel–Crafts reaction and [3 + 2] cycloaddition, stereoselectivity could be switched based on reaction conditions. These ligands were particularly prominent in the remote controls of enantioselection such as the conjugate additions to alkylidene malonates and ring-opening/cyclization cascades of cyclopropanes, for which high stereoselectivity is usually difficult to achieve due to the poor chiral communication. The works by us and other groups have demonstrated that the side arm strategy can be employed as a general principle for ligand and catalyst design and should not be limited to the BOX scaffolds and the reactions described in this Account. Wide application of the new strategy in organometallic homogeneous catalysis can be anticipated.

1. INTRODUCTION

The development of efficient and highly stereoselective catalysts is of central importance in asymmetric catalysis. Because stereocontrol over an asymmetric reaction is a delicate process (ca. 3.0 kcal/mol difference in transition states can lead to >99/1 enantiomeric selectivity at room temperature),[1] it requires fine-tuning of the electronic nature of the central metal together with a precisely forged cavity to accommodate the substrates and reagents. Accordingly, the catalyst design is to find an easy and effective way to control these factors.

C_2-Symmetric bisoxazolines (BOX) have been established as a kind of powerful ligand in asymmetric catalysis.[2−4] Inspired by the versatility of BOX, C_3-symmetric trisoxazolines have also been developed and successfully applied in several asymmetric reactions,[5−14] in particular, for elegant Trisox developed by Gade et al.[8−13] (Scheme 1). Because an extra coordination group in an organometallic complex will strongly influence the shape, the space, and the electronic properties of the central metal, we introduced a side arm (SA) strategy based on bisoxazolines for ligand/catalyst design.[15,16] This strategy is initiated from the asymmetric Friedel–Crafts reactions of indole with electron-deficient olefins. We noticed that ^{t}Bu-BOX/Cu(II) afforded up to 99.5% ee in the reaction of indoles with unsaturated α-ketoesters (eq 1, Scheme 2)[17] but only gave a moderate enantioselectivity (up to 69% ee) in a similar

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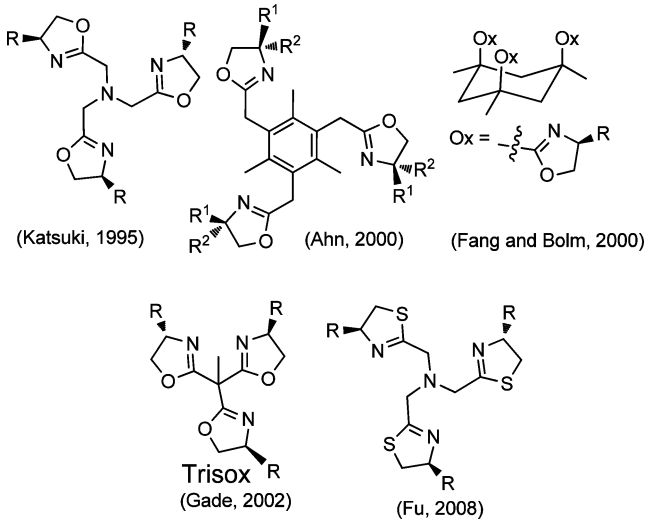
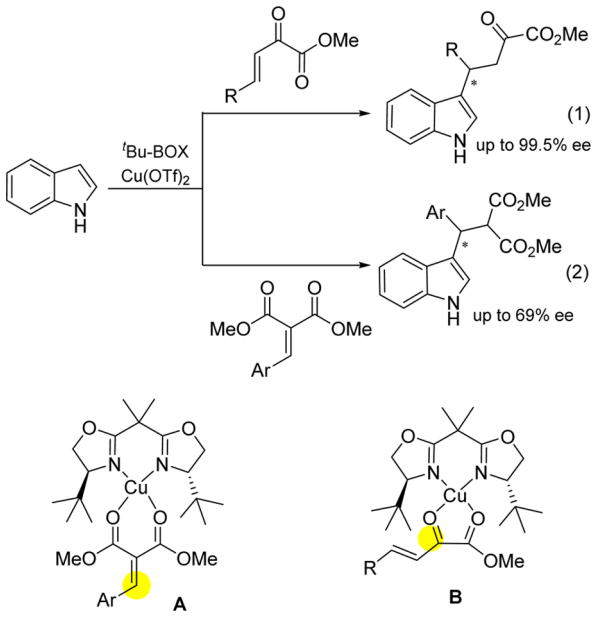
Scheme 1. Representative C_3-Symmetric Trisoxazoline Ligands



Scheme 2. Asymmetric Friedel–Crafts Reactions of Indole with Electron-Deficient Olefins



reaction with alkylidene malonates (eq 2).[18] The low enantioselectivity in the latter case could be ascribed to the fact that the electrophilic carbon is far from the chiral inducing center of the ligand (model A). In comparison, one face of the prochiral double bond of the β,γ-unsaturated α-ketoesters was effectively shielded by the bulky *tert*-butyl group (model B). We conceived that installation of a pendant oxazoline group (SA group) at the bridge carbon of the BOX ligands might modulate the shape, the space, and the electronic properties of the catalytic site as shown in Figure 1. Supposedly, the side arm can act in different roles depending on the properties of the chosen groups. For example, the side arm could exert only a steric effect by virtue of its steric hindrance or bind to the metal like a pendant ligand. Besides, the side arm may also behave as a directing group to assist in the stereochemical control and reagent/substrate activation. In a sense, the side arm behaves as a controller-like group for catalyst performance, providing

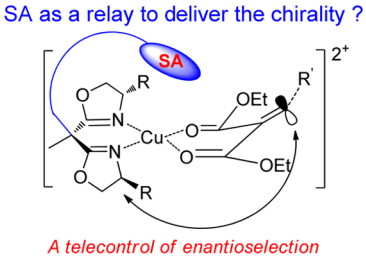
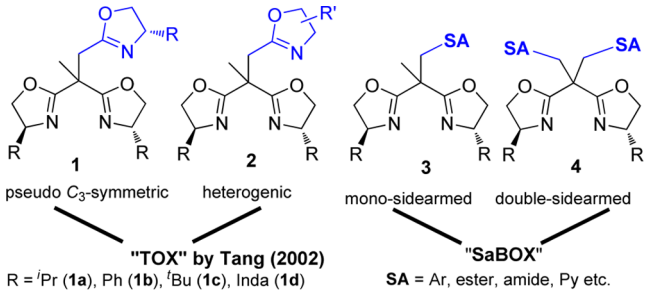


Figure 1. Relay the chirality by side arm group (SA).

access to new catalysts for the improvement of reaction selectivity and efficiency.

On the basis of this idea, we have successfully constituted two series of ligands (Scheme 3): (1) pseudo-C_3-symmetric

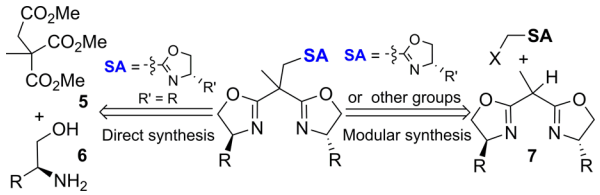
Scheme 3. TOX and SaBOX Ligands



trisoxazolines[15] (TOX) with a pendant oxazoline group located at the bridge carbon and (2) side armed bisoxazolines (SaBOX) with one or two pendant groups other than oxazoline at the bridge (SA ≠ oxazoline).

These ligands can be readily synthesized in 10 g scale via a direct synthetic route[15] or modular synthesis[19] as shown in Scheme 4. Typically, pseudo-C_3-symmetric trisoxazolines such

Scheme 4. Synthesis of TOX and SaBOX



as ^{i}Pr-TOX (R = ^{i}Pr, **1a**) can be prepared in two steps from the corresponding triester **5** and chiral amino alcohols **6** (left, Scheme 4). For the synthesis of other types of ligands in which the SA group is different from the backbone oxazoline such as heterogenic TOX ligands **2** and SaBOX ligands **3** and **4** (SA ≠ oxazoline), three- or four-step modular synthetic approaches from BOX **7**, which was first developed by Gade et al. for the synthesis of Trisox,[8] are employed (right, Scheme 4).

These ligands have been successfully applied to a number of asymmetric reactions such as Friedel–Crafts reaction,[15,19−23] [3 + 2] cycloaddition reaction,[24] Nazarov reaction,[25] Kinugasa reaction,[26−28] 1,2-Stevens rearrangement,[29] Cannizzaro reaction,[30] cyclopropanation,[31−33] etc. In particular, they are very effective in remote stereocontrols involving long distance communication between the chiral center of the catalyst and the reaction site of the substrate, such as asymmetric reactions with alkylidene malonates[15,19−23] and annulation reactions[34−38]

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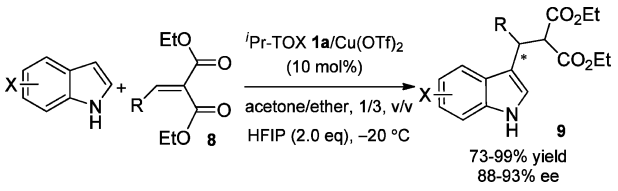
based on ring-opening reactions of D−A cyclopropane 1,1-dicarboxylates. Compared with the corresponding parent bisoxazolines, these TOX and SaBOX ligands exhibited higher efficiency and selectivity, as well as a better tolerance to impurities. In this Account, we summarize the evolution of this side arm strategy and its applications in the catalytic asymmetric transformations.

2. ASYMMETRIC REACTIONS OF ALKYLIDENE MALONATES AND RELATED TRANSFORMATIONS

2.1. The Asymmetric Friedel−Crafts Reaction with Indoles[15,19−23]

For the Friedel−Crafts reaction of indoles with alkylidene manolates, typical BOX ligands such as ^{t}Bu-BOX and Ph-BOX only afforded moderate enantioselectivities in this type of tele-stereocontrol,[18] while TOX **1a**, which contains an oxazoline side arm could furnish up to 93% ee (Scheme 5).[15] Remarkably,

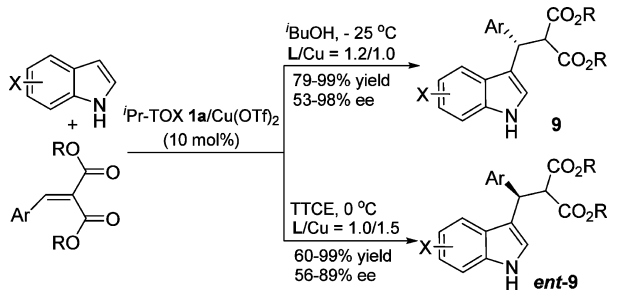
Scheme 5. TOX 1a/Cu(II) Catalyzed Asymmetric Friedel−Crafts Reaction of Indoles with Alkylidene Manolates



the reaction could be carried out under air atmosphere and was insensitive to moisture (e.g., after adding 50 equiv of water relative to the catalyst, the reaction could also deliver the product in 75% yield with 90% ee). Various indoles and alkylidene malonates (**8**, R = Ar) were well accommodated, and ethylidene malonates (R = Me) could also convert with 85% ee at −78 °C.[21]

An interesting phenomenon is that the enantioselectivity observed in alcohols was opposite to that obtained in noncoordinating solvents like 1,1,2,2-tetrachloroethane (TTCE), probably resulting from the coordination pattern change of the catalytic species in different solvents.[21] Consequently, both *R* and *S* alkylation products **9** are accessible with high enantioselectivity using **1a**/Cu(OTf)$_2$ (Scheme 6).

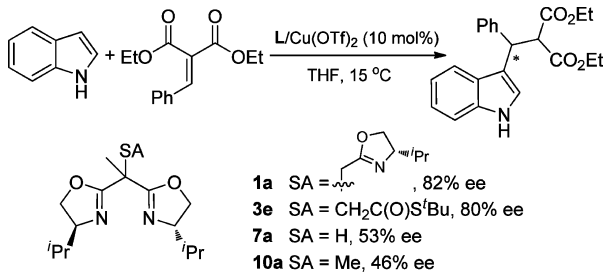
Scheme 6. Solvent Promoted Reversal of Enantioselectivity



Notably the ligand/metal ratios influenced the enantioselectivity;[21] the probable reason is that coordination patterns of the catalytic species changed, and the detailed mechanism awaits further investigation.

The side arm effect was further systematically studied by comparing a spectrum of TOX and SaBOX ligands. Both ^{i}Pr-TOX **1a** and SaBOX ligand **3e** were found to give much higher selectivity than ^{i}Pr-BOX **10a** and **7a** in THF (Scheme 7).[20] In 2006, Gade et al. studied the influence of the side arms in the

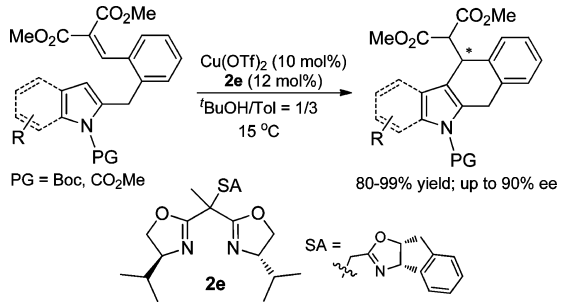
Scheme 7



bisoxazoline/copper complexes on their catalyst behaviors in the asymmetric allylic oxidation of cyclohexene. They found that the side arms did not interfere directly in this reaction but most probably play an indirect role by virtue of their steric demand.[11]

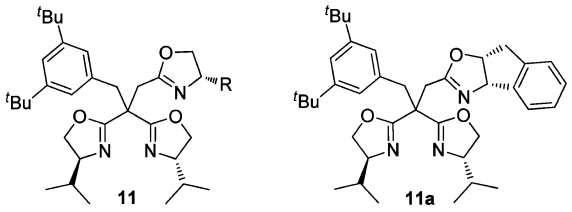
TOX/Cu(II) was also efficient for the intramolecular Friedel−Crafts alkylation reaction, and up to 90% ee could be obtained with heterogenic TOX ligand **2e** (Scheme 8).[39]

Scheme 8. TOX 2e/Cu(II) Catalyzed Intramolecular Friedel−Crafts Alkylation Reaction



Recently, we developed a type of benzyl substituted TOX, ligands **11** (Scheme 9), which are solids at room temperature

Scheme 9. TOX 11 and 11a



and much more convenient to handle than pasty ^{i}Pr-TOX. Ligands **11** were very efficient, and in the reactions of indoles with alkylidene malonates, the catalyst loading (**11a**/Cu-(OTf)$_2$) can be reduced to 0.5 mol % without loss of enantioselectivity.[40]

2.2. Asymmetric Cycloaddition Reaction with Nitrones[24]

As demonstrated in the Friedel−Crafts reaction, the TOX ligands exhibited good discrimination between the two enantiotopic faces of the double bond of alkylidene malonates. Encouraged by this result, we attempted to apply TOX ligands to the cycloaddition of 1,3-dipolar nitrones **12** with alkylidene malonates. As shown in Scheme 10, a strong side arm effect was

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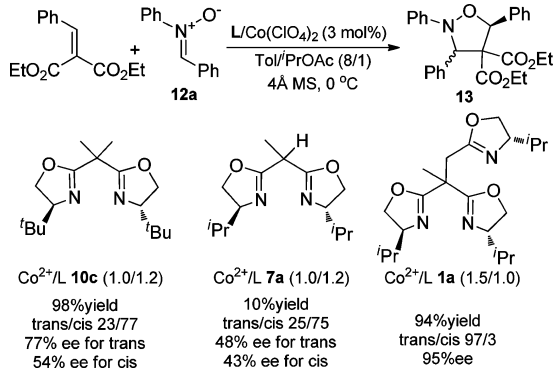
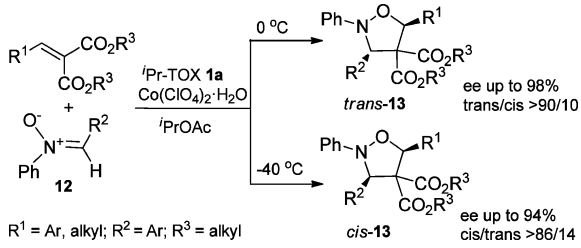
Scheme 10. Asymmetric Cycloaddition Reaction with Nitrones



also observed in this Co(II)-catalyzed cycloaddition reaction. In contrast to the poor stereoselectivity with ^{t}Bu-BOX **10c** and BOX **7a**, ^{i}Pr-TOX **1a** gave 95% ee with excellent diastereoselectivity.

Of note is that the diastereoselectivity in this reaction was temperature-dependent and both *cis*- and *trans*-isoxazolidines are accessible with high enantioselectivity (Scheme 11). Upon the cleavage of the N−O bond, the products can be easily converted to *β*-lactams and *β*′-hydroxy-*β*-amino acids.[24]

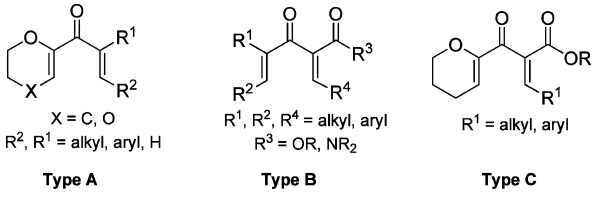
Scheme 11. Temperature-Reversed Diastereoselectivity of 1,3-Dipolar Cycloaddition of Nitrones



2.3. Asymmetric Nazarov Reaction[25]

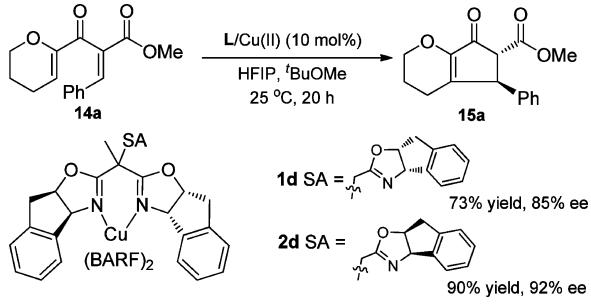
Previously PyBOX-derived complexes have been reported to deliver high enantioselectivity in the Nazarov reaction of type A and B substrates,[41,42] but they were inferior for type C (Scheme 12).[25]

Scheme 12. Representative Divinyl Ketones Used in the Nazarov Reaction



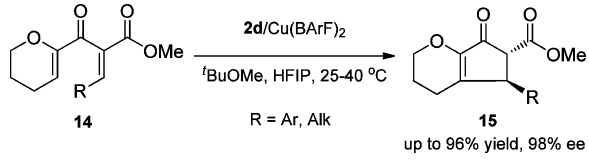
For example, in the Nazarov reaction of **14a**, In-PyBOX/$Sc(OTf)_3$ and ^{i}Pr-PyBOX/($CuBr_2$/$AgSbF_6$) both gave poor enantioselectivities (27−33% ee). Indane-derived BOX/Cu(II) and TOX/Cu(II) were found to be much more efficient. The pendant side arm significantly affected the stereoselectivity; heterochiral In-TOX **2d** was found to be more selective than homochiral **1d** (Scheme 13).

Scheme 13. Side Arm Effect in the TOX/Cu(II) Catalyzed Asymmetric Nazarov Reaction



Excellent dr (>99:1) and ee values (92−98%) were consistently obtained (Scheme 14). In all cases, trans-products **15** were isolated as a single diastereoisomer.

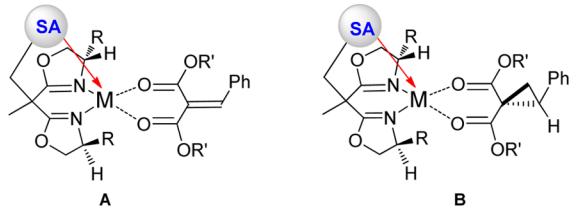
Scheme 14. Asymmetric Nazarov Reaction Catalyzed by 2d/Cu(II)



3. ASYMMETRIC RING-OPENING AND ANNULATION REACTIONS OF D−A CYCLOPROPANES

In the aforementioned Friedel−Crafts reaction, the coordination of both ester groups of malonate to the metal center, forming a rigid six-member ring (Scheme 15, model A), is

Scheme 15. Activation Fashion of Alkylidene Malonates and Cyclopropanes with SaBOX/TOX



crucial for the activation of substrates. Similarly, cyclopropane-1,1-dicarboxylates could also bind to the metal center (Scheme 15, model B), and good recognition between the two enantiomers of cyclopropane could probably be established with the assistance of side arm groups, thus enabling asymmetric transformations based on (dynamic) kinetic resolution of racemic 2-substituted cyclopropane-1,1-dicarboxylates.

3.1. Asymmetric Formal [3 + 3] Cycloaddition with Nitrones[34]

The formal [3 + 3] cycloaddition of cyclopropane-1,1-dicarboxylates with nitrones is a useful type of transformation in the synthesis of natural products.[43] DBFOX/Ni(II) was reported to afford a high enantioselectivity with cis/trans selectivity in the range of 1.0/1.4−0.8.[44] In comparison, TOX **2e**/$Ni(ClO_4)_2$·$6H_2O$ delivered both high enantio- and high diastereoselectivity (Scheme 16).[34]

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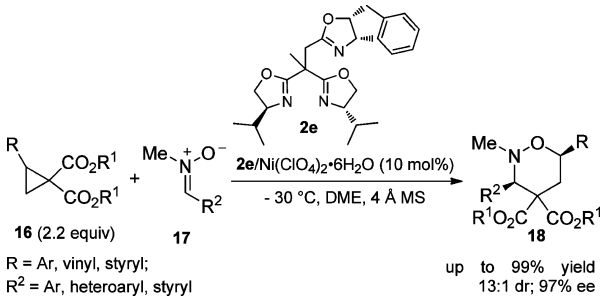
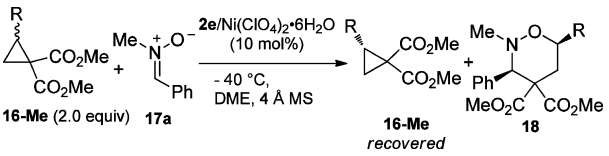
Scheme 16. Formal Cycloaddition of Cyclopropane-1,1-dicarboxylates with Nitrones



This reaction also provided an efficient protocol for the kinetic resolution of cyclopropanes (Table 1).

Table 1. Kinetic Resolution of Cyclopropanes

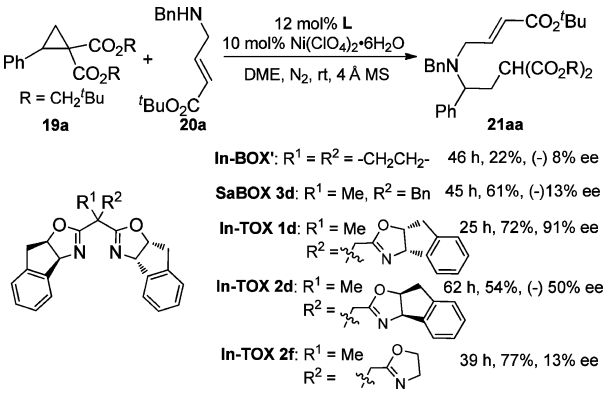


					16-Me (recovered)	
entry	R	17a (mmol)	*S*	*T* (h)	ee (%)	yield (%)
1	Ph	0.40	16	30	91	43
2	4-MeC_6H_4	0.25	97	48	96	49
3	4-BrC_6H_4	0.23	81	67	95	49
4	4-$CF_3C_6H_4$	0.23	97	168	96	49
5	4-$NO_2C_6H_4$	0.23	36	96	97	45
6	4-ClC_6H_4	0.23	70	72	94	49
7	4-$MeOC_6H_4$	0.23	13	48	92	40

3.2. Asymmetric Nucleophilic Ring-Opening with Amines[35]

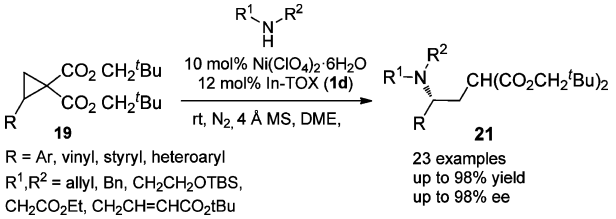
Although many examples of this ring-opening reaction have been reported, most of them invariably run under rigorous conditions such as elevated temperature even in the presence of Lewis acids. The reason is that the coordination of amines to Lewis acids will severely poison the catalysts.[45] We envisioned that introduction of a side arm oxazoline to BOX might modulate the steric and electronic nature of the nickel center and increase its tolerance toward amines. As shown in Scheme 17, using indene-derived bisoxazoline (In-BOX′), the product **21aa** was obtained in 22% yield and (−) 8% ee only even after prolonging the reaction time to 2 days. The indane−trisoxazoline (In-TOX) ligand **1d** bearing a chiral oxazoline group as a coordinating side arm significantly sped up the reaction, providing **21aa** in 72% yield with 91% ee in 25 h. Of note is that the enantioselectivity obtained with In-BOX′ and SaBOX **3d** was opposite to that with In-TOX **1d**. This critical influence of the side arm oxazolinyl group on the sense of enantioselectivity was unprecedented and intriguing. For comparison, we prepared heterochiral ligand In-TOX **2d** and nonsubstituted In-TOX **2f**. Remarkably, changing the side arm chirality could reverse the enantioselectivity (**2d** vs **1d**), while **2f** almost lost its stereoinduction, showing a strong side arm effect in this reaction.

Scheme 17. Influence of Side Arm on the Asymmetric Nucleophilic Ring-Opening of Cyclopropanes with Amines



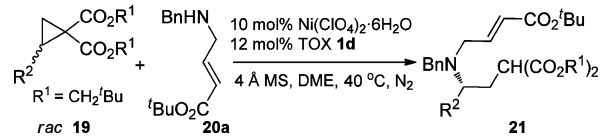
Various amines such as dibenzylamine, benzylamines, and anilines were well tolerated under these conditions. The products can be readily converted into γ-amino acid derivatives (Scheme 18).[35]

Scheme 18. Asymmetric Nucleophilic Ring-Opening of Cyclopropanes with Amines



The reaction could also proceed with an efficient concurrent kinetic resolution of cyclopropanes (Table 2).

Table 2. Kinetic Resolution of Cyclopropanes via Ring-Opening with Amines[35]



			(*R*)-19		21		
entry	R^2	conv (%)	yield (%)	ee (%)	yield (%)	ee (%)	*S*
1	Ph	57	42	93	39	90	18
2	*p*-ClC_6H_4	55	43	95	40	94	29
3	*p*-BrC_6H_4	55	46	93	40	97	25
4	*p*-MeC_6H_4	50	49	88	46	92	47
5	*m*-MeC_6H_4	57	41	93	42	96	18

3.3. Asymmetric [3 + 3] Annulation Reaction with Aromatic Azomethine Imines[36]

The In-TOX **1d**/Ni(II) complex was also efficient for the asymmetric annulations of cyclopropanes with azomethine imines **22** (Table 3). For this reaction, the DBFOX/Ni(II) catalytic system gave 30% ee only, while PyBOX/MgI_2 was almost inactive. In-BOX′ with a cyclopropylidene spacer gave a smooth reaction, but the product was nearly racemic (2% ee, entry 1). Interestingly, the sense of asymmetric induction was also reversed (entry 4) when In-TOX **1d** was replaced by In-BOX **3d** or **7d**. Using neo-pentyl ester and introducing an ortho CF_3 group to the benzoyl ring improved the ee to an excellent level (entry 8).

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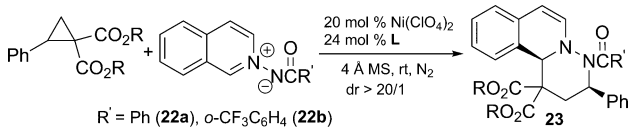
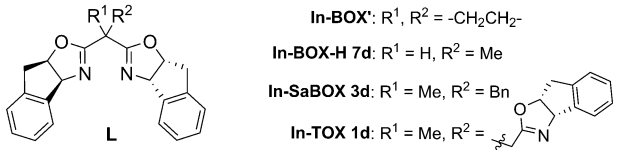
Table 3. Influence of Side Arm on the Asymmetric [3 + 3] Annulation Reaction with Aromatic Azomethine Imines





entry	R^1	L	t (h)	conv (%)	ee (%)
1	Me (**22a**)	In-BOX′	19	96	−2
2	Me (**22a**)	**7d**	11	>99	−35
3	Me (**22a**)	**3d**	65	97	−31
4	Me (**22a**)	**1d**	20	>99	56
5	Et (**22a**)	**1d**	54	70	65
6	^{i}Bu (**22a**)	**1d**	120	26	72
7	^{t}BuCH$_2$ (**22a**)	**1d**	120	15	79
8	^{t}BuCH$_2$ (**22b**)	**1d**	42	99	95

A single crystal of In-TOX **2f**/Ni(II) was developed to probe the role of the pendant oxazoline group. As shown in Figure 2,

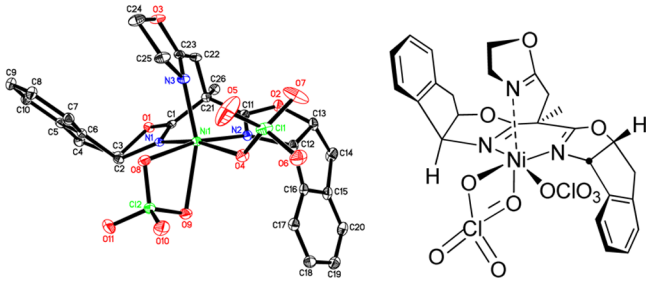


Figure 2. X-ray structure of [**2f**/Ni](ClO$_4$)$_2$ (hydrogen atoms omitted for clarity).

2f/Ni(II) adopted octahedral coordination with all three oxazoline nitrogen atoms binding to the nickel. The oxazoline side arm lies on the top of the Ni−bisoxazoline plane, thus allowing its approximation to the coordinated substrates and participation in the stereocontrol, which is well reflected by the strong side arm effect.

DFT study was also performed to understand the enantioselectivity in the [3 + 3] annulation reaction of cyclopropanes with the azomethine imines. A stable triplet six-coordinated model of the TOX **1d**/Ni^{II} catalysts and substrates was obtained, with one molecule of isoquinoline azomethine imine **22b** binding from the bottom. This octahedral coordination model is consistent with the crystal structure shown above. Notably, a strong $\pi-\pi$ interaction between the aromatic part of the side arm oxazoline and the phenyl substituent at the cyclopropane substrate was found in complex-*S*, which makes it more favored than complex-*R* by 1.7 kcal/mol (Figure 3). In complex-*R*, the two aromatic rings are too far to reach an effective $\pi-\pi$ interaction. This $\pi-\pi$ interaction could also explain the reversed sense of asymmetric induction in the two reactions mentioned above when In-TOX **1d** was replaced with BOX ligands without the indane−oxazoline side arm group.

To further verify the influence of the $\pi-\pi$ stacking interaction, control experiments were designed and conducted (Scheme 19). When the indane−oxazoline side arm was replaced with an isopropyl oxazoline group (TOX **2g**) that lacks an aromatic moiety, the enantioselectivity dramatically decreased to 42% ee. On the other hand, *o*-MeOC$_6$H$_4$ substituted cyclopropane also gave a low ee, as a result of weakened $\pi-\pi$ interaction by the hindered *ortho*-methoxy group. In fact, the methyl substituted cyclopropane was converted with significantly lower enantioselectivity, due to the absence of $\pi-\pi$ stacking interaction. This strong and beneficial directing effect of the side arm group also provides an inspiration for the design of new bifunctional catalysts.

3.4. Asymmetric [3 + 2] Annulation with Enol Ethers[37]

[*n*,3,0]-Carbobicycles containing a tertiary alcohol moiety at the bridge carbon are found in plenty of biologically active compounds. Recently, we developed a [3 + 2] annulation of cyclic enol ethers **24** with cyclopropanes, which constitutes an effective approach to these structures.[46] Although initial attempts of chiral Ph-PYBOX and Ph-DBFOX gave poor results, the use of benzyl modified BOX ligands such as SaBOX **3e** could reach a high degree of diastereo- and enantioselectivity (Scheme 20).[37] The reaction worked well with five-, six-, and seven-membered enol ethers, affording a range of [*n*,3,0] (*n* = 3−5) bicycles **26** in high enantiopurity. Remarkably, excellent diastereoselectivities (>99/1) were consistently observed with 5−6-membered substrates, and both conjugate and isolated dienol silyl ethers as well as benzene-fused ones are also suitable substrates.

3.5. Enantioselective Cyclopentannulation with Indoles[38]

SaBOX ligands were also found to be quite effective in the [3 + 2] annulation of indoles with donor−acceptor (D−A) cyclopropanes, which provides a facile route to C2,C3-fused cyclopentaindolines. The introduction of two *bulky* side arm groups (**4e**) was crucial for the high enantioselectivity. As revealed by the crystal structure of **4e**/CuBr$_2$, **4e** adopted a cage-like conformation with the two side arm groups bending over the copper center (Scheme 21). The reaction showed a broad substrate scope and was also applicable to the constructions of [3,3,3,0]-tetracyclic indolines, which contain two quaternary chiral bridging carbons.

This reaction provided a short asymmetric synthetic route for the construction of the tetracyclic core of borreverine (Scheme 22).

On the basis of the crystal structure of **4e**/CuBr$_2$ complex, a working model was proposed to elucidate the origin of the enantioselectivity (Figure 4). Considering the steric demand in both the nucleophilic attack of C3-substituted indoles to a sp^3 carbon and the donor group (PMP) stabilizing effect, the C2 carbon in cyclopropanes must have a significant carbenium ion character.[47] The approach of the *Si* face of indole to the transient (*R*)-cyclopropane (left) should experience less steric interactions with the ligand indanyl substituent. The preference for (*R*)-cyclopropane is in line with the kinetic resolution experiments, in which the recovered cyclopropanes were (*S*)-configured.

4. ASYMMETRIC CYCLOPROPANATION REACTIONS

Since Nozaki et al.[48] reported the first enantioselective cyclopropanation reaction via copper-catalyzed carbene transfer to olefins, extensive research efforts have been devoted to this area in the past decades. However, so far, few examples of

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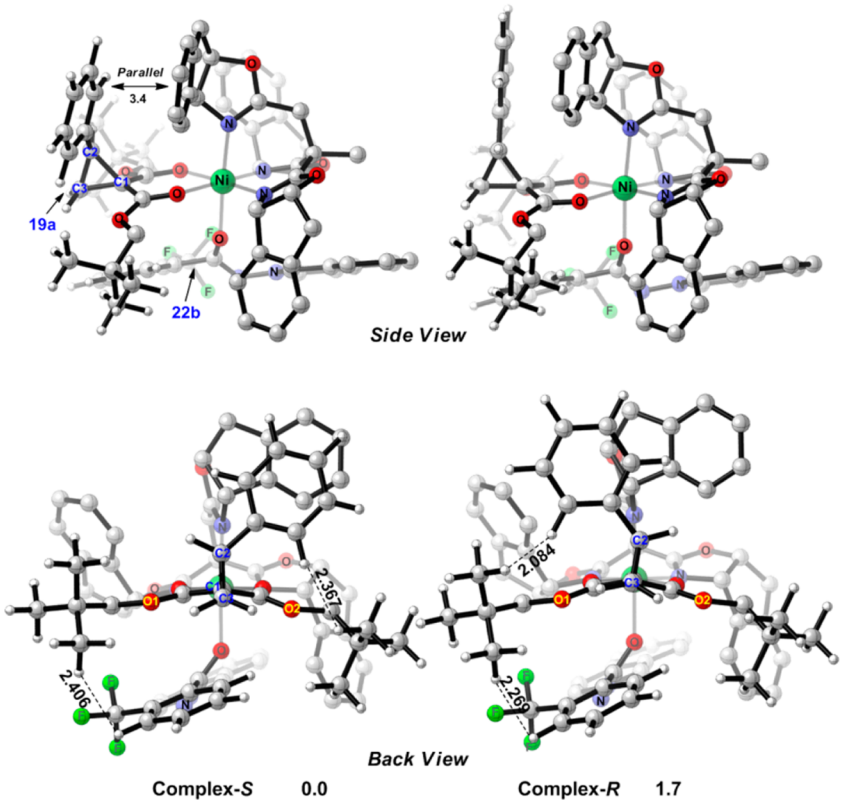
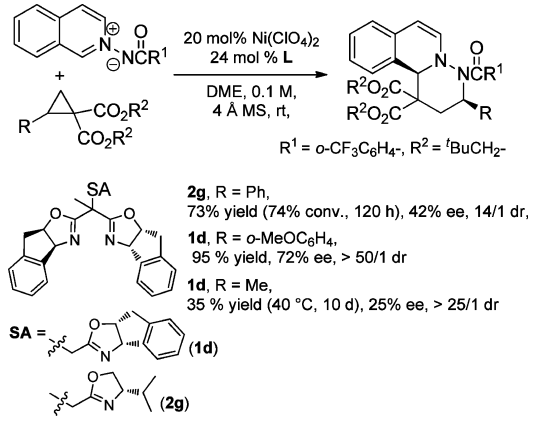
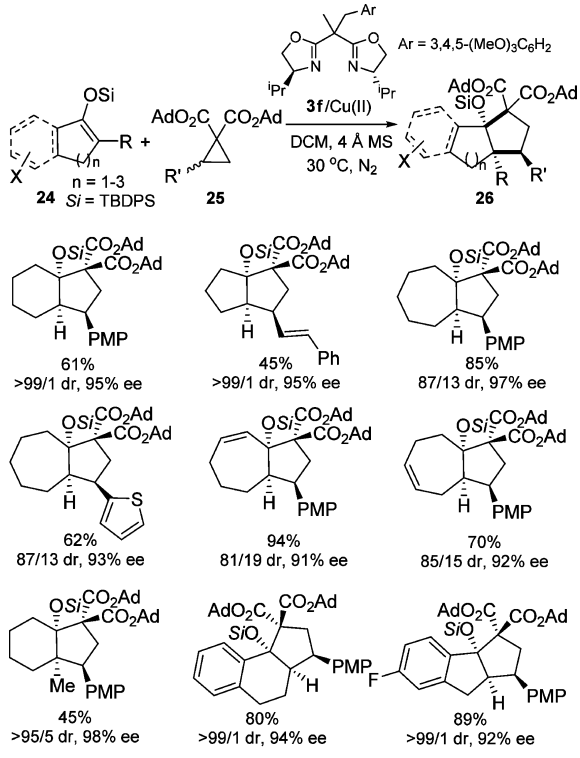


Figure 3. Optimized structures of complex-*S* and complex-*R*.

Scheme 19. Asymmetric [3 + 3] Annulation Reaction with Aromatic Azomethine Imines



Scheme 20. 3f/Cu(II) Catalyzed Asymmetric [3 + 2] Annulation with Enol Ethers



internal olefins have been reported with both high diastereo- and enantioselectivity, in sharp contrast to the great success with terminal olefins.[49,50] Gade et al. reported that heterochiral trisox might be more versatile than homochiral trisox in better compatibility with catalytic intermediate to obtain higher enantioselectivity in the cyclopropanation of olefin.[8] We found a strong side arm effect of BOX-ligand in the cyclopropanation of olefins.[31] In particular, we found that BOX ligands with a benzyl side arm such as ^{i}Pr-SaBOX **3a** were superior for *cis*-1,2-disubstituted alkenes (Scheme 23).[32]

By use of benzyl side armed Ph-BOX **3b**, *trans*-1,2-substituted alkenes could also be accomplished with excellent enantioselectivity. In particular, the generality and high diastereoselectivity are unprecedented (Table 4). Remarkably, the reaction can be scaled up to 50 mmol without loss of any efficiency and stereoselectivity. And the reaction can be carried out with as low as 0.05 mol % catalyst without loss of enantioselectivity (98% ee).

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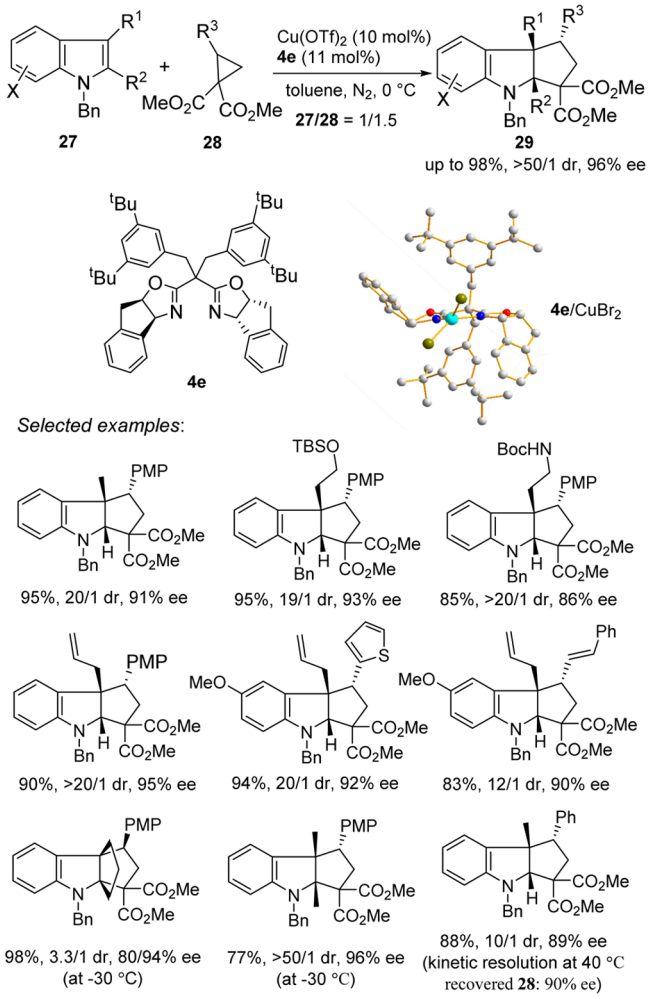
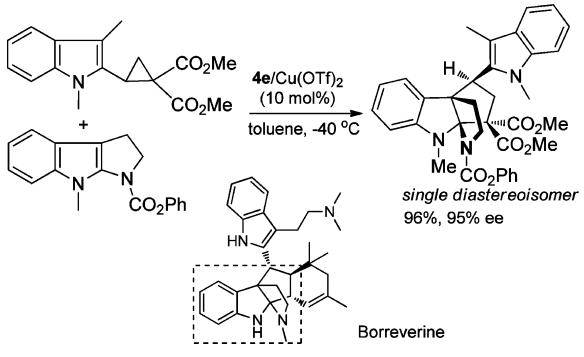
Scheme 21. SaBOX 4e/Cu(II) Catalyzed Enantioselective Cyclopentannulation with Indoles



Scheme 22. Asymmetric Synthesis of the Tetracyclic Core of Borreverine



In sharp contrast, the ligand without the benzyl side arm group only gave 60% ee (Scheme 24).

Spurred by this success, the more challenging asymmetric cyclopropanation of olefins with malonate-derived metallocarbenes has been explored, which represents effective access to useful enantioenriched 1,1-cyclopropane dicarboxylates.[51] Although the asymmetric cyclopropanation of olefins with unsymmetric disubstituted metal carbenes has been extensively studied, few examples with terminal olefins using malonate-derived metallocarbenes have been achieved with high

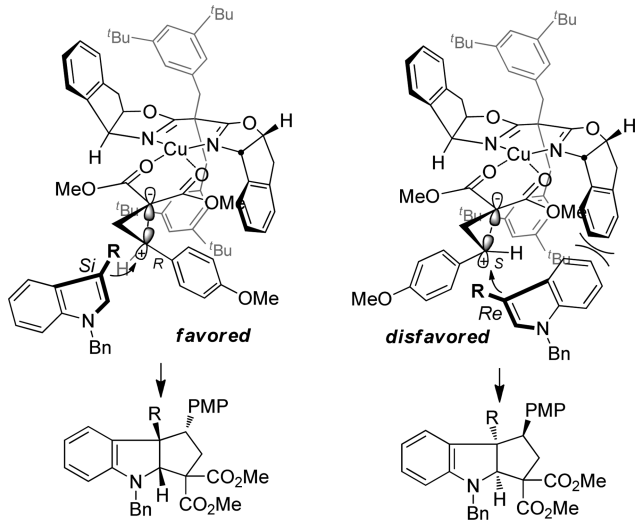
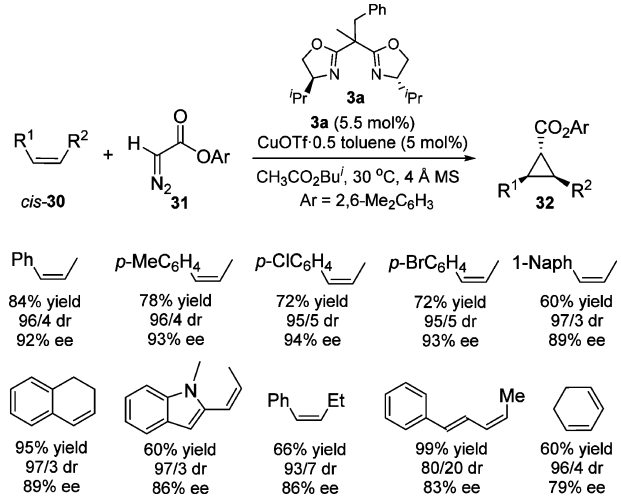


Figure 4. Stereochemical model for [3 + 2] annulation with indoles.

Scheme 23. Asymmetric Cyclopropanation of *cis*-1,2-Disubstituted Alkenes



stereoselectivity, and no internal alkenes have been disclosed with high enantioselectivity.[52]

Recently, we found that SaBOX **4f** with a double side arm modification could promote the cyclopropanation of a series of alkenes such as terminal, internal, and trisubstituted olefins with phenyliodonium ylide malonate **33** with unprecedented high enantioselectivity (up to >99% ee) (Scheme 25).[33]

The double side arms are crucial for the high enantioselectivity. As shown in Scheme 26, Ph-BOX/$Cu(CH_3CN)_4PF_6$ afforded 66% ee, while benzyl SaBOX **3b** gave a similar result. Surprisingly, installation of two benzyl groups (**4b**) dramatically increased the enantioselectivity to 86% ee. SaBOX **4f** with two bulky side arm groups was even more selective. Lowering the temperature could further increase the enantioselectivity to 95% ee.

X-ray crystallographic analysis shows that $Cu(CH_3CN)_4PF_6$/**4f** (Figure 5) adopted a distorted square-planar coordination, with the sum of bond angles of N3−Cu−N1, N3−Cu−N2, and N1−Cu−N2 being 359.99°. Both pendant phenyl groups swing toward the copper center and shield the upper and lower faces of coordination plane. It unveiled that this complex is in fact a *C*1-symmetric chiral cage, because the bond angle of N3−Cu−

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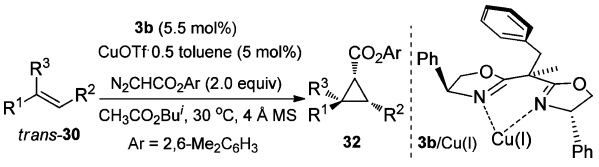
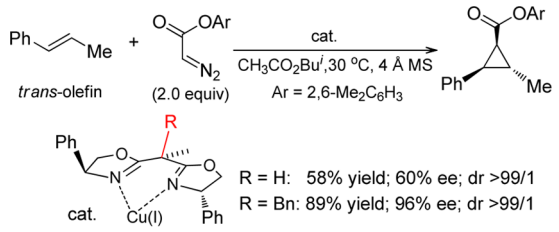
Table 4. Asymmetric Cyclopropanation of *trans*-Alkenes



entry	alkene	yield (%)	*trans*/*cis*	ee (%)
1	Ph, Me	89	>99/1	96
2	*p*-MeC$_6$H$_4$, Me	99	>99/1	96
3	*p*-MeOC$_6$H$_4$, Me	96	>99/1	94
4	*p*-ClC$_6$H$_4$, Me	96	>99/1	97
5	*p*-BrC$_6$H$_4$, Me	73	>99/1	96
6	1-Naph, Me	60	>99/1	96
7	Ph, Me	97	93/7	96
8	Ph, OTBS	64	>99/1	98
9	Ph, Et	84	>99/1	97
10	Ph	82	>99/1	96

Scheme 24. Influence of the Benzyl Side Arm on the Cyclopropanation Reaction



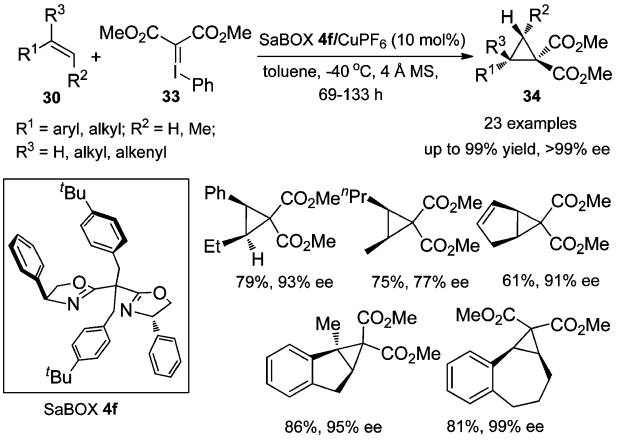
N1 is distinctively larger than that of N3−Cu−N2 (148.38(10)° vs 118.69(10)°) and the bond length of Cu−N1 is shorter than that of Cu−N2 (1.945(2) vs 2.012(2) Å). This *C*2- to *C*1-symmetry distortion probably enhanced the stereoselectivity.

5. OTHER ASYMMETRIC TRANSFORMATIONS

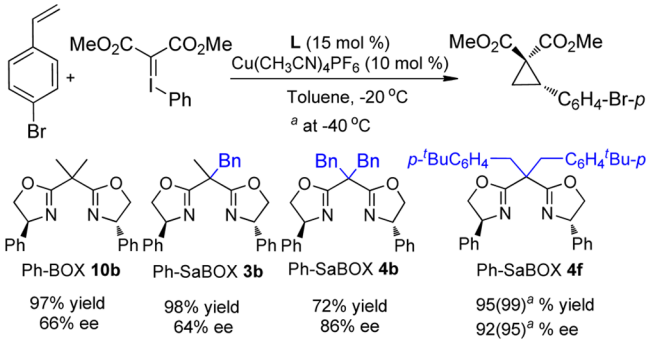
5.1. Asymmetric Kinugasa Reactions[26−28]

Enantioselective catalytic Kinugasa reaction of alkynes with nitrones as an appealing synthetic route to chiral β-lactams has attracted considerable research interest. Typical BOX **10a−c** were in fact employed by Miura et al. in the first catalytic asymmetric Kinugasa reaction, but only moderate enantioselectivity (up to 57% ee) was obtained.[53] ^{i}Pr-TOX **1a**, with a

Scheme 25. Cyclopropanation of Terminal, Internal, and Trisubstituted Olefins with Phenyliodonium Ylide Malonate



Scheme 26. Crucial Effect of the Double Side Arms for High Enantioselectivity



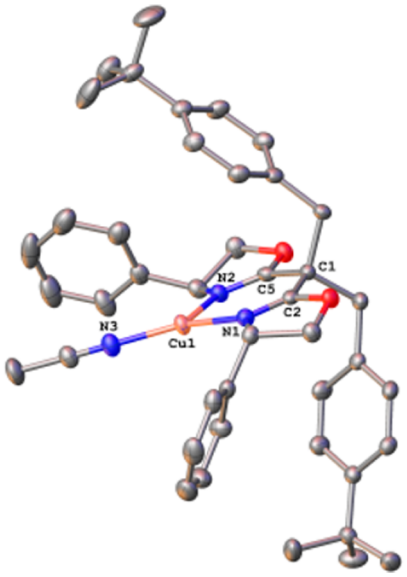


Figure 5. Molecular structure of **4f**/Cu(CH$_3$CN)$_4$PF$_6$.

side arm modification, was found to be much more selective than the BOX ligands for this reaction, giving 82% ee and 15/1 dr (Scheme 27).[26,27] Notably, Cu(II) salts can be directly employed, and the reaction can be conducted even under an air atmosphere without rigorously dry conditions.

The indanyl framework (In-TOX **1d**) was later identified to be much more selective for this reaction and improved the ee to

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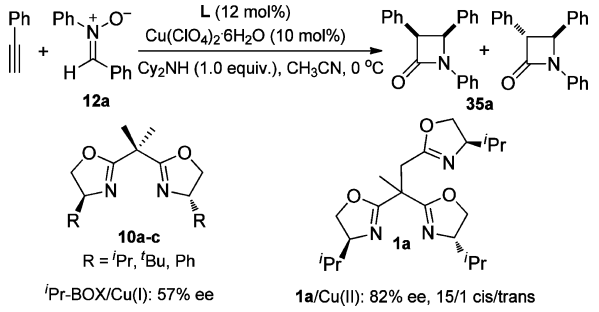
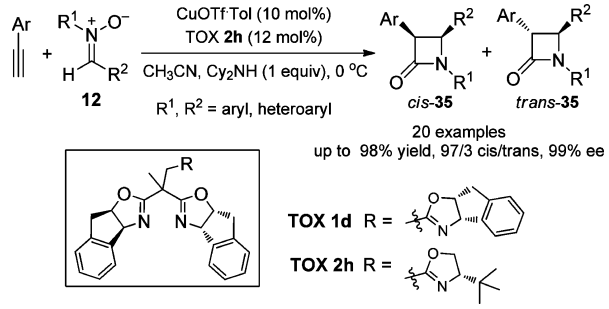
Scheme 27. Comparison of BOX and TOX Ligands on the Asymmetric Kinugasa Reaction



a 90% level. In-TOX **2h**, containing a bulky side arm oxazoline, was found to be even more efficient (Scheme 28).[28] To our

Scheme 28. TOX/Cu(I) Catalyzed Asymmetric Kinugasa Reaction



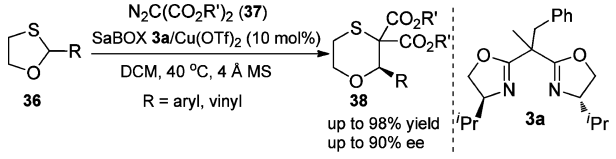
knowledge, the diastereo- and enantioselectivity obtained with the TOX/Cu(I) catalyst are among the best results so far. Evans et al.[54] also reported a high enantioselectivity with In-BOX ligands, while the current TOX system with a preference toward *C*-arylnitrones (**12**, R^2 = Ar) afforded a good complement to their reaction scope.

The ^{13}C NMR technique was employed to investigate the role of the side arm oxazoline.[27] In this case, CuCl was used instead of $Cu(ClO_4)_2{\cdot}6H_2O$. In the absence of CuCl, the ^{13}C chemical shifts of the three sp^2 carbon atom of oxazolines in TOX **1a** appeared at 163.71, 167.38, and 167.43 ppm. However, after contact with CuCl, the three ^{13}C signals merged at 164.32 ppm. These results suggested that all three nitrogen atoms of TOX **1a** might coordinate to copper. Upon addition of equimolar phenylacetylene and Cy_2NH to the mixture, the single signal of the ^{13}C signals of three sp^2 carbon of oxazolines and the O- and N-bound sp^3 carbons split again into three peaks, indicating that decoordination of the pendant oxazoline might occur.

5.2. Asymmetric [1,2]-Stevens Rearrangement[29]

Recently, we found that SaBOX **3a**/$Cu(OTf)_2$ could effectively catalyze the asymmetric [1,2]-Stevens rearrangement reaction of 1,3-oxathiolane **36** with diazo malonates **37** under mild conditions (Scheme 29). It provides facile access to optically active 1,4-oxathianes **38** (up to 90% ee). Notably, the enantioselectivity obtained with **3a** was much better than that with ^{i}Pr-BOX **10a**, indicating that a beneficial side arm effect exists.

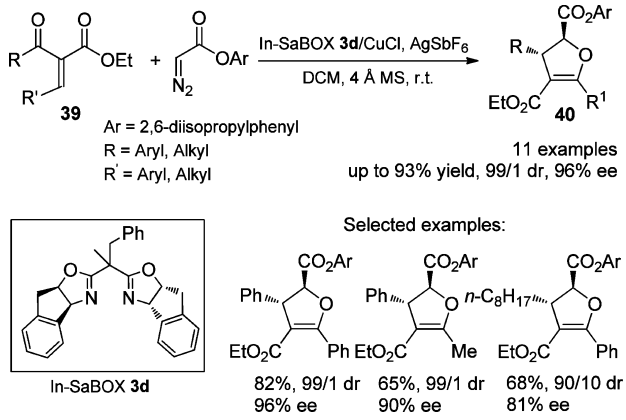
Scheme 29. Asymmetric [1,2]-Stevens Rearrangement



5.3. Asymmetric Carbene Transfer Reactions to Carbonyl Compounds[55,56]

The carbene transfer to α,β-unsaturated carbonyl compounds, followed by the addition of the transient carbonyl ylides to the C−C double bond represents convenient access to multiple functionalized 2,3-dihydrofurans.[57] In 2011, we developed a tunable reaction of α-benzylidene-β-dicarbonyls **39** with diazoacetate, which could furnish both the seven-membered heterocyclic products and the normal dihydrofurans by choosing a suitable diimine ligand or a bisoxazoline ligand.[55] Recently, we found that in the present of chiral ligand SaBOX **3d**, the reaction could also proceed with high diastereo- and enantioselectivity to afford 2,3-dihydrofurans **40** (Scheme 30).[56]

Scheme 30. 3d/Cu(I) Catalyzed Asymmetric Carbene Transfer to Carbonyl Compounds



5.4. Asymmetric Cannizarro Reaction of Glyoxals[30]

The asymmetric Cannizzaro reactions of α-keto aldehydes provide unique access to useful α-hydroxy carboxylic acid derivatives. However, the enantioselective control of this reaction is quite challenging, and the best results so far remain at a moderate level (54% ee).[58] Recently, we found that a congested TOX ligand **2i** exhibited high efficiency for this reaction, giving α-hydroxy esters **43** with unprecedented high levels of enantioselectivity (Scheme 31). Further investigation showed that the step of enantioselective addition of alcohols to glyoxals **42** contributes most to the stereoselectivity, other than contribution from the dynamic kinetic resolution of hemiacetal intermediates.[59]

6. CONCLUSIONS

During the past decade, we demonstrated the utility of the side arm strategy for chiral catalyst design. Based on this strategy, we developed a series of trisoxazoline (TOX) and side armed bisoxazoline (SaBOX) ligands, which readily complex with many metal cations such as Cu(II), Cu(I), Co(II), and Ni(II) and show excellent performance in a number of enantiose-

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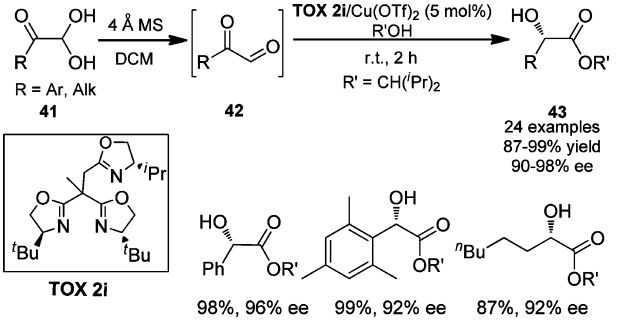
Scheme 31. Asymmetric Cannizzaro Reactions of α-Keto Aldehydes



lective reactions described in this Account. In almost all the reactions described above, compared with the corresponding parent BOX ligands, TOX or SaBOX ligands normally afforded higher reactivity and stereoselectivity, and also exhibited better stability and tolerance to impurities such as moisture and air. It is worth mentioning that the side arm strategy has also been successfully applied to the design of olefin polymerization catalysts[60] and Wittig olefination catalysts.[61] These results unequivocally indicate that the introduction of a side arm group to the parent ligands could be a useful approach for the design and development of new catalysts. As already demonstrated by us and other groups,[11,62,63] this strategy and the underlying principles should not be limited to the BOX scaffolds and the types of reactions described in this Account. Wide applications of this strategy can be expected.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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Xiu-Li Sun was born in 1971 in Inner Mongolia, China. She received her Ph.D. degree from Nankai University in 2000 under the supervision of Prof. Xiu-Zhong Zhou. Since 2000, she joined Prof. Tang's group in Shanghai Institute of Organic Chemistry, CAS. In 2013, she was promoted to a full Professor. Her research interests are development of organometallic complexes and their applications.

Yong Tang was born in September 1964 in Sichuan, China. He received his Ph.D. degree in 1996 at Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, under the supervision of Prof. Yao-Zeng Huang and Prof. Li-Xin Dai. Having spent three years as a postdoctoral researcher in the USA, he joined Shanghai Institute of Organic Chemistry, CAS, in 1999 as an associate Professor. He was promoted to a full Professor in 2000. His current research interests are the development of new synthetic methodologies and the design and synthesis of olefin polymerization catalysts.

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