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Copper-Catalyzed Enantioselective Cyclopropanation of Internal Olefins with Diazomalonates

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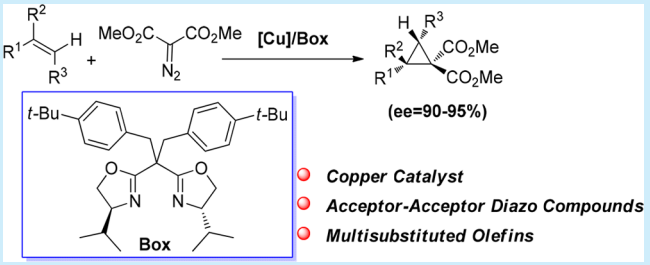
Supporting Information

ABSTRACT: The first enantioselective copper catalyzed cyclopropanation of internal olefins with diazomalonates is reported. This process provides a new method for the synthesis of chiral 1,1-cyclopropane diesters. With a chiral bi-side arm bisoxazoline−copper(I) complex, the reaction performed well over a series of substrates, giving the desired products in good yields (up to 95%) and excellent enantioselectivities (90−95% ee).



The catalytic enantioselective construction of chiral 1,1-cyclopropane diesters using copper and diazomalonates remains a difficult problem in synthetic chemistry.[1] Due to the fact that diazomalonate derivatives are substantially less reactive to the transition-metal-catalyzed decomposition, high reaction temperature is required to generate metal-carbene species. The two identical substituents on the carbene precursor minimize the discrimination of the two prochiral faces and increase the steric hindrance in the asymmetric induction of cyclopropanation, which causes a negative effect to both the enantiocontrol and the reactivity. However, asymmetric cyclopropanation between olefins and metallocarbenes of the malonate groups is very useful in organic synthesis since the resulting optically active 1,1-cyclopropane diesters are valuable intermediates that are widely applied in the total synthesis of biologically active natural products[2] as well as the synthesis of important chiral building blocks through ring-opening and ring-expansion reactions, for example, reaction with enol silyl ethers,[3] amines,[4] azomethine imines,[5] aldehydes,[6] nitrones,[7] imine,[8] indole,[9] and others.[10] Although this area is of great interest, until now there have been no reports of copper-catalyzed asymmetric cyclopropanation with dizaomalonate. In 2012, we reported a chiral bisoxzoline ligand bearing two pendent side arms which can be successfully utilized to realize the asymmetric cyclopropanation reactions between various olefins and phenyliodonium ylide.[11] However, the strategy led to the formation of one equivalent of iodobenzene as byproduct and requires much more phenyliodonium ylide due to its poor stability.[1b,12] Herein, we wish to report the copper/chiral bi-side arm bisoxazoline catalyzed enantioselective cyclopropanation of internal alkenes with diazomalonate.

In carbene-transfer reactions, diazo compounds usually act as carbene precursor.[13] In the presence of Rh or Cu(I) complexes, metallocarbenes could be generated by the decomposition of the diazomalonates derived from dimethyl malonate. In 2010, Hayashi reported that C_1-symmetric chiral diene−rhodium(I) proved to be a good catalyst system for enantiselective cyclopropanation of terminal olefins with diazomalonate.[14] In this context, we are interested in the possibility of using the cheaper Cu(I) complex to catalyze this asymmetric cyclopropanation with internal alkenes.

Initially, various chiral bisoxazoline ligands containing different side arm groups were considered, and several trends were observed. Installing one pendant benzyl side arm on the bisoxazoline, when $Cu(CH_3CN)_4PF_6$/**L2** was employed, led to a a dramatic increase in the enantioselectivity (89% yield, 90% ee, Table 1, entry 2). Encouraged by this results, then we installed two pendant benzyl side arms on the bisoxazoline ligand **L3**. Compared to **L2**, when **L3** was used, both the yield and enantioselectivity were improved from 89% yield with 90% ee to 95% yield with 92% ee (Table 1, entries 2 and 3). Moreover, changing chiral ligands from **L3** to **L4**, the ee value increased from 92% to 94%, showing that steric hindrance of the pendant group played an important role in promoting the enantioselectivity. (Table 1, entries 3 and 4). When the substituent on the side arm was an electron-withdrawing group (*p*-trifluoromethyl), **L5** led to a slightly decreased ee value (93% ee) (Table 1, entry 5).With the bulky side arm groups on modified ligand **L6**, the ee value also decreased (91% ee, Table 1, entry 6).

After the chiral ligand screening, we studied the reaction conditions with the in situ prepared $Cu(CH_3CN)_4PF_6$/**L4** complex to catalyze asymmetric cyclopropanation of indene

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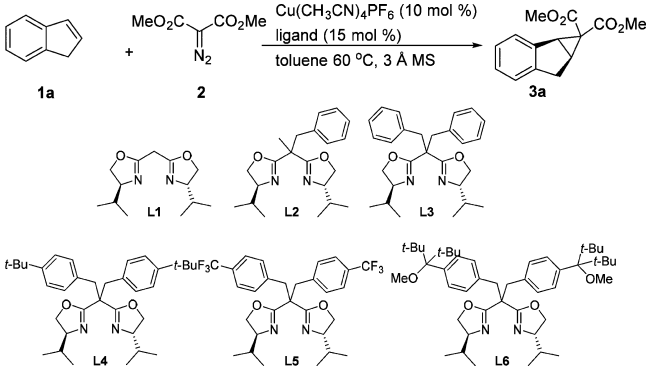
Table 1. Scope of the Ligands in the Catalytic Asymmetric Cyclopropanation[a]

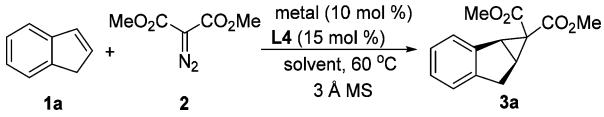


entry	ligand	time (h)	yield[b] (%)	ee[c] (%)
1	**L1**	46	55	65
2	**L2**	23	89	90
3	**L3**	23	95	92
4	**L4**	47	88	94
5	**L5**	47	90	93
6	**L6**	49	92	91

[a]Unless otherwise noted, reactions were carried out under argon atmosphere with **1a** (0.40 mmol, 1.0 equiv), **2** (0.80 mmol, 2.0 equiv), metal (0.04 mmol, 0.1 equiv), ligand (0.06 mmol, 0.15 equiv), and 3 Å MS (200 mg), at 60 °C, c = 0.1 mol/L. [b]Isolated yield. [c]Determined by chiral HPLC analysis (Chiralcel IC-3).

with dimethyl dizaomalonate. Without molecular sieves as additive, the yield was sharply decreased (Table 2, entry 2).

Table 2. Optimization of the Reaction Conditions[a]



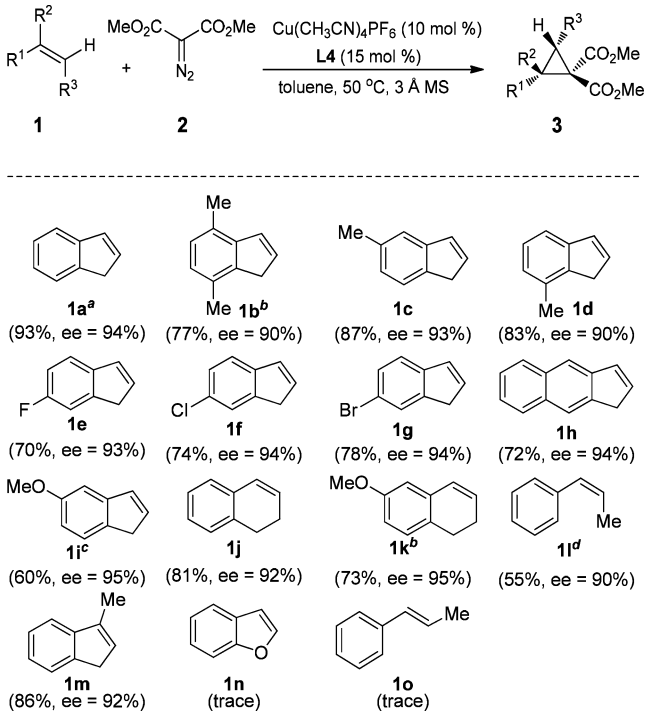
entry	metal	solvent	yield[b] (%)	ee[c] (%)
1	$Cu(CH_3CN)_4PF_6$	toluene	88	94
2[d]	$Cu(CH_3CN)_4PF_6$	toluene	33	95
3	$Cu(CH_3CN)_4PF_6$	DCE	80	92
4	$Cu(CH_3CN)_4PF_6$	*t*-BuOAc	23	9
5	$Cu(CH_3CN)_4PF_6$	DME	trace	
6	$Cu(OTf)_2$	toluene	trace	
7	CuOTf/0.5tol	toluene	trace	
8[e]	$Cu(CH_3CN)_4PF_6$	toluene	95	94
9[e,f]	$Cu(CH_3CN)_4PF_6$	toluene	90	91

[a]Unless otherwise noted, reactions were carried out under argon atmosphere with **1a** (0.40 mmol, 1.0 equiv), **2** (0.80 mmol, 2.0 equiv), metal (0.04 mmol, 0.1 equiv), ligand (0.06 mmol, 0.15 equiv), and 3 Å MS (200 mg), at 60 °C for 62 h, c = 0.1 mol/L. [b]Isolated yield. [c]Determined by chiral HPLC analysis (Chiralcel IC-3). [d]No molecular sieves. [e]At 50 °C. [f]With 5 mol % catalyst.

Studies on the solvent effect showed that 1.2-dichloroethane, *tert*-butyl acetate, and 1,2-dimethoxyethane (DME) could lower the reactivity (Table 2, entries 3−5). Meanwhile, $Cu(OTf)_2$/**L4** and CuOTf/**L4** showed almost no reactivity (Table 2, entries 6 and 7). When the reaction temperature was decreased to 50 °C, 95% yield with 94% ee was obtained (Table 2, entry 8). Furthermore, with 5 mol % catalyst, the cyclopropanation also worked well, leading to the desired product in 90% yield with 91% ee after 72 h (Table 2, entry 9).

With the optimal reaction conditions in hand, the substrate scope was investigated, showing that the current catalytic system exhibited excellent enantiocontrol ability for internal olefins. The results are summarized in Scheme 1. With

Scheme 1. Scope of the Internal Alkenes in the Catalytic Asymmetric Cyclopropanation[*,a,b,c,d]



[*]Unless otherwise noted, reactions were carried out under argon atmosphere with **1** (0.40 mmol, 1.0 equiv), **2** (0.80 mmol, 2.0 equiv), copper (0.04 mmol, 0.1 equiv), L4 (0.06 mmol, 0.15 equiv), toluene (4.0 mL), and 3 Å MS (200 mg), at 50 °C, c = 0.1 mol/L. Isolated yield. Determined by chiral HPLC analysis. [a]At 1.0 mmol scale. [b]At 40 °C. [c]**2** (2.0 mmol, 5.0 equiv). [d]**2** (1.2 mmol, 3.0 equiv).

diazomalonate **2**, various electron-poor and -rich indenes **1a**−**i** reacted smoothly, resulting in the corresponding cyclopropanes in good to high yields with excellent enantioselectivities (70−95% yields, 90−95% ee). Six-membered cyclic alkene **1j** was tolerated in this transformation, which led to a 81% yield with 92% ee. In contrast to cyclic olefins, acyclic *cis*-alkenes **1l** was also a suitable substrate for the cyclopropanations, affording **3l** in 55% yield with 90% ee. Moreover, trisubstituted alkene **1m** was also studied, giving rise to product **3m** with 92% ee. However, both benzofuran and acyclic *trans*-alkenes showed almost no reactivity. The absolute configuration of **3e** was determined as *S*,*S* by comparing the optical rotation with the literature.[11]

To demonstrate the synthetic potential of this method, a transformation was carried out. As shown in Scheme 2, reaction of cyclopropane **3l** with 4-methoxybenzaldehyde through [3 + 2] cycloaddition proceeded successfully in excellent yield without loss of optical purity. This transformation provides a facile strategy for the construction of multisubstituted tetrahedron furan derivatives.

In summary, we report the copper-catalyzed enantioselective cyclopropanation reaction of internal olefins with dimethyl diazomalonate. Remarkably, with chiral bi-side arm bisoxazoline−copper(I) complex, the reaction performed well over a

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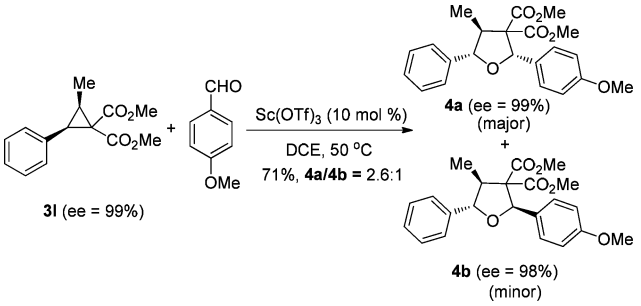
Scheme 2. Chemical Transformation of 1,1-Cyclopropane Diesters 3l



series of internal alkenes to give the desired products in excellent yields (up to 95%) and enantioselectivities (up to 95% ee). This protocol provides an effective access to the synthesis of chiral 1,1-cyclopropane diesters.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02694.

Experimental details, full spectroscopic data for all new compounds, and analytical data of ee values of products (PDF)

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Notes

The authors declare no competing financial interest.

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