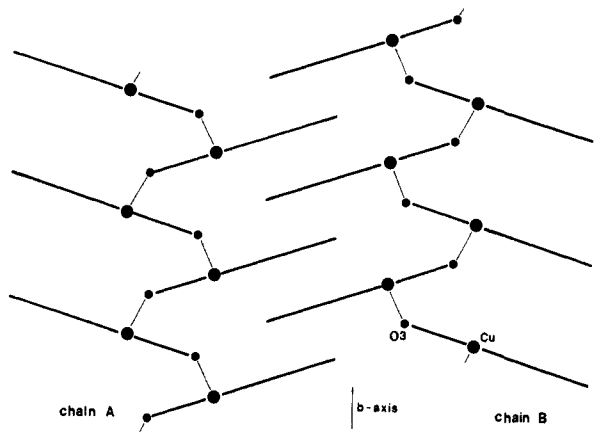

Figure 1. View normal to two chain axes which shows the antiparallel packing of the chains and the interleaving of the molecular units.

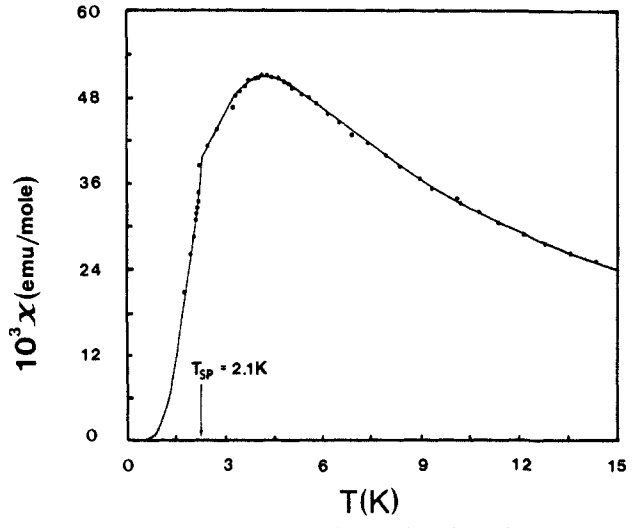

Figure 2. Magnetic susceptibility data which show the spin-Peierls transition. Solid lines were generated by the theoretical expressions and parameters described in the text.

Isothermal magnetization data show the expected behavior for an SP transition. Uniform chain magnetization behavior is observed at 4.2 and 2.4 K, but at 2.1 K and lower temperatures the magnetization behavior is characteristic of an alternating chain. Isofield magnetization data show an abrupt change in magnetization at T_{SP} which is dependent on the applied magnetic field, T_{SP} being 2.1 K at 1 T and ~1.8 K at 4 T. The magnetization behavior is complex above 4.4 T.

The magnetic susceptibility data for CuNSG may be fit by the $S = {}^1/_2$ 1-D Heisenberg theory[8] by using $J = -1.55$ cm^{-1}. The fit is improved if a slightly temperature-dependent exchange coupling constant is used below $T = 5.5$ K. Temperature-dependent exchange coupling was also found in TTF-Cu[1]BDT.[3b]

Below T_{SP} the spin chain is an alternating chain, and the degree of alternation is temperature-dependent. If T_{SP} is taken as the temperature of maximum $d\chi/dT$,[3] the data in Figure 2 indicate that $T_{SP} = 2.1$ K. Below T_{SP} the magnetic susceptibility cannot be fit by either the static alternating chain model,[4] or the temperature-dependent alternating chain model of Bulaevskii.[9] This is probably due to large spin-phonon coupling in CuNSG. The magnetic susceptibility below T_{SP} may be fit by the expression

$$\chi_M = (Ng^2\beta^2/3kT)A \exp[-2J(1 - T/T_c)/kT]$$

where the parameter $A = 0.75$ is the $S(S + 1)$ value for $S = {}^1/_2$, and the temperature parameter T_c in the Boltzmann term qualitatively accounts for the progressive dimerization in CuNSG. The best fit of $T_c = 5.8$ K is nearly the temperature at which the correction to the Bonner-Fisher chain result becomes important. A quantitative description of the dimerization in CuNSG will require a more accurate description of the variation of the exchange energies with structural parameters.

Acknowledgment. This work was supported in part by the National Science Foundation through Grant CHE 83 08129 and by the John Simon Guggenheim Memorial Foundation. High-field magnetization measurements were made at the Francis Bitter National Magnet Laboratory, which is supported at M.I.T by the National Science Foundation. We thank J. C. Bonner and L. J. de Jongh for helpful discussions, and L. G. Rubin and B. Brandt for their invaluable help.

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Enantioselective Deprotonation by Chiral Lithium Amide Bases: Asymmetric Synthesis of Trimethylsilyl Enol Ethers from 4-Alkylcyclohexanones

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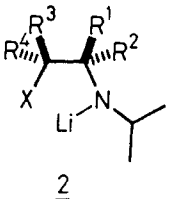
Highly selective transformations of enantiotopic groups in prochiral or meso compounds having a σ-plane are well-known in enzymatic processes.[1] Chemical approaches have also been made mainly by diastereoselective methods,[2] and a few enan-



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	R^1	R^2	R^3	R^4	X
a	H	Pr^i	H	H	OMe
b	H	Bzl	H	H	OMe
c	Bu^t	H	H	H	OMe
d	Ph	H	H	H	OMe
e	Ph	H	H	H	NMe_2
f	Ph	H	H	H	N⬠
g	Ph	H	H	H	N⬡
h	Ph	H	H	H	N◯NMe
i	Me	H	Ph	H	OMe
j	Me	H	H	Ph	OMe
k	H	Ph	H	H	H
l	1-Naph	H	H	H	H

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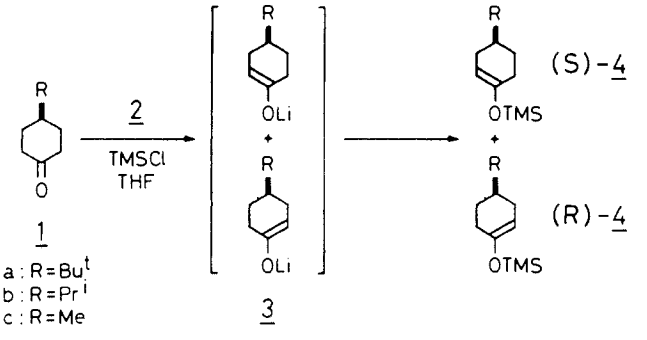
Table I. Enantioselective Synthesis of **4**[a]

entry	ketone	base	HMPA,[b] equiv	product	isolated yield, %	$[\alpha]_{365}$,[c] deg	ee, %[d]	config
1	**1a**	**2a**	2.0	**4a**	88	−55.3	26	*S*
2	**1a**	**2b**	2.0	**4a**	65	−78.7	36	*S*
3	**1a**	**2c**	2.0	**4a**	91	+84.6	39	*R*
4	**1a**	**2d**	2.0	**4a**	90	+103	47	*R*
5	**1a**	**2d**	0	**4a**	87	−15.7	7	*S*
6	**1a**	**2e**	2.0	**4a**	35	+109	51	*R*
7	**1a**	**2f**	2.0	**4a**	52	+158	73	*R*
8	**1a**	**2g**	2.0	**4a**	67	+182	84	*R*
9	**1a**	**2g**	0	**4a**	89	+157	73	*R*
10	**1a**	**2h**	1.0	**4a**	87	+182	84	*R*
11[e]	**1a**	**2h**	1.0	**4a**	51	+210	97	*R*
12	**1a**	**2h**	0	**4a**	65	+173	80	*R*
13	**1a**	**2i**	2.0	**4a**	74	+79.0	37	*R*
14	**1a**	**2j**	2.0	**4a**	32	+95.0	44	*R*
15	**1a**	**2k**	3.0	**4a**	63	−151	70	*S*
16	**1a**	**2k**	0	**4a**	88	−181	84	*S*
17	**1a**	**2l**	3.0	**4a**	31	+156	72	*R*
18	**1b**	**2h**	1.0	**4b**	85	+178	66	*R*
19	**1b**	**2k**	0	**4b**	65	−180	67	*S*
20	**1c**	**2h**	1.0	**4c**	68	+152	50	*R*
21	**1c**	**2k**	0	**4c**	69	−175	58	*S*

[a] For procedure, see the text. [b] Relative amount to **2**. [c] *c* 1.5 in benzene at 25 ± 2 °C. [d] Calculated by optical rotation. [e] The reaction was performed at −105 °C.

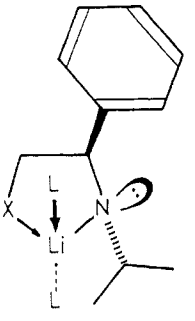
Scheme I



tioselective methods[3] are now known. We describe here the first example of enantioselective deprotonation of prochiral 4-alkylcyclohexanones **1** by chiral lithium amide bases **2** to generate chiral lithium enolates **3**, which were isolated as their corresponding trimethylsilyl enol ethers **4** (Scheme I).

All reactions were carried out by Corey's internal quench method[4] and are summarized in Table I. A typical experimental procedure (entry 8) is as follows. A solution of lithium amide **2g** was prepared under argon atmosphere by adding a solution of *n*-butyllithium (2.4 mmol) in hexane (approximately 1.5 M solution) to a solution of the corresponding amine (2.5 mmol) in tetrahydrofuran (THF) (50 mL) under stirring at −78 °C. After 5 min, hexamethylphosphoric triamide (HMPA) (4.8 mmol)[5] was added and the mixture was warmed to room temperature and then recooled to −78 °C. Trimethylsilyl chloride (10 mmol) was added, and then 4-*tert*-butylcyclohexanone (**1a**) (2.0 mmol) in THF (4 mL) was added dropwise during 3 min. Stirring was continued at −78 °C for 10 min. After addition of triethylamine (4 mL) and saturated aqueous sodium bicarbonate (10 mL), the product was isolated by the usual workup and purification (column chromatography (silica gel, pentane) followed by bulb-to-bulb distillation (150 °C/2 mmHg)) to give (*R*)-4-*tert*-butyl-1-[(trimethylsilyl)oxy]cyclohexene ((*R*)-(+)-**4a**) in 84% ee (67% chemical yield).

Absolute configurations and maximum rotations of trimethylsilyl enol ethers ($[\alpha]^{25}_{365}$ −216° (*c*, 1.45, benzene) for (*S*)-**4a**, $[\alpha]^{25}_{365}$ +268° (*c*, 1.52, benzene) for (*R*)-**4b**, $[\alpha]^{26}_{365}$ +303° (*c*, 1.83, benzene) for (*R*)-**4c**) were determined by chemical correlation to the known compounds **6**,[6a] **7**,[6b] **8**[6c]) as depicted in Scheme II.



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It is shown that the degree of asymmetric induction is highly dependent on the structures of chiral bases used and also on the bulkiness of the alkyl groups in cyclohexanones. In a case when

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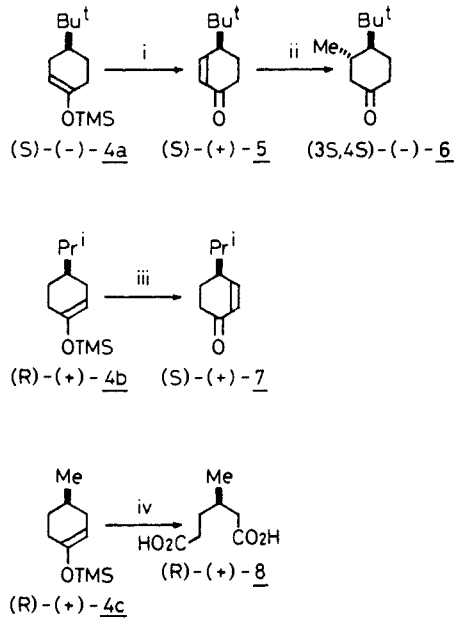
(6) (a) (*S*)-**4a** ($[\alpha]^{25}_{365}$ −120° (*c* 1.45, benzene)) afforded (3*S*,4*S*)-**6** ($[\alpha]^{20}_{D}$ −137° (*c* 0.46, $CHCl_3$)). (3*R*,4*R*)-**6** is reported to show $[\alpha]^{20}_{D}$ +247.8° (*c* 0.45, $CHCl_3$). Konopelsky, J. P.; Sundararaman, P.; Barth, G.; Djerassi, C. *J. Am. Chem. Soc.* **1980**, *102*, 2737–2745. Enantiomeric purity of (3*S*,4*S*)-(−)-**6** obtained here was independently confirmed to be 56% ee by converting it to the corresponding acetal with (2*R*,3*R*)-(−)-butanediol (97% conversion by GC). (b) (*R*)-**4b** ($[\alpha]^{25}_{365}$ +178° (*c* 1.52, benzene) afforded (*S*)-**7** ($[\alpha]^{20}_{D}$ +79.3° (*c* 2.40, EtOH)). Optically pure (*R*)-**7** is reported to show $[\alpha]^{20}_{D}$ −119.3° (*c* 2.0, EtOH). Galloway, A. S.; Dewar, J.; Read, J. *J. Chem. Soc.* **1936**, 1595–1597. (c) (*R*)-**4c** ($[\alpha]^{26}_{365}$ +152° (*c* 1.83, benzene)) afforded (*R*)-**8** ($[\alpha]^{26}_{D}$ +5.77° (*c* 3.59, $CHCl_3$)). Maximum rotation reported to date for (*R*)-**8** is $[\alpha]^{26}_{D}$ +11.5° (*c* 9.38, $CHCl_3$)). Semmler, W. *Ber.* **1892**, *25*, 3513–3520. Cf.: Irwin, A. J.; Jones, J. B. *J. Am. Chem. Soc.* **1977**, *99*, 556–561.

Scheme II[a]



[a] (i) $Pd(OAc)_2$, CH_3CN, 87%. (ii) Me_2CuLi, Et_2O, 84%. (iii) $Pd(OAc)_2$, CH_3CN, 79%. (iv) $MoO_2(acac)_2$, *t*-BuOOH, C_6H_6, 60%.

1a was deprotonated with **2h** in the presence of HMPA in THF at −105 °C, **4a** was obtained in 97% ee.

Five-membered chelated structures are expected to be formed for the lithium amides **2a–j** as in **9**, where the isopropoyl group on nitrogen should be exclusively trans to the bulky substituent on the chiral carbon for steric reasons. This infers that the direction of the lone pair on chiral nitrogen to be used for deprotonation is fixed. It is known that axial α-hydrogens are lost in preference to equatorial α-hydrogens in enolization of cyclohexanones due to stereoelectronic effect.[7] For deprotonation to occur by synchronous proton and lithium ion transfer,[8] the carbonyl group in **1** will coordinate to the lithium from the same side as the lone pair. Correlation of configuration between the chiral center of the chiral base and that of the product may become possible as work advances. It should be noted that higher asymmetric induction was observed in the presence of HMPA. The effect of HMPA is likely to destroy aggregation of lithium amide bases and to generate more effective species[9] for selective deprotonation.

Interestingly, simple lithium amide bases **2k,l** having no additional ligation sites also caused fairly high asymmetric induction (entries 15–17, 19, 21). In these cases, however, higher asymmetric induction was observed in the absence of HMPA.[10]

The method outlined above represents a new approach to enantioselective asymmetric synthesis of chiral enol ethers **4**, which should be useful as synthons for the synthesis of optically active compounds.

Acknowledgment. Partial financial support from the Ministry of Education, Science and Culture, Japan (Grant-in-aid for Scientific Research, No. 60870075), is acknowledged.

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Structure of the Complex between an Unexpectedly Hydrolyzed Phosphonamidate Inhibitor and Carboxypeptidase A

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Recent high-resolution crystal structures of enzyme–inhibitor complexes[1] involving the metalloenzyme carboxypeptidase A (CPA)[2] have provided new three-dimensional insight as to potential catalytic conformations[3] of this zinc exopeptidase. Such X-ray crystallographic methods serve as powerful complements to studies of the enzyme in solution. We now report the structure of the complex between CPA and the unexpectedly hydrolyzed phosphonamidate inhibitor *N*-[[[(benzyloxycarbonyl)amino]-methyl]hydroxyphosphinyl]-L-phenylalanine (ZGP′; a possible transition-state analogue of the dipeptide substrate Cbz-Gly-L-Phe),[4] where the corresponding phosphonic acid occupies the S_1 subsite and phenylalanine occupies the S_1' subsite. The observed structure resembles a product/product analogue complex of the cleaved moieites bound to the enzyme, yet still resembles a possible transition-state analogue complex by virtue of the tetrahedral phosphorous moiety bound to the zinc ion.

Crystals of CPA were prepared and cross-linked as described,[1a] and then soaked in a buffer solution [0.2 M LiCl, 0.02 M Veronal-LiOH (pH 7.5)] containing a 7 mM concentration of ZGP′ for 5 days at 4° C. Data collection, reduction, and refinement procedures have been described.[1a] Model building was facilitated by the use of the Evans and Sutherland PS300 interfaced with a VAX 11/780, with graphics software developed by Jones[5] (FRODO). The final crystallographic *R* factor[6] was calculated to be 0.176 at 1.82-Å resolution.[7]

The carbobenzoxy carbonyl of the cleaved phosphonate does not make a hydrogen bond with Arg-71 in the S_2 subsite, as might be predicted from the interaction of CPA with the 39-amino acid inhibitor from the potato.[8] Instead, this portion of the inhibitor lies in the "aromatic" region of S_2 and S_3 (the area around Tyr-198 and Phe-279). An oxygen of the tetrahedral phosphonate moiety hydrogen bonds with Glu-270 (3.4 Å, yet still within experimental error of a hydrogen bond), and it is the only oxygen of the phosphonate to coordinate to zinc (the Zn–O distance is 2.2 Å). The long hydrogen bond to Glu-270 may reflect a particular state of ionization of the polyprotic phosphonic acid. Another phosphonate oxygen accepts a hydrogen bond from one of the guanidinium nitrogens of Arg-127 (2.7 Å; see Figure 1). This is the first observed interaction of Arg-127 with a zinc-bound inhibitor. Although this interaction does not involve the phosphonate oxygen which is also coordinated to zinc, it does support a role for Arg-127 proposed[1a] as a hydrogen bond donor to a transient intermediate in proteolytic reactions. Arg-127 might serve as an electrophilic catalyst through hydrogen bond donation, with or without the

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(6) $R = \sum||F_o| - |F_c||/\sum|F_o|$, where $|F_o|$ and $|F_c|$ are observed and calculated structure factor amplitudes, respectively.
(7) An rms error in atomic positions was estimated to be about 0.2 Å on the basis of relationships derived by Luzatti; see: Luzzati, V. *Acta Crystallogr.* **1952**, *5*, 802–810.
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