of $[\theta]_{222}$ on P/M was not influenced by the differences in the polymerization degree and in the optical activity of the polymers. When we chose $[\theta]_{222} = -2000$ and -28400 deg cm^2 dmol^{-1} for the disordered and helical structures of melittin, respectively,[3,11] the proportion of helical structure was estimated to be 75% beyond $P/M = 1$.

As is known, PLGA and PDGA adopt helical structures at acidic pH. However, these polymers did not induce helix formation in melittin at pH 2.3 because of loss of their original negative charges (the solution was clear). On the contrary, upon subtracting the spectrum of PLGA or PDGA from that of the mixture, we obtained the spectrum of melittin alone, indicative of a more disordered structure (−26 000 deg cm^2 dmol^{-1} around 195 nm) at the acidic pH than at neutral pH (Figure 1A). This might suggest that melittin has a slight amount of helices at neutral pH.

On the other hand, helix formation was not induced in melittin by the coexistence (<5 mM) of a simple anionic amino acid, glutamic acid. The polymers appear likely also to provide a place for the helix formation of melittin. A similar situation can be anticipated for melittin in surfactant solutions. The nonpolar tails of surfactants bound to cationic residues of melittin must strongly interact with one another, forming a micelle-like structure.[3] This micelle-like aggregate appears likely to supply a similar place for the helix formation. At neutral pH, some of six cationic charges of melittin might be neutralized on PLGA and PDGA. Then, the helical moiety, with four continuous cationic residues in the C-terminal, are considered to be entwined with PLGA or PDGA. Probably related to this, the disordered state might be required for the polymers to twine around the helical rod. Interestingly, the value of $[\theta]_{222}$ becomes almost constant above $P/M = 1$ (Figure 2), while polymerization degrees of the present polymers are much larger than the residue number, 26, of the protein. We speculate that a considerable amount of helical melittin molecules hang on each of the homopolypeptide chains.

The present results tend to indicate that the short polypeptide melittin presents a useful model for the studies of polypeptide–polypeptide interactions as well.

(11) (a) Greenfield, N.; Fasman, G. D. *Biochemistry* **1969**, *8*, 4108. (b) Chen, Y.-H.; Yang, J. T.; Martinez, H. M. *Biochemistry* **1972**, *11*, 4120. (c) Chen, Y.-H.; Yang, J. T.; Chau, K. H. *Biochemistry* **1974**, *13*, 3350. (d) Chang, C. T.; Wu, C.-S. C.; Yang, J. T. *Anal. Biochem.* **1978**, *91*, 13.

Catalytic Asymmetric Aldol Reactions. Use of a Chiral (Acyloxy)borane Complex as a Versatile Lewis Acid Catalyst

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The development of chiral catalysts that mediate the asymmetric aldol condensations in a highly stereocontrolled and truly catalytic manner has been a challenging goal in synthetic organic chemistry. Although much fascinating chemistry has been exploited on this problem, which provided excellent methods for chirality transfer from chiral substrates or auxiliaries to prochiral molecules, it has not led to an ultimate means of propagating chirality with a nonstoichiometric amount of a chiral source, except in a few special cases.[1] We report now a successful solution to this problem.

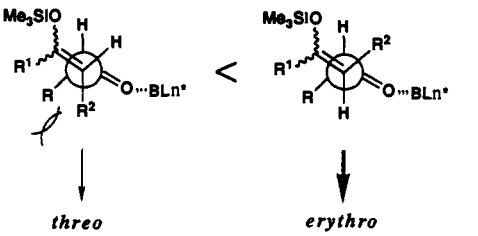
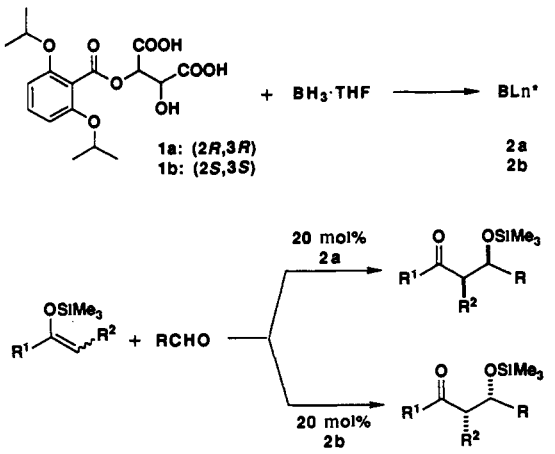


Figure 1. Extended transition state model.

Scheme I



Our method uses a chiral (acyloxy)borane (CAB) complex[2] as a Lewis acid catalyst for the Mukaiyama condensation of simple chiral enol silyl ethers of ketones with various aldehydes.[3] This CAB-catalyzed aldol process allows the formation of adducts in a highly diastereo- and enantioselective manner (up to 96% ee) under mild reaction conditions. Furthermore, the reactions are catalytic, thus only 20 mol % of catalyst is needed for efficient conversions, and the chiral source is recoverable and reusable.

Chiral (acyloxy)borane complex **2** was easily prepared in situ from tartaric acid derivative **1** and BH_3·THF complex in propionitrile solution at 0 °C[4] (Scheme I). The aldol reactions of ketone enol silyl ethers with aldehydes were promoted by 20 mol % of this catalyst solution at low temperature.[5] After a usual workup, the crude product mixture (mostly silylated β-hydroxy ketones) was treated with diluted hydrochloric acid to afford desilylated aldol adducts. Product diastereomer ratios were determined by analytical HPLC and ^{1}H NMR spectroscopy of the adducts and/or the corresponding MTPA esters. The stereochemical assignments (relative stereochemistries) were made from the analyses of the ^{1}H NMR spectra, and the absolute configurations were determined by comparison of the specific rotation values with those of the literature. Some results are summarized in Table I.

The relative stereochemistry of the major adducts was assigned as erythro, and predominant *re*-face attack of enol ethers at the aldehyde carbonyl carbon was confirmed in cases where a natural tartaric acid derivative was used as a Lewis acid ligand. The use of an unnatural form of tartaric acid as a chiral source afforded the other enantiomer as expected (entry 8). Almost perfect asymmetric inductions were achieved in the erythro adducts, reaching 96% ee, although a slight reduction in both the enantio-

(1) (a) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3. (b) Paterson, I.; Goodman, J. M.; Lister, M. A.; Schumann, R. C.; McClure, C. K.; Norcross, R. D. *Tetrahedron* **1990**, *46*, 4663 and references cited therein. Recently, Mukaiyama et al. reported catalytic asymmetric aldol-type reactions of silyl ethers of propanethioate mediated by a chiral tin reagent. (c) Mukaiyama, T.; Kobayashi, S.; Uchiro, H.; Shiina, I. *Chem. Lett.* **1990**, 129. (d) Kobayashi, S.; Fujishita, Y.; Mukaiyama, T. *Chem. Lett.* **1990**, 1455.

(2) For precedent applications of CAB catalysts to asymmetric reactions, see: (a) Furuta, K.; Miwa, Y.; Iwanaga, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 6254. (b) Furuta, K.; Shimizu, S.; Miwa, Y.; Yamamoto, H. *J. Org. Chem.* **1989**, *54*, 1481. (c) Furuta, K.; Kanematsu, A.; Yamamoto, H.; Takaoka, S. *Tetrahedron Lett.* **1989**, *30*, 7231.

(3) For a review of the Mukaiyama aldol reaction, see: Mukaiyama, T. *Org. React. (N.Y.)* **1982**, *28*, 203.

(4) Tartaric acid **1** was prepared by the monoacylation of dibenzyl tartrate followed by hydrogenolysis.

(5) The use of 10 mol % catalyst for the reaction resulted in a significant decrease in reactivity.

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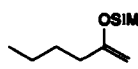
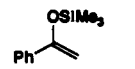
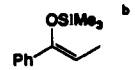
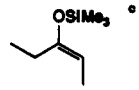
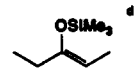
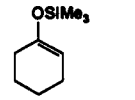
Table I. CAB-Catalyzed Asymmetric Aldol Reactions of Ketone Silyl Ethers with Aldehydes[a]

entry	silyl ethers	RCHO[e]	yield (%)	erythro /threo	ee(%)[j,k] (config)
1		A	81	-	85(I)
2		B	70	-	80(I)
3		A	98	-	85(R)
4		C	88	-	83(I)
5	 [b]	A	86	95/ 5	95(I)
6		D	62	88/12[l]	80(I)
7	 [c]	A	96	94/ 6	96(R)
8		A [f]	99	94/ 6	96(S)
9		A [g]	95	88/12	90(R)
10		A [h]	55	82/18	77(R)
11		E	79	>94/ 6[l]	93(R)
12		D	61	80/20	88(S)
13	 [d]	A	97	93/ 7	94(R)
14		A	57	>95/ 5[l]	>95(I)

[a] Conditions as in ref 9. [b] Mixture of two isomers (E/Z = 2/98). [c] Mixture of two isomers (E/Z = 4/1). [d] Mixture of two isomers (E/Z = 1/6). [e] A: benzaldehyde. B: pentanal. C: cinnamaldehyde. D: butanal. E: crotonaldehyde. [f] **1b** was used as a ligand. [g] Nitroethane was used as a solvent. [h] Dichloromethane was used as a solvent. [i] The diastereomer ratio was determined by analysis of 500-MHz ^{1}H NMR spectra. [j] The values correspond to the major isomers. [k] Reference 10. [l] Not determined.

and diastereoselectivities was observed in the reactions with saturated aldehydes. It is noteworthy that, regardless of the stereochemistry (E or Z) of starting enol silyl ethers generated from ethyl ketones, erythro aldols were highly selectively obtained in the present reactions.[6] The observed unprecedentedly high erythro selectivities together with their independence of the stereochemistry of silyl ethers in the CAB-catalyzed reactions are fully consistent with Noyori's TMSOTf-catalyzed aldol reactions of acetals and, thus, may reflect the acyclic extended transition state mechanism postulated in the latter reactions (Figure 1).[7] It was of considerable interest to us that the diastereoselectivities of these reactions showed significant solvent dependency; thus, in CH_2Cl_2 (standard solvent for this type of reaction) the ratio dropped to 82/18 (entry 10). The polar solvent should be helpful for the polarized extended transition state model.[8] Judging from the product configurations, CAB catalyst (from natural tartaric acid) should effectively cover the *si* face of carbonyl on its coordination and the selective approach of nucleophiles from the *re* face should result. That behavior is totally systematic and in good agreement with the results of previously reported CAB-catalyzed Diels-Alder reactions.[2] Thus it follows that the sense of asymmetric induction of CAB-catalyzed reactions is the same for all aldehydes examined. Although the enol ethers derived from methyl ketones exhibited modest asymmetric induction (entries 1-4), this reaction would be generally applicable to various ketone silyl ethers and aldehydes.[9] Further studies of the reaction mechanism and the scope of these transformations are in progress.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan.

(6) The reaction of a silyl ether of *tert*-butyl ethyl ketone (Z form) exceptionally gave the threo adduct predominantly (74/26 ratio). See ref 7.

(7) (a) Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 3248. (b) Noyori, R.; Murata, S.; Suzuki, M. *Tetrahedron* **1981**, *37*, 3899. In the case of the reaction of *tert*-butyl ethyl ketone (R^1 = *t*-Bu, R^2 = Me, Z form, in Figure 1), it could be considered that the steric repulsion between R and R^1 (=*t*-Bu) in the erythro transition state becomes more significant than that between R and R^2 in the threo transition state.

(8) The superiority of propionitrile as a solvent for catalytic asymmetric aldol-type reactions has been reported: see ref 1d.

(9) The following experiment is typical: To a solution of monoacylated tartaric acid **1** (74 mg, 0.2 mmol) in propionitrile (1 mL) was added BH_3·THF (0.12 mL of 1.68 M solution in THF, 0.2 mmol) at 0 °C under Ar. The reaction mixture was stirred for 1 h at that temperature, during which period the evolution of hydrogen gas ceased, and then the solution was cooled to -78 °C. To this were introduced 3-(trimethylsiloxy)-2-pentene (190 mg, 1.2 mmol, E/Z = 4/1) and benzaldehyde (102 μL, 1.0 mmol) successively. After stirring for 2 h, the solution was poured into diluted hydrochloric acid and the product was extracted with ether. The solvent was evaporated, and the residue was treated with 1 N HCl-THF solution (2 mL, 1/1 in vol). Usual workup followed by chromatographic separation gave aldol adducts (185 mg, 96% yield).

(10) (a) Iwasawa, N.; Mukaiyama, T. *Chem. Lett.* **1982**, 1441. (b) Mashraqui, S. H.; Kellogg, R. M. *J. Org. Chem.* **1984**, *49*, 2513. (c) Muraoka, M.; Kawasaki, H.; Koga, K. *Tetrahedron Lett.* **1988**, *29*, 337. (d) Enders, D.; Lohray, B. B. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 581. (e) Reference 1b.

Transformation of C-Terminal Serine and Threonine Extended Precursors into C-Terminal α-Amidated Peptides: A Possible Chemical Model for the α-Amidating Action of Pituitary Enzymes

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The primary amide functionality present at the carboxyl terminus in the majority of polypeptide hormones and in many bioactive neuropeptides[1] is known[2] to be derived from a glycine (Gly) residue at the C-terminus of their Gly extended precursors.[3]

We present here a practical, in vitro model for the terminal amidation reaction using either a serine (Ser) or threonine (Thr)[4]

(1) Mains, R. E.; Eipper, B. A.; Glembotski, C. G.; Dores, R. M. *Trends NeuroSci. (Personal edt.)* **1983**, *6*, 229.

(2) Bradbury, A. F.; Finnie, M. D. A.; Smyth, D. G. *Nature* **1982**, *298*, 686. Eipper, B. A.; Mains, R. E.; Glembotski, C. G. *Proc. Natl. Acad. Sci. U.S.A.* **1983**, *80*, 5144.

(3) This reaction is catalyzed by the peptidylglycine α-amidating enzyme (PAM). Although not conclusive, it is believed that the process involves α-hydroxylation to carbinolamides, which can be nonenzymatically transformed to terminal amides. The α-hydroxylation can be effected either directly or through an *N*-acylimine. A subsequent "retroaminal" process would result in amide. (For leading references, see: Bradbury, A. F.; Smyth, D. G. *Biosci. Rep.* **1987**, *7*, 907. Eipper, B. A.; Mains, R. E. *Annu. Rev. Physiol.* **1988**, *50*, 333. Bateman, R. C., Jr.; Youngblood, W. W.; Busbuy, W. H., Jr.; Kizer, J. S. *J. Biol. Chem.* **1985**, *260*, 9088. Bradbury, A. F.; Smyth, D. G. *Eur. J. Biochem.* **1987**, *169*, 579. Ramer, S. E.; Cheng, H.; Palcic, M. M.; Vederas, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 8582. Kaiopodis, A. G.; May, S. W. *Biochemistry* **1990**, *29*, 4541. Reddy, K. V.; Jin, S.-J.; Arora, P. K.; Sfeir, D. S.; Maloney, S. C.; Maloney, F.; Urbach, F. L.; Sayre, L. M. *J. Am. Chem. Soc.* **1990**, *112*, 2332. Young, S. D.; Tamburini, P. P. *J. Am. Chem. Soc.* **1989**, *111*, 1933. Tajima, M.; Iida, T.; Yoshida, S.; Komatsu, K.; Namba, R.; Yanagi, M.; Noguchi, M.; Okamoto, H. *J. Biol. Chem.* **1990**, *265*, 9602.) We are grateful to a referee for bringing to our notice very pertinent recent references.

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