

# Highly Enantioselective Asymmetric 1,3-Dipolar Cycloaddition of Azomethine Ylide Catalyzed by a Copper(I)/ClickFerrophos Complex

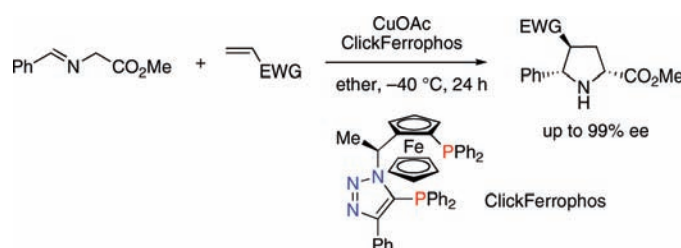
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## ABSTRACT



A copper(I)/ClickFerrophos complex catalyzed the asymmetric 1,3-dipolar cycloaddition reaction of methyl *N*-benzylideneglycinate (the source of azomethine ylides) with vinyl sulfone to give the *exo*-2,4,5-trisubstituted pyrrolidine in good yield with high enantioselectivity (99% ee). The complex also effectively catalyzed reactions of other dipolarophiles such as acrylates, maleate, and maleimides to give the *exo*-2,4,5-, and 2,3,4,5-substituted pyrrolidine derivatives with high diastereo- and enantioselectivities.

Catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides with alkenes is currently of interest, as the reaction is one of the most useful convergent strategies for stereoselective synthesis of optically active five-membered heterocycles such as pyrrolidine and proline derivatives, whose ring systems are key building blocks for many pharmaceuticals and biologically active natural products. Several effective chiral metal complex catalysts have thus far been reported.<sup>1</sup> The development of more effective catalysts for the reaction is of great importance, and proposed chiral metal complex catalysts include silver,<sup>2</sup> copper,<sup>3</sup> zinc,<sup>4</sup> and nickel.<sup>5</sup> The reaction of methyl *N*-benzylideneglycinate (the source of azomethine ylides) with acrylate, maleate, or maleimide gives tri- and tetra-substituted *exo* and/or *endo* pyrrolidines, with

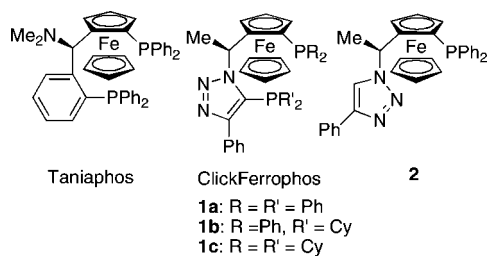
diastereoselectivity dependent on the metal complex catalyst employed; Cu/P,P-ligand and Ag/P,N-ligand complexes, respectively, give the *exo* and *endo* isomers exclusively.<sup>1</sup>

In previous work, we developed a new chiral ferrocenyl ligand, ClickFerrophos, using click chemistry methodology, and reported that its rhodium and ruthenium complexes efficiently catalyzed asymmetric hydrogenation of alkenes and ketones with excellent enantioselectivity (up to 99.7% ee).<sup>6</sup> ClickFerrophos is a 1,5-diphosphine whose structure is similar to that of Taniaphos but which gives higher

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enantioselectivities in some cases (Figure 1).<sup>7</sup> We are interested in the 1,3-dipolar addition reaction of azomethine ylide with vinyl sulfone, which gives 4-sulfonylpyrrolidines. A Cu/Taniaphos complex was found to catalyze the reaction with high enantioselectivity and was highly effective compared to other phosphine ligands.<sup>8</sup> This reaction is expected to be useful for obtaining 2,5-disubstituted pyrrolidines, since the sulfone group can be removed by reduction. In this work, we used ClickFerrophos for Cu (or Ag)-catalyzed asymmetric 1,3-dipolar cycloaddition and found that the complex is sometimes more effective than Taniaphos for this reaction. Reactions using other dipolarophiles such as acrylates, maleate, and maleimide were also studied.



**Figure 1.** Taniaphos and ClickFerrophos.

We first investigated the reaction of methyl *N*-benzylideneglycinate (**3a**) with vinyl phenyl sulfone (**4**) using a combination of ClickFerrophos **1a–c**, **2**, and various metal complexes; the metal salts used were CuOAc, Cu(MeCN)<sub>4</sub>ClO<sub>4</sub>, Cu(OTf)·C<sub>6</sub>H<sub>6</sub>, Cu(OTf)<sub>2</sub>, and AgOAc. A typical reaction was carried out in toluene at 0 °C for 24 h using a ClickFerrophos metal complex (5 mol %), and the ee % of the product was determined by HPLC (Chiralcel AS-H). As shown in Table 1, the combination of CuOAc or Cu(OTf)·C<sub>6</sub>H<sub>6</sub> with **1a** was the most effective for the reaction, giving only the *exo* 4-sulfonyl pyrrolidine **5a** in good yield (87%) with high enantioselectivity (96–97% ee) (entries 1 and 4), while the other metal salts gave the product with good enantioselectivity but unsatisfactory yields. Cu(MeCN)<sub>4</sub>ClO<sub>4</sub> was another possible choice for the metal salt as it gave the product with high enantioselectivity (entry 5)—higher than that of Taniaphos (entry 6)—but for reasons of safety (Cu(MeCN)<sub>4</sub>ClO<sub>4</sub> is potentially explosive) and economy, we

chose the inexpensive CuOAc as the metal salt for subsequent investigations. CuOAc has an additional advantage over other copper salts in that the reaction did not require the addition of amine, which was required for the other copper salt catalyst systems. Combinations of other Click-Ferrophos variations (**1b** and **1c**) with CuOAc were examined, but these were not as effective as **1a** (entries 2–3). The complex with AgOAc somewhat effective but gave a lower yield and ee % than CuOAc (entry 8). It was previously reported that Ag salts are suitable for combining with P,N-ligands,<sup>1</sup> therefore, a combination of AgOAc with **2** was examined, but this gave a poor result (entry 9).

**Table 1.** Reaction of **3a** with Vinyl Sulfone Catalyzed by Metal Salt/ClickFerrophos<sup>a</sup>

| entry          | metal salt           | ligand (L) | yield (%) <sup>b</sup> | ee (%) <sup>c</sup> |
|----------------|----------------------|------------|------------------------|---------------------|
| 1 <sup>d</sup> | CuOAc                | <b>1a</b>  | 87                     | 96                  |
| 2 <sup>d</sup> | CuOAc                | <b>1b</b>  | 68                     | 76                  |
| 3 <sup>d</sup> | CuOAc                | <b>1c</b>  | 78                     | 82                  |
| 4              | CuOTf                | <b>1a</b>  | 87                     | 97                  |
| 5              | CuClO <sub>4</sub>   | <b>1a</b>  | 80                     | 98                  |
| 6 <sup>e</sup> | CuClO <sub>4</sub>   | Taniaphos  | 87                     | 83                  |
| 7              | Cu(OTf) <sub>2</sub> | <b>1a</b>  | 48                     | 83                  |
| 8              | AgOAc                | <b>1a</b>  | 75                     | 82                  |
| 9              | AgOAc                | <b>2</b>   | 23                     | 24                  |

<sup>a</sup> Reactions run using **3a** (0.2 mmol), **4** (0.2 mmol), metal salt (0.01 mmol), L (0.011 mmol), Et<sub>3</sub>N (0.018 mmol), and toluene (2 mL). <sup>b</sup> Isolated yield. <sup>c</sup> Determined by HPLC. <sup>d</sup> Without Et<sub>3</sub>N. <sup>e</sup> Data from ref 3.

Next, we optimized the reaction by employing CuOAc/**1a** as a catalyst under various reaction conditions. Diethyl ether was found to be the most suitable solvent for the reaction, with a high yield (94%) and enantioselectivity of up to 99.9% at –40 °C. These results are summarized in Table 2.

With the reaction conditions thus optimized, the reaction with vinyl sulfone was expanded to substituted azomethine ylide precursors (dipoles), including 4-substituted phenyl derivatives, 2-naphthyl, and cyclohexyl derivatives, in diethyl ether at –40 °C (Table 3). Similarly to the reaction with **3a**, the *exo* products were obtained in good yield and with high enantioselectivity (up to 99% ee) as single diastereomers. In the reaction with  $\alpha$ -substituted dipole **3f**, the 2,2-disubstituted pyrrolidine containing an ester group *cis* to the phenyl group was produced almost as the sole product in good yield with high enantioselectivity. The CuOAc/**1a** catalyst gave high enantioselectivities, similar to those

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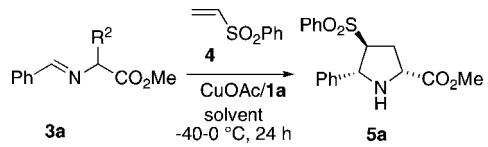
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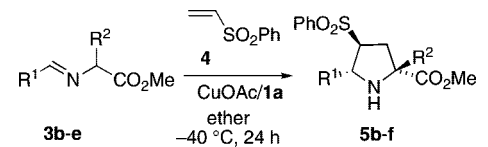
(6) Fukuzawa, S.-i.; Oki, H.; Hosaka, M.; Sugasawa, J.; Kikuchi, S. *Org. Lett.* **2007**, *9*, 5557–5560.

**Table 2.** Reaction of **3a** with Vinyl Sulfone<sup>a</sup> Catalyzed by CuOAc/ClickFerrophos **1a**

| entry | solvent                         | temp (°C) | yield (%) <sup>b</sup> | ee (%) <sup>c</sup> |
|-------|---------------------------------|-----------|------------------------|---------------------|
| 1     | toluene                         | 0         | 87                     | 96                  |
| 2     | CH <sub>2</sub> Cl <sub>2</sub> | 0         | 50                     | 94                  |
| 3     | THF                             | 0         | 95                     | 94                  |
| 4     | Et <sub>2</sub> O               | 0         | 90                     | 90                  |
| 5     | Et <sub>2</sub> O               | -20       | 90                     | 98                  |
| 6     | Et <sub>2</sub> O               | -40       | 94                     | >99.9               |

<sup>a</sup> Reactions run using **3a** (0.2 mmol), **4** (0.2 mmol), CuOAc (0.01 mmol), **1a** (0.011 mmol), and solvent (2 mL). <sup>b</sup> Isolated yield. <sup>c</sup> Determined by HPLC.

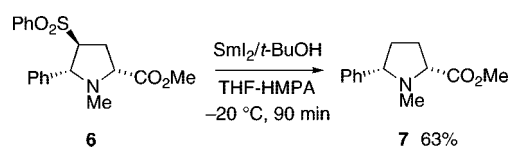
obtained using Cu(I)/Taniaphos, even gave higher yields and % ee in reactions with certain dipolarophiles, such as **3d**, in which Cu(I)/Taniaphos is less effective.<sup>8</sup>

**Table 3.** Reactions with Various Dipoles<sup>a</sup>

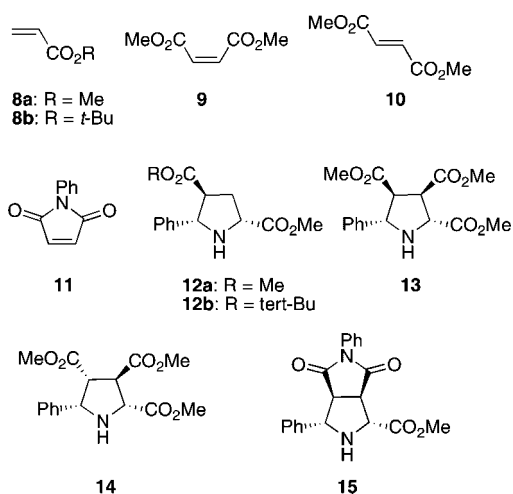
| entry | dipole    | R <sup>1</sup>                     | R <sup>2</sup> | yield (%) <sup>b</sup> | ee (%) <sup>c</sup> |
|-------|-----------|------------------------------------|----------------|------------------------|---------------------|
| 1     | <b>3b</b> | 4-FC <sub>6</sub> H <sub>4</sub>   | H              | 80                     | 95                  |
| 2     | <b>3c</b> | 4-MeOC <sub>6</sub> H <sub>4</sub> | H              | 91                     | 96                  |
| 3     | <b>3d</b> | 2-C <sub>8</sub> H <sub>9</sub>    | H              | 87                     | 94                  |
| 4     | <b>3e</b> | Cy                                 | H              | 81                     | 99                  |
| 5     | <b>3f</b> | Ph                                 | Me             | 83                     | 93                  |

<sup>a</sup> Reactions run using dipole (0.2 mmol), **4** (0.2 mmol), CuOAc (0.01 mmol), **1a** (0.011 mmol), and diethyl ether (2 mL). <sup>b</sup> Isolated yield. <sup>c</sup> Determined by HPLC.

The sulfonyl group of *N*-methyl derivative **6** was removed by reduction with samarium(II) iodide/THF-HMPA rather than the Carretero desulfonylation method using Na(Hg)/NaHPO<sub>4</sub>, as the former method does not require the use of harmful mercury,<sup>8</sup> and *cis*-2,5-disubstituted pyrrolidine **7** was obtained in good yield without loss of optical purity (Scheme 1).<sup>9</sup>

**Scheme 1.** Desulfonylation of **6**

Finally, we used the CuOAc/**1a** catalyst in reactions of **3a** with a variety of dipolarophiles, including methyl and *tert*-butyl

**Figure 2.** Dipolarophiles and pyrrolidine products.**Table 4.** Reaction of **3a** with Various Dipolarophiles<sup>a</sup>

| entry | dipolarophile | product    | yield (%) <sup>b</sup> ,<br>exo/endo <sup>c</sup> | ee (%) (exo) <sup>d</sup> |
|-------|---------------|------------|---|---------------------------|
| 1     | <b>8a</b>     | <b>12a</b> | 89, 70/30   | 96                        |
| 2     | <b>8b</b>     | <b>12b</b> | 87, 95/5  | 91                        |
| 3     | <b>9</b>      | <b>13</b>  | 66, 98/2  | 80                        |
| 4     | <b>10</b>     | <b>14</b>  | 71, 2/98  | 91                        |
| 5     | <b>11</b>     | <b>15</b>  | 95, 75/25   | 91                        |

<sup>a</sup> Reactions run using **3a** (0.2 mmol), dipolarophile (0.2 mmol), CuOAc (0.01 mmol), **1a** (0.011 mmol), diethyl ether (2 mL). <sup>b</sup> Total isolated yield. <sup>c</sup> Determined by <sup>1</sup>H NMR. <sup>d</sup> Determined by HPLC.

acrylate, maleate, fumarate, and maleimide (Figure 2). The results are outlined in Table 4. In the reaction with methyl acrylate **8a**, the exo cycloadduct **12a** was obtained preferentially in high enantioselectivities (96% ee), although accompanied by significant amounts of the endo isomer (exo/endo = 70:30) (entry 1). In the reaction with *tert*-butyl acrylate **8b**, exo diastereoselectivity was improved (exo/endo = 95:5) with high ee% (entry 2). In the reactions with dimethyl maleate **9** the exo isomers **13** was obtained predominantly (exo/endo = 98:2) with high enantioselectivity (80% ee, entry 3). Zhang et al. reported that high diastereoselectivity and enantioselectivity can be achieved in the reaction of azomethine ylide with **8b** and **9** using a Cu(I)/chiral ferrocenyloxazoline phosphine complex in which the phosphinyl substituent is a bulky 3,5-xylyl group.<sup>3</sup> The phosphinyl substituent of ClickFerrophos used here was a simple phenyl group, which implies that the structure of ClickFerrophos itself is effective for asymmetric induction. On the other hand, with fumarate (**10**), the endo cycloadduct **14** was obtained exclusively with 91% ee (entry 4). The reaction with *N*-phenylmaleimide (**11**) gave the exo adduct **15** with moderate diastereoselectivity (exo/endo = 75:25) and 91% ee (entry 5).

(9) Künzer, H.; Stahnke, M.; Sauer, G.; Wiechert, R. *Tetrahedron Lett.* **1991**, 32, 1949–1952. The cleavage of C–N bond was accompanied to yield (*E*)-methyl 2-(methylamino)-5-phenylpent-4-enoate (10% yield).

In conclusion, Cu(I)/ClickFerrophos complex was found to be an efficient catalyst for asymmetric 1,3-dipolar cycloaddition of azomethine ylide with dipolarophiles. In reactions with vinyl sulfone, acrylates, maleate, and maleimide, the *exo* isomers were produced predominantly, with high enantioselectivity (up to 99.9% ee).

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**Supporting Information Available:** Full experimental procedures, characterization data, HPLC analyses, and  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra (PDF) for pyrrolidine derivatives **5a–5f**, **6,7**, **12a,b**, **13–15**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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