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Copper-catalyzed enantioselective conjugate addition of triethylaluminum to 2-cyclopentenone

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Abstract—Bidentate phosphites were prepared starting from BINOL, H_8-BINOL or 3,3′, 5,5′-tetra-*tert*-butyl-2,2′-biphenol. Utilization of these ligands in the copper-catalyzed enantioselective conjugate addition of triethylaluminum to 2-cyclopentenone afforded 3-ethylcyclopentanone in up to 94.0% ee.

1. Introduction

The enantioselective conjugate addition of organometallic reagents to α,β-unsaturated compounds is a powerful tool for the formation of carbon–carbon bonds simultaneously introducing new stereogenic centers the substrate.[1] High enantioselectivities have been obtained in the copper-catalyzed Michael addition[2] of Grignard and organozinc reagents to enones and other α,β-unsaturated carbonyl compounds using phosphorus ligands such as phosphorus amidites,[3] diphosphite[4] and oxazoline-phosphite[5] ligands. In contrast, only a few examples of conjugate additions using trialkylaluminum reagents have been reported with moderate yields and enantioselectivities. Iwata et al.[6] showed that when trimethylaluminum reacted with 3-methyl-cyclohexa-2,5-dienone in the presence of chiral oxazoline ligands, Cu(OTf) and TMSOTf, the conjugate addition proceeded at the less substituted double bond in up to 68% ee. Woodward et al.[7] utilized Kubas compound, $[Cu(MeCN)_4]BF_4$, with (*S*)-binaphthol derivatives of thiourethane in the addition of trimethylaluminum to acyclic enones to give products in up to 51% ee. Dieguez et al.[8] reported a phosphine-phosphite ligand that gave 62% ee in the reaction of triethylaluminum with 2-cyclohexenones. Recently we found that diphosphite ligand **6** gave 96% ee in the addition of trimethylaluminum to 2-cyclohexenone.[26]

The catalytic enantioselective 1,4-addition to 2-cyclopentenone is of interest because the products are relevant to natural products such as prostaglandin 11-deoxy-PGF1a[9] and (−)-PGE1 methyl ester.[10] Unfortunately, cyclopentenone poses additional problems related to the lower reactivity and the tendency to undergo a Michael reaction with the enolate resulting from the conjugate addition of the organozinc reagent. Thus, in contrast to the large number of good systems for the 1,4-addition of diethylzinc to cyclohexenone, there are few reports on enantioselective 1,4-addition to cyclopentenone.[10] We have previously found that diphosphite ligand **1**[4] gave up to 89% ee on the addition of $ZnEt_2$ to cyclopentenone. Feringa utilized TADDOL-based phosphoramidite ligands **2**[11] and **3**[12] in the same reaction and obtained 62 and 83% ee, respectively. Pfaltz et al. achieved 94% ee using a chiral oxazoline-phosphite ligand **4**.[5] Hoveyda et al.[13] reported ee values up to 97% using a chiral peptide-based phosphine ligand **5** in the 1,4-addition of diethylzinc to 2-cyclopentenone, but in practice only the *R* enantiomer of the product can be easily obtained due to the less accessibility of the non-natural amino acids. Recently, we used diphosphite **6** in the conjugate addition of diethylzinc to cyclopentenone with ee up to 98%.[27] The 1,4-addition of alkylaluminum to cyclopentenone is still an interesting challenge.

Alkylaluminum compounds have been extensively investigated on account of their use as olefin polymerization co-catalysts and chemical intermediates. The commercial synthesis of triethylaluminum and higher homologues is via the reaction of H_2 and an appropriate alkene with aluminum metal at elevated pressure and temperature:[28]

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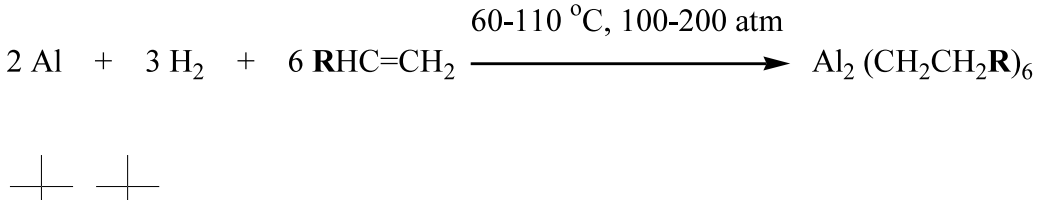
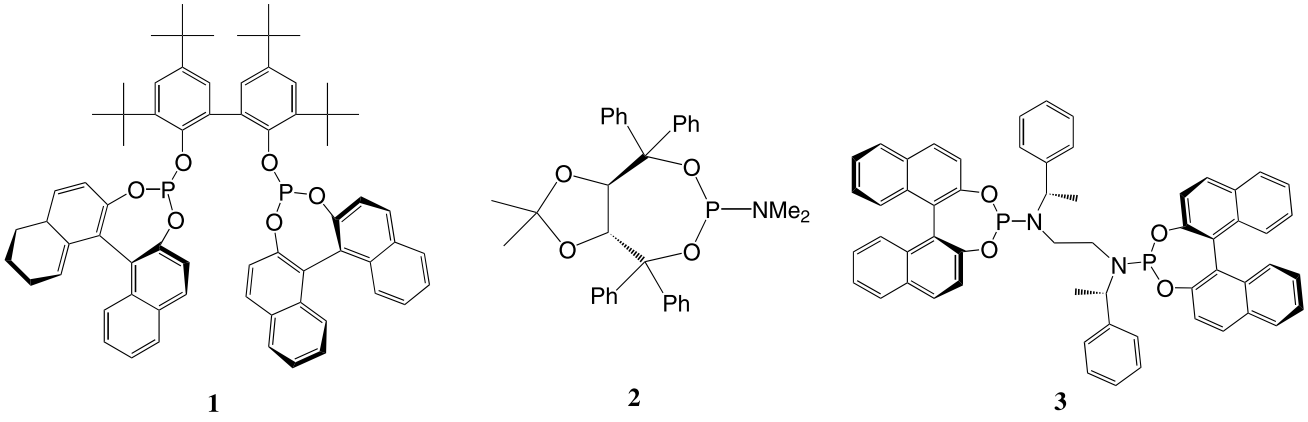




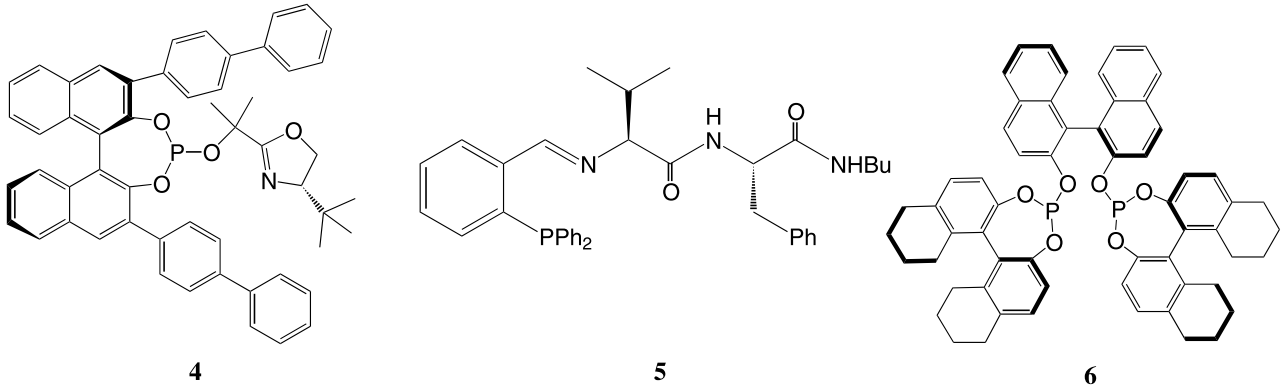
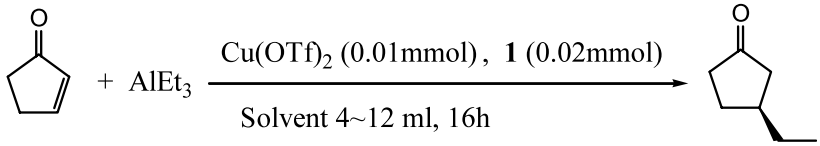


Table 1. 1,4-Addition of triethylaluminum to cyclopentenone using chiral ligand **1**



10 **11**

Entry	Solvents	Catalyst concentration (10^{-3} M)	Substrate to catalyst ratio	Temp. (°C)	Yield[a] (%)	Ee[b] (%) (*S*)[c]
1	Toluene	1.25	100	0	92	84.2
2	CH_2Cl_2	1.25	100	0	90	60.7
3	Ether	1.25	100	0	90	92.8
4	THF	1.25	100	0	53	44.3
5	1,4-Dioxane	1.25	100	25	57	63.4
6	Ether	1.25	100	25	88	90.7
7	Ether	1.25	100	−20	89	89.2
8	Ether	1.25	150	0	85	74.8
9	Ether	1.25	50	0	87	90.9
10	Ether	2.50	100	0	90	83.2
11	Ether	0.83	100	0	92	94.0

[a] Determined by GC, using dodecane as an internal standard.
[b] Determined by GC (CHIRALDEX A-TA Column 50 m×0.25 mm).
[c] The absolute configuration was determined by comparing the result with those from Ref. 25.

Table 2. 1,4-addition of triethylaluminum to cyclopentenone using ligands **7**–**9**

Entry	Ligands	Yields (%)	Ee (%)
1	**7**	78	66.8
2	**8**	66	59.4
3	**9**	69	65.5

Conditions: 0.01 mmol $Cu(OTf)_2$, 0.02 mmol ligand, 1.0 mmol cyclopentenone, 1.5 mmol $AlEt_3$ in 8 ml ether; reaction temp. = 0°C; reaction time = 16 h.

This economical synthesis method makes alkylaluminum compounds readily available in large quantities. From both scientific and practical standpoints, it is of interest to study the use of triethylaluminum as a reagent for the conjugate addition to 2-cyclopentenone. Herein, we report the enantioselective conjugation addition of triethylaluminum to 2-cyclopentenones in the presence of $Cu(OTf)_2$ and chiral diphosphite ligands with up to 94% ee. This approach was proved to be an effective method for the asymmetric addition of an ethyl moiety to cyclopentenone.

2. Results and discussion

The bidentate phosphite **1** was synthesized according to a previously published method.[4] The ligand was tested for the conjugate addition of triethylaluminum to cyclopentenone in different solvent systems and the results were summarized in Table 1. High enantioselectivities and yields were observed in toluene and ether at 0°C. Both the substrate-to-catalyst ratio and the catalyst concentration had some influence on the enantioselectivity of the reaction. The best ee (94%) in a preliminary screening was obtained with a substrate-to-catalyst ratio of 100 and a catalyst concentration of 8.3×10^{-4} M (entry 11).

Previous studies by ourselves[14–18] and others[19–23] showed that chiral catalysts derived from partially hydrogenated binaphthyl species, 5,5′,6,6′,7,7′,8,8′-octahydro-1,1-bi-2-naphthyl exhibited higher activity and enantioselectivity than those prepared from binaphthol in certain asymmetric reactions due to the steric and electronic modulation in the H_8-binaphthyl backbone. In order to test this effect on the conjugate addition of triethylaluminum to cyclopentenone, we replaced the binaphthyl moieties of diphosphite **1** with H_8-binaphthyl to give ligand **7**. Unfortunately, only moderate enantioselectivities and yields were obtained with this ligand (entry 1, Table 2).

Since no positive effect was observed in changing the binaphthyl moieties of **1** to H_8-binaphthyl, we further modified the structure of **1** by changing the bridging unit of the ligand. By replacing the non-chiral 3,3′,5,5′-tetra-*tert*-butylbiphenol bridge of **1** to (*S*)-binaphthol, compound **8** was obtained.[24] When **8** was used as the chiral ligand for the conjugate addition of triethylaluminum to cyclopentenone, only moderate enantioselectivity and yield were obtained (entry 2, Table 2). Diphosphite **9** was obtained by changing the chirality of the bridging unit of **8** from *S* to *R* and the ligand was tested in the conjugate addition. No significant cooperative effect between the chirality of the bridging unit with those of the terminal unit was observed. The enantioselectivity and yield were enhanced only slightly in comparison with the use of **8** (entries 2, 3 of Table 2).

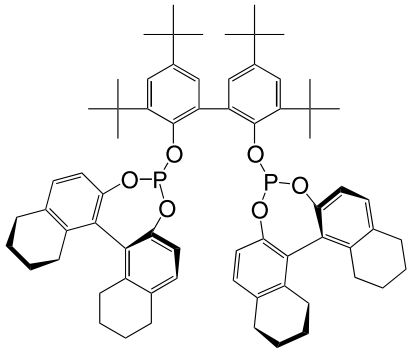
3. Conclusion

High enantioselectivity in the 1,4-addition of triethylaluminum to 2-cyclopentenone was achieved using chiral diphosphite ligand **1**. The chirality of the bridging unit in the ligand was found to have little influence on the enantioselectivity of the reaction.

4. Experimental

4.1. General

Unless otherwise indicated, all experiments were carried out under dry N_2 atmosphere. Toluene, diethyl ether, THF and 1,4-dioxane were dried over sodium and distilled immediately before use. Dichloromethane was distilled over CaH_2. PCl_3 was distilled and BINOL was dried by toluene azeotrope before use. Commercially available 2-cyclopentenone (98%, ACROS), $Cu(OTf)_2$ (98%, ACROS), $AlEt_3$ (93%, Aldrich) were used without further purification. ^{31}P, ^{1}H and ^{13}C NMR spectra were recorded on a Varian AS500 spectrometer. Enantiomeric excesses were determined by chiral GC analy-



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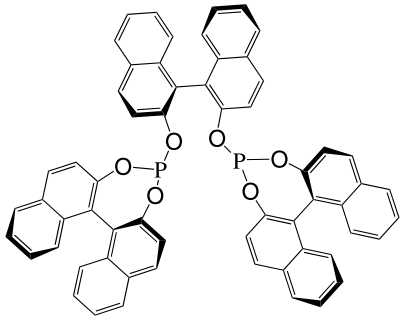
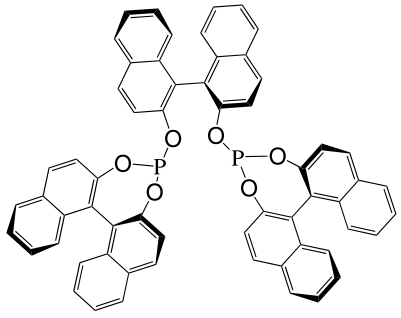


(*S*,*S*,*S*)-**8**



(*S*,*R*,*S*)-**9**

sis (Chiraldex A-TA column 50 m×0.25 mm). 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.

Ligands **1** and **8** were synthesized according to previously reported methods.[4,24]

4.2. Synthesis of 7

A solution of (*S*)-H_8-BINOL (882 mg, 3.0 mmol) in toluene (25.0 ml) was added dropwise to a solution mixture of PCl_3 (0.27 ml, 3.0 mmol) and Et_3N (0.86 ml, 6.0 mmol) in toluene (5.0 ml) over 5 min at −20°C with stirring. The reaction mixture was stirred for 2 h at −20°C and at room temperature for another 3 h. The content was then filtered and the filtrate was treated with a mixture of Et_3N (0.43 ml, 3.0 mmol), 3,3′,5,5′-tetra-*tert*-butyl-2,2′-biphenol (615 mg, 1.4 mmol), and DMAP (catalytic amount, 45.0 mg) in toluene (25 ml) at 0°C. The mixture was allowed to stand at ambient temperature for 6 h and then filtered. The filtrate was concentrated, and purified using chromatography (silica gel, hexane/EA: 3/1) to give the pure product of (*S*,*S*)-**7** (82% yield): ^{31}P NMR ($CDCl_3$): δ 142.97(s), 142.40(s) ppm; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40–7.38 (d, 2H), 7.20–7.17 (m, 2H), 7.15–7.05 (m, 4H), 6.98–6.76 (m, 4H), 2.80–2.60 (m, 8H), 2.38–2.04 (m, 8H), 1.78–1.52 (m, 16H), 1.36–1.34 (t, 27H), 1.18 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$): δ 147.74, 147.70, 147.14, 147.07, 146.47, 146.19, 146.06, 146.03, 145.96, 140.89, 140.25, 138.37, 137.94, 137.65, 137.50, 137.03, 134.54, 133.49, 133.06, 133.00, 129.74, 129.70, 129.16, 129.05, 128.86, 128.82, 128.35, 128.26, 128.24, 127.69, 126.73, 126.66, 126.26, 126.18, 124.22, 124.14, 124.02, 123.94, 119.24, 119.13, 117.87, 117.79, 35.37, 35.27, 34.71, 34.65, 31.64, 31.62, 31.59, 31.57, 31.18, 31.14, 31.00, 30.98, 29.63, 29.58, 29.47, 29.23, 29.19, 28.01, 27.84, 27.53, 23.02, 22.92, 22.89, 22.80, 22.73, 22.64, 22.54 ppm; $[\alpha]_D^{20}$ = +121.6 (*c* 1.0, toluene); HRMS calcd for $C_{68}H_{80}O_6P_2$: 1054.54, found: 1054.48.

4.3. Synthesis of (*S*,*R*,*S*)-9

Ligand (*S*,*R*,*S*)-**9** was synthesized via a similar procedure as that for the preparation of **7**.

(*S*,*R*,*S*)-**9**: ^{31}P NMR ($CDCl_3$): δ 146.47(s) ppm; ^{1}H NMR ($CDCl_3$): δ 8.11–8.05 (m, 4H), 7.87–7.85 (m, 4H), 7.73–7.71 (d, 2H), 7.59–7.57 (d, 2H), 7.55–7.52 (m, 2H), 7.40-7.15 (m, 20H), 5.77–5.75 (d, 2H) ppm; ^{13}C NMR ($CDCl_3$): δ 148.30, 148.27, 148.24, 147.39, 147.07, 134.10, 132.73, 132.15, 131.48, 131.14, 131.01, 130.37, 130.24, 130.21, 129.26, 129.18, 129.11, 128.31, 128.28, 128.20, 128.16, 128.10, 127.21, 127.15, 126.99, 126.89, 126.85, 126.77, 126.35, 126.32, 126.24, 126.15, 125.92, 125.83, 125.34, 125.29, 125.07, 125.00, 124.76, 124.69, 124.29, 123.14, 122.46, 121.75, 121.67, 121.54, 121.44, 121.18 ppm; $[\alpha]_D^{20}$ = +278.5 (*c* 1.0, toluene); HRMS calcd for $C_{60}H_{36}O_6P_2$: 914.20, found: 914.31.

4.4. General procedure for the reaction of 2-cyclopentenone with triethylaluminum

$Cu(OTf)_2$ (3.7 mg, 0.01 mmol) and ligand **1** (21.0 mg, 0.02 mmol) was dissolved in dry ether (8 ml). The solution was stirred for 20 min at ambient temperature under a nitrogen atmosphere, and cyclopentenone (1.0 mmol) was added. The reaction mixture was cooled to 0°C and triethylaluminum solution (93%, 1.5 mmol) was added dropwise over a period of 2 min by using gas-tight syringe. After stirring for 16 h at 0°C, the intermediate was hydrolyzed by the addition of saturated NH_4Cl solution (2.0 ml) followed by diluted HCl solution (2N, 2.5 ml). The content was allowed to warm up to room temperature. Water and Et_2O (2.0 ml each) were added, and the mixture was stirred for 10 min. The aqueous phase was separated and extracted with Et_2O (3×3 ml). The combined organic phases were dried over $MgSO_4$. The solvent was removed at reduced pressure to give a crude product which was purified using flash column chromatography to afford the 3-ethylcyclopentanone as a colorless liquid. The ee value of the product (*S*)-(-)-**11** was determined using chiral GC (Chiraldex A-TA chiral capillary column, 50 m× 0.25 mm).

Acknowledgements

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