A Chiral Cagelike Copper(I) Catalyst for the Highly Enantioselective Synthesis of 1,1-Cyclopropane Diesters**

Chao Deng, Li-Jia Wang, Jun Zhu, and Yong Tang*

Optically active 1,1-cyclopropane dicarboxylates are widely applied in the total synthesis of natural products, as well as important chiral building blocks in organic synthesis.[1-2] Asymmetric cyclopropanation of olefins with metalcarbenes of malonate provides an easy and direct access to these compounds.[3] Although the asymmetric cyclopropanation of olefins with unsymmetric disubstituted metal carbenes,[4] such as those derived from aryl diazoacetates,[4a,b,d] α-nitrodiazoacetates,[4c,d] and α-cyanodiazoacetates,[4e] has proven efficient for the highly enantioselective synthesis of 1,1-disubstituted cyclopropanes, only a very few examples of the cyclopropanation of malonate-derived metalcarbenes,[5] have been achieved with high enantioselectivity and diastereoselectivity.[5a-c] The main reason might be that the carbon atom of the malonate metalcarbenes is not pro-stereogenic, which causes a negative effect on the enantiocontrol.[4i] Thus, the design of chiral ligands that discriminate the two prochiral faces during asymmetric cyclopropanation is regarded as quite a challenging problem.[4] The research groups of Hayashi and Müller designed C- symmetric chiral diene-rhodium(I)[5d] and -rhodium(II) carboxylates[5b] respectively, which proved to be elegant catalysts for the enantioselective cyclopropanation of terminal olefins with metalcarbenes of malonate (16-96% yield, 29-90% ee[5b,c] and 56-75% yield, 65-98% ee[5a]). To date, the cyclopropanation of multisubstituted olefins with metalcarbenes of malonate has been rarely explored and has proved to be less enantioselective (25% ee).[5d] Very recently, we designed a cagelike bisoxazoline-derived Cu(I) catalyst and found it can promote the asymmetric cyclopropanation reaction of malonate-derived metalcarbenes with both terminal and multisubstituted olefins with high selectivity (Scheme 1). Herein, we wish to report the preliminary results.

We employed phenyliodonium ylide 2[6] as the carbene transfer reagent for the study it had previously been shown to be more active than diazomalonate for the formation of metalcarbenes.[7] As shown in Table 1, the in situ prepared bisoxazoline [Cu(L1)](CH3CN)4PF6[8] could catalyze the cyclopropanation of p-bromostyrene with phenyliodonium ylide malonate to afford 3a in 97% yield with 66% ee (entry 1). Ligand 2, bearing a pendant benzyl group, was able to promote the cyclopropanation in 98% yield with 64% ee (entry 2). Installing two pendant benzyl groups at the bridged carbon atom of the phenyl-bisoxazoline resulted in the enantioselectivity dramatically increasing (72% yield, 86% ee; entry 3). Further study showed that steric hindrance of the pendant group also played an important role in promoting both the enantioselectivity and reactivity. For example, the highly sterically demanding ligand 4, which possessed two large bulky side arms, turned out to be the optimal one (95% yield, 92% ee; entry 4). Increasing the steric hindrance of the pendant group further destroyed the enantioselectivity (80% yield, 88% ee; entry 5) versus...
The reaction of terminal alkenes with phenyliodonium ylide. 

Table 2: Reaction of terminal alkenes with phenyliodonium ylide. 

<table>
<thead>
<tr>
<th>Entry</th>
<th>R₁, R₂</th>
<th>Yield [%]</th>
<th>ee [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>p-BrC₆H₄, H</td>
<td>99 (3a)</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>Ph, H</td>
<td>85 (3b)</td>
<td>91 (5)</td>
</tr>
<tr>
<td>3</td>
<td>p-CIC₆H₄, H</td>
<td>93 (3c)</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>p-CF₂C₆H₄, H</td>
<td>99 (3d)</td>
<td>96</td>
</tr>
<tr>
<td>5</td>
<td>p-ClC₆H₄, H</td>
<td>79 (3e)</td>
<td>94</td>
</tr>
<tr>
<td>6</td>
<td>p-MeC₆H₄, H</td>
<td>99 (3f)</td>
<td>92</td>
</tr>
<tr>
<td>7</td>
<td>o-MeC₆H₄, H</td>
<td>99 (3g)</td>
<td>92</td>
</tr>
<tr>
<td>8</td>
<td>m-MeC₆H₄, H</td>
<td>97 (3h)</td>
<td>93</td>
</tr>
<tr>
<td>9</td>
<td>p-MeOC₆H₄, H</td>
<td>96 (3i)</td>
<td>87</td>
</tr>
<tr>
<td>10</td>
<td>p-PhC₆H₄, H</td>
<td>95 (3j)</td>
<td>92</td>
</tr>
<tr>
<td>11</td>
<td>PhOCH₂C₆H₄, H</td>
<td>21 (3k)</td>
<td>80</td>
</tr>
</tbody>
</table>

[a] 1 (0.40 mmol), 2 (400 mg, 1.20 mmol), Cu(14.9 mg, 0.04 mmol), L₄ (35.9 mg, 0.06 mmol), toluene (4.0 mL) and 3 Å MS (300 mg), at −40°C, c = 0.1 mol L⁻¹, reaction time: 50–133 h. Yield of isolated product. The ee values were determined by HPLC analysis on a chiral stationary phase. [b] The absolute configuration of 3b was determined as S by comparing the optical rotation with the literature values. [c] 40 mol% of catalyst; L₆ = iPr-bisoxazoline, R² = R¹ = p-BuC₆H₄.

efficient enantioselectivities (87–96% ee) were obtained (entries 1–10) for both electron-withdrawing and -donating groups at the para, ortho, and meta positions of the phenyl ring of substrates 1a–1j. Aliphatic substrate 1k showed lower reactivity and gave the cyclopropane 3k in 21% yield with 80% ee (entry 11).

Further studies showed that the current catalytic system exhibited excellent enantiocontrol for nonterminal olefins (Scheme 2). Various electron-poor and -rich indenes 4a–4f with different substitution patterns on the aromatic ring reacted smoothly with phenyliodonium ylide malonate (2) to give the corresponding cyclopropanes in good to high yields with excellent enantioselectivities (70–99% yields, 97–> 99% ee). Six- and seven-membered cyclic alkenes 4g and 4h readily participated in this transformation, and almost enantiopure products were obtained in high yields. Moreover, trisubstituted alkene 4i gave rise to product 5i with 95% ee. The acyclic cis-alkenes 4j and 4k were also suitable substrates for the cyclopropanations, and led to 5j in 84% yield with 99% ee and 5k in 79% yield with 93% ee, respectively. Cyclopentadiene (4i) and 1,3-cyclohexadiene (4m) also worked well, affording the monocyclopropanation products in moderate yield with up to 91% ee. In addition, aliphatic-substituted olefin 4n afforded cyclopropane 5n in 75% yield and 77% ee.

To understand the asymmetric induction of the current reaction, a single crystal of the [Cu(CH₃CN)₄]PF₆/L₄ complex was analyzed by X-ray crystallography (Figure 1). The copper center adopts a distorted square-planar geometry, with N1 and N2 of ligand L₄ and a nitrile molecule (the sum of the bond angles of N₃-Cu-N₁, N₃-Cu-N₂, and N₁-Cu-N₂ is 359.99°). Both pendant phenyl groups swing towards the copper center and shield both the upper and lower faces of the

![Figure 1. X-ray structure of [Cu(L₄)(CH₃CN)]⁺ (unless labeled, hydrogen atoms and PF₆⁻ are omitted for clarity).](https://www.angewandte.org/11621)
bisoazoline–copper(I) coordination plane (N1-Cu-N2-C5-C1-C2). As the bond angle of N3-Cu-N1 is distinctively larger than that of N3-Cu-N2 (148.38(10)° versus 118.69(10)°) and the Cu–N1 bond is shorter than that of Cu–N2 (1.945(2) Å versus 2.012(2) Å), a nonsymmetric chiral cage is formed.

According to previous studies by the research groups of Doyle and Charette, malonate-derived metallocarbenes can adopt three different conformations (out-out, in-out, and in-in).[13] The in-out arrangement was regarded as the reactive conformation because one of the ester groups prefers to adopt an out-of plane conformation that could stabilize the partial positive charge formed on the β carbon of the alkene.[8b]

On the basis of these results, and by combining the molecular structure of [Cu(CH3CN)4]PF6/ L4 with the model developed by Pfaltz and co-workers,[13] a stereocontrol model has been developed to explain the stereochemistry of the reaction. As shown in Figure 2, two competing transition-state structures of the [Cu(CH3CN)4]PF6/ L4 complex led to a proposed stereochemical model. The readily accessible starting material, cheap catalyst, high diastereo- and enantioselectivities make the present reaction potentially useful in organic synthesis. Further application of this method in useful transformations is underway.

**Experimental Section**

Typical procedure for the asymmetric cyclopropanation (3a as an example): A mixture of [Cu(CH3CN)4]PF6 (14.9 mg, 0.04 mmol) and the ligand (L4, 35.9 mg, 0.06 mmol) in toluene (4 mL) with activated 3 Å MS (300 mg) was stirred at room temperature for 2 h under nitrogen. Alkene 1a (53 μL, 0.4 mmol) was then added and the resulting mixture cooled to −40°C. After stirring the mixture for 10 min, the phenyliodonium ylide (400 mg, 1.20 mmol) was added in one portion. After the reaction was complete (monitored by TLC), the suspension was filtered through a glass funnel with a thin layer (20 mm) of silica gel (100-200 mesh) and eluted with CH2Cl2 (ca. 150 mL). The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography to afford 3a (124.7 mg), as a colorless oil (20%).

Received: August 8, 2012
Published online: October 12, 2012

**Keywords:** asymmetric catalysis • carbenes • copper • cyclopropanation • homogeneous catalysis

---


[10] For details, see the Supporting Information.

[11] CCDC 894923 ([Cu(CH3CN)4]PF6) and 894922 (5b) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[12] a) M. P. Doyle, J. H. Griffin, V. Bagheri, R. L. Dorow, Organometallics 1984, 3, 53–61; b) see Refs [3a,4f] and [4i].