

# Thioether–phosphinite and diphosphinite ligands derived from D-xylose for the copper-catalyzed asymmetric 1,4-addition to 2-cyclohexenone

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**Abstract**—A series of thioether–phosphinite **1–3** and diphosphinite **4** and **5** ligands, derived from inexpensive D-(+)-xylose, were tested for the first time in the Cu-catalyzed asymmetric 1,4-addition to 2-cyclohexenone **6**. Good enantioselectivities (up to 72%) and activities [TOF up to >1225 mol (mol h<sup>-1</sup>)] combined with excellent selectivity in the 1,4 product were obtained. Our results show that activity and selectivity (chemo- and enantioselectivity) depend strongly on the type of functional group at the C-5 position of the carbohydrate backbone, the steric properties of the substituent in the thioether moiety, the catalyst precursor and the alkylating agent.

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## 1. Introduction

The enantioselective conjugate addition of organometallic reagents to  $\alpha,\beta$ -unsaturated substrates catalyzed by chiral transition metal complexes is a useful synthetic process for asymmetric carbon–carbon bond formation.<sup>1</sup> A prominent position in the rapid development of this process is occupied by the copper-catalyzed, ligand-accelerated, 1,4-addition of organozinc reagents.<sup>1</sup> Trialkylaluminum reagents were tested in only a few cases but these represent an interesting alternative.<sup>2</sup> The selection of chiral ligands for the highly enantioselective conjugate addition of organozinc reagents to  $\alpha,\beta$ -unsaturated compounds has mainly focused on P-donor and mixed P,N-donor ligands.<sup>1f–h,3</sup> Most phosphorus ligands are of the phosphite (mainly monophosphite) and phosphoramidite type.<sup>1f–h</sup> Non-phosphorus ligands have scarcely been used with dialkylzinc reagents.<sup>1f</sup> More research is therefore required to study the possibilities offered by other classes of ligands in this process. Carbohydrates are particularly advantageous for this purpose because they are inexpensive and their modular constructions are easy. Although they have been successfully used in other

enantioselective reactions,<sup>4</sup> there have been few reports on the highly enantioselective 1,4-addition using these systems. Notable examples, however, include monophosphonite,<sup>5</sup> monophosphite,<sup>3c,5,6</sup> and mixed amino-thiolate<sup>7</sup> ligands derived from TADDOL, and furanoside diphosphite ligands.<sup>8</sup> Other carbohydrate ligands, such as phosphoroamidite<sup>3c,5,6,9</sup> and mixed S–O,<sup>10</sup> N–P,<sup>11</sup> S–P,<sup>12</sup> and P–P<sup>11,12</sup> heterodonor ligands, have also been tested with low-to-moderate enantioselectivities.

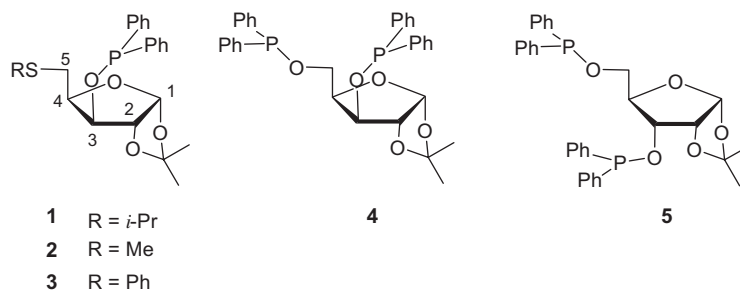
Following our interest in carbohydrates as an inexpensive and highly modular chiral source for preparing ligands,<sup>4</sup> and encouraged by the success of the furanoside diphosphite<sup>8</sup> ligands in this process, we tested their thioether–phosphinite **1–3** and diphosphinite **4** and **5** counterparts (Fig. 1) in the enantioselective copper-catalyzed 1,4-addition to 2-cyclohexenone. To the best of our knowledge, diphosphinite and thioether–phosphinite ligands have not previously been applied in this process.

## 2. Results and discussion

### 2.1. Ligand design

Ligands **1–5**, which were easily prepared in a few steps from inexpensive D-(+)-xylose,<sup>13</sup> consist of chiral 1,2-*O*-protected xylo- and ribo-furanoside backbones,

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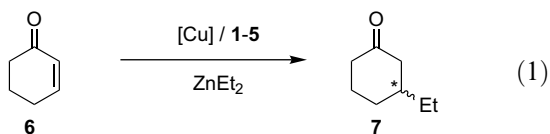
**Figure 1.** Furanoside thioether–phosphinite **1–3** and diphosphinite **4** and **5** ligands.

which determines their underlying structure with either thioether (ligands **1–3**) or phosphinite (ligands **4** and **5**) groups at the C-5 position.

We studied the influence of various substituents at the thioether groups using ligands **1–3**, which have the same phosphinite moiety. We then used ligands **4** and **5** to study how a phosphinite moiety rather than the thioether functionality affected catalytic performance. We also looked at how the configuration of the C-3 stereogenic center of the ligand backbone was affected by comparing ligands **4** and **5**, which have opposite configurations at C-3.

## 2.2. Asymmetric conjugate 1,4-addition of ZnEt<sub>2</sub>

In the first set of experiments, we tested furanoside ligands **1–5** in the copper-catalyzed conjugate addition of diethylzinc to 2-cyclohexenone **6** (Eq. 1). The latter was chosen as a substrate because this reaction has been performed with a wide range of ligands with several donor groups enabling the direct comparison of the efficiency of the various ligands systems.<sup>1</sup> The catalytic system was generated in situ by adding the corresponding ligand to a suspension of catalyst precursor. The results are shown in Table 1.



The effect of several reaction parameters, such as solvent, ligand-to-copper ratio and catalyst precursor, were studied using ligand **1** (entries 1–8). Our results showed that the efficiency of the process depended on the nature of the solvent (entries 1–3). Therefore, the selectivity (chemoselectivity in the 1,4-product and enantioselectivity) was best when dichloromethane was used. Adding one-fold excess of ligand led to a higher chemoselectivity in the 1,4-product and enantioselectivity (entry 4). However, the outcome of the reaction was not affected when a greater excess of ligand was added (entry 5).

Varying the catalyst precursor showed an effect on the selectivity of the process (entries 6–8). The best trade-off between chemoselectivities and enantioselectivities was therefore achieved with the catalyst precursors

CuCN and [Cu(MeCN)<sub>4</sub>]BF<sub>4</sub>. Interestingly, the sense of the asymmetric induction obtained with these catalyst precursors was the opposite of that for the catalyst precursor Cu(OTf)<sub>2</sub>. The nature of the catalyst precursor is therefore also important in determining the enantioselectivity.

Under the optimized conditions, we then studied how the thioether substituents affected the catalytic performance with ligands **2** and **3**. Using ligand **2** with a methyl substituent in the thioether moiety showed lower enantioselectivities (entries 9–10). Using ligand **3** with a phenyl substituent in the thioether moiety showed the lowest asymmetric induction (entries 11 and 12).

The influence of the phosphinite moiety rather than the thioether functionality was studied with ligands **4** and **5** (entries 13–15). In general, these ligands led to lower enantioselectivities and chemoselectivities with higher activities. Interestingly, the sense of asymmetric induction was the opposite of that obtained with the catalytic systems Cu/**1–3**. Also, if we compare the results obtained with ligands **4** and **5** we can see that the configuration of C-3 of the carbohydrate backbone had no effect on the catalytic performance of the process (entries 14 and 15).

Finally, we also studied how the temperature affected the outcome of the reaction with ligand **1**. Lowering the temperature to 0 °C increased enantioselectivity (up to 72%) (entry 7 vs 16). This phenomenon was also observed for related furanoside Cu–thioether–phosphite systems.<sup>12</sup>

## 2.3. Asymmetric conjugate 1,4-addition of AlEt<sub>3</sub>

Michael additions of organolithium, Grignard and diorganozinc reagents to enones have been widely studied in the last decade but very little attention has been paid to trialkylaluminum reagents.<sup>1,2</sup> Bearing in mind the positive effect when we used triethylaluminum rather than diethylzinc as the alkylating reagent, we also studied the use of triethylaluminum. Table 2 shows the results of the copper-catalyzed conjugate addition of trialkylaluminum to 2-cyclohexenone **6** (Eq. 2) using the thioether–phosphinite **1–3** and diphosphinite **4** and **5** ligands. The catalytic system was generated in situ by adding the corresponding ligand to a suspension of catalyst precursor.

**Table 1.** Cu-catalyzed asymmetric 1,4-addition of diethylzinc to 2-cyclohexenone **6** using ligands **1–5**<sup>a</sup>

| Entry             | Ligand   | Solvent                         | Catalyst precursor                      | % Conv (h) <sup>b</sup> | 1,4-Product (%) <sup>c</sup> | % ee <sup>d</sup> |
|-------------------|----------|---------------------------------|---|-------------------------|------------------------------|-------------------|
| 1                 | <b>1</b> | CH <sub>2</sub> Cl <sub>2</sub> | Cu(OTf) <sub>2</sub>                    | 100 (2)                 | 55                           | 25 ( <i>S</i> )   |
| 2                 | <b>1</b> | Toluene                         | Cu(OTf) <sub>2</sub>                    | 100 (2)                 | 45                           | 10 ( <i>S</i> )   |
| 3                 | <b>1</b> | THF                             | Cu(OTf) <sub>2</sub>                    | 100 (2)                 | 45                           | 12 ( <i>S</i> )   |
| 4 <sup>e</sup>    | <b>1</b> | CH <sub>2</sub> Cl <sub>2</sub> | Cu(OTf) <sub>2</sub>                    | 100 (2)                 | 60                           | 34 ( <i>S</i> )   |
| 5 <sup>f</sup>    | <b>1</b> | CH <sub>2</sub> Cl <sub>2</sub> | Cu(OTf) <sub>2</sub>                    | 100 (2)                 | 59                           | 33 ( <i>S</i> )   |
| 6 <sup>e</sup>    | <b>1</b> | CH <sub>2</sub> Cl <sub>2</sub> | CuI                                     | 100 (2)                 | 100                          | 55 ( <i>R</i> )   |
| 7 <sup>e</sup>    | <b>1</b> | CH <sub>2</sub> Cl <sub>2</sub> | CuCN                                    | 100 (2)                 | 100                          | 64 ( <i>R</i> )   |
| 8 <sup>e</sup>    | <b>1</b> | CH <sub>2</sub> Cl <sub>2</sub> | [Cu(MeCN) <sub>4</sub> ]BF <sub>4</sub> | 100 (2)                 | 100                          | 63 ( <i>R</i> )   |
| 9 <sup>e</sup>    | <b>2</b> | CH <sub>2</sub> Cl <sub>2</sub> | CuCN                                    | 100 (2)                 | 85                           | 26 ( <i>R</i> )   |
| 10 <sup>e</sup>   | <b>2</b> | CH <sub>2</sub> Cl <sub>2</sub> | [Cu(MeCN) <sub>4</sub> ]BF <sub>4</sub> | 100 (2)                 | 100                          | 53 ( <i>R</i> )   |
| 11 <sup>e</sup>   | <b>3</b> | CH <sub>2</sub> Cl <sub>2</sub> | CuCN                                    | 100 (2)                 | 98                           | 2 ( <i>R</i> )    |
| 12 <sup>e</sup>   | <b>3</b> | CH <sub>2</sub> Cl <sub>2</sub> | [Cu(MeCN) <sub>4</sub> ]BF <sub>4</sub> | 100 (2)                 | 100                          | 15 ( <i>R</i> )   |
| 13                | <b>4</b> | CH <sub>2</sub> Cl <sub>2</sub> | CuCN                                    | 97 (1.30)               | 38                           | 17 ( <i>S</i> )   |
| 14                | <b>4</b> | CH <sub>2</sub> Cl <sub>2</sub> | [Cu(MeCN) <sub>4</sub> ]BF <sub>4</sub> | 97 (1)                  | 69                           | 25 ( <i>S</i> )   |
| 15                | <b>5</b> | CH <sub>2</sub> Cl <sub>2</sub> | [Cu(MeCN) <sub>4</sub> ]BF <sub>4</sub> | 96 (1)                  | 68                           | 29 ( <i>S</i> )   |
| 16 <sup>e,g</sup> | <b>1</b> | CH <sub>2</sub> Cl <sub>2</sub> | CuCN                                    | 63 (2)                  | 100                          | 72 ( <i>R</i> )   |

<sup>a</sup> Reaction conditions: catalyst precursor (0.025 mmol), ligand (0.025 mmol), ZnEt<sub>2</sub> (3.5 mmol), substrate (2.5 mmol), solvent (6 mL), room temperature.

<sup>b</sup> Measured by GC using undecane as internal standard. Reaction time in hours shown in parentheses.

<sup>c</sup> Chemoselectivity in 1,4-product determined by GC using undecane as internal standard.

<sup>d</sup> Determined by GC using Lipodex-A column. Absolute configuration drawn in parentheses.

<sup>e</sup> L/Cu = 2.

<sup>f</sup> L/Cu = 4.

<sup>g</sup> T = 0 °C.

**Table 2.** Cu-catalyzed asymmetric 1,4-addition of triethylaluminum to 2-cyclohexenone **6** using ligands **1–5**<sup>a</sup>

| Entry             | Ligand   | Solvent                         | Catalyst precursor                      | % Conv (min) <sup>b</sup> | 1,4-Product (%) <sup>c</sup> | % ee <sup>d</sup> |
|-------------------|----------|---------------------------------|---|---------------------------|------------------------------|-------------------|
| 1                 | <b>1</b> | CH <sub>2</sub> Cl <sub>2</sub> | Cu(OTf) <sub>2</sub>                    | 100 (20)                  | 65                           | 9 ( <i>R</i> )    |
| 2                 | <b>1</b> | Toluene                         | Cu(OTf) <sub>2</sub>                    | 100 (20)                  | 60                           | 8 ( <i>S</i> )    |
| 3                 | <b>1</b> | THF                             | Cu(OTf) <sub>2</sub>                    | 100 (20)                  | 55                           | 3 ( <i>R</i> )    |
| 4 <sup>e</sup>    | <b>1</b> | CH <sub>2</sub> Cl <sub>2</sub> | Cu(OTf) <sub>2</sub>                    | 100 (20)                  | 100                          | 9 ( <i>R</i> )    |
| 5 <sup>e</sup>    | <b>1</b> | CH <sub>2</sub> Cl <sub>2</sub> | CuI                                     | 100 (20)                  | 95                           | 1 ( <i>R</i> )    |
| 6 <sup>e</sup>    | <b>1</b> | CH <sub>2</sub> Cl <sub>2</sub> | CuCN                                    | 100 (20)                  | 94                           | 5 ( <i>S</i> )    |
| 7 <sup>e</sup>    | <b>1</b> | CH <sub>2</sub> Cl <sub>2</sub> | [Cu(MeCN) <sub>4</sub> ]BF <sub>4</sub> | 100 (20)                  | 100                          | 10 ( <i>R</i> )   |
| 8 <sup>e</sup>    | <b>2</b> | CH <sub>2</sub> Cl <sub>2</sub> | Cu(OTf) <sub>2</sub>                    | 100 (20)                  | 95                           | 15 ( <i>S</i> )   |
| 9 <sup>e</sup>    | <b>2</b> | CH <sub>2</sub> Cl <sub>2</sub> | [Cu(MeCN) <sub>4</sub> ]BF <sub>4</sub> | 100 (20)                  | 100                          | 33 ( <i>S</i> )   |
| 10 <sup>e</sup>   | <b>3</b> | CH <sub>2</sub> Cl <sub>2</sub> | Cu(OTf) <sub>2</sub>                    | 100 (20)                  | 95                           | 27 ( <i>R</i> )   |
| 11 <sup>e</sup>   | <b>3</b> | CH <sub>2</sub> Cl <sub>2</sub> | [Cu(MeCN) <sub>4</sub> ]BF <sub>4</sub> | 100 (20)                  | 100                          | 36 ( <i>S</i> )   |
| 12                | <b>4</b> | CH <sub>2</sub> Cl <sub>2</sub> | Cu(OTf) <sub>2</sub>                    | 91 (5)                    | 48                           | 12 ( <i>S</i> )   |
| 13                | <b>4</b> | CH <sub>2</sub> Cl <sub>2</sub> | [Cu(MeCN) <sub>4</sub> ]BF <sub>4</sub> | 94 (5)                    | 100                          | 24 ( <i>S</i> )   |
| 14                | <b>5</b> | CH <sub>2</sub> Cl <sub>2</sub> | [Cu(MeCN) <sub>4</sub> ]BF <sub>4</sub> | 97 (5)                    | 100                          | 32 ( <i>S</i> )   |
| 15 <sup>e</sup>   | <b>5</b> | CH <sub>2</sub> Cl <sub>2</sub> | [Cu(MeCN) <sub>4</sub> ]BF <sub>4</sub> | 91 (10)                   | 65                           | 14 ( <i>S</i> )   |
| 16 <sup>f</sup>   | <b>5</b> | CH <sub>2</sub> Cl <sub>2</sub> | [Cu(MeCN) <sub>4</sub> ]BF <sub>4</sub> | 93 (10)                   | 62                           | 20 ( <i>S</i> )   |
| 17 <sup>e,g</sup> | <b>3</b> | CH <sub>2</sub> Cl <sub>2</sub> | [Cu(MeCN) <sub>4</sub> ]BF <sub>4</sub> | 100 (60)                  | 100                          | 48 ( <i>S</i> )   |

<sup>a</sup> Reaction conditions: catalyst precursor (0.025 mmol), ligand (0.025 mmol), AlEt<sub>3</sub> (3.5 mmol), substrate (2.5 mmol), solvent (6 mL), room temperature.

<sup>b</sup> Measured by GC using undecane as internal standard. Reaction time in minutes shown in parentheses.

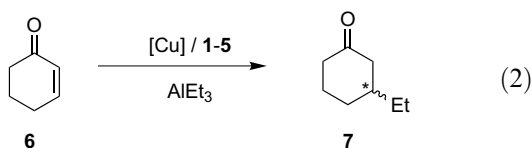
<sup>c</sup> Chemoselectivity in 1,4-product determined by GC using undecane as internal standard.

<sup>d</sup> Determined by GC using Lipodex-A column. Absolute configuration shown in parentheses.

<sup>e</sup> L/Cu = 2.

<sup>f</sup> L/Cu = 0.5.

<sup>g</sup> T = 0 °C.



trade-off between chemoselectivities and enantioselectivities was obtained when dichloromethane was used as solvent, the ligand-to-copper ratio was 2, and Cu(OTf)<sub>2</sub> and [Cu(MeCN)<sub>4</sub>]BF<sub>4</sub> were used as catalyst precursor (entries 4 and 7).

Our preliminary investigations into the solvent effects, the ligand-to-copper ratio and catalyst precursor using ligand **1** (Table 2, entries 1–7) indicated that the opti-

Under optimized conditions, the results with ligands **1–3** (Table 2, entries 4 and 7–11) indicate that the chemoselectivities and enantioselectivities followed a different

trend to those for the copper-catalyzed conjugate addition of diethylzinc to 2-cyclohexenone **6** (Table 1, entries 7–12). Enantioselectivity was therefore best with ligand **3**, which contains a phenyl substituent in the thioether moiety, while ligand **1** provided the lowest asymmetric induction in this case. Note that with ligands **2** and **3**, the best catalyst precursor was  $[\text{Cu}(\text{MeCN})_4]\text{BF}_4$ .

In general, diphosphinite ligands **4** and **5** showed much higher reaction rates [TOF up to  $>1225 \text{ mol}(\text{mol h}^{-1})$ ] but lower enantioselectivities than the Cu–thioether–phosphinite ligand systems (entries 12–16). Unlike thioether–phosphinite ligands, with diphosphinite ligands excess of ligand decreased activity, chemoselectivity and enantioselectivity (entry 14 vs 15). The same effect was observed by decreasing the catalyst loading (entry 16). If we compare entries 13 and 14, we can see that the configuration at C-3 affected the product outcome. Therefore, ligand **5**, with an (*R*)-configuration at C-3, obtained a better enantioselectivity than the catalytic system Cu/**4**.

We studied how temperature affected the outcome of the reaction with ligand **3**. Lowering the temperature to 0 °C increased the enantioselectivity (up to 48%) (entry 11 vs 17).

If we compare the results of using  $\text{AlEt}_3$  with the results of using  $\text{ZnEt}_2$ , we can conclude that with thioether–phosphinite ligands, activity was higher but enantioselectivity was lower using  $\text{AlEt}_3$ . However, for diphosphinite ligands  $\text{AlEt}_3$  produced much higher activities and chemoselectivities in the 1,4-product than  $\text{ZnEt}_2$  with similar enantioselectivity.

### 3. Conclusions

A series of thioether–phosphinite **1–3** and diphosphinite **4** and **5** ligands, derived from inexpensive and readily available D-(+)-xylose, were tested in the Cu-catalyzed asymmetric 1,4-addition to 2-cyclohexenone **6**. Good enantioselectivities (up to 72%) and activities [TOF up to  $>1225 \text{ mol}(\text{mol h}^{-1})$ ] combined with high chemo- and regioselectivity in 1,4 product were obtained. Systematically varying the functional groups at the C-5 position (thioether and phosphinite) and different substituents in the thioether moieties had a strong effect on the rate and enantioselectivity. The best enantioselectivity was achieved with the catalyst precursor containing the thioether–phosphinite ligand **1**, which has an isopropyl substituent in the thioether moiety. However, the activity was best with the diphosphinite ligands **4** and **5**.

Our results also showed that the nature of the catalyst precursor and alkylating agent also plays an important role in determining activity and selectivity (chemo- and enantioselectivity).

Encouraged by the promising behavior with ligand **1**, we are currently performing further studies aimed at developing a more efficient ligand by exploiting the fact that these sugar ligands can be so easily modified.

## 4. Experimental

### 4.1. General

All syntheses were performed using the standard Schlenk techniques under argon atmosphere. Solvents were purified by standard procedures. Thioether–phosphinites **1–3**<sup>13b</sup> and diphosphinites **4** and **5**<sup>13a</sup> were prepared by previously described methods. All other reagents were used as commercially available.

**4.1.1. Typical procedure for the catalytic conjugate addition of diethylzinc to 2-cyclohexenone, 6.** In a typical procedure, a solution of copper-catalyst precursor (0.025 mmol) and furanoside ligand (0.025 mL) in dichloromethane (3 mL) was stirred for 30 min at room temperature. After cooling to 0 °C, diethylzinc (1 M soln in hexanes, 3.5 mL, 3.5 mmol) was added. A solution of 2-cyclohexenone (0.24 mL, 2.5 mmol) and undecane as GC internal standard (0.25 mL) in dichloromethane (3 mL) was then added at the corresponding reaction temperature. The reaction was monitored by GC. The reaction was quenched with HCl (2 M) and filtered twice through flash silica. Conversion, chemoselectivity and enantioselectivity were obtained by GC using a Lipodex-A column.

**4.1.2. Typical procedure for the catalytic conjugate addition of triethylaluminum to 2-cyclohexenone, 6.** In a typical procedure, a solution of copper-catalyst precursor (0.025 mL) and furanoside ligand (0.025 mL) in dichloromethane (3 mL) was stirred for 30 min at room temperature. Triethylaluminum (1 M soln in hexanes, 3.5 mL, 3.5 mmol) was added at the corresponding temperature. A solution of 2-cyclohexenone (0.24 mL, 2.5 mmol) and undecane as GC internal standard (0.25 mL) in dichloromethane (3 mL) was then added. The reaction was monitored by GC. The reaction was quenched with HCl (2 M) and filtered twice through flash silica. Conversion, chemoselectivity and enantioselectivity were obtained by GC using a Lipodex-A column.

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