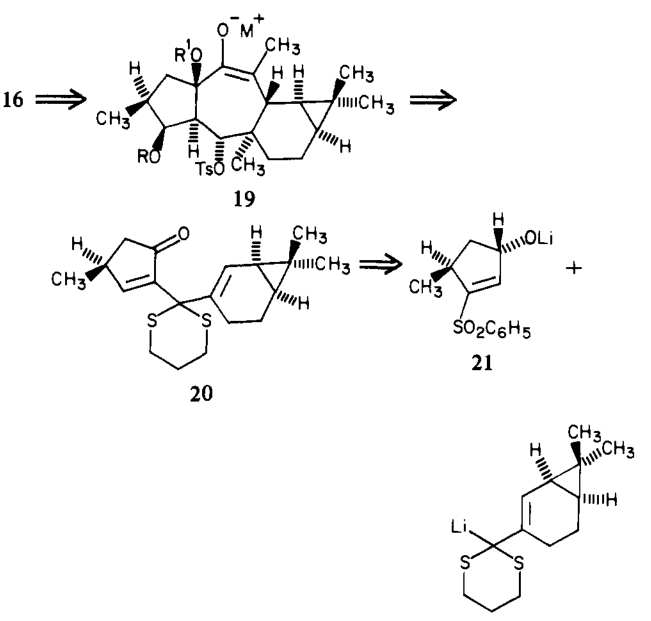
Scheme V



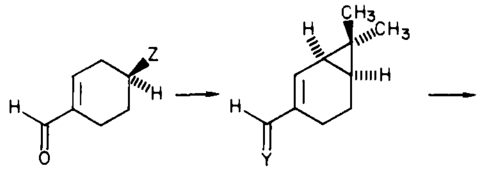
19

20

21

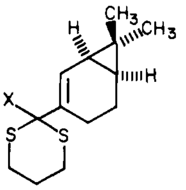
22

a quantitative yield of “crude” chloride **24a**[4,16] as a colorless oil. Tertiary halide **24a** was not further purified but dissolved in THF and added to a suspension of potassium *tert*-butoxide (107 mmol) in THF at 0 °C to afford a 94% yield of cyclopropyl aldehyde **25** [$[\alpha]^{25}_{D}$ +120° (*c* 1.50, $CHCl_3$)].[4,17] Aldehyde **25** had been previously prepared (41% yield) in an analogous manner from the very labile tertiary bromide **24b** by Büchi.[17] Treatment of **25** with 1,3-propanedithiol in the presence of a catalytic amount of boron trifluoride etherate (0.08 equiv) in methlene chloride produced dithiane **26a**[4] [$[\alpha]^{25}_{D}$ +26° (*c* 2.0, $CHCl_3$)] in 68% yield after purification by plug filtration on silica gel. Reaction of **26a** in THF at −78 °C with *n*-butyllithium for 1 h smoothly afforded anion **22** as evidenced by CH_3OD quenching studies to yield **26b** (90%).

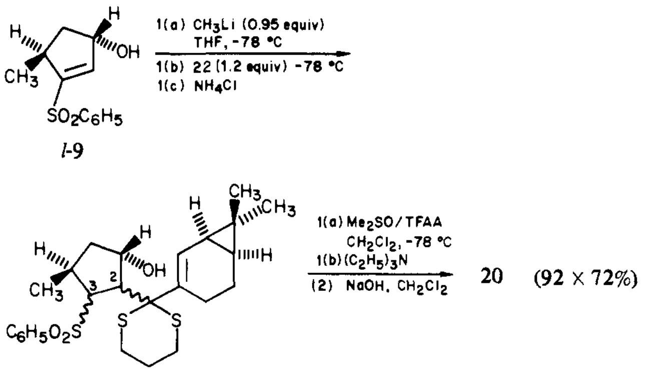


23, $Z = CCH_3{=}CH_2$
24a, $Z = C(CH_3)_2Cl$
b, $Z = C(CH_3)_2Br$

25, Y = 0
26, $Y = S(CH_2)_3S$



26a, X = H
22, X = Li
26b, X = D



27 (65%)

Treatment of *l*-**9** in THF at −78 °C with methyllithium (0.95 equiv) affords a solution of **21** which is further reacted with **22** (1.2 equiv) and quenched with ammonium chloride to provide a 65% yield of sulfone alcohol **27** after chromatographic purification[4,18] (stereochemistry at C-2 and C-3 undefined). Swern oxidation[19] and base treatment then affords chiral enone [$[\alpha]^{25}_{D}$ −48° (*c* 1.65, $CHCl_3$)].[4,20]

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research (11617-AC1). The ^{13}C NMR used in this investigation was obtained on the departmental CFT-20 instrument provided by NSF Grant 7842. We thank the Purdue University Biological Magnetic Resonance Laboratory for access to the 360-MHz ^1H NMR spectrometer (NIH RR01077).

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[16] Olefin **25** was inert to HCl addition in numerous other solvents.

[17] G. Büchi, W. Hofheinz, and J. V. Paukstelis, *J. Am. Chem. Soc.*, **91**, 6473 (1969). [$[\alpha]^{25}_{D}$ 108° (*c* 4.0, $CHCl_3$)].

[18] A small amount (ca. 15%) of γ addition of heteroallyl anion **22** to vinyl sulfone **21** is also observed in this reaction.

[19] S. L. Huang, K. Omura, and D. Swern, *J. Org. Chem.*, **41**, 3329 (1976).

[20] Reaction of *dl*-**9** with chiral **22** followed by oxidation and elimination affords a mixture of enones which are diasteromeric at the γ-methyl position [$[\alpha]^{25}_{D}$ 1.0° (*c* 0.95, $CHCl_3$)]. The only spectral characteristic which is diagnostic of this mixture is the quaternary vinyl carbon on the six-membered ring which can be observed in the ^{13}C NMR spectra. In the diastereomeric mixture this carbon appears as 1:1 pair of singlets at 134.9 and 134.7 ppm, while chiral enone **20** only exhibits the higher field peak. Control studies demonstrate that γ epimerization does not occur under the basic conditions necessary to β eliminate the phenylsulfinic acid in the synthesis of enone **20**.

Reaction of Allylically Substituted Enolates with Organometallic Reagents: A Convenient Source of Enolonium Ion Equivalents

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Received December 22, 1980

The importance of the enolate group in organic synthesis is largely attributable to its considerable service as a nucleophile in carbon–carbon bond-forming reactions.[1] We describe herein a new chemistry for allylically substituted enolates in which their classical role as a nucleophile in such reactions is reversed to that of an electrophile through a change only in reaction conditions.

The present study emerged from our interest in effecting the conversion of an α,β-epoxy ketone to an α-alkyl-β-hydroxy ketone, as generalized by **1** → **2** (Scheme I), with a starting substrate[2] whose attendant functionality attenuated the effectiveness of reductive alkylation methodology[3] and precluded the use of

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[†] A. P. Sloan Foundation Fellow, 1979–1981; Camille and Henry Dreyfus Teacher-Scholar Award Recipient, 1980–1985.

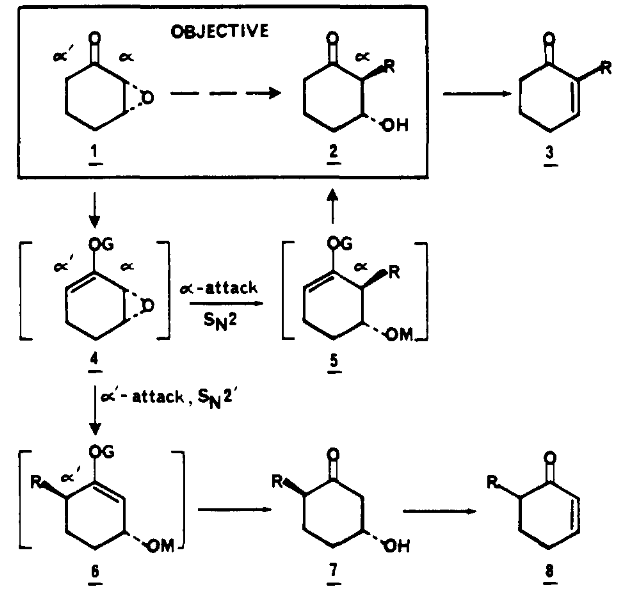
[1] d'Angelo, J. *Tetrahedron* **1976**, *32*, 2979. House, H. O., “Modern Synthetic Reactions”, W. A. Benjamin: Reading, MA, 1972; p 492 ff.

[2] Wender, P. A.; Lechleiter, J. C. *J. Am. Chem. Soc.* **1980**, *102*, 6340.

[3] (a) Szajewski, R. P. *J. Org. Chem.* **1978**, *43*, 1819. (b) McChesney, J. D.; Wypalek, A. F. *J. Chem. Soc., Chem. Commun.* **1971**, 542.

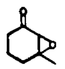
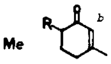
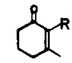
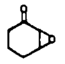
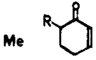
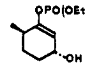
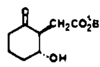
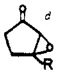
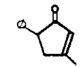
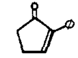
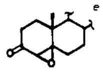
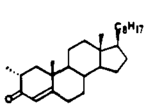
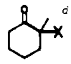
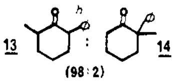
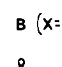
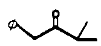
0002-7863/81/1503-2114$01.25/0

Scheme I



chemistry based on hydrazone and oxime derived enolonium ion (α-ketocarbonium ion) equivalents.[4] In the formulation of an alternative approach, it was reasoned[5] that an enol ether derivative (cf. **4**) of an epoxy ketone would function as a diene monoepoxide in its reactions with carbon nucleophiles to provide, depending on the type of nucleophile, the product(s) of S_N2 (α attack, cf. **5**) and/or S_N2' (α' attack, cf. **6**)[6] addition. In accord with this analysis, reaction of the readily prepared trimethylsilyl enol ether **4** (G = SiMe$_3$)[7-9] with Me$_2$CuLi provided, after hydrolysis of the initially formed hydroxy enol ether, 6-methylcyclohex-2-enone (**8**, R = Me) in 55% yield. While this result established a basis for a useful α'-substitution method,[10] it served a more significant purpose in lending credibility to an operationally more expedient and regiochemically versatile method. Specifically, since the ^{13}C NMR resonance for the α'-carbon of enol ether **4** (G = SiMe$_3$, δ 104.7) and that of the corresponding lithium enolate **4** (G = Li, δ 88.7)[11] suggest that the latter is only slightly more π-electron rich than the former,[12] it was expected that the commonly nu-

Table I

ENTRY	SUBSTRATE/ METHOD[a]	ORGANO-METALLIC	PRODUCTS	YIELD %
				
1:	A	Me$_2$CuLi	$\underline{9}$, R = Me  [b]	97 (GC)
2:	B	Me$_2$CuLi	$\underline{9}$, R = Me[b]	80 (GC)
3:	B	MeLi	$\underline{10}$, R = Me  [b]	93 (GC)
4:	A	ϕ_2CuLi	$\underline{9}$, R = ϕ[c]	95
5:	B	ϕ_2CuLi	$\underline{9}$, R = ϕ[c]	72
6:	B	ϕLi	$\underline{10}$, R = ϕ[c]	63
7:	B	ϕMgBr	$\underline{10}$, R = ϕ[c]	56
8:	A	//\MgBr·CuI (2:1)	$\underline{9}$, R = CH$_2$=CH–[b]	93
	 $\underline{1}$			
9:	A	Me$_2$CuLi	$\underline{8}$, R = Me  [b]	55 (GC)
10:	B	Me$_2$CuLi	$\underline{8}$, R = Me[b]	65 (GC)
11:	C	Me$_2$CuLi	$\underline{11}$ 	83
12:	B	MeLi	$\underline{3}$, R = Me[b]	99 (GC)
13:	B	ϕLi	$\underline{3}$, R = ϕ[c]	64
14:	B	LiCH$_2$CO$_2$^{t}Bu		65
	 [d]			
15:	B (R = Me)	ϕ_2CuLi		40
16:	B (R = H)	ϕLi		62
	 [e]			
17:	B	Me$_2$CuLi	 [b]	83
	 [d,e]			
18:	B (X = OCOϕ)	ϕ_2CuLi	$\underline{13}$  $\underline{14}$ [h] (98:2)	65
19:	B (X = Cl)	ϕ_2CuLi[f]	$\underline{13}$[h] : $\underline{14}$ (97:3)	34
20:	B (X = Cl)	ϕLi[f]	$\underline{13}$[h] : $\underline{14}$ (2:1)	32
	 [d]			
21:	B (X = OCOϕ)	ϕ_2CuLi[g]	$\underline{15}$ 	trace
22:	B (X = Cl)	ϕ_2CuLi	$\underline{15}$	44

[a] Method A: Corresponding trimethylsilyl enol ether[7] used as substrate. Method B: Corresponding enolate[7] used as substrate. Method C: Corresponding enol phosphate[7] used as substrate. [b] After TsOH/PhH (reflux, 15 min) dehydration. [c] After 3 N HCl/EtOH (1:1, 60 °C, 30 min) dehydration. [d] Reaction conducted at −45 °C, instead of −23 °C. [e] LiHMDS used as base. [f] ca. 2 equiv of base and 3 equiv of organometallic used. [g] Reaction warmed to room temperature before quenching. [h] cis/trans mixture. [i] Isolated yields unless otherwise noted.

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(4) (a) Corey, E. J.; Melvin, L. S.; Haslanger, M. F. *Tetrahedron Lett.* **1975**, 3117. (b) Fuchs, P. L. *J. Org. Chem.* **1976**, *41*, 2935. (c) Stork, G.; Ponaras, A. A. *Ibid.* **1976**, *41*, 2937.

(5) The basis for this reasoning is found in studies on the reaction of nucleophiles with enolizable α,β-epoxy and α-halo ketones, e.g., see: (a) Caton, M. P. L.; Darnbrough, G.; Parker, T., *Synth. Commun.* **1978**, *8*, 155. (b) Paisley, J. K.; Weiler, L. *Tetrahedron Lett.* **1972**, 261. (c) Cox, J. S. G. *J. Chem. Soc.* **1960**, 4508. (d) Bordwell, F. G.; Carlson, M. W. *J. Am. Chem. Soc.* **1970**, *92*, 3370, 3377.

(6) (a) Staroscik, J.; Rickborn, B. *J. Am. Chem. Soc.* **1971**, *93*, 3046. (b) Wieland, D. M.; Johnson, C. R. *Ibid.* **1971**, *93*, 3047. (c) Marino, J. P.; Floyd, D. M. *Tetrahedron Lett.* **1979**, 675.

(7) (a) A typical experimental procedure is as follows: a solution of the ketone[7b] in THF (ca. 1 M) was added dropwise over 7 min to a solution of ca. 1.2 equiv of LDA (unless otherwise noted) in THF (ca. 0.6 M) at −78 °C. The mixture was stirred for 0.5 h at −78 °C (at this point, the enolate could be diverted to enol ether formation, vide infra), followed by addition of the organometallic reagent (ca. 2.4 equiv), stirring at −23 °C for 2 h, and quenching with saturated NH$_4$Cl solution at 0 °C. The enol ethers were formed by addition of the appropriate chloride [Me$_3$SiCl or ClPO(OEt)$_2$] to the enolate at −78 °C and warming to 0 °C (over ca. 1 h). An aqueous quench, extractive workup, and flash column chromatography or distillation provided the desired product. Reactions of these enol ethers with organometallic reagents followed the procedure outlined above for enolates. The resulting hydroxy trimethylsilyl enol ethers could be isolated, if desired, with some loss due to hydrolysis. (b) Epoxy ketones were generally made according to: Wasson, R. L.; House, H. O., *Org. Synth.* **1957**, *37*, 58. It should be noted that 2,3-epoxycyclohexanone forms a hydrate indicated by a broad peak at δ 3.3 (CDCl$_3$) in the ^{1}H NMR. The water is most easily removed by azeotropic distillation.

(8) All new compounds were homogeneous by TLC and gave satisfactory NMR, IR, and UV spectra and exact mass analysis. GC yields and analyses were determined on a $^1/_8$-in. × 20-ft OV-210 column by using biphenyl as an internal standard.

(9) For a review of the uses of silyl enol ethers in synthesis, see: Rasmussen, J. K. *Synthesis* **1977**, 91.

(10) For independent studies on the reactions of silyl enol ethers with organometallic reagents, see: (a) Marino, J. P.; Hatanaka, N. *J. Org. Chem.* **1979**, *44*, 4467. (b) Sakurai, H.; Shirahata, A.; Araki, Y.; Hosomi, A. *Tetrahedron Lett.* **1980**, 2325. (c) Schlecht, Matthew Ph.D. Thesis, Columbia University, New York, 1980.

cleophilic enolate **4** would serve in the relatively unexplored role of an electrophile in the above reaction. Indeed, when the epoxy enolate **4** (G = Li) was treated with Me_2CuLi and the resulting product subjected to acidic hydrolysis, 6-methylcyclohex-2-enone (**8**, R = Me), the product of S_N2' attack, was obtained in 65% yield, free of any regioisomeric product. That the regiochemical course (S_N2 vs. S_N2') of this addition can be cleanly controlled by the type of organometallic reagent used was demonstrated by the reaction of the same epoxy enolate **4** (G = Li) with methyllithium which provided, after acidic workup, only the product of S_N2 addition, i.e., 2-methylcyclohex-2-enone (**3**, R = Me) in 99% yield.[13]

Further synthetic and mechanistic aspects of this chemistry are reflected, in part, in Table I. In general, it is seen that organocuprate reagents, irrespective of their hybridization, react in an S_N2' fashion with both epoxy enol ethers and epoxy enolates, while the corresponding organolithium and organomagnesium reagents react with the enolates to provide the products resulting from an S_N2 mode of attack. Of particular note in the latter group is the reaction of the lithium enolate of *tert*-butyl acetate with **4** (G = Li, Scheme I; cf. Table I, entry 14) which provides the basis for a convenient solution to the hydroxymethylene lactone problem associated with numerous natural products which exhibit cytotoxic activity.[14]

Several important substrate related variations are also revealed in the tabulated data and support studies. In general, this methodology is applicable to five- and six-membered ring systems. However, the change from cyclic to acyclic epoxy enolate substrates reveals an important mechanistic feature in that the latter, as evidenced in the case of the enolate of mesityl oxide epoxide, failed to react. Presumably, counterion coordination by the bidentate substrate results in an unfavorable orbital alignment between the enolate π system and the allylically disposed carbon-oxygen bond.[15] Variations in the leaving group can also be made (e.g., entries 18-22) although, once again, the acyclic system is unreactive if the group, such as benzoyloxy, can strongly coordinate the counterion. However, with a halide group, and presumably other weakly or noncoordinating groups, both acyclic and cyclic systems (i.e., α-halo ketone enolates) function equally well as enolonium ion equivalents. Finally, it is synthetically noteworthy that the group on oxygen can be widely varied. Thus, in addition to enolates and silyl enol ethers, the readily prepared enol phosphates[7] function as particularly effective substrates for cuprate reagents (Table I, entry 11). Since reduction of the hydroxy enol phosphate product **11** provides only *trans*-4-methylcyclohex-2-enol (**12**), the epoxy ketone functionality serves, through this chemistry, as a readily available cycloalkadiene monoepoxide equivalent whose reactions are stereo- and regiocontrolled. This regioselectivity is contrasted by the reaction of the parent cyclohexadiene monoepoxide with Me_2CuLi which provides allylic alcohol **12** as well as the product of S_N2 opening in a nearly regiorandom manner.[6a,b]

In summary, this chemistry provides a convenient source of enolonium ion, dienolonium ion, and diene monoepoxide equivalents which service a number of important objectives in synthesis.[16] Further studies on this fundamentally novel enolate chemistry are in progress.

Acknowledgment. This investigation was supported by Grant CA 21136, awarded by the National Cancer Institute.

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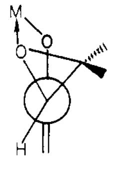
[11] The enol ether spectrum was recorded in THF at 25.2 MHz at ambient temperature. The enolate was prepared in a manner similar to that used for its reactions with organometallic reagents. The enolate showed only an insignificant temperature dependence of its chemical shifts from -60 to -20 °C.

[12] (a) House, H. O.; Prabhu, A. U.; Phillips, W. V. *J. Org. Chem.* **1976**, *41*, 1209. (b) Jackman, L. M.; Szeverenyi, N. M. *J. Am. Chem. Soc.* **1977**, *99*, 4954. (c) Meyer, R.; Gorrichon, L.; Maroni, P. *J. Organomet. Chem.* **1977**, *129*, C7. (d) Lauterbur, P. G. *Tetrahedron Lett.* **1961**, 274.

[13] The *trans*-3-hydroxy-2-methylcyclohexanone[4a] can be isolated by column chromatography with some loss due to dehydration.

[14] (a) Chavdarian, C. G.; Woo, S. L.; Clark, R. D.; Heathcock, C. H. *Tetrahedron Lett.* **1976**, 1769. (b) Grieco, P. A.; Nishizawa, M.; Burke, S. D.; Marinovic, N. *J. Am. Chem. Soc.* **1976**, *98*, 1612. (c) Danishefsky, S.; Schuda, P. F.; Kitahara, T.; Etheredge, S. J. *Ibid.* **1977**, *99*, 6066. (d) Kieczykowski, G. R.; Schlessinger, R. H. *Ibid.* **1978**, 100, 1938. (e) Iio, H.; Isobe, M.; Kawai, T.; Goto, T. *Ibid.* **1978**, 100, 1940.

[15] A reasonable representation of the unreactive chelated epoxy enolate is depicted below. Geometrical constraints preclude the formation of such chelated structures for the cyclic epoxy enolates.



[16] It is noteworthy that this method also allows for regiospecific generation of enolates as demonstrated by the trapping of **5** (G = M = Li) as its bis(trimethylsilyl) ether.

Temperature Dependence of Carbene-Carbene Rearrangements. A New Method for the Generation of Carbenes[1]

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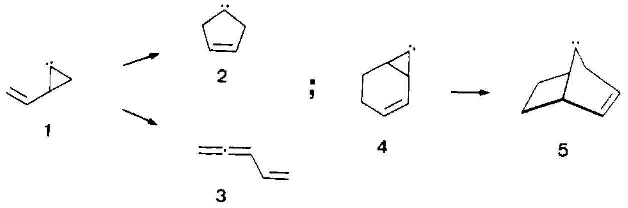
Received December 24, 1980

Among carbene-carbene rearrangements with a skeletal reorganization of the type **1** → **2**,[2] the 7-norcar-2-enylidene-7-norbornenylidene rearrangement **4** → **5**[3] is the least understood.



This reaction, discovered by Skattebøl,[3] is known to give *syn*-7-bromo-7-methylnorbornene (**6**) on treatment of 7,7-dibromonorcar-2-ene (**7**) with methyllithium at -78 °C as nearly the exclusive product. The mechanism for the stereoselective formation of **6** is still unsettled.[4] This rearrangement has recently been reinvestigated.[5,6] The decomposition of potassium *anti*-7-norcar-2-enediazotate[5] and 7-*exo*-norcar-2-ene-*N*-nitrosourea[6] in methanol gave *anti*-7-methoxynorbornene and *endo*-2-methoxytricyclo[4.1.0.$0^{3,7}$]heptane which probably derive from the 7-norbornenyl cation thought to arise from protonation of the re-

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[1] Carbene Rearrangements, part 7. Part 6: Brinker, U. H.; König, L. *J. Am. Chem. Soc.* **1981**, *103*, 212.

[2] (a) Skattebøl, L. *Chem. Ind.* (*London*) **1962**, 2146. (b) Kirmse, W. *Org. Chem.* (*N.Y.*) **1971**, *1*, 465. (c) Baird, M. S.; Reese, C. B. *Tetrahedron Lett.* **1976**, 2895. (d) Jones, W. M.; Brinker, U. H. In "Pericyclic Reactions"; Marchand, A. P., Lehr, R. E., Eds.; Academic Press: New York, 1977; pp 159-165. (e) Holm, K. H.; Skattebøl, L. *Tetrahedron Lett.* **1977**, 2347. (f) Butler, D. N.; Gupta, I. *Can. J. Chem.* **1978**, *56*, 80. (g) Schoeller, W. W.; Brinker, U. H. *J. Am. Chem. Soc.* **1978**, *100*, 6012. (h) Brinker, U. H.; Fleischhauer, I. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 396. (i) Jäggi, F. J.; Ganter, C. *Helv. Chim. Acta* **1980**, *63*, 214. (j) Schleyer, P. v. R.; Grubmüller, P.; Maier, W. F.; Vostrowsky, O.; Skattebøl, L.; Holm, K. H. *Tetrahedron Lett.* **1980**, 921. (k) Jones, W. H. *Org. Chem.* (*N.Y.*) **1980**, *42*, Chapter 3. (l) Brinker, U. H.; Fleischhauer, I. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 304.

[3] Skattebøl, L. *Tetrahedron* **1967**, *23*, 1107.

[4] However, for a related system see: (a) Warner, P.; Chang, S.-C. *Tetrahedron Lett.* **1978**, 3981. (b) *Ibid.* **1979**, 4141.

[5] Holm, K. H.; Skattebøl, L. *J. Am. Chem. Soc.* **1977**, *99*, 5480.

[6] Kirmse, W.; Jendralla, H. *Chem. Ber.* **1978**, *111*, 1873.

0002-7863/81/1503-2116$01.25/0