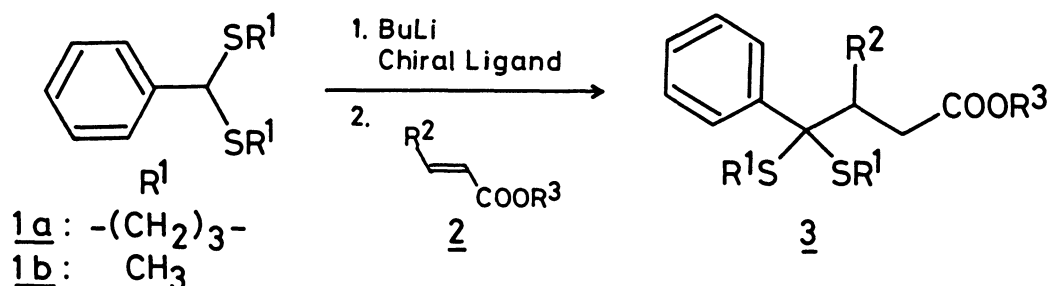


ENANTIOSELECTIVE CONJUGATE ADDITION REACTION
MEDIATED BY CHIRAL LIGANDS

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Chiral ligand mediated enantioselective conjugate addition reaction of lithiated dithioacetal derivative with prochiral α,β -unsaturated ester gives the corresponding adduct in 67% enantiomeric excess.

The addition of organometallics to the carbon-carbon double bond of α,β -unsaturated carbonyl compounds, a process known as 1,4-conjugate addition or the Michael reaction, is a versatile method of synthesis. Application of this process to asymmetric synthesis is a focused and exciting area of current investigations.^{1,2)} Most of the successful applications involve the diastereoface-differentiating reactions in which the chiral auxiliaries should be bound to either of reaction partners by covalent bond.^{2,3)} On the contrary, enantioface-differentiating conjugate addition of achiral organometallics to prochiral acceptors by the mediation of chiral solvents or complexing ligands has remained the challenge^{2,4,5)} and only two successful asymmetric additions (achieving over 60% enantiomeric excess (ee)) of methylcuprate to chalcone with an aid of L-proline-based ligands have been reported.⁴⁾ Since this type of reaction holds promise for significant efficiency in that asymmetric conjugate addition reaction



can be realized simply by adding the chiral ligand to the reaction medium, we

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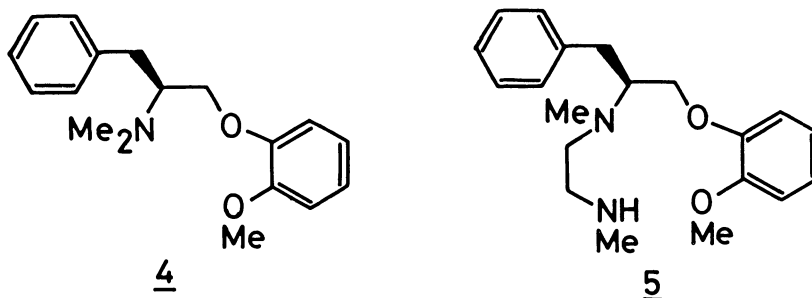
decided to develop the new chiral ligands for the reaction of organolithium reagents.⁶⁾ We report herein the enantioselective conjugate addition reaction of the dithioacetal derivatives (1) with α,β -unsaturated esters (2) in the presence of new chiral ligands (4,5) which enter into the reaction as intermediate complex or solvate for organolithium reagent, providing 3 of either antipode with up to 67% ee.

The chiral ligands 4 and 5 were prepared from L-phenylalanine.^{7,8)} The ligand 4 ($[\alpha]_D^{20} +61.8^\circ(\text{CHCl}_3)$) was designed to bear the three coordination sites, one nitrogen and two phenolic oxygens. The ligand 5 ($[\alpha]_D^{24} +20.1^\circ(\text{CHCl}_3)$) bears an additional coordination site, the secondary amino-nitrogen, and is also expected to work as a strong lithium amide base by internal chelation. It was also expected that the ligands 4 and 5 form the differently organized complexes with the lithiated 1, leading to the opposite enantioface selection.⁹⁾

Since the reaction scheme (1 + 2 \rightarrow 3) consists of two steps (lithiation of 1 and subsequent conjugate addition of lithiated 1 to 2), lithiation of 1b with BuLi was first studied. The reaction was quenched with CH_3OD and the ratio of D incorporation was determined by ^1H NMR. It was found that, when 1b was treated with BuLi in the presence of 1.1 equiv. of ligand 4 at -78°C in toluene, 1b was successfully lithiated to form a yellow precipitate, probably a complex with the ligand 4, while lithiation of 1b failed completely without a ligand even in a mixture of ether-toluene (1:1 (v/v)) at -78°C . Activation of BuLi and complex formation with lithiated 1b by the use of 4 suggest the ability of 4 working as a ligand for the lithium cation.¹⁰⁾

A typical experimental procedure is as follows (Run 1): A hexane solution of BuLi (1.2 ml, 1.7 mmol) was added to a solution of 1a (333 mg, 1.7 mmol) and 4 (571 mg, 2.0 mmol) in toluene¹¹⁾ (11 ml) at -78°C and the mixture was stirred for 1 h at the same temperature.¹²⁾ A solution of methyl crotonate (2 ($\text{R}^2=\text{R}^3=\text{Me}$)) (150 mg, 1.5 mmol) in toluene (1 ml) was then added. After stirring for 15 min at -78°C , the reaction was quenched with aqueous ammonium chloride solution. Standard work-up and silica-gel column chromatography (eluted with a 1:1 mixture of ether and hexane) afforded (S)-3 of 50% ee in 40% yield. The degree of asymmetric induction was determined by ^1H NMR analysis in the presence of $\text{Eu}(\text{hfc})_3$.¹³⁾ The absolute configuration of the product was determined by the conversion into known compound. The chiral ligand was recovered for reuse without any loss of optical purity by a simple extraction procedure.

In a similar manner, asymmetric reaction was conducted using chiral ligands 4 and 5. These results are summarized in Table 1. A moderate to good enantioface selection was realized in the reaction of 1 with α,β -unsaturated esters (2) bearing methyl, isopropyl, and phenyl β -substituents. It is noteworthy that the ligands 4 and 5 clearly showed the opposite sense of enantioface selection as shown in Table 1. Continuing studies are in progress in our laboratory.

Table 1. Enantioselective Asymmetric Synthesis of 3

Run	Ligand	<u>1</u>	R ²	R ³	Yield/% ^{a)}	[α] _D ²⁰ / ^{°b)}	ee/% ^{c)}	Conf'n
1	<u>4</u>	<u>1a</u>	Me	Me	40	-16.1	50	S ^{e)}
2	<u>4</u>	<u>1a</u>	i-Pr	Et	32(36) ^{d)}	-16.6	67	R ^{f)}
3	<u>4</u>	<u>1a</u>	Ph	Et	22(37) ^{d)}	-18.7	53	R ^{g)}
4	<u>4</u>	<u>1b</u>	Ph	Et	53	-11.1	36	R ^{g)}
5	<u>5</u>	<u>1a</u>	Me	Me	36	+10.4	32	R ^{e)}
6	<u>5</u>	<u>1a</u>	i-Pr	Et	38(61) ^{d)}	+10.2	41	S ^{f)}
7	<u>5</u>	<u>1b</u>	i-Pr	Et	76	-21.5	38	S ^{f)}
8	<u>5</u>	<u>1b</u>	Ph	Et	81	+13.1	43	S ^{g)}

a) Yields are not optimized. Yields in parentheses are the corrected ones based on the consumed 2. b) Taken in CHCl₃. c) Enantiomeric excess was determined by ¹H NMR analysis in the presence of Eu(hfc)₃. d) A comparable amount of 1,2-addition product was obtained. e) Absolute configuration was determined by the conversion of (-)-3 (Raney nickel in EtOH) into (R)-(+)-methyl 3-methyl-4-phenylbutyrate; K. B. Wiberg and T. W. Hutton, J. Am. Chem. Soc., **78**, 1640 (1956). f) Absolute configuration was determined by the conversion of (-)-3 (Run 7) (i. Raney nickel in EtOH; ii. RuCl₃-NaIO₄ in aq. CH₃CN-CCl₄; iii. B₂H₆-THF) into (S)-(-)-3-isopropylpentan-5-olide; A. J. Irwin and J. B. Jones, J. Am. Chem. Soc., **99**, 556 (1977). g) Absolute configuration was determined by the conversion of (-)-3 (i. Raney nickel in EtOH; ii. aq. NaOH) into (R)-(+)-3,4-diphenylbutyric acid, of which antipode ((S)-(-)) was obtained from (R)-(-)-2,3-diphenylpropionic acid (LiAlH₄ in THF; ii. p-TsCl in pyridine; iii. NaCN in DMSO; iv. aq. HCl-HCOOH); M. B. Watson and G. W. Youngson, J. Chem. Soc., C, **1968**, 258.

References

- 1) a) "Asymmetric Synthesis," ed by J. D. Morrison, Academic Press, New York (1983-1984), Vol. 1-4; b) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions," Prentice-Hall, Inc., New Jersey (1971).
- 2) K. Tomioka and K. Koga, in ref. 1a, Vol. 2 (1983), p.201; G. H. Posner, *ibid.*, Vol. 2 (1983), p.225; K. A. Lutomoski and A. I. Meyers, *ibid.*, Vol. 3 (1984), p.213.
- 3) D. Enders and K. Papadopoulos, *Tetrahedron Lett.*, 24, 4967 (1983); K. Yamamoto, M. Iijima, Y. Ogimura, and J. Tsuji, *ibid.*, 25, 2813 (1984).
- 4) F. Leyendecker and D. Laucher, *Tetrahedron Lett.*, 24, 3517 (1983); F. Leyendecker, F. Jesser, and B. Rubland, *ibid.*, 22, 3601 (1981); T. Imamoto and T. Mukaiyama, *Chem. Lett.*, 1980, 45.
- 5) W. Langer and D. Seebach, *Helv. Chim. Acta*, 62, 1710 (1979); D. Seebach, G. Crass, E.-M. Wilka, D. Hilvert, and E. Brunner, *ibid.*, 62, 2695 (1979).
- 6) Significant success in the enantioselective addition reaction of organometallics with carbonyl compounds by the use of chiral ligands has been reviewed: G. Solladié, in ref. 1a, Vol. 2 (1983), p. 157; Asymmetric Michael reaction of β -keto esters by the use of chiral crown-ether catalysts has been reported: D. J. Cram and G. D. Y. Sogah, *J. Chem. Soc., Chem. Commun.*, 1981, 625.
- 7) Details will be reported in due course. The authors are grateful to Mr. K. Shiina for his assistance in preparing the ligand 4.
- 8) All new compounds described in this paper provided the satisfactory spectroscopic and analytical data.
- 9) It is possible to speculate that the ligand 4 forms a chelate with lithium cation using nitrogen and two phenolic oxygens, while 5 forms a similar one using two nitrogens and one phenolic oxygen.
- 10) Lithiated 1a was proved by X-ray crystallographic analysis to form a 1:1:1 complex with the bidentate ligand tetramethylethylenediamine and THF: R. Amustutz, J. D. Dunitz, and D. Seebach, *Angew. Chem., Int. Ed. Engl.*, 20, 465 (1981).
- 11) We are currently using toluene as a solvent of choice for asymmetric reaction based on the chelation control. K. Tomioka, K. Ando, Y. Takemasa, and K. Koga, *J. Am. Chem. Soc.*, 106, 2718 (1984); *Tetrahedron Lett.*, 25, 5677 (1984).
- 12) When ligand 5 was used, it was first treated with BuLi and then dithioacetal was added.
- 13) When 1a was used, ee of 3 was determined by the optical rotation of the desulfurized compound, which was also obtained from 3 derived by the reaction of 1b. When 1b and 2 ($R^3=Me$) were used, ee was determined by 1H NMR analysis of 3 in the presence of $Eu(hfc)_3$.

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