by base-specific chemical cleavage method of Maxam and Gilbert.[19] The nucleotide sequence of each oligomer was found to be as expected.

Acknowledgment. We are grateful to Eugene Nowoswiat for providing unpublished information regarding procedures used in solid support phosphite methodology and to Warren McComas for his help in sequencing the oligonucleotides.

Supplementary Material Available: Table I (proton NMR of **2a-f** and **3a-f**) and Table II (proton NMR of **5a-d** and **6a-r**) (3 pages). Ordering information is given on any current masthead page.

Stereochemistry of Dithianyllithium Addition to Cyclohexanone[1]

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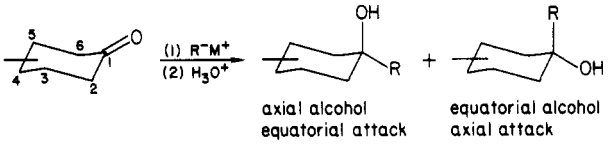
The reaction of 2-phenyl-1,3-dithianyllithium (1-Li) with 4-*tert*-butylcyclohexanone in cyclohexane and tetrahydrofuran may proceed either with kinetic or thermodynamic control. In the latter case carbinol formation involves exclusively equatorial attack. In contrast, only kinetic control is seen in the reaction of the same ketone with 1,3-dithianyllithium (2-Li) or its mono-*S*-oxide (3-Li). No addition but only enolate formation occurs in solvent hexamethylphosphoric triamide; with 1-[2-phenyl-2-(1,3-dithianyl)]-4-*tert*-butylcyclohexanol reversal of the addition reaction is seen in this solvent.

Introduction

In contrast to the significant effort dedicated to the study of the reduction of cyclohexanones by metal hydrides,[3,4] reports concerning the course of addition of organometallic compounds to give isomeric alcohols are limited.[5] This in spite of the fact that the addition of carbanions to ketones has important stereochemical aspects.



It is now well-established that the steric hindrance introduced by the axial hydrogens (or substituents) at C(3,5) tends to direct the nucleophile to approach the carbonyl from the equatorial side.[6] It is also clear that an opposing nonsteric factor may lead to a preference for axial attack.[3,4]

The nature of the second factor is not well understood. It has been suggested that the thermodynamic stability of the products,[7] the torsional strain engendered during equatorial approach,[8] the configuration of the frontier orbitals,[9,10] the hardness vs. softness of the nucleophile,[11] and the importance of two-electron stabilizing interactions[12,13] are responsible for the unexpected ratio of axial addition.

Table I. Products of the Reaction of 1-Li with 4 as a Function of Reaction Time

entry	solvent	time, h	5:6
1	THF	"zero"[a]	79:21
2	THF	1.5[a]	86:14
3	THF	4[b]	100:0
4	C_6H_{12}	"zero"[c]	76:24
5	C_6H_{12}	2[c]	82:18
6	C_6H_{12}	20[c]	95:5
7	C_6H_{12}	48[c]	98.2:1.8
8	HMPTA	16.5[d]	

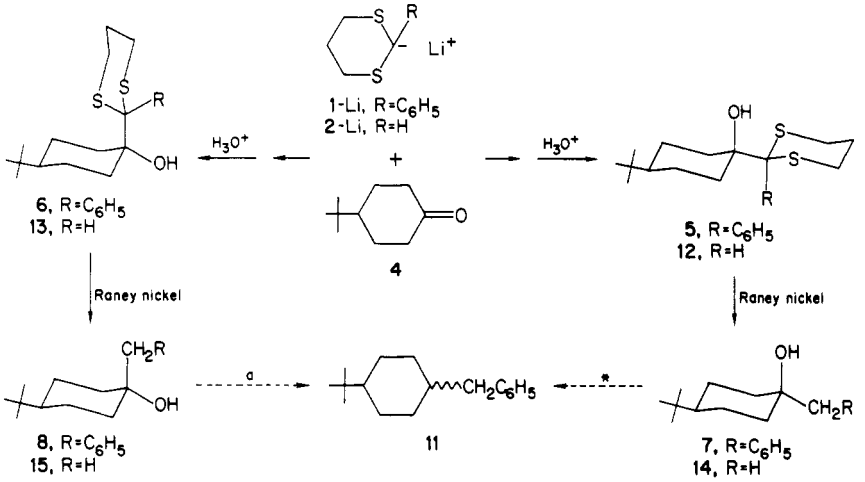
[a] At -20 °C. [b] 1.5 h at -20 °C plus 2.5 h at 25 °C. [c] At 25 °C. [d] 15 h at 0 °C plus 15 h at 25 °C.

1,3-Dithianyllithium and its 2-substituted derivatives are widely used organometallics in organic synthesis,[14] and their addition to ketones affords the corresponding carbinols in high yields.[15] This paper reports the results of a stereochemical study of the addition of the lithium salt of the parent 1,3-dithiane, as well as its 2-phenyl derivative to the anancomeric[16] 4-*tert*-butylcyclohexanone. Since spectral evidence suggests[17] that 2-phenyl-2-lithio-1,3-dithiane (1-Li) exists as a tight ion pair in tetrahydrofuran (THF) or cyclohexane (C_6H_{12}) but as a solvent-separated, delocalized ion pair in hexamethylphosphoric triamide (HMPTA), it can be argued that the species present in HMPTA should be the softer base. Analysis of the solvent effect (THF or C_6H_{12} vs. HMPTA) thus appeared of in-

(1) A preliminary report on this work has appeared: Juaristi, E.; Eliel, E. L. *Tetrahedron Lett.* **1977**, 543-546.
(2) (a) University of North Carolina and Instituto Politécnico Nacional. Address correspondence to this author in Mexico City. (b) Instituto Politécnico Nacional.
(3) Wigfield, D. C. *Tetrahedron* **1979**, *35*, 449-462.
(4) Boone, J. R.; Ashby, E. C. *Top. Stereochem.* **1979**, *11*, 53-95.
(5) Ashby, E. C.; Laemmle, J. T. *Chem. Rev.* **1975**, *75*, 521-546. There has, of course, recently been much work on the stereoselective addition of organometallic compounds to acyclic aldehydes. See, for example: Heathcock, C. H. *Science* **1981**, *214*, 395-400.
(6) Kamernitskii, A. V.; Akhrem, A. A. *Tetrahedron* **1962**, *18*, 708-750.
(7) Dauben, W. G.; Fonken, G. J.; Noyce, D. S. *J. Am. Chem. Soc.* **1956**, *78*, 2579-2581.
(8) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199-2204. Cherest, M.; Felkin, H. *Ibid.* **1968**, 2205-2208. Cherest, M. *Tetrahedron* **1980**, *36*, 1593-1598.
(9) Klein, J. *Tetrahedron Lett.* **1973**, 4307-4310. Klein, J. *Tetrahedron* **1974**, *30*, 3349-3353.
(10) See also: Liotta, C. L. *Tetrahedron Lett.* **1975**, 519-522.
(11) Maroni-Barnaud, Y.; Roux-Schmitt, M. C.; Seyden-Penne, J. *Tetrahedron Lett.* **1974**, 3129-3132.
(12) Anh, N. T.; Eisenstein, O. *Tetrahedron Lett.* **1976**, 155-158. Huet, J.; Maroni-Barnaud, Y.; Anh, N. T.; Seyden-Penne, J. *Tetrahedron Lett.* **1976**, 159-162. See also: Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61-70.
(13) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540-4552.
(14) Gröbel, B.-T.; Seebach, D. *Synthesis* **1977**, 357-402.
(15) Corey, E. J.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 1075-1077.
(16) Anteunis, M. J. O. "Conformational Analysis, Scope and Present Limitations"; Academic Press: New York, 1971; p 32.
(17) Abatjoglou, A. G.; Eliel, E. L.; Kuyper, L. F. *J. Am. Chem. Soc.* **1977**, *99*, 8262-8269.

0022-3263/84/1949-4912$01.50/0

Scheme I[a]



[a] (a) For R = C_6H_5, see Table II.

terest in order to test the hypothesis that the steric course of nucleophile addition should depend on the hardness or softness of the nucleophile.[11,18]

In addition, study of the stereochemistry of the addition of the mono-*S*-oxide of 1,3-dithianyl lithium to 4-*tert*-butylcyclohexanone is pertinent in relation to the proposed importance of $\sigma_{C_{2,6}-H}/\sigma^*_{Nu-C_1}$ two-electron stabilizing interactions.[13]

As it turns out, our findings provide little evidence in favor of or against the theoretical prediction, because other factors (thermodynamic vs. kinetic control, enolate formation) determine the reaction course.

Results and Discussion

A. 2-Phenyl-2-lithio-1,3-dithiane (1-Li). Scheme I presents the reaction between 1-Li and 4-*tert*-butylcyclohexanone (**4**), which affords the diastereomeric alcohols **5** and **6**. Analysis of the product mixture was effected by a combination of proton and carbon-13 NMR. Configuration was ascertained by hydrogenolysis of the products (**5** and **6**) to the known[19] 1-benzyl-4-*tert*-butylcyclohexanols (**7** and **8**, Scheme I) whose proportion, determined by gas chromatography, also provided a check on the original product composition.

The outcome of the reaction of 1-Li with **4** as initially observed is summarized in Table I, entries 3, 5, and 8.

The reaction in THF is totally stereoselective, contrary to that in C_6H_{12}. This is a gratifying result since high stereoselectivity of nucleophilic attack to cyclohexanones is normally found only with very bulky reagents.[5,19,20] No reaction occurs in HMPTA.

Our suspicion that the reaction proceeds in the reverse direction in HMPTA was confirmed when we converted the equatorial adduct (axial alcohol) **5** to its lithio derivative in HMPTA. The pale yellow solution of **5** in HMPTA instantaneously turned bright orange red upon addition of 1 equiv of *n*-butyllithium. Upon quenching, starting materials **1** and **4** were quantitatively recovered.

In contrast to other reversible nucleophic additions to ketones[21] rapid reverse quenching (by pouring the reaction mixture into vigorously stirred aqueous methanolic HCl) did not enable us to isolate any of the desired carbinols **5** and **6** in HMPTA. This result rules out the possibility that, upon gradual acidification, the more basic (phenyldithianyl)lithium 1-Li is neutralized first while equilibrium has time to reestablish itself, so that eventually **1** and **4** are recovered on slow neutralization.

The finding that addition is reversible in HMPTA suggested that addition in the other two solvents was also reversible but with the equilibrium largely on the side of the adducts. This hypothesis was confirmed when the product composition in the addition of 1-Li to **4** in THF and C_6H_{12} was followed as a function of time (Table I).

The thermodynamically controlled product **5** accumulated more rapidly in the more polar solvent THF.[22] Since the equilibrium lies entirely on the side of the lithio derivative of **5**, this appears to be a convenient method for the totally stereoselective syntheses of axial alcohols.[23]

Equilibration of products in the addition of nucleophiles to ketones has also been found elsewhere.[25] In a closely parallel situation, 1-Li adds reversibly to cyclohexenones largely 1,2 in hexane-THF mixtures at −78 °C, whereas in pure THF substantial amounts of 1,4-adduct are formed (irreversibly) even at −78 °C; at room temperature, only the thermodynamically controlled 1,4-addition product is found.[26]

The high predominance of **5**-Li over **6**-Li can be rationalized in terms of severe steric interactions in the latter. It is also clear from inspection of Dreiding models, that the Li^+ ion may be coordinated to one of the sulfur atoms in **5**-Li.[27] This coordination is not likely to be present in **6**-Li because the conformations allowing for $Li^+\cdots S^{\delta-}$

(18) See also: Kyriakakou, G.; Roux-Schmitt, M. C.; Seyden-Penne, J. *Tetrahedron* **1975**, *31*, 1883–1888. Gaudemar, M. *Ibid.* **1976**, *32*, 1689–1691. Bellassoued, M.; Dardoize, F.; Gaudemar-Bardone, F.; Gaudemar, M.; Boasdoue, N. *Ibid.* **1976**, *32*, 2713–2717.

(19) Meakins, G. D.; Percy, R. K.; Richards, E. E.; Young, R. N. *J. Chem. Soc. C* **1968**, 1106–1109.

(20) McDonald, T. L.; Still, W. C. *J. Am. Chem. Soc.* **1975**, *97*, 5280–5281. Still, W. C. *J. Org. Chem.* **1976**, *41*, 3063–3064.

(21) Hamrick, P. J.; Hauser, C. R. *J. Am. Chem. Soc.* **1959**, *81*, 2096–2099, 3144–3147.

(22) Conversion of the adduct **5** to its lithio derivative in C_6H_{12} did not lead to the formation of any of its epimer **6**. It is then suggested that the equilibrium **5**-Li ⇄ **6**-Li also lies entirely on the side of **5**-Li in this solvent.

(23) The phenyldithianyl moiety can be readily hydrolyzed[24] into a benzoyl group or reduced to a benzyl derivative.

(24) Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553–3560 and references cited therein.

(25) For example: Koudsi, Y.; Maroni-Barnaud, Y. *C. R. Acad. Sci. Paris* **1975**, *280 C*, 153–156, 313–315, 399–401.

(26) Ostrowski, P. C.; Kane, V. V. *Tetrahedron Lett.* **1977**, 3549–3552.

(27) Dunitz, Seebach, et al. have recently studied the structure (by X-ray crystallography) of a couple of dithianyllithiums and have, indeed, found that there is coordination of Li^+ to S: Amstutz, R.; Seebach, D.; Seiler, P.; Schweizer, B.; Dunitz, J. D. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 53–54. Amstutz, R.; Dunitz, J. D.; Seebach, D. *Ibid.* **1981**, *20*, 465–466.

Scheme II

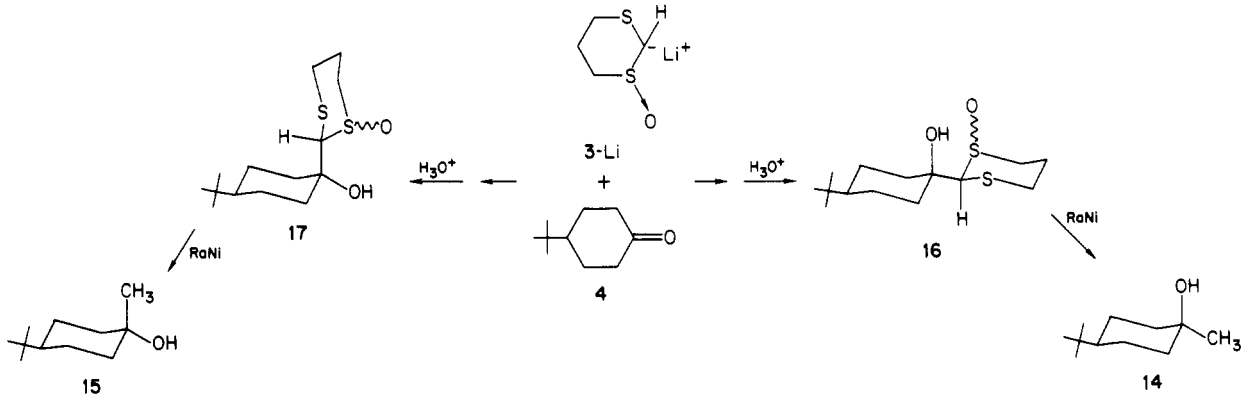
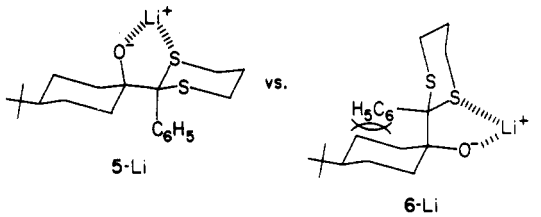


Table II. Extent of Homobenzylic Hydrogenolysis Encountered during the Desulfurization of 5 and 6 with Raney Nickel W-2 in Ethanol under Various Conditions

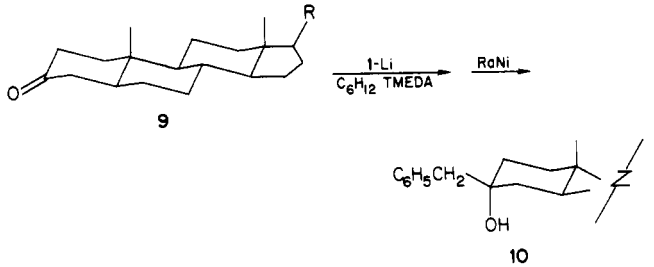
nickel cat	T, °C	reactn time, h	%7 and 8	%11
W-2	85	2	32.1	67.9
W-2[a]	85	0.25	75.6	24.4
W-2	25	24	71.8	28.2
W-2	25	2	78.4	21.6
W-2[a]	25	2	83.3	16.7
W-2	0	5	96.7	3.1

[a] Deactivated with aqueous 0.1% AcOH.[32]

proximity also involve very significant steric crowding of the phenyl moiety of the axial hydrogens of the cyclohexyl ring.



The fact that equilibration (5-Li ⇄ 6-Li) is faster in the more polar THF that in C_6H_{12} suggests that solvation of the lithium ion facilitates the movement of electrons that regenerates the starting reagents. Indeed, when the addition of 1-Li to 4 was carried out in C_6H_{12} in the presence of 1 equiv of tetramethylethylenediamine (TMEDA) the thermodynamically controlled alkoxide 5-Li was the only product after 2 h at 0 °C plus 3 h at 25 °C, compared with 48+ h in C_6H_{12} alone. In an application of this finding, 5α-cholestan-3-one (9) was converted to 3β-benzyl-5α-cholestan-3-α-ol (10) with over 95% stereoselectivity.[28]



Although desulfurization of carbinols 5 and 6 (Scheme I) is readily accomplished with Raney nickel W-2[29] in ethanol, care must be exercised because the homobenzylic alcohols initially obtained (7 and 8) can be further hydrogenolyzed to a ca. 80:20 mixture of *cis*- and *trans*-1-benzyl-4-*tert*-butylcyclohexanes[30] (*cis*- and *trans*-11, Scheme I).[31]

Table III. Products of the Reaction of 2-Li with 4 in Various Solvents[a]

solvent	C_6H_{12}	THF	TMEDA	HMPTA
yield, %	71	99	8	0
12:13	49:51	40:60	58:42	

[a] Product composition (12:13) was constant with time.

Table IV. Reaction of 4-*tert*-Butylcyclohexanone (4) with 2-Lithio-1,3-dithiane Mono-*S*-oxide (3-Li)

solvent	T, °C	16:17
THF	−78[a]	51.4:48.6
THF	−20[b]	43.7:56.3
C_6H_{12}	0[c]	44.4:55.6

[a] At "zero" time; essentially the same ratio (51.2:48.8) was observed after three days (−78 → 25 °C). [b] 1 h at −20 °C plus 24 h at 25 °C. [c] 1 h at 0 °C.

Table II shows the extent to which hydrogenolysis takes place under various conditions.

Although no significant inhibition of the undesired reaction was attained with deactivated catalyst, highly satisfactory yields of the desired products were observed when the reaction temperature was kept at 0 °C (yield of 7 and 8 is 95–99%).

B. 2-Lithio-1,3-dithiane (2-Li). Little if any stereoselectivity was found in any of the solvents studied when the parent compound was allowed to react with 4 (Scheme I) *nor was there any change of composition with time* (Table III).

Product composition in Table III was determined by gas chromatography and by ^1H and ^{13}C NMR. The configuration of epimers was assigned by Raney nickel hydrogenolysis to the known 1-methyl-4-*tert*-butylcyclohexanols.[19,33,34]

(28) Proton NMR detection limit: Standard samples of 3α- and 3β-benzyl-5α-cholestan-3-ols were prepared by the reaction of benzylmagnesium chloride and 9;[19] the ^1H NMR shifts (90 MHz, $CDCl_3$) for the benzylic methylenes are 2.83 and 2.67 ppm, respectively.

(29) Preparation of Raney nickel W-2: Mozingo, R. In "Organic Syntheses"; John Wiley and Sons: New York, 1955; Collect. Vol. III, p 181.

(30) Garbish, E. W. *J. Chem. Soc., Chem. Commun.* **1967**, 806–807.

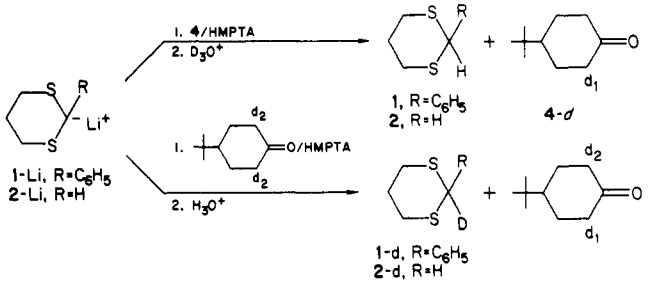
(31) We, also,[30] have found that in competitive hydrogenolysis of the substrate pair 7 and 8 with Raney nickel W-2 in ethanol, benzylic alcohol 8 reacts faster than its epimer 7.

(32) "Organikum"; Deutscher Verlag der Wissenschaften: Berlin, 1967; p 632.

(33) Cross, B.; Whitham, G. H. *J. Chem. Soc.* **1960**, 3892–3895.

(34) The configurational assignments of the benzyl[19] and methyl[19,33] tertiary carbinols were confirmed by carbon-13 NMR: $C_6H_5CH_2$, axial, 42.50 ppm, equatorial, 50.42 ppm; CH_3, axial, 25.30 ppm, equatorial, 31.41 ppm.

Scheme III



In view of the sometimes low yields, the observed product variations may not be significant (vide infra), but it is significant that the reaction with 2-Li, like that with 1-Li, fails to give adduct in HMPTA but that, unlike that with 1-Li, it is irreversible. The latter point was confirmed by converting a mixture of 12 and 13 to its lithio derivative in THF (65 °C) or HMPTA (25 °C): upon quenching the unchanged mixture was recovered.

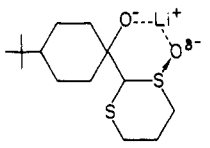
Two factors may be responsible for the irreversibility observed in the addition of 2-Li to 4: (1) The reverse reaction is not favored by the stability of the dithianyl carbanion because, in contrast to 1-Li, delocalization of the negative charge in 2-Li is much less important in the absence of the α-phenyl substituent.[35,36] (2) Steric hindrance in the adducts of 2-Li is less severe than in the adducts of 1-Li.

2-Lithio-1,3-dithiane Mono-*S*-oxide (3-Li). Scheme II shows the reactions effected in order to establish the stereochemistry of the addition of 3-Li to 4-*tert*-butylcyclohexanone.

Analysis of the product mixture (16 and 17) was effected by hydrogenolysis to the known[19,33,34] 1-methyl-4-*tert*-butylcyclohexanols (14 and 15) whose proportion was determined by gas chromatography. The outcome of the reaction of 3-Li with 4 is summarized in Table IV.

Monosulfoxide 3-Li, like 2-Li, adds *irreversibly* to 4. This was shown when the carbinol ratio (16:17) was measured as a function of time: essentially the same proportion was found at "zero" time and after 3–4 days. [See footnote *a* in Table IV].

The irreversibility here is surprising in view of the great acidity of 3 (high stability of 3-Li) which might have facilitated the reversal 16 and/or 17 → 3-Li and 4 (vide supra). As a conciliatory argument, it could be speculated that strong complexing of Li^+ in product by $^{\delta+}S\rightarrow O^{\delta-}$ prevents the disconnection of the adducts.



D. Course of the Reaction of HMPTA. The question arises why the reaction of 1-Li or 2-Li with ketone 4 fails to give adduct in HMPTA but proceeds in the reverse direction. When 4 is treated with 1-Li in this solvent and the mixture is quenched in D_3O^+,[37] the products are 1 (rather than 1-*d*) and 4-*d* (95.2% monodeuterated by mass spectrometry). Similarly, 2-Li and 4 in HMPTA yielded 1,3-dithiane (2) (rather than 2-*d*) after quenching in D_3O^+[37] (Scheme III).

Table V. Extent of Enolization in the Reaction of *n*-Butyllithium with 4-*tert*-Butylcyclohexanone (4) in C_6H_{12}, THF, and HMPTA

solvent	% addition[a]	% enolization
C_6H_{12}[b]	64.0	36.0
THF[c]	62.1	37.9
HMPTA[d]	12.8	87.2

[a] A ca. 77:23 mixture of the epimeric alcohols was obtained in all solvents studied. [b] At 25 °C for 2 h. [c] 1 h at −20 °C plus 1 h at 25 °C. [d] 1 h at 0 °C plus 1 h at 25 °C.

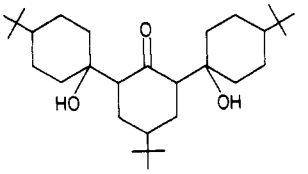
The logical conclusion is that 1-Li and 2-Li react with 4 in HMPTA not by addition but by enolate formation.[38] This hypothesis was confirmed as shown in the lower part of Scheme III.

Since in the addition of 1-Li to 4 thermodynamic control obtains, the enolate is evidently more stable than the adduct in HMPTA but not in THF of C_6H_{12}. In the case of 2-Li, since addition is irreversible, exclusive formation of the enolate in HMPTA must indicate that the transition state to enolate formation is of substantially lower energy than that to addition; thus the energies of the transition states reflect those of the products.

We were interested to determine if enolization is also favored over addition when sterically unhindered, more reactive nucleophiles are allowed to react with 4 in HMPTA. Table V shows the relative amounts of enolization and addition when *n*-butyllithium is added to 4-*tert*-butylcyclohexanone (4) in various solvents. In order to verify that the recovered ketone had indeed originated from its enolate derivative, reaction mixtures were quenched in D_3O^+.[37] The amount of deuterium incorporation in recovered 4 was then determined by mass spectrometry. The observed amount of undeuterated ketone 4 was less than 9%.

In contrast to the reaction in C_6H_{12} or THF, the reaction in HMPTA leads to a high proportion of enolate formation. It is suggested then that preparative methods of enolates[39] may be improved by the use of HMPTA as solvent.

During the addition of 1-Li or 2-Li to 4 in HMPTA a single aldol condensation product is isolated in 25% yield. Proton and carbon-13 NMR, as well as elemental analysis confirmed its structure as *meso*-2,6-bis(1-hydroxy-4-*tert*-butylcyclohexyl)-4-*tert*-butylcyclohexanone (18). While this product may arise from two consecutive aldol condensations, it could also have originated from dianion 19.[40-42]



18 19

(35) 2-Phenyl-1,3-dithiane is indeed more acidic than the parent dithiane: 29.6 vs. 31.1 pK.[36]

(36) Streitwieser, A., Jr.; Ewing, S. P. *J. Am. Chem. Soc.* **1975**, *97*, 190–191. See also: Streitwieser, A., Jr.; Juaristi, E.; Nebenzahl, L. L. In "Comprehensive Carbanion Chemistry"; Buncel, E., Durst, T., Eds.; Elsevier: Amsterdam, 1980; p 357.

(37) Quenching was effected by dropwise addition of the reaction mixture into a vigorously stirred solution of deuterioacetic acid in deuterium oxide (pH = 5.0). Under these conditions no significant H^+/D^+ exchange is expected: House, H. O.; Tefertiller, B. A.; Olmstead, H. D. *J. Org. Chem.* **1968**, *33*, 935–942.

(38) Pierre, J. L.; Handel, H.; Perraud, R. *Tetrahedron Lett.* **1977**, 2013–2014. These authors find that complexation of the metal by crown ethers increases the energy of activation for addition to the carbonyl function. In our case, the HMPTA solvent is very probably causing the same effect.

(39) Cf. Carruthers, N. "Some Modern Methods of Organic Synthesis"; Cambridge University Press: London, 1971; pp. 17–27.

(40) Juaristi, E. Ph.D. Dissertation, University of North Carolina at Chapel Hill, 1977, pp. 143–145.

Experimental Section

Melting points, determined with a Mel-Temp or an Electrothermal apparatus, are uncorrected. Infrared (IR) spectra were recorded with a Perkin Elmer 257 or a Nicolet MX-1-FT spectrometer calibrated against the 1601 cm^{-1} band of styrene. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on a JEOL C-60HL, Varian XL-100, or Varian EM-390 spectrometer. Chemical shifts are expressed in δ units relative to 1% tetramethylsilane as an internal standard. Mass data were obtained on a Hitachi-Perkin Elmer RMU-6E mass spectrometer. The deuterium content of deuterated material was calculated on the basis of the increase of the M + 1 peak height with respect to that of the nondeuterated compound in the low voltage spectra (13–15 eV) of the molecular ion region. The microanalyses were performed by Galbraith Laboratories, Inc.

Pure samples, reaction products, and equilibrium mixtures were analyzed on a Hewlett-Packard Model 5750 or Varian Model 1420 Research Chromatograph equipped with a dual thermal conductivity detector and provided with stainless steel columns ($^1/_8$ in. ID), and a Moseley 7127 A 1.0 mV recorder. The injection block was maintained at 220 °C, and the detector at 250 °C. The inlet pressure was kept at either 40 or 50 psi of helium.

Flasks, stirring bars, and hypodermic needles used for the generation and reactions of alkyllithiums were dried for ca. 12 h at 120 °C and allowed to cool in a desiccator over anhydrous calcium sulfate. Anhydrous solvents were obtained by distillation over lithium aluminum hydride (ethers) or calcium hydride (amines or hydrocarbons). The molarity of commercial solutions of *n*-butyllithium was determined by the titration methods of Gilman,[43] Kofron and Baclawski,[44] or Juaristi et al.[45]

General Procedure for the Reaction of Organoalkali Reagents with 4-*tert*-Butylcyclohexanone (4). The experimental procedure is detailed here for the reaction of 2-lithio-2-phenyl-1,3-dithiane (1-Li) with **4** in THF.

2-Phenyl-1,3-dithiane (**1**, 5 mmol, 0.98 g) was placed in a dry 50-mL round-bottom flask containing a teflon-coated magnetic bar. The flask was capped with a sleeve-type rubber septum, secured with copper wire, and flushed with dry nitrogen, introduced to and vented from it by means of hypodermic needles. Freshly distilled (over lithium aluminum hydride) THF (20 mL) was introduced into the flask via cannula under positive pressure of nitrogen, and the mixture was cooled to −20 °C. A 5% excess of *n*-butyllithium (2.66 mL of a 2.0 M solution in *n*-hexane) was added slowly with a syringe, and the mixture was stirred at −20 °C for 90–120 min. The reaction was completed by addition of the solution of the intermediate to a solution of 0.77 g (5 mmol) of 4-*tert*-butylcyclohexanone (**4**) in ca. 15 mL of THF contained in another flask, capped with a rubber septum, and flushed with nitrogen. The transfer was effected by siphoning through a stainless steel hypodermic needle tubing under positive nitrogen pressure. The reaction mixture was stirred at −20 °C for 90 min and then at room temperature for 3.5 additional h. The reaction mixture was quenched by direct transfer via cannula to a flask containing saturated aqueous ammonium chloride. The product (**5**) was extracted with three 25-mL portions of ether, and the combined ether extracts were washed with two 25-mL portions of water, dried over anhydrous magnesium sulfate, filtered, and concentrated in a rotary evaporator.

***cis*-1-[2-Phenyl-2-(1,3-dithianyl)]-4-*tert*-butylcyclohexanol (5).** A ca. 80:20 mixture of carbinols **5** and **6** (obtained from the reaction of 1-Li to **4** in cyclohexane, 2-h reaction time) was separated by preparative TLC (ca. 100 mg of mixture per 20 × 40 × 0.14 cm plate) on aluminum oxide with hexane–benzene–ether (60:30:10) as eluent; R_f (**5**) 0.36, R_f (**6**) 0.31. Extraction of the former afforded a yellowish oil which was crystallized from CH_3OH–H_2O (9:1) into white crystals: mp 123–125 °C; ^1H NMR ($CDCl_3$, 100 MHz) δ 0.80 (s, 9 H), 0.86 (m, 1 H), 1.58 (m, 11 H), 2.61 (m, 4 H), 7.38 (m, 3 H), 8.06 (m, 2 H); IR (KBr) 3493 (s), 2955 (vs), 1470 (m), 1432 (s), 1041 (s). Anal. Calcd for $C_{20}H_{30}OS_2$: C, 68.52; H, 8.63. Found: C, 68.55; H, 8.71. ^{13}C NMR in Table VI (supplementary material).

***trans*-1-[2-Phenyl-2-(1,3-dithianyl)]-4-*tert*-butylcyclohexanol (6).** Extraction of the material with R_f 0.31 afforded **6** which was crystallized from CH_3OH–H_2O (9:1) to yield fine, white needles: mp 76.5–78 °C. Calcd for $C_{20}H_{30}OS_2$: C, 68.52; H, 8.63. Found: C, 68.67; H, 8.73. ^1H NMR ($CDCl_3$, 100 MHz) δ 0.75 (s, 9 H), 1.34 (m, 7 H), 1.87 (m, 3 H), 2.18 (m, 2 H), 2.63 (m, 4 H), 7.38 (m, 3 H), 8.10 (m, 2 H). ^{13}C NMR in Table VI (supplementary material).

Separation of *cis*- and *trans*-1-[2-(1,3-Dithianyl)]-4-*tert*-butylcyclohexanols (12 and 13). Fractional crystallization from hexane of a ca. 50:50 mixture of carbinols **12** and **13** (prepared by the reaction of **2**-Li and **4** in cyclohexane) afforded white crystals of **13**, mp 96–98 °C. Carbinol **12** was obtained from the slow crystallization of the filtrate, mp 109–111 °C.

***cis*-1-[2-(1,3-Dithianyl)]-4-*tert*-butylcyclohexanol (12).** Anal. Calcd for $C_{14}H_{26}OS_2$: C, 61.26; H, 9.55. Found: C, 61.33; H, 9.85. ^1H NMR ($CDCl_3$, 60 MHz) δ 0.88 (s, 9 H), 0.97–2.43 (m, 12 H), 2.83 (m, 4 H), 4.08 (s, 1 H). ^{13}C NMR in Table VI (supplementary material).

***trans*-1-[2-(1,3-Dithianyl)]-4-*tert*-butylcyclohexanol (13).** Anal. Calcd for $C_{14}H_{26}OS_2$: C, 61.26; H, 9.55. Found, C, 61.27; H, 10.06. ^1H NMR ($CDCl_3$, 60 MHz) δ 0.88 (s, 9 H), 0.97–2.30 (m, 12 H), 2.87 (m, 4 H), 4.42 (s, 1 H). ^{13}C NMR in Table VI (supplementary material).

Procedure for the Desulfurization of *cis*- and *trans*-1-[2-Phenyl-2-(1,3-dithianyl)]-4-*tert*-butylcyclohexanols (5 and 6) to 7 and 8. The phenyldithianyl derivative (**5** and/or **6**, 42 mg, 0.12 mmol) was dissolved in 10 mL of absolute ethanol and vigorously stirred at 0 °C with 0.5 g of freshly prepared Raney nickel W-2.[29] The mixture was then filtered, through glass fiber filter, and the ethanolic filtrate evaporated. Analysis of the desulfurized material (**7** and/or **8**) was accomplished by gas chromatography (20 ft column, 30% QF-1 on chromosorb W, 80/100 mesh) with a gas flow of 40 mL/min and programmed temperature (140 °C for 20 min and then at 170 °C for 20 additional minutes).

Addition of 2-Lithio-1,3-dithiane Mono-*S*-oxide (3-Li) to 4-*tert*-Butylcyclohexanone (4). Monosulfoxide **3** was prepared according to the method of Carlson and Helquist,[46] and its lithium derivative was prepared as suggested by Carey et al.[47] before it was added to **4** following the general procedure (vide supra).

Procedure for the Desulfurization of *cis*- and *trans*-1-(1,3-Dithian-2-yl)-4-*tert*-butylcyclohexanols (12 and 13) and Monosulfoxides 16 and 17. The dithianyl derivative (0.1 mmol) in ethanol (10 mL) was heated under reflux for 3 h with freshly prepared Raney nickel W-2[29] (0.5 g). Removal of the catalyst and concentration (rotary evaporator) furnished the desulfurized product (**14** and/or **15**), which was analyzed by gas chromatography (20 ft column, 30% QF-1 on chromosorb W, 80/100 mesh) at 110 °C and 30 mL/min gas flow.

Preparation and Separation of *cis*- and *trans*-1-Benzyl-4-*tert*-butylcyclohexanols (7 and 8). The procedure of Meakins et al.[19] was followed. The ^{13}C NMR spectra are listed in Table VI (supplementary material).

Isolation of a *meso*-2,6-Bis(1-hydroxy-4-*tert*-butylcyclohexyl)-4-*tert*-butylcyclohexanone (18). Repeated crystallization of the product mixture obtained from the reaction of 1-Li (0.98 g, 5 mmol) and **4** (0.77 g, 5 mmol) afforded 65 mg (25% of theoretical yield) of a white solid, mp 176.5–177.5 °C, characterized as a meso aldol product **18**. Anal. Calcd for $C_{30}H_{54}O_3$: C, 77.87; H, 11.76. Found: C, 77.84; H, 12.09. ^1H NMR ($CDCl_3$, 100 MHz) δ 0.86 (s, 18 H), 0.92 (s, 9 H), 1.0–2.01 (m, 23 H), 2.08–2.48 (m, 4 H), 3.25 (broad s, 2 H). ^{13}C NMR in Table VI (supplementary material).

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(42) It is also significant that while in the addition of *n*-butyllithium to **4** in THF quenching in D_3O^+ leads almost exclusively to monodeuterated recovered ketone (**4**-d_1, ca. 90%), similar analysis of **4** after a similar sequence in HMPTA shows ca. 33% of *di*deuterated ketone (**4**-d_2).

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Registry No. 1, 505-23-7; 1-*d*, 14664-88-1; 1-Li, 53178-41-9; 2, 5425-44-5; 2-*d*, 74447-48-6; 2-Li, 36049-90-8; 3-Li, 60349-88-4; 4, 98-53-3; 4-*d*, 2979-37-5; 5, 92787-88-7; 6, 92787-89-8; 7, 17181-81-6; 8, 17181-80-5; 9, 566-88-1; 10, 19490-62-1; 12, 40615-42-7; 13, 40615-41-6; 14, 16980-55-5; 15, 16980-56-6; 16, 92787-90-1; 17, 92787-91-2; 18, 92787-92-3.

Supplementary Material Available: ^{13}C chemical shift data for 5–8, 12, 13, and 18 (2 pages). Ordering information is given on any current masthead page.

Sulfonation of Three Symmetrical 2,6-Dialkylphenols, 2,6-Dichlorophenol, Phenol, and 2,6-Dimethylanisole. Sulfation and Sulfonation Product Distributions and Mechanisms[1]

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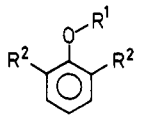
The sulfonation of four symmetrically 2,6-disubstituted phenols, phenol, and 2,6-dimethylanisole with SO_3 in aprotic solvents was studied. With the phenols the initial product is the phenyl hydrogen sulfate, which is slowly converted into the phenolsulfonic acids via O-desulfonation and subsequent C-sulfonation if the phenol is in excess and via C-sulfonation and subsequent O-desulfonation if the SO_3 is in excess. The ratio of partial rate factors for 3- and 4-sulfonation (f_3/f_4) for 2,6-dimethylphenol (1) in nitromethane strongly decreases on replacing the methyl groups by *i*-Pr, *t*-Bu (steric effects), and Cl (electronic effects). The strong increase of f_3/f_4 on increasing the SO_3:1 ratio from 0.9 to 6.0 is ascribed to increasing sulfonation of the phenyl hydrogen sulfate for which because of steric inhibition of resonance f_3/f_4 is higher (3.9) than that of the phenol 1 (<0.01) and of 2,6-dimethylanisole (5) (<0.01). The protic sulfonation of 1 and 5 in concentrated sulfuric acid was also studied. The large variations in f_3/f_4 with increasing sulfuric acid concentration are discussed in terms of steric inhibition of resonance for the entities undergoing sulfonation, viz., 1, its hydrogen sulfate, and 5 by the various sulfonating entities in the sulfuric acid range 75–107% H_2SO_4.

Recently Miller et al. reported that the benzylation of 2,6-dimethylphenol (1) and its methyl ether (5) yields in



1 R^1= H ; R^2= Me
2 R^1= H ; R^2= Pr^i
3 R^1= H ; R^2= Bu^t
4 R^1= H ; R^2= Cl
5 R^1= R^2= Me
6 R^1= R^2= H
7 R^1= Me ; R^2= H

addition to the expected 4-benzyl derivative substantial amounts of the 3-benzyl derivative (ca. 40% and 70% respectively),[2] and further that the allylation of these substrates also leads to both 3- and 4-substitution.[3] A search of the literature failed to reveal a single instance of an electrophilic substitution reaction of a simple phenol or aryl ether with unsubstituted positions ortho or para to the oxygen atom in which significant amounts of meta substitution occurred.[2] Most of the cited literature is rather outdated and not always conclusive. For instance, the sulfonation of 1 with 85% sulfuric acid[4] and its nitration with 80% nitric acid[5] led to the 4-substituted product in isolated yields of only ca. 40% and 50%, respectively.

2,6-Dialkylphenols and their methyl ethers are intriguing, as they may be considered both as a phenol and its ether (for which the electrophilic substitution is strongly directed to the 2- and 4-positions) and as a *m*-dialkylbenzene (which directs strongly to the 3-position). The substituent constant σ^+ for substitution para to the OH and OMe substituents are −0.92 and −0.78, respectively,[6] whereas the overall substituent constant for substitution at the 4-position of *m*-xylene is $\sigma^+_{o\text{-Me}} + \sigma^+_{p\text{-Me}} = -0.19^7 + -0.28^6 = -0.47$. Thus with the 2,6-dimethyl derivatives of phenol and anisole the effects of the OH and OMe substituents strongly dominate over the directing effect of the two methyls provided that the former substituents can fully exert their conjugative effect, i.e., that the OH hydrogen and the OMe carbon are in the plane of the phenyl ring. Any tordation of the OH and OMe substituents because of steric hindrance with the adjacent alkyl groups will reduce the mesomeric conjugation between the OH and OMe substituents and the cationic cyclohexadienyl structure in the transition state that leads to 4-substitution. This will then allow the much slower 3-substitution to become a competing reaction.

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