

# Highly Enantioselective Synthesis of Multifunctionalized Dihydrofurans by Copper-Catalyzed Asymmetric [4 + 1] Cycloadditions of $\alpha$ -Benzylidene- $\beta$ -ketoester with Diazo Compound

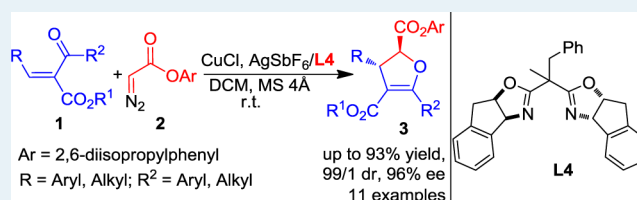
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## S Supporting Information

**ABSTRACT:** Highly efficient synthesis of chiral tetrasubstituted 2,3-dihydrofuran derivatives has been realized by Cu-catalyzed asymmetric [4 + 1] cycloadditions of  $\alpha$ -benzylidene- $\beta$ -ketoester with a diazo compound. Following this methodology, a series of optically active multifunctionalized dihydrofurans were prepared in high yield with up to 96% ee and 99/1 dr.

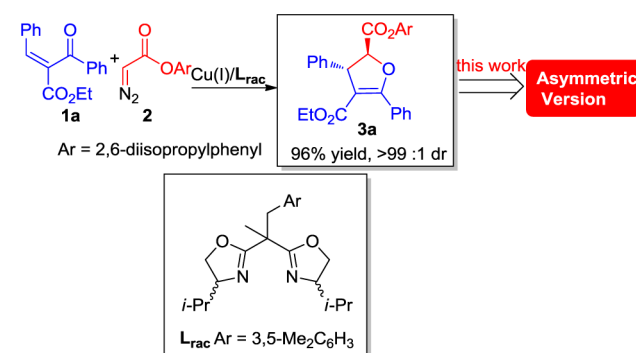
**KEYWORDS:** asymmetric, copper carbene, [4 + 1] cycloadditions, dihydrofurans



Synthesis of oxygenated heterocycles via transition-metal-catalyzed decomposition of diazo compounds generated by transient carbonyl ylides has proved to be one of the most efficient and practical protocols and has drawn considerable interest.<sup>1,2</sup> Of those studies, the carbonyl ylides-involved 1,3-dipolar cycloaddition reactions have been well developed.<sup>3,4</sup> However, [4 + 1] cycloadditions of  $\alpha,\beta$ -unsaturated carbonyl compounds with diazo compounds, which provide a facile access to multifunctionalized 2,3-dihydrofurans, has been less explored. In 1967, Spencer et al. pioneered CuSO<sub>4</sub>-catalyzed [4 + 1] cycloadditions of  $\beta$ -methoxy- $\alpha,\beta$ -unsaturated ketones with ethyl diazoacetate.<sup>5</sup> Since then, great efforts have been devoted to the exploitation of such a cycloaddition,<sup>6</sup> but none of these investigations has realized the enantioselective version until Fu's work in 2007,<sup>7a</sup> leading to optically active 2,3,5-trisubstituted 2,3-dihydrofurans<sup>7</sup> with good efficiency and stereoselectivity under the catalysis of the Cu(I)/[(-)-bpy\*] complex. In view of dihydrofurans containing molecular skeletons being key subunits of various biologically active compounds as well as versatile intermediates for the construction of complex molecules,<sup>8,9</sup> they are of considerable synthetic value, and efficient methodologies for the catalytic enantioselective synthesis of chiral multifunctionalized 2,3-dihydrofurans are still highly demanded.

In 2011, we developed a tunable carbonyl ylide reaction: in the presence of side-arm-modified *rac*-<sup>i</sup>PrBox L<sub>rac</sub>/Cu (I), the reaction of a  $\alpha$ -benzylidene- $\beta$ -dicarbonyl compound with a diazo 2,6-diisopropylphenyl ester can furnish 2,3,4,5-tetrasubstituted 2,3-dihydrofurans with high chemoselectivity in excellent yields and with high diastereocontrol (Scheme 1).<sup>10</sup> Recently, our attempts on the asymmetric version achieved promising enantioselectivity to afford optically active 2,3,4,5-tetrasubstituted 2,3-dihydrofuran products. In this letter, we present our preliminary results on this subject.

## Scheme 1. Synthesis of 2,3,4,5-Tetrasubstituted 2,3-dihydrofurans

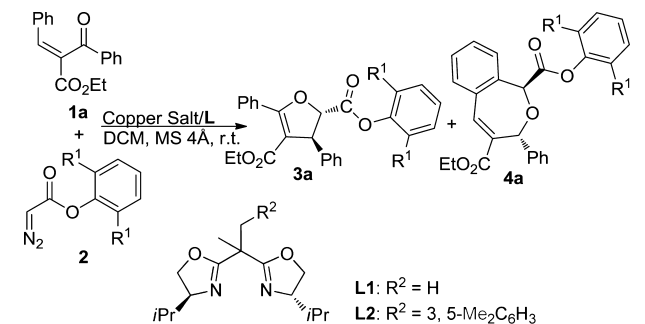


Initially, a control experiment was carried out with non-side arm <sup>i</sup>PrBox L1 and side arm-modified <sup>i</sup>PrBox L2, which indicated that installing an aryl side arm at the bridge of the bisoxazoline ligand could increase the enantioselectivity of this reaction obviously (Table 1, entry 1 vs 2). In the case of L2 as a ligand, we examined the cycloadditions of  $\alpha$ -benzylidene- $\beta$ -ketoester **1a** with diazo compound **2** in the presence of a variety of commonly used copper salts. As shown in Table 1, the reaction was carried out smoothly in good yield with 88% ee for the major diastereoisomer when CuPF<sub>6</sub>(CH<sub>3</sub>CN)<sub>4</sub> was used, but 14% yield of **4a** was also detected by <sup>1</sup>H NMR analysis (entry 2).<sup>10</sup> Both CuBARf (CuCl + NaBARf) and CuSbF<sub>6</sub> (CuCl + AgSbF<sub>6</sub>) could give the desired 2,3-dihydrofuran **3a** in excellent yields with high enantioselectivities (92% yield with 90% ee and 94% yield with 91% ee,

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

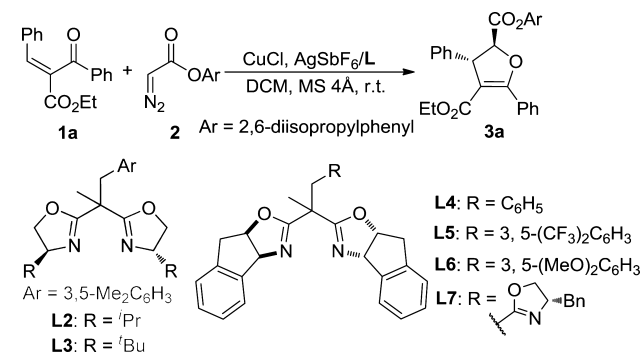
entry	copper salt	R <sup>1</sup>	L	yield of 3a (%) <sup>b</sup>	ee (%) <sup>c</sup>
1	CuPF <sub>6</sub> (MeCN) <sub>4</sub>	<sup>i</sup> Pr	L1	90	75
2	CuPF <sub>6</sub> (MeCN) <sub>4</sub>	<sup>i</sup> Pr	L2	85 <sup>d</sup>	88
3	CuCl + NaBARF <sup>f</sup>	<sup>i</sup> Pr	L2	94 (92) <sup>e</sup>	90
4	CuCl + AgSbF <sub>6</sub>	Me	L2	90	89
5	CuCl + AgSbF <sub>6</sub>	<sup>t</sup> Bu <sup>g</sup>	L2	94	89
6	CuCl + AgSbF <sub>6</sub>	<sup>i</sup> Pr	L2	94 (94) <sup>e</sup>	91

<sup>a</sup>Reaction conditions: Copper salt (5 mol %), L (5.2 mol %), MS 4 Å (100 mg/mL), DCM, r.t., 1a (0.5 mmol), 2 (2.0 mmol). <sup>b</sup>Determined by <sup>1</sup>H NMR. <sup>c</sup>For major diastereomer; determined by chiral HPLC. <sup>d</sup>4a was observed from <sup>1</sup>H NMR in 14% yield with 53% ee. <sup>e</sup>Isolated yield. <sup>f</sup>BARF<sup>-</sup> = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate. <sup>g</sup>Diazo 2,6-di-<sup>t</sup>Bu-4-Me-Phenyl ester and (E)-ethyl 2-benzoyl-3-(4-chlorophenyl)acrylate used.

respectively, entries 3 and 6). The impact of the diazo ester was next investigated, and it was found that the nature of the diazo compounds influences the yield and stereoselectivity.<sup>11</sup> Further study showed that the diazo 2,6-diisopropylphenyl ester provided the best combination of both yield and ee (94% yield, 91% ee, entry 6).

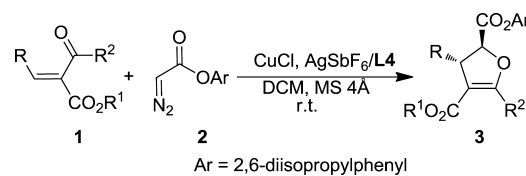
Further investigation was focused on the ligand effects of modified bisoxazolines on the enantioselectivity.<sup>12,13</sup> As outlined in Table 2, comparing with the <sup>i</sup>PrBox L2 and <sup>t</sup>Bu-Box L3, ligands L4–L7 with indane skeletons gave a better result. For example, the enantioselectivity could be increased to 96% ee with a slight decrease in the isolated yield when InBox L4 was employed (entry 3). By the use of chiral InBox L5 with a 3,5-ditrifluoromethylbenzyl group as a side arm, 95% ee could also be afforded (entry 4). In contrast, chiral ligand L6 with 3,5-dimethoxybenzyl, which contains an electron-rich side arm, led to an obvious decline in the ee value (84% ee, entry 5). In addition, good enantioselectivity could also be achieved with the chiral In-TOX ligand L7 (94% ee, entry 6).

Under the optimized conditions, we evaluated the generality of the current asymmetric reaction. As shown in Table 3, a variety of substrates were examined. When R and R<sup>2</sup> were a phenyl or substituted phenyl group, the reaction displayed excellent stereoselectivity and chemoselectivity. All substrates completed the reaction smoothly to afford optically active 2,3-dihydrofuran derivatives in up to 96% yield with extremely high diastereoselectivities (>99/1) as well as excellent enantioselectivities (90–96%), regardless of the electronic nature and the position of the substituent on phenyl group R (entries 1–7). Further studies show that alkyl-substituted substrates are suitable to this catalysis. For instance, when R<sup>2</sup> was <sup>i</sup>Pr, the reaction could furnish the desired 3h with 79% yield in up to 99/1 dr and 89% ee (entry 8). Using the Me group instead of the <sup>i</sup>Pr group, the high diastereoselectivity and enantioselectivity were maintained, albeit with a slight decrease in the yield

Table 2. Survey of Ligands<sup>a</sup>

entry	ligand	yield (%) <sup>b</sup>	ee (%) <sup>c</sup>
1	L2	94 (94) <sup>d</sup>	91
2	L3	45 <sup>e</sup>	99
3	L4	93 (82) <sup>d</sup>	96
4	L5	88	95
5	L6	88	84
6	L7	86 <sup>f</sup>	94

<sup>a</sup>Reaction conditions: CuCl (2.5 mg, 0.025 mmol, 5 mol %), AgSbF<sub>6</sub> (8.7 mg, 0.025 mmol, 5 mol %), ligand (0.026 mmol, 5.2 mol %), MS 4 Å (100 mg/mL), DCM, r.t., 1a (0.5 mmol), 2 (2.0 mmol). <sup>b</sup>Determined by <sup>1</sup>H NMR. <sup>c</sup>For major diastereomer; determined by chiral HPLC. <sup>d</sup>Isolated yield. <sup>e</sup>4a was observed by <sup>1</sup>H NMR in 55% yield with 24% ee. <sup>f</sup>4a was observed by <sup>1</sup>H NMR in 13% yield with 38% ee.

Table 3. Substrate Scope<sup>a</sup>

entry	substrate (R, R <sup>1</sup> , R <sup>2</sup> )	yield <sup>b</sup>	dr <sup>c</sup>	ee <sup>d</sup> (%)
1	1a (Ph, Et, Ph)	3a, 82%	99/1	96
2	1b (o-Me-C <sub>6</sub> H <sub>4</sub> , Et, Ph)	3b, 71%	99/1	95
3	1c (p-Me-C <sub>6</sub> H <sub>4</sub> , Et, Ph)	3c, 89%	99/1	95
4 <sup>e</sup>	1d (p-MeO-C <sub>6</sub> H <sub>4</sub> , Et, Ph)	3d, 85%	99/1	90
5	1e (p-CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> , Et, Ph)	3e, 82%	99/1	90
6	1f (p-Cl-C <sub>6</sub> H <sub>4</sub> , Et, Ph)	3f, 93%	99/1	96
7	1g (p-Br-C <sub>6</sub> H <sub>4</sub> , Et, Ph)	3g, 81%	99/1	96
8	1h (Ph, Me, <sup>i</sup> Pr)	3h, 79%	99/1	89
9	1i (Ph, Et, Me)	3i, 65%	99/1	90
10 <sup>f</sup>	1j (n-C <sub>8</sub> H <sub>17</sub> , Et, Ph)	3j, 68%	90/10	81
11 <sup>f</sup>	1k (n-C <sub>12</sub> H <sub>25</sub> , Et, Ph)	3k, 74%	92/8	78

<sup>a</sup>Reaction conditions: CuCl (2.5 mg, 0.025 mmol, 5 mol %), AgSbF<sub>6</sub> (8.7 mg, 0.025 mmol, 5 mol %), ligand (0.026 mmol, 5.2 mol %), MS 4 Å (100 mg/mL) and DCM, r.t., 1 (0.5 mmol), 2 (2.0 mmol). <sup>b</sup>Isolated yield. <sup>c</sup>Determined by <sup>1</sup>H NMR. <sup>d</sup>Determined by chiral HPLC. <sup>e</sup>Ligand = L3. <sup>f</sup>Ligand = L7, 10 mol % catalyst.

(entry 9). When R was n-C<sub>8</sub>H<sub>17</sub> and n-C<sub>12</sub>H<sub>25</sub>, good stereoselectivities and isolated yields were obtained, giving 68% yield with 90/10 dr and 81% ee and 74% yield with 92/8 dr and 78% ee, respectively (entry 10 and 11). The absolute configuration of 3g was established as 2S, 3S by X-ray crystallography (Figure 1).<sup>14</sup>

Previous study of the structure of side-armed BOX–metal complexes showed that the pendant aryl groups of BOX–metal complexes always bend toward the metal center.<sup>15</sup> In

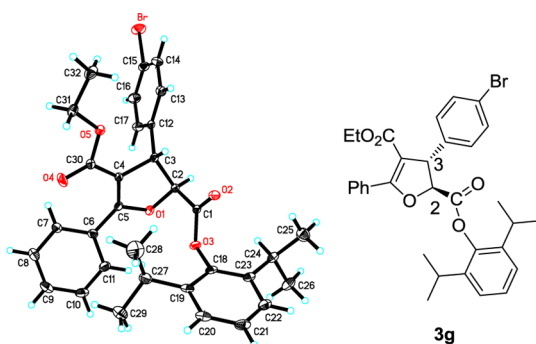
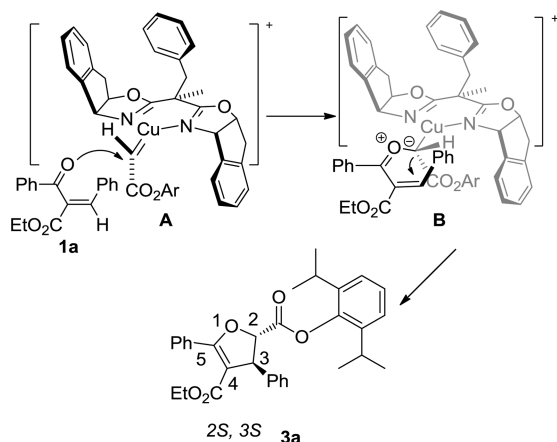


Figure 1. X-ray crystal structure of **3g**.

combination with our previous computational study<sup>10</sup> and the aforementioned experimental results, the stereoinductive model shown in Scheme 2 was proposed to account for the observed

### Scheme 2. Proposed Stereochemical Model



enantioselectivity. In this model, the top of the Cu(I)/oxazoline ring square is blocked by the phenyl-ring side arm, and the top left corner as well as the lower right corner are blocked by an indanyl ring. We proposed that in the presence of the Cu(I) complex, the diazo compound decomposed to form copper carbene **A** first, followed by the formation of the accepted metal-associated carbonyl ylide **B** by attack of the carbonyl group from the lower left corner of the copper carbene with a less steric hindrance. Consequently, 1,5-cyclization takes place by the ylide attack from the *si* face of the benzylidene plate (Scheme 2). To our delight, this model is consistent with stereochemical results.

In conclusion, we have developed an efficient and practical protocol to construct chiral multifunctionalized 2,3-dihydrofurans by combining a  $\alpha$ -benzylidene- $\beta$ -ketoester with a diazo compound. Following this methodology, a series of optically active tetrasubstituted 2,3-dihydrofurans were achieved with good to excellent stereoselectivity (90/10–99/1 dr and 78–96% ee) in good to excellent yields (65–93%). In addition, a rational stereoinductive model was developed. The present reaction will be helpful for the understanding of the Cu(I)/side-armed BOX-catalyzed reactions and provide useful information for the rational design of new ligands to control selectivities in related asymmetric reactions.

## ■ ASSOCIATED CONTENT

### Supporting Information

<sup>1</sup>H NMR and <sup>13</sup>C NMR spectroscopic data of new compounds and analytic data of the compounds **3** are included. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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(14) CCDC 915948 (**3g**) contains 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](http://www.ccdc.cam.ac.uk/data_request/cif). See the Supporting Information.

(15) See refs 13e, 13f, 13m, and 13n.