

# Highly Diastereoselective and Enantioselective Formal [4 + 3] Cycloaddition of Donor–Acceptor Cyclobutanes with Nitrones

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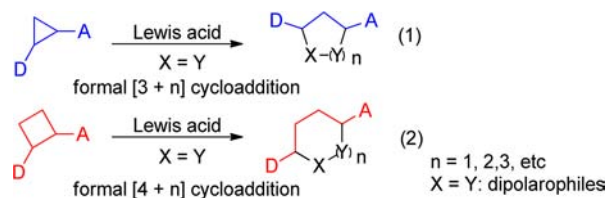
**S** Supporting Information

**ABSTRACT:** The first highly diastereoselective and enantioselective catalytic formal [4 + 3] cycloaddition of 1,1-cyclobutane diester with nitrone has been developed. Sterically hindered chiral SaBOX/Cu(II) complex promotes the reaction efficiently with a broad substrate scope, producing a range of multifunctionalized optically active 1,2-oxazepanes with excellent stereocontrol (up to >99/1 dr and 97% ee).



The ring opening and formal [3 + *n*] cycloaddition reactions of donor–acceptor (D–A) cyclopropanes<sup>1</sup> (eq 1, Scheme 1) have been developed and achieved significant success on both

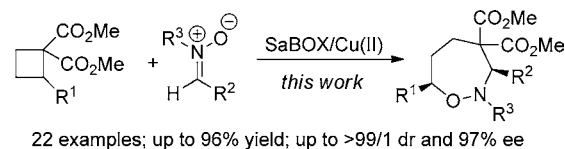
**Scheme 1. Cycloaddition of Cyclopropane and Cyclobutane**



enantioselective catalysis<sup>2</sup> and natural product synthesis,<sup>3</sup> involving efficient catalyst systems. In contrast, the transformations of their analogue D–A cyclobutanes which show lower reactivity<sup>4</sup> probably due to their puckered structures and a slightly lower strain energy compared with that of cyclopropane (27.5 kcal/mol vs 26.3 kcal/mol)<sup>5</sup> are less studied. Saigo demonstrated their pioneering study of formal [4 + 2] cycloadditions of D–A cyclobutanes with aldehydes in 1991,<sup>6a</sup> formal [4 + *n*] cycloadditions with different dipolarophiles, such as aldehydes, ketones, imines, and nitrones, emerged and attracted increasing attention (eq 2, Scheme 1).<sup>6</sup> For example, Christie and Pritchard,<sup>6c</sup> Johnson,<sup>6d</sup> Pagenkopf,<sup>6e–h</sup> and Matsuo<sup>6i,7</sup> have, respectively, established effective methods in the construction of various racemic formal [4 + *n*] cycloadducts. However, as far as we know, the catalytic asymmetric version of D–A cyclobutanes involved formal [4 + *n*] cycloadditions has not been reported. Recently, we developed a series of side arm modified bisoxazolines (TOX and SaBOX),<sup>8,9</sup> which improve both the reactivity and stereoselectivity in the asymmetric ring opening and formal cycloaddition of D–A cyclopropanes.<sup>2f–i</sup> Given our interest in the strained ring asymmetric transformations, herein, we uncover the first catalytic asymmetric formal [4 + 3] cycloaddition of 1,1-cyclobutane diester with

nitrone,<sup>10</sup> producing multifunctionalized optically active 1,2-oxazepanes<sup>11</sup> in high yields with excellent stereocontrol (Scheme 2).

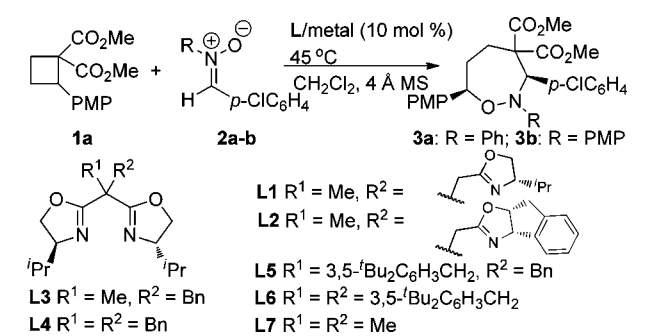
**Scheme 2. Asymmetric Annulation of h D–A Cyclobutane**



Since (*S*)-Ph-DBFOX and (*S*)-4-Cl-<sup>t</sup>Bu-PYBOX have shown excellent performance in asymmetric annulations of D–A cyclopropanes with nitrones<sup>2a</sup> and aldehydes,<sup>2c</sup> respectively, we initially used these two ligands to investigate the cycloaddition of D–A cyclobutane with nitrone. Unfortunately, neither of them could promote this reaction.<sup>12</sup> Then we carried out the formal [4 + 3] cycloaddition of 1,1-cyclobutane diester **1a** with nitrone **2a** in CH<sub>2</sub>Cl<sub>2</sub> at 45 °C using 10 mol % of metal salts and 12 mol % of <sup>i</sup>Pr-trisoxazoline ligand **L1** as catalysts. As shown in Table 1, although TOX/Ni(II)<sup>2b</sup> and TOX/Co(II)<sup>8g</sup> complexes was successfully employed in the asymmetric cycloaddition of nitrone with D–A cyclopropanes and alkylidene malonates, poor results were obtained with the D–A cyclobutane (entries 1 and 2). After screening of various metals with several counterions,<sup>12</sup> Cu(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O was found to be a suitable metal salt, promoting the desired 1,2-oxazepane product **3a** in 86% yield with 90/10 *cis/trans* and 82% ee (entry 3). TOX ligand **L2** was proved to be more efficient on the stereocontrol of cycloaddition of D–A cyclopropane with nitrone, however, a slight decrease of the ee value was observed in this reaction (entry 4). Then we turned to examine a series of SaBOX ligands **L3–6**

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

entry	Lewis acid	L	3	yield (%) <sup>b</sup>	dr( <i>cis/trans</i> ) <sup>c</sup>	ee (%) <sup>d</sup>
1	Ni(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	L1	3a	0	-	-
2	Co(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	L1	3a	77	77/23	14
3	Cu(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	L1	3a	86	90/10	82
4	Cu(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	L2	3a	91	90/10	79
5	Cu(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	L3	3a	85	87/13	74
6	Cu(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	L4	3a	39	89/11	84
7	Cu(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	L5	3a	94	90/10	90
8	Cu(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	L6	3a	82	93/7	91
9	Cu(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	L7	3a	72	93/7	57
10	Cu(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	L6	3b	65	>99/1	93
11 <sup>e</sup>	Cu(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	L6	3b	87	>99/1	95
12 <sup>e,f</sup>	Cu(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	L6	3b	82	>99/1	96
13 <sup>e,f,g</sup>	Cu(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	L6	3b	87	>99/1	94

<sup>a</sup>1a/2a–b = 1/1 and [1a] = 0.1 M in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) under N<sub>2</sub>, 1–24 h. PMP = *p*-methoxyphenyl. <sup>b</sup>Isolated yield. <sup>c</sup>Determined by <sup>1</sup>H NMR analysis. <sup>d</sup>Determined by chiral HPLC. <sup>e</sup>At –5 °C. <sup>f</sup>[1a] = 0.025 M. <sup>g</sup>2 mol % of L6/Cu(II); nitrone was added dropwise.

bearing versatile benzyl side arms, and found obvious trends to improve the enantioselectivity. Compared with L3, L4 with two benzyl side arms led to a better enantiocontrol despite an obvious decrease to the yield (85% yield, 87/13 dr and 74% ee vs 39% yield 89/11 dr and 84% ee, entries 5 vs 6). With the more bulky 3,5-di-*tert*-butylbenzyl side arm, L5 gave rise to great improvements on both the reactivity and the enantioselectivity, affording the product 3a in 94% yield with 90/10 dr and 90% ee within 5 h (entry 7). Furthermore, when we continue to increase the steric hindrance of side arm, the dr and ee values were promoted to 93/7 dr and 91% ee (entry 8). Notably, in comparison with TOX and SaBOX, BOX ligand L7 delivered only 57% ee (entry 9). When PMP-substituted nitrone 2b was employed, *cis*-diastereomer 3b was obtained exclusively in 93% ee (entry 10). The reaction was carried out at –5 °C, furnishing *cis*-3b in 87% yield with 95% ee (entry 11). The best enantioselectivity was afforded as 96% ee, when the concentration of 1a was in a 0.025 M solution (entry 12). In addition, a test on the application potential of the current catalyst system showed that this process was readily scalable even with lower catalyst loading. With 2 mol % of catalyst, 1.41 g of product 3b was obtained in 87% yield, >99/1 dr, and 94% ee (entry 13).

Under optimal reaction conditions, the substrate scope was next explored. Using D–A cyclobutane 1a, a broad range of nitrones 2b–h derived from versatile *para*-substituted benzaldehydes, such as –F, –Cl, –Br, –CF<sub>3</sub>, –NO<sub>2</sub> and –Me, worked well under the current reaction system generally regardless of the electronic nature of the aryl groups. As shown in Table 2, high yields of single diastereomer of *cis*-product 3b–h were obtained

Table 2. Nitronne Scope<sup>a</sup>

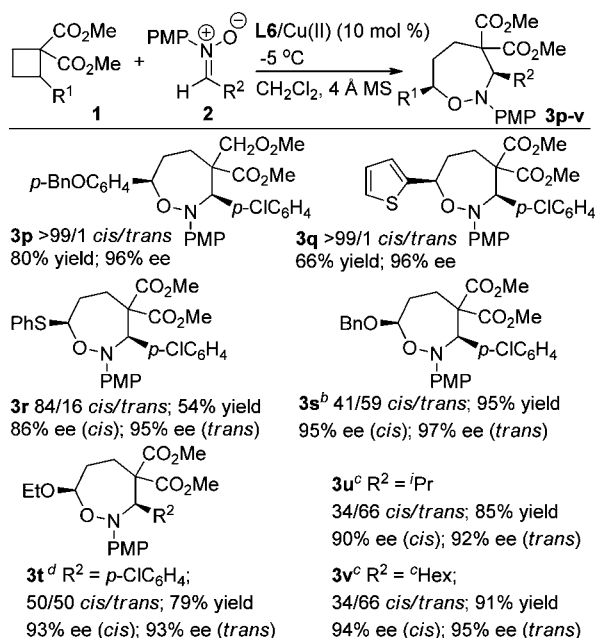
entry	R <sup>1</sup> ; R <sup>2</sup> ; (3)	yield (%) <sup>b</sup>	dr ( <i>cis/trans</i> ) <sup>c</sup>	ee (%) <sup>d</sup>
1	PMP; <i>p</i> -ClC <sub>6</sub> H <sub>4</sub> ; (3b)	82	>99/1	96
2	PMP; <i>p</i> -FC <sub>6</sub> H <sub>4</sub> ; (3c)	93	>99/1	96
3	PMP; <i>p</i> -BrC <sub>6</sub> H <sub>4</sub> ; (3d)	89	>99/1	96 <sup>e</sup>
4	PMP; <i>p</i> -CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> ; (3e)	81	>99/1	96
5	PMP; <i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> ; (3f)	56	>99/1	96
6	PMP; Ph; (3g)	77	>99/1	95
7	PMP; <i>p</i> -MeC <sub>6</sub> H <sub>4</sub> ; (3h)	92	>99/1	93
8	PMP; <i>m</i> -ClC <sub>6</sub> H <sub>4</sub> ; (3i)	77	>99/1	94
9	PMP; 3,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub> ; (3j)	72	>99/1	94
10	PMP; 2-furyl; (3k)	92	93/7	81
11	PMP; 2-thienyl; (3l)	84	>99/1	96
12	Ph; <i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> ; (3m)	96	97/3	88
13	Ph; <i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> ; (3n)	89	95/5	92
14	Ph; <i>p</i> -CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> ; (3o)	84	97/3	91
15	Ph; <i>p</i> -ClC <sub>6</sub> H <sub>4</sub> ; (3a)	96	97/3	95

<sup>a</sup>1/2 = 1/1 and [1a] = 0.025 M in CH<sub>2</sub>Cl<sub>2</sub> (8 mL) under N<sub>2</sub>, 2–96 h. <sup>b</sup>Isolated yield. <sup>c</sup>Determined by <sup>1</sup>H NMR analysis. <sup>d</sup>Determined by chiral HPLC. <sup>e</sup>The absolute configuration of 3d was determined as 3*R*,7*R* by X-ray crystallography.

with 93–96% ee, except that *p*-nitrophenyl-substituted nitrone 2f gave moderate yield, probably due to the instability of nitrone (entries 1–7). Meta-substituted and 3,4-disubstituted substrates 2i and 2j could also be used to generate functionalized 1,2-oxazepane compounds 3i and 3j in good yields and excellent diastereo- and enantioselectivities (>99/1 dr, 94% ee), and decreased stereoselectivity was observed with 2-furyl-substituted substrate 2k; 84% yield, >99/1 dr, and 96% ee was achieved by using 2-thienyl-substituted substrate 2l (entries 10 and 11). In addition, *N*-phenylnitrones 2m–o and 2a were tolerated, furnishing the corresponding 3m–o and 3a in 84–96% yields with up to 97/3 dr and 88–95% ee (entries 12–15).

Various D–A cyclobutanes encompassing simple and functionalized phenyl, 2-thienyl, phenylthioxy, and alkoxy motifs are readily accommodated, giving functionalized 1,2-oxazepanes 3p–v in good to high yields with excellent ee values (Scheme 3). Notably, for alkoxy-substituted cyclobutanes, the diastereoselectivities are not good, probably due to the fact that the *cis*-isomers are liable to isomerize to *trans*-isomers under the current reaction conditions.<sup>12</sup> Both the *cis*- and *trans*-isomers 3s–v could be isolated in high yields with excellent enantioselectivity.

According to previous studies by Johnson, the cycloaddition of aldehyde with D–A cyclopropane occurs via an aldehyde attacking nucleophilic substitution mechanism, because of which the electron-rich aldehydes lead to a higher reactivity.<sup>2,c,d</sup> During the examination of the reaction substrate scope, we found that the electron-deficient nitrones apparently perform a higher reactivity. For example, comparing *p*-CF<sub>3</sub>C<sub>6</sub>H<sub>4</sub>-substituted nitrone 2e with the one substituted by *p*-MeC<sub>6</sub>H<sub>4</sub> 2h, the former finished after 2 h, while the latter need 11 h to complete the reaction. It was the same case with nitrones 2m and 2o (34 h vs 4.5 h). The above-mentioned observation intrigued us to carry out a series of competition experiments (Table 3). After 4.5 h, the 1a was consumed; however, we found that compared with

Scheme 3. D–A Cyclobutane Scope<sup>a</sup>

<sup>a</sup>1/2 = 1/1 and [1a] = 0.025 M in CH<sub>2</sub>Cl<sub>2</sub> (8 mL) under N<sub>2</sub>, 2–96 h; isolated yield; dr was determined by <sup>1</sup>H NMR analysis; ee was determined by chiral HPLC. <sup>b</sup>At -30 °C. <sup>c</sup>Using Cu(OTf)<sub>2</sub>; 20 mol % of L6/Cu(II) at 0 °C. <sup>d</sup>The relative configuration of *cis*-3t was determined by X-ray crystallography.

Table 3. Competition Experiments

entry	Ar <sup>1</sup>	Ar <sup>2</sup>	conv <sup>a</sup> (%)	A/B <sup>a</sup> (ratio)
1	Ph	<i>p</i> -CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	>99	1.84/1
2	Ph	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	20	1/1.20
3	Ph	Ph	>99	
4	Ph	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	<1	

<sup>a</sup>Determined by <sup>1</sup>H NMR spectroscopy.

phenyl-substituted nitronium, the one with a *p*-CF<sub>3</sub>C<sub>6</sub>H<sub>4</sub> group resulted in a lower reactivity (A/B = 1.84/1, entry 1). In the case of phenyl-substituted nitronium versus the one with a *p*-MeC<sub>6</sub>H<sub>4</sub> group, the ratio of the corresponding product is 1/1.2, though the conversion of D–A cyclobutane was only 20% after 4.5 h (entry 2). In dramatic contrast to the poor reactivity of this trial, 2 equiv of phenyl-substituted nitronium was subjected to the control experiment. Interestingly, full conversion of the D–A cyclobutane was observed in 4.5 h (entry 3). These results suggested that the ring-opening step of cyclobutane attacked by nitronium might be the rate-determining step in this formal [4 + 3] annulation, indicating that the cycloaddition of nitronium with D–A cyclobutane might occur via a nitronium attacking nucleophilic substitution mechanism. The apparently observed lower reactivity with electron-rich nitronium might be caused by the poisoning effect of the nitronium toward Lewis acid.<sup>6d</sup> Further investigation by using more electron-rich *p*-MeOC<sub>6</sub>H<sub>4</sub> sub-

stituted nitronium led to almost no reaction, which was in accordance with our hypothesis (entry 4).

In summary, although several ring-opening reactions of cyclobutane 1,1-dicarboxylates have been reported, few asymmetric versions have been developed. We found that SaBOX/Cu(II) could catalyze the asymmetric formal [4 + 3] cycloaddition of 1,1-cyclobutane diester with nitronium with high enantioselectivity, which represents the first example of the enantioselective transformations of cyclobutane 1,1-dicarboxylates. The mild reaction conditions, high enantioselectivity, high yield, readily accessible catalyst, and easily scaling up make the current method synthetically useful.

## ASSOCIATED CONTENT

### Supporting Information

Experimental procedures and characterization data for all new compounds and crystallographic data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01077.

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### Notes

The authors declare no competing financial interest.

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