

## Highly enantioselective cyclopropanation of trisubstituted olefins

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Received November 3, 2017; accepted December 24, 2017; published online January 24, 2018

A highly efficient asymmetric cyclopropanation of trisubstituted olefins with methyl diazoacetate has been developed in terms of an elaborate modified chiral bisoxazoline/copper complex as a catalyst. A broad scope of substrates is compatible with this catalyst system, including various trisubstituted olefins bearing different aryl-, fused aryl- and alkyl-substituents, providing an easy access to optically active 1,1-dimethyl cyclopropanes in good yields with excellent diastereo- and enantio-selectivity.

**cyclopropanation, enantioselective, bisoxazoline, copper, diazoacetate**

**Citation:** Li J, Zheng L, Chen H, Wang L, Sun XL, Zhu J, Tang Y. Highly enantioselective cyclopropanation of trisubstituted olefins. *Sci China Chem*, 2018, 61, <https://doi.org/10.1007/s11426-017-9200-9>

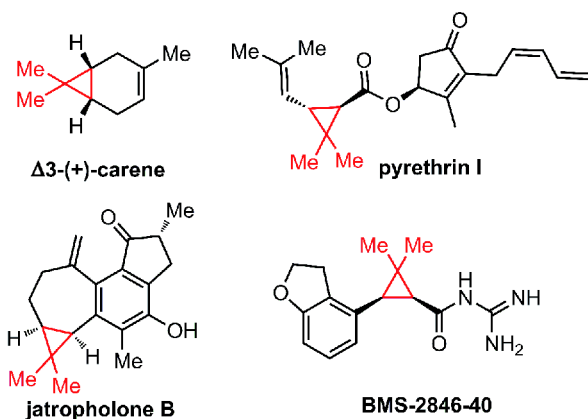
1,1-Dimethyl cyclopropanes are a class of important scaffolds, which widely exist in natural products, such as  $\Delta^3$ -(+)-carene, jatrophenolone B and pyrethrin I (Figure 1). Those natural products were usually found to be biologically useful compounds [1]. For example, since optically active pyrethrin and its analogs exhibited impressive insecticidal activity, many insecticides that are effective, low toxicity and low residue have been developed base on the 1,1-dimethyl cyclopropane skeleton [2]. Besides, enantiopure artificial molecules containing the 1,1-dimethyl cyclopropane backbone, such as BMS-2846-40, was also found significant NHE-1 inhibitory activity [3]. Asymmetric catalytic cyclopropanation of trisubstituted olefins bearing 1,1-dimethyl moiety with metal carbene generated from diazo acetates [4] provides a straightforward access to the optically active 1,1-dimethyl cyclopropanes. Therefore, developing highly efficient methods for the stereospecific cyclopropanation increasingly becomes of great interests to many chemists.

Aratani and co-workers [5] demonstrated their pioneering study on the double asymmetric induction of Schiff base/

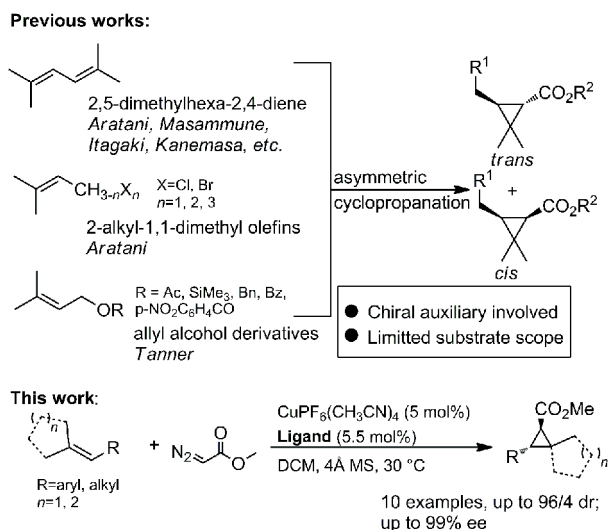
copper catalyzed asymmetric cyclopropanation of 2,5-dimethylhexa-2,4-diene with optically active *l*-menthyl diazoacetate in 1977, affording the mono cyclic product in 75% yield with 93/7 dr and 94% ee. Since then, a variety of efficient catalyst systems have been developed for the cyclopropanation of 2,5-dimethylhexa-2,4-diene, such as chiral bisoxazoline (BOX)/copper catalysts developed by Masamune *et al.* [6b] and Itagaki *et al.* [6e,6f] respectively, and chiral diamine/copper catalyst reported by Kanemasa *et al.* [6c]. However, for other trisubstituted alkenes in the enantioselective cyclopropanation, relatively less studies have been reported. Aratani *et al.* [7] studied the double asymmetric induction of cyclopropanation with 2-alkyl-1,1-dimethyl olefins, resulted in 47%–73% yield with 85%–95% ee for major *cis* isomer. Recently, Tanner *et al.* [8] reported the BOX/copper catalyzed asymmetric cyclopropanation of allyl alcohol derivatives with ethyl diazoacetate, obtaining 10%–95% ee and 50/50–88/12 dr. Although many asymmetric catalytic methodologies have been developed, the trisubstituted olefin substrates are limited to the aforementioned three types (Scheme 1) [9,10]. Furthermore, with regard to the substrate scope generality, those reported

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**Figure 1** Useful biologically active compounds bearing 1,1-dimethyl cyclopropane scaffold (color online).



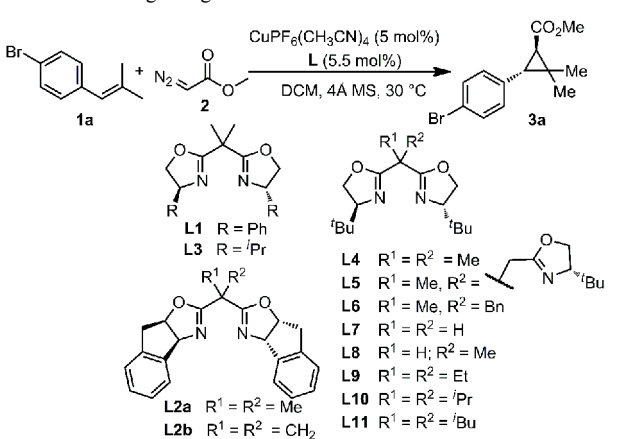
**Scheme 1** Trisubstituted olefins in asymmetric 1,1-dimethyl cyclopropanation.

methods are specific to one or one type of olefins. Moreover, due to the high sensitivity of metallocarbenes to the steric hindrance and geometry of the alkenes, for more steric bulky trisubstituted olefins bearing different aryl groups, the enantioselective cyclopropanation has rarely been realized yet. Accordingly, in consideration of the versatility of 1,1-dimethyl cyclopropanes in drugs development, a new chiral catalyst system, that is highly efficient on both reactivity and enantioselectivity, as well as with abroad substrate scopes, is still in eager demand. Here, we report our efforts on this subject.

In a metal complex involved asymmetric catalysis, the chiral ligands usually proved to be crucial for both the reactivity and the stereo selectivity. Recently, we have developed a series of side arm modified chiral bisoxazoline ligands [11], which were successfully applied in the enantioselective cyclopropanation of terminal olefins and 1,2-disubstituted olefins with different copper carbenes such as

donor-acceptor carbenes [12a], carbene acetates [12b] and carbene malonates [12c]. Our study began with the screening of a number of BOX and TOX ligands. As shown in Table 1, BOX ligands L1–L4 bearing different chiral backbones were initially examined, and *L-tert-Leucine* derivatives L4 proved to be the optimal ligand, giving the desired cyclopropane 3a in 56% yield with 88/12 dr and 79% ee (entry 5). Based on our previous study on the complex structures of TOX/nickel [13a] and SaBOX/copper [12c,13b], the pendant side-arm groups swing towards the copper center, which may force the coordinated parent oxazoline groups and allow a more suitable space to accommodate the substrates and release the products. However, in this reaction, when TOX ligand L5 and SaBOX ligand L6 were employed, both the yields and enantioselectivity declined (entries 6 and 7).

Based on the previously reported works, the bridge angle of the two oxazolines in a chiral BOX ligand has significant effects on the enantioselectivity of a reaction. For example, Davies *et al.* [14a] found that the increasing bridge angles of the chiral BOX ligands led to the increasing enantioselectivity in the In-BOX/Cu(II) catalyzed asymmetric Diels-Alder reaction. Denmark and coworkers [14b,14c] also demonstrated that when bulkier substituents were installed on the bridge carbon of the chiral BOX ligands, the corresponding bridge angles were smaller, and the enantioselectivities of the asymmetric reactions promoted by these chiral BOX ligands were increased, for some substrates in the enantioselective additions of organolithium to imines. In our recent studies on the catalytic asymmetric [2+2] tandem cyclization reactions, we utilized a strong Thorpe-Ingold effect to modify the chiral ligands, which by means of increasing the steric hindrance of the substituents on the bridge carbon of chiral BOX ligand, the enantioselectivity of the reaction could be improved [14d]. In this cyclopropanation, we noticed that, in comparison of L2a with L2b, L2b with a cyclopropyl group led to an obviously drop on both the yield and ee value (entry 2 vs. entry 3, Table 1). These results suggested that the reaction was quite sensitive to the steric demand of R<sup>1</sup> and R<sup>2</sup>, and that drove us to the screening of ligands with different R<sup>1</sup> and R<sup>2</sup> groups. With L7 and L8, containing less hindered R<sup>1</sup> and R<sup>2</sup> groups, 38% and 50% yields with 77/23 dr as well as 73% ee and 72% ee were obtained respectively (entries 8 and 9). Inspiringly, 91/9 dr and 87% ee were achieved with a diethyl substituted ligand L9 (entry 10). Further increasing the steric hindrance with diisopropyl substituents (L10) allowed the current reaction to give an 89/11 dr with 91% enantioselectivity (entry 11). However, with diisobutyl substituted ligand L11, the stereo control of this reaction was destroyed (entry 12). To our delight, both the yield and enantioselectivity of the desired cyclopropane could be increased in terms of lowering the reaction temperature to 0 °C, and gave 76% yield, 95/5 dr and 95% ee (entry 13), probably due to the lower temperature

**Table 1** Screening of ligands <sup>a)</sup>


Entry	L	Yield (%) <sup>b)</sup>	Time (h)	dr <sup>c)</sup>	ee (%) <sup>d)</sup>
1	L1	54	12	82/18	26
2	L2a	34	12	86/14	64
3	L2b	22	11	90/10	30
4	L3	31	12	82/18	47
5	L4	56	22	88/12	79
6	L5	18	12	70/30	47
7	L6	23	13	75/25	73
8	L7	38	12	77/23	73
9	L8	50	12	77/23	72
10	L9	35	12	91/9	87
11	L10	24	13	89/11	91
12	L11	25	12	80/20	78
13 <sup>e)</sup>	L10	76	12	95/5	95
14 <sup>f)</sup>	L10	49	13	95/5	96

a) Performed with 1-bromo-4-(2-methylprop-1-enyl)benzene (0.5 mmol), methyl 2-diazoacetate (1.0 mmol),  $\text{CuPF}_6(\text{CH}_3\text{CN})_4$  (0.025 mmol), L (0.0275 mmol), at 30 °C, in DCM (4.5 mL); b) isolated yield; c) determined by  $^1\text{H}$  NMR of the crude products; d) determined by Chiral HPLC; e) at 0 °C; f) at -20 °C.

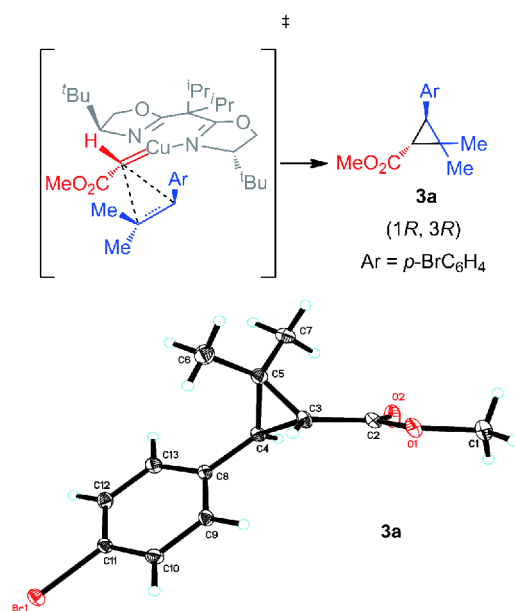
diminishing the side reactions in this catalytic system. When the reaction was carried out at -20 °C, the reaction was slow down and resulted in 49% yield with 95/5 dr in 96% ee (entry 14).

Under the optimized reaction conditions, a variety of trisubstituted olefins bearing different functional groups were subjected to the current catalytic system. As shown in Table 2, both the electron rich and poor alkenes proceeded smoothly, providing the corresponding multisubstituted cyclopropanes **3a–3e** in good yields with excellent diastereoselectivity and enantioselectivity (76%–85% yields, 91/9–95/5 dr and 94%–97% ee, entries 1–5). Remarkably, 1-naphthyl substituted cyclopropane **3f** and 2-naphthyl substituted cyclopropane **3g** could also be obtained in 81%–83% yield with 96/4–93/7 dr and 95%–99% ee (entries 6 and 7). The catalyst also proved to be highly efficient for the five- and six-membered cyclic substrates, furnishing the rigid

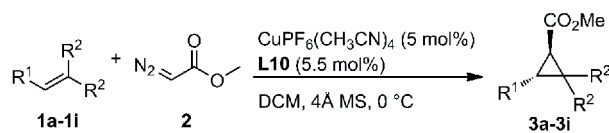
spiro products **3h** and **3i** in 95/5 dr and excellent ee value (entries 8, 9). In addition, aliphatic olefin substrate **1j** was also tolerated in the current catalytic system, affording the product **3j** in 41% yield with 95/5 dr and 85% ee (entry 10).

The enantioinduction model shown in Figure 2 was proposed to explain the accomplished high enantioselectivity. According to our previous studies on the structure of a diisopropyl substituted *L*-phenylglycine derived BOX ligand/copper complex (for details, see the Supporting Information online), the isopropyl groups on the bridge carbon are always far away from the metal center. In this model, effected by the steric hindrance from the two methyl groups of the olefin substrates, the less hindered mono-substituted carbon of the olefin substrate keep close to the copper complex. Owing to the steric repulsion between the ester group of the metal carbene and the aryl group of the olefin substrate, these two groups adopt the opposite direction. In addition, the observed enantioselectivity of the cyclopropanation could be attributed to the steric hindrance between the aryl group of the olefin and the bulky *tert*-butyl group on the chiral ligand. This model is consistent with stereochemical results and the configuration of the cyclopropane determined by X-ray crystallographic analysis [15].

In conclusion, we developed a highly efficient asymmetric cyclopropanation of trisubstituted olefins with methyl diazoacetate in terms of an elaborate modified chiral bisoxazolone/copper complex as catalyst. A broad scope of substrates was compatible with this catalyst system, including various trisubstituted olefins bearing different aryl-, fused aryl- and alkyl-substituents, providing a number of optically active multi-functionalized cyclopropanes in good



**Figure 2** Proposed enantioinduction model and crystal structure of **3a** (color online).

**Table 2** Substrate scope <sup>a)</sup>

Entry	Alkene	3	Time (h)	Yield (%) <sup>b)</sup>	dr <sup>c)</sup>	ee (%) <sup>d)</sup>
1 <sup>e)</sup>		<b>3a</b>	12	76	95/5	95
2		<b>3b</b>	12	79	95/5	97
3		<b>3c</b>	12	78	91/9	94
4		<b>3d</b>	13	81	94/6	94
5 <sup>f)</sup>		<b>3e</b>	13	85	95/5	94
6		<b>3f</b>	13	81	96/4	99
7		<b>3g</b>	10	83	93/7	95
8 <sup>f)</sup>		<b>3h</b>	12	72	95/5	92
9		<b>3i</b>	13	59	95/5	98
10		<b>3j</b>	12	41	95/5	85

a) Performed with 1-bromo-4-(2-methylprop-1-enyl)benzene (0.5 mmol), methyl 2-diazoacetate (1.0 mmol),  $\text{CuPF}_6(\text{CH}_3\text{CN})_4$  (0.025 mmol), **L** (0.0275 mmol), at 30 °C, in DCM (4.5 mL); b) isolated yield; c) determined by  $^1\text{H}$  NMR of the crude products; d) determined by Chiral HPLC; e) the absolute configuration of **3a** was determined by X-ray diffraction analysis as *1R*, *3R*, as shown in Figure 2 [15]; f) at -20 °C, with 1.5 mmol of methyl 2-diazoacetate.

yields with excellent diastereo- and enantio-selectivity. Further study on asymmetric cyclopropanation involving diacceptor diazo compounds as carbene precursor is still in progress in our laboratory.

**Acknowledgements** This work was supported by the National Natural Science Foundation of China (21432011, 21772224), Key Research Program of Frontier Sciences of Chinese Academy of Sciences (QYZDY-SSW-SLH016), the Strategic Priority Research Program of the Chinese Academy of Sciences (XDB20000000), the Youth Innovation Promotion Association CAS (2017301) and the National Basic Research Program of China (2015CB856600). We thank Dr. Xue-Bing, Leng (SIOC) and Mr. Jie, Sun (SIOC) for X-ray crystal analysis.

**Conflict of interest** The authors declare that they have no conflict of interest.

**Supporting information** The supporting information is available online at <http://chem.scichina.com> and <http://link.springer.com/journal/11426>. The supporting materials are published as submitted, without typesetting or editing. The responsibility for scientific accuracy and content remains entirely with the authors.

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- 15 CCDC 1032475 (**3a**) contains the supplementary crystallographic data. These data can be obtained free of charge from the Cambridge crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif)