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# Copper-catalysed asymmetric conjugate addition of organometallic reagents to enones using S,O-ligands with a xylofuranose backbone

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**Abstract**

The copper-catalysed enantioselective 1,4-addition reactions of diethylzinc to cyclohexenone and trimethylaluminium to *E*-non-3-en-2-one in the presence of thioether-alcohol ligands, which are easily prepared from D-(+)-xylose, resulted in e.e.s of up to 62% for cyclohexenone and 34% for *E*-non-3-en-2-one. © 2000 Elsevier Science Ltd. All rights reserved.

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## 1. Introduction

The enantioselective conjugate addition of organometallic reagents to α-β-unsaturated substrates,[1] and in particular, the addition of organocuprates to enones, is still to be of considerable synthetic interest.[2] Excellent enantioselectivities have been obtained in the copper-catalysed Michael addition of Grignard and diorganozinc reagents to enones and other α-β-unsaturated carbonyl compounds using phosphorus ligands[3–16] such as phosphorus amidites,[3–10] oxazoline–phosphite[11] and phosphite ligands[12–14] (Fig. 1). However, one important limitation is that they exhibit high substrate specificity. Further efforts are therefore required to design new chiral catalysts which can be applied more generally to different sizes of cyclic and acyclic substrates.

Despite the early promising results obtained with thiolate ligands in the asymmetric copper-catalysed Michael addition to enones,[17–20] sulphur ligands have been less studied than their phosphorus counterparts. As far as we know, thioether-based catalysts have never been applied in the copper-catalysed 1,4-addition of soft organometallics, e.g. $ZnR_2$ and $AlR_3$, to enones.

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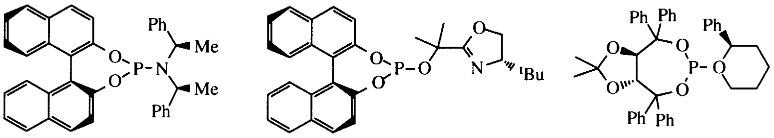
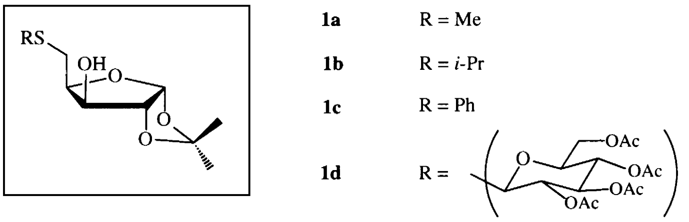


Fig. 1.

In this paper we report the synthesis of a new thioether-alcohol ligand containing both a xylose and a glucose backbone. We discuss the results of using this ligand and a family of thioether-alcohol ligands with a xylofuranose backbone in the asymmetric copper addition of diethylzinc and trimethylaluminium to 2-cyclohexenone and *E*-non-3-en-2-one, respectively (Scheme 1).

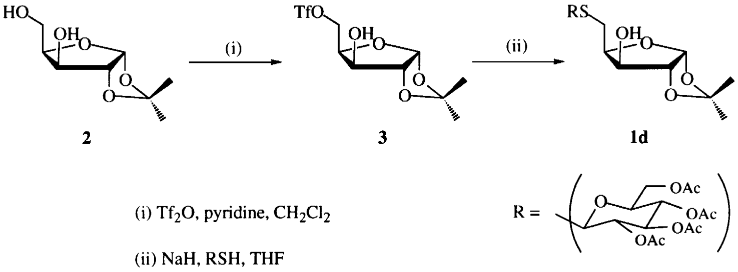


Scheme 1.

## 2. Results and discussion

### 2.1. Synthesis of ligand **1d**

Thioether–alcohol **1d** was synthesised from xylose via compound **2** (Scheme 2) using a slightly modified literature method for **1a**–**c**.[21] The diol **2** was converted to the monotriflate **3** by the reaction of a dichloromethane solution of **2** with triflic anhydride and pyridine. Treating compound **3** with a stoichiometric amount of NaH and 1-thio-β-D-glucose tetraacetate at −78°C afforded ligand **1d**. Higher temperatures led to the elimination of the triflyl group as a secondary reaction.

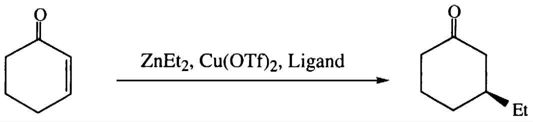


Scheme 2. Synthesis of ligand **1d**

### 2.2. Conjugate addition of 2-cyclohexenone

Ligands **1a**–**d** were used in the copper-catalysed conjugate addition of diethylzinc to 2-cyclohexenone (Table 1). The catalytic system was generated in situ by adding two equivalents of the corresponding ligands to a solution of $Cu(OTf)_2$ followed by addition of diethylzinc. In general, conversions and regioselectivities in the 1,4-product were good for all ligands. There was no 1,2-product observed.

Table 1
Catalytic conjugate addition reactions of $ZnEt_2$ to 2-cyclohexenone[a]



| Entry | Ligand | t (min) | Solvent | T[K] | % conv.[b] | % 1,4[c] | % ee[d] |
|---|---|---|---|---|---|---|---|
| 1 | **1c** | 60 | $CH_2Cl_2$ | 273 | 75 | 92 | 61 (S) |
| 2 | **1c** | 60 | Toluene | 273 | 80 | 87 | 62 (S) |
| 3 | **1c** | 60 | THF | 273 | 63 | 71 | 59 (S) |
| 4[e] | **1c** | 60 | $CH_2Cl_2$ | 273 | 100 | 92 | 60 (S) |
| 5[f] | **1c** | 60 | $CH_2Cl_2$ | 273 | 100 | 12 | 3 (S) |
| 6 | **1c** | 5 | $CH_2Cl_2$ | 298 | 67 | 91 | 54 (S) |
| 7 | **1c** | 60 | $CH_2Cl_2$ | 253 | 54 | 89 | 38 (S) |
| 8 | **1c** | 60 | $CH_2Cl_2$ | 233 | 39 | 89 | 29 (S) |
| 9 | **1b** | 60 | $CH_2Cl_2$ | 273 | 98 | 94 | 44 (S) |
| 10 | **1a** | 60 | $CH_2Cl_2$ | 273 | 78 | 89 | 49 (S) |
| 11 | **1d** | 60 | $CH_2Cl_2$ | 273 | 41 | 82 | 20 (S) |

[a] Reaction conditions: [$Cu(OTf)_2$] (0.025 mmol), solvent (6 mL), $ZnEt_2$ (3.5 mmol), 2-cyclohexenone (2.5 mmol). [b] % Conversion of 2-cyclohexenenone determined by GC using undecane as internal standard. [c] % Regioselectivity in 1,4-product. [d] % Enantiomeric excess measured by GC using a Lipodex A column. [e] [$Cu(OTf)_2$] (0.05 mmol), [substrate]/[Cu] = 25. [f] TMSCl (2.5 mmol) added.

The effect of the reaction temperature was studied for the system with ligand **1c**. As reported for the related Cu–diphosphite catalytic system[22] the best enantiomeric excesses were obtained at 273 K (entry 1), and these decreased considerably when the reaction temperature was lowered (Fig. 2).

Increasing the catalyst loading increased the chemical yield but the 1,4-regio- and enantioselectivity were not affected (entry 4 vs entry 1). Attempts to increase the catalytic activity at 273 K by adding a Lewis acid promoter strongly suppressed both regio- and enantioselectivity (entry 5 vs entry 1).

The addition of diethylzinc proceeded with similar enantioselectivities in solvents of both lower and higher polarity (entries 1–3). However, regioselectivities in favour of the 1,4-product were lower when toluene, and especially THF, were used as solvents.

Changing the substituent of the thioether moiety produces an important effect on the rate and stereoselectivities. Conversions are higher for the catalyst precursor containing the electron-rich **1b**

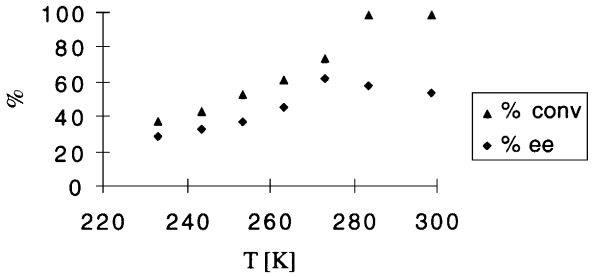


Fig. 2. Variation of conversion and enantioselectivity vs temperature using ligand **1c**

ligand (entry 9) while better enantioselectivities have been obtained with the catalyst precursor containing ligand **1c** (entry 1). The presence of a bulky substituent **1d** has a detrimental effect on conversion and enantioselectivity (entry 11). The formation of ligand-free copper aggregates could be responsible for this.

### *2.3. Conjugate addition of* E*-non-3-en-2-one*

Linear enones possessing only aliphatic substituents are a demanding substrate class for asymmetric conjugate addition.[23] The only highly enantioselective catalytic conjugate additions of this substrate class are rhodium-catalysed.[24] The enantioselective addition of alkyl groups has been successfully obtained only recently.[23]

Table 2 shows the results of the thioether/copper-catalysed conjugate addition of trimethylaluminium to *E*-non-3-en-2-one. There was no 1,2-product. It is noteworthy that better results have been obtained using $[Cu(MeCN)_4]BF_4$ instead of $Cu(OTF)_2$ as a catalyst precursor and when tetrahydrofuran was used as a solvent.

As previously observed for 2-cyclohexenone, the introduction of sterically demanding groups in the thioether moiety had a negative effect on selectivity, while at low temperature selectivities were better than at 273 K (entries 3, 4 vs 5). This is in contrast with cyclohexenone addition, probably because of the formation of different aggregates. Catalyst precursors containing the electron-rich ligands **1a** and **1b** gave better conversions, while, as observed for 2-cyclohexenone, better enantioselectivities have been obtained with the catalyst precursor that contained ligand **1c** (entries 1, 2 vs 3).

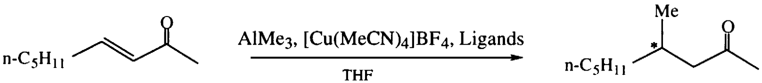
In summary, chiral dithioether ligands are active in the enantioselective copper-catalysed 1,4-addition of diethylzinc to cyclohexenone and produce enantiomeric excesses of up to 62% and have also shown promising results (e.e.s of up to 34%) in the addition of trimethylaluminium to *E*-non-3-en-2-one. Further investigation is in progress to delineate the scope and utility of the mixed thioether-alcohol ligands.

## 3. Experimental

### *3.1. General comments*

All experiments were carried out under an argon atmosphere. All solvents were dried by standard published methods and distilled prior to use. 1,2-*O*-Isopropylidenexylofuranose,[26,27] 1,2-*O*-isopropylidene-5-*O*-trifluoromethanesulfanyl-α-D-(−)-xylofuranose[21] and thioether-alcohol ligands **1a**–**c**[21] were prepared by previously described methods. Elemental analyses were performed on a Carlo Erba EA-1108 instrument. $^1H$ and $^{13}C\{^1H\}$ NMR spectra were recorded on a Varian Gemini 300 MHz spectrometer. Chemical shifts are relative to $SiMe_4$ ($^1H$ and $^{13}C$) as internal standard. All assignments in NMR spectra

Table 2
Catalytic conjugate addition reactions of $AlMe_3$ to *E*-non-3-en-2-one[a]



| Entry | Ligand | t (min) | T[K] | % conv.[b] | % 1,4[c] | % ee[d] |
|---|---|---|---|---|---|---|
| 1 | **1a** | 20 | 253 | 73 | 92 | 6 (R) |
| 2 | **1b** | 20 | 253 | 53 | 83 | 15 (R) |
| 3 | **1c** | 20 | 253 | 40 | 80 | 22 (R) |
| 4 | **1c** | 20 | 233 | 10 | 80 | 34 (R) |
| 5 | **1c** | 20 | 273 | 55 | 70 | 9 (R) |
| 6 | **1d** | 20 | 253 | 45 | 72 | 2 (S) |

[a] Reaction conditions: $[Cu(MeCN)_4]BF_4$ (0.05 mmol), THF (2 mL), $AlMe_3$ (0.7 mmol), *E*-non-3-en-2-one (0.5 mmol). [b] % Conversion of *E*-3-nonen-2-one determined by GC using undecane as internal standard. [c] % Regioselectivity in 1,4-product. [d] % Enantiomeric excess measured by GC using an *oktakis*-(6-*O*-methyl-2,3-di-*O*-pentyl)-γ-cyclodextrin.[25]

were determined by means of COSY and HETCOR spectra. Gas chromatographic analyses were run on a Hewlett–Packard HP 5890A instrument equipped with a Hewlett–Packard HP 3396 series II integrator. Optical rotations were measured at 20°C on a Perkin–Elmer 241 MC polarimeter. The specific rotations are given in deg $cm^3$ $g^{-1}$ $dm^{-1}$ units.

### 3.2. *1,2-*O*-Isopropylidene-5-(1′-thio-2′,3′,4′,6′-tetra-*O*-acetyl-β-*D*-glucopyranosyl)-α-*D*-(−)-xylo-furanose* ***1d***

A solution of 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose (1 g, 2.7 mmol) in THF (6 mL) was added to a suspension of NaH (108 mg, 2.7 mmol) in THF (6 mL) at −78°C. After 30 min at −78°C, the suspension was warmed to room temperature and a solution of **2** (0.8 g, 2.7 mmol) in THF (6 mL) was added. After 90 min, water (50 mL) was added, the solvent was evaporated and the residue was extracted with dichloromethane (3×50 mL). The extract was dried over magnesium sulfate and concentrated. The residue was purified by column chromatography (hexane:ethyl acetate, 2:1) to give 1.01 g (70%) as a white solid (decomposes at 130°C). Anal. calcd for $C_{22}H_{32}O_{13}S$: C, 49.25; H, 6.01; S, 5.98. Found: C, 49.88; H, 6.11; S, 5.79. $^1H$ NMR ($CDCl_3$): $\delta$ 1.28 (m, 3H, CMe), 1.47 (s, 3H, CMe), 1.99 (s, 3H, OAc), 2.03 (s, 3H, OAc), 2.06 (s, 3H, OAc), 2.08 (s, 3H, OAc), 2.79 (m, 1H, OH), 2.82 (dd, 1H, H-5b, $^2J_{5b\text{-}5a}$=12.9 Hz, $^3J_{5b\text{-}4}$=10.2 Hz), 3.14 (dd, 1H, H-5a, $^2J_{5a\text{-}5b}$=12.9 Hz, $^3J_{5a\text{-}4}$=4.5 Hz), 3.72 (m, 1H, H-5′), 4.15 (m, 2H, H-6′), 4.22 (m, 1H, H-4), 4.28 (m, 1H, H-3), 4.51 (d, 1H, H-2, $^3J_{2\text{-}1}$=3.6 Hz), 4.58 (d, 1H, H-1′, $^3J_{1'\text{-}2'}$=10.2 Hz), 5.02 (t, 1H, H-4′, *J*=9.4 Hz), 5.12 (m, 1H, H-2′), 5.21 (t, 1H, H-3′, *J*=9.4 Hz), 5.88 (d, 1H, H-1, $^3J_{1\text{-}2}$=3.3Hz). $^{13}C$ NMR ($CDCl_3$): $\delta$ 20.4 (CO*Me*), 26.0 (C*Me*), 26.6 (C*Me*), 27.2

(C-5), 62.1 (C-6′), 68.2 (C-4′), 69.8 (C-2′), 73.5 (C-3′), 74.0 (C-3), 75.9 (C-5′), 79.8 (C-4), 83.9 (C-1′), 84.9 (C-2), 104.9 (C-1), 113.2 (*C*Me), 169.5, 169.9, 170.2, 170.8 (CO). $[\alpha]_D^{20}=-20.6$ (c=1, $CHCl_3$).

### 3.3. Typical procedure for the catalytic conjugate addition of diethylzinc to 2-cyclohexenone

A solution of $Cu(OTf)_2$ (9 mg, 0.025 mmol) and thioether (0.05 mmol) in dichloromethane (3 mL) was stirred for 30 min at room temperature. After cooling to 273 K, diethylzinc (1 M sol. 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. The reaction was monitored by GC. After 1 h the reaction was quenched with HCl (2 M) and filtered twice through flash silica. The chemical yield and enantiomeric excesses were obtained by GC using a Lipodex-A column.

### 3.4. Typical procedure for the catalytic conjugate addition of trimethylaluminium to E-non-3-en-2-one

Trimethylaluminium solution (1 M sol., 100 μL, 0.1 mmol) was added to a THF solution (1 mL) containing thioether (0.1 mmol) and $[Cu(MeCN)_4]BF_4$ (15.7 mg, 0.05 mmol) at 253 K. After 1 min the trimethylaluminium (1 M sol., 0.75 mL, 0.75 mmol) and enone (0.6 M sol. in THF, 0.75 mL, 0.5 mmol) were introduced sequentially and in a dropwise manner over 20 min. After 20 min the reaction was quenched with HCl (2 M) and undecane as GC internal standard (50 μL) was added. The organic layer was filtered twice through flash silica. The chemical yield and e.e.s were obtained by GC using an *oktakis*-(6-*O*-methyl-2,3-di-*O*-pentyl)-γ-cyclodextrin column.

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