

# Asymmetric Copper-Catalyzed Carbozincation of Cyclopropenes en Route to the Formation of Diastereo- and Enantiomerically Enriched Polysubstituted Cyclopropanes

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**S** Supporting Information

**ABSTRACT:** The enantioselective synthesis of cyclopropylzinc reagents has been achieved via a copper-catalyzed carbozincation of 3,3-disubstituted cyclopropenes with diorganozinc reagents. The obtained organozinc compounds can be easily functionalized with a broad range of electrophiles, including palladium-catalyzed cross-couplings, affording highly substituted cyclopropanes. The operationally simple procedure using very low quantities of a commercially available and inexpensive copper catalyst provides a new tool for the synthesis of highly enantioenriched cyclopropanes as single diastereoisomers.

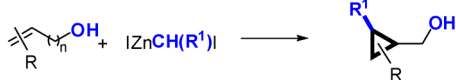
Cyclopropanes are important structural motifs found in a broad range of biologically active compounds and pharmaceuticals.<sup>1</sup> As a consequence, over the last few decades great progress has been made in constructing enantiomerically enriched substituted cyclopropanes<sup>2</sup> using one of the main methods summarized in Scheme 1. The catalytic metal-

## Scheme 1. General Approaches for the Enantioselective Formation of Cyclopropanes

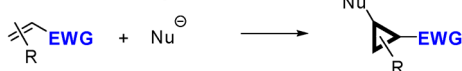
- Transition metal-catalyzed decomposition of diazoalkanes



- Simmons-Smith cyclopropanation reaction



- Michael-initiated ring closure



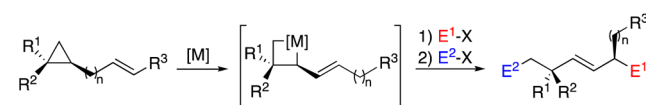
catalyzed decomposition of diazoalkanes is generally highly enantioselective and can be performed with a large variety of different transition metal species with very low catalyst loadings when monosubstituted alkenes are used.<sup>3</sup> On the contrary, the Simmons–Smith–Furukawa cyclopropanation of allylic alcohols<sup>4</sup> and more recently homoallylic ethers<sup>5</sup> is often highly diastereo- and enantioselective and allows the preparation of chiral cyclopropanes possessing a large variety of substituents on the cyclopropyl ring. Because of the flexibility of the olefin pattern, this method has been extensively used in synthesis

despite the fact that a stoichiometric, or in some cases substoichiometric, amount of chiral ligand is required.<sup>6</sup> Finally, important progress has been made in the addition of nucleophiles across activated alkenes followed by 1,3-elimination reactions.<sup>7</sup> It should be noted that these three methods lead to the formation of functionalized cyclopropanes, which may be an advantage if one needs to perform further chemical functionalization.

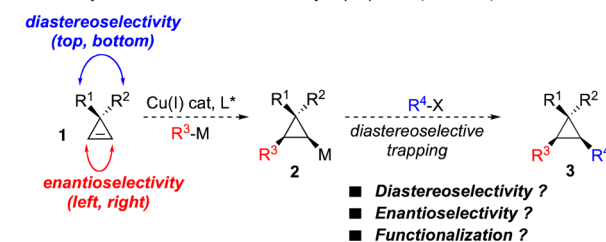
As we are interested in the exploitation of the multifold reactivity of organometallic species to merge allylic C–H and C–C bond activations of pure hydrocarbons,<sup>8</sup> we have recently reported this combined reaction to transform ω-ene cyclopropanes into acyclic compounds possessing challenging quaternary carbon stereogenic centers<sup>9</sup> (Scheme 2, path A).

## Scheme 2. Proposed Asymmetric Catalytic Carbometalation of Cyclopropenes en Route to the Diastereo- and Enantioselective Preparation of Cyclopropanes

**Path A** Allylic C–H bond activation and selective C–C bond cleavage



**Path B** Asymmetric carbometalation of cyclopropenes (this work)



In this context, we soon realized that the diastereo- and enantioselective preparation of cyclopropanes possessing only hydrocarbon chains (therefore composed of C and H) required tedious manipulations of any functionalized cyclopropanes reported in Scheme 1. It became clear that a catalytic method leading to the formation of variously enantioenriched substituted cyclopropanes composed of only hydrocarbon chains as single diastereoisomers and enantiomers was in its

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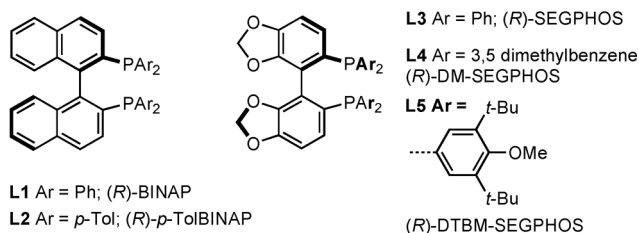
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infancy<sup>10</sup> and therefore highly desirable. Having studied the diastereoselective carbometalation reactions of cyclopropenyl esters<sup>11</sup> and following the pioneering work of Nakamura, Lautens, Fox, Tortosa, and Endo<sup>12</sup> we anticipated that the enantioselective carbometalation of cyclopropenes would be an ideal approach to access polysubstituted enantioenriched cyclopropane structures as single diastereoisomers (Scheme 2, path B).

For our initial studies, we chose achiral cyclopropene **1** (Scheme 2, path B), as it requires the chiral catalyst to perform a double facial selection: (i) enantiotopic face selection (left or right) and (ii) diastereotopic face selection (top or bottom). Moreover, as cyclopropyl metal species **2** is known to be configurationally stable and react with retention of configuration,<sup>13</sup> the addition of an electrophile should lead to the formation of cyclopropane **3** containing three stereocenters, including the carbon quaternary stereocenter. We began our investigation by performing the copper-catalyzed carbозincation reaction, and a rapid screening of chiral phosphorus ligands and copper salts led us to identify the combination of copper(I) thiophene-2-carboxylate (CuTC) with (*R*)-BINAP as an excellent initial combination.<sup>14</sup> Under these conditions, cyclopropane **3a** was obtained with good diastereoselectivity and an enantiomeric ratio of 84:16 (Table 1, entry 1), albeit accompanied by the formation of the dimer **A**, which was very likely formed through a Cu-catalyzed [2 + 2] addition.<sup>15,12d</sup> Further optimization showed that the enantioselectivity as well as the diastereoselectivity could be improved at lower temperature (entry 2), where full conversion was achieved within 3 h at -78 °C with 5 mol % Cu catalyst.

Table 1. Reaction Optimization<sup>a</sup>

Entry	CuX / (mol%)	L	Reaction conditions	dr <sup>[b]</sup>	er <sup>[c]</sup>	A <sup>[b,d]</sup>
1	CuTC / 5	L1	Et <sub>2</sub> O, 0 °C	15:1	84:16	15%
2	CuTC / 5	L1	Et <sub>2</sub> O, -78 °C	>99:1	92:8	14%
3 <sup>e</sup>	CuTC / 5	L2	Et <sub>2</sub> O, -78 °C to 0 °C	67:1	86:14	23%
4 <sup>e</sup>	CuTC / 5	L3	Et <sub>2</sub> O, -78 °C to 0 °C	24:1	91:9	22%
5	CuTC / 5	L4	Et <sub>2</sub> O, -78 °C	94:1	88:12	19%
6	CuTC / 5	L5	Et <sub>2</sub> O, -78 °C	>99:1	93:7	4%
7	CuTC / 10	L5	Et <sub>2</sub> O, -78 °C	>99:1	93:7	<2%
g <sup>f</sup>	Cu(CH <sub>3</sub> CN) <sub>4</sub> PF <sub>6</sub> / 5	L5	THF, 0 °C	>99:1	93:7	<2%
g <sup>f</sup>	Cu(CH <sub>3</sub> CN) <sub>4</sub> PF <sub>6</sub> / 3	L5	THF, 0 °C	>99:1	93:7	<2%
10	Cu(CH <sub>3</sub> CN) <sub>4</sub> PF <sub>6</sub> / 3	--	THF, 0 °C	5:1	--	40%

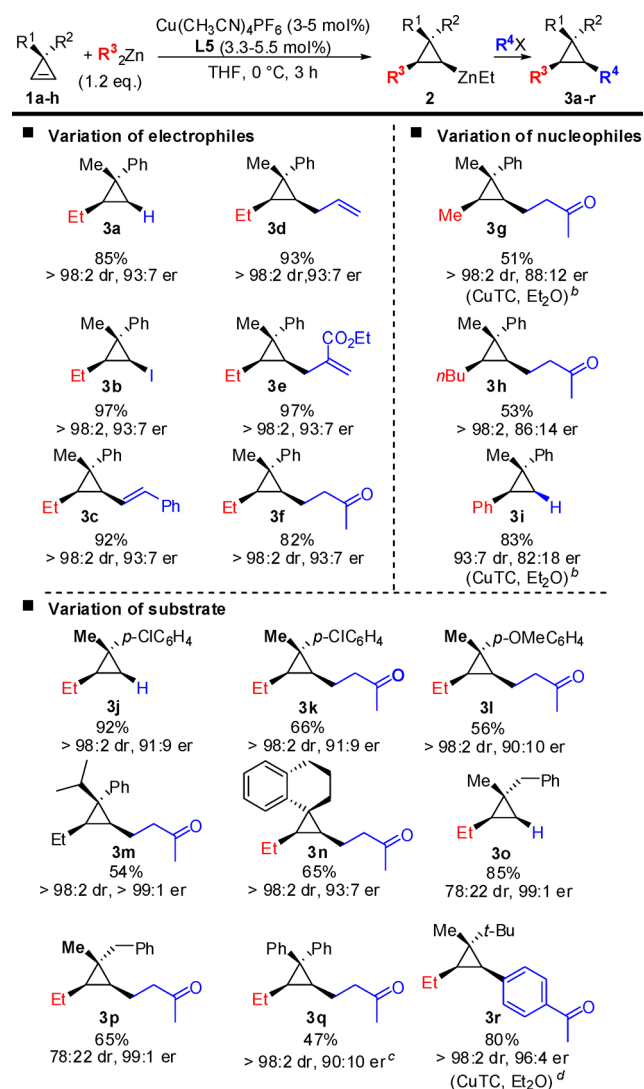


<sup>a</sup>The reactions were run on a 0.25 mmol scale, and full conversion was observed by GC analysis. <sup>b</sup>Estimated by GC-MS analysis. <sup>c</sup>Determined by chiral GC. <sup>d</sup>Combined integration of all diastereoisomers with *m/z* = 260 (mass for dimeric compounds). <sup>e</sup><20% conversion after 3 h at -78 °C. <sup>f</sup>Full conversion was achieved within 15 min. <sup>g</sup>1.2 equiv of Et<sub>2</sub>Zn.

Examination of ligands of the BINAP family showed that (*R*)-DTBM-SEGPHOS completely suppressed the dimeric side product **A** and increased the enantioselectivity (entry 7).<sup>12d</sup> Further improvement could be obtained by using Cu-(CH<sub>3</sub>CN)<sub>4</sub>PF<sub>6</sub> in THF and warming the reaction mixture to 0 °C, which gave full conversion within 15 min (entry 8). Although the enantiomeric ratio did not improve under these new experimental conditions (compare entries 7 and 8), the higher reaction temperature greatly improved the practicality of the reaction. Finally, we found that only 1.2 equiv of Et<sub>2</sub>Zn and 3 mol % catalyst are necessary to ensure complete conversion (entry 9). A control experiment emphasized the importance of the copper complex for selective, efficient, and clean reactions (entry 10).

With the optimized conditions in hand (Table 1, entry 9), we then explored the scope of the reaction. Our first goal was to investigate the reactivity of the configurationally stable cyclopropylzinc species **2** resulting from the asymmetric copper-catalyzed ethylzincation reaction with various electrophiles, as described in Scheme 3.<sup>14</sup> Addition of I<sub>2</sub> delivered cyclopropyl iodide **3b** in high yield, whereas addition of Buchwald's SPhos ligand in combination with Pd(OAc)<sub>2</sub> smoothly catalyzed the Negishi cross-coupling with styrenyl bromide to afford **3c** in excellent yield.<sup>16</sup> Cyclopropylzinc species **2** could also be transmetalated to copper and undergo smooth allylation and 1,4-addition reactions, providing **3d-f** in good to excellent yields.<sup>18</sup> It should be noted that all of the cyclopropanes **3b-f** were obtained as single diastereoisomers, confirming that the transmetalation proceeds with complete retention of configuration, with the same enantiomeric ratio of 93:7. When different commercially available diorganozinc reagents such as Me<sub>2</sub>Zn, Bu<sub>2</sub>Zn, and Ph<sub>2</sub>Zn, were tested in the copper-catalyzed carbозincation of cyclopropene **1a**, we were pleased to see that the carbозincation also proceeded smoothly, albeit with slightly lower enantioselectivity (formation of **3g-i**; Scheme 3), and the products were still obtained as single diastereoisomers after transmetalation and reaction with methyl vinyl ketone. For the reactions leading to cyclopropanes **3g** and **3i**, we found that the combination CuTC with (*R*)-DTM-SEGPHOS (as discussed in Table 1, entry 7) provides better enantiomeric ratio and diastereoselectivity compared with the standard method (Table 1, entry 9).<sup>17</sup> Comparison of the NMR spectra and optical rotation of **3i** with those of an authentic sample known in the literature confirmed the absolute and relative configurations.<sup>12d</sup>

Finally, we extended our copper-catalyzed carbозincation reaction to cyclopropenes bearing different quaternary carbon centers (Scheme 3). Cyclopropanes **3j** and **3k** having electron-deficient aryl groups and product **3l** with an electron-donating aryl group were obtained with similar enantioselectivities compared to the parent substrate (Table 1, entry 9) as single diastereoisomers. Even when the discrimination between the two diastereotopic faces was very challenging (*i*Pr vs Ph), the organometallic complex reacted with complete diastereoselectivity, leading to **3m** with an outstanding enantiomeric ratio (99.7:0.3 er). Cyclopropane **3n** with a more rigid backbone and cyclopropane **3o** with a more flexible benzyl substituent were also obtained with good to excellent enantioselectivities, respectively. In the latter case, the possible lower steric differentiation of the two diastereotopic faces of the parent cyclopropene produces the two diastereoisomers as a 4:1 mixture but with almost complete enantiocontrol (99.3:0.7 er). Interestingly, the carbometalation of cyclopropene leading to

Scheme 3. Scope of the Asymmetric Cu-Catalyzed Carbozincation of Cyclopropenes<sup>a</sup>

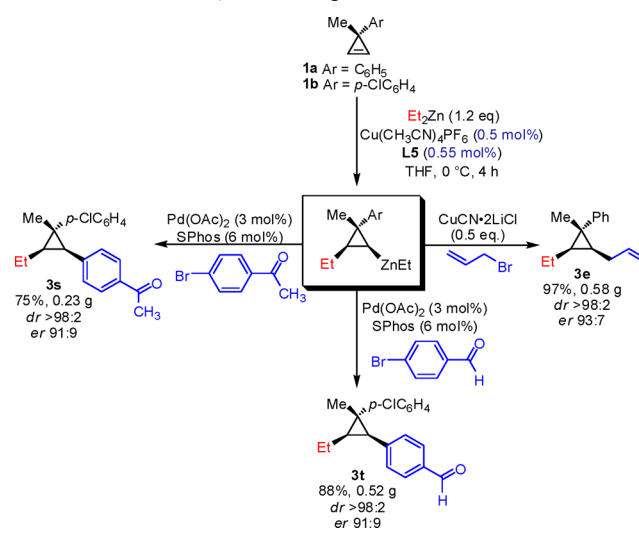
<sup>a</sup>Isolated yields on a 0.5–1.0 mmol scale are reported. Conditions for functionalization of the cyclopropylzinc reagent are described in the Supporting Information. Enantiomeric ratios were determined by chiral HPLC or GC analysis. <sup>b</sup>Changed reaction conditions: CuTC (5 mol %), L5 (5.5 mol %), Et<sub>2</sub>O, –78 °C, 3 h. <sup>c</sup>8 h at 0 °C. <sup>d</sup>Changed reaction conditions: CuTC (10 mol %), L5 (11 mol %), Et<sub>2</sub>O, –78 °C, 3 h, then warmed for 3 h at 0 °C.

the formation of **3q** was very sluggish under our best experimental conditions (Table 1, entry 9), resulting in the formation of cyclopropane **3q** with low conversion (<20%), suggesting the reluctance of the chiral copper catalyst to deliver the organic substituent syn to the phenyl group at the 3-position. Better conversion could be achieved only after significantly prolonged reaction times (8 h instead of 15 min) in the presence of 5 mol % catalyst. Finally, when a parent cyclopropene without an aromatic group was used (i.e., the formation of **3r**), a moderate enantioselectivity (80:20 er) was obtained under the experimental conditions described in Table 1, entry 9 (not shown in Scheme 3). However, changing to the complex of CuTC with (*R*)-DTM-SEGPHOS in Et<sub>2</sub>O (Table 1, entry 7) led to a strong improvement in the enantiomeric ratio (96:4 er), and a single diastereoisomer was obtained after

the palladium cross-coupling reaction with *p*-bromoacetophenone. This example impressively shows the ability of the chiral catalyst to differentiate the two enantiotopic faces without any significant bonding to the substituents at the 3-position of the cyclopropene and to react chemoselectively with functionalized electrophiles.

To demonstrate the robustness and scalability of this method, we performed the copper-catalyzed carbozincation on a larger scale and were delighted to see that the reaction still proceeds efficiently with as little as 0.5 mol % copper catalyst to produce the expected cyclopropanes in excellent enantiomeric ratios as unique diastereoisomers (Scheme 4). The high functional group tolerance of these couplings is showcased by the syntheses of **3s** and **3t** presenting ketone and aldehyde moieties, respectively.<sup>18</sup>

## Scheme 4. Enantioselective Cu-Catalyzed Carbozincation with a Lower Catalyst Loading



In summary, the copper-catalyzed enantioselective carbozincation of cyclopropenes affords highly enantioenriched and configurationally stable cyclopropylzinc reagents. Facile functionalization reactions through either copper- or palladium-catalyzed transformations provide a large variety of substituted cyclopropanes as single diastereoisomers. Hence, a great number of cyclopropanes can be accessed from a single enantiomerically enriched cyclopropylzinc precursor. We are currently investigating alternative nucleophiles, monosubstituted cyclopropenes, and cyclopropenes leading to biologically significant motifs as well as further transformations of the in situ-generated cyclopropylzinc reagents.

## ■ ASSOCIATED CONTENT

## S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b11220.

Optimization reactions, experimental procedures, and characterization data (<sup>1</sup>H NMR, <sup>13</sup>C NMR, HRMS) for all new compounds (PDF)

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## Notes

The authors declare no competing financial interest.

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- (18) Importantly, the chiral Cu(I) catalyst already present in the reaction medium was inefficient in catalyzing the reaction, and  $\text{CuCN}\cdot 2\text{LiCl}$  (0.5 equiv) was added before addition of allyl bromide.