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Enantioselective conjugate addition of diethylzinc to cyclic enones with chiral aryl diphosphite-copper catalysts

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Abstract

A series of C_2-symmetric aryl diphosphites based on chiral binaphthol were prepared and their copper complexes were found to be efficient catalysts for the conjugate addition of diethylzinc to cyclic enones. Good enantioselectivities (up to 89.8 and 88.7% ee, respectively) were obtained in the conjugate addition of diethylzinc to 2-cyclohexenone and 2-cyclopentenone. © 1999 Elsevier Science Ltd. All rights reserved.

The conjugate addition of organometallic reagents to enones catalyzed by chiral transition metal complexes is a useful synthetic method for asymmetric carbon–carbon bond formation.[1] The application of organozinc reagents in these reactions is of special value due to their high tolerance of many functional groups.[2] Copper catalysts, with a variety of chiral phosphorus ligands, were found to be efficient in the asymmetric conjugate addition of organozinc reagents to cyclic enones.[3] Excellent enantioselectivities were achieved in the addition of organozinc reagents to six-membered ring enones using the copper complexes of chiral phosphorus amidites,[4] phosphite-oxazolines[5] and phosphites[6] as chiral catalysts. Unfortunately, the application of these catalysts to the conjugate addition of dialkylzinc to 2-cyclopentenone has been less successful.[7] Since the 1,4-adducts of this class of five-membered ring enones are key intermediates for the preparation of physiologically important prostaglandin analogues, it is highly desirable to develop more efficient methods for the asymmetric conjugate addition of organozinc reagents to 2-cyclopentenone.[8] Recently, we found the C_2-symmetric aryl diphosphite **1** to be an efficient ligand for the copper-catalyzed conjugate addition of diethylzinc to 2-cyclohexenone and 2-cyclopentenone (up to 90.2 and 76.6% ee, respectively).[9] In this paper we report the synthesis and application of a series of C_2-symmetric aryl diphosphites, based on binaphthol, in the catalytic conjugate addition of diethylzinc to cyclic enones.

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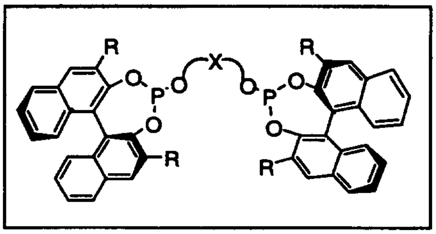

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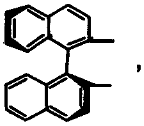

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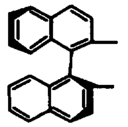

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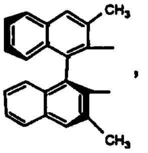

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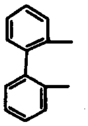

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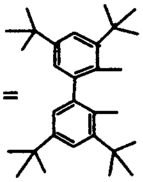

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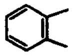
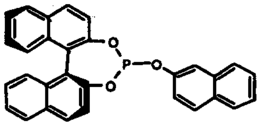


, R = H

7



Chiral aryl diphosphites **1–6** were prepared from the reaction of the corresponding (*S*)-chlorophosphites with aryl diols and were purified by recrystallization or flash chromatography.[10] In order to investigate the importance of the chelate effect in ligand **1**, the mono-phosphite **7** was also prepared. The $Cu(OTf)_2$ complexes of these ligands were used as catalysts in the conjugate addition of diethylzinc to 2-cyclohexenone **8a** and 2-cyclopentenone **8b** and the results are summarized in Table 1.

$Cu(OTf)_2$-**7** showed good catalytic activity but much lower enantioselectivity than $Cu(OTf)_2$-**1** in the conjugate addition of diethylzinc to 2-cyclohexenone and 2-cyclopentenone (entry 1 versus 3, entry 2 versus 4).[†] The bidentate diphosphite ligands are expected to provide more efficient enantiocontrol. The modifications of the structure of ligand **1** were made on the bridge or terminal binaphthol units. Introduction of methyl groups onto the 3,3′-sites of the bridge binaphthyl unit or to the terminal binaphthyl unit of ligand **1** provided ligands **2** and **3**. These two ligands gave rather low enantioselectivities as well as catalytic activities for the conjugate addition of diethylzinc to 2-cyclopentenone (entries 6, 8). Replacing the bridging (*S*)-binaphthol ring of ligand **1** with an (*R*)-binaphthol ring was found to be detrimental.[9] When 2,2′-biphenol was used as the bridge unit, the resulting ligand **4** afforded very low enantioselectivity (entries 9, 10). The ^{31}P NMR spectrum of ligand **4** showed rather complex splitting at around 145 ppm. The result was consistent with the presence of atropisomers due to the rotation around the biphenyl C–C linkage. The introduction of a bulky *tert*-butyl group to the 4,4′ and 6,6′ site of 2,2′-biphenol backbone prevented the rotation around the C–C bond and the ^{31}P NMR spectrum of ligand **5** showed two peaks at 143.0 and 141.6 ppm. This result revealed that the steric hindrance effect prevented ligand **5** from adopting a C_2-symmetric arrangement at the two phosphorus atoms. $Cu(OTf)_2$-**5** gave good enantioselectivity in the conjugate addition of diethylzinc to 2-cyclohexenone and 2-cyclopentenone (entries 11, 12, 13). When a more rigid bridge unit was introduced, the resulting complex $Cu(OTf)_2$-**6** also gave good enantioselectivities in the conjugate addition of diethylzinc to 2-cyclohexenone and 2-cyclopentenone (entries 14, 15). Ligands **1**, **5** and **6** gave similar levels of enantioselectivity in

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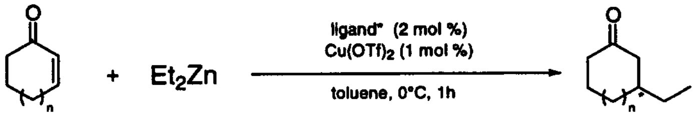
[†] A typical procedure for the catalytic conjugate addition reaction is as follows: A solution of 12.4 mg $Cu(OTf)_2$ (0.034 mmol) and 70 mg **5** (0.068 mmol) in toluene (20 ml) was stirred under N_2 atmosphere at room temperature for 0.5 h. The flask was placed in an ice-bath. Diethylzinc (1.1 M solution in toluene, 4.7 ml, 5.1 mmol) and a solution of enone (3.4 mmol enone in 5 ml toluene) were added sequentially. After stirring for 1 h the mixture was poured into a 1N HCl solution (20 ml) and was extracted with ethyl acetate (25 ml×2). The combined organic layer was washed with brine twice (20 ml×2) and was dried over $MgSO_4$. After the solvent was evaporated, a colorless oil was obtained and was purified by column chromatography (SiO_2, hexane:ethyl acetate=8:1).The ee values of the products were determined according to the methods reported in the text.

Table 1
The enantioselective conjugate addition of diethylzinc to **8a** and **8b** catalyzed by the Cu(OTf)$_2$ complexes of ligands **1**–**7**[a]



n=1, **8a**
n=0, **8b**

9a
9b

Entry	Ligand	Enone	Conversion (%)[b]	E.e. (%)[b]	Configuration[c]
1	**7**	**8a**	100	29.1	*S*
2	**7**	**8b**	100	11.7	*R*
3[c]	**1**	**8a**	100	90.2	*S*
4[c]	**1**	**8b**	100	76.6	*S*
5	**2**	**8a**	100	42.1	*S*
6	**2**	**8b**	53.5	10.5	*R*
7	**3**	**8a**	100	69.2	*S*
8	**3**	**8b**	7.4	3	*S*
9	**4**	**8a**	100	3.6	*S*
10	**4**	**8b**	21.2	0	/
11	**5**	**8a**	100	**89.8**	*S*
12	**5**	**8b**	100	84.0	*S*
13[d]	**5**	**8b**	100	**88.7**	*S*
14	**6**	**8a**	100	88.3	*S*
15	**6**	**8b**	100	83.0	*S*

a) The reactions were carried out in toluene at 0°C for 1h (enone: copper: ligand: Et$_2$Zn= 1: 0.01: 0.02: 1.5). b) The data on conversion and ee values of **9a** and **9b** were determined by GC with a Chiraldex A-TA column (30m × 0.25mm). c) These data had been reported in a previous paper.[9] d) The reaction was carried out at 10 °C.

the conjugate addition to 2-cyclohexenone, but ligand **5** afforded much better enantioselectivity than ligand **1** in the conjugate addition to 2-cyclopentenone. The rate and enantioselectivity of the copper-catalyzed conjugate addition of diethylzinc to enones were strongly dependent on the choice of solvent, reaction temperature and the concentration of the copper complex.[9] The addition of diethylzinc to 2-cyclopentenone with Cu(OTf)$_2$-**5** catalyst gave rather poor enantioselectivity and catalytic activity at –20°C (7.6% ee, 23.7% conversion). The enantioselectivity was higher at 20°C (88.1% ee, 100% conversion) than at 0°C (entry 12) with the Cu(OTf)$_2$-**5** catalyst and the optimal reaction temperature was found to be about 10°C (entry 13).

Cu(OTf)$_2$-**1** and Cu(OTf)$_2$-**5** were also tested in the conjugate addition of diethylzinc to 2-cycloheptenone **8c**, 4,4-dimethyl-2-cyclohexenone **8d**, 4,4-dimethyl-2-cyclopentenone **8e**. Moderate enantioselectivities were achieved with Cu(OTf)$_2$-**1** and Cu(OTf)$_2$-**5** in the addition of diethylzinc to **8c**, but Cu(OTf)$_2$-**5** displayed higher catalytic activity than Cu(OTf)$_2$-**1** (100% conversion, 47.3% ee versus 40% conversion, 56.0% ee). Very low catalytic activities were observed in the addition of diethylzinc to **8d** and **8e** with Cu(OTf)$_2$-**1** and Cu(OTf)$_2$-**5**, but Cu(OTf)$_2$-**5** provided higher enantioselectivities for **8d** and **8e** than Cu(OTf)$_2$-**1** (33.3 versus 0% ee and 66.0 versus 20.0% ee, respectively). Considering the steric hindrance of ligands **1** and **5**, it is reasonable to expect the catalyst systems to be sensitive to the steric environment of enones.

In conclusion, we have demonstrated that C_2-symmetric aryl diphosphites are efficient ligands for the copper-catalyzed conjugate addition of diethylzinc to cyclic enones. The enantioselective conjugate addition of diethylzinc to 2-cyclopentenone has been achieved with over 88% ee using Cu(OTf)$_2$-**5** catalyst. To the best of our knowledge, this is the best ee value achieved for this reaction to date.

Acknowledgements

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10. Selected spectral data for **5**: HRMS calculated for $C_{68}H_{64}O_6P_2$: 1038.4178; found: 1038.4150. ^{31}P NMR (CDCl$_3$): 141.6(s), 143.0(s) ppm. ^{1}H NMR (CDCl$_3$, 400 MHz): 1.17 (s, 9H), 1.32 (s, 9H), 1.43 (s, 9H), 1.55 (s, 9H), 6.77 (d, J=8.4 Hz, 1H), 7.12 (d, J=8.4 Hz, 1H), 7.19–7.23 (m, 8H), 7.31–7.40 (m, 8H), 7.53 (d, J=2.4 Hz, 1H), 7.60–7.63 (m, 2H), 7.67 (d, J=8.4 Hz, 1H), 7.75 (d, J=8.4 Hz, 1H), 7.81–7.86 (m, 5H). ^{13}C NMR (CDCl$_3$): 30.52, 31.02, 31.30, 31.69, 34.52, 34.68, 35.46, 35.72, 122.06, 122.30, 122.52, 122.76, 122.88, 124.51, 124.58, 124.88, 124.95, 125.71, 125.90, 125.99, 127.09, 128.15, 128.24, 128.33, 129.17, 129.33, 129.42, 129.76, 130.12, 130.74, 130.93, 131.34, 131.42, 132.39, 132.45, 132.66, 132.71, 140.49, 140.78, 145.04, 145.40, 146.84, 147.12, 147.77, 148.38, 148.71 ppm. M.p. 250–252°C. $[\alpha]_D^{20}$=+170.9 (*c* 1.0, benzene).