here, the overvoltage for the production of hydrogen at the tungsten electrode is 0.85 V (H_2O, pH 7.8, 0.1 M Na_2SO_4), and dihydrogen evolution becomes rapid at −1.7 V (vs. SCE). We use a mixture of Lip^{ox} and DTT^{ox} in Scheme I to increase the overall rate of cathodic disulfide reduction. DTT^{ox} is reduced approximately twice as rapidly as Lip^{ox} at −1.0 V, and a major pathway in the reductions of a mixture of the two disulfides is one in which DTT^{ox} is converted to DTT^{red}, and this DTT^{red} in turn reduces Lip^{ox} to Lip^{red} by thiol–disulfide interchange.[8] DTT^{red} is not a substrate for LipDH.

We illustrate the operation of the regeneration sequence summarized in Scheme I with the synthesis of L-lactate from pyruvate. A 2-L, three-necked, round-bottomed flask containing a stirring bar and attached to an argon line was used as the reaction vessel. The working electrode was 40 ft of coiled tungsten wire[9] (0.030-in. diameter, surface area approximately 300 cm^2) and the reference electrode was an unexceptional SCE. The counter electrode was 3 ft of coiled platinum wire (0.040-in. diameter), separated from the working solution by a porous ceramic Soxhlet extraction thimble (VWR) inserted in the center neck of the flask. During electrolysis, the solution in the anode compartment was purged with a slow stream of Ar to remove any O_2 formed.[10] The flask was charged with 500 mL of imidazole (Im)–H_2SO_4 buffer (50 mM, pH 7.8). D,L-Lipoamide (2.05 g, 10 mmol),[11] DTT^{ox} (1.52 g, 10 mmol), sodium pyruvate (0.55 g, 5 mmol), and xanthine (0.3 g, 2 mmol)[12] were added, and the solution was readjusted to pH 7.8. LipDH (EC 1.6.4.3, from torula yeast) and L-LDH (EC 1.1.1.27) were coimmobilized in PAN gel:[13] 140 mL of swollen gel added to the reactor contained 340 U (μmol min^{-1}) of LipDH and 460 U of L-LDH. NAD (0.14 mmol) was added, the potential of the tungsten electrode was adjusted to −1.0 V (vs. SCE), and sodium pyruvate (14.3 g, 130 mmol, in 100 mL of Im·H_2SO_4 buffer) was added at 1.5 mmol h^{-1}. Reaction was complete in 3.5 days; under these conditions the cathodic reduction of disulfides was overall rate limiting, at least at the start of the reaction.[14] The gel was allowed to settle, the supernatant decanted, and the lactic acid produced isolated as its zinc salt as described previously[15] (13.8 g, 96% pure, 115 mmol, 85% yield based on pyruvate, 96% ee). The turnover numbers[16] (and recovered activities) of the components were as follows: LipDH, 2.6×10^7 (88%); L-LDH, 3.6×10^7 (90%); NAD, 920; Lip, 13. No effort was made to recover Lip or NAD. Only approximately 5% of the NAD(H) originally added to the reaction mixture remained active at the conclusion of the reaction; most of the Lip was still present in active form.

This synthesis demonstrates one practical procedure for the electrochemical regeneration of NAD. The efficient reduction of stable disulfides to strongly reducing dithiols represents a new electrochemical reaction and should be useful in other areas of enzymology, especially in protection of enzymes against autoxidation. The isolation of enantiomerically enriched product establishes that the ultimate reduction step—pyruvate to L-lactate—is enzymatic. The immobilization of the enzyme seems to be important to the success of the procedure: immobilization protects the enzymes against deactivation at the electrode surface and protects the electrode surface against poisoning by adsorbed proteins.

The present limitations of this regeneration procedure are that the system is specific for NAD,[17] that the turnover number achieved for NAD is lower by factors of 2–5 than those observed in comparable preparations of L- or D-lactic acid using purely enzymatic regeneration systems[15,18,19] (probably because of electrochemical reduction of NAD to a biologically-inactive product), and that, in common with many electrochemical syntheses, the reaction is complicated by the equipment required.

Acknowledgment. This research was supported by the National Institutes of Health (GM 26543) and the National Science Foundation (80-12722 CHE and DMR 78-24185). We thank our colleague Bob DiCosimo for measurements of H_2 overvoltage.

Registry No. NADH, 58-68-4; NAD, 53-84-9.

(8) Szajewski, R. P.; Whitesides, G. M. *J. Am. Chem. Soc.* **1980**, *102*, 2011–2026. The equilibrium constant for reduction of NAD to NADH by DTT^{red} is ~1.3.

(9) Molybdenum is also an effective cathode for disulfide reduction but gives lower current efficiencies than tungsten.

(10) The anodic products of reaction were not identified.

(11) The presence of Lip^{ox} in large excess (5–10 times the solubility of Lip^{ox} in the buffer employed) resulted in greater selectivity of the tungsten cathode against NAD and pyruvate reduction.

(12) Inclusion of nitrogen heterocycles (nicotinamide, nicotinic acid, AMP, adenine, xanthine) in the reaction mixture substantially reduced the rate of cathodic reduction of NAD, probably by competition for sites active for the reduction of heterocycles on the electrode surface (see Bresmahan et al.[1]).

(13) Pollak, A.; Blumenfield, H.; Wax, M.; Baughn, R. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1980**, *102*, 6324–6336.

(14) This method of conducting the reaction results in a high steady-state value for [NAD]/[NADH]. NAD is intrinsically more stable than NADH under these solution conditions but more rapidly destroyed by cathodic reduction.[15] We believe that electrochemical reduction limits the lifetime of NAD(H) in this system.

(15) Wong, C.-H.; Whitesides, G. M. *J. Am. Chem. Soc.*, **1981**, *103*, 4890.

(16) Turnover number = mole of lactate isolated per mole of enzyme (cofactor).

(17) Williams, C. H., Jr., In "The Enzymes", 3rd ed.; Academic: New York, 1976; Vol. 13, pp 106–129.

(18) Wong, C.-H.; Daniels, L.; Orme-Johnson, W.; Whitesides, G. M. *J. Am. Chem. Soc.*, manuscript submitted (H_2/hydrogenase).

(19) Shaked, Z.; Whitesides, G. M. *J. Am. Chem. Soc.* **1980**, *102*, 7104–7105 (formate/formate dehydrogenase).

Ze'ev Shaked, James J. Barber
George M. Whitesides*
Department of Chemistry
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139
Received July 31, 1981

A Stereoselective Approach to Acyclic Systems via Condensations of α-Lithiosulfinyl Carbanions and Aldehydes

Summary: The stereochemical outcome of condensations of α-lithiosulfinyl carbanions with aldehydes is presented, and demonstrates useful methodology for generating 1,2-asymmetry, as well as construction of 1,3-asymmetric relationships in acyclic systems.

Sir: Development of synthetic methodology for relative asymmetric induction has been recognized as a challenging problem in the chemistry of complex acyclic molecules. In part, as an outgrowth of interest in the synthesis of ionophore antibiotics, new methods have recently demonstrated relative asymmetric induction in acyclic systems.[1] Although a number of procedures establish 1,2-asymmetry,[2] construction of 1,3-asymmetric relationships presents

(1) For an excellent review on acyclic stereocontrol, see: Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2.

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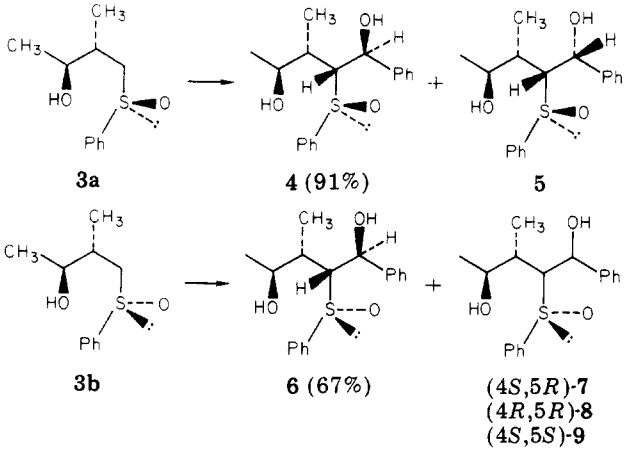
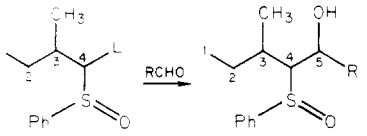
Scheme I



a more difficult problem.[3] Our explorations of condensations of α-sulfinyl carbanions with aldehyde substrates demonstrate a useful strategy for developing relative stereochemistry for acyclic molecules.

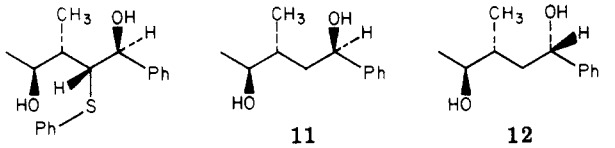
From the outset, we had anticipated that α-sulfinyl carbanions, such as 1, would undergo condensations with aldehydes, yielding the β-hydroxy sulfoxides 2, thus generating two asymmetric centers at C-4 and C-5 with a stereoselective attack controlled by the chirality at sulfur.[4]



Recent reports presenting some simple examples of condensations of chiral sulfoxides with aldehydes were encouraging.[5] However, the role of an additional feature of asymmetry at the β-position to sulfur, while of paramount importance for control of relative asymmetry, was clearly difficult to assess.[6]

The racemic sulfoxides **3ab** were prepared as a diastereomeric mixture by oxidation of the corresponding sulfide,[7] and after a simple chromatographic separation, each isomer was rapidly deprotonated with lithium diisopropylamide (2 equiv) in tetrahydrofuran at −78 °C (1 min). Quenching the α-sulfinyl carbanion with benzaldehyde (stirring 30 s) followed by addition of aqueous ammonium chloride at −78 °C led to a mixture of adducts, which were separated and characterized. Thus, sulfoxide **3a** gave adducts **4** and **5** in 85% isolated yield in a 91:9 ratio, whereas the diastereomer **3b** gave four adducts, **6**, **7**, **8**, and **9**, in 94% yield of 67:17:13:3 composition, respectively (Scheme I).

Longer reaction times for deprotonation and condensation did not alter product ratios. Although proton magnetic resonance spectra of each isomer displayed distinctive chemical shifts and coupling constants for the methine hydrogens at C-3, C-4, and C-5, assignments of stereochemistry using these data were not initially feasible. An X-ray crystallographic analysis of major product **4** revealed the stereochemical features as illustrated,[8] and further reductive transformations led to the assignments of all stereoisomers. Thus, the major condensation products **4** and **6** resulting from diastereomeric sulfoxides **3ab** gave the same sulfide **10** upon reduction with borane in tetrahydrofuran (25 °C, 24 h, 95%). Desulfurizations with Raney nickel at 22 °C in absolute ethanol proceeded in high yields (90–96%) and demonstrated that **4**, **6**, and **9** each afforded the same diol **11**, while isomer **12** was produced by reduction of **5**, **7**, and **8**. Likewise reduction of **5** and **8** gave identical sulfides, whereas each of the phenyl sulfides from **7** and **9** were stereochemically unique.[9]



In similar fashion, condensations of racemic sulfoxides **13ab**, which have inverted configuration of the β-methyl substituent at C-3, afforded 85–90% yields with benzaldehyde, and as before, studies of stereochemical relationships among the products led to assignments as indicated in Scheme II.[9] Note that major products, **14** and **16**, as well as **4** and **6** from Scheme I, share the *same relative stereochemistry along the carbon backbone, in spite of the inversions of sulfoxide configuration.* These reactions illustrate an interesting reversal of the usual

(2) Some recent developments presenting different synthetic strategies for 1,2-asymmetry: Still, W. C.; Schneider, J. *Tetrahedron Lett.* **1980**, 1035. Hasan, J.; Kishi, Y. *Ibid.* **1980**, 4229. Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099. Isobe, M.; Kitamura, M.; Goto, T. *Tetrahedron Lett.* **1980**, 4727. Yamamoto, Y.; Yatagai, H.; Naruta, Y.; Maruyama, K. *J. Am. Chem. Soc.* **1980**, *102*, 7107.

(3) Bartlett, P. A.; Jernsedt, K. K. *J. Am. Chem. Soc.* **1977**, *99*, 4829. Still, W. C.; Darst, K. P. *Ibid.* **1980**, *102*, 7385.

(4) For a review, see: Durst, T.; Viau, R. *Intra-Sci. Chem. Rep.* **1973**, *7*, 63.

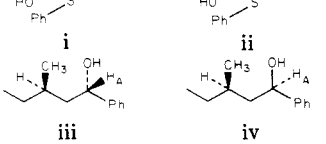
(5) Miokowski, C.; Solladie, G. *Tetrahedron* **1980**, *36*, 227. Farum, D. G.; Veysoghu, T.; Cardé, A. M.; Duhl-Emswiler, B.; Pancoast, T. A.; Reitz, T. J.; Cardé, R. T. *Tetrahedron Lett.* **1977**, 4409. Colombo, L.; Gennari, G.; Scolastico, C. *Chem. Commun.* **1979**, 591.

(6) The stereoselective alkylation of β-aminoalkyl sulfones has been reported; Eisch, J. J.; Galle, J. E. *J. Org. Chem.* **1980**, *45*, 4534. For stereoselective reactivity of β-oxido ylides, see: Corey, E. J.; Ulrich, P.; Venkateswarlu, A. *Tetrahedron Lett.* **1977**, 3231.

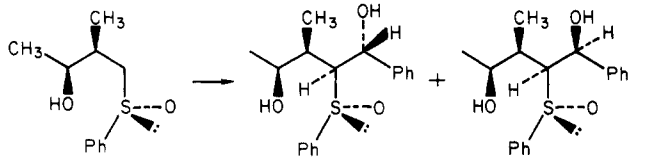
(7) Sodium *m*-periodate in aqueous methanol–tetrahydrofuran (80:20 by volume) at 22 °C for 16–24 h gave yields of 85–95%.

(8) Structure **4** was determined as its diacetate by single crystal analysis (−172 °C). Crystal data are: space group $P2/a$; a = 7.139 (4), b = 34.280 (4), c = 8.366 (4) Å, β = 97.29 (3)°, Z = 4. The structure was solved by direct methods, using 2867 intensities of amplitudes ≥2.33(I) as obtained from θ–2θ scan techniques using Mo K_α radiation. Experimental detail and data reduction were previously described (Huffman, J. C.; Lewis, L. N.; Caulton, K. G. *Inorg. Chem.* **1980**, *19*, 2755). Atoms were located (including hydrogens) and refined by full-matrix techniques to final residuals of $R(F)$ = 0.046 and $R_w(F)$ = 0.055. Complete crystallographic data are available from Indiana University Chemistry Library, Molecular Structure Center Report 8041.

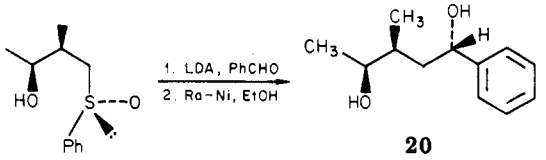
(9) All products were fully characterized by infrared, nuclear magnetic resonance, and mass spectral analysis. Two diagnostic features, which seem especially noteworthy for recognition of stereochemical relationships, became apparent in the ^{1}H NMR spectra of our products from borane and Raney nickel reductions. In all cases, the "erythro" (R,S) relationship of methine hydrogens H_B and H_C in the sulfides (i) is indicated by substantial downfield chemical shift position (δ 0.5–0.2) of H_C by comparison to the corresponding "threo" (R,R) isomers (ii). For the diols, a 1,3-syn-(R,R) stereorelationship (iv) led to the observation of a distorted triplet for benzylic hydrogen H_A, whereas the 1,3-anti-(R,S) relationship (iii) gave rise to a clear doublet of doublets pattern for H_A. The proton spectra were recorded on 220- and 270-MHz instruments in $CDCl_3$ (0.1% Me_4Si) solutions. ^{1}H NMR data, while too extensive for inclusion here, has been submitted as supplementary material and will be presented in the full paper to follow for all compounds.



Scheme II



scheme for 1,2-asymmetric induction with attack of an asymmetric carbanion at a symmetrical carbonyl. Moreover, the carbon–sulfur bond is cleaved in nearly quantitative yield to provide for 1,3-asymmetric induction, in which the major adducts each display the 1,3-substituents in an anti relationship (as illustrated in the extended or zig-zag conformations). Thus, pure diol **11** is produced in 74% yield in two steps from starting sulfoxide **3a**, and likewise diol **20** is prepared in 62% overall yield from sulfoxide **13a**.



The reaction products reveal an apparent preference of carbanion configuration which is dependent upon the asymmetry at the β-position (C-3) as well as the chirality of sulfur. A rationale for this behavior is not well understood and deserves detailed mechanistic studies. However, the general mode of addition of the carbanion to the carbonyl demonstrates the same preference for "erythro" orientations at C-4 and C-5 as in the case of phosphorous ylides, and other anion-carbonyl reactions which presumably *do not involve cyclic, chairlike, transition-state mechanisms with a preferred pseudoequatorial disposition of bulky substituents.*

Methodology has previously been reported which allows for preparation of olefins and epoxides from α-hydroxysulfoxides and sulfides with efficient stereocontrol.[10,11] Stereospecific eliminations can produce α,β-unsaturated sulfoxides of known configuration which may also serve as substrates for asymmetric synthesis.[12] Further novel applications and the use of this methodology for natural product synthesis are currently underway.

Acknowledgment. This work was supported by an NIH Biomedical Sciences Support Grant and, in part, by the National Institutes of Health (Award RO1 AI 17668). We acknowledge the M.H. Wruble Computing Center for use of computing facilities.

(10) Lythgoe, B.; Waterhouse, I. *Tetrahedron Lett.* **1977**, 4223. Mukaiyama, T.; Imaoke, M. *Chem. Lett.* **1978**, 413.
(11) Kano, S.; Yodomatsu, T.; Shibuya, S. *Chem. Commun.* **1978**, 785 and references therein.
(12) Tsuchihashi, G.; Mitamura, S.; Ogura, K. *Tetrahedron Lett.* **1976**, 855. Abbott, D. J.; Colonna, S.; Stirling, C. J. M. *J. Chem. Soc., Perkin Trans 1* **1976**, 492.

Registry No. (±)-**3a**, 78822-84-1; (±)-**3a** α-lithio, 78822-85-2; (±)-**3b**, 78855-50-2; (±)-**3b**- α-lithio, 78855-51-3; (±)-**4**, 78822-86-3; (±)-**5**, 78855-52-4; (±)-**6**, 78855-53-5; (±)-**7**, 78855-54-6; (±)-**8**, 78855-55-7; (±)-**9**, 78855-56-8; (±)-**10**, 78822-87-4; (±)-**11**, 78822-88-5; (±)-**12**, 78855-57-9; (±)-**13a**, 78855-58-0; (±)-**13b**, 78855-59-1; (±)-**14**, 78855-60-4; (±)-**15**, 78855-61-5; (±)-**16**, 78855-62-6; (±)-**17**, 78855-63-7; (±)-**18**, 78855-64-8; (±)-**19**, 78855-65-9; (±)-**20**, 78855-66-0; (±)-*threo*-4-(phenylthio)-3-methyl-2-butanol, 78837-34-0.

Supplementary Material Available: Tables of fractional coordinates, thermal parameters, bond distances, bond angles, and stereoscopic view; proton NMR information of sulfoxides (8 pages). Ordering information is given on any current masthead page.

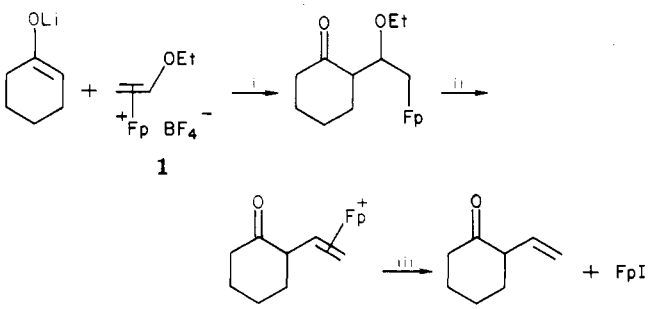
David R. Williams,* James G. Phillips
Department of Chemistry
Indiana University
Bloomington, Indiana 47405

John C. Huffman
Molecular Structure Center
Department of Chemistry
Indiana University
Bloomington, Indiana 47405
Received May 5, 1981

α-Isopropenylation of Ketones. Use of an Enol Ether–Iron Complex as an Isopropenyl Cation Equivalent

Summary: The complex $C_5H_5Fe(CO)_2$(ethyl isopropenyl ether)$^+BF_4^-$ functions as an isopropenyl cation equivalent in the isopropenylation of cyclohexanone enolates.

Sir: We recently reported the use of the organoiron complex **1** [$F_p = C_5H_5Fe(CO)_2$] for the synthesis of α-vinylcyclohexanones[1] through the sequence:



i, THF, −78 °C; ii, HBF_4, CH_2Cl_2, −78 °C; iii, NaI, acetone, 25 °C

Since the number of reagents which function as vinyl cation equivalents is comparatively limited,[2] we were prompted to extend the sequence above to the isopropenylation of ketones, especially as this C_3 unit is a strcutural feature common to many terpenes.[3] We now report the application of **2b** to the α-isopropenylation of ketones and illustrate its use in the efficient synthesis of isopiperitenone, isopulegone, and isoisopulegone.

The requisite cationic synthon **2**, like **1**, is readily prepared on a 10-g or larger scale and can be stored indefinitely at 0 °C. A detailed preparation of the methyl ether complex **2a** from bromoacetone dimethyl ketal has recently

(1) Chang, T. C. T.; Rosenblum, M.; Samuels, S. B. *J. Am. Chem. Soc.* **1980**, *102*, 5930.
(2) Kowalski, C. J.; Dung, J.-S. *J. Am. Chem. Soc.* **1980**, *102*, 7950.
(3) Devon, T. K.; Scott, A. I. "Handbook of Naturally Occurring Compounds"; Academic Press: New York, 1972; Vol. II.

0022-3263/81/1946-4103$01.25/0