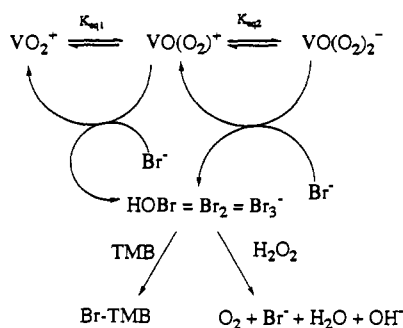


Figure 3. Dioxygen formation in the bromide-assisted disproportionation of hydrogen peroxide. Conditions are the same as in Figure 1. O_2 was measured with a YSI Clark-type electrode. (a) $VO_2^+ + Br^- + H_2O_2$; (b) $VO_2^+ + H_2O_2$; (c) $Br^- + H_2O_2$; (d) $VO_2^+ + Br^- + H_2O_2 + TMB$. Note: The solubility of O_2 in this reaction solution is ca. 0.345 mM; the limited solubility prevents determination of the stoichiometry under these conditions.

Scheme II



Dioxovanadium(V) also catalyzes the oxidation of iodide and chloride by H_2O_2 in acid. Peroxovanadium(V) species oxidize iodide; however, dioxovanadium(V) is reduced by iodide in acid,⁹ consistent with the observed decrease in the ^{51}V NMR signal over time of the reaction solution under catalytic conditions (data not shown). Further, we have found that dioxovanadium(V) catalyzes the oxidation of chloride by hydrogen peroxide, and the formation of chlorotrimethoxybenzene (Cl-TMB; $M^+ m/e$ 202, 204), although the chlorination rate is slower than that for bromination.

Thus we have shown that dioxovanadium(V) catalyzes the bromination of TMB and the bromide-assisted disproportionation of hydrogen peroxide, analogous to the reactivity of the V-BrPO enzyme (Scheme II; in this scheme, HOBr, Br_2 and Br_3^- are in rapid equilibration). In this biomimetic system, dioxovanadium(V) coordinates H_2O_2 forming the monoperoxo or diperoxo species, in ratios dependent on the hydrogen peroxide and acid concentrations (Figure 2).⁸ The peroxovanadium(V) species then oxidize the halide, although the detailed mechanism of this reaction is not yet known: the halide could be oxidized directly by bound peroxide, retaining the vanadium(V) moiety, or the halide could coordinate or reduce vanadium(V), before reduction of bound peroxide occurs. The two main differences between the biomimetic system and V-BrPO are the rate of catalysis and the pH dependence, with a much greater enzyme rate at higher pH. Further mechanistic studies are in progress to address the role of the protein in the enzymatic activity by investigating the role of oxo-

vanadium(V) ligands in mediating the rate of halide oxidation and the pH dependence.

Acknowledgment. This work was supported by the National Institutes of Health (GM-38130). We thank J. V. Walker for her results on the TMB analysis.

Supplementary Material Available: Listing of details of experimental procedures for Figures 1-3 (2 pages). Ordering information is given on any current masthead page.

Crystallographic and 6Li and ^{15}N NMR Studies of a Chiral Bidentate Lithium Amide. An Effect of Aggregation States on an Enantioselective Deprotonation Reaction

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Asymmetric synthesis using chiral lithium amides has received much attention in recent years.² Previously we reported highly enantioselective reactions involving deprotonation of cycloalkanones,³ aldol condensation,⁴ and alkylation⁵ by employing chiral bidentate lithium amides ((R) -1, $Y = OR, NR_2$). On the basis of our earlier studies on diastereoselective alkylation of chiral chelated lithio enamines,⁶ we designed (R)-1 using the following three hypotheses: (1) five-membered chelated structures will be formed as shown in (R)-2; (2) a chiral amide nitrogen will be formed efficiently since a bulky alkyl group on the amide nitrogen should be exclusively trans to the bulky phenyl group on the chiral carbon for steric reasons, i.e., the lone pair on amide nitrogen will be fixed cis to the phenyl group; and (3) the aggregation state of (R)-1 in solution can be controlled by adding an external ligand such as HMPA (hexamethylphosphoric triamide) to satisfy the

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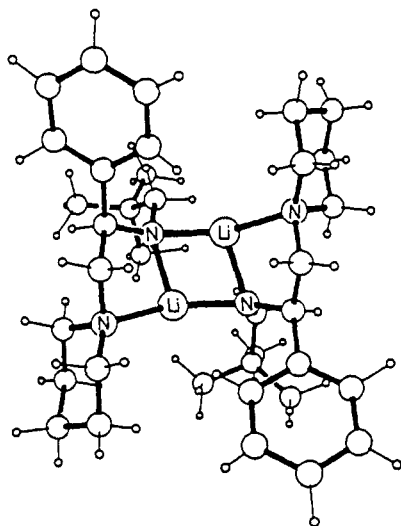


Figure 1. X-ray structure of (*R*)-1a.

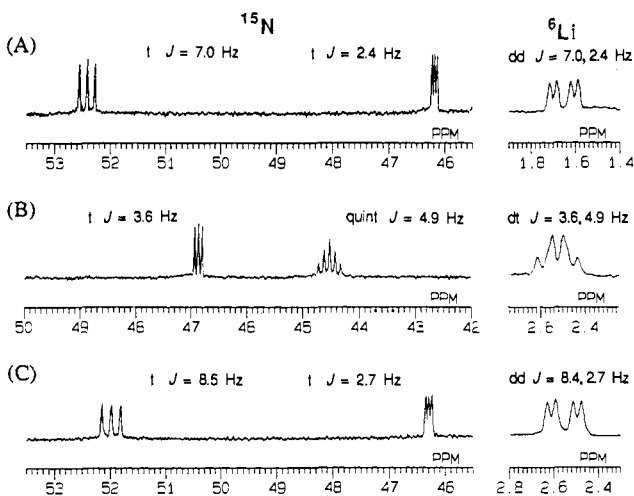
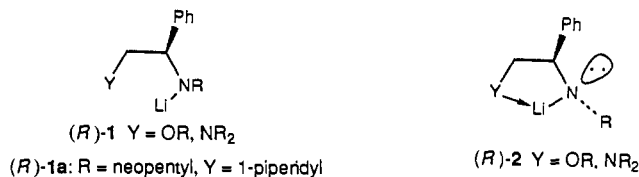


Figure 2. (A) ^{15}N and ^6Li NMR spectra of $[\text{}^6\text{Li}, \text{}^{15}\text{N}_2]\text{-(R)-1a}$ in $\text{THF-}d_8$ (Table I, entry 1); (B) in $\text{toluene-}d_8$ (Table I, entry 6); (C) in $\text{toluene-}d_8$ with 2 equiv of HMPA (Table I, entry 7).

coordination of lithium. We obtained support for these hypotheses by X-ray diffraction⁷ and ^6Li and ^{15}N NMR studies⁸ on (*R*)-1a.



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Scheme I

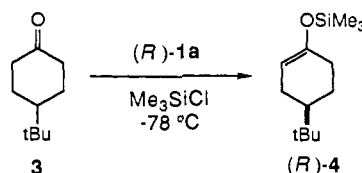


Table I. Solvent Effect on Synthesis of (*R*)-4 (Scheme I)^a

entry	solvent	HMPA (equiv)	yield, %	ee, ^b %
1	THF	0	86	84
2	THF	2	82	82
3	DME	0	86	70
4	DME	2	87	81
5	toluene	0	12	58
6	toluene	2	87	82
7	ether	0	8	64
8	ether	2	89	82

^a For procedure of asymmetric deprotonation reaction, see ref 3a. ^b Maximum rotation for (*R*)-4 is $[\alpha]_{365}^{25} +237^\circ$ (*c* 1.5, benzene). Aoki, K.; Nakajima, M.; Tomioka, K.; Koga, K., unpublished results.

Air-sensitive crystals of (*R*)-1a were obtained from ether-toluene (4:1) as colorless prisms.⁹ Its X-ray structure is given in Figure 1.¹⁰ The structure is a dimer having a tricyclic [5.3.0.0] ring system. The core of the dimer is an approximately diamond-shaped Li-N-Li-N four-membered ring. Both lithium atoms are tricoordinated. A five-membered chelate is formed in each monomer that constitutes a dimer. The conformation of each monomer is very similar. The flexible neopentyl groups on amide nitrogen adopt a slightly different conformation and are trans to the phenyl group. This means that the lone pair on amide nitrogen is fixed cis to the phenyl group as expected, and the dimer is formed by coordination of the lone pair on amide nitrogen with the vacant orbital on the lithium atom from the same side of the phenyl group on chiral carbon.

The ^6Li and ^{15}N NMR studies of $[\text{}^6\text{Li}, \text{}^{15}\text{N}_2]\text{-(R)-1a}$ were carried out in several solvents at -80°C .¹¹ In $\text{THF-}d_8$ or $\text{DME-toluene-}d_8$ (4:1), the ^6Li NMR spectrum of $[\text{}^6\text{Li}, \text{}^{15}\text{N}_2]\text{-(R)-1a}$ showed a doublet of doublets (Figure 2A), indicative of coupling to two neighboring ^{15}N nuclei (^{15}N : spin $1/2$). The corresponding ^{15}N spectrum displayed two sets of triplets (1:1:1), indicating that each nitrogen atom couples to one neighboring ^6Li nucleus (^6Li : spin 1). This requires that each nitrogen is attached to one lithium. This observation also shows that a five-membered chelated structure is formed as a monomer in these solvents. In $\text{toluene-}d_8$ or $\text{ether-toluene-}d_8$ (4:1), the ^6Li NMR spectrum of $[\text{}^6\text{Li}, \text{}^{15}\text{N}_2]\text{-(R)-1a}$ showed a doublet of triplets (Figure 2B), indicative of coupling to three neighboring ^{15}N nuclei. The corresponding ^{15}N spectrum displayed a triplet (1:1:1) and a quintet (1:2:3:2:1), indicating that one nitrogen couples to one neighboring lithium, while the other nitrogen couples to two neighboring lithiums. Thus, one nitrogen is connected to one lithium, and the other nitrogen is connected to two lithiums. It is therefore concluded that, in $\text{toluene-}d_8$ or $\text{ether-toluene-}d_8$ (4:1), (*R*)-1a exists as a dimer, as was observed by X-ray analysis of the crystal

(9) (*R*)-*N*-Neopentyl-1-phenyl-2-piperidinoethylamine was deprotonated with 1 equiv of butyllithium in ether at -78°C . Lithium amide crystallized at -20°C in ether-toluene (4:1) in 3 days.

(10) The dimer crystallized in the orthorhombic space group $P2_12_12_1$ with unit cell parameters $a = 29.163$ (2) Å, $b = 11.469$ (1) Å, $c = 10.722$ (1) Å, and $D_{\text{calc}} = 1.038$ g/cm³. A total of 3024 reflections were observed using graphite-monochromated Cu Kα radiation (2θ values in the range of 0–120°), and the temperature of the crystal was kept at 253 K. The structure was solved by direct methods using the computer program SIR 88 and the difference Fourier method. The final values are $R = 0.047$ and $R_w = 0.046$. No absorption corrections were applied. Specific details of the diffraction analysis along with tables of atomic coordinates and structural parameters have been submitted as supplementary material.

(11) Samples were prepared by treatment of $[\text{}^{15}\text{N}_2]\text{-(R)-N}$ -neopentyl-1-phenyl-2-piperidinoethylamine with 1 equiv of $[\text{}^6\text{Li}]$ butyllithium/hexane solution at -78°C .

structure. HMPA changed this situation dramatically.¹² In all the solvents tested, addition of 2 equiv of HMPA caused (*R*)-**1a** to exist as a chelated monomer. The ⁶Li NMR spectrum of [⁶Li,¹⁵N₂]-(*R*)-**1a** shows a doublet of doublets, and the corresponding ¹⁵N spectrum displays two sets of triplets (Figure 2C). Addition of a large excess of HMPA (13 equiv) to the [⁶Li,¹⁵N₂]-(*R*)-**1a** in THF-*d*₈ did not affect the five-membered chelate structure.

The asymmetric deprotonation of 4-*tert*-butylcyclohexanone (**3**) using (*R*)-**1a** (Scheme I) showed remarkable solvent effects as shown in Table I. In THF or DME, the reaction proceeded with good chemical yield and good enantioselectivity (especially in THF). On the other hand, the reaction itself did not proceed well and enantioselectivities were somewhat decreased in toluene or ether. HMPA also showed a marked effect on the reaction as an external ligand.^{3a,12} In the presence of 2 equiv of HMPA, chemical and optical yields became high and independent of the solvent used. It is concluded that the five-membered chelated monomeric form of (*R*)-**1a** is higher in reactivity and gives higher enantioselectivity in deprotonation than the dimeric form of (*R*)-**1a**, and that the function of HMPA is to destroy the dimeric form and to generate the monomeric form of (*R*)-**1a**.

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Supplementary Material Available: Details of the diffraction analysis, plots of atom labels, and tables of atomic coordinates and equivalent isotropic thermal parameters, bond lengths, and bond angles for the dimeric form of (*R*)-**1a** and complete ⁶Li and ¹⁵N NMR spectroscopic data of [⁶Li,¹⁵N₂]-(*R*)-**1a** (10 pages). Ordering information is given on any current masthead page.

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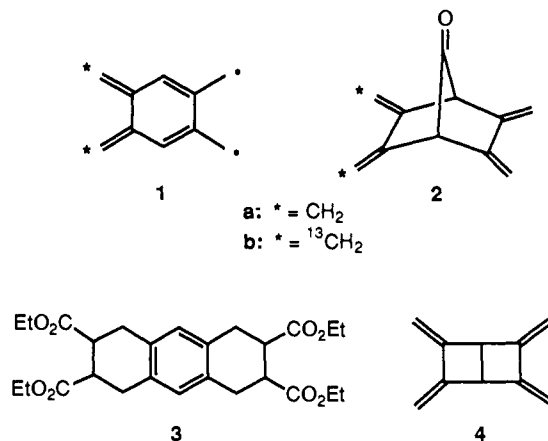
A Kinetically Stable Singlet State of 1,2,4,5-Tetramethylenebenzene

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The atomic connectivity^{1,2} of the 1,2,4,5-tetramethylenebenzene (TMB) biradical **1a** permits its two nominally nonbonding electrons to reside in "disjoint" molecular orbitals, confining to separate spatial domains.³ According to both semiempirical⁴ and ab initio⁵ theory, **1a** should have a singlet ground state. The highest level calculations done so far^{5b} predict the singlet to be favored by 5–7 kcal/mol with respect to the triplet.

Previous experimental studies, however, have favored a triplet ground state for **1a**.⁶ Photolysis of ketone **2a** in Ar matrix at



15 K gave rise to CO and to a UV-vis spectrum with a strong band near 480 nm (ϵ not specified) and weak bands at 530, 560, and 600 nm ($\epsilon \sim 600, 600,$ and 400 , respectively). The weak bands were assigned⁶ to the dipole-forbidden transition at 570 nm predicted^{5b} for the triplet of **1a**. A preparation of **2a** in adamantane matrix irradiated at 15 K gave a strong, narrow ESR signal near 3404 G and a weak half-field transition near 1693 G. The ESR signal intensity was linear in $1/T$ between 15 and 80 K. These observations led to the assignment of a triplet ground state for **1a**.⁶ The formation of product **3** in the thermal (80 °C) reaction of ketone **2a** in solution with fumaric ester was interpreted as chemical trapping of the biradical **1a** formed by loss of CO from **2a**.⁶

Our work leads to different conclusions. First, we find that the biradical **1a** is not a significant intermediate in the thermal **2a** \rightarrow **3** reaction. Ketone **2a** alone is stable in benzene solution at 80 °C, and its reaction with diethyl fumarate is kinetically second-order. These observations conform to the mechanism described⁷ for the reaction of **2a** with tetracyanoethylene: two successive conventional Diels-Alder reactions followed by decarbonylation.

By irradiation at 77 K of ketone **2a**, prepared by either of the literature^{6,7} routes, in glassy media or in adamantane matrix prepared by cosublimation, we observe an intense purple color and a UV-vis spectrum (major absorption near 490 nm, $\epsilon \sim 4200$) essentially the same in all features as that reported.⁶ Purple samples from **2a** show an ESR signal near 3280 G at a microwave frequency of 9.27 GHz whose intensity is variable and is not correlated with that of the UV-vis absorption. At 77 K, a half-field signal near 1650 G is not visible, even at 1.8 mM concentration of the biradical. Allowing the matrix to thaw results in complete destruction of ketone **2a** and disappearance of the purple color. Refreezing and rephotolyzing this sample give the same ESR signal as before, but the purple color and the UV-vis spectrum featuring the 490-nm band are absent. The implication is strong that the carrier of the ESR signal is not the species responsible for the purple color and the UV-vis spectrum.

Ketone precursor 2-2,3-*di*-¹³CH₂ (**2b**) was synthesized as described elsewhere.⁸ Figure 1A shows the solid-state CP MAS ¹³C NMR spectrum of **2b** immobilized in 2-methyltetrahydrofuran (MTHF) glass at 77 K. Irradiation at 310 nm produces a new species with a resonance at 113 ppm (Figure 1B). This chemical shift corresponds well to that expected⁹ for a singlet biradical (compare the shifts of the terminal CH₂ carbons of 3,4-dimethylenefuran^{9a} and 3,4-dimethylenethiophene,^{9bc} $\delta = 102$ and 105 ppm, respectively) and cannot be attributed to a triplet, which would not be observable under these conditions.⁹ Integration of the difference spectrum (1B - 1A) shows that the decrease in

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