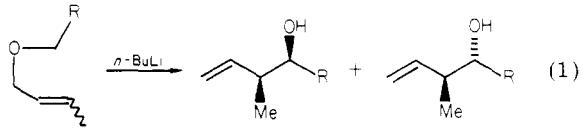
Acyclic Stereocontrol through Diastereo- and Enantioselective [2,3] Sigmatropic Wittig Rearrangements[1]

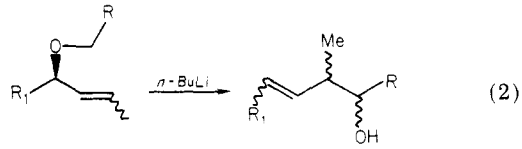
Summary: High diastereoselection and complete transfer of chirality is observed in the [2,3] Wittig rearrangements of optically active allyl (*Z*)-2-methylhex-4-en-3-yl ether. The acyclic stereoselection in the [2,3] Wittig rearrangement of other (*E*)- and (*Z*)-allylic ethers is also examined.

Sir: Over the last several years considerable progress has been achieved in controlling acyclic stereochemistry.[2] Recently the [2,3] sigmatropic rearrangement has been used for stereochemical control with a high degree of success.[3] The [2,3] Wittig rearrangement of primary allylic ethers examined intensively by Nakai (eq 1),[4] can be



(1)

highly diastereoselective. However, the ability to control olefin geometry, diastereoselectivity, and chirality transfer in the secondary allic ether systems (eq 2) had not been examined at the time that we commenced this study.[4e]

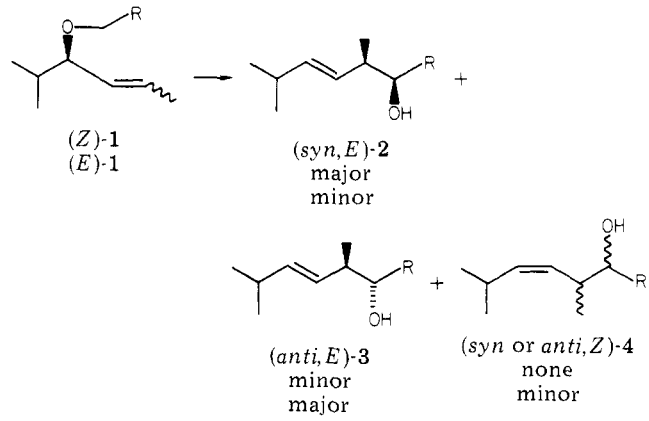


(2)

Our ability to produce secondary propargyl alcohols in high optical purity and our interest in the asymmetric synthesis of biologically active molecules encouraged us to investigate the stereoselectivity of this reaction. We now report that the [2,3] Wittig rearrangement of optically active (*Z*)-allylic ether **1a** provides allylic alcohol (3*R*,4*R*)-2a with complete control of olefin geometry and chirality transfer and a high degree of diastereoselectivity.

The olefin geometry and diastereoselectivity in the [2,3] Wittig rearrangement of racemic allylic ethers (*E*)- and (*Z*)-**1a–e** was examined (Scheme I).[5] The rearrangement was easily accomplished in tetrahydrofuran (THF) by using *n*-butyllithium as the base to give the alcohols in good yield.[6] Rearrangement of either the (*E*)- or (*Z*)-allylic ethers gives the (*E*)-olefin as either the exclusive or the major product.[7] All of the (*Z*)-allylic ethers examined exhibit syn stereoselection, whereas the (*E*)-allylic ethers

Scheme I[a]



[a] a, R = CH=CH$_2$; b, R = C(CH$_3$)=CH$_2$; c, R = Ph; d, R = C≡CH; e, R = C≡CSiMe$_3$.

Scheme II

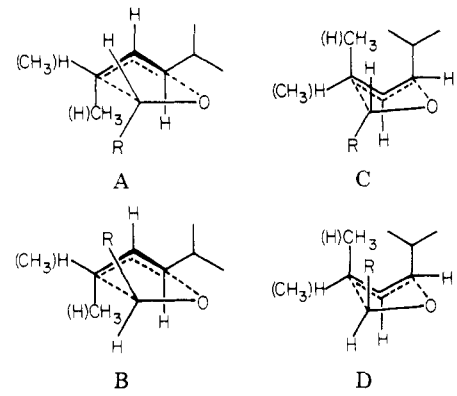


Table I. Stereoselectivity in the [2,3] Wittig Rearrangement

substrate	1*E*:1*Z*	yield, % (isolated)	stereoselectivity[a] 2/3/4
1a, R = CH=CH$_2$	0:100	84	92/8/0
	100:0	75	40/60/0
1b, R = C(CH$_3$)=CH$_2$	0:100	93	93/7/0
	100:0	89	40/50/10
1c, R = Ph	0:100	89	93/7/0
	100:0	95	20/62/18
1d, R = C≡CH[b]	0:100	89	91/9/0
	100:0	63	10/82/8
1e, R = C≡CSiMe$_3$	0:100	62	>98/2/0

[a] Ratio was determined by HPLC and confirmed by ^{1}H and/or ^{13}C NMR analysis (cf. ref 6). [b] Two equivalents of *n*-BuLi were used.

(1) Presented in part at the 184th National Meeting of the American Chemical Society, Washington, D.C., Aug 29–Sept 2, 1983.

(2) For reviews on stereoselective synthesis of acyclic compounds, see: (a) Masamune, S.; Choy, W. *Aldrichichimica Acta* **1982**, *15*, 47. (b) Evans, D. A.; Nelson, J. V.; Taber, T. R. In *Top. Stereochem.* **1982**, *13*, 1. (c) Heathcock, C. H. *Science (Washington, D.C.)* **1981**, *214*, 395. (d) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 555. (e) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 3 and references cited therein.

(3) (a) For a review on [2,3] sigmatropic rearrangements, see: Hoffman, R. W. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 563. (b) Still, W. C.; Mitra, A. *J. Am. Chem. Soc.* **1978**, *100*, 1927. (c) Chan, K.; Saucy, G. *J. Org. Chem.* **1977**, *42*, 3828. (d) Baldwin, J. E.; Patrick, J. E. *J. Am. Chem. Soc.* **1971**, *93*, 3556.

(4) (a) Mikami, K.; Kimura, Y.; Kishi, N.; Nakai, T. *J. Org. Chem.* **1983**, *48*, 279. (b) Mikami, K.; Fujimoto, K.; Nakai, T. *Tetrahedron Lett.* **1983**, *24*, 513. (c) Sayo, N.; Kimura, Y.; Nakai, T. *Ibid.* **1982**, *23*, 3931. (d) Nakai, T.; Mikami, T.; Taya, S.; Fujita, Y. *J. Am. Chem. Soc.* **1981**, *103*, 6492 and references cited therein. (e) An enantioselective [2,3] Wittig rearrangement was also reported at the American Chemical Society meeting by Nakai.[1] (f) Sayo, N.; Azuma, K.; Mikami, K.; Nakai, T. *Tetrahedron Lett.* **1984**, *25*, 565.

(5) The allylic ethers **1a–d** were easily prepared from (*E*)- and (*Z*)-allylic alcohols and allyl chloride, 2-methyl allyl chloride, benzyl chloride, and propargyl bromide, respectively, in the presence of sodium hydride in refluxing THF in good yield (70–95%). The (trimethylsilyl)propargyl allylic ether **1e** was prepared from **1d** via treatment with *n*-butyllithium followed by trimethylsilyl chloride.

(6) For the sake of clarity, we have used the prefixes syn and anti according to the nomenclature of Masamune: Masamune, S.; Ali, S.A.; Snitman, D. L.; Garvey, D. S. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 557. 200-MHz ^{1}H NMR data of the product and its isomers in Table I are as follows. Chemical shifts, not important in the structural determination, are omitted. **2a** (*syn,E*), 3.98 (t, 5.6 Hz); **3a** (*anti,E*), 3.78 (t, 7.1 Hz); **2b** (*syn,E*), 3.88 (d, 5.9 Hz); **3b** (*anti,E*), 3.66 (d, 8.3 Hz); **4b** (*syn* or *anti,Z*), 3.87 (d, 6.3 Hz); **2c** (*syn,E*), 4.55 (d, 5.9 Hz); **3c** (*anti,E*), 4.25 (d, 8.3 Hz); **4c** (*syn* or *anti,Z*), 4.43 (d, 7.3 Hz); **2d** (*syn,E*), 4.23 (dd, 4.9 and 2.0 Hz); **3d** (*anti,E*), 4.14 (dd, 6.4 and 2.0 Hz); **4d** (*syn* or *anti,Z*), 4.25 (m); **2e** (*syn,E*), 4.20 (d, 4.9 Hz). Ratios were determined by HPLC and confirmed by ^{1}H and/or ^{13}C NMR analysis.

(7) Previous examples show that [2,3] sigmatropic rearrangements of (*Z*)-allylic alcohol derivatives generally lead to (*E*)-olefins with a high degree of selectivity. Rearrangements of the (*E*)-allylic alcohol derivatives, however, give mixtures of (*E*)- and (*Z*)-olefins (cf. ref 3).

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show anti stereoselection.[8] The results are shown in Table I.

In order to study the chirality transfer in these systems, optically active (*R*),(*Z*)-**1a** and **1c** were prepared. Asymmetric reduction of 2-methyl-4-hexyn-3-one with *B*-3-pinanyl-9-borabicyclo[3.3.1]nonane (*R*-Alpine-Borane)[9] afforded (*R*)-2-methyl-4-hexyn-3-ol of 91% ee in good yield.[10] Partial hydrogenation of the secondary propargylic alcohol gave (*R*),(*Z*)-2-methyl-4-hexen-3-ol without detectable racemization.[11] The optically active (*R*),(*Z*)-allylic ethers **1a** ($[\alpha]^{24}_D$ −0.3° (*c* 2.28, THF)) and **1c** ($[\alpha]^{25}_D$ +10.60° (*c* 2.52, THF)) were easily prepared from the alcohol and allyl and benzyl chloride, respectively, in the presence of sodium hydride in refluxing THF.

The [2,3] Wittig rearrangement of (*R*),(*Z*)-allylic ethers **1a** and **1c** produced (*syn*,*E*)-**2a** and (*anti*,*E*)-**3a** in a 11:1 ratio and (*syn*,*E*)-**2c** and (*anti*,*E*)-**3c** in a 13:1 ratio, respectively. The assignment of syn and anti stereochemistry by NMR may be misleading.[12] Therefore, the relative and absolute stereochemistry was determined by conversion of optically active (*syn*,*E*)-**2c**[13] ($[\alpha]^{24}_D$ +15.67° (*c* 2.33, EtOAc)) to the known (2*S*,3*S*)-3-hydroxy-2-methyl-3-phenylpropanoic acid[14] and is in agreement with the prediction from the five-membered cyclic transition state.[3,4] NMR lanthanide shift study, Eu(hfc)$_3$, of the optically active (3*R*,4*R*),(*E*)-**2a** ($[\alpha]^{25}_D$ +29.89° (*c* 1.79, THF)) showed the alcohol was 91% ee. Since the enantiomeric purity is identical with that of the starting material the rearrangement proceeded with essentially 100% transmission of chirality.

The mechanism of this reaction is not fully understood.[3,4] Presumably the relative stereochemistry is fixed with a high degree of control by way of the five-membered cyclic transition state (Scheme II). For the rearrangement of (*Z*)-allylic ethers, the isopropyl group is less hindered in the equatorial position (transition states A and B) and leads to the (*E*)-olefin with a high degree of selectivity. The substituent *R* is also less hindered in transition state A and thus leads to (*syn*,*E*)-**2** as the major product. Due to the severe interactions in transition states C and D, none of the *cis*-olefin was observed. The reason for the poor diastereoselectivity observed with the (*E*)-allylic ether is somewhat less obvious and must await further information.[15] However, transition state A predicts the major product. In rearrangment of the optically active ether, the chirality of the starting material fully determines the face of double bond on which the new carbon–carbon bond forms (i.e., *re* face for (*R*),(*Z*)-**1a**).

The enantiomeric purity of the product (3*R*,4*R*)-**2a** is essentially the same as the enantiomeric purity of the α-pinene. Thus the chirality of the pinene is transferred to the two new centers of alcohol **2a** with nearly 100% efficiency. Since both enantiomers of optically pure α-pinene can be obtained and recycled,[16] both enantiomers of the optically pure **2a** should be available. The development of a more diastereoselective process and the application of this reaction to the synthesis of natural products are in progress.

Acknowledgment. We thank the Herman Frasch Foundation, administered by the American Chemical Society, the National Institutes of Health (GM24517), and the Cancer Research Coordinating Committee of the University of California for financial support.

(8) Previous examples show that [2,3] sigmatropic rearrangements of *Z* substrates exhibit syn stereoselection, whereas the *E* substrates show anti stereoselection (cf. ref 4).

(9) Reductions of alkynyl ketones with *R*-Alpine-Borane (prepared from 91.3% (+)-α-pinene and 9-BBN) always give (*R*)-propargyl alcohols. (a) Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A. *J. Am. Chem. Soc.* **1980**, *102*, 867. (b) Midland, M. M.; Graham, R. S. *Org. Synth.*, submitted for publication. (c) Brown, H. C.; Pai, G. G. *J. Org. Chem.* **1982**, *47*, 1606. (d) Midland, M. M.; Tramontano, A.; Kazubski, A.; Graham, R. S.; Tsai, D. J. S.; Cardin, D. B. *Tetrahedron*, in press.

(10) NMR lanthanide shift study with Eu(hfc)$_3$ showed the alcohol to be 95.6% *R* and 4.4% *S*, 91% ee. The absolute configuration was confirmed by conversion to the known β-methyl-γ-lactone (cf. ref 9d).

(11) (a) Lindlar, H.; Dubuis, R. *Org. Synth.* **1966**, *46*, 89. (b) Chan, K. K.; Cohen, N.; DeNobel, J. P.; Specian, A. C.; Saucy, G. *J. Org. Chem.* **1976**, 3497.

(12) Heng, K. K.; Simpson, J.; Smith, R. A. J.; Robinson, W. T. *J. Org. Chem.* **1981**, *46*, 2932.

(13) NMR lanthanide shift study of optically active (*syn*,*E*)-**2b** with Eu(hfc)$_3$ showed the alcohol was 88% ee.

(14) (a) Evans, D. A.; McGee, L. R. *J. Am. Chem. Soc.* **1981**, *103*, 2876. (b) Masamune, S.; Choy, W.; Kerdesky, F.; Imperiali, B. *J. Am. Chem. Soc.* **1981**, *103*, 1566. (c) Heathcock, C. H.; White, C. T.; Morrison, J. J.; Van Derveer, D. *J. Org. Chem.* **1981**, *46*, 1296.

(15) For example, the structure of the allylic anion may play an important role. Hartmann, J.; Muthukrishnan, R.; Sclosser, M. *Helv. Chim. Acta* **1974**, *57*, 2261.

(16) Brown, H. C.; Jadhav, P. K.; Desai, M. C. *J. Org. Chem.* **1982**, *47*, 4583. Enriched α-pinene is also available from Aldrich Chemical Co.

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Peroxide Radical Cations in Solution

Summary: Bicyclic bis(tertiary) peroxides **2** and **3** give long-lived radical cations at room temperature, despite their high oxidation potentials ($E^{\circ\prime}$ = 2.18 and 2.29 V vs. SCE, respectively). The ESR spectra of the radical cations are reported, and the reason for oxidation being so much harder for peroxides than for hydrazines is discussed.

Sir: Davies and co-workers[2a] suggested that the broad singlet ESR spectrum with g = 2.0091 detected upon photolysis of di-*tert*-butyl peroxide (**1**) in solvents containing trifluoroacetic acid was $\mathbf{1}^+$, and Symons and coworkers[2b] recently have obtained the g tensor components for radiolytically generated $\mathbf{1}^+$ in a $CFCl_3$ matrix at 77 K (g_{av} = 2.0084). We have recently observed ESR spectra of radical cations of dioxetanes from tetraalkyl-substituted olefins.[3] We report here that although $\mathbf{1}^+$ is unstable at room temperature, two tertiary dialkyl peroxides that have COOC angles held near 0° by bicyclic strutures give long-lived radical cations at room temperature, allowing measurement of the thermodynamically significant formal potential for electron loss ($E^{\circ\prime}$) by using cyclic voltammetry. Although electron removal is thermodynamically difficult, the radical cations of dihydroascaridole (**2**) and 1,5-dimethyl-6,7-dioxabicyclo[3.2.1]octane (**3**)[4] prove to be long-lived in 20:1:1 CH_2Cl_2:CF_3CO_2H:$(CF_3CO)_2O$.[5] The

(1) (a) University of Wisconsin. (b) University of Cincinnati.

(2) (a) Cookson, P. G.; Davies, A. G.; Roberts, B. P.; Tse, M.-W. *J. Chem. Soc., Chem. Commun.* **1976**, 1002. (b) Chandra, H.; Rao, D. N. R.; Symons, M. C. R. *J. Chem. Res. Synop.* **1983**, 68.

(3) Lopez, J. Ph.D. Thesis, University of Basel, 1982. Kapp, D. L., unpublished work.

(4) Wilson, R. M.; Rekers, J. W. *J. Am. Chem. Soc.* **1981**, *103*, 206.

(5) Cyclic voltammetry blanks in CH_2Cl_2 show substantial current above +2 V vs. SCE. Addition of trifluoroacetic acid and anhydride (see Hammerich, O.; Parker, V. D. *Electrochim. Acta* **1973**, *18*, 537) allows scanning to much higher potential, presumably because of removal of trace impurities.

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