



Copper-catalyzed highly enantioselective 1,4-conjugate addition of trimethylaluminum to 2-cyclohexenone

Liang Liang^{a,b} and Albert S. C. Chan^{a,*}

^a*Open Laboratory of Chirotechnology of the Institute of Molecular Technology for Drug Discovery and Synthesis[†] and Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hong Kong, China*

^b*Faculty of Chemical Engineering and Light Industry, Guangdong University of Technology, Guangzhou, China*

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Abstract—New bidentate phosphites were prepared starting from BINOL and H₈-BINOL. Utilization of these ligands in the copper-catalyzed enantioselective conjugate addition of trimethylaluminum to 2-cyclohexenone afforded 3-methylcyclohexanone with up to 96% e.e. The scope of this process using various copper sources was investigated. © 2002 Published by Elsevier Science Ltd.

1. Introduction

The 1,4-conjugate addition of organometallic reagents to α,β -unsaturated ketones is a useful method for the introduction of a hydrocarbon unit to the β -position of a carbonyl function.¹ In recent years considerable progress has been achieved in the development of the copper-mediated catalytic versions of the enantioselective 1,4-addition of organozinc reagents to enones.^{2–4} Among the different chiral ligands used for this purpose, phosphoramidites,⁵ peptide-based phosphines,⁶ BINOL-based diphosphites,⁷ phosphites,⁸ TADDOL-derivatives,⁹ and oxazoline-phosphites¹⁰ have proven to be effective chirality sources in the reaction of dialkylzinc compounds with cyclic enones and acyclic enones. However, the development of effective ligands for the asymmetric conjugate addition to enones, in particular using trialkylaluminum reagents is still a challenge. Although the asymmetric 1,4-additions of many

organometallic reagents to cyclic enones have been widely studied in the last decade, very little attention has been paid to the 1,4-additions of trialkylaluminum reagents. Since trialkylaluminums are produced on industrial scales, new chemistry using these reagents may generate more practical applications. Recently, Dieguez et al reported an effective phosphine–phosphite ligand that gave 62% e.e. in the reaction of triethylaluminum with 2-cyclohexenones.¹¹ Herein, we report an effective catalytic enantioselective conjugate addition of trimethylaluminum to 2-cyclohexenone.

2. Results and discussion

A new family of chiral aryl diphosphite ligands, **1–3**, were prepared in our studies of diphosphite ligands containing binaphthyl and H₈-binaphthyl moieties (Fig. 1).

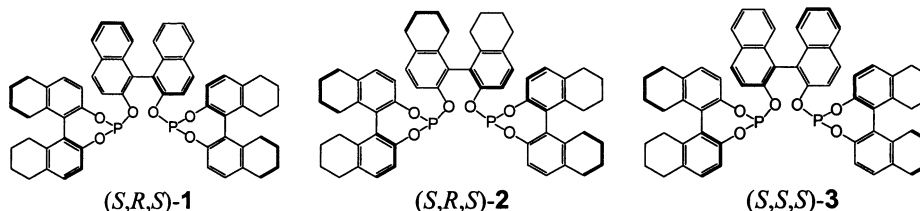


Figure 1.

* Corresponding author. E-mail: bcachan@polyu.edu.hk

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These new ligands were synthesized in a one-step reaction from the chlorophosphite of (*S*)-H₈-BINOL with (*R*)- or (*S*)-BINOL or (*S*)-H₈-BINOL. As a model reaction, the copper-catalyzed 1,4-conjugate addition of trimethylaluminum to 2-cyclohexenone **4** was examined by using ligands **1–3** with a number of copper sources including Cu(OTf)₂, (CuOTf)₂·C₆H₆ and Cu(CH₃CN)₄·BF₄ as catalyst precursor. All reactions were carried out at 0°C in the presence of 1 mol% of CuX and 2 mol% of ligand under nitrogen atmosphere. Table 1 summarized the preliminary results obtained by using (CuOTf)₂·C₆H₆ with **1–3** in the 1,4-addition of trimethylaluminum to 2-cyclohexenone in dichloromethane. The results indicated that **1–3** were effective ligands in the 1,4-addition reaction. Ligand **1** was particularly effective, giving the desired product in 91% e.e. at 83% yield (entry 1). It was obvious from Table 1 that the bridging moiety profoundly affected the enantioselectivity of the asymmetric catalytic reaction: when the configuration of the bridging moiety of the ligand was changed from *S* to *R* (entries 1 and 3, from ligand **1** to ligand **3**), the catalyst exhibited higher enantioselectivity (91% e.e.) in the catalytic reaction. This result was consistent with the expectation that the alkylation reaction with trimethylaluminum was sensitive to the steric properties of the ligand. The experimental results also indicated that the asymmetric induction

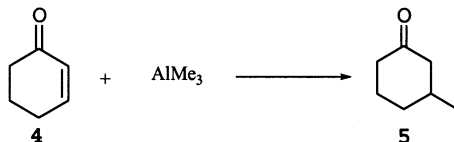
was dominated by the end groups of the chiral ligand.

Table 2 shows more detailed results from the experiments under various conditions by using ligand **1**. The influence of different copper sources was observed in the reaction (entries 2, 6 and 7). For example, when [Cu(CH₃CN)₄] BF₄ was used as the copper source the reaction proceeded smoothly with high enantioselectivity. The highest e.e. value of **5** 96% was obtained using copper(II) triflate. The effect of the solvent on the enantioselectivity of the reaction was also examined (entries 2–5). Toluene, dichloromethane and diethyl ether were found to give good results (>90% e.e.) while the use of a more polar solvent such as tetrahydrofuran gave less satisfactory results (entry 5, 62% e.e.).

3. Conclusion

In conclusion, the present investigation reveals that the application of a new diphosphite ligand in the copper-catalyzed 1,4-conjugate addition of trimethylaluminum to 2-cyclohexenone induces high enantioselectivity. To the best of our knowledge, the new catalyst system gives the best e.e. value achieved to date in this reaction.

Table 1. The effect of ligands **1–3** on the 1,4-addition of trimethylaluminum to 2-cyclohexenones



Entry	(CuOTf) ₂ ·C ₆ H ₆ (mol%)	Ligands (mol%)	Yield ^{a,b,c} of 1,4-product (%)	E.e. (%) / configuration ^d
1	1	(<i>S,R,S</i>)- 1 (2)	83	91 (–)/ <i>S</i>
2	1	(<i>S,R,S</i>)- 2 (2)	85	68 (–)/ <i>S</i>
3	1	(<i>S,S,S</i>)- 3 (2)	83	69 (–)/ <i>S</i>

^a The reaction of 2-cyclohexenone (0.5 mmol) and AlMe₃ (0.5 mmol) was performed in CH₂Cl₂ at 0°C for 6 h (the molar ratio of 2-cyclohexenone, trimethylaluminum, and (CuOTf)₂·C₆H₆ was 100:100:1).

^b The yields and e.e. values were determined by GC with a Chiraldex A-TA column (50 m×0.25 mm) using dodecane as an internal standard.

^c A trace amount of the 1,2-product was formed.

^d The absolute configuration was determined by the specific rotation (Ref. 13).

Table 2. The effect of solvents and copper source on the 1,4-addition of trimethylaluminum to 2-cyclohexenone

Entry	Catalyst (mol%)	(<i>S,R,S</i>)- 1 (mol%)	Solvents	Yield ^{a,b} (%) (1,4-product)	E.e. (%) / configuration
1	[Cu(CH ₃ CN) ₄]·BF ₄ (1)	–	CH ₂ Cl ₂	48	<i>rac</i>
2	[Cu(CH ₃ CN) ₄]·BF ₄ (1)	2	CH ₂ Cl ₂	81	96 (–)/ <i>S</i>
3	[Cu(CH ₃ CN) ₄]·BF ₄ (1)	2	Toluene	56	91 (–)/ <i>S</i>
4	[Cu(CH ₃ CN) ₄]·BF ₄ (1)	2	Et ₂ O	64	91 (–)/ <i>S</i>
5	[Cu(CH ₃ CN) ₄]·BF ₄ (1)	2	THF	69	62 (–)/ <i>S</i>
6	(CuOTf) ₂ ·C ₆ H ₆ (1)	2	CH ₂ Cl ₂	83	91 (–)/ <i>S</i>
7	Cu(OTf) ₂ (1)	2	CH ₂ Cl ₂	60	95 (–)/ <i>S</i>

^a The reactions were performed at 0°C for 6 h.

^b Trace 1,2-product was formed.

4. Experimental

4.1. General

Unless otherwise indicated, all experiments were carried out under dry N₂ atmosphere. Toluene and diethyl ether were distilled from sodium and dichloromethane was distilled from CaH₂. 2-Cyclohexenone **4** (ACROS) and PCl₃ were distilled before use. BINOL was dried by toluene azeotrope before use. The following substances were from commercial sources and were used without further purification: (CuOTf)₂·C₆H₆, Cu(OTf)₂, AlMe₃ (97%, Aldrich).

³¹P, ¹H and ¹³C NMR spectra were recorded on a Varian AS500 spectrometer. E.e. values were determined by chiral GC analysis (Chiraldex A-TA column 50 m×0.25 mm) in comparison with authentic materials (3-methylcyclohexanone, ACROS). High-resolution mass spectrometry was performed using a Finnigan MAT 95S model spectrometer. Optical rotations were measured on a Perkin–Elmer 241 MC (at 20°C). GC analyses were performed on an HP 5890 apparatus equipped with FID.

4.2. Synthesis of (S,R,S)-1

A solution of (S)-H₈-BINOL (882 mg, 3 mmol) in toluene (25 mL) at ambient temperature was added to a cooled solution (–60°C) of PCl₃ (270 μL, 3 mmol) and Et₃N (860 μL, 6 mmol), in toluene (5 mL) over 5 min. The reaction mixture was stirred for 2 h, warmed to room temperature, and filtered. The filtrate was treated with a solution of Et₃N (290 μL, 2.9 mmol), (R)-BINOL (400 mg, 1.4 mmol), and 40 mg DMAP in toluene (25 mL) at 0°C and the temperature of the mixture was allowed to rise to ambient temperature. After 6 h at room temperature, the reaction mixture was filtered, concentrated, and purified by chromatography (silica gel, hexane/EA: 3/1) to give the pure product, (S,R,S)-**1** (85% yield): ³¹P NMR (CDCl₃): δ 138.3 ppm; ¹H NMR (500 MHz, CD₂Cl₂): δ 8.05–8.04 (d, 2H), 8.00–7.99 (d, 2H), 7.49–7.47 (m, 4H), 7.30–7.28 (t, 2H), 7.20–7.18 (m, 2H), 6.95–6.94 (d, 2H), 6.73–6.72 (d, 2H), 6.42–6.41 (d, 2H), 5.3–5.28 (d, 2H), 2.71–2.47 (m, 12H), 2.09–2.04 (m, 4H), 1.69–1.61 (m, 12H), 1.45–1.41 (m, 4H); ¹³C NMR (CD₂Cl₂): δ 22.45, 22.51, 22.65, 22.68, 27.67, 27.75, 29.07, 29.13, 118.50, 118.79, 123.11, 125.31, 126.11, 127.10, 127.48, 128.23, 128.78, 129.07, 129.29, 130.28, 121.38, 131.24, 134.00, 134.21, 135.16, 137.14, 138.06, 138.54, 145.82, 148.37 ppm; mp 167°C; [α]_D²⁰ = +87.9 (c 1.0, toluene); HRMS calcd for C₆₀H₅₂O₆P₂: 930.3241, found: 930.3306.

4.3. Synthesis of (S,R,S)-2 and (S,S,S)-3

Ligands (S,R,S)-**2** and (S,S,S)-**3** were synthesized via similar procedures.

(S,R,S)-**2**: ³¹P NMR (CDCl₃): δ 141.17 ppm; ¹H NMR (CD₂Cl₂): δ 7.30–6.91 (m, 10H), 6.09–6.08 (d, 2H), 3.03–2.70 (m, 12H), 2.40–2.17 (m, 12H), 1.82–1.57 (m, 24H); ¹³C NMR (CD₂Cl₂): δ 22.54, 22.64, 22.73, 22.83,

23.02, 23.09, 27.62, 27.79, 27.85, 29.18, 29.27, 29.76, 117.90, 118.91, 119.17, 127.82, 128.27, 129.04, 129.33, 129.53, 133.82, 133.99, 135.05, 137.21, 138.04, 138.58, 145.70, 146.16, 147.25 ppm; [α]_D²⁰ = +91.1 (c 1.0, toluene); HRMS calcd for C₆₀H₆₀O₆P₂: 938.3865, found: 938.4191.

(S,S,S)-**3**: ³¹P NMR (CD₂Cl₂): δ 138.39 ppm; ¹H NMR (CD₂Cl₂): δ 8.09–8.07 (d, 2H), 7.99–7.97 (d, 2H), 7.56–7.55 (d, 2H), 7.45–7.44 (t, 2H), 7.32–7.20 (m, 6H), 7.01–7.00 (d, 2H), 6.85–6.83 (d, 2H), 6.03–6.02 (d, 2H), 2.82–2.60 (m, 8H), 2.57–2.53 (m, 4H), 2.16–2.07 (m, 4H), 1.80–1.66 (m, 12H), 1.49–1.42 (m, 4H); ¹³C NMR (CD₂Cl₂): δ 22.48, 22.67, 27.72, 29.14, 118.65, 118.89, 120.03, 122.58, 125.21, 125.91, 126.97, 127.64, 128.20, 128.25, 129.11, 129.27, 130.09, 130.98, 134.06, 134.19, 135.08, 137.56, 138.50, 145.52, 145.86; [α]_D²⁰ = +98.0 (c 1.0, toluene); HRMS calcd for C₆₀H₅₂O₆P₂: 930.3241, found: 930.3161.

4.4. General procedure for the reaction of 2-cyclohexenone with trimethylaluminum

A solution of [Cu(CH₃CN)₄]⁺BF₄[–] (0.005 mmol) and **1** (0.01 mmol) in CH₂Cl₂ (5 mL) was stirred under a nitrogen atmosphere at ambient temperature for 0.5 h. The resulting mixture was then treated with 2-cyclohexenone (0.5 mmol). The reaction mixture was cooled to 0°C and trimethylaluminum (97%, 0.6 mmol) was added via gas-tight syringe. The stirring was continued at 0°C for 6 h and the reaction mixture was quenched by adding saturated of NH₄Cl solution (2 mL). After extraction with Et₂O (3×2.0 mL), the organic layers were combined. The solvent was removed under reduced pressure after the solution was dried with MgSO₄. Purification by flash column chromatography afforded the pure product as a clear oil. [α]_D²⁰ = –12.7 (c 0.7, CHCl₃). The e.e. values of the resulting (S)-(-)-**5** were determined by chiral GC (Chiraldex A-TA chiral capillary column, 50 m×0.25 mm, 80°C, 165 kPa, N₂, t_R = 26.4 (S), 27.2 min (R), internal standard dodecane t_R = 35.3 min).

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