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Enantioselective conjugate addition of diethylzinc to acyclic enones using a copper phosphino-phenol complex as catalyst

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Abstract—Newly designed phosphino-phenol **1c** was found to be an efficient chiral auxiliary for copper-mediated asymmetric conjugate addition of diethylzinc to acyclic enones. High enantioselectivity up to >99% ee was achieved in the reaction of acyclic α,β-enones.

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Conjugate addition of organometallic reagent to enones is a potent method for carbon–carbon bond formation and is widely used in various organic syntheses. Thus, much effort has been directed towards asymmetrization of the addition reaction.[1] In seminal studies of the asymmetric addition, alkyllithium, Grignard and organocuprate reagents were used as organometallic reagent in the presence of a catalytic or stoichiometric amount of a chiral auxiliary.[1] In 1993, Alexakis et al. reported copper-mediated asymmetric conjugate addition of dialkylzinc to enones in the presence of chiral phosphorus ligands.[2] The phosphorus ligand has been proposed to coordinate with the copper(I) ion and to accelerate the addition reaction.[1a] Subsequently, various mono- and multi-dentate chiral phosphorus ligands have been extensively studied as the chiral auxiliary for the reactions.[3] As the results, many phosphorus ligands have been successfully applied to the reactions of cyclic enones,[1] but a relatively small number of chiral ligands are effective for the reactions of acyclic enones.[3a,b,e–g,i–l,q–s,w,x] Of such ligands, P,N-ligands bearing a binaphthyl structure as the chiral unit are highly efficient for the latter reactions.[3a,k,w] Although the detailed mechanism of copper- mediated conjugate addition of dialkylzinc to enones has not been clarified, it has been proposed that its catalytic cycle involves a monoalkyl copper(I) species:[1c,3p,u] π-complexation of the copper(I) species with enone and coordination of its carbonyl oxygen to a Lewis acidic zinc species are essential for alkyl transfer from copper(I) to enone.[1c,3p] Taking into account the mechanism of copper-mediated alkylzinc addition and oxygenophilicity of the zinc ion, we expected that a P,O-ligand bearing a binaphthyl skeleton could also be an effective chiral ligand for conjugate addition of alkylzinc to enones (Scheme 1).[4] In particular, simple phosphino-phenols **1** attracted our attention, because they are readily available and their methoxy derivative (MOP) has been proven to be an excellent chiral auxiliary for various reactions.[5] According to the reported procedure for the synthesis of **1e**,[5b] ligands **1a**–**d** were also synthesized from (*R*)-1,1′-binaphthol (Scheme 2).

With chiral ligands **1a**–**e** in hand, we first examined the addition reaction of diethylzinc to chalcone that can adopt *s-cis* conformation, with the copper complexes of **1a**–**e** as catalyst in dichloromethane (Table 1).[6] The substituent on the phosphorus atom of the ligands was found to exert strong influence on yield and enantioselectivity. In general, ligands **1a**,**c**,**d** bearing a primary alkyl group at the phosphorus atom induced moderate to good enantioselectivities; among them, **1c** was the most effective (entries 1, 3 and 4), while **1b** bearing an isopropyl group induced poor enantioselectivity (entry 2). Ligand **1e** was found to be far less efficient than **1c** for this reaction in terms of yield and enantioselectivity (entry 5). Thus, we next examined the effect of the

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Keywords: Copper; Asymmetric catalysis; Phosphino-phenol; Conjugate addition.

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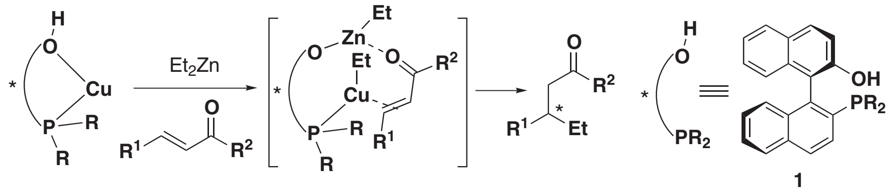
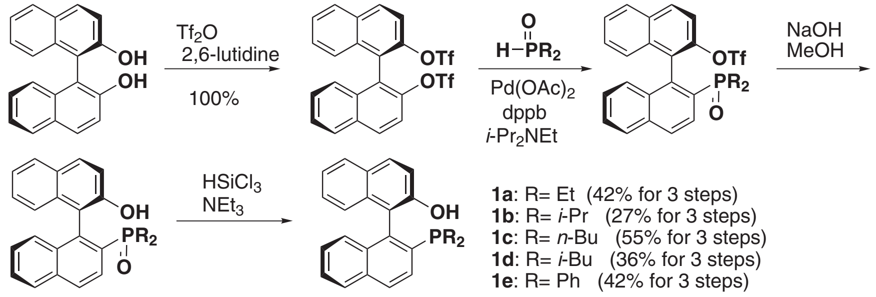
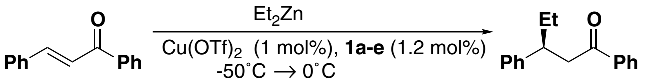


Scheme 1.



Scheme 2.

Table 1. Copper-mediated asymmetric conjugate addition of diethylzinc to chalcone using **1a–e** as chiral ligand[a]



Entry	Ligand	Solvent	Time (h)	Yield (%)	% ee[b]	Confign.[c]
1	**1a**	CH_2Cl_2	24	57	72	*S*
2	**1b**	CH_2Cl_2	24	25	14	*S*
3	**1c**	CH_2Cl_2	3.5	46	88	*S*
4	**1d**	CH_2Cl_2	36	14	60	*S*
5	**1e**	CH_2Cl_2	24	10	44	*S*
6	**1c**	Toluene	72	68	83	*S*
7	**1c**	Et_2O	20	60	85	*S*
8	**1c**	THF	18	67	94	*S*
9	**1c**	AcOEt	24	69	89	*S*
10	**1c**	DMF	1	84	>99	*S*

[a] All reactions were carried out with molar ratio of chalcone/diethylzinc/Cu(OTf)$_2$/**1** = 1:1.1:0.01:0.012.

[b] Determined by HPLC analysis using chiral stationary phase column (Daicel Chiralpak AD-H; hexane: *i*-PrOH = 99:1).

[c] Absolute configuration was determined by chiroptical comparison with the published value (Ref. 8).

solvent on enantioselectivity by using **1c** as the chiral ligand. Use of toluene and diethyl ether somewhat diminished enantioselectivity (entries 6 and 7). To our surprise, higher enantioselectivities were observed in the reactions in more polar solvents and, in particular, the reaction in *N,N*-dimethylformamide (DMF) showed remarkably improved enantioselectivity of >99% ee together with good yield (entry 10).[7] This is different from the previously reported copper-mediated conjugate addition reactions that generally show high enantioselectivity in a less polar solvent such as dichloromethane or toluene.[1,3] To get some insight into the role of the polar solvent, we studied non-linearity between % ee of the product and % ee of the ligand (Fig. 1). Reactions in both toluene and DMF showed a negative non-linear effect, indicating that the copper ion and the ligand forms a *meso*-2:1 ligand/Cu species preferentially.[9,10] Although enantioselectivity of the two reactions was different, they showed similar non-linear effect and it is likely that the same active species participates, regardless of polarity of the solvent. However, a polar solvent more strongly coordinates with the Lewis acidic part of the catalyst and favourably effects its asymmetric induction.

Under the optimized conditions, the reactions of other acyclic enones **2–8** were examined and the results are summarized in Table 2. The reactions of aromatic enones **2–4** showed good enantioselectivities, though the reaction rate of **3** bearing an electron-donating methoxy group was slow and the yield was moderate (entries 1–3). By lowering the reaction temperature, enantioselectivities were improved in the reaction of **2** and **4** (entries 2 and 5). On the other hand, the reaction of enone **5** (R^2 = methyl) in DMF gave the addition product in poor yield due to formation of messy side products,[11] though the enantioselectivity was good

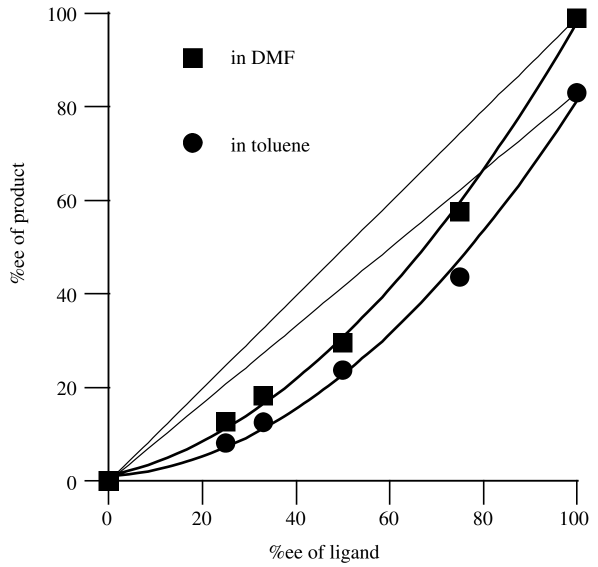
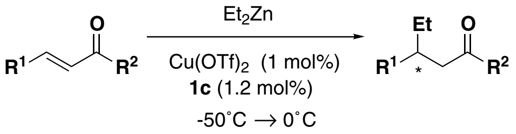


Figure 1. Non-linear effects for the addition reaction of diethylzinc to chalcone in DMF and toluene.

(entry 6). Taking into account the donor numbers of DMF and THF, it was considered that the enolate generated by conjugate addition in DMF should be more reactive than that in THF and this might be reflected in the side product formation.[12] Thus, we examined the reaction in THF and found that not only the yield of the desired ketone but also enantioselectivity was somewhat improved (entry 7). By using 5 mol % of catalyst, the yield was further improved to 62% (entry 8). We next examined the reaction of **6** (R^2 = ethyl) in DMF. Although no undesired side reaction was observed and enantioselectivity was good, the reaction stopped at 15% conversion (entry 9). The yield was improved to some extent when the catalyst loading was increased to 5 mol % (entries 11 and 12). Again, chemical yield and enantioselectivity were improved, when the reaction was performed in THF (entries 9-12). The reactions of alkyl enones **7** and **8** also proceeded with high enantioselectivity in moderate to good yields. Differing from the above two examples, slightly better enantioselectivity was observed in DMF than in THF (entries 13–16). The determined configuration of the products was all *S*.[8] It is noteworthy that the reactions using other P–N ligands bearing the same binaphthyl unit give the corresponding *R*-products.[3a,x]

We also examined the reaction of 2-cyclohexenone that has been widely used as substrate, under the present conditions, but the reaction was slow and the enantioselectivity was modest (40% ee, 49% yield after 64 h). Cyclohexenone is impossible to take *s-cis*-configuration and this result is considered to support the proposed reaction mechanism (Scheme 1).

Table 2. Copper-mediated asymmetric conjugate addition of diethylzinc to various acyclic enones using **1c** as chiral ligand[a]



2: R^1= 4-Cl-C_6H_4, R^2= C_6H_5
3: R^1= 4-MeO-C_6H_4, R^2= C_6H_5
4: R^1= *n*-C_5H_{11}, R^2= C_6H_5
5: R^1= C_6H_5, R^2= CH_3
6: R^1= C_6H_5, R^2= C_2H_5
7: R^1= *n*-C_5H_{11}, R^2= C_2H_5
8: R^1= *c*-C_6H_{11}, R^2= C_2H_5

Entry	Substrate	Solvent	Time (h)	Yield (%)	% ee	Confign.
1	**2**	DMF	0.5	85	98[b]	*S*[c]
2[d]	**2**	DMF	0.5	84	>99[b]	*S*[c]
3	**3**	DMF	48	56	94[b]	*S*[c]
4	**4**	DMF	0.5	72	96[e]	—[f]
5[d]	**4**	DMF	2	72	98[e]	—[f]
6	**5**	DMF	40	23	86[b]	*S*[c]
7	**5**	THF	40	33	90[b]	*S*[c]
8[g]	**5**	THF	24	62	90[b]	*S*[c]
9	**6**	DMF	6	15	85[h]	*S*[c]
10	**6**	THF	20	30	95[h]	*S*[c]
11[g]	**6**	DMF	20	40	90[h]	*S*[c]
12[g]	**6**	THF	18	72	93[h]	*S*[c]
13[g]	**7**	DMF	24	72	90[i]	—[f]
14[g]	**7**	THF	18	84	85[i]	—[f]
15[g]	**8**	DMF	24	40	91[j]	—[f]
16[g]	**8**	THF	18	39	89[j]	—[f]

[a] All reactions were carried out in DMF with molar ratio of enone/diethylzinc/Cu(OTf)$_2$/**1** = 1:1.1:0.01:0.012, unless otherwise mentioned.

[b] Determined by HPLC analysis using chiral stationary phase column (Daicel Chiralpak AD-H; hexane: *i*-PrOH = 99:1).

[c] Absolute configuration was determined by chiroptical comparison with the published value (Ref. 8).

[d] Reaction was performed at −50 → −40 °C.

[e] Determined by HPLC analysis using chiral stationary phase column (Daicel Chiralcel OD-H; hexane).

[f] Absolute configuration was not determined.

[g] Enone/diethylzinc/Cu(OTf)$_2$/**1** molar ratio = 1:1.1:0.05:0.06.

[h] Determined by HPLC analysis using chiral stationary phase column (Daicel Chiralpak AD-H; hexane: *i*-PrOH = 99.7:0.3).

[i] Determined by GC using chiral stationary phase column (SPERCO γ-DEX 225; 75 °C constant).

[j] Determined by GC using chiral stationary phase column (SPERCO γ-DEX 225; 85 °C constant).

In conclusion, we have demonstrated that the newly designed phosphino-phenol **1c** is an efficient chiral ligand for copper-mediated asymmetric conjugate addition of diethylzinc to acyclic enones. Further studies on the optimization of the ligand and the reaction mechanism are in progress in our laboratory.

Acknowledgements

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4. Copper complex of P-stereogenic phosphino-phenol ligand, a different type of chiral P,O-ligand, has been reported to catalyze addition of diethylzinc to enones with good enantioselectivity of 85% ee: Takahashi, Y.; Katagiri, K.; Danjo, H.; Imamoto, T. In *Abstracts of the 84th Spring Meeting of the Chemical Society of Japan*, 2004; Vol. 2, p 761.
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6. In the present study, a hexane solution of diethylzinc was slowly added to the solution including Cu–**1c** complex and enone at −50 °C and, after the addition, the reaction temperature was immediately raised to 0 °C, because the enantioselectivity was unreproducible when the solution of diethylzinc was directly added at 0 °C. The addition reaction was sluggish at −50 °C.
7. Typical experimental procedure was exemplified by asymmetric conjugate addition of diethylzinc to chalcone: Copper(II) triflate (1.4 mg, 4.0 μmol) was placed in a flask under nitrogen and to this flask was added **1c** (2.0 mg, 4.8 μmol) in DMF (2.0 ml). After being stirred for 1 h at room temperature, chalcone (83.3 mg, 0.4 mmol) was added and the mixture was cooled to −50 °C. Diethylzinc (0.43 ml, 1.02 mol dm^{-3} in hexane) was added dropwise at the temperature and, then, immediately raised to 0 °C. After being stirred for another hour at the temperature, the mixture was quenched with 1 N HCl, allowed to warm to room temperature and extracted with ethyl acetate. The organic extract was washed three times with water, dried over anhydrous $MgSO_4$ and concentrated. Silica gel chromatography of the residue (hexane–ethyl acetate = 30:1) gave the desired product (80.1 mg, 84%) as an oil. Enantiomeric excess of the product was determined to be >99% by HPLC using chiral stationary phase column. All the new compounds obtained in this study gave satisfactory spectroscopic data.
8. The specific rotations of the products are given below: (a) 1,3-diphenyl-1-pentanone (99% ee): $[\alpha]_D^{22}$ +4.6 (*c* 1.26, EtOH); lit.[3r] [86% ee (*S*)-isomer]; $[\alpha]_D^{20}$ +7.3 (*c* 1.52, EtOH); (b) 3-(4-chlorophenyl)-1-phenyl-1-pentanone (99% ee): $[\alpha]_D^{24}$ +1.5 (*c* 1.13, EtOH); lit.[3r] [80% ee (*S*)-isomer]; $[\alpha]_D^{20}$ +2.0 (*c* 2.00, EtOH); (c) 3-(4-methoxyphenyl)-1-phenyl-1-pentanone (94% ee): $[\alpha]_D^{23}$ +14.9 (*c* 0.26, EtOH); lit.[3r] [90% ee (*S*)-isomer]; $[\alpha]_D^{20}$ +15.2 (*c* 1.67, EtOH); (d) 3-ethyl-1-phenyl-1-octanone (98% ee): $[\alpha]_D^{24}$ +2.8 (*c* 1.20, EtOH); lit.[3r] [61% ee]; $[\alpha]_D^{20}$ +1.7 (*c* 1.60, EtOH); (e) 4-phenyl-2-hexanone (90% ee): $[\alpha]_D^{24}$ +25.4 (*c* 0.16, EtOH); lit.[3r] [81% ee (*S*)-isomer]; $[\alpha]_D^{20}$ +27.0 (*c* 1.32, EtOH); (f) 5-phenyl-3-heptanone (93% ee): $[\alpha]_D^{23}$ +81.3 (*c* 1.10, benzene); lit.[13] [52% ee (*S*)-isomer]; $[\alpha]_D^{22}$ +37.6 (*c* 1.026, benzene); (g) 5-ethyl-3-decanone (90% ee): $[\alpha]_D^{25}$ +3.3 (*c* 0.45, $CHCl_3$); (h) 5-cyclohexyl-3-heptanone (91% ee): $[\alpha]_D^{20}$ +1.5 (*c* 0.63, $CHCl_3$).
9. Negative non-linear effect has also been reported in copper-mediated conjugate addition of diethylzinc to enones (Refs. 3m and 3r). Despite the observation of this non-linearity, it is likely that the present addition is catalyzed not by a 2:1 but by a 1:1 ligand/Cu species, because the reaction with the molar ratio of ligand/Cu = 2.2:1 was sluggish.
10. For the review of non-linear effect, see: Kagan, H. B.; Luukas, T. O. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Vol. 1, Chapter 4.1.
11. MS analysis of the mixture suggested that the side products were generated by Michael addition and aldol

reactions between the unreacted enone and the enolate formed by diethylzinc addition.

12. (a) A solvent of a large donor number is strongly coordinated to metal ion and weakens metal–oxygen bond, increasing reactivity of enolate species. For definition of donor number, see: Mayer, U.; Gutmann, V.; Gerger, W. *Monatsh. Chem.* **1975**, *106*, 1235–1257; (b) Parker, A. J.; Mayer, U.; Schmid, R.; Gutmann, V. *J. Org. Chem.* **1978**, *43*, 1843–1854.
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