scribed temperature and 2.0 mmol of *N*-(2-butylidene)benzenesulfenamide (3)[4] in 2.0 mL of the appropriate solvent was added dropwise over 0.5 h. After stirring for the required time, 6.0 mmol of iodomethane was added dropwise and the stirring was continued for an additional 2 h. The reaction was quenched with 30 mL of water and the ether solution was dried over anhydrous $MgSO_4$. Sulfenimines 7 and 8 were analyzed by gas chromatography.

Acknowledgment. This investigation was supported by Public Health Service Research Grant No. CA-14341 from the National Cancer Institute.

Registry No.—8, 65276-71-3.

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On the Mechanism of the Thermal Isomerization of 1,2-Diolates. Is the Pinacol Coupling Reaction Reversible?

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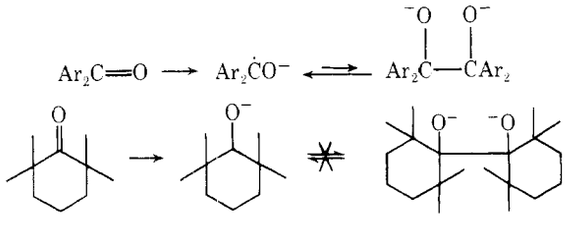
1,2-Diols containing at least one α proton will isomerize when heated to 155 °C as their dilithium salts. The mechanism of the isomerization is shown to be an oxidation–reduction rather than a reverse pinacol coupling as had been suggested by earlier workers. Evidence in support of the proposed mechanism is presented.

The pinacol coupling reaction is a potentially powerful method of carbon–carbon bond formation which has received little attention from synthesis chemists.[1] We have been interested for some time in the synthetic uses of the pinacol reaction,[2,3] and one of the questions which we wished to answer involved the reversibility (or lack thereof) of the reaction. Such information could be valuable if, for example, one wished to plan the stereospecific synthesis of a cyclic 1,2-diol by internal pinacol cyclization.[4]

It has long been known that *certain* pinacol couplings are readily reversible when, for some reason, the central carbon–carbon bond is unusually weak. Such, for example, is the case when diaryl ketones are reductively coupled to tetraarylethanediols.[5] Similarly, although for steric rather than electronic reasons, 2,2,6,6-tetramethylcyclohexanone cannot be reductively coupled to a pinacol because its ketyl will not dimerize.[6]



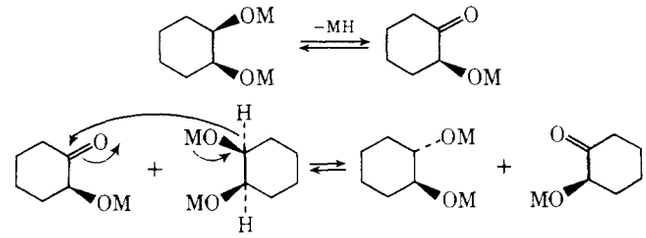
The situation for saturated, sterically uncrowded 1,2-diols is less clear, however. Schlosser, in a 1970 communication, reported the thermal isomerization of a series of dilithium 1,2-diolates and proposed a bond homolysis mechanism (reverse pinacol coupling) to account for his results.[7] *cis*-1,2-Dihydroxycyclohexane, for example, isomerized nearly completely (97%) to its trans isomer when heated as its dilithium salt for 17 h at 155 °C.

Yet a further example was reported sometime later by Sharpless.[8]

In considering the Schlosser report, we were struck by the fact that all of the cases examined were disecondary 1,2-diols and that an alternative oxidation–reduction mechanism, perhaps initiated by a trace amount of ketone, could also account for the observed results. We therefore investigated the isomerization of a selected 1,2-diol, *cis*-1,2-dihydroxycyclohexane (1), in more detail. Our results are summarized in Table I.

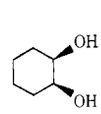
Runs 1–3 were carried out to establish the minimum condition necessary to achieve diol equilibration, and we verified the Schlosser report in this respect. In order to establish whether or not the observed equilibration was due to a catalytic amount of O_2 initiating a redox process, we next (runs 4 and 5) attempted equilibration using scrupulously oxygen-free conditions (freeze–thaw deoxygenation of solvents; sealed tube) under both nitrogen and argon atmospheres. Although the equilibration seemed qualitatively somewhat slower, and although higher yields of recovered products were obtained, it was nevertheless clear that diol equilibration still occurred readily in the absence of oxygen.

An alternative means of generating a trace amount of oxidized material necessary to start the catalytic redox cycle



0022-3263/78/1943-1800$01.00/0

Table I. Isomerization of Some Diols by Thermal Equilibration of Dimetallo Salts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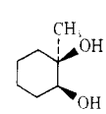
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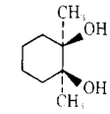

3

Run	Diol	Base	Conditions	Products, %	Yield, %
1	1[a]	*n*-BuLi	Diglyme; N_2; rt; 20 h	100 cis 0 trans	75
2		*n*-Buli	Diglyme; N_2; 155 °C; 1.5 h	17 cis 83 trans	40
3		*n*-BuLi	Diglyme; N_2; 155 °C; 3 h	0 cis 100 trans	40
4		*n*-BuLi	Freeze–thaw degassed diglyme; N_2; 155 °C; 42 h	4 cis 96 trans	60
5		*n*-BuLi	Freeze–thaw degassed diglyme; Ar; 155 °C; 40 h	4 cis 96 trans	90
6		NaH	Diglyme; N_2; 155 °C; 2 h	10 cis 90 trans	33
7		LDA	Diglyme; N_2; 155 °C; 2 h	15 cis 85 trans	35
8		KH	Diglyme; N_2; 155 °C; 3.5 h	97 cis 3 trans	45
9		*n*-BuLi	Freeze–thaw degassed diglyme; Ar; 155 °C; 45 h; 10 mol % $NaBH_4$ present	81 cis 19 trans	52
10	2[b]	*n*-BuLi	Diglyme; N_2; 155 °C; 6 h	43 cis 57 trans	69
11	3[c]	*n*-BuLi	Diglyme; N_2; 205 °C; 2 h	100 cis	70
12		LDA	Diglyme; N_2; 155 °C; 2 h	100 cis	92
13		NaH	Diglyme; N_2; 155 °C; 2 h	100 cis	88
14		*n*-BuLi	Diglyme; N_2; 305 °C (sealed tube); 24 h		0

[a] Registry no. 1792-81-0. [b] Registry no. 52718-65-7. [c] Registry no. 33046-21-8.

would be to assume that a small amount of diolate undergoes loss of metal hydride.[9]

The ketone product then acts as a hydride acceptor for a second diolate, and the catalytic cycle commences. One would expect the feasibility of the initial loss of metal hydride to be dependent on the nature of the counterion, and runs 6 and 8 indicate that this is so. Although sodium hydride as base is nearly as effective as *n*-BuLi and lithium diisopropylamide, potassium hydride is ineffective even under forcing conditions. If the diolate equilibration were occurring by a bond homolysis (reverse pinacol) mechanism, one might expect a dipotassium diolate to be more reactive than disodium or dilithium.[10] If, however, loss of metal hydride occurs to initiate a redox cycle, then loss of the more covalent lithium hydride might be expected to be easier than loss of potassium hydride since bond energies of the alkali hydrides occur in the order LiH (56.9 kcal/mol) > NaH (48 kcal/mol) > KH (43.8 kcal/mol).[11]

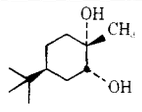
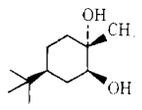
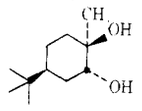
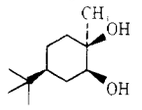
If a trace amount of carbonyl is involved in catalyzing the equilibration, we reasoned that we ought to be able to quench the reaction by adding a carbonyl scavenger to the reaction. Run 9 was therefore carried out under oxygen-free conditions in the presence of 10 mol % $NaBH_4$. Equilibration was, in fact, greatly diminished under these conditions but nevertheless still occurred to a modest degree. Although this result is not clear cut, it would seem to argue for a redox mechanism of equilibration, especially in light of the recent report that borohydride reduction may be reversible under some conditions.[12]

The evidence thus far is inconclusive, and we felt that more definitive results might be found if attempts were made to equilibrate more substituted diols. *cis*-1,2-Dihydroxy-1-methylcyclohexane should be capable of equilibrating by either mechanism, and indeed, we found that its dilithium salt equilibrates readily (run 10). A ditertiary 1,2-diol, however, should be able to equilibrate only by a reverse pinacol mechanism and not by a redox cycle since no α hydrogens are present. Runs 11–14 indicate that under no conditions found does *cis*-1,2-dihydroxy-1,2-dimethylcyclohexane equilibrate with its trans isomer even when the reaction temperature is raised to the point of solvent decomposition. A priori, one might have predicted a ditertiary diol to react faster than a disecondary diol due to steric effects if the reverse pinacol mechanism were operative (see, for example, our earlier comments about the 2,2,6,6-tetramethylcyclohexanone pinacol). The fact that we see no equilibration is good evidence against such a mechanism.

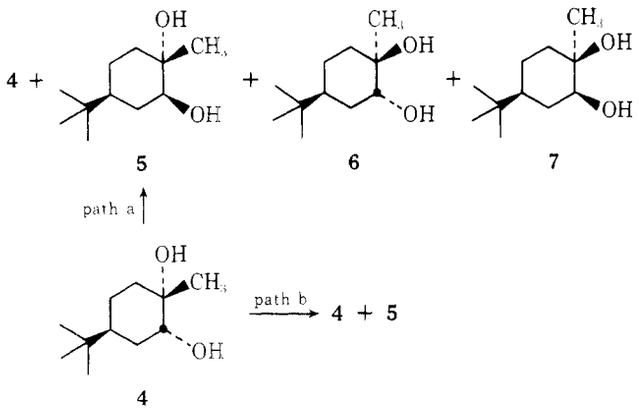
Negative evidence, while strongly indicative, is never as compelling as positive evidence, and we therefore considered experiments which would lead to unambiguous positive results. One such experiment is the attempted equilibration of a secondary–tertiary diol such as **4** in which isomerization relative to another internal chiral center can be followed. We have already established that a secondary–tertiary diol such as **2** undergoes isomerization. If isomerization of **4** occurs by a reverse pinacol mechanism, both hydroxyl containing centers should be epimerized leading to a mixture of four possible products (path a). If isomerization occurs by a redox mechanism, only the secondary hydroxyl should be epimerized and two products result (Scheme I, path b). Our results are summarized in Table II.

All four of the known isomeric diols **4–7** were synthesized and submitted to isomerization conditions. The results are compatible only with isomerization through a redox mechanism. As predicted, compounds **4** and **5** were readily interconverted by epimerization at the secondary center. Only in the case of diol **4** does a small amount of isomerization at the tertiary hydroxyl occur, and we thus cannot completely rule out a reverse pinacol mechanism competing to a slight extent with a redox mechanism. We find it surprising that trans diols **6** and **7** evidence no isomerization, but this does not seem to have bearing on the reverse pinacol vs. redox question since neither is occurring.

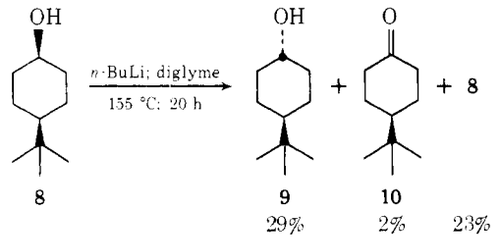
Table II. Isomerization of 1,2-Dihydroxy-4-*tert*-butyl-1-methylcyclohexanes

Starting diol	Registry no.	Products (%)	Yield, %
 4	33817-491	4 (24.4) 5 (67.5) 6 (0) 7 (8.1)	38
 5	43089-39-0	4 (27.5) 5 (72.3) 6 (0) 7 (tr)	75
 6	43089-35-6	4 (0) 5 (2.3) 7 (2.4) 6 (95.3)	33
 7	5951-25-7	4 (0) 5 (0) 6 (0) 7 (100)	57

Scheme I

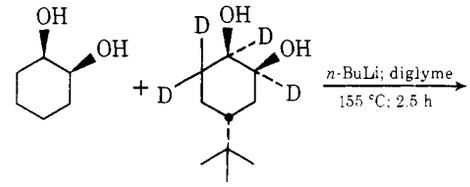


Final proof of the redox mechanism for isomerization of 1,2-diols was gathered by two additional experiments. In the first of these, we hypothesized that a mono alkoxide should be able to undergo a redox isomerization as well as a dialkoxide (though obviously not a reverse pinacol isomerization). We therefore synthesized *cis*-4-*tert*-butylcyclohexanol (**8**) and submitted its lithium salt to standard conditions. Heating the lithium salt of **8** under N_2 atmosphere to 155 °C for 20 h in diglyme yielded a 44:56 mixture of cis and trans isomers in 52% yield, along with about 2% 4-*tert*-butylcyclohexanone—clear evidence of redox processes occurring:



The final and concluding experiment involved coisomerization of a mixture of *cis*-1,2-dihydroxycyclohexane (**1**) and *cis*-1,2,6,6-tetradeuterio-1,2-dihydroxy-4-*tert*-butylcyclohexane (**14**). Both diols should isomerize but if a reverse pinacol mechanism were operative (intramolecular), no deuterium should be exchanged between the two compounds. If a redox mechanism were operative (intermolecular) deuterium should be scrambled between the diols. The synthesis of deuterated diol **14** is given in Scheme II, and the results of the coisomerization experiment are given in Table III.

Table III. Coisomerization (%) of a Deuterated and a Nondeuterated 1,2-Diol



OH	D^0	D^1	D^2	D^3	D^4
1					
Before reaction	100	0	0	0	0
After reaction	34	30	23	10	3
14					
Before reaction	2	5	14	35	43
After reaction	17	28	25	18	10

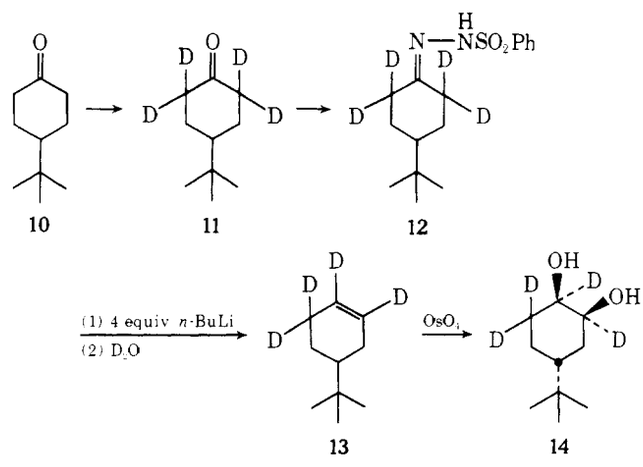
Although separation of products into individual stereoisomers was not carried out, the results clearly indicate a large amount of intermolecular deuterium scrambling consistent only with a redox mechanism.

In conclusion, we feel that our evidence for the mechanism of 1,2-diolate isomerization is compatible only with a redox pathway and not with the reverse pinacol coupling pathway originally proposed by Schlosser. From a synthesis point of view, our results clearly indicate that isomerization can be achieved only at secondary centers and not at tertiary centers; synthetic schemes incorporating a pinacol coupling reaction will therefore have to be constructed with this fact in mind.

Experimental Section

General. Melting points (uncorrected) were obtained on a Thomas-Hoover Unimelt apparatus. ^1H NMR spectra were determined on a Varian A56/60A (60 MHz) or a Jeolco Minimar (60 MHz) instrument. ^{13}C NMR spectra were determined on a Jeolco PFT-100 instrument operating at 25.1 MHz. Chemical shifts were reported in δ downfield from Me_4Si (δ 0). IR spectra were recorded on Perkin-Elmer 237 B or Perkin-Elmer 337 grating spectrophotometers. Analytical vapor phase chromatography (VPC) was performed on a Varian A-200 (FID) instrument using 10% carbowax 20 M on Chromosorb W 60/80 columns (10 ft. × ⅛ in.). Preparative VPC was performed on an Aerograph 90-P instrument employing 20% SE-30 on Chromosorb W 80/100 column (6 ft. × ¼ in.). Isotopic compositions were determined by gas chromatography/mass spectroscopy on a Finnegan Model 4000 instrument operating with ionization potential at 70 eV and utilizing a 3% OV-1 Chromosorb W glass column (4 ft. × ⅛ in.). High-pressure liquid chromatography (HPLC) was performed on a Water Associates Model ALC 201 instrument employing Porasil-A

Scheme II



packed columns (6 ft. × ¼ in.) and utilizing ethyl acetate/petroleum ether (bp 30–60 °C) solvent system (2/3).

n-BuLi (Alfa) was titrated by the method of Watson.[13] L-Selectride (Aldrich) was used as purchased. *N,N,N',N'*-Tetramethyl-1,2-ethylenediamine (TMEDA, Aldrich) was distilled from CaH_2. Diglyme (Matteson Coleman Bell) was predried by standing over anhydrous $CaCl_2$ and then distilled from CaH_2. Diglyme was dried by stirring over molten potassium metal for an overnight period and then distilled in vacuo. D_2O (99.8%) was purchased from Bio-Rad.

Known cis diols **1**,[14] **2**,[15] and **3**[16] and their trans isomers were prepared according to the literature procedures. Diols **4, 5, 6,** and **7** were prepared according to Barili, Bellucci, Macchia, and Parmigiani[17] and were then purified on HPLC. ^{13}C NMR spectra ($CDCl_3$) of **4, 5, 6,** and **7** were consistent with their structures.[18] Alcohol **8** (96% isomeric purity) was obtained according to the procedure of Brown.[19]

Organic phases from extraction were dried over anhydrous Na_2SO_4. All reactions were performed in oven-dried glassware assembled hot under an N_2 atmosphere except where indicated.

2,2,6,6-Tetradeuterio-4-*tert*-butylcyclohexanone (11). Deuterated cyclohexanone-2,2,6,6-d_4 was prepared by the deuterium exchange procedure of Eliel;[20] mp 49–50 °C. Isotopic composition: 0% d_0, 0.4% d_1, 3.3% d_2, 24.6% d_3, and 71.8% d_4.

2,2,6,6-Tetradeuterio-4-*tert*-butylcyclohexanone Phenylsulfonylhydrazone (12). Ketone **11** (1.58 g, 10 mmol) was added to a magnetically stirred hot saturated methanolic solution (10 mL) of phenylsulfonylhydrazide (1.72 g, 10 mmol). After being allowed to cool and being stirred at 20 °C for 1 h, no carbonyl was detected by infrared spectroscopy. The solution was refrigerated to induce crystallization, and the white solid was filtered, washed with four portions of H_2O, and dried in vacuo to yield 2.22 g (71%) of product, mp 129–131 °C (lit.[21] mp for undeuterated product 128–130 °C).

1,2,6,6-Tetradeuterio-4-*tert*-butylcyclohexene (13).[22] Into a 100-mL flask fitted with a rubber stopple, a magnetic stirring bar, and an inserted thermometer was placed dry TMEDA (60 mL) and hydrazone **12** (1.87g, 6 mmol). The solution was cooled to −45 °C (internal temperature) and, via syringe, *n*-BuLi (10 mL, 24 mmol) was added at such a rate that internal temperature never exceeded −35 °C. External cooling was removed and the deep red solution was allowed to warm to 20 °C. After stirring for 1.5 h, N_2 evolution had ceased and D_2O (6 mL) was added dropwise to the orange solution cooled by an external H_2O bath. The suspension was poured into H_2O (50 mL). After being saturated with NaCl, the aqueous mixture was extracted with pentane (4 × 30 mL). The combined pentane extracts were washed with saturated NH_4Cl solution (2 × 40 mL), dried, filtered, and concentrated on a rotary evaporator. Preparative VPC of the liquid residue yielded 354 mg (41%) of **13.** Integration of the vinyl proton at δ 5.65 indicated ~90% deuteration.

1,2,6,6-Tetradeuterio-4β-*tert*-butyl-1α,2α-dihydroxycyclohexane (14). Diol **14** was prepared according to the literature procedure[23] for the protio analogue. Isotopic content is given in Table III, mp (hexane) 113–5 °C (lit.[23] mp for undeuterated **9** 117–9 °C).

General Procedure for Isomerization of Diols. The appropriate diol (1.0 mmol) was dissolved in 10 mL of diglyme and a slight excess (2.2 mmol) of base was added. The reaction was then placed under inert atmosphere by successive evacuations and fillings with nitrogen. The reaction mixture was stirred at room temperature for 0.5 h, heated to 155 °C for the proper length of time, cooled, and diluted with water. The aqueous solutions were extracted three times with ethyl acetate, and the extracts were combined, washed with saturated brine, dried (Na_2SO_4), and concentrated at the rotary evaporation. Analysis was carried out by GLC as detailed above. The specific runs are indicated in Tables I–III.

All freeze–thaw reactions (runs 4, 5, 9; Table I) were carried out in thick-walled Pyrex tubing. The proper reaction mixtures were placed in the tubes, frozen in liquid N_2 under high vacuum, and allowed to thaw. After five freeze–thaw cycles, the tubes were sealed under high vacuum. After heating for the appropriate time, the tubes were opened, and the contents were analyzed as above.

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Registry No.—**11,** 15649-46-4; **12,** 65253-49-8; **14,** 65253-50-1.

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