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Highly enantioselective 1,4-conjugate addition of dialkylzinc to α,β-unsaturated lactone catalyzed by diphosphite–copper complexes

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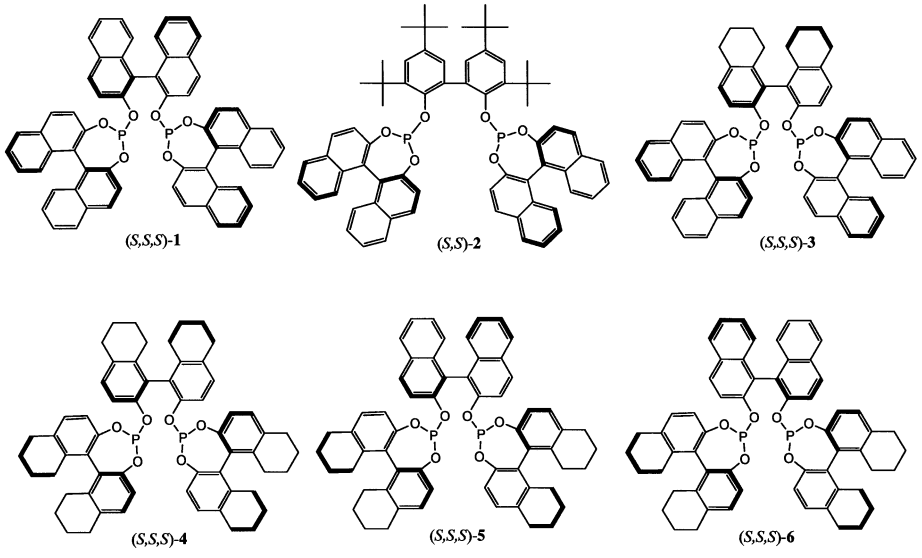
Abstract—The 1,4-addition of diethylzinc and dimethylzinc to 5,6-hydro-2*H*-pyran-2-one using new chiral diphosphite–copper catalysts gave products in up to 98% ee.

The enantioselective 1,4-conjugate addition to α,β-unsaturated lactones is a reaction of high interest because the chiral lactone products constitute important subunits in many natural products such as sesquiterpenes,[1] α-methylene lactones[2] and macrolides.[3] In addition, many lactone compounds exhibit important biological properties and function as semiochemicals, flavours and fragrances, or as antibiotics or cytostatics. Enders et al. reported the preparation of β-stereogenic lactone derivatives via reagent-controlled asymmetric Michael addition of a stoichiometric amount of chiral reagent to a non-chiral acceptor.[4]

The investigation of accessing chiral lactone compounds by catalytic asymmetric synthetic method with non-chiral starting material and catalytic amount of



Keywords: asymmetric catalysis; 1,4-conjugate addition; stereoselective synthesis; diphosphite ligands; α,β-unsaturated lactones.
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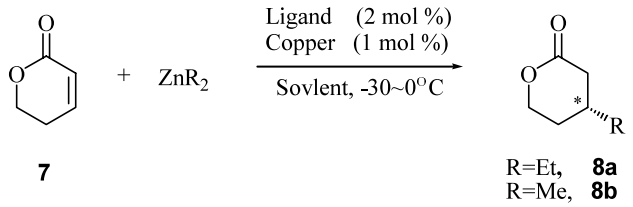
chiral source should be of high scientific and commercial interest. The first attempt on that was reported in 1981 by Yoshikawa et al. who obtained lactones via catalytic asymmetric hydrogenation of cyclic anhydrides with ee's up to 20%.[5] Thereafter, another route was employed for chiral lactones with ee's up to 94% via DIOP-Rh catalyzed asymmetric hydrogenation of itaconic acid esters, followed by selective hydride reduction.[6] Doyle et al. developed a highly enantioselective carbene insertion into an unactivated C–H bond of diazoacetate with up to 96% ee by using a chiral dirhodium(II) carboxamidate catalyst.[7] Tomioka et al. reported an enantioselective conjugate addition route in which Grinard reagents reacted with 5,6-dihydro-2*H*-pyran-2-one in the presence of 32 mol% of proline-based chiral amidophosphines with up to 90% ee.[8] Previously we also reported the enantioselective conjugate addition of diethylzinc to α,β-unsaturated lactones with high enantioselectivities in the presence of copper salts and chiral diphosphite ligands (2 mol%) derived from binaphthol. When (*S*,*S*,*S*)-**1** was used as chiral ligand in the reaction, **8a** was obtained in 73% ee. Replacing the bridging part of (*S*,*S*,*S*)-**1** from *S*-binaphthol to achiral 3,3′,5′,5-tetra-*tert*butyl-1,1′-bi-2-phenol afforded (*S*,*S*)-**2**, which was utilized as chiral ligand in the same reaction to give the chiral lactone in up to 92% ee.[9] Recently Reetz et al. reported the second example in conjugate addition of $ZnEt_2$ to lactones with ee's up to 88% by using ferrocene-based diphosphonites and copper salts.[10] In this paper, we report our recent study on the copper-catalyzed enantioselective conjugate addition of dialkylzinc to 5,6-dihydro-2*H*-pyran-2-one (Scheme 1).



Scheme 1.

Previous studies by us[11] and others[12] 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. Based on this phenomenon and our previous observation of the effectiveness of (*S*,*S*,*S*)-**1** and (*S*,*S*)-**2**, it was of interest to modify (*S*,*S*,*S*)-**1** by replacing some or all *S*-binaphthol units to *S*-H_8-binaphthol. (*S*,*S*,*S*)-**3** was obtained by replacing the bridging *S*-BINOL group to *S*-H_8-BINOL group.[14] This modified ligand gave only 65% ee in the conjugate addition (entry 1 of Table 1). Replacing the terminal parts of (*S*,*S*,*S*)-**3** from *S*-binaphthol to *S*-H_8-binaphthol gave (*S*,*S*,*S*)-**4**, which gave higher ee value (81%) than those from using (*S*,*S*,*S*)-**1** or (*S*,*S*,*S*)-**3** in the conjugate addition of diethylzinc to **7**. Further ligand modification led to the more effective ligand (*S*,*S*,*S*)-**5** and (*S*,*R*,*S*)-**6** which gave up to 98% ee in the reaction. The results of the catalytic reactions are summarized in Tables 1 and 2. When the absolute configuration of the bridging BINOL was different from the terminal H_8-BINOL, the catalyst exhibited significantly higher enantioselectivity in the reaction (entries 3 versus 6 and 4 verus 5 in Table 1). Interestingly the same configuration of **8a** was obtained whether **4**, **5** or **6** was used, indicating the dominant effect of the terminal moieties in the chiral ligand. In the investigation of the factors governing the rate and enantioselectivity of the reaction by using **5** and **6**, a profound solvent effect was observed. In toluene, ethyl acetate, dichloromethane and diethyl ether, the reaction proceeded smoothly with good yield and high enantioselectivity (Table 1, entries 7, 9, 10 and 12). The effect of catalyst concentration on the enantioselectivity was examined and it was found that lower catalyst

Table 1. Enantioselective 1,4-addition of diethylzinc to 5,6-dihydro-2*H*-pyran-2-one

Entry[a]	Ligand	[Cu] (10^{-3}M)	Solvent	Yield (%)	ee[c] (%) (+, *R*)[d]
1	(*S*,*S*,*S*)-**3**	4.00	Et_2O	81	65
2	(*S*,*S*,*S*)-**4**	4.00	Et_2O	78	81
3	(*S*,*S*,*S*)-**5**	4.00	Et_2O	76	90
4[b]	(*S*,*S*,*S*)-**5**	4.00	Et_2O	77	91
5[b]	(*S*,*R*,*S*)-**6**	4.00	Et_2O	70	97
6	(*S*,*R*,*S*)-**6**	4.00	Et_2O	79	96
7	(*S*,*R*,*S*)-**6**	1.67	Et_2O	81	97
8	(*S*,*R*,*S*)-**6**	1.25	Et_2O	82	98
9	(*S*,*R*,*S*)-**6**	1.67	Toluene	97	94
10	(*S*,*R*,*S*)-**6**	1.67	EA	82	95
11	(*S*,*R*,*S*)-**6**	1.67	THF	13	61
12	(*S*,*R*,*S*)-**6**	1.67	CH_2Cl_2	64	93
13	(*S*,*R*,*S*)-**6**	1.67	1,4-Dioxane	44	83

[a] All reactions were carried out at −30°C for 18 h; substrate:copper:ligand:Zt_2Zn = 100:1:2:150–200 (molar ratio); CuOTf was used as copper source unless otherwise indicated.

[b] $Cu(OTf)_2$ was used as copper source.

[c] The ee values of **8a** was determined by GC with a Chiraldex A-AT column (30 m×0.25 mm).

[d] The absolute configuration was assigned by comparing the optical rotation value with the result in Ref. 13.

Table 2. Enantioselective 1,4-addition of dimethylzinc to 5,6-dihydro-2*H*-pyran-2-one

Entry[a]	Ligand	[Cu] (10^{-3}M)	Solvent (mL)	Time (h)	Yield (%)	ee[c,d] (%)
1	(*S*,*S*,*S*)-**3**	5.00	Toulene	28	57	43
2	(*S*,*S*,*S*)-**4**	5.00	Toulene	28	51	54
3	(*S*,*S*,*S*)-**5**	5.00	Toulene	28	66	69
4[b]	(*S*,*S*,*S*)-**5**	5.00	Toulene	28	48	69
5	(*S*,*R*,*S*)-**6**	5.00	Toulene	28	56	82
6[b]	(*S*,*R*,*S*)-**6**	5.00	Toulene	28	39	75
7	(*S*,*R*,*S*)-**6**	1.66	Toulene	34	49	85
8	(*S*,*R*,*S*)-**6**	5.00	Et_2O	34	25	68
9	(*S*,*R*,*S*)-**6**	5.00	EA	34	10	63
10	(*S*,*R*,*S*)-**6**	5.00	CH_2Cl_2	34	60	72

[a] All reactions were carried out at 0°C with CuOTf as copper source except otherwise indicated; substrate:copper:ligand = 100:1:2 (molar rate).
[b] $Cu(OTf)_2$ was used as copper source.
[c] The ee values of **8b** was determined by GC with a Chiraldex A-AT column (50 m×0.25 mm).
[d] The absolute configurations of all the products were found to be *R* by comparimg the corresponding optical rotation values with that of Ref. 5.

concentration gave better product ee's (Table 1, entries 6–8). The highest enantioselectivity obtained was 98%.

The effect of copper source for the catalyst was relatively insignificant (Table 1, entries 3 versus 4 and 5 versus 6).

The 1,4-conjugate addition of dimethylzinc to 5,6-dihydro-2*H*-pyran-2-one (**7**) was also investigated. Table 2 summarized the results obtained under various reaction conditions. Ligand **6** always exhibited better enantioselectivity than those obtained by using ligands **3**, **4** or **5** under otherwise identical conditions. The enantioselectivity of the reaction was found to be strongly affected by the solvent used. Among the four different solvents (toluene, diethyl ether, ethyl acetate and dichloromethane) used, toluene gave the best product ee.

In summary, new chiral diphosphite ligands derived from H_8-binaphthol were found to be effective in the enantioselective copper-catalyzed 1,4-addition of diethylzinc and dimethylzinc to 5,6-dihydro-2*H*-pyran-2-one, giving rise to enantiomeric excesses of up to 98% and 85%, respectively. To the best of our knowledge, these are the best ee values achieved for these reactions to date.

Acknowledgements

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References

1. Yoshioka, H.; Mabry, T. J.; Timmermann, B. N. *Sesquiterpene Lactones*; University of Tokyo Press: Tokyo, 1973.
2. For reviews, see: (a) Grieco, P. A. *Synthesis* **1975**, 67–82; (b) Hoffmann, H. M. R.; Rabe, J. *Angew. Chem.* **1985**, *97*, 96–108; *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 94–110; (c) Sarma, J. C.; Sharma, R. P. *Heterocycles* **1986**, 441–457; (d) Ito, M. *Pure Appl. Chem.* **1991**, *63*, 13–22.
3. For reviews, see: (a) Nicolaou, K. C. *Tetrahedron* **1977**, *33*, 683–710; (b) Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 587–588; (c) Rossa, L.; Vögtle, F. *Top. Curr. Chem.* **1983**, *113*, 1–83; (d) Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569–3624; (e) Boeckmann, R. K., Jr.; Goldstein, S. W. In *The Total Synthesis of Natural Products*; Simon, J. A., Ed.; Wiley: New York, 1988; Vol. 7; p. 1.
4. (a) Enders, D.; Gröbner, R.; Runsink, J. *Synthesis* **1995**, 947–951; (b) Enders, D.; Teschner, P.; Gröbner, R.; Raabe, G. *Synthesis* **1999**, 237–242; (c) Enders, D.; Sun, H.; Leusink, F. R. *Tetrahedron* **1999**, *55*, 6129–6138.
5. Osakada, K.; Obana, M.; Ikariya, T.; Saburi, M.; Yoshikawa, S. *Tetrahedron Lett.* **1981**, *22*, 4297–4300.
6. (a) Tanaka, M.; Mukaiyama, C.; Mitsuhashi, H.; Maruno, M.; Wakamatsu, T. *J. Org. Chem.* **1995**, *60*, 4339–4352; (b) Landais, Y.; Robin, J. P.; Lebrun, A. *Tetrahedron* **1991**, *47*, 3787–3804; (c) Kosugi, H.; Tagami, K.; Takahashi, A.; Kanna, H.; Uda, H. *J. Chem. Soc., Perkin Trans. 1* **1989**, 935–943.
7. (a) Bode, J. W.; Doyle, M. P.; Protopopova, M. N.; Zhou, Q.-L. *J. Org. Chem.* **1996**, *61*, 9146–9155; (b) Doyle, M. P.; Protopopova, M. N.; Zhou, Q.-L.; Bode, J. W.; Simonsen, S. H.; Lynch, V. *J. Org. Chem.* **1995**, *60*, 6654–6655.
8. Kanai, M.; Tomioka, K. *Tetrahedron Lett.* **1995**, *36*, 4275–4278.
9. Yan, M.; Zhou, Z. Y.; Chan, A. S. C. *Chem. Commun.* **2000**, 115–116.
10. Reetz, M.; Gosberg, T. A.; Moulin, D. *Tetrahedron Lett.* **2002**, *43*, 1189–1191.
11. (a) Zhang, F.-Y.; Kwok, W. H.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2001**, *12*, 2337–2342; (b) Zhang, F.-Y.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1997**, *8*, 3651–3655; (c) Chan, A. S. C.; Zhang, F.-Y.; Yip, C.-W. *J. Am. Chem. Soc.* **1997**, *119*, 4080–4081; (d) Zhang, F.-Y.; Pai, C.-C.; Chan, A. S. C. *J. Am. Chem. Soc.* **1998**, *120*, 5808–5809; (e) Zhang, F.-Y.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1998**, *9*, 1179–1182.

12. (a) Zhang, X.; Taketomi, T.; Yoshizumi, T.; Kumobayashi, H.; Akutagawa, S.; Mashima, K.; Takaya, H. *J. Am. Chem. Soc.* **1993**, *115*, 3318–3319; (b) Zhang, X.; Uemura, T.; Matsumura, K.; Kumobayashi, H.; Sayo, N.; Takaya, H. *Synlett* **1994**, *1*, 501–503; (c) Uemura, T.; Zhang, X.; Matsumura, K.; Sayo, N.; Kumobayashi, H.; Ohta, T.; Nozaki, K.; Takaya, H. *J. Org. Chem.* **1996**, *61*, 5510–5516; (d) Liu, G.-B.; Tsukinoki, T.; Kanda, T.; Mitoma, Y.; Tashiro, M. *Tetrahedron Lett.* **1998**, *39*, 5991–5994; (e) Wang, Y.; Guo, H.; Ding, K. *Tetrahedron: Asymmetry* **2000**, *11*, 4153–4162.
13. Meyers, A. I.; Whitten, C. E. *Tetrahedron Lett.* **1976**, *17*, 1947–1950.
14. Experimental section: 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 method before use. Commercially available 5,6-dihydro-2*H*-pyran-2-one (98%, ACROS), $Cu(OTf)_2$ (98%, ACROS), $ZnEt_2$ (Pure, Aldrich) were used without further purification. ^{31}P, ^{1}H and ^{13}C NMR spectra were recorded on a Varian AS500 spectrometer. Enantiomer excess values were determined by chiral GC analysis (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. **Typical experimental procedure for the Cu-catalyzed conjugate addition of organozinc reagents to 5,6-hydro-2*H*-pyran-2-one**: The reaction was carried out under nitrogen atmosphere using dried glassware. The catalyst was prepared in situ by stirring 1 mol% of $(CuOTf)_2{\cdot}C_6H_6$ (or $Cu(OTf)_2$) and 2 mol% of ligand in 2–8 mL of dry Et_2O for 20–30 min and then at −30 to 0°C substrate (1.0 equiv.) and 1.5 equiv. of neat Et_2Zn were added sequentially. The reaction was quenched by the addition of 1.5–2 mL of a saturated solution of NH_4Cl. The product was extracted with Et_2O (three times, 2.0 mL each), dried with $MgSO_4$, followed by the removal of volatiles in vacuo. The yield and ee value of the product were determined by GC with a chiral capillary column using dodecane as an internal standard. Ligands **3**–**6** were synthesized according to our previously reported method[9] by using H_8-BINOL to replace the appropriate BINOL units. **[[(*S*)-1,1′-bi-2-naphthol]bi[(*S*)-2,2′-dihydroxy-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl]bisphosphite] (5)**: ^{1}H NMR (CD_2Cl_2): δ 8.08 (d, $J=8.5$ Hz, **2**H), 7.98 (d, $J=8.5$ Hz, **2**H), 7.56 (d, $J=9.0$ Hz, **2**H), 7.44 (t, $J=7.0$ Hz, **2**H), 7.32–7.20 (m, **6**H), 7.01 (d, $J=8.5$ Hz, **2**H), 6.84 (d, $J=8.0$ Hz, **2**H), 6.03 (d, $J=7.5$ Hz, **2**H), 2.82–2.60 (m, **8**H), 2.57–2.53 (m, **4**H), 2.16–2.07 (m, **4**H), 1.80–1.66 (m, **12**H), 1.49–1.42 (m, **4**H); ^{13}C NMR (CD_2Cl_2) δ 145.9, 145.5, 138.5, 137.6, 135.1, 134.2, 134.1, 131.0, 130.1, 129.3, 129.1, 128.3, 128.2, 127.6, 127.0, 125.9, 125.2, 122.6, 120.0, 118.9, 118.7, 29.1, 27.7, 22.7, 22.5 ppm; ^{31}P NMR (CD_2Cl_2) δ 138.39 ppm; $[\alpha]_D^{20}=+98.0$ ($c=1.0$, toluene); HRMS calcd for $C_{60}H_{52}O_6P_2$: 930.3239, found: 930.3161. **[[(*R*)-1,1′-bi-2-naphthol]bi[(*S*)-2,2′-dihydroxy-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl]bisphosphite] (6)**: mp 167°C; ^{1}H NMR (CD_2Cl_2): δ 8.05 (d, $J=9.0$ Hz, 2H), 8.00 (d, $J=8.0$ Hz, **2**H), 7.49–7.47 (m, **4**H), 7.29 (td, $J=7.3$, 1.5 Hz, **2**H), 7.20–7.18 (m, **2**H), 6.95 (d, $J=8.0$ Hz, **2**H), 6.73 (d, $J=7.0$ Hz, **2**H), 6.42 (d, $J=8.0$ Hz, **2**H), 5.3 (d, $J=8.5$ Hz, **2**H), 2.71–2.47 (m, **12**H), 2.09–2.04 (m, **4**H), 1.69–1.61 (m, **12**H), 1.45–1.41 (m, **4**H); ^{13}C NMR (CD_2Cl_2): δ 148.4, 145.8, 138.54, 138.1, 137.1, 135.2, 134.2, 134.0, 131.2, 130.3, 129.3, 129.1, 128.8, 128.2, 127.5, 127.1, 126.1, 125.3, 123.1, 121.4, 118.8, 118.5, 29.1, 29.1, 27.8, 27.7, 22.7, 22.7, 22.5, 22.5 ppm; $[\alpha]_D^{20}=+87.9$ ($c=1.0$, toluene); HRMS calcd for $C_{60}H_{52}P_2O_6$: 930.3239, found: 930.3306.