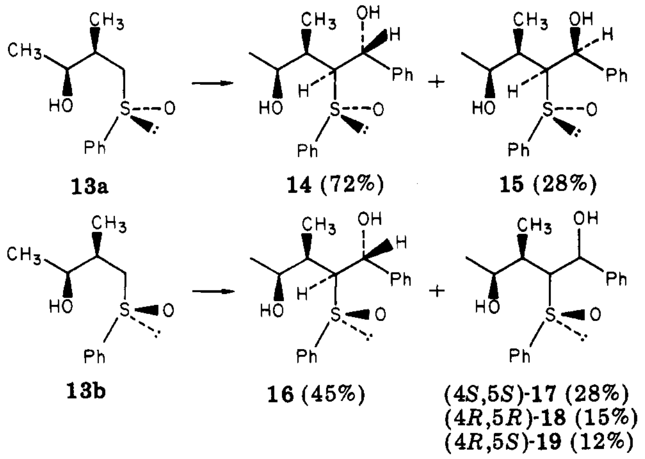
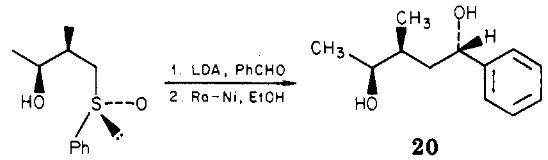
Scheme II



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.

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

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[10] Lythgoe, B.; Waterhouse, I. *Tetrahedron Lett.* **1977**, 4223. Mukaiyama, T.; Imaoke, M. *Chem. Lett.* **1978**, 413.

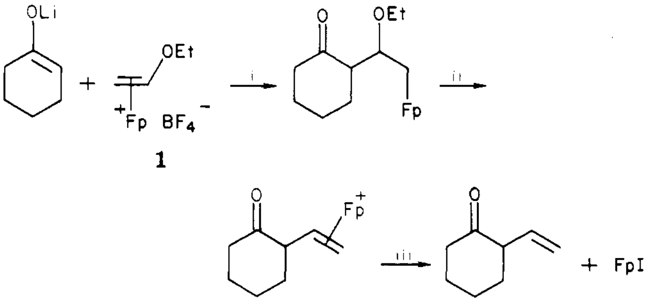
[11] Kano, S.; Yodomatsu, T.; Shibuya, S. *Chem. Commun.* **1978**, 785 and references therein.

[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.

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

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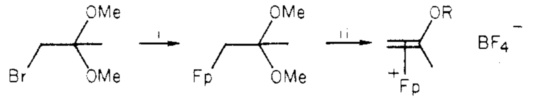
[1] Chang, T. C. T.; Rosenblum, M.; Samuels, S. B. *J. Am. Chem. Soc.* **1980**, *102*, 5930.

[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.

been given by Abram and Baker[4] (eq 1).

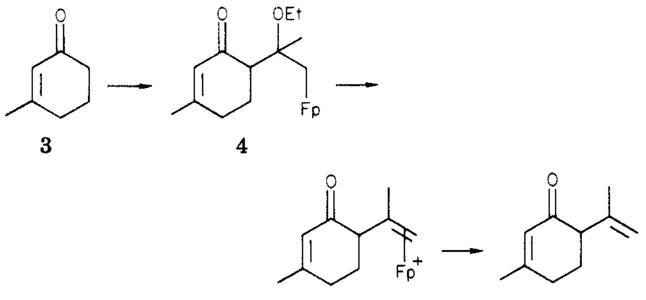


2a, R = Me
b, R = Et

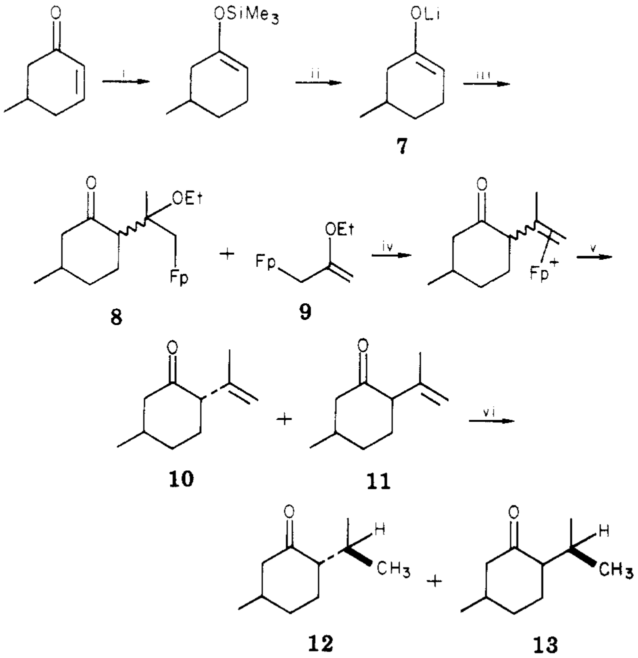
i, NaFp, THF, 0-25 °C; ii, HBF_4, THF, −78 °C; Et_2O

Since **2a** functions competitively with nucleophiles as a methylating reagent, it is advantageous to use the ethyl ether complex **2b** instead in the vinylation sequence. The latter may be prepared either from the bromo diethyl ketal, or from **2a** itself by dissolution in ethanol–acetone solution, concentration, and precipitation of the exchanged product with ether.[5]

Isopiperitenone, previously obtained in low yield along with carvone by oxidation of limonene,[6] is readily prepared from 3-methyl-2-cyclohexenone (**3**). The kinetic enolate, prepared from **3** and lithium diisopropylamide in THF, smoothly reacts with **2b** at −78 °C for 1 h to give the adduct **4**[7] in 93% yield after purification by chromatography on alumina. Treatment of **4** in methylene chloride solution at −78 °C with $HBF_4{\cdot}Et_2O$ gave the salt **5** (91%),[8] and this was demetalated by exposure to tetraethylammonium bromide in methylene chloride at room temperature for 30 min. Purification of the product by Kugelrohr distillation gave isopiperitenone (**6**, 95%, identified by ^1H NMR spectral comparison with that in literature.[9]



3 **4** **5** **6**

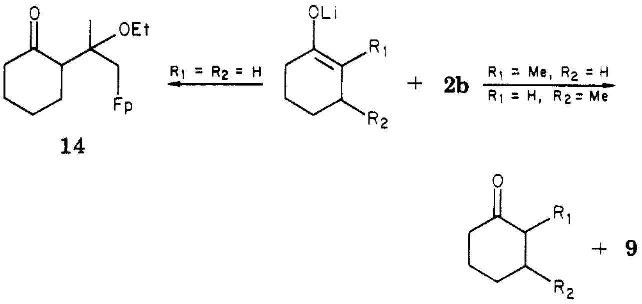


7 **8** **9** **10** **11** **12** **13**

i, Me_3SiH, $Rh(PPh_3)_3Cl$, PhH, 65 °C, 6 h; ii, BuLi, THF, 25 °C; iii, **2b**, −78 °C, 3.5 h; iv, $HBF_4{\cdot}Et_2O$, CH_2Cl_2, −78 °C, 0.3 h; Et_2O; v, NaI, acetone, 25 °C, 0.5 h; vi, Pd/C, H_2

A mixture of isopulegone and isoisopulegone[10] is similarly prepared by isopropenylation of lithium 5-methylcyclohexanone enolate (**7**), obtained by desilylation of the corresponding silyl ether. The latter was conveniently prepared by hydrosilation[11] of 5-methyl-2-cyclohexenone[12] in the presence of Wilkinson's catalyst. The adduct **8**, obtained as a mixture of stereoisomers, was freed chromatographically from **9**, the product of proton transfer, and isolated in 60% yield. Conversion of **8** through low-temperature protonation and demetalation gave a mixture of isopulegone (**10**) and isoisopulegone (**11** 88%). These were characterized by hydrogenation over palladium on carbon to give a 5:2 mixture of menthone (**12**) and isomenthone (**13**), identified by comparison of their ^{13}C NMR spectra with those in the literature.[13]

Alternatively, advantage may be taken of the observation that hindered enolates react with **2b** by proton transfer to give **9** rather than alkylation product. Thus, while cyclohexanone lithium enolate reacts with **2b** to give the adduct **14** (77%),[14] both 2- or 3-methylcyclohexanone enolates afford only **9** and the corresponding ketone on treatment with **2b**.[15]



14

Treatment of 3-methylcyclohexanone with either lithium tetramethylpiperidide or trityllithium[16] at −78 °C gives a

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[4] Abram, T. S.; Baker, R. *Synth. React. Inorg. Met-Org. Chem.* **1979**, *9*, 471.

[5] Other primary and secondary ethers may be obtained in this way, among them allyl, cyclohexyl, neopentyl, and L-menthyl.

[6] Dauben, W. G.; Lorber, M.; Fullerton, D. S. *J. Org. Chem.* **1969**, *34*, 3587.

[7] IR (CH_2Cl_2) 1995, 1940 (C≡O), 1710 cm^{-1} (C=O); NMR $CDCl_3$) δ 4.8 (s, 5, Cp), 3.5–3.1 (m, 2, OCH_2Me), 1.9 (s, 3, $CH_3C{=}$), 1.10 (s, 3, CH_3CO), 1.14 (t, 3, J = 7 Hz, OCH_2CH_3).

[8] This material is obtained as a thermally unstable yellow solid which isomerizes rapidly to the carbonyl coordinated complex. IR (CH_2Cl_2) 2080, 2020 (C≡O), 1580 cm^{-1} ($C{=}O{\cdots}{}^{+}Fp$). Foxman, B. M.; Klemarczyk, P. T.; Liptrot, R. E.; Rosenblum, M. *J. Organometal. Chem.* **1980**, *187*, 253.

[9] Tori, K.; Horibe, I.; Shigemoto, H.; Umemoto, K. *Tetrahedron Lett.* **1975**, 2199. NMR ($CDCl_3$) δ 5.92 (m, 1, H-2), 4.96 (m, 1, H-8), 4.77 (m, 1, H-8), 2.97 (t, 1, J = 8 Hz, H-6), 1.95 (s, 3, CH_3), 1.76 (s, 3, CH_3).

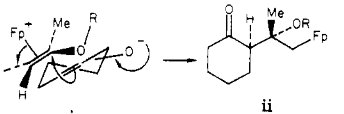
[10] Ohloff, G.; Osiecki, J.; Djerassi, C. *Helv. Chim. Acta* **1962**, *95*, 1400. Hawkes, G. E.; Herwig, K.; Roberts, J. D. *J. Org. Chem.* **1974**, *39*, 1017.

[11] Iwo, O.; Kogure, T. *Tetrahedron Lett.* **1972**, 5035.

[12] Blanchard, J. P.; Goering, H. L. *J. Am. Chem. Soc.* **1951**, *73*, 5863.

[13] Geoffrey, E.; Hawkes, K. H.; Roberts, J. D. *J. Org. Chem.* **1974**, *34*, 1017.

[14] The adduct **14** is obtained as a mixture of diastereomers (84:16) on the basis of a ^{13}C NMR spectrum of the product. The related neopentyl isopropenyl ether complex **2** (R = neopentyl) shows greater diastereoselectivity (ratio of isomers 96:4). On this basis the major diastereomer is tentatively assigned structure ii, assuming orientation of reacting components in the activated complex to be that shown in i, and with the larger OR group exo to the enolate ring.



i ii

[15] The less sterically demanding cation **1**, which is also not capable of proton transfer, reacts normally with these crowded enolates.

mixture of regioisomeric enolates of which only **7** is alkylated by **2b**. Employing these bases, the adduct **8** was obtained in 71 and 53% yield, respectively, after chromatography on activity IV, neutral alumina with ether–petroleum ether (5:95). Finally, it is convenient, but not essential, to isolate and purify the adducts from the initial alkylation reaction. A detailed procedure given below for the preparation of **10** and **11** illustrates this point.

A solution of lithium 2,2,6,6-tetramethylpiperidide, prepared from 7.2 g (0.05 mol) of amine and *n*-butyllithium in 100 mL of THF, was cooled to −78 °C and 5.6 g (0.05 mol) of 3-methylcyclohexanone was added dropwise. The enolate solution was then transferred by canula to a slurry of **2b** (17.2 g, 0.05 mol) in 100 mL of THF cooled to −78 °C. After 3.5 h, the solution was allowed to warm to 25 °C, THF was removed, and the residue was taken up in ether. Ether was removed and the residue was taken up in methylene chloride. This was cooled to 0 °C and then treated with 7 mL of 48% aqueous HBF_4 (0.05 mol), dissolved in 40 mL of acetic anhydride. Reaction was continued for 30 min at 0 °C and then 500 mL of ether was added. The red oily product, which separated, was washed with ether and then taken up in 100 mL of acetone and treated with 7.5 g (0.05 mol) of sodium iodide for 30 min. Acetone was removed in vacuo and the residue was extracted with ether. The ether solution was concentrated to 10 mL, petroleum ether (200 mL) was added, and the solution was filtered. Removal of solvent and Kugelrohr distillation of the residue (0.1 mm, 25–60 °C) gave 3.5 g (46%) of a mixture of **10** and **11** (2:1) as a pale yellow oil.

Further applications of Fp(vinyl ether)BF_4 salts in synthesis are being pursued.

Acknowledgment. This work was supported by a grant from the National Institutes of Health (GM-16395).

Registry No. 2b, 78782-37-3; **3**, 1193-18-6; **4**, 78782-38-4; **5**, 78782-40-8; **6**, 529-01-1; **7**, 78782-00-0; **8**, 78782-41-9; **9**, 78782-42-0; **10**, 29606-79-9; **11**, 52152-10-0; **12**, 89-80-5; **13**, 491-07-6; **14** (isomer 1), 78791-20-5; **14** (isomer 2), 78853-56-2; (2-methylcyclohexanone)lithium enolate, 13670-84-3; (3-methylcyclohexanone)lithium enolate, 54526-74-8; 2-methylcyclohexanone, 583-60-8; 3-methylcyclohexanone, 591-24-2.

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(16) Anthony, A.; Maloney, T. *J. Org. Chem.* **1972**, *37*, 1055. The kinetic ratio of 3-methyl to 5-methyl enolates with trityllithium in monoglyme was found to be 18:82.

Tony C. T. Chang, Myron Rosenblum*
Department of Chemistry
Brandeis University
Waltham, Massachusetts 02254

Received June 18, 1981

Interaction of Triphenylphosphine with 2,3-Dioxabicyclo[2.2.1]heptane

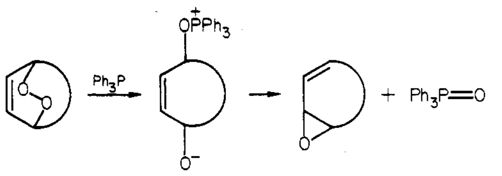
Summary: The reaction of triphenylphosphine with 2,3-dioxabicyclo[2.2.1]heptane resulted in the formation of a phosphorane that decomposed in the presence of water to give triphenylphosphine oxide and *trans*-1,3-cyclopentanediol.

Sir: The study of the interaction of triphenylphosphine (Ph_3P) with peroxides have been extensive. Peroxides that have been investigated include diacyl peroxides,[1] peresters,[2] dialkyl peroxides,[3] hydroperoxy endoperoxides,[4] ozonides,[5] and dioxetanes,[6] all of which react with formation of triphenylphosphine oxide and loss of one oxygen from the substrate. The reactions of Ph_3P with several unsaturated bicyclic peroxides have also been reported.[7] These reactions proceed by initial cleavage of the oxygen–oxygen bond followed by Sn2′ displacement to give the unsaturated epoxide and triphenylphosphine oxide (eq 1).

Table I. Rate Constants for the Reaction of Triphenylphosphine and Peroxides[a]

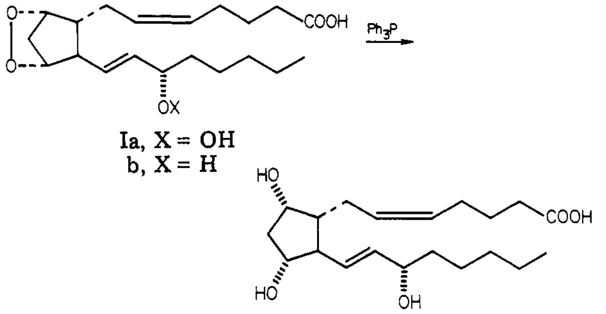
compound (X)	[X], M × 10^{-3}	$[Ph_3P]$, M × 10^{-3}	solvent	10^2k_2, M^{-1} s^{-1}
II	10	0.1	$CHCl_2$[b]	0.99 ± 0.06[c,d]
II	10	0.1	benzene[b]	0.93 ± 0.06[c,d]
IV[e]	6.6	70	benzene	100 ± 10[f]
IV[e]	6.1	65	benzene/CH_3CN	100 ± 10[f]

[a] Disappearance of Ph_3P was pseudo first order through at least 3 half-lives (T = 24 °C). [b] Distilled off of EDTA before use. [c] Disappearance of Ph_3P monitored by observing decrease in absorbance at 290 nm. [d] The rate constants are the average of three experiments. [e] IV = tetramethyldioxetane. [f] Reference 6.



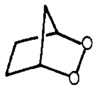
(1)

Hamberg and Samuelsson[8] in 1973 reported the first reactions of Ph_3P with two saturated bicyclic endoperoxides, PGG_2 and PGH_2 (I_a and $_b$). The product of the reactions was reported to be the cis 1,3-diol (eq 2). but no mechanistic details were given. We report here the first mechanistic study of the reaction of Ph_3P with a saturated bicyclic endoperoxide, the prostaglandin endoperoxide model compound, 2,3-dioxabicyclo[2.2.1]heptane[9] (II).



Ia, X = OH
b, X = H

(2)



II

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(1) (a) Greenbaum, M. A.; Denney, D. B.; Hoffmann, A. K. *J. Am. Chem. Soc.* **1956**, *78*, 2563. (b) Denney, D. B.; Greenbaum, M. A. *Ibid.* **1957**, *79*, 979.

(2) Denney, D. B.; Goodyear, W. F.; Goldstein, B. *J. Am. Chem. Soc.* **1961**, *83*, 1726.

(3) Denney, D. B.; Relles, H. M. *J. Am. Chem. Soc.* **1964**, *86*, 3897.

(4) Porter, N. A.; Funk, M. O.; Gilmore, D.; Isaac, R.; Nixon, J. *J. Am. Chem. Soc.* **1976**, *98*, 6000.

(5) Carles, J.; Fliszar, S. *Can. J. Chem.* **1969**, *47*, 1113.

(6) Bartlett, P. D.; Baumstark, A. L.; Landis, M. E.; Lerman, C. L. *J. Am. Chem. Soc.* **1974**, *96*, 5267.

(7) Balci, M. *Chem. Rev.* **1981**, *81*, 91.

(8) Hamberg, M.; Svensson, J.; Samuelsson, B. *Proc. Natl. Acad. Sci. U.S.A.* **1974**, *71*, 3400.

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