The results of a number of interconversions are summarized in Table IV. The melting points of the products are given and

TABLE IV
RESULTS OF INTERCONVERSION OF ISOMERS OF [3]FERROCENOPHANE

Starting isomer	Product	Yield, %	Mp, °C
9 (9:PhCHO; 1:1.5)	17	30	162–164
	9	18	132–134
	25	25	203–207
9 (9:PhCHO; 1:10)	25	61	205–207
12	5	64	113–114
13	6	64	93–96
14	7	53	145–146
15	5	51	110–113
17	9	66	131–134
18	6	64	94–96
22	5	78	112–114
25	17	57	163–165
	9	Trace	

in all cases the nmr spectra of the products were identical with those of the isomer assigned.

Conversion of 2,3′-Diacetyl[3]ferrocenophane (5) to 2-[3][3]-1,3-ferrocenophanylpropionic Acid.—A mixture of 2.38 g (7.6 mmol) of **5** was converted to 1.56 g (55%) of 2,3′-[3]ferrocenophanyldipropionic acid (**26**), mp 158–162°, according to the procedure of Rinehart, *et al.*[2]

The diacid **26** (1.56 g, 4.2 mmol) was dissolved in 100 ml of dry methylene chloride and added slowly to a solution of 5 g (26 mmol) of trifluoroacetic anhydride in 50 ml of cold methylene chloride. The solution was maintained at 0° in a nitrogen atmosphere for 22 hr, then quenched by the addition of 100 ml of 5% sodium bicarbonate. The pH of the solution was adjusted to 6 so that the acid would remain in the organic layer. After separation of the organic layer and the extraction of the aqueous layer, the combined organic fractions were dried ($MgSO_4$) and concentrated. The material was chromatographed on a silica gel column packed in chloroform. Four bands developed. The first band, eluted with chloroform, and the second band, eluted with chloroform–ethyl acetate (3:1), were unidentified. The third band, also eluted with the chloroform–ethyl acetate mixture, yielded 0.63 g (43%) of the crude yellow oily dibridged keto acid. The fourth band, eluted with methanol, was probably a mixture of decomposition products. The keto acid was dissolved in 50 ml of acetic acid and hydrogenated over 0.5 g of platinum oxide at 52 psi for 65 hr. After work-up, a yield of 0.57 g of oil was obtained. Repeated recrystallization from petroleum ether gave 0.28 g (46%) of 2-[3][3]-1,3-ferrocenophanylpropionic acid (**27**), mp 146–148°.

Anal. Calcd for $C_{19}H_{22}O_2Fe$: C, 67.47; H, 6.56; Fe, 16.51. Found: C, 67.63; H, 6.60; Fe, 16.41.

Preparation of 27 from 2-Acetyl[3][3]-1,3-ferrocenophane.—A solution of 3.0 g (11 mmol) of [3][3]-1,3-ferrocenophane (**28**, synthesized according to Rinehart, *et al.*[2]) and 2.75 ml of acetic anhydride in 50 ml of dry methylene chloride was cooled to 0° under nitrogen. BF_3 etherate (4 ml) was added and the solution was stirred at 0° for 30 min and then at 25° for 16 hr. The reaction was quenched by pouring into 50 ml of ice water. After work-up, the crude product was transferred to an alumina column and eluted with petroleum ether (bp 20–40°) to remove a trace of starting material and then 0.60 g (17%) of 2-acetyl[3][3]-1,3-ferrocenophane (**28**). Recrystallization of **28** from hexane yielded orange rods, mp 101–102° (lit.[2] mp 101–102.5°). A third band, eluted with petroleum ether–ether (4:1), yielded 1.9 g (55%) of 4-acetyl[3][3]-1,3-ferrocenophane, mp 148–149° (lit.[2] mp 148.5–149.5°).

A mixture of 0.5 g (1.6 mmol) of **28**, 32 mmol of sodium hydride, and 0.6 g (4.8 mmol) of diethyl carbonate in 30 ml of dry benzene was heated at reflux for 48 hr in a nitrogen atmosphere. After the usual work-up, the crude keto acid was dissolved in 50 ml of acetic acid and hydrogenated over 0.3 g of platinum oxide at 52 psi for 48 hr. The reduced ester was isolated and saponified in refluxing ethanolic 2 *N* sodium hydroxide (1:1 ethanol–water). The crude acid obtained after work-up was purified on a silica gel column packed in chloroform. The first fraction, eluted with chloroform, was a mixture of nonacidic compounds. The acid was eluted with chloroform–ethyl acetate (3:1). Recrystallization from hexane yielded 0.25 g (46%) of yellow needles, mp 146.5–148°, whose nmr and infrared spectra were identical with those of **27** obtained from **5** described above.

Anal. Calcd for $C_{19}H_{22}O_2Fe$: C, 67.47; H, 6.56; Fe, 16.51. Found: C, 67.64; H, 6.59; Fe, 16.53.

The Base-Induced Rearrangement of Epoxides. IV. Reaction of Cyclohexene Oxide with Various Lithium Alkylamides[1]

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The effect of variation of base structure in the reaction with cyclohexene oxide has been explored. The yields of the products 2-cyclohexenol, cyclohexanone, and amino alcohol (nucleophilic substitution) were determined for an extensive series of lithium alkylamides. The yield of 2-cyclohexenol is maximized with lithium di(primary alkyl)amide, being effectively quantitative with lithium di-*n*-propylamide and di-*n*-butylamide. Lithium monoalkylamides in general give low to moderate yields of the allylic alcohol, very little ketone, and extensive amino alcohol adduct formation. Bulky bases favor the formation of ketone at the expense of allylic alcohol. Certain bases cause the rearrangement of 2-cyclohexenol to 3-cyclohexenol, and the mechanism of this transformation has been briefly explored.

The reaction of epoxides with strong bases can occur by at least three major pathways, *viz.*, rearrangement to allylic alcohol, to ketone, or by direct nucleophilic substitution. Our earlier studies have been directed to the first process.[1b] The regiospecificity and stereospecificity exhibited in the reaction of a number of epoxides with lithium diethylamide to give allylic alcohol suggest the considerable synthetic potential of this procedure. This paper describes the results of treating a single model system, cyclohexene oxide, with a wide range of lithium alkylamides, to test the effect of structural variation of the base on the yields of the various possible products.

Results and Discussion

The lithium alkylamide reagents were prepared by treating the appropriate amine in ether with *n*-butyllithium in hexane; 2.5 mol of base were used for each mole of epoxide. The excess of base was used because

(1) (a) Support by the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged. (b) Part III: R. P. Thummel and B. Rickborn, *J. Org. Chem.*, **36**, 1365 (1971).

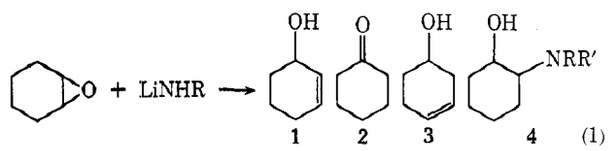
TABLE I

Registry no.	Run	LiNHR, R =	Time, hr[a]	% 1	% 2	% 3	% 4
34566-51-3	1[b]	$C_6H_5CH_2$	24	26	0	0	70
34566-52-4	2[b]	*n*-C_3H_7	17	15	0.5	Trace	77
34566-53-5	3	$C_6H_5CH_2CH_2$	12	42	0	2	49
34566-54-6	4	*i*-C_4H_9	48	77	0	4	19
26372-63-4	5	*c*-C_6H_{11}	52	47	1	9	40
34566-56-8	6[c]	$C_6H_5CH_2(CH_3)CH$	21	53	0	4	39
34566-57-9	7	*i*-C_3H_7	41	75	0.5	5	10
34566-58-0	8	*sec*-C_4H_9	41	69	0	8	20
34566-59-1	9	*t*-C_4H_9	27[d]	60[d]	4	0	2

[a] The time required for loss of >93% of epoxide in all cases except run 9. Yields were determined by peak area measurement of vpc traces, using an inert internal standard as reference. [b] Cyclohexanol was also observed in some runs as follows: run 1, 3%; 2, 1.2%; 7, 0.6%. [c] *trans*-β-methylstyrene was formed in this reaction, presumably by base-induced elimination of either $LiNH_2$ or Li_2NH. [d] 66% of the epoxide was consumed in this time.

of a side reaction, the fragmentation of the ether solvent,[2] which consumes some of the amide reagent.

Lithium monoalkylamides provide a considerable range in yield of the 2-cyclohexenol product, with most of the remainder of the material balance appearing as amino alcohol adduct (these products were in most instances not specifically identified, but inferred from a relatively long retention time peak in the vpc trace). The data for the reaction shown in eq 1 are displayed in Table I. Several generalizations can be made. The primary alkylamides tend to give mostly adduct **4**, although the relatively bulky lithium isobutylamide does furnish 77% of the allylic alcohol **1**. The mono-



(1)

alkylamides, with one exception, do not give significant amounts of cyclohexanone. The exception is the only mono-*tert*-alkylamide examined (entry 9 in Table I). The rates of formation of adduct **4**, as judged from yields and the time required for reaction, vary in a manner consistent with a reaction having significant steric requirements. It appears that a major factor in the reaction of cyclohexene oxide with monoalkylamides is not the enhanced rate of formation of **4**, but rather the diminished rate (compared to lithium dialkylamide reactions) of the processes leading to **1** and **2**.

The relatively long times required for the reactions listed in Table I appear in part to be responsible for an interesting side reaction, the formation of homoallylic alcohol **3**. This process, described in greater detail later in this paper, occurs by further rearrangement of the initially formed 2-cyclohexenol.

The results obtained on treatment of cyclohexene oxide with a number of lithium dialkylamides are shown in Table II. In all instances the reactions are considerably faster than with the lithium monoalkylamides, requiring from 0.5 to 4 hr for complete consumption of the epoxide starting material.

The historically most widely used base, lithium diethylamide, gives a high yield of **1** (run 10), accompanied by a small amount of **2** and 10% of amino alcohol adduct. Although it might be thought difficult to improve on this already excellent yield, both lithium di-*n*-propylamide and di-*n*-butylamide furnish **1** in effectively quantitative yield. The significant advantage in the use of either of these bases over lithium diethylamide is not so much in diminished amino alcohol adduct formation (this material is easily separated from the allylic alcohol), but rather the absence of the isomeric products **2** and **3**, which in practice are difficult to separate from **1**. These two bases (runs 11 and 12) thus are the recommended reagents when a high yield of pure allylic alcohol is desired.

The further rearrangement of **1** to **3** fails to occur with a number of lithium dialkylamides, and in particular lithium diethylamide and di-*sec*-butylamide show negligible formation of **3** even on prolonged (>200 hr) treatment of **1**. Initially this observation led to the suspicion that an NH grouping was required in the lithium amide base to effect this rearrangement, but the data from runs 13, 14, 15, and 21 show that this is not the case. In fact, cyclic dialkylamides, exemplified best by *N*-lithiopyrrolidine (run 13), are the most effective of the bases examined in this work for carrying out the rearrangement of **1** to **3**, as well as the reverse reaction.

Although in some instances ketone may be formed by subsequent rearrangement of allylic alcohol under the basic reaction conditions,[3,4] this was not the case in the present study. The proportions of **1** and **2** shown in Table II remain constant through the course of the reactions, and in general the allylic alcohol is not converted to cyclohexanone even under extended treatment. The ketone is thus a primary product, presumably formed *via* the α-abstraction mechanism originally proposed by Cope[5] and more recently examined in detail by Crandall.[6] It is interesting that the competition between α- and β-proton abstraction increasingly favors the former process as the bulk of the lithium dialkylamide is increased. In the only di-*tert*-alkylamide examined (run 23), ketone formation clearly predominates. Although it is tempting to speculate that this effect is due to the greater steric requirements for β-proton abstraction (leading to allylic alcohol), this view is not supported by the relative rates as estimated from the reaction times shown in Table II. In other words, it does not appear that ketone

(2) Unpublished work of Brian H. Williams; ethanol has been identified as a product of this fragmentation. The longer times required for some reactions lead to the formation of lithium ethoxide, which appears as a white solid precipitate. The limited solubility of many lithium alkylamides mitigates against the use of hydrocarbon solvent alone. Recently we have found that THF can serve as an unreactive substitute for diethyl ether.

(3) J. K. Crandall and L. C. Lin, *J. Org. Chem.*, **33**, 2375 (1968).
(4) B. Rickborn and R. P. Thummel, *ibid.*, **34**, 3583 (1969).
(5) A. C. Cope and B. D. Tiffany, *J. Amer. Chem. Soc.*, **73**, 4158 (1951).
(6) J. K. Crandall, L. C. Crawley, D. B. Banks, and L. C. Lin, *J. Org. Chem.*, **36**, 510 (1971).

TABLE II

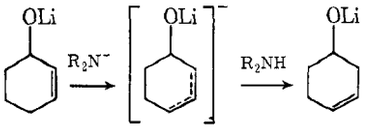
Registry no.	Run	R_2NLi	Time, hr[a]	% 1[b]	% 2	% 3	% 4
25347-30-2	10	$(C_2H_6)_2N$	2	86	3	0	10
34566-61-5	11	$(n\text{-}C_3H_7)_2N$	2	>99	<0.5	<0.5	0
34566-62-6	12	$(n\text{-}C_4H_9)_2N$	4	97	0	<0.5	3
34566-63-7	13[c]		1	63	0	17	15
24316-38-9	14		1	72	Trace	8	11
34566-65-9	15	$(i\text{-}C_4H_9)_2N$	2	68	10	5	18
34566-66-0	16[d]	$C_6H_5CH_2CH(CH_3)N(CH_3)$	4	79	0	0	20
26396-97-4	17[e]	$(i\text{-}C_3H_7)_2N$	3	38	33	0	28
34566-16-0	18[e]	$(sec\text{-}C_4H_9)_2N$	2	40	46	0	13
34566-17-1	19[c,e]	$(c\text{-}C_6H_{11})_2N$	2	54	39	<1	3
34566-18-2	20[e]		2	58	8	0	32
34566-19-3	21[e]		3	75	2	4	14
34566-20-6	22[c,e]	$(c\text{-}C_6H_{11})N(i\text{-}C_3H_7)$	2	46	38	0	12
34566-21-7	23[e]		0.5	31	62	0	7

[a] The time required for loss of >97% of epoxide. [b] Yields as determined by vpc analysis using mesitylene as an internal standard. [c] A small amount of material with retention time identical with that of 2-cyclohexenone was observed in runs 13, 19, and 22. [d] *trans*-β-Methylstyrene was also formed in this run. [e] A small amount (0.5–2%) of cyclohexanol was formed in runs 17–23.

formation is associated with a lower rate of formation of allylic alcohol. The basis for the observed selectivity thus remains in doubt. It is also worth noting that even the most bulky bases still lead to some substitution product **4**; in fact, this process is minimized with the relatively unhindered lithium di-*n*-alkylamides.

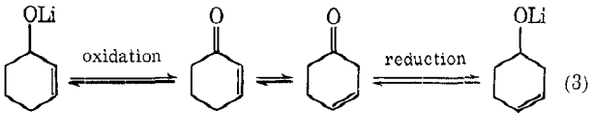
Cyclohexylisopropylamide (run 22) was included in this study after seeing it recommended for a novel ester alkylation procedure by Rathke and Lindert.[7] In the present work it offers no particular advantage over other di-*sec*-alkylamides.

The mechanism of the rearrangement of **1** to **3** was examined in some detail, particularly because of our interest in determining the potential of the base-induced rearrangement of epoxides to generate optically active allylic alcohols by asymmetric induction. At least two reasonable pathways may be considered for the conversion of **1** to **3**. One would involve proton abstraction to give an allylic carbanion with subsequent reprotonation to give the rearranged material (eq 2). Alternatively, one might envision the lithium



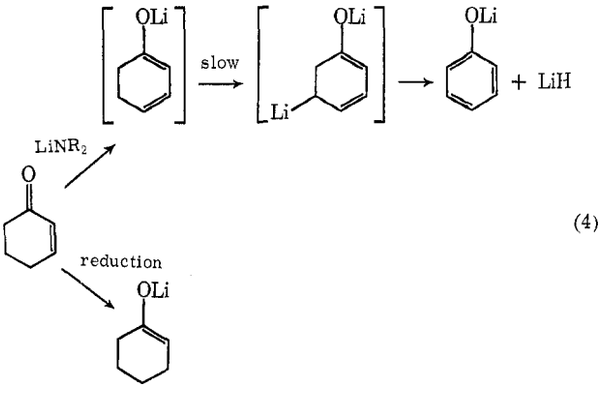
(2)

salt of **1** acting as a hydride donor for any available reducible species (*e.g.*, epoxide, ketone). The 2-cyclohexenone generated in this manner could undergo base-catalyzed equilibration to 3-cyclohexenone, which, acting in turn as a hydride acceptor, would lead to 3-cyclohexenol (eq 3). Rearrangement by this mechanism would necessarily involve loss of asymmetry. Several experiments were carried out to probe this mechanistic question.



(3)

When the possible intermediate 2-cyclohexenone is added to a solution of lithium dialkylamide, it is consumed with formation of cyclohexanone and phenol. Although these are the products anticipated from a disproportionation of the enolate of 2-cyclohexenone, in fact such a process does not appear to be important. Substantial yields of phenol were formed with the several bases used, but the yields of cyclohexanone were variable, and always too low to be accounted for by this disproportionation. Furthermore, the saturated ketone was formed rapidly on mixing the reagents, while the yield of phenol increased with time. Finally, evidence was obtained for the formation of LiH (evolution of hydrogen on quenching); taken together these data suggest the following course for the reaction of 2-cyclohexenone with lithium dialkylamide (eq 4).[8]



(4)

(7) M. Rathke and A. Lindert, *J. Amer. Chem. Soc.*, **93**, 2318 (1971).

(8) The aromatization of this system and others through the loss of LiH has been confirmed by Brian H. Williams (unpublished work).

Thus the cyclohexanone is formed *via* conjugate reduction of the enone, with lithium alkylamide providing the necessary hydride.[9] Very likely the traces of cyclohexanol observed in many of the reactions described in Tables I and II are formed in similar fashion by reduction of cyclohexene oxide. Of primary concern to the present mechanistic question, however, is the fact that in no instance did 2-cyclohexenone generate measurable quantities of either 2-cyclohexenol or 3-cyclohexenol under the basic reaction conditions. This clearly rules out the mechanism shown in eq 3 as a viable pathway for the rearrangement of **1** to **3**, leaving eq 2 as the preferred depiction.

Two experiments were carried out in an attempt to establish the equilibrium concentrations of **1** and **3** (as their lithium salts). Treatment of **1** with 2.5 equiv of lithium *sec*-butylamide for 405 hr gave a mixture of 52% of **1** and 48% of **3**. Similar treatment of **3** after 435 hr gave 19% of **1** and 81% of **3**. While these data do not accurately establish the position of equilibrium, they suggest that **3** is slightly favored, probably comprising 70 ± 10% of the mixture at equilibrium.

Finally, some experiments were carried out to explore the effects of changing solvent, initial concentration of base, and other variables on the reaction with cyclohexene oxide. The data are shown in Table III. Com-

TABLE III

Run	Base (equiv)	Time, hr	% 1	% 2	% 4
24	$LiN(C_2H_5)_2$ (2.5) Ether solvent	10	83	0	15
25	$LiN(C_2H_5)_2$ (1.5)	3	95	0.5	4.5
26	$LiN(i\text{-}C_4H_9)_2$ (1.5)	5	83	4	11
27	$LiN(i\text{-}C_3H_7)_2$ (1.5)	3	75	23	0
28	$LiN(sec\text{-}C_4H_9)_2$ (1.5)	3	55	41	0.5
29	$LiN(sec\text{-}C_4H_9)_2$ (1.5) $n\text{-}C_4H_9Li$ (1.5)	3	51	48	0.5
30	$LiN(sec\text{-}C_4H_9)_2$ (1.5) $HN(C_4H_9)_2$ (1.5)	3	64	34	2
31	$n\text{-}C_4H_9Li$ (1.5)	4	89	11	

parison of run 24 with run 10 (Table I) shows that diethyl ether alone as solvent slows down the reaction somewhat, but does not greatly affect the product distribution relative to the reaction carried out in the usual ether–hexane mixture.

The effect of lower initial concentration of base (compare runs 25, 26, 27, and 28 with their counterpart runs 10, 15, 17, and 18) is to enhance the formation of **1** at the expense of both **2** and **4**.

(9) This is the nitrogen analog of the Meerwein–Ponndorf–Verley reduction; hydride transfer reduction processes involving lithium alkylamides have been described in the work of G. Wittig and A. Hesse, *Justus Liebigs Ann. Chem.*, **746**, 174 (1971).

The last four entries in Table III examine the effects of excess amine or butyllithium on the reaction with cyclohexene oxide. Butyllithium alone (run 31) gives no measurable alkylation product under these reaction conditions; the proportion of ketone formed is somewhat larger than with lithium diethylamide, but less than that formed with the bulkier amides (*cf.* run 28). Excess free amine does not appreciably alter the rate of reaction, although a small change in product distribution occurs.[10]

Experimental Section

The cyclohexene oxide used in this study was prepared by the peracetic acid method[12] from the olefin in 87% distilled yield, bp 130–132°, and was shown by vpc and spectral analysis to be free of impurities.

With the exceptions noted below, all amines were commercial materials purified by distillation from KOH pellets before use. When this purification procedure was followed, all of the lithium alkylamides subsequently formed were completely soluble in the ether–hexane reaction mixtures.

Di-*sec*-Butylamine.—*sec*-Butylamine (40 mmol) and 40 mmol of 2-bromobutane were refluxed together without solvent for 24 hr. On cooling, a pale yellow, crystalline solid was obtained, which was carefully added to concentrated aqueous KOH solution. The organic layer was separated and distilled from KOH pellets at atmospheric pressure to give 5.0 g (97%) of di-*sec*-butylamine, bp 132–134° (lit.[13] bp 132–134°), picrate mp 107–109° (lit.[14] mp 111°).

Cyclohexylisopropylamine.—To a mixture of 1.0 mol of cyclohexylamine and 1.1 mol of acetone were added five drops of concentrated hydrochloric acid and 7 g of 4A molecular sieve. This mixture was stirred for 30 hr at ambient temperature; KOH pellets were added and the mixture was distilled to give 92 g (97%) of the imine, bp 96–100° (59 Torr).[15] A sample, 6.9 g (50 mmol), of the imine was reduced by adding it to a solution of 1.9 g (50 mmol) of sodium borohydride in 100 ml of isopropyl alcohol at 0°. After 10 min, 10 ml of concentrated aqueous sodium hydroxide was added, and the organic phase was separated and distilled to give 6.3 g (90%) of cyclohexylisopropylamine, bp 55–57° (9 Torr).[15]

Epoxide Rearrangements.—To a solution of 0.025 mol of the appropriate amine in 10 ml of anhydrous ether was added 15.5 ml of commercial 15% *n*-butyllithium in hexane. The epoxide (0.98 g, 0.01 mol) was then added and the mixture was refluxed; the course of the reaction was followed by removing aliquots, quenching with water (salt saturated), and vpc analysis of the organic phase, using a Carbowax 6M column. In several instances the amino alcohol adduct was isolated by preparative vpc; although not fully characterized, these materials exhibited the anticipated nmr and ir spectral features.

Registry No.—Cyclohexene oxide, 286-20-4.

(10) A complex composed of 1 mol of lithium diethylamide and 2 mol of diethylamine has recently been identified as the active species in the addition reaction to butadiene.[11]

(11) N. Imai, T. Narita, and T. Tsuruta, *Tetrahedron Lett.*, 3517 (1971).

(12) M. Korach, D. R. Nielsen, and W. H. Rideout, *J. Amer. Chem. Soc.*, **82**, 4328 (1960).

(13) A. Fleury-Larsonneau, *Bull. Soc. Chim. Fr.*, **6**, 1567 (1939).

(14) J. Mitchell, Jr., and W. M. D. Bryant, *J. Amer. Chem. Soc.*, **65**, 128 (1943).

(15) D. G. Norton, V. E. Haury, F. C. Davis, L. J. Mitchell, and S. A. Ballard, *J. Org. Chem.*, **19**, 1054 (1954).