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ENANTIOSELECTIVE CONJUGATE ADDITION REACTION MEDIATED BY CHIRAL LIGANDS

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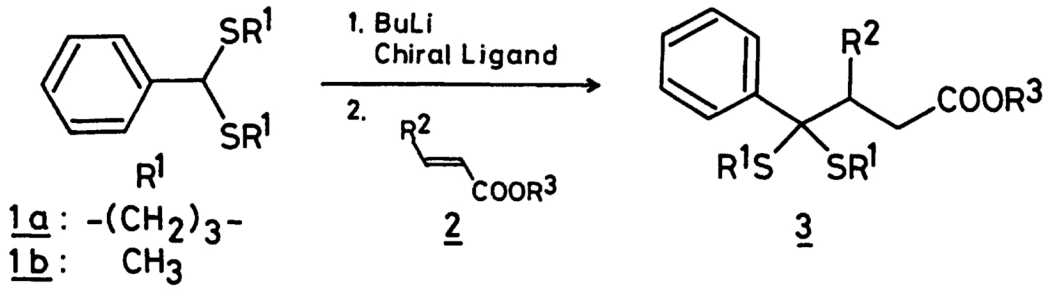
Chiral ligand mediated enantioselective conjugate addition reaction of lithiated dithioacetal derivative with prochiral α,β-unsaturated ester gives the corresponding adduct in 67% enantiomeric excess.

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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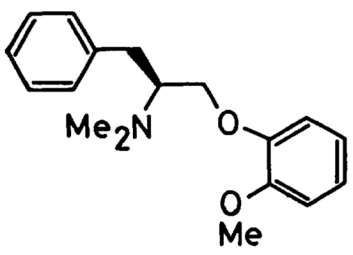
decided to develop the new chiral ligands for the reaction of organolithium reagents.[6] We report herein the enantioselective conjugate addition reaction of the dithioacetal derivatives (1) with α,β-unsaturated esters (2) in the presence of new chiral ligands (4,5) which enter into the reaction as intermediate 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°($CHCl_3$)) was designed to bear the three coordination sites, one nitrogen and two phenolic oxygens. The ligand 5 ($[\alpha]_D^{24}$+20.1°($CHCl_3$)) 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 → 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 toluene[11] (11 ml) at -78°C and the mixture was stirred for 1 h at the same temperature.[12] A solution of methyl crotonate (2 (R^2=R^3=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 $Eu(hfc)_3$.[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.



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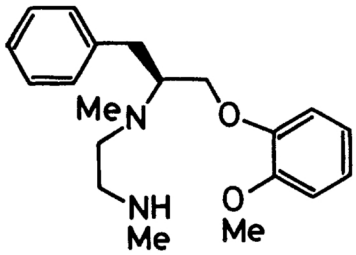

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Table 1. Enantioselective Asymmetric Synthesis of 3

Run	Ligand	1	R^2	R^3	Yield/%[a]	$[\alpha]_D^{20}$/°[b]	ee/%[c]	Conf'n
1	4	1a	Me	Me	40	-16.1	50	S[e]
2	4	1a	i-Pr	Et	32(36)[d]	-16.6	67	R[f]
3	4	1a	Ph	Et	22(37)[d]	-18.7	53	R[g]
4	4	1b	Ph	Et	53	-11.1	36	R[g]
5	5	1a	Me	Me	36	+10.4	32	R[e]
6	5	1a	i-Pr	Et	38(61)[d]	+10.2	41	S[f]
7	5	1b	i-Pr	Et	76	-21.5	38	S[f]
8	5	1b	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 $CHCl_3$. 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. $RuCl_3$-$NaIO_4$ in aq. CH_3CN-CCl_4; iii. B_2H_6-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 ($LiAlH_4$ 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.

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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 ^{1}H NMR analysis of 3 in the presence of Eu(hfc)$_3$.

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